Technische Universität München
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Retrospective Analysis of Clinical Features and ECG Changes after Out-Of-Hospital Cardiac Arrest due to Myocardial Infarction and Their Impact on Survival

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Abbreviations

ACS	Acute Coronary Syndrome
AED	Automated external defibrillator
AF	Atrial fibrillation
AMI	Acute myocardial infarction
AV	Atrioventricular
BBB	Bundle branch block
BMS	Bare metal stent
b.p.m	Beats per minute
CA	Cardiac arrest
CAG	Coronary angiography
CAD	Coronary artery disease
CI	Confidence interval
CL	Culprit Lesion
CM	Cardiomyopathy
COPD	Chronic obstructive pulmonary disease
CPR	Cardiopulmonary resuscitation
cTN	Cardiac troponin values
CVRF	Cardiovascular risk factors
DES	Drug eluting stent
ECG	Electrocardiogram
ELAD	Extreme left axis deviation
EMS	Emergency Medical Services
ER	Early repolarization
ERAD	Extreme right axis deviation
EuReCa	European Registry of Cardiac Arrest
HR	Hazard ratio
ICD	Implantable cardioverter defibrillator
IHCA	In – hospital cardiac arrest
IQR	Interquartile range
LAFB	Left anterior fascicular block
LBBB	Left bundle branch block

LAD	Left anterior descending artery
LCA	Left coronary artery
LCX	Left circumflex artery
LVEF	Left ventricular ejection fraction
LVH	Left ventricular hypertrophy
MI	Myocardial infarction
NSTE	Non – ST – segment elevation
NSTEMI	Non – ST – elevation myocardial infarction
OHCA	Out – of – hospital cardiac arrest
PAC	Premature atrial contraction
PCI	Percutaneous coronary intervention
PQd	PQ duration
PTCA	Percutaneous transluminal coronary angioplasty
PVC	Premature ventricular contraction
QRSd	QRS duration
QTc	QT duration corrected for the heart rate
QTd	QT duration
RBBB	Right bundle branch block
RCA	Right coronary artery
ROSC	Return of spontaneous circulation
RT	Reperfusion therapy
SCA	Sudden cardiac arrest
SCD	Sudden cardiac death
SD	Standard deviation
SR	Sinus rhythm
STE	ST – segment elevation
STEMI	ST – Elevation myocardial infarction
SUDS	Sudden Unexpected Death Study
TpTe	T peak to T end interval
TpTec	T peak to T end interval corrected for the heart rate
TTM	Targeted temperature management
VA	Ventricular arrhythmia
VF	Ventricular fibrillation

VT	Ventricular tachycardia

1 Introduction

1.1 Sudden Cardiac Arrest and Sudden Cardiac Death

1.1.1 Definition

Sudden cardiac arrest (SCA) is the sudden stop of all cardiac activity, resulting in haemodynamic collapse. A cardiac cause for the arrest is presumed unless there is a likely or known non-cardiac cause such as respiratory failure or trauma. (Al-Khatib et al., 2018; Zeppenfeld et al., 2022). According to the setting the SCA occurs in, SCA is further differentiated into in-hospital cardiac arrest (IHCA) and out-of-hospital cardiac arrest (OHCA), which differ in survival rates. (Gräsner et al., 2021) If resuscitation efforts after SCA prove to be unsuccessful, sudden cardiac death (SCD) is the consequence.

Sudden death is defined as a fatal event in a healthy subject, that occurs up to one hour after the onset of symptoms. If the event is not witnessed, but the victim was in good health 24 hours before, the death is also considered sudden. Sudden cardiac death requires the death to not only occur sudden but due to a cardiac cause. This is the case if the patient was suffering from a potentially fatal cardiac condition, the autopsy identified a cardiac cause, or no obvious extra-cardiac cause could be found. (Zeppenfeld et al., 2022)

In earlier studies, criteria for SCD have been less strict, considering deaths within 24 hours of the onset of symptoms as sudden (el Fawal et al., 1987). More recent studies, however, use the definitions as written above, which are found in current guidelines.

1.1.2 Epidemiology

There is an estimated number of 300,000 people who suffer a SCA in Europe each year (Zeppenfeld et al., 2022). The reported annual incidence of OHCA in Europe ranges between 64 to 170 per 100,000 inhabitants and varies greatly between and within countries. However, the true incidence remains unknown, due to lack of national registries in many countries and the literature being largely based on OHCA attended by emergency medical services (EMS) only. (Gräsner et al., 2021) The most comprehensive information concerning the epidemiology of OHCA is provided by the European Registry of Cardiac Arrest (EuReCa). There have been two prospective studies, EuReCa ONE and TWO which included 27 and 28 European countries respectively. EuReCa ONE investigated the incidence and outcome of OHCA in Europe over the period of one

month. They estimated an annual incidence of 84 OHCA per 100,000 inhabitants, with a range between 28 to 160 (Gräsner et al., 2016). The EuReCa TWO study looked at a period of three months and reported a similar incidence of 89 per 100,000 inhabitants per year, with a range between 53 to 166 (Gräsner et al., 2020). Resuscitation is attempted in approximately 50 – 60% of cases by EMS, again with a great variability between countries (Gräsner et al., 2021).

In the US about 356,461 people suffer a SCA annually. The Cardiac Arrest Registry to Enhance Survival continuously investigates the incidence of OHCA in the United States treated by EMS. In 2019 they reported an incidence of 76.5 per 100,000, varying from 41.8 to 126.1 (Virani et al., 2021). Resuscitation attempts are reported in 52% of cases (Virani et al., 2021). Overall numbers reported in the US and Europe show similar incidences.

IHCA is reported to occur in an estimated 1.5 to 2.8 patients per 1,000 hospital admissions in Europe. The Swedish Cardiopulmonary Resuscitation Register estimates the ratio of OHCA to IHCA at 1.7 to 1. (Gräsner et al., 2021) In the US incidence numbers are reported to be higher with 10.6 cases of IHCA per 1,000 hospital admissions (Virani et al., 2021). However there has also been a multicentre study reporting a median of 4 IHCA per 1,000 hospital admissions (Bradley et al., 2017).

Not only incidences but also survival rates differ between in and out-of-hospital cardiac arrest. Typically, survival after IHCA is better than after OHCA as treatment is more readily available in the hospital setting. In Europe 15 – 34% of patients survive to hospital discharge/30 days after IHCA (Gräsner et al., 2021).

Overall, only about 10% of patients survive a sudden cardiac arrest occurring out-of-hospital. (Empana et al., 2018) The survival rate again differs greatly between and within countries. In Europe a range between 0 and 18% has been reported. (Gräsner et al., 2021) The EuReCa TWO study shows a survival rate of 8% overall. (Gräsner et al., 2020) In the US in 2019 numbers showed, 10.5% of patients survived to hospital discharge after suffering an OHCA. (Virani et al., 2021) A systematic review and meta–analysis of studies worldwide found a rate of survival to hospital admission of 22% and to hospital discharge of 8.8%. Survival was better if patients received bystander cardiopulmonary resuscitation (CPR) and among patients in Western Countries. (Yan et al., 2020)

Survival after OHCA depends on many different factors. Some unmodifiable like age, gender, existing comorbidities, specific cause of arrest, and initial arrest rhythm.

However, quality of treatment has an impact on survival as well, for example whether bystander CPR is performed, whether an automated external defibrillator (AED) is used and whether specific post-resuscitation measures are available, like percutaneous coronary intervention (PCI). (Gräsner et al., 2021)

With survival after SCA being so low, its epidemiology is necessarily connected with the occurrence of SCD. Just like with SCA, the absolute numbers reported for SCD vary, depending on the epidemiological methods and exact definitions used to assess the population burden. The ESC Guideline on the prevention of SCD reports an incidence of 50 per 100,000 person years in individuals in the fifth to sixth decade of life. While the incidence rate is drastically lower in childhood with 1 per 100,000 person years, it reaches a minimum of 200 per 100,000 person years in the eighth decade of life. (Zeppenfeld et al., 2022) Overall, SCD is estimated to account for 10-20% of deaths in Europe. (Lynge et al., 2021; Zeppenfeld et al., 2022)

The guidelines published by the AHA/ACC/HRS on the same topic, make SCD responsible for approximately 230,000 to 350,000 deaths in the USA annually, with a range of 170,000 to 450,000 (Al-Khatib et al., 2018)

Chugh estimates 350,000 sudden cardiac deaths per year in the USA, 700,000 in Europe and four to five million worldwide (Chugh, 2017).

How greatly the method used influences the incidence reported, is shown by Chugh et al. comparing a retrospective and prospective analysis of SCD cases. For the prospective approach, protocols of EMS, family doctors and hospitals as well as autopsy reports were used to analyse the circumstances of death. They found an incidence rate of 53 SCD per 100,000/year. The retrospective analysis of death certificates however yielded an incidence rate of 153/100,000/year. This almost three-fold difference highlights the difficulty of assessing SCD incidence. (Chugh et al., 2004)

There have been several community-based studies, evaluating the incidence of sudden cardiac death. Martens et al. retrospectively analysed data from the EMS in the city of Aurich, Germany, identifying all cases of SCD. The results showed an incidence rate of 81 cases per 100,000 persons per year. This rate proved to be stable over the whole eight-year period. (Martens, E. et al., 2014)

One of the largest epidemiological studies on sudden cardiac death, is the Oregon Sudden Unexpected Death Study (SUDS), which has been started in 2002 and is still ongoing. In this prospective study all sudden cardiac deaths or arrests in Multnomah

County, Oregon are identified. The emergency medical response system, the county medical examiner's office and 16 area hospitals are used as sources and every potential case is carefully screened to make sure it meets the criteria for SCD. (Chugh et al., 2004) In 2006 they reported an SCD incidence of 54/100,000/year (Stecker et al., 2006).

There has been a downwards trend in SCD numbers between 2004 and 2011. Since 2012 however, the incidence rate is on the rise again, along with a rise in cardiovascular mortality overall. (Benjamin et al., 2019; Reinier et al., 2020)

Despite the differences in the absolute SCD numbers reported in the literature, it is widely accepted that SCD accounts for around 50% of all cardiovascular deaths (Goldberger et al., 2011; Myerburg & Junttila, 2012; Zeppenfeld et al., 2022). Additionally, up to 50% are first symptomatic cardiac events, in people with no previously diagnosed heart disease or patients with an individual risk prediction suggesting a low risk (Fishman et al., 2010; Myerburg, 2001; Myerburg & Junttila, 2012; Zeppenfeld et al., 2022).

With cardiovascular disease being the number one cause of death worldwide (WHO, 2017) this highlights that sudden cardiac arrest and death are a major public health problem that needs to be addressed.

Looking at women and men separately, they are differently affected by sudden cardiac death. Overall two thirds of all SCD cases occur in men (Krokhaleva & Vaseghi, 2019).

Most recent findings in the Oregon SUDS showed incidence rates of 30/100,000/year in women and 58/100,000/year in men (Reinier et al., 2020). Martens et al. reported similar numbers with 55/100,000/year and 25/100,000/year for men and women respectively. A study in Denmark showed an incidence rate ratio of 1.99 between men and women, that were aged 75 years or younger. (Ågesen et al., 2021)

Furthermore, as can be seen in the incidence numbers above, increasing age is a risk factor for SCA, even though the association is not linear. Adults and children under 35 years of age have an annual risk of SCD of 1/100,000 overall. This is in contrast to the much higher risk of 1 case of SCD per 1000 people every year in the general population over 35, with a lower incidence at the younger end of the spectrum and an increasing risk in the elderly. (Myerburg, 2001)

In the German population of Aurich, the incidence rate peaked for the group aged 70 – 80 years (Martens, E. et al., 2014). However, a lifetime risk analysis suggested, that the

incidence for SCD decreases again in the very old, especially in people over 75 years of age (Bogle et al., 2016).

Even though the burden of SCD is higher in older people, 34% of all patients are still under 65 years of age (Martens, E. et al., 2014).

Overall numbers show, that SCA and consequently SCD constitute a major health issue, which concerns a large number of people of all ages. The very poor survival rates of SCA make it necessary to improve risk prediction and treatment options, in order to reduce SCD.

1.1.3 Pathophysiology

SCD has a big variety of underlying conditions, from coronary artery disease (CAD) to congestive heart failure, cardiomyopathy (CM), myocarditis or hereditary electrical heart diseases, as can be seen in Figure 1. The leading cause is CAD, accounting for 70 – 80% overall. CAD mostly manifests as acute coronary syndrome (ACS). ACS is responsible for about 60% of OHCA. Beyond CAD the pathology is very heterogenous, including different types of CM, inherited electrical heart diseases, valvular heart diseases, hypertrophy and more. In approximately 5% of cases no cause can be identified, even after autopsy. (Geri et al., 2017; Hayashi et al., 2015; Myerburg & Junttila, 2012; Zeppenfeld et al., 2022)

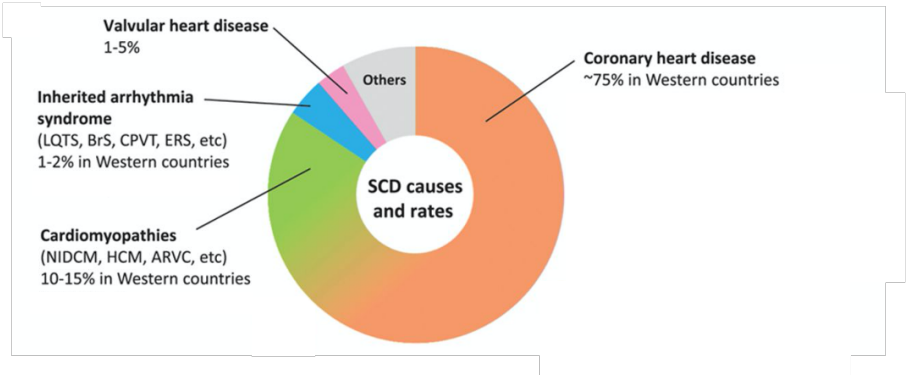

Figure 1 Causes of Sudden cardiac death modified from (Hayashi et al., 2015)

NIDCM = non – ischemic dilated cardiomyopathy, HCM = hypertrophic cardiomyopathy, ARVC = arrhythmogenic right ventricular cardiomyopathy, LQTS = long – QT syndrome, BrS = Brugada syndrome, CPVT = catecholaminergic polymorphic ventricular tachycardia, ERS = early repolarisation syndrome

The diseases associated with SCD differ between the different age groups, which is illustrated in Figure 2. Chronic degenerative diseases, such as CAD, valvular heart diseases and heart failure predominate in older populations. In younger adults and

children primary ion channelopathies, hypertrophic cardiomyopathies, coronary artery anomalies, myocarditis and arrhythmogenic right ventricular cardiomyopathy as well as substance abuse play a more important role. (Hayashi et al., 2015; Priori et al., 2015; Zeppenfeld et al., 2022)

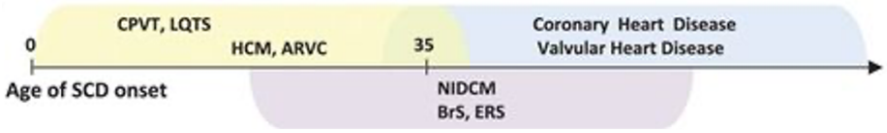

Figure 2 Age of SCD onset in different diseases (Hayashi et al., 2015)

NIDCM = non – ischemic dilated cardiomyopathy, HCM = hypertrophic cardiomyopathy, ARVC = arrhythmogenic right ventricular cardiomyopathy, LQTS = long – QT syndrome, BrS = Brugada syndrome, CPVT = catecholaminergic polymorphic ventricular tachycardia, ERS = early repolarisation syndrome

However recent data has shown, that CAD is the predominant cause for SCA and death in young adults as well. (Waldmann et al., 2019) This corresponds to the rise in CAD and myocardial infarction in young adults over the last 20 years. (Arora et al., 2019) Waldmann et. al. investigated the aetiology in patients between 18 and 40 years of age. They found that 40.8% had CAD as underlying cause for the arrest. In patients aged between 30 and 40 years, the percentage was even greater with 53.7%. CAD presents itself in the form of acute coronary syndrome (ACS) in 86.2% of times in these patients. Potentially due to the lack of collateral circulation, young patients have a greater risk of myocardial infarction (MI) related SCA. (Waldmann et al., 2019)

Causes of SCD do not just vary with age but also with gender. CAD is found more often in men than in women, while women are more likely to have a non – ischemic cause of SCD. The Fingesture study collected clinical and autopsy data from subjects with SCD in Northern Finland between 1998 and 2017. They compared the causes of death determined in the autopsy between men and women. Ischemic heart disease was found in 72% of women and 76% of men, while there was a non – ischemic cause in 28% and 24% in women and men respectively. (Haukilahti et al., 2019)

Earlier studies found an even greater difference with CAD in 40 – 50% of women as opposed to 80 – 90% in men. (Albert et al., 1996; Spain et al., 1960)

Even though CAD is still the most common cause of SCD, the proportion of SCDs attributable to ischemic heart disease overall, is decreasing. Meanwhile the proportion associated with both hypertensive heart disease and myocardial fibrosis has increased.

(Junttila et al., 2016) Non-ischemic SCD is most commonly caused by various types of cardiomyopathies, with obesity-related-CM, alcoholic-CM, hypertensive-CM and idiopathic-fibrotic-CM making up the largest proportions. (Hookana et al., 2011) In addition, recent trends showed, that victims of out-of-hospital cardiac arrest that were admitted to a hospital alive, are becoming more likely to have cardiovascular risk factors such as diabetes mellitus, hypertension and dyslipidaemia. At the same time, they are less likely to have manifest cardiovascular disease. (Wong et al., 2014)

The underlying mechanism in all these various conditions is presumed to be an electrical instability that leads to a lethal arrythmia. (Hayashi et al., 2015) The arrythmia is a result of the interaction between an arrhythmogenic substrate, an exacerbating factor, and a triggering event. A structural abnormality, such as CAD, left ventricular hypertrophy (LVH), myopathic ventricles or primary arrhythmic diseases, serves as the substrate. Ischemia, systemic factors (e.g., electrolyte disturbances, hemodynamic dysfunction, etc.), autonomic fluctuations or drugs can lead to electrical instability and destabilise the myocardial membrane. This combination then makes the heart susceptible to a simple triggering event, such as a premature ventricular contraction (PVC) and results in ventricular tachycardia or fibrillation. (Hata et al., 2003; Myerburg et al., 1992)

1.1.4 Risk Factors

Manifest structural or electrical heart disease is of course associated with a higher risk of SCA and SCD. However as mentioned above, the majority of cases occurs in individuals without diagnosed cardiovascular diseases, making it necessary to find other risk factors than manifest disease. (Hayashi et al., 2015)

Due to CAD being the principal cause for SCA, the most effective risk prediction in the general population, is by identifying risk factors for the development of CAD. (Zeppenfeld et al., 2022) Major risk factors include hypertension, smoking, obesity, hypercholesterolemia, diabetes mellitus and a positive family history. (Adabag et al., 2010; Visseren et al., 2021) Old age and male gender also constitute important risk factors, as is evident from the incidence numbers presented above. (Adabag et al., 2010; Al-Khatib et al., 2018) Although models for risk stratification in the general population have been proposed, currently there is no evidence for a clear benefit of mass screening programs. (Zeppenfeld et al., 2022)

Individual risk prediction is a big challenge, complicated by the fact, that even though there is a large number of SCA in the population overall, the individual risk remains low. (Al-Khatib et al., 2018) There have been many predictors suggested by researchers, including non-invasive markers like heart rate variability, abnormal electrocardiogram (ECG) and LV dysfunction, but none of them have been integrated into clinical practice. (Adabag et al., 2010; Zeppenfeld et al., 2022)

1.1.5 Diagnostic Evaluation and Treatment

The key to treating a sudden cardiac arrest, is the immediate start of CPR, in every unconscious person with abnormal or no breathing. Basic life support should be applied, with 30 chest compressions and 2 rescue breaths as soon as possible, and an AED should be used. (Olasveengen et al., 2021)

It is clear in the literature, that bystander CPR is one of the most important measures when it comes to improving survival, as it limits the time without circulation. Consequently, it also improves neurological outcome. (Hasselqvist-Ax et al., 2015) The use of an AED has been shown to improve survival as well. (Hallstrom et al., 2004)

When EMS arrive, advanced life support, according to current ERC guidelines, should be initiated immediately. (Soar et al., 2021)

There is some evidence for improved survival if patients are transported to a cardiac arrest center. There is no clear definition for such institutions, however it is usually described as a facility that can provide evidence-based resuscitation treatment with 24/7 availability of PCI, imaging facilities and a critical care unit. (Nolan et al., 2021)

The most important diagnostic tool when return of spontaneous circulation (ROSC) is achieved, is a 12-lead ECG, as it is readily available and can confirm a cardiac cause, such as a ST-elevation myocardial infarction (STEMI). (Nolan et al., 2021; Zeppenfeld et al., 2022)

If an ST-elevation is identified, immediate Coronary angiography (CAG) and PCI are indicated to identify and treat the culprit lesion (CL). (Nolan et al., 2021; Zeppenfeld et al., 2022) Several metanalyses (Khan, M. S. et al., 2017; Meng-Chang et al., 2020; Welsford et al., 2018) and two prospective observational studies (Dumas et al., 2016; Vadeboncoeur et al., 2018) have found a benefit of immediate CAG in patients presenting with Non-ST-elevation myocardial infarction (NSTEMI) as well. However recently, three large randomized controlled trials found no benefit in immediate CAG in

patients with cardiac arrest (CA) without ST-elevation compared to delayed CAG. (Desch et al., 2021; Hauw-Berlemont et al., 2022; Lemkes et al., 2020) Given the high proportion of coronary occlusions in SCA patients, the current ESC Guidelines still recommend CAG in patients without ST-elevations, if they exhibit electrical instability that is likely due to myocardial infarction and if there is a high suspicion of ongoing myocardial ischemia (e.g., uncertain or abnormal ECG, CAD in patient history or chest pain prior to arrest). (Ibanez et al., 2018; Zeppenfeld et al., 2022)

Nevertheless, in patients without ST-elevation, a quick evaluation for extra cardiac causes (such as pulmonary embolism, cerebrovascular events or intoxication) is considered sensible. Especially the performance of an echocardiography is recommended immediately after the ECG, as it can show wall motion abnormalities suggestive of myocardial infarction as well as alternative pathologies like right ventricular dilatation (indicating pulmonary embolism) or aortic dissection. (Collet et al., 2021; Ibanez et al., 2018)

If there are no signs for a cardiac cause, brain and chest CT scans should be performed, together with a toxicological blood analysis. (Nolan et al., 2021; Zeppenfeld et al., 2022) Figure 3 shows the algorithm for early evaluation and treatment of SCA as presented in the 2022 ESC Guidelines.

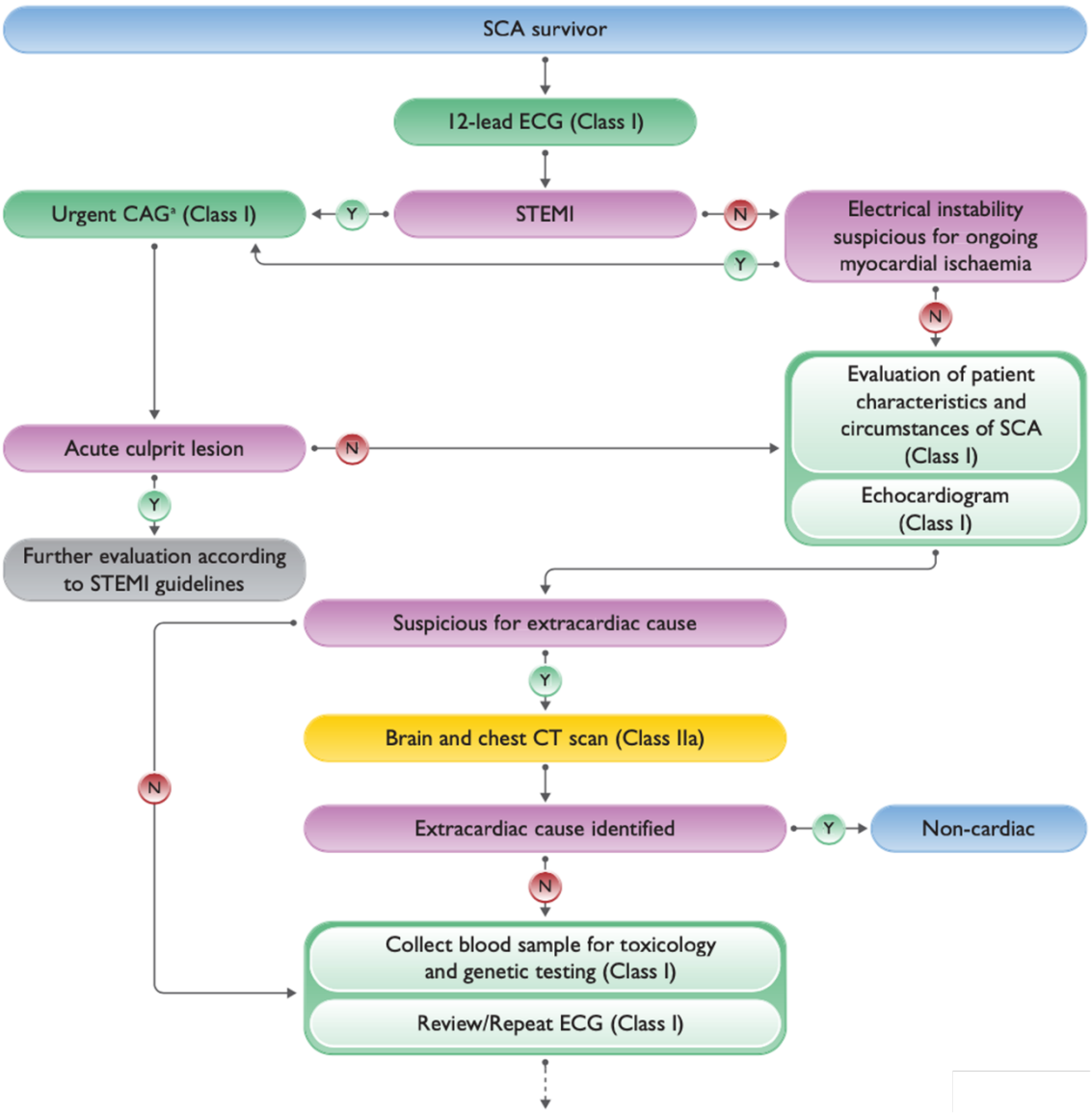

Figure 3 Early diagnostic steps and treatment of SCA (Zeppenfeld et al., 2022)

CAG = coronary angiogram; CT = computed tomography; ECG = electrocardiogram; SCA = sudden cardiac arrest; STEMI = ST elevation myocardial infarction; a The 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation

Another important component in the treatment of SCA survivors is targeted temperature management (TTM), which is indicated in all patients that remain unresponsive after ROSC. The patient temperature should be kept between 32 and 36°C for 24 hours and fever should be avoided for 72 hours after ROSC. TTM should be initiated early after resuscitation but should not delay PCI if indicated. (Ibanez et al., 2018; Nolan et al., 2021)

Patients should be cared for in an intensive care unit, where neuroprotective measures should be taken, such as maintaining normoxia and avoiding hypotension. (Nolan et al., 2021) Additional diagnostic tests should be performed in case the underlying cause has

not been identified, such as further imaging studies, provocation tests and genetic testing, in accordance with ESC Guidelines. (Zeppenfeld et al., 2022)

As mentioned above, immediate CPR is crucial in improving survival after SCA. (Hasselqvist-Ax et al., 2015) However, specific post-resuscitation measures and their availability play an important role as well. (Zeppenfeld et al., 2022) Two interventions proved to be especially closely associated with better outcomes after CA, namely CAG and TTM. (Aissaoui et al., 2018; Cronier et al., 2011; Dumas et al., 2016; Geri et al., 2015; Gräsner et al., 2011; Vadeboncoeur et al., 2018)

1.2 Myocardial Infarction as the Cause of Sudden Cardiac Arrest and Death

As has been outlined above myocardial infarction is one of the most common causes of sudden cardiac arrest and death. Therefore, the next section focuses on MI and its relationship with SCA.

1.2.1 Myocardial Infarction

To give an overview of myocardial infarction, the definition, symptoms, diagnostic evaluation and treatment is described below.

1.2.1.1 Definition

On a pathological level, MI is defined as the death of myocardial cells due to ischemia. According to the Fourth universal definition of myocardial infarction, acute myocardial infarction (AMI) consists of two aspects: acute myocardial injury and clinical evidence of acute myocardial ischaemia. (Thygesen et al., 2018)

Myocardial injury is present, if cardiac troponin values (cTN) are elevated and at least one value is greater than the 99th percentile upper reference limit. If the cTN values show a dynamic over time with a rise and/or fall, the myocardial injury is considered to be acute. (Thygesen et al., 2018)

For clinical evidence of acute myocardial ischaemia at least one of the following must be present (Thygesen et al., 2018):

- Identification of a coronary thrombus
- Symptoms of myocardial ischaemia (e.g., chest pain)
- New changes in the ECG suggestive of ischaemia

- Pathological Q – waves
- Imaging evidence of new regional wall motion abnormalities or new loss of myocardium, consistent with ischaemia

Based on pathological differences, influencing prognosis and treatment, the Fourth universal definition of myocardial infarction distinguishes 5 different types of MI.

Type 1 MI is caused by atherothrombotic CAD. Rupture, ulceration, erosion, or fissure of an atherosclerotic plaque lead to the formation of a thrombus. The thrombus partially or totally occludes the coronary artery and may also lead to embolization of a more distal coronary artery. Resulting in reduced blood flow to the myocardium, myocardial necrosis is the consequence. (Collet et al., 2021; Thygesen et al., 2018)

Type 2 MI is the occurrence of myocardial necrosis due to a mismatch between oxygen supply and demand. By definition, this mismatch may not be caused by a plaque disruption. There are many different mechanisms leading to an insufficient oxygen supply. A stressor causes myocardial oxygen supply to be reduced. Depending on the ischaemic threshold, this causes myocardial cell death, if the oxygen demand of the cells is no longer met. Ischaemic threshold is dependent on cardiac structural abnormalities, presence of CAD, comorbidities, and the extent of the stressor. Examples for causes of Type 2 MI include, fixed atherosclerosis, coronary vasospasm, coronary artery dissection, arrhythmias, anaemia, or hypotension. (Thygesen et al., 2018)

Type 3 MI is diagnosed in patients presenting with symptoms suggestive of myocardial ischaemia and new ischaemic ECG changes or ventricular fibrillation, who die before increases in cardiac biomarkers can be found or blood tests can be performed. (Thygesen et al., 2018)

Type 4 and 5 MI are associated with coronary interventions. Type 4 MI is further categorized into 3 subtypes. Type 4a is a myocardial infarction occurring during and up to 48 hours after PCI. Stent thrombosis associated with PCI is labeled Type 4b MI. Type 4c MI is defined as MI that can only be explained by restenosis following CAG. MI associated with coronary artery bypass grafting constitutes Type 5 MI. (Thygesen et al., 2018)

In a clinical setting, another system to classify AMI is used to initiate the right treatment course for each patient. A spectrum of conditions compatible with myocardial ischemia are summarized under the concept of acute coronary syndrome (ACS). (Amsterdam et al., 2014)

ACS encompasses three conditions: ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI) and unstable angina (Figure 4). (Byrne et al., 2023; Kotecha & Rakhit, 2016)

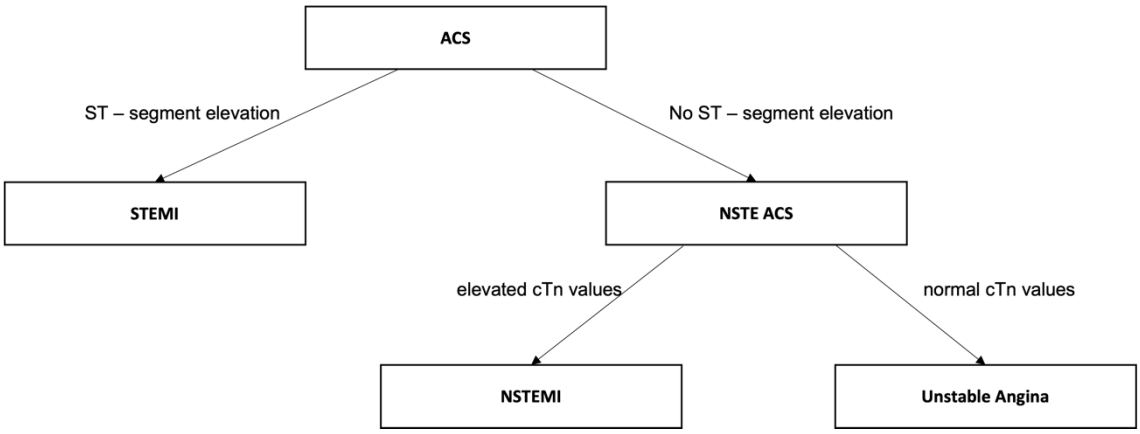

Figure 4 Acute coronary syndrome (according to (Collet et al., 2021))

ACS = acute coronary syndrome; NSTEMI = Non-ST-elevation myocardial infarction; NSTE ACS = Non-ST-elevation acute coronary syndrome; STEMI = ST-elevation myocardial infarction; cTN = cardiac Troponins

First patients should be separated in two groups based on the ECG. STEMI is diagnosed in patients with persistent ST-segment elevation (STE) in their ECG, characteristically localized to a vessel territory. STEMI usually reflects the total occlusion of one or several coronary arteries, leading to a transmural infarction. Thus, it requires immediate reperfusion therapy. (Byrne et al., 2023; Collet et al., 2021; Kotecha & Rakhit, 2016)

Patients without persistent ST-segment elevation suffer from non-ST-segment elevation (NSTE) ACS, which is usually associated with incomplete or transient vessel occlusion. If there is actual myocardial necrosis, indicated by a release of cardiac enzymes, NSTEMI is diagnosed. Patients without enzyme release but with typical symptoms are diagnosed with unstable angina. Typical symptoms include persistent chest pain at rest for more than 20 minutes, new angina since less than 3 months and/or worsening symptoms. Patients with NSTEMI or unstable angina my also show changes in the ECG, such as ST-depression, T-inversion, flat T-waves or transient ST-elevation. However, the ECG can also be completely normal. (Collet et al., 2021; Kotecha & Rakhit, 2016)

While the incidence of NSTEMI is on the rise, the numbers of STEMI are falling. Consequently, the proportion of patients with NSTEMI among all patients with AMI is growing. (McManus et al., 2011; Puymirat et al., 2017) STEMI is more common in younger than older patients and more common in men than in women as well. (Ibanez et al., 2018; Khera et al., 2015)

1.2.1.2 Symptoms

ACS can present itself in a variety of ways. The most common symptom is acute chest discomfort, which is often described as retrosternal pressure, tightness, pain and burning. The pain may radiate to the upper extremity, the jaw, or the neck. The discomfort is typically diffuse and is not affected by position or movement of the region. The likelihood of myocardial ischemia is increased if the symptoms are exacerbated by physical strain and mitigated at rest. In some patients the complications of ACS may be the first symptom, such as cardiac arrest, electrical instability with different arrhythmias or cardiogenic shock, for example due to mechanical complications like mitral regurgitation. (Byrne et al., 2023; Collet et al., 2021; Ibanez et al., 2018; Thygesen et al., 2018)

Women and older patients are significantly more likely to present with atypical symptoms such as dyspnea, diaphoresis, epigastric pain, nausea and vomiting, palpitations and syncope, in the absence of chest pain. (Collet et al., 2021) Atypical presentation leads to misdiagnosis and undertreatment, even though the probability of ischemic changes on the ECG is not influenced by the nature of the presenting symptom. (Brieger et al., 2004; Collet et al., 2021; McGarry & Shenvi, 2021)

1.2.1.3 Diagnostic Evaluation and Invasive Treatment

The most important diagnostic tool in assessing patients with symptoms suggestive of ACS is the 12-lead ECG. It should be performed within 10 minutes of first medical contact, whether that is EMS personnel, general practitioners, or hospital staff. (Byrne et al., 2023)

If the 12-lead ECG shows ST-segment elevation, that meets the criteria as stated in the fourth universal definition of myocardial infarction, STEMI is diagnosed. A STEMI diagnosis is the indication for immediate primary PCI. Patients should be brought to a PCI-capable facility and PCI should be performed within 90 minutes of diagnosis. The only exception is, if PCI cannot be performed within 120 minutes of diagnosis, in which case immediate fibrinolysis (within 10 minutes) is recommended. (Byrne et al., 2023; Ibanez et al., 2018; Thygesen et al., 2018)

Left bundle branch block (LBBB) complicates the interpretation of the ECG, as the conduction disturbance itself leads to changes in the ST-segment. Sgarbossas' criteria (Sgarbossa et al., 1996) can help identify AMI even in the presence of LBBB. However, patients presenting with LBBB and symptoms suggestive of AMI should be treated like STEMI patients, whether the LBBB has been previously known or not. The same is true for patients with right bundle branch block (RBBB). Patients that are hemodynamically unstable, have life – threatening arrhythmias or acute heart failure should also receive primary PCI. Should the ECG be inconclusive, additional ECGs have to be acquired. (Byrne et al., 2023; Collet et al., 2021; Ibanez et al., 2018)

As well as performing an ECG, blood samples for high-sensitivity cardiac troponin assays must be taken. Troponin is usually elevated in patients with AMI within 1 hour after symptom onset. Current Guidelines recommend assessing cTN at admission and again after one hour, in order to distinguish between unstable angina and NSTEMI. Strongly elevated cTN values and/or dynamic changes should lead to patients being ruled in for AMI. If the values at 0h and 1h are inconclusive, an additional blood sample should be acquired after 3h. (Byrne et al., 2023)

Echocardiography can and should be used to detect wall motion abnormalities and rule out differential diagnosis, such as pulmonary embolism or aortic dissection. (Byrne et al., 2023)

Patients diagnosed with NSTE-ACS, have to be further stratified according to their respective risk factors, in order to decide at which timepoint PCI should be employed. The ESC Guideline identifies 7 very high-risk criteria, such as hemodynamic instability, life threatening arrythmias or acute heart failure. If at least one of those criteria is present, patients should undergo PCI immediately, meaning in under 2 hours, irrespective of biomarker findings and ECG-changes. Similarly, in case at least 1 of 4 high-risk criteria is present, an early invasive strategy is indicated, with PCI within 24 hours. The high-risk criteria include established NSTEMI diagnosis or transient ST-elevation. Among patients that have been successfully resuscitated after SCA and do not exhibit ST-elevation or hemodynamic instability, a delayed PCI should be considered as well. In Patients exhibiting neither very high, nor high-risk criteria, a selective invasive strategy should be followed. In these cases, stress echocardiography and stress cardiac magnetic resonance imaging should be used to further assess likelihood and extent of CAD, before invasive measures are taken. (Byrne et al., 2023; Collet et al., 2021)

1.2.2 SCA and SCD in the Context of Acute MI

AMI can lead to sudden cardiac arrest and death. In some patients, CA even is the first symptom of AMI, as opposed to the classic chest pain. (Collet et al., 2021; Zeppenfeld et al., 2022) CA occurs mostly due to ventricular arrhythmias (VA), namely ventricular tachycardia (VT) and ventricular fibrillation (VF), that are caused by the myocardial ischemia and subsequent ionic imbalance. (Gorenek et al., 2014; Zeppenfeld et al., 2022) More specifically, the differences between the electrophysiology of the myocardium in the infarct and peri-infarct region can lead to the formation of re-entrant loops, which in turn can cause CA. (Myerburg & Junttila, 2012)

During the first month after onset of MI, SCD-risk is highest, while it decreases afterwards. (Adabag et al., 2010; Adabag et al., 2008) Within the first 48 hours approximately 4 – 12% of STEMI patients develop VA. (Demirel et al., 2015; Jabbari et al., 2015; Zeppenfeld et al., 2022)

Jabbari et al. reports that 11.6% of STEMI patients experienced VF before undergoing PCI, with 83% of those cases already occurring out-of-hospital. In the study conducted by Demidova et al. 7% of patients with ST-elevation had VT/VF in the first 48 hours and 96% of those events occurred within the first 24 hours after STEMI. This suggests a higher risk for VF early after onset of AMI. (Demidova et al., 2012; Jabbari et al., 2015)

Demirel et al. focuses specifically on OHCA in patients with STEMI, and reports that 7% of STEMI patients admitted had OHCA. Patients with OHCA were younger and more likely to exhibit the CL in the left main artery or the left descending artery (LAD). In-hospital mortality was higher after OHCA. (Demirel et al., 2015) Similar observations were made in other studies. (Demidova et al., 2012; Jabbari et al., 2015)

Most of the studies focus on SCA and SCD after STEMI, however the majority with up to two-thirds of OHCA patients, shows no sign of ST-segment elevation on their ECG. (Dumas et al., 2016) This population poses particular difficulties when it comes to treatment decisions. For patients with OHCA and STEMI, treatment is clear. As stated above, immediate reperfusion therapy is indicated, as the ischemia caused by the underlying coronary occlusion is a trigger for arrhythmias. (Zeppenfeld et al., 2022) If there is no evidence for ST-elevation on the patient ECG, cause and therefore treatment is less clear. As mentioned before, there is a high rate of coronary occlusions in patients presenting with OHCA, as CAD is a major underlying cause. Even in patients not fulfilling

STEMI criteria on their ECG, up to 53% were found to have acute coronary occlusion. (Dumas et al., 2016) Several observational studies and metanalyses have found, that immediate CAG and if necessary, PCI, led to better outcome in patients without ST-elevation as well. (Dumas et al., 2016; Meng-Chang et al., 2020; Vadeboncoeur et al., 2018; Welsford et al., 2018)

Recently three large randomized controlled trials, the COACT trial, the TOMAHAWK trial and the Emerge trial, have been conducted to further investigate whether immediate PCI after OHCA leads to better outcome in patients without ST-segment elevation. All three studies found no significant difference between an immediate or delayed strategy. However, in the Emerge Trial the survival rate at 180 days in the immediate CAG group was higher than in the delayed CAG group (36.2% vs. 33.3% respectively), even though the difference did not reach statistical significance. (Desch et al., 2021; Hauw-Berlemont et al., 2022; Lemkes et al., 2019; Lemkes et al., 2020)

2 Objective

As explained above, SCA is a major public health problem with a large number of victims every year. Many studies have been conducted to improve the prediction and prevention of such events. However, since the SCA often is the first manifestation of heart disease, this is extremely difficult (Fishman et al., 2010; Myerburg, 2001; Myerburg & Junttila, 2012; Zeppenfeld et al., 2022). Given this, the focus cannot only be on the prevention of SCA but has to be extended to improving the outcome of SCA victims.

To achieve this goal, patients with especially high risk of death must be identified to allow treatment to be intensified and adjusted to the patients' specific needs.

There is a substantial amount of evidence on the impact of resuscitation factors on survival after out-of-hospital cardiac arrest. This includes the beneficial influence of bystander CPR and witnessed status as well as the differing effects of initial presenting rhythms. (Dumas & Rea, 2012; Gräsner et al., 2021; Hasselqvist-Ax et al., 2015; Mader et al., 2012; Sasson et al., 2010) But even though these factors are well established, survival after OHCA has not considerably improved over the last decades, making it necessary to look for other features predictive of survival. (Sasson et al., 2010)

Therefore, the aim of this study is to investigate the impact of clinical characteristics and post-resuscitative ECG parameters on 30-day mortality after out-of-hospital cardiac arrest, as both of them are an integral part of diagnostics and patient care. Additionally, with acute myocardial infarction being one of the most common causes, the study looked at patients suffering OHCA due to an AMI, in order to further specify the population. (Martens, Eimo et al.)

3 Methods

3.1 Study design

The study has a retrospective design. Patients were admitted to the Department of Cardiology, Klinikum Rechts der Isar, Technical University of Munich (RDI) between March 2003 and March 2018 after suffering an out-of-hospital cardiac arrest in the context of an acute coronary syndrome (ACS). Patients who met the inclusion criteria were selected and the first 12-lead ECG after ROSC recorded at admission was interpreted. Additionally, several clinical parameters were collected and analysed. The data were extracted from the written files of the patients, as well as the "Filemaker", the documentation program of the I. Medical Clinic. The patients all received treatment according to current guidelines, which was not affected by the study. Patient data was pseudonymised, to protect patient identities. The study (number 2022-562-S-NP) was approved by the ethics committee of the Technical University Munich. (Martens, Eimo et al.)

3.2 Study population

The study population was based on a list of all patients admitted to RDI after out of hospital cardiac arrest which was believed to have a cardiac cause, containing 257 patients overall. All of them were treated in the Department of Cardiology, Klinikum Rechts der Isar, Technical University of Munich between March 2003 and March 2018. As the study focuses on SCA due to myocardial infarction, only patients with proven acute myocardial ischemia were included. These patients were identified on the basis of a lesion in their coronary arteries, that warranted reperfusion therapy (RT), and was deemed responsible for the myocardial ischemia resulting in sudden cardiac arrest. (Martens, Eimo et al.)

The following inclusion criteria were applied:

- The patient underwent coronary angiography which resulted in RT. RT was defined as percutaneous coronary intervention (PCI) with and without stent implantation.
- RT was performed on the day of admission
- The file of the patient included the 12-lead ECG recorded at admission

130 patients were subject to RT, as defined above. The files of 119 of those patients included a 12-lead ECG recorded at admission and were included in the study. The inclusion process is shown in figure 5. (Martens, Eimo et al.)

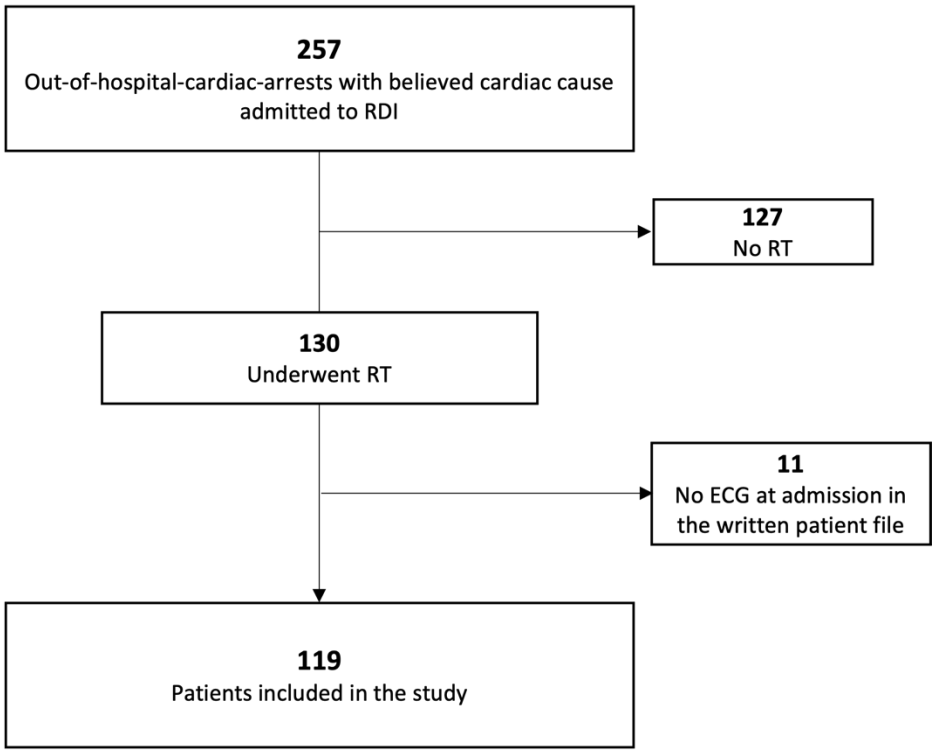

Figure 5 Patient Inclusion

3.3 Clinical Data

Clinical parameters were collected of all patients selected for the study. As mentioned above, the data were taken from both the documentation program of the I. Medical Clinic (Filemaker) and the written files. All parameters that were documented are listed in Table 1.

Table 1 Clinical data

Personal data	Date of birth Sex Weight Height
Hospital stay	Date of admission Date of discharge
Outcome	30-day mortality
Event	Medical professional present at time of cardiac arrest
Coronary angiography and Reperfusion Therapy	Successful reperfusion Culprit lesion (including grade of stenosis) Coronary artery disease (Grade 1 – 3) Stent implantation Percutaneous transluminal coronary angioplasty Type of stent (bare metal stent, drug eluting stent) Left ventricular ejection fraction (LVEF)
Cardiovascular risk factors	Arterial hypertension Smoking High cholesterol Positive family history Diabetes mellitus (with and without insulin dependency) Obesity (BMI > 30)
Pre - existing conditions	Cardiac arrhythmias
Previous cardiovascular events	Myocardial infarction Previous interventions (stent implantation, coronary artery bypass)
Pre – existing medication	QT-prolonging drugs Antiarrhythmic drugs (Vaughan Williams classification)
Pacemaker	Pre-existing pacemaker (type, date of implantation) Pacemaker implanted after sudden cardiac arrest (type, date of implantation)

To characterise the patients included in the study, personal data as well as data concerning pre-existing conditions and medication were collected. All pre-existing cardiac arrythmias were documented, so they could be taken into consideration during ECG analysation. If the patients already had a pacemaker or ICD before experiencing SCA, information about the type of pacemaker and the date of implantation was collected. Antiarrhythmic drugs were assigned to Class 1 - 4, according to the Vaughan Williams classification (Lei, M. et al., 2018). The total number of antiarrhythmic drugs

taken was documented as well. All drugs taken by the patient previous to the sudden cardiac arrest were checked for QT-prolonging properties (Woosley, n.d.). As all patients suffered an AMI, special attention was paid to known cardiovascular risk factors (CVRF) and previous cardiovascular events. CVRF were considered present if they were explicitly mentioned in the patient file. The patient was also considered obese if his body mass index (BMI) was at least 30. Furthermore, it was documented whether the patients had already undergone PCI or cardiovascular bypass previously.

To further characterise the event, the length of the hospital stay was documented. It was also checked whether a medical professional was present at the time of cardiac arrest and thus resuscitation was started immediately. Doctors as well as EMS personnel were considered to be medical professionals.

Findings in the coronary angiography, and details about the reperfusion therapy were described. This included the grade of coronary artery disease (CAD), by distinguishing how many of the three main branches of the coronary arteries were affected. The main branches are the right coronary artery (RCA), the left anterior descending artery (LAD) and the left circumflex artery (LCX). Based on the number of branches affected, CAD was classified as grade 1 – 3 respectively (Herold, 2020).

The localization of the culprit lesion (the coronary blockage deemed responsible for the acute myocardial ischemia) and its grade of stenosis, the presence of stenosis in other coronary arteries and whether a stent was implanted, or only percutaneous transluminal coronary angioplasty (PTCA) was employed for reperfusion, was documented as well. It was also noted, which type of stent was used.

Bedside echocardiography was performed to visually assess left ventricular function and to classify left ventricular ejection fraction (LVEF) by eye. In a proportion of patients, LVEF was quantified from the LV angiogram. If that was not the case, it was documented, whether LVEF was normal (>55%), impaired (35-55%) or highly impaired (<35%). (Martens, Eimo et al.)This classification was chosen because it was also used in the older patient records. Thus, there was insufficient information on which category the patients' LVEF would belong to according to the current classification. (McDonagh et al., 2022)

If patients received an implantable cardioverter defibrillator (ICD) during their treatment, information was gathered on the type of ICD and the date of implantation.

The primary outcome parameter was 30-day mortality.

3.4 ECG Analysis

3.4.1 Analyzed Parameters

A comprehensive list of parameters was analysed in each ECG. An overview is shown below in Table 2.

Table 2 ECG Parameters (Martens, Eimo et al.)

Heart rate	Beats per minute
Rhythm	SR with and without AV-block I Bigeminy Trigeminy Atrial fibrillation or flutter Junctional escape rhythm Idioventricular rhythm Accelerated idioventricular rhythm VT Stimulated rhythm (atrial/ventricular)
Axis	Intermediate type (30° - 60°) Vertical type (60° - 90°) Horizontal type (-30° - 30°) Right axis deviation (90 - 120°) Extreme left axis deviation (-90° - -30°) Extreme right axis deviation (120° - 210°)
PVC and PAC	Monomorph/polymorph
PQ-duration	PQ-duration
QRS - complex	Duration and amplitude of the QRS-complex QRSd QRS dispersion Pathological Q-wave
Intraventricular conduction defects	LBBB LAFB RBBB Bifascicular BBB
ST - segment	ST-Elevation ST-depression Sgarbossa criteria Brugada sign
QT - segment	QT-duration QTd QTc QT-dispersion
Repolarization	T-wave inversion Isoelectric T-wave TpTe interval TpTec Early repolarization

SR = sinus rhythm, AV-Block = atrioventricular block, VT = ventricular tachycardia, PVC = premature ventricular contractions, PAC = premature atrial contractions, QRSd = QRS-duration, LBBB = left bundle branch block, LAFB = left anterior fascicular block, RBBB = right bundle branch block, bifascicular BBB = bifascicular bundle branch block, QTd = QT-duration, TpTe = T peak to T end interval

The heart rate was assessed by measuring the RR-interval, which is the distance between two following R waves. In order to calculate the heart rate in beats per minute (b.p.m), 60 was divided by the duration of the RR-interval in seconds.

For each ECG the rhythm was identified. Sinus rhythm (SR) was considered to be present, if there were regular, normal oriented p-waves, each one followed by a QRS-complex (Surawicz & Knilans, 2008). If the duration between beginning of the p-wave and onset of the QRS-complex exceeded 200 ms, atrioventricular-block I (AV-Block I) was diagnosed (Aro, 2016). If the RR-intervals were irregularly irregular and there were no discernable repeating p-waves, but rather irregular atrial activations, atrial fibrillation (AF) was identified (Hindricks et al., 2020). Atrial flutter was considered to be present, if there was an atrial activation from 250 – 330 b.p.m with a saw tooth pattern (Brugada et al., 2020). Junctional escape rhythm was defined as a regular rhythm, with narrow QRS-complexes and no regular p-waves (Surawicz & Knilans, 2008). If the rhythm was regular, but the QRS-complexes were wide and of ventricular origin, it was considered to be an idioventricular rhythm. If the heart rate was over 50 and under 100 b.p.m the idioventricular rhythm was classified as accelerated (Buxton et al., 2006; Surawicz & Knilans, 2008). A ventricular tachycardia was identified when there were three or more consecutive complexes originating in the ventricles, independent from atrial or atrioventricular conduction, with a rate of > 100 b.p.m (Zeppenfeld et al., 2022). A premature ventricular contraction (PVC) was noted, if an abnormal QRS complex was present, that occurred prematurely and without a preceding p-wave. If there was more than one PVC on the ECG, monomorphic PVCs and polymorphic PVCs were distinguished. Monomorphic PVCs were defined as having one single QRS morphology, while polymorphic PVCs showed different QRS morphologies (Zeppenfeld et al., 2022). A complex similar to the QRS-morphology of a sinus beat originating from the atrium, but with a shorter coupling interval was considered to be a premature atrial contraction (PAC) accordingly (Durmaz et al., 2020). PVCs appearing in a stable pattern of each sinus beat alternating with a PVC or every second sinus beat followed by a PVC were labeled bigeminy and trigeminy respectively (Surawicz & Knilans, 2008). Lastly, the heart rhythm was considered to be stimulated if the sharp, narrow spikes of a pacemaker impulse could be identified in the ECG. Atrial and ventricular pacing were differentiated, by the presence of a p-wave after the impulse. (Surawicz & Knilans, 2008)

The electrical cardiac axis is the main vector of the ventricular depolarization in the vertical plane. If the lead axis is parallel to the main vector, a high voltage is registered in this lead. In contrast, no deflection can be seen if the lead axis is perpendicular to the main vector. By assessing the amplitude of the QRS-complex in the six limb leads, the cardiac axis was determined, as can be seen in Figure 6 (Meek & Morris, 2002; Surawicz & Knilans, 2008).

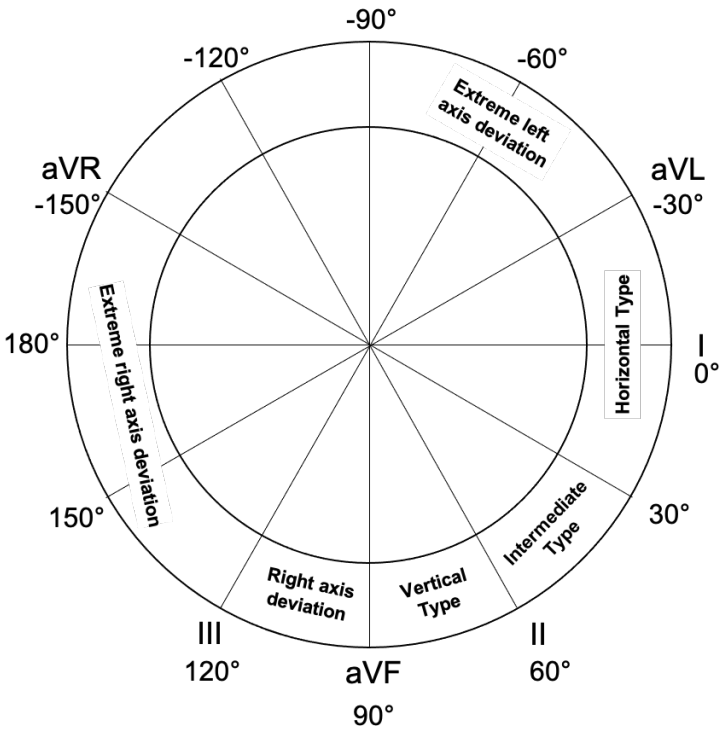

Figure 6 Cardiac Axis modified from (Meek & Morris, 2002)

The PQ-interval was measured from the beginning of the p-wave until the onset of the QRS-complex. Everything between 120-200 ms was considered normal. (Holmqvist et al., 2015)

The duration of the QRS-complex was measured in each lead separately. To calculate the mean QRS-duration (QRSd), all durations were summed up and divided by the number of leads. The QRS-dispersion is the difference between the maximum and minimum QRSd measured (Jain et al., 2019). In addition to the duration, the amplitude of the QRS-complex was measured.

The classical criteria for pathological Q-waves were used, with a duration ≥ 40 ms and an amplitude ≥ ¼ of the R-wave in the same lead being classified as pathological (Delewi et al., 2013).

Interventricular conduction defects were identified, if the QRSd was prolonged. Left bundle branch block (LBBB) was defined as a broad notched or slurred R-wave in leads I, aVL, V5 and V6, as well as a normal R-peak time in V1-V3 but > 60 ms in V5 and V6. LBBB was considered to be complete if the QRSd was ≥ 120 ms, and incomplete with a QRSd between 110 – 119 ms. Left anterior fascicular block (LAFB) was identified, if the ECG showed an extreme left axis deviation (ELAD), a qR pattern and R-peak time of ≥ 45 ms in lead aVL and a S-Persistence up to lead V6. Right bundle branch block (RBBB) was defined as a rsr'/rsR'/rSR' pattern in leads V1 and V2 as well as an S- wave > 40 ms or wider than the R-wave in leads V5 and V6. If there was only a dominant R wave present in V1, R-peak time in V1 had to be greater than 50 ms, while being normal in leads V5 and V6. Same as for LBBB, RBBB was considered complete if the QRSd was ≥ 120 ms, and incomplete with a QRSd between 110 – 119 ms. (Surawicz et al., 2009). Bifascicular bundle branch block (bifascicular BBB) was noted, if there was an LAFB, as well as a complete RBBB.

Elevation or depression of the ST-segment was evaluated for each lead. The magnitude of the ST-segment shift was identified at the J-Point, with the onset of the QRS-complex as a reference point (Figure 3). The J-Point is the junction between QRS termination and ST-segment onset. (Thygesen et al., 2018)

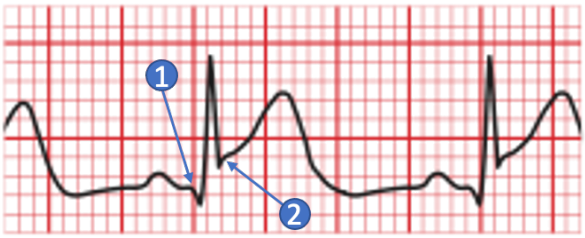

Figure 7 Example of ST - segment elevation modified from (Thygesen et al., 2018) ; Arrow 1 indicates the onset of the QRS, Arrow 2 shows the J – point

For ST-elevation, suggestive of acute myocardial ischemia, to be considered present, there had to be an elevation at the J-Point in two contiguous leads ≧ 0,1 mV in all leads except V2 and V3. Here the following cut-points apply (Thygesen et al., 2018):

- ≥ 0.15 mV in women regardless of age
- ≥ 0.20 mV in men ≥ 40 years
- ≥ 0.25 mV in men < 40 years

ST – depression suggestive of acute myocardial ischemia was considered to be present if there was a down sloping or horizontal depression of the ST-segment at the J-Point in two contiguous leads ≥ 0.05 mV. (Thygesen et al., 2018)

LBBB leads to secondary repolarisation changes which may conceal the changes associated with acute myocardial ischemia. Therefore, if an ECG exhibited LBBB, it was checked for the presence of the Sgarbossa criteria. They consist of three different electrocardiographic criteria, each one with its own score. They are listed in Table 3. If the total score is at least 3, Sgarbossa et al. reported a positive predictive value of 89% for an AMI. (Sgarbossa et al., 1996)

Table 3 Sgarbossa criteria modified from (Sgarbossa et al., 1996)

Criterion	**Score**
ST – segment elevation ≥ 0,1 mV and concordant with the QRS – complex	5
ST – segment depression ≥ 0,1 mV in lead V1, V2 or V3	3
ST – segment elevation ≥ 0,5 mV and disconcordant with the QRS – complex	2

Type 1 Brugada pattern was defined as a ST-segment elevation ≥ 0.2 mV in ≥ 1 right precordial lead (V1, V2) (Juan Sieira, 2017).

The duration of the QT-interval was measured in each lead and the mean QT-duration (QTd) was calculated. Using Bazett's formula the QT-interval was adjusted for heart rate, by dividing the mean QTd by the square root of the RR-interval in seconds:

$$QTc = \frac{QTd}{\sqrt[2]{RR - interval}}$$

QTc longer then 500ms was considered prolonged. Short QTc was defined as shorter than 390 ms. For QT-dispersion the difference between the maximal and minimal QTd was calculated. (Rautaharju et al., 2009)

Repolarisation was also further characterised. T-inversion was defined as a negative T-wave in two contiguous leads, with an amplitude of at least 0.1 mV, in leads with a prominent R-wave or R/S ratio > 1. (Thygesen et al., 2018)

The T-peak-to-T-end-interval (TpTe) was measured as a correlate of dispersion of ventricular repolarization. In lead V2 the interval between the peak of the T-wave and the end of the T-wave was measured. The tangent method was used to identify the end of the T-wave. (Rosenthal et al., 2018) TpTe was then also corrected for heart rate (TpTec) using Bazett's formula, as it was reported, that TpTec has a better predictive value for SCA risk assessment than TpTe alone. (Chua et al., 2016)

$$TpTec = \frac{TpTe}{\sqrt[2]{RR - interval}}$$

For early repolarization (ER) the definition proposed by Macfarlane et al. was used. ER is present, if there is an end-QRS notch or slur on the downslope of the R-wave of an QRS-complex with a QRSd < 120 ms. The elevation of this notch or slur must be $\geq$ 0.1 mV in 2 or more contiguous leads, excluding the right precordial leads (V1 – V3). (Macfarlane et al., 2015)

3.4.2 Measurement

All ECGs had a calibration of 10mm/mV and most of them a paper speed of 50 mm/s. 2 ECGs were recorded with a paper speed of 25 mm/s. In order to allow precise measurements of durations and amplitudes in the ECGs the program Image J (Public domain, https://github.com/imagej/ImageJ) was used (Schneider et al., 2012). (Martens, Eimo et al.) The ECGs were scanned and uploaded into the program. First of all, considering the paper speed and the ECG graph paper, a scale was set. This provided the program with the information how many pixels on the scanned ECG corresponded to how many seconds (s) or millivolts (mV) respectively. After setting the scale all intervals could be measured, as shown in Figure 8.

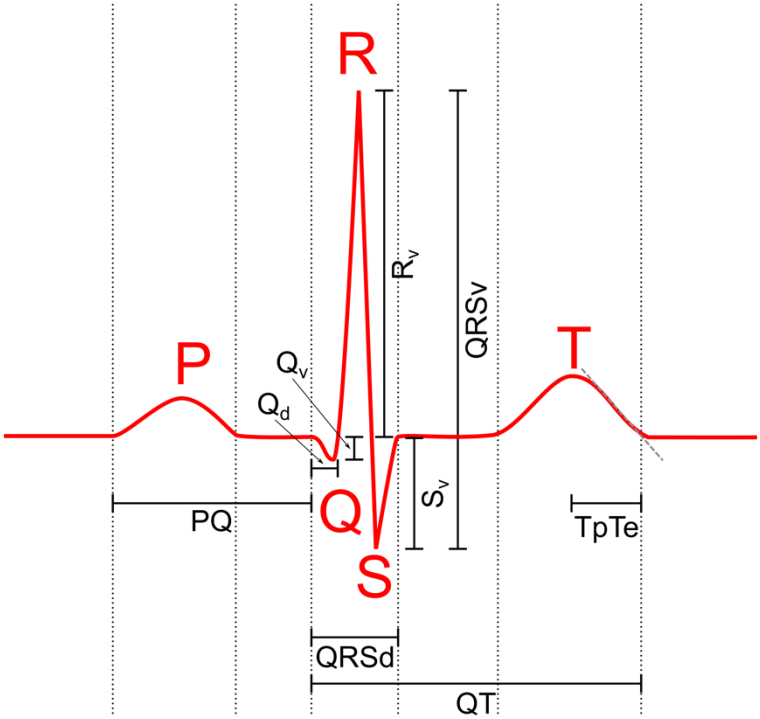

Figure 8 Measurement of durations and amplitudes in a Sample - ECG

PQ = duration of the PQ-interval; Q_d = duration of the Q-wave; Q_v = voltage of the Q-wave; QRSd = duration of the QRS-complex; QRSv = voltage of the QRS complex; R_v = voltage of the R-wave; S_v = voltage of the S-wave; TpTe = duration of the Tpeak-to-Tend-interval

A large number of the analysed ECGs were already several years old. This resulted in faded ink on the ECG paper, making the analysis difficult. Additionally, several ECGs were recorded poorly (with parts not visible, etc.) or had substantial artefacts. In order to obtain precise and correct measurements, in each lead one complex was chosen that allowed the best result due to the best visibility and no neighbouring artefacts influencing the measured waves.

3.5 Statistical Analysis

For the statistical analysis SPSS 27.0 was used. Categorical variables were reported with absolute values and percentages. Continuous variables were further differentiated into normally and not normally distributed variables. This was done using graphical (histogram and box plot) testing. For continuous variables median and interquartile range (IQR) were reported. (Spriestersbach et al., 2009)

As the main goal was to look for variables impacting survival, Cox Regression analysis was used to look for significant associations between different variables and 30-day mortality. (Martens, Eimo et al.) Hazard ratios (HR) were presented with 95% confidence

intervals (CI). Given the relatively small number of deaths in our population within 30 days, we focused on univariate analyses. (Ziegler A. , 2007a) In order to calculate 30-day mortality for categorical variables, Kaplan-Meier estimators were employed. (Ziegler A. , 2007b).

To test for significant differences between two groups unpaired t-test was used for normally distributed variables.

Two-sided p-values < 0.05 were considered statistically significant.

4 Results

4.1 Patient Characteristics

Overall, 119 patients were included in the analysis. They were all admitted to the Department of Cardiology, Klinikum Rechts der Isar, Technical University of Munich after suffering an OHCA due to AMI. The cardiac arrest was witnessed by a medical professional in 21 cases (17.6%). (Martens, Eimo et al.)

They had a median age of 66 years, with a relatively broad range from 29 years to 90 years. 20 patients were female, while the vast majority was male (99 patients). (Martens, Eimo et al.) Median weight was 80.0 kg and median height 178 cm. This puts the average BMI at 25,2 kg/m^2.

Table 4 Age, Sex, Weight, and Height in the patient population (Martens, Eimo et al.)

patient characteristics	**n (%) or median (IQR)**
Age (years)	
median	66.0
interquartile range	57.0 – 77.0
Sex	
female	20 (16.8%)
male	99 (83.2%)
Weight (kg) (n=116)	
median	80.0
interquartile range	75.0 – 90.0
Height (cm) (n=116)	
median	178.0
interquartile range	170.3 – 180.0

Pre-existing CVRF were also looked at, which can be found in Table 5. A little over two thirds of the population suffered from arterial hypertension (68.1%). 37 patients (31.1%) were active smokers, and 16 patients (13.4%) were ex-smokers. Almost a third of the population was obese (30.1%) and almost two thirds were previously diagnosed with hypercholesterolemia (65.5%). 24 patients were known to have diabetes mellitus, 2 of which were insulin dependent (20.2% and 1.7% respectively). 14.3% had a positive family history. (Martens, Eimo et al.)

Table 5 Cardiovascular Risk Factors (Martens, Eimo et al.)

CVRF	**n (%) (N=119)**
Hypertension	
yes	81 (68.1%)
no	38 (31.9%)
Smoker	
current smoker	37 (31.1%)
ex-smoker	16 (13.4%)
no	66 (55.5%)
Overweight (BMI>30)	
yes	36 (30.3%)
no	83 (69.7%)
Hypercholesterolemia	
yes	78 (65.5%)
no	41 (34.5%)
Family history	
yes	17 (14.3%)
no	102 (85.7%)
Diabetes mellitus	
yes	24 (20.2%)
insulin dependent	2 (1.7%)
non-insulin dependent	22 (18.5%)
no	95 (79.8%)

CVRF = cardiovascular risk factors

Concerning previously diagnosed illnesses and procedures, cardiac arrhythmias, and myocardial infarction as well as previous coronary interventions and ICD or pacemaker implantations were documented.

Almost a quarter of patients had a pre-diagnosed ECG alterations (29 patients). Most common were atrial fibrillation/flutter and left bundle branch block, which were present in 18 and 5 patients respectivley. All prediagnosed ECG changes present before the event can be seen in the figure below.

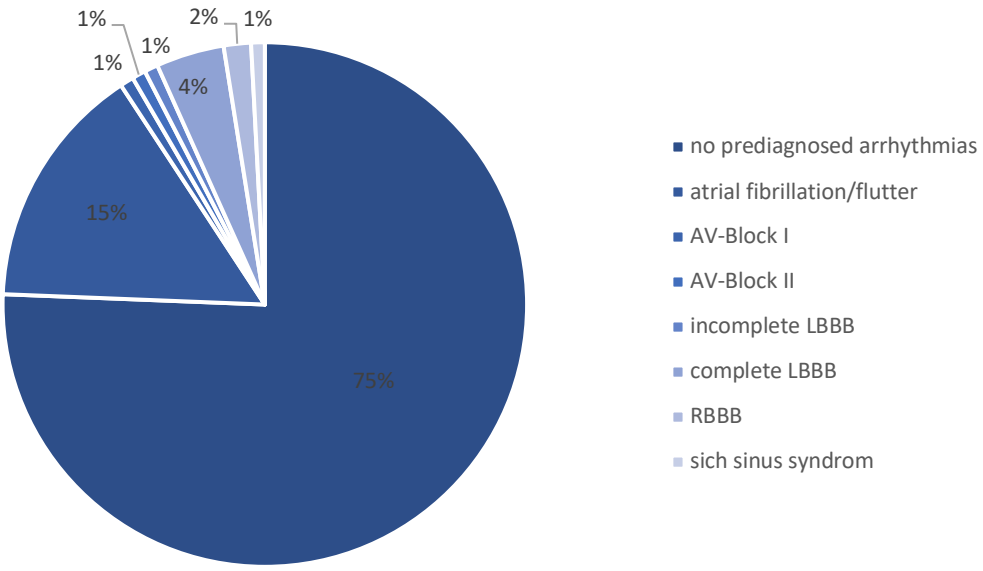

Figure 9 Pre-diagnosed cardiac arrhythmias

As the study specifically focused on OHCA due to AMI, data on previous MI and coronary interventions was collected. With 96 patients (80.7%), the majority of the population had not suffered an MI prior to the event. However, a quarter of all patients had undergone a coronary intervention before. Among all patients with a prior coronary intervention, 43.3% (13 patients total) received a coronary bypass. A small number of patients already had an ICD, or a pacemaker implanted before the event. The exact numbers can be seen in Table 6. (Martens, Eimo et al.)

Table 6 Previous MI, coronary intervention and pacemaker/ICD implantation (Martens, Eimo et al.)

Previous MI, coronary intervention, pacemaker and ICD	**n (%) (N=119)**
History of MI	
yes	23 (19.3%)
no	96 (80.7%)
Previous coronary intervention	
no	89 (74.8%)
one	28 (23.5)
Stent implantation	17 (14.3%)
Bypass	11 (9.2%)
several (both including coronary bypass)	2 (1.7%)
Prearrest ICD/pacemaker	
yes	5 (4.2%)
DDD	1 (0.8%)
DDDR	1 (0.8%)
VVI-ICD	1 (0.8%)

		DDD-ICD	2 (1.7%)

MI = myocardial infarction, ICD = internal cardioverter defibrillator

Two types of pre-existing medications were documented, QT-prolonging drugs and antiarrhythmic drugs (Table7). 11 of the 119 patients took QT prolonging medication (9.2%). The antiarrhythmic drugs were divided into the four classes of the Vaughan Williams classification. Overall, 44 patients (36.9%) were medicated with antiarrhythmic drugs prior to the event. (Martens, Eimo et al.) One patient was taking a Na-channel blocker, one was taking both a beta-blocker and a K-channel blocker and the majority was only prescribed a beta-blocker.

Table 7 Pre-existing medication (Martens, Eimo et al.)

Pre-existing medication			**n (%) (N=119)**
Antiarrhythmic drugs			
	yes		44 (36.9%)
		class I	1 (0.8%)
		class II	43 (36.1%)
		class III	1 (0.8%)
		class IV	0 (0%)
		more than one	1 (0.8%)
	no		75 (63.1%)
QT prolonging drugs			
	yes		11 (9.2%)
	no		108 (90.8%)

4.2 Coronary angiography and Intervention

All patients received a CAG on the day of admission and were found to have a coronary lesion responsible for the OHCA, as stated in the inclusion criteria. 117 patients received a stent, which was a drug eluting stent (DES) in 94.8% of the time. In 6 patients a bare metal stent (BMS) was used. The remaining 2 patients only received a percutaneous transluminal coronary angioplasty (PTCA). The median number of stents implanted per patient was 2. The intervention of the culprit lesion was successful 97.5% of the time. Only in three patients the CL could not be revascularized. In another three patients a reintervention was necessary due to stent thrombosis, which was successful in two of the three cases.

Over half of the population had three-vessel coronary artery disease (CAD), 30.3% had two-vessel CAD and 16% had one-vessel CAD. (Martens, Eimo et al.)

Table 8 Characteristics of the Coronary Angiography (Martens, Eimo et al.)

Coronary angiographic characteristics		**n (%) (N=119)**
Coronary artery disease		119 (100%)
	One-vessel CAD	19 (16%)
	Two-vessel CAD	36 (30.3%)
	Three-vessel CAD	64 (53.8%)
Success of the intervention of the CL		
	Successful	116 (97.5%)
	Not successful	1 (0.8%)
	No reflow	2 (1.7%)
Reintervention due to stent thrombosis		3 (2.5%)
Culprit Lesion		
	RCA	37 (31.1%)
	LCA	7 (5.9%)
	LAD	50 (42%)
	LCX	21 (17.6%)
	Bypass > RCA	1 (0.8%)
	Bypass > LAD	2 (1.7%)
	Bypass > LCX	1 (0.8%)
Blockage of the Culprit lesion		
	75	5 (4.2%)
	90	38 (31.9%)
	99	24 (20.2%)
	100	52 (43.7%)
Type of stent		
	BMS	6 (5.1%)
	DES	109 (93.2%)
	No stent	2 (1.7%)
Number of stents (N=117), median (IQR)		2 (2)

CAD = coronary artery disease, CL = culprit lesion, RCA = right coronary artery, LCA = left coronary artery, LAD = left anterior descending artery, LCX = left circumflex artery, BMS = bare metal stent, DES = drug eluting stent

The left anterior descending artery (LAD) was the most common CL in 50 patients (42.0%), followed by the right coronary artery (RCA) with 37 patients (31.3%), the left circumflex artery (LCX) with 21 patients (17.6%) and the main left coronary artery (LCA) with 7 patients (5.9%). In 4 patients the CL was localized to a pre-existing bypass. (Figure 11) (Martens, Eimo et al.) In most cases the CL showed a blockage of 90% or more, in 5 patients however the blockage was no more than 75%.

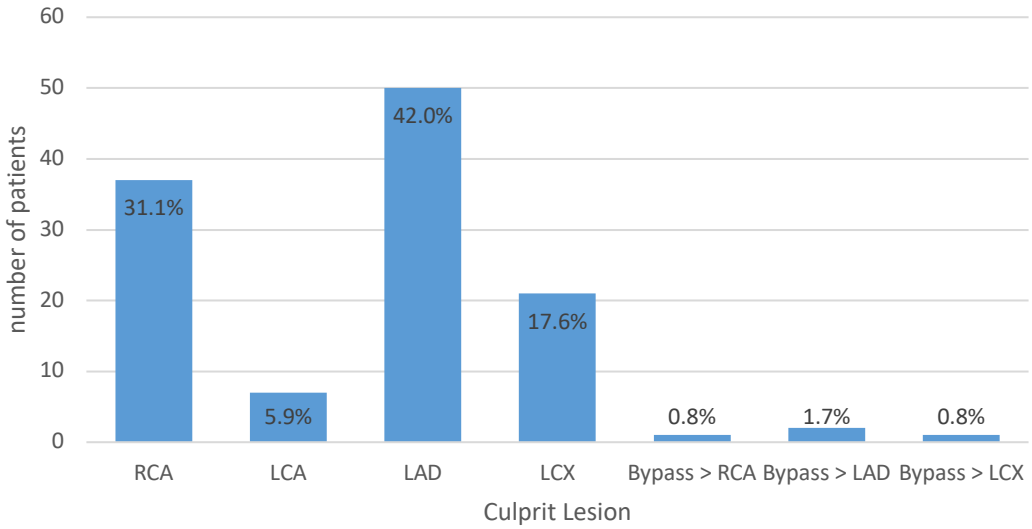

Figure 10 Distribution of the Culprit Lesion

RCA = right coronary artery, LCA = left coronary artery, LAD = left anterior descending artery, LCX = left circumflex artery

In 33 patients (27.7%), the intervention was not limited to the CL, and two or more coronary arteries were addressed. In line with being the most common CL, the LAD was subject to intervention most often, in over half of the population (66 patients, 55.5%). The RCA and LCX were addressed in 39 patients (32.8%) each, while there was an intervention in the LCA in 19 patients (16%). For each main coronary artery Figure 12 shows the number and percentage of patients with an intervention in the respective vessel.

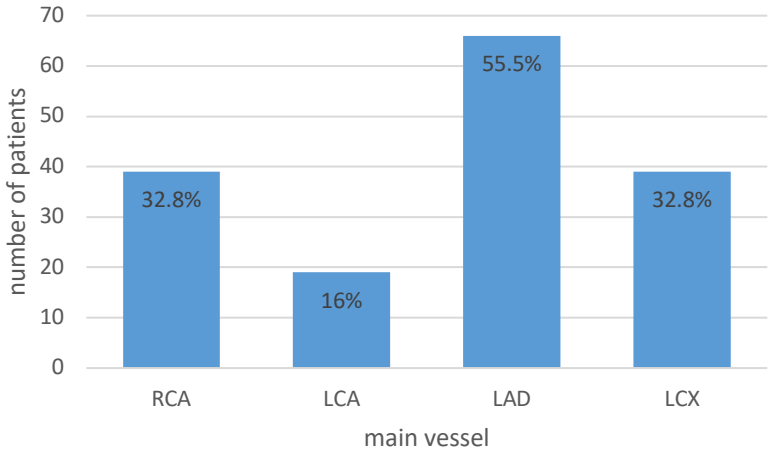

Figure 11 Number of patients with an intervention in each main coronary artery (includes patients with interventions in more than one vessel)

RCA = right coronary artery, LCA = left coronary artery, LAD = left anterior descending artery, LCX = left circumflex artery

LVEF was recorded as well, using bedside echocardiography, and whenever documented left ventricular – angiography (LV-angiography). In 3 patients LVEF could not be measured, because the patients died, before echocardiography was performed. LVEF was highly reduced in 39 patients (32.8%), reduced in 64 patients (53.8%) and normal in 13 patients (10.9%) of the population. A quantified LVEF from LV-angiogram was only documented in 84 of the patient records. For these 84 patients, LVEF on average was reduced, with a median of 40% (IQR 16%).

Table 9 Left ventricular ejection fraction (Martens, Eimo et al.)

Echocardiographic characteristics		**n (%) (N=119)**
LVEF (%) (N=84), median ± IQR		40 (33 – 49)
LVEF categorized		
	> 55%	13 (10.9%)
	35 – 55%	64 (53.8%)
	< 35%	39 (32.8%)
	Dead before measurement	3 (2.5%)

LVEF = left ventricular ejection fraction

4.3 ECG characteristics

As described in the methods section, each ECG was analyzed with respect to a large number of parameters. An Overview of all parameters can be seen in Table 10.

Table 10 Overview of all analysed ECG parameters (Martens, Eimo et al.)

ECG on admission		**n (%), N=119**
Heart rate (beats per minute), median (IQR)		90 (75 – 107)
Rhythm		
	Sinus Rhythm	80 (67.2%)
	Sinus Rhythm with AV - Block 1	17 (14.3%)
	Bigeminy	2 (1.7%)
	Trigeminy	1 (0.8%)
	Atrial fibrillation/flutter	29 (24.4%)
	Junctional rhythm	4 (3.4%)
	Idioventricular rhythm	1 (0.8%)
	Accelerated idioventricular rhythm	1 (0.8%)
	Ventricular tachycardia	2 (1.7%)
	Atrial stimulated rhythm	1 (0.8%)
	Ventricular stimulated rhythm	1 (0.8%)

Premature ventricular contraction (PVC)		30 (25.2%)
	1 PVC	17 (14.3%)
	Several monomorphic PVC	9 (7.6%)
	Polymorphic PVC	4 (3.4%)
Premature atrial contraction		4 (3.4%)
Axis (N=118)		
	Intermediate type (30°-60°)	19 (16.1%)
	Vertical type (60°- 90°)	25 (21.2%)
	Horizontal type (-30°-30°)	37 (31.4%)
	Right axis deviation (90°-120°)	12 (10.2%)
	Extreme left axis deviation (-90°- -30°)	21 (17.8%)
	Extreme right axis deviation (120°-210°)	4 (3.4%)
PQd (N=80), median (IQR)		180 (155 – 201)
QRSd (N=118), median (IQR)		104 (89 – 134)
QRS Dispersion (N=118), median (IQR)		37 (28 – 46)
LBBB (N=118)		36 (30.5%)
	incomplete	18 (15.3%)
	complete	18 (15.3%)
LAFB (N=118)		17 (14.4%)
RBBB (N=118)		31 (26.3%)
	incomplete	3 (2.5%)
	complete	28 (23.7%)
Bifascicular BBB (N=118)		10 (8.5%)
ECG criteria for STEMI (N=118)		59 (50%)
ECG criteria for ST depression (N=118)		94 (79.7%)
Sgarbossa criteria (N=18)		
	Sgarbossa I	4 (22.2%)
	Sgarbossa II	4 (22.2%)
	Sgarbossa III	4 (22.2%)
	$\geq$ 3 points total	6 (33.3%)
QTd (N=118), median (IQR)		367 (326 – 402)
QTc (N=118), median (IQR)		448 (415 – 482)
QT Dispersion (N=118), median (IQR)		60 (45 – 86)
TpTe (N=105), median (IQR)		93 (79 – 109)
TpTec (N=105), median (IQR)		115 (96 – 139)
Pathological q waves (N=118)		65 (55.1%)
	More than one	51 (43.2%)
	Isolated	14 (11.9%)
Early repolarization		7 (5.9%)
Isoelectric T wave (N=118)		9 (7.6%)
	Isoelectric T wave in 1 lead	4 (3.4%)
	Isoelectric T wave in more than 1 lead	5 (4.2%)
T-inversion according to ESC Guidelines (N=118)		56 (47.5%)

LBBB = left bundle branch block, RBBB = right bundle branch block, Bifascicular BBB = bifascicular bundle branch block, STEMI = ST-elevation myocardial infarction

The population had a slightly elevated heart rate with a median of 90/min. The most common rhythm was sinus rhythm in 80 patients (67.2%). Atrial fibrillation or flutter was

the most frequent arrhythmia (29 patients, 24.4%). Looking strictly at atrial fibrillation in the admission ECG six (22.2%) of these patients were already diagnosed with AF previously, while 21 (77.8%) had new-onset AF.

Out of the 15 patients that had been pre-diagnosed with AF before the event, only 6 (40%) also presented with AF in their admission ECG. The remaining 9 patients presented with atrial flutter (1 patient), SR (3 patients), SR with AV block I (3 patients), junctional rhythm (1 patient) and VT (1 patient).

One of the two patients with a VT in their ECG could not be further analysed for most of the other ECG parameters, as no clear QRS complexes could be distinguished.

Only 4 patients (3.4%) had PACs. A quarter of the population had at least one PVC (30 patients, 25.2%) and in 4 of those patients (13.3%) the PVCs were polymorph.

Most patients presented with a normal heart axis in their ECG, including intermediate (19 patients (16.1%)), vertical (25 patients (21.2%)) and horizontal type (37 patients (31.4%)). A relatively large subgroup presented with extreme left axis deviation (ELAD) (21 patients (17.8%)). Only 12 patients showed right axis deviation (10.2%), and four extreme right axis deviation (ERAD) (3.4%).

The duration of the PQ-interval could be measured in 80 patients. The remaining patients did not exhibit regular p-waves followed by a QRS-complex. Median PQ-duration (PQd) was 180ms with a IQR of 45.8ms. So overall the population had a normal PQd.

Median QRS-duration (QRSd) was only marginally prolonged with 104ms. QRS-dispersion was a median of 37ms with a IQR of 18ms.

More than half of the population presented with pathological Q-waves (65 (55.1%)). Of those patients 51 had more than one (78.5%), 14 only presented an isolated pathological Q-wave (21.5%).

A majority of the population (75 patients (63.6%)) presented with intraventricular conduction defects. 36 patients had a left bundle branch block (30.5%), including 18 patients with incomplete LBBB and 18 patients with complete LBBB (15.3% each). 14 patients presented with a LAFB (11.9%). 31 patients showed a right bundle branch block (26.3%), including three with an incomplete RBBB (9.7%) and 28 with a complete RBBB (90.3%).

Only 59 patients (50%) fulfilled the ESC ECG criteria for a STEMI, thus presenting signs of a transmural infarction. 94 patients (79.7%) presented an ST-Depression. 19 patients

(16%) showed no ST-changes at all (Figure 13). (Martens, Eimo et al.) For the 18 patients presenting with a complete LBBB, the Sgarbossa criteria were calculated. 6 of these patients (33.3%) had 3 or more points, and thus had a risk sign for AMI in their ECG.

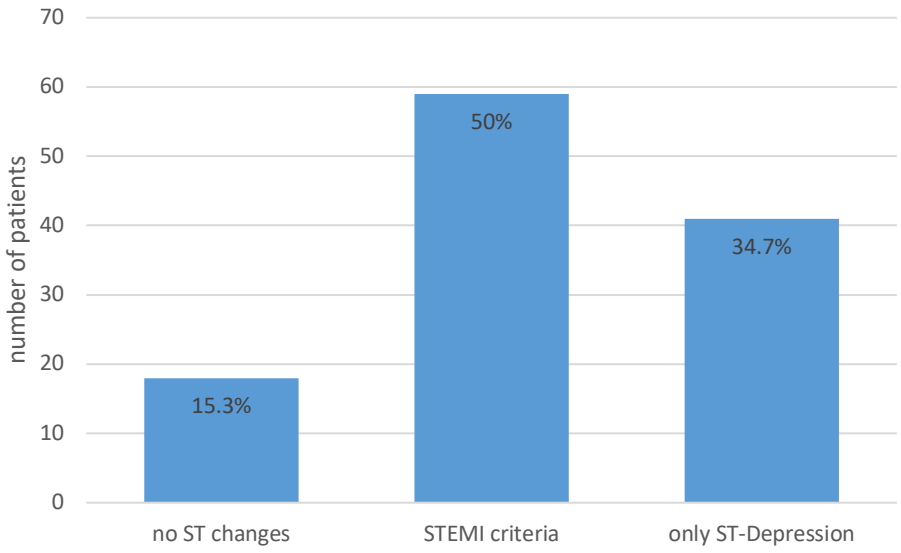

Figure 12 ST Changes

The QT-duration (QTd) was measured as well, with a median of 367ms. QTd was corrected for the heart rate with Bazett's formula (QTc). Median QTc was 448ms. QT dispersion had a median of 60ms. 11 patients were already taking QT prolonging medication prior to the event. Both median QTd (399ms vs 362ms) and QTc (492ms vs. 450ms) were longer in this group of patients compared to patients that did not take such drugs. However, the difference did not reach statistical significance (p=0.317 and p=0.069 for QTd and QTc respectively).

T-wave configuration was assessed. 9 patients (7.6%) showed one or more isoelectric T-waves. 56 patients (47.5%), so almost half of the population presented with T-wave inversions according to ESC guidelines. TpTe interval was measured and had a median of 93 ms. Median TpTe corrected for heart rate (TpTec) was 115ms. Only 7 (5.9%) patients presented with an early repolarization pattern in their ECG.

4.4 Outcome

Primary outcome measure was 30-day mortality, which was 30.3% (36 patients). (Martens, Eimo et al.) As expected, the number of survivors decreased markedly over time. After 24 hours, patients (10.1%) were dead, 17 patients (14.3%) died until 48 hours after admission and 35 patients (29.4%) died before discharge. After discharge 29 patients were lost to follow up.

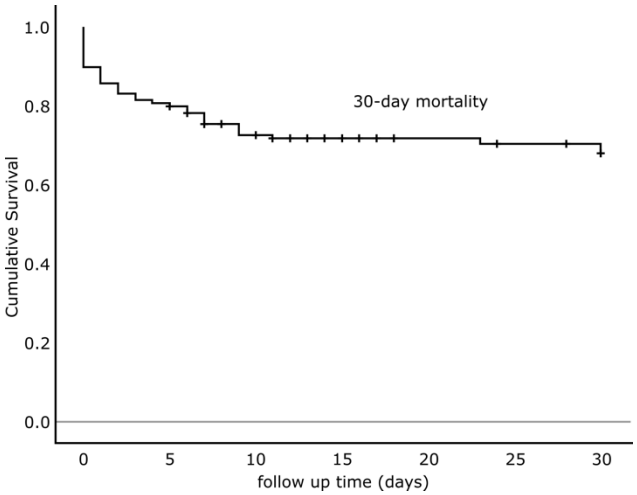

Figure 13 Kaplan-Meier curve for 30-day mortality

Patients spent a median number of 10 days in the hospital, before they were discharged. However, there was no information on the duration of possibly following rehabilitative treatments and hospital stays.

17 patients (14.3%) received an ICD for secondary prevention of recurring SCA. For another 2 patients an ICD was recommended, but there was no information whether the implantation took place. The majority of the 17 patients received a VVI-ICD (12 Patients, 70.6%), 4 patients received a DDD-ICD (23.5%), and 1 patient was fitted with a CRT-ICD (5.9%).

4.5 Determinators of patient outcome

All parameters collected were assessed for an association 30-day mortality using Cox-regression analysis. Kaplan-Meier curves are shown for some categorical variables to illustrate the difference in 30-day mortality between groups.

4.5.1 Patients Characteristics and Survival

Table 11 shows the association of clinical characteristics and pre-conditions with the 30-day mortality. Higher age led to higher mortality. Cox regression revealed a hazard ratio of 1.04 (95% CI 1.01 – 1.07, p = 0.003). Only two other variables showed a significant, but inverse, association with mortality: hypercholesterolaemia and smoking status. Patients with hypercholesterolaemia or smokers had a lower risk of death with hazard ratios of 0.39 (95% CI 0.20 – 0.75, p = 0.005) and 0.41 (95% CI 0.20 – 0.84, p = 0.02) respectively. 81.1% of smokers survived up to thirty days compared to 60.6% of non-smokers. Patients with hypercholesterolemia had a 30-day survival rate of 78.2%, while only 53.7% without hypercholesterolemia lived that long. No other CVRF had a significant impact on survival.

Table 11 Association between patient characteristics and survival

Univariable Cox analysis	**HR (95% CI)**	**p-value**
Age, n	**1.042 (1.014 – 1.070)**	**0.003**
Female, y/n	1.755 (0.825 – 3.733)	0.144
Weight, n	0.960 (0.921 – 1.000)	0.052
Height, n	0.996 (0.972 – 1.020)	0.748
Medical professional present, y/n	0.547 (0.193 – 1.546)	0.255
Arterial hypertension, y/n	1.207 (0.582 – 2.504)	0.613
Smoker, y/n	**0.405 (0.195 – 0.843)**	**0.016**
Hypercholesterolemia, y/n	**0.389 (0.202 – 0.750)**	**0.005**
Diabetes mellitus, y/n	0.925 (0.405 – 2.111)	0.853
Family history, y/n	0.139 (0.019 – 1.017)	0.052
Obesity (BMI >30), y/n	0.996 (0.490 – 2.024)	0.990
Class II antiarrhythmic agents, y/n	0.601 (0.290 – 1.248)	0.172
QT-prolonging drugs, y/n	2.155 (0.896 – 5.182)	0.086
Previous myocardial infarction, y/n	1.071 (0.488 – 2.353)	0.863
Previous coronary intervention, y/n	1.211 (0.596 – 2.463)	0.596
Pre-diagnosed arrhythmias, y/n	1.199 (0.578 - 2.486)	0.626
Pre-diagnosed atrial fibrillation/flutter, y/n	1.422 (0.622 – 3.247)	0.404
Pre-existing ICDs/pacemakers, y/n	1.382 (0.332 – 5.759)	0.657

BMI = body mass index, ICD = internal cardioverter defibrillator

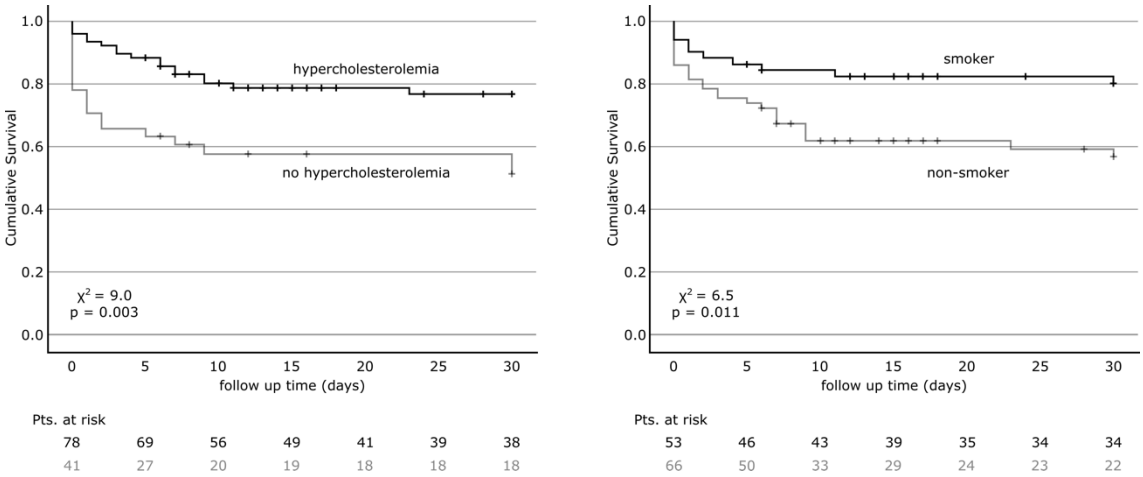

Figure 14 Kaplan-Meier curves for hypercholesterolemia and smoking status

The female gender tended to have a worse outcome, while the 30-day survival rate for women was 55%, almost 73% of men survived to 30 days. However, this was not significant (HR 1.76 (95% CI 0.83 - 3.73, p = 0.144)) (see figure 15). The same was true when the cardiac arrest was witnessed by a healthcare professional. The Kaplan-Meier-curve showed a trend that these patients were more likely to survive, but the difference was not significant (HR 0.55 [95% CI 0.19 - 1.55], p = 0.255).

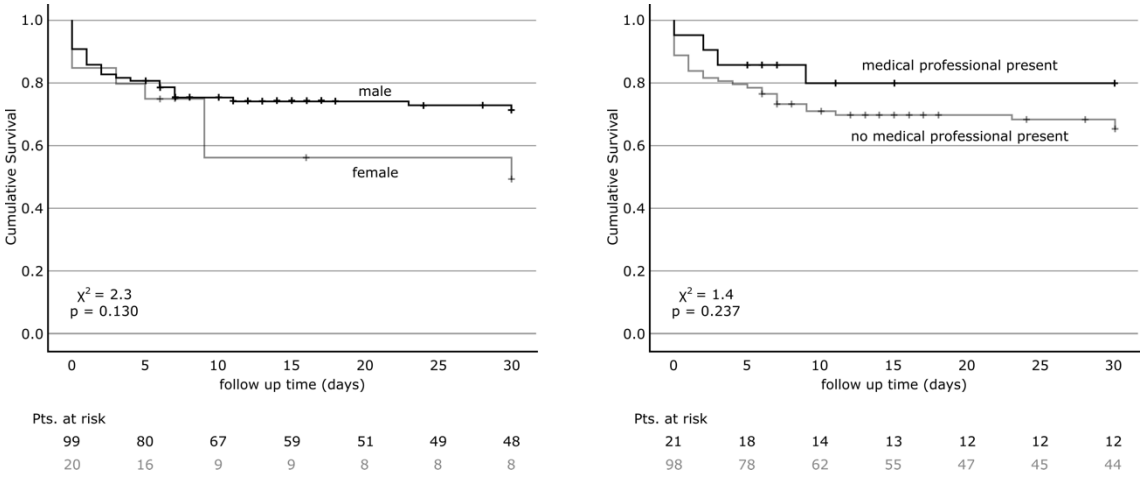

Figure 15 Kaplan-Meier curve for female sex and presence of a medical professional

The influence of pre-existing medication was also investigated (Figure 16). Almost all patients pre-medicated with antiarrhythmic drugs received beta blockers, which seemed to be beneficial for survival, but didn't show statistical significance (HR 0.60 (95% CI 0.29 – 1.25, p = 0.172)). QT prolonging drugs lead to a trend of higher 30-day mortality, which again wasn't significant (HR 2.16 (95% CI 0.90 – 5.18, p = 0.086).

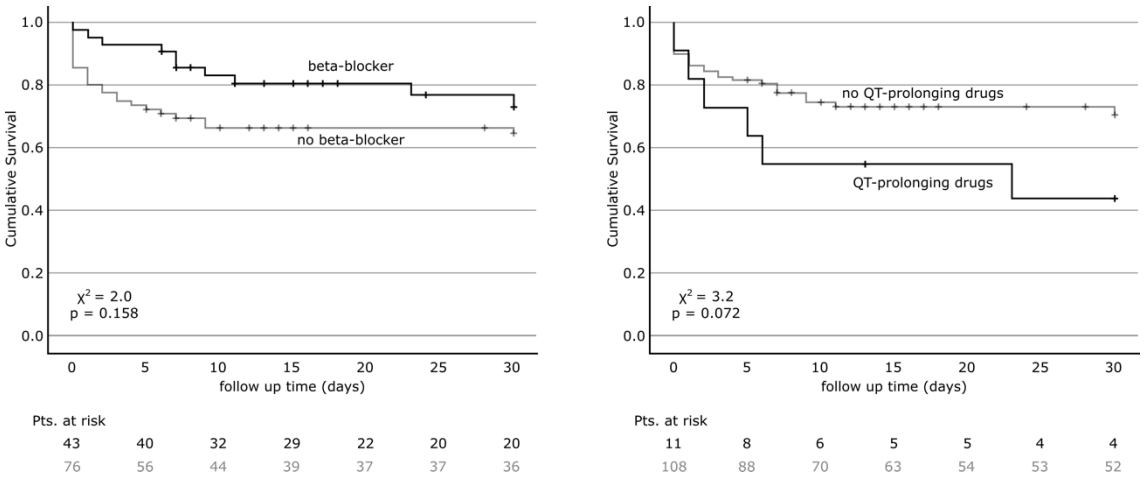

Figure 16 Kaplan-Meier curves for pre-existing medication: beta blockers and QT prolonging drugs

Previous interventions, myocardial infarctions and pre-diagnosed arrhythmias did not influence survival. The same was true for pre-existing ICDs/pacemakers.

4.5.2 Angiographic characteristics

Every patient underwent CAG and reperfusion therapy, as stated in the inclusion criteria. The Hazard Ratios for the tested parameters can be found in the table below.

Table 12 Association between angiographic characteristics and survival

Univariable Cox analysis	**HR (95% CI)**	**p-value**
Coronary artery disease		
One-vessel CAD, y/n	1.379 (0.604 – 3.151)	0.446
Two-vessel CAD, y/n	0.755 (0.355 – 1.605)	0.465
Three-vessel CAD, y/n	1.045 (0.541 – 2.018)	0.895
Success of the intervention of the CL, y/n	**9.364 (2.704 – 32.433)**	**<0.001**
Reintervention due to stent thrombosis, y/n	1.225 (0.168 – 8.949)	0.841
Culprit Lesion localization		
RCA, y/n	1.175 (0.588 – 2.351)	0.648
LCA, y/n	1.440 (0.441 -4.698)	0.546
LAD, y/n	**0.420 (0.197 – 0.894)**	**0.024**
LCX, y/n	**2.213 (1.088 – 4.503)**	**0.028**
Bypass, y/n	0.809 (0.111 – 5.907)	0.835
Stenosis of the CL (%)	1.001 (0.950 – 1.055)	0.959
Number of stents, y/n	0.994 (0.774 – 1.276)	0.960
Type of stent, BMS/DES	0.822 (0.197 – 3.429)	0.788

CAD = coronary artery disease, CL = culprit lesion, RCA = right coronary artery, LCA = left coronary artery, LAD = left descending artery, LCX = left circumflex artery, BMS = bare metal stent, DES = drug eluting stent

The success of the intervention of the CL was unsurprisingly associated with survival, with a significantly higher mortality in patients with an unsuccessful intervention (HR 9.364 (95% CI 2.704 – 32.433, p <0.001)). However, the intervention was not successful in only three patients.

The need for a reintervention due to a stent thrombosis was not associated with survival. All patients had CAD. The distribution of one, two and three vessel CAD didn't significantly impact mortality.

Both a CL in the LAD and the LCX influenced survival. While a CL in the LAD was protective, with a HR of 0.420 (95% CI 0.197 – 0.894, p = 0.024), a CL in the LCX was linked with a higher mortality, reflected by a HR of 2.213 (95% CI 1.088 – 4.503, p= 0.028). Kaplan Meier Curves are shown in the figure below.

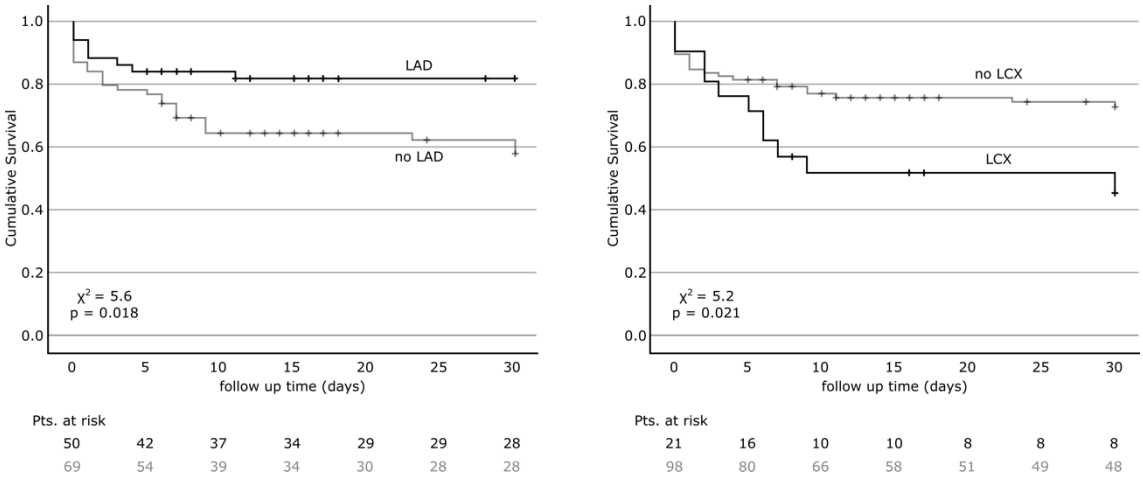

Figure 17 Kaplan Meier curves for left anterior descending artery (LAD) and left circumflex artery (LCX)

There was no significant difference for a CL in the RCA, LCA and within a pre-existing bypass. Survival was not associated with the grade of the stenosis of the CL.

Neither the number of stents nor the type of stent implanted influenced survival.

4.5.3 LVEF

We locked at both mean LVEF and categorized LVEF as a quantified LVEF was only documented for 84 patients. Neither mean LVEF nor normal, reduced or significantly reduced LVEF showed a significant impact on survival in our population. All Hazard ratios can be seen in the table below.

Table 13 Association between LVEF and survival

Univariable Cox analysis	**HR (95% CI)**	**p-value**
LVEF, n	0.973 (0.940 – 1.008)	0.126
LVEF visually categorized		
Normal	1.286 (0.392 – 4.216)	0.678
Impaired vs. normal	0.994 (0.288 – 3.435)	0.992
Highly impaired vs. normal	1.821 (0.527 – 6.293)	0.344

LVEF = left ventricular ejection fraction

4.5.4 ECG characteristics

As the 12-lead ECG was one of the main focuses of the study, a lot of different ECG features were analysed, and we found some to significantly impact survival. In the Table below there is an overview of the HR for the various parameters.

Table 14 Association between ECG characteristics and survival (Martens, Eimo et al.)

Univariable Cox analysis	**HR (95% CI)**	**p-value**
Heart rate, n	0.999 (0.986 – 1.012)	0.847
Sinus rhythm, yes/no	**0.492 (0.255 – 0.946)**	**0.034**
Atrial fibrillation/flutter, yes/no	**2.294 (1.172 – 4.487)**	**0.015**
PVC during ECG at admission, yes/no	1.164 (0.561 – 2.414)	0.684
Normal axis (-30°-90°), yes/no	1.669 (0.860 – 3.241)	0.130
Right axis deviation (90°-120°), yes/no	0.993 (0.386 – 2.555)	0.989
Extreme left axis deviation (-90°- -30°), yes/no	2.022 (0.973 – 4.200)	0.059
Pathological q waves, y/n	0.801 (0.416 – 1.539)	0.505
Complete RBBB, yes/no	**2.226 (1.137 – 4.358)**	**0.020**
Complete LBBB, yes/no	0.648 (0.229 – 1.833)	0.414
Bifascicular BBB, yes/no	**2.517 (1.045 – 6.059)**	**0.040**
ECG criteria for STEMI, yes/no	1.054 (0.548 – 2.026)	0.875
ECG criteria for ST depression, yes/no	0.789 (0.359 – 1.732)	0.554
Sgarbossa criteria ≥ 3 points, yes/no	0.851 (0.088 – 8.242)	0.889
Early repolarization, yes/no	1.533 (0.470 – 5.000)	0.479
T inversion (ESC Guidelines), yes/no	**2.019 (1.023 – 3.987)**	**0.043**
PQd, n	1.005 (0.996 – 1.014)	0.299
QRSd, n	1.007 (0.996 – 1.018)	0.204
QRS Dispersion, n	1.004 (0.982 – 1.026)	0.731
QTc, n	1.006 (1.000 - 1.012)	0.070
QTc ≥ 500 ms, yes/no	**2.208 (1.102 – 4.423)**	**0.025**
QT Dispersion, n	1.007 (0.998 – 1.017)	0.125
QT Dispersion ≥ 100ms, yes/no	**2.107 (1.015 – 4.372)**	**0.045**
TpTe, n	0.999 (0.987 – 1.011)	0.906
TpTec, n	0.998 (0.987 – 1.010)	0.791

PVC = premature ventricular contraction, ECG = electrocardiogram, RBBB = right bundle branch block, LBBB = left bundle branch block, BBB = bundle branch block, STEMI = ST-elevation myocardial infarction, PQd = PQ duration, QRSd = QRS duration, QTc = QT duration corrected for heart rate, TpTe = T peak to T end interval, TpTec = T peak to T end interval corrected for the heart rate

The heart rate didn't influence mortality. Presenting rhythm however had an impact on survival. If patients showed atrial fibrillation or atrial flutter on their admission ECG, they had a higher 30-day mortality with a HR of 2.294 (95% CI 1.172 – 4.487, p = 0.015). Conversely, sinus rhythm was protective, reflected by a HR of 0.492 (95% CI 0.255 – 0.946, p = 0.034). (Martens, Eimo et al.)

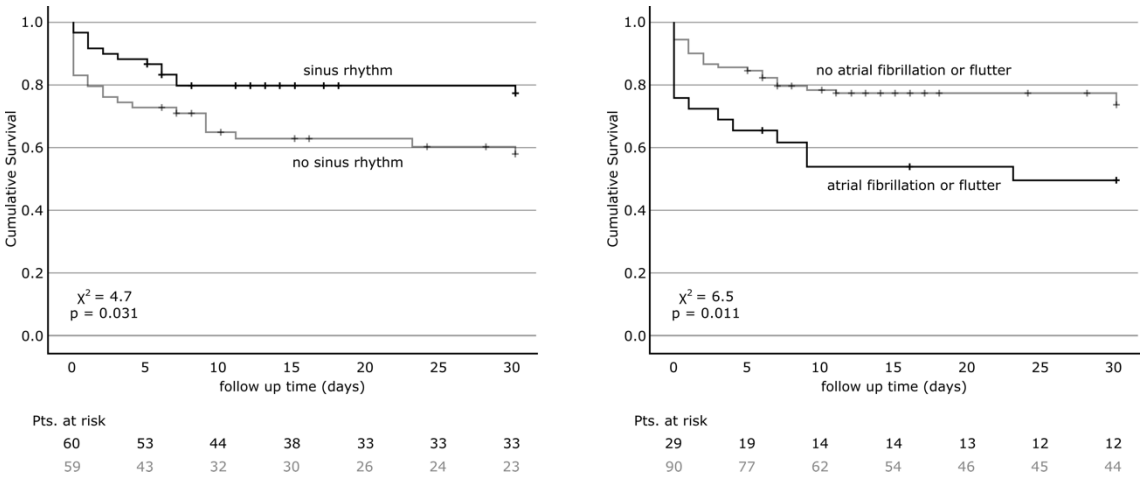

Figure 18 Kaplan Meier curves for Sinus rhythm and atrial fibrillation and flutter (Martens, Eimo et al.)

Looking at premature beats there was no significant difference for PVCs on the admission ECG.

Having an extreme left axis deviation (ELAD), was linked with worse 30-day mortality, however, it just missed being statistically significant (HR 2.022 (95% CI 0.973 – 4.200, p = 0.059)). (Martens, Eimo et al.) Right axis deviation and normal axis didn't influence survival.

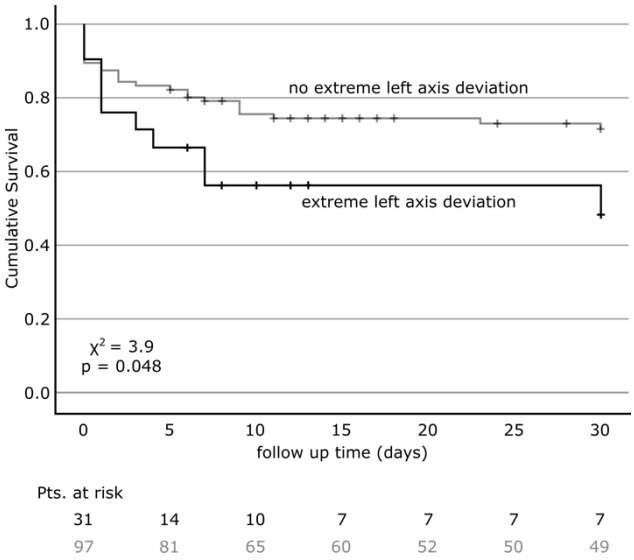

Figure 19 Kaplan Meier curve for extreme left axis deviation (Martens, Eimo et al.)

Neither PQ duration, QRS duration nor QRS dispersion had an impact on 30-day mortality. The same is true for pathological q-waves.

Intraventricular conduction defects on the other hand seem to impact survival significantly, as shown in the Kaplan Meier curves below. Both a complete RBBB and a bifascicular BBB (defined as complete RBBB and left anterior fascicular block) were linked with worse survival with a HR of 2.226 (95% CI 1.137 – 4.358, p = 0.020) and 2.517 (95% CI 1.045 – 6.059, p = 0.040) respectively. Only LBBB didn't significantly influence the 30-day mortality (HR 0.648 (95% CI 0.229 – 1.833, p = 0.414)). (Martens, Eimo et al.)

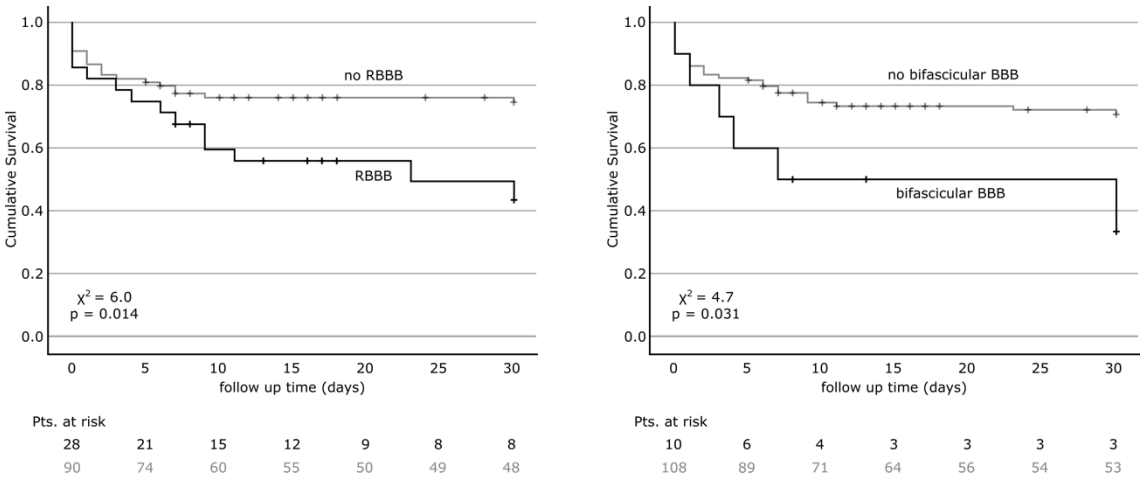

Figure 20 Kaplan-Meier Curves for right bundle branch block (RBBB) and bifascicular bundle branch block (bifascicular BBB) (Martens, Eimo et al.)

Changes to the ST-segment, namely the presence of STEMI criteria, ST-Depression or positive Sgarbossa criteria in patients with LBBB, didn't impact the outcome.
QTc-duration wasn't linked with survival. Looking at a prolonged QTc ≥ 500 ms however, there was a statistically significant association with a higher 30-day mortality (HR 2.208 (95% CI 1.102 – 4.423, p = 0.025)). (Martens, Eimo et al.)

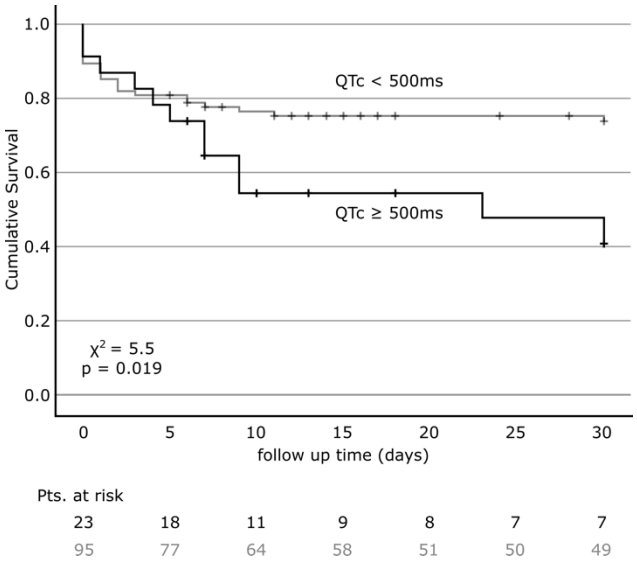

Figure 21 Kaplan Meier curve for a QTc greater or equal to 500ms (Martens, Eimo et al.)

Absolute QT-dispersion again showed no association with survival. Comparing patients with and without a QT dispersion ≥ 100ms, survival was worse among patients with a higher QT dispersion (HR 2.107 (95% CI 1.015 – 4.372, p = 0.045)). (Martens, Eimo et al.)

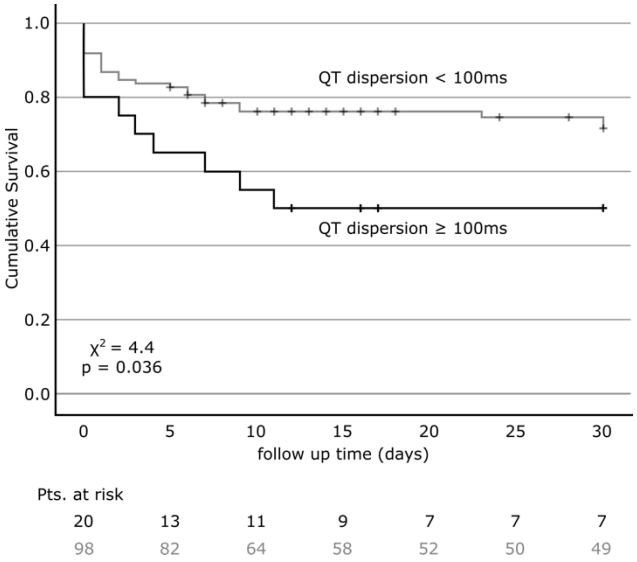

Figure 22 Kaplan Meier curve for QT-dispersion greater or equal to 100ms (Martens, Eimo et al.)

Neither the TpTe nor the TpTec interval was linked with survival.

T-inversions according to ESC guidelines however were associated with a significantly higher 30-day mortality, with a HR of 2.019 (95% CI 1.023 – 3.987, p = 0.043). (Martens, Eimo et al.)

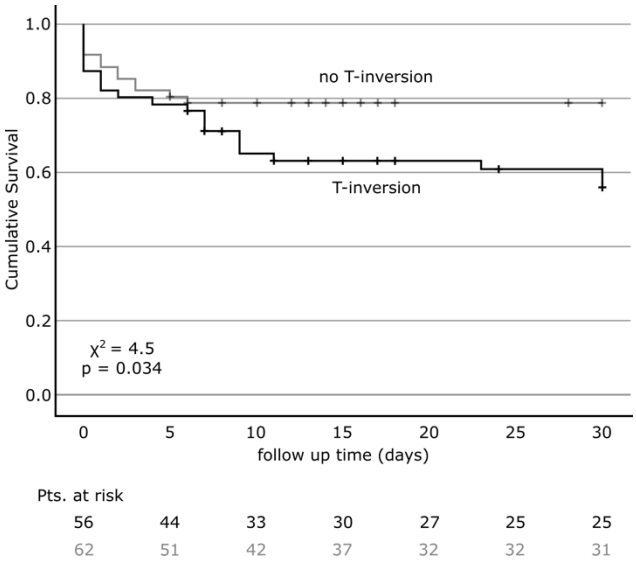

Figure 23 Kaplan Meier curve for T-inversion

5 Discussion

Looking at the overall outcome in the study, one first has to note that survival was much higher than is reported after OHCA in general. (Empana et al., 2018; Gräsner et al., 2020; Sasson et al., 2010; Yan et al., 2020) The study looked at a highly selected subset of patients with a myocardial infarction, thus treatable, underlying cause of the arrest. All patients included in the study achieved ROSC and lived long enough to undergo CAG. Additionally, the patients suffered their cardiac arrest in Munich, a big city with a high number of hospitals providing maximum care. Furthermore, response times of emergency medical services (EMS) are short within the city. Mell et al. found the median time between the call to EMS and their arrival to be 6 minutes in urban areas, while it was 13 minutes in rural areas. So, depending on your location, arrival of EMS can take more than twice as long. (Mell et al., 2017). Thus, the patients underwent quick resuscitation by the EMS and a highly standardised level of care upon arrival at the hospital. In conclusion, the population was only a selected subgroup of OHCA victims in general. (Martens, Eimo et al.)

The here presented study showed that older patients have a worse outcome which is in line with many previous findings. Several studies have shown that age is a risk factor for worse survival after OHCA both short and long term. (Pleskot et al., 2011; Pleskot et al., 2009; Zanders et al., 2021)

Additionally, in the studied population female sex was associated with a higher mortality, even though it missed being statistically significant. There is supporting evidence for this as well. Women have a significantly lower chance of survival to hospital discharge compared to men after OHCA in general (Blom et al., 2019; Lei, H. et al., 2020). Outcome for women is reported to be worse after STEMI as well (Ibanez et al., 2018). However, a recent metanalysis by Malik et al. on the effect of sex on the outcome after OHCA showed no association between female sex and survival to discharge (Malik, A. et al., 2022).

There is only a very limited number of studies investigating the effect of CVRFs on survival after OHCA. There is evidence that CVRF, a history of CAD and comorbidities are generally associated with worse outcomes after OHCA (Kroupa et al., 2017; Lee et al.,

2011). Diabetes mellitus is also associated with lower survival after cardiac arrest (Herlitz et al., 2003; Kroupa et al., 2017).

In this studied population both hypercholesterolemia and smoking were significantly linked with a lower 30-day mortality, whereas hypertension, Diabetes mellitus and family history of MI did not show a significant association with the endpoint. The reason for this finding is a matter of speculation. One possible explanation is, that patients with known hypercholesterinemia are already being treated, most of them with statins, which are speculated to have pleiotropic effects above their cholesterol lowering effect and which are known to reduce long-term-mortality risk in post-infarction patients. (Chou et al., 2016; Kytö et al., 2023; Oesterle et al., 2017) Other studies have also shown that treatment with lipid-lowering drugs improves the chances of survival after an OHCA (Herlitz et al., 2003; Hung et al., 2017; Stecker et al., 2014). Roth at al. reported hypercholesterolemia to adversely affect survival after OHCA, contrary to the findings in this study. However, their primary endpoint was success of initial resuscitation, while in this population all patients achieved return of spontaneous circulation (ROSC) and primary endpoint was 30-day mortality. (Roth et al., 2000)

Although smoking is a risk factor for coronary heart disease, many studies have shown that, paradoxically, smokers have a better prognosis after a myocardial infarction. The reasons discussed are that smokers are younger at the time of the infarction, have fewer comorbidities, have less multivessel disease and have a higher out-of-hospital mortality rate. (Andrikopoulos et al., 2001; Ottesen et al., 1999) Herlitz et al. studied OHCA victims, that were admitted to the hospital alive, similarly to this population. They reported an association between improved survival in those patients and a history of smoking (Herlitz et al., 2003).

Looking also at pre-diagnosed heart disease and not only at CVRFs, a few more studies can be found. Van Dongen et al. investigated whether reported pre-diagnosed heart disease influenced survival in OHCA patients. They found improved survival to hospital admission and hospital discharge, however only the former reached statistical significance. The investigators hypothesized that the benefit of earlier cardiologic treatment could be the underlying cause (van Dongen et al., 2021). Stecker et al. also found, that pre-diagnosed CAD led to a 50% higher chance of survival from resuscitated SCA (Stecker et al., 2014). In this study however, pre-diagnosed MI or previous coronary interventions didn’t impact survival.

Thus, at the moment there is no conclusive data on the impact of CVRF on survival after OHCA.

The impact of pre-arrest medication with antiarrhythmic agents on survival was investigated in this study and an association between beta-blockers and a trend towards improved survival was found, which however didn't reach statistical significance. Yoshie et al. similarly found prior use of beta-blockers in patients with ventricular arrhythmia (VA) and hemodynamic collapse to improve survival to hospital discharge (Yoshie et al., 2021). Beta-blockers can prevent VA and are indicated in acute MI both for prevention and treatment of such arrhythmias (Zeppenfeld et al., 2022). It has also been suggested that the prevention of ventricular tachycardia and fibrillation by beta-blockers is dose dependent (Ruwald et al., 2018). If patients already took beta-blockers pre-arrest, they might have a higher drug level and therefore better protection against recurring fatal arrhythmias. In patients older than 65 years, however, the favourable effect of pre-arrest betablockers seems to be abolished. (Czarnecki et al., 2015)

Characteristics concerning the coronary angiography also influenced survival in this study. While a culprit lesion in the LAD proved to be protective, a lesion in the LCX led to worse outcome in the studied population.

Existing evidence on these findings is scarce and conflicting. Velders at al. found that the localization of the culprit lesion influences the likelihood of OHCA in STEMI patients in general, with a higher risk for lesions in the left coronary artery, especially proximally. Additionally, OHCA patients with proximal left culprit lesion had higher in-hospital mortality. (Velders et al., 2013) However Stone et al. reports patients with a myocardial infarction due to a culprit lesion in the LAD to have a worse outcome due to the extent of myocardial ischemia, in contrast to the results of this study (Stone et al., 1988)

Bertic et al. looked at the influence of LAD involvement in STEMI patients with and without OHCA. While they also found a higher mortality in patients without OHCA and a culprit lesion in the LAD, no such association was apparent in OHCA patients. There was even a trend to higher survival in patients with a culprit lesion in the LAD, suffering from OHCA. (Bertic et al., 2020) These findings support the presented results and show

that the impact of infarction territory may be different, depending on whether AMI patients present with OHCA or not.

As previous studies have only focused on the LCA in general or the LAD in particular, the findings concerning the LCX are even more difficult to interpret. AMI with the LCX as culprit lesion is more commonly manifesting as NSTEMI, which might impact treatment and therefore prognosis. (Kobo et al., 2021). More studies are needed to further characterize the impact of the LCX as culprit lesion on survival after OHCA due to AMI.

Several ECG characteristics had a significant effect on survival in the studied population. For one, the rhythm in the admission ECG was linked with survival. If the patients in the study exhibited atrial fibrillation/flutter, they had a worse outcome, while sinus rhythm was protective. (Martens, Eimo et al.) Pathophysiological, AF may be suggestive of a more damaged heart and higher number of comorbidities (Hindricks et al., 2020). Furthermore, it has adverse hemodynamical effects (Bosch et al., 2018). Sinus rhythm in contrast speaks to a normal electrical conduction. There is very little evidence on the relationship between survival after OHCA and the rhythm in the admission ECG, but it supports the findings in this study. Gupta et al. found AF at any point during the index hospitalization to be an independent predictor of long-term mortality after SCA (Gupta et al., 2018). In children as well as adults that suffered OHCA, sinus rhythm in the first ECG on admission was linked to a better survival to hospital discharge (Herlitz et al., 2003; Lin et al., 2010).

A detrimental effect of ELAD on survival was observed in the studied population, just missing statistical significance. As the ECG electrodes are always placed in the same manner, a pre-existing axis deviation of the heart can lead to substantial changes in body surface potentials (MacLeod et al., 2000). Therefore, it can be hypothesized, that ST-elevations may not show up on the ECG to the same extent, which may lead to a delay in treatment and consequently worse outcome. However, the extreme axis deviation could also simply be the acute result of a more extensive loss of myocardium due to the infarction which also leads to worse survival. Bellamoli et al. conducted a study on the effect of new-onset extreme right axis deviation (ERAD) in AMI and suggested that the extensive myocardial damage was the reason for the extreme dislocation of the axis (Bellamoli et al., 2020). A similar mechanism could lead to ELAD, especially as ELAD and

ERAD merge into each other (Bellamoli et al., 2020). There is some evidence on axis deviation in the setting of AMI, but none of these studies have been conducted in AMI patients presenting with OHCA. The TACOS study found that both right and left axis deviation lead to higher short and long-term all-cause mortality in ACS patients, with right axis deviation being the strongest predictor of mortality (Punkka et al., 2022). Similarly, Bellamoli et al. reported a high in-hospital mortality for patients with ERAD in acute MI (Bellamoli et al., 2020). In this population of OHCA victims however, only left axis deviation was associated with higher mortality.

Intraventricular conduction disturbances impacted survival in this population. Both RBBB and bifascicular BBB led to a higher 30-day mortality. LBBB however didn't seem to impact survival in the same way as the other types of BBB. (Martens, Eimo et al.) There is little and conflicting evidence on the impact of RBBB on survival. Grand et al. also reports RBBB to be directly associated with higher mortality after OHCA (Grand et al., 2016). Patients suffering from acute MI without OHCA also seem to have a higher mortality if they present with RBBB (Ibanez et al., 2018). Sarak et al. however found no connection between RBBB and mortality in ACS patients presenting with OHCA (Sarak et al., 2018). Meanwhile no study to date has examined the impact of bifascicular BBB on survival after OHCA. There is however very limited evidence on bifascicular BBB leading to worse outcome in acute myocardial infarction, which supports our findings. (Lévy, 2018; Neumann et al., 2019)

As mentioned above LBBB didn't impact survival in the studied population. While Sarak et al. didn't find a connection between RBBB and mortality in ACS patients presenting with OHCA, LBBB was associated with a higher mortality, both in-hospital and after 6 months. (Sarak et al., 2018) But again Grand et al. supports our findings. In his study, there was also no influence of LBBB on survival after 6 months in OHCA patients. Neumann et al. looked at BBB in patients with suspected AMI. While patients with LBBB more often really had a myocardial infarction than patients with RBBB or bifascicular BBB, one year mortality was markedly higher in patients with RBBB or bifascicular BBB than in those with LBBB. (Neumann et al., 2019)

Overall, to date there is no clear evidence on the impact of BBB on survival after OHCA.

The presence of STEMI criteria in the ECG on admission didn't influence survival in this study. Surprisingly however, only 50% of the whole population fulfilled the criteria for STEMI in their ECG, as stated in the current guidelines. (Thygesen et al., 2018) Even though all patients included in the study had a myocardial infarction as underlying cause of the OHCA, requiring immediate reperfusion. Whether or not OHCA victims without ST-elevations on their ECG should receive immediate CAG has been a focus in the literature in recent years. This question is of very high importance as the majority of OHCA patients presents without ST-elevation (STE). However, up to 53% of these patients not fulfilling STEMI criteria still have an acute coronary occlusion, which aligns with this study's results. (Dumas et al., 2016) Nevertheless the evidence on the benefits of an immediate CAG strategy in OHCA due to NSTEMI is conflicting. While there are many metanalyses and observational studies that found immediate CAG and PCI led to better outcome (Dumas et al., 2016; Meng-Chang et al., 2020; Vadeboncoeur et al., 2018; Welsford et al., 2018), three recently conducted large randomized controlled trials found no significant difference between an immediate or delayed strategy. Primary endpoint differed between all three trials, with survival after 90 days and 1 year in the COACT trial, survival with minimal neurological deficits after 180 days in the Emerge trial and all cause death after 30 days in the TOMAHAWK trial (Desch et al., 2021; Hauw-Berlemont et al., 2022; Lemkes et al., 2019; Lemkes et al., 2020). Only in the Emerge Trial the survival rate was higher in the immediate CAG group than in the delayed CAG group (36.2% vs. 33.3% respectively), but the difference did not reach statistical significance (Hauw-Berlemont et al., 2022). Both the COACT trial and the Tomahawk trial reported TTM to have started later in the group of patients receiving immediate CAG, which may have been a confounder (Desch et al., 2021; Lemkes et al., 2020).

There may be various reasons for the conflicting evidence. First of all, the exact patient population could be different for each study resulting in different results. Furthermore, the percentage of patients suffering from a relevant coronary lesion even though they do not present with STE may also be different in each population. Consequently, whether the patients as a group profit from the early intervention varies from study to study. This is supported by the fact, that the rates of reported acute coronary occlusions range from 21% to 53% depending on the study. (Dumas et al., 2016; Hollenbeck et al., 2014; Peberdy et al., 2013; Strote et al., 2012) However, even if the proportion of

patients without an ST elevation with an acute coronary occlusion as cause for their AMI is small, it is still a substantial number of people that could profit from an early CAG.
Using STEMI as a surrogate for a complete or near occlusion AMI, goes back to studies conducted in the thrombolytic era. (Group, 1994) There have since been no further studies examining the relation between STE and reperfusion by intervention (Aslanger et al., 2020; Pendell Meyers et al., 2021). 25 – 30% of NSTEMI patients suffer from unrecognized coronary occlusion and therefore do not receive emergent reperfusion therapy (Aslanger et al., 2020; Khan, A. R. et al., 2017). Given these findings, and the fact that half of the population in this study did not present with STEMI criteria despite having a coronary occlusion, the STEMI criteria might not be the best tool to identify patients in need of reperfusion therapy, both for patients with myocardial infarction itself and OHCA victims.

A QTc interval equal to or above 500ms was found to lead to a higher mortality in the studied population. (Martens, Eimo et al.) There is some evidence pointing to worse survival in patients with MI or suspected MI with a prolonged QTc duration (Cupa et al., 2018; Hetland et al., 2014). Only very little evidence can be found on survival after OHCA specifically and the studies that did look at the QTc duration in association with survival after OHCA, didn't find it to be predictive of the outcome (Bunch et al., 2004; Kosmopoulos et al., 2020).

QT-dispersion is considered to be an indirect measure of the heterogeneity in the ventricular repolarization. But due to difficulties in localizing the end of the T wave, QT-dispersion is subject to a large measurement error. Malik et al. suggests that only values $\geq$ 100 ms, which are outside the range of possible errors in measurement, point to an abnormal repolarization with practical implications. (Malik, M. & Batchvarov, 2000)
In line with this, patients in the presented study with a QT dispersion $\geq$ 100 ms had a significantly higher 30-day mortality. (Martens, Eimo et al.) QT-dispersion has been reported as a risk factor for SCA (Goldberger et al., 2008), but evidence on the impact on survival after OHCA is scarce. Kosmopoulos et al. reported a significantly lower QT-dispersion in OHCA patients who survived to hospital discharge as well. While the mean dispersion in survivors was below 100 ms, QT-dispersion in the deceased patients considerably exceeded 100 ms with a mean of 166 ms. (Kosmopoulos et al., 2020) The

underlying mechanism for these findings could be an association between the prolongation of QT-dispersion and the severity of myocardial ischemia, which has been reported previously (Stierle et al., 1998).

In the studied population T inversion on the admission ECG proved to be significantly associated with worse survival. (Martens, Eimo et al.) There is evidence supporting T wave inversion to be associated with a higher risk of sudden death (Laukkanen et al., 2014). However, there is almost no evidence on the impact of T inversion on the outcome after OHCA. A sub-study of the COACT trial, looked at post arrest ischemic ECG patterns (ST-depression and T-wave inversion) and 90-day survival. 90-day survival was worse in patients with ST depression or T-wave inversion in the first in-hospital ECG after ROSC. However, they didn't distinguish between the two ECG patterns, so the exact impact of T-wave inversion on survival remains unclear. (Spoormans et al., 2022)

There are limitations to the study, that need to be taken into account, when interpreting the results. The data were acquired retrospectively, using written and digital patient files. As the data originally were not documented for research, some data are inevitably missing. Patients were included over a timeframe of 15 years, thus different people were involved in patient care and data entry, leading to an additional lack of homogeneity, which might further impair the quality of the data. With data potentially missing, unknown confounding factors could stay unrecognised, which might lead to false associations.

Furthermore, the ECGs that were analysed were sometimes of limited quality. A lot of them had been stored for a long time, causing the ink to fade. Additionally, as they were written in an acute setting, some ECGs had a high number of artifacts. This made the analysis more difficult and although the complexes best visible were used to measure intervals, errors cannot be ruled out.

The population size was relatively small, leading to limited power. Therefore, other parameters that may have been associated with survival did not reach statistical significance. Finally, a selection bias cannot be ruled out as only patients that achieved ROSC and lived long enough to undergo PCI were included.

Overall, this study shows, that there is an association between both clinical features and ECG characteristics and 30-day mortality after OHCA due to AMI. Pre-diagnosed CVRF seem to have a counterintuitive positive effect on survival. More established risk factors like age and female sex, were associated with worse survival. Additionally, several parameters of the first 12-lead ECG after admission, such as rhythm, BBB, ELAD and QT dispersion and QTc, are related to survival. (Martens, Eimo et al.) This means that both clinical and ECG characteristics should be taken into greater consideration in the decision-making process after patient admission in order to identify patients at high risk of death.

6 Conclusion

OHCA is a major public health problem that affects a large number of people every year and has a very poor prognosis. The annual incidence ranges from 64 to 170 per 100,000 inhabitants. (Gräsner et al., 2021) Only 50-60% of the victims are even resuscitated by EMS and the survival rate is as low as 8-10%. (Empana et al., 2018; Gräsner et al., 2021; Gräsner et al., 2020; Sasson et al., 2010; Yan et al., 2020) There are large efforts to improve the prevention of SCA by better predicting such events. However, this remains extremely difficult, as in many patients SCA is the first manifestation of heart disease. (Fishman et al., 2010; Myerburg, 2001; Myerburg & Junttila, 2012; Zeppenfeld et al., 2022) Consequently, prediction of the occurrence of OHCA in general is not enough. The treatment and prediction of patients at especially high risk of death has to be improved as well, to reduce the number of fatalities. The literature in this area has focused mostly on the impact of pre-hospital resuscitation factors, such as initial presenting rhythm, witnessed status and bystander CPR. (Gräsner et al., 2021) Nevertheless, the mortality rate has shown no real improvement over the last decades. (Sasson et al., 2010) Therefore, the aim of this study was to investigate the impact of clinical characteristics and post-resuscitative ECG changes on the survival after OHCA, as both are an integral and basic part of patient care. With CAD, most often presenting as ACS, being the cause for 70-80% of all SCA cases, the study specifically focused on patients with OHCA due to myocardial infarction. (Geri et al., 2017; Hayashi et al., 2015; Zeppenfeld et al., 2022)

The clinical data and 12-lead post-resuscitative ECGs of 119 patients admitted after OHCA due to AMI were analysed. AMI was considered to be the cause of arrest, if the patients showed an acute obstructive lesion in their coronary arteries that warranted reperfusion therapy (RT). Patients without a documented 12-lead ECG on admission were excluded. The first 12-lead ECG after ROSC was analysed and several clinical features such as pre-diagnosed CVRF, comorbidities and pre-existing antiarrhythmic medications were extracted from patient files. 30-day mortality was the primary endpoint. Statistical tests were used to look for significant associations between clinical characteristics and post-resuscitative changes in the electrocardiogram and survival. 30-day mortality was 30.3% (36 patients). (Martens, Eimo et al.)

A considerable number of variables were found to be associated with survival.

Features linked with worse survival included atrial fibrillation/flutter (HR 2.29 (95% CI 1.17 – 4.49, p = 0.015)), right bundle branch block (HR 2.23 (95% CI 1.14 – 4.56, p = 0.020)), bifascicular bundle branch block (HR 2.517 (95% CI 1.045 – 6.059, p = 0.040)), T-inversion (HR 2.012 (95% CI 1.02 – 3.99, p = 0.043)), QTc duration ≥ 500ms (HR 2.21 (95% CI 1.10 – 4.42, p = 0.025)), QT dispersion ≥ 100 ms (HR 2.11 (95% CI 1.02 – 4.37, p = 0.045)), higher age (HR 1.04 (95% CI 1.01 – 1.07, p = 0.003)) and a CL in the LCX (HR 2.213 (95% CI 1.088 – 4.503, p= 0.028)). (Martens, Eimo et al.)

Sinus rhythm (HR 0.492 (95% CI 0.255 – 0.946, p = 0.034)), a CL in the LAD (HR 0.420 (95% CI 0.197 – 0.894, p = 0.024)), a history of smoking (HR 0.405 (95% CI 0.195 – 0.843, p = 0.016)) and hypercholesterolemia (HR 0.389 (95% CI 0.202 – 0.750, p = 0.005)) were associated with a lower 30-day mortality. (Martens, Eimo et al.)

This shows, that both clinical characteristics and post-resuscitative ECG changes impact survival significantly. In the future not only pre-resuscitative factors but both clinical and ECG characteristics should be considered more closely, in order to identify patients at higher risk of death. This could help to intensify treatment of high-risk patients and in turn improve survival after OHCA.

7 Publication

Parts of the thesis have been previously published in:

E. Martens et al., Out-of-hospital cardiac arrest 30-day-outcomes: The importance of the first electrocardiogram after successful resuscitation, Journal of Emergency Medicine, https://doi.org/10.1016/j.jemermed.2024.09.010

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