Cardiac arrest with emphasis on comorbidity and choice of treatment in acute coronary syndrome in the elderly

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Statistics can be made to prove anything—

even the truth

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ABSTRACT

Background and aim: More data is required on survival and neurological outcome after in-hospital cardiac arrest (IHCA) in the elderly. The influence of comorbidity is often neglected in cardiac arrest research, particularly after out-of-hospital cardiac arrest (OHCA). The treatment strategy of non - ST elevation - acute coronary syndrome (NSTE-ACS) in the very elderly is debatable. Thus, the aim of this thesis was to determine the following aspects:

1) The 30-day survival and neurological outcome of elderly patients after IHCA.
2) The impact of comorbidity on 30-day survival after OHCA.
3) Whether comorbidity impacts the effect of bystander cardio-pulmonary resuscitation (CPR) on 30-day survival after OHCA.
4) The impact between two treatment strategies in the very elderly with NSTE-ACS.

Methods: Data from the Swedish Registry of Cardiopulmonary Resuscitation (SRCR) was used for analysis; IHCA (I) and OHCA (II-III). Data from the National Patient Registry (NPR) was merged with the SRCR (II-III). Study IV was a randomized controlled trial in which patients aged ≥80 years with NSTE-ACS were randomized to an invasive strategy or a conservative strategy.

Results: In Study I, we found that 30-day survival decreased among the elderly with advancing age; however, among survivors, no significant association was found between age and a favourable neurological outcome. In Study II, we found that with increasing comorbidity, the likelihood of a 30-day survival after OHCA decreased. In Study III, we showed that comorbidity had no marked influence on the association between bystander CPR and 30-day survival after OHCA and that there was still a strong association between bystander CPR and 30-day survival even when adjusting for comorbidity. In Study IV, we showed that at the 12-month follow up, there was no statistically significant difference between the invasive strategy group compared to the conservative strategy group in major adverse cardiac and cerebrovascular events (MACCE) in the very elderly with NSTE-ACS.

Conclusion: A decrease in survival among the elderly with advancing age but most elderly survivors from IHCA had a favourable neurological outcome. Increasing comorbidity was associated with a decreased chance of 30-day survival, but the degree of comorbidity did not affect the association of bystander CPR with 30-day survival after OHCA. No significant difference was found between the invasive and the conservative strategy group in terms of MACCE in the very elderly with NSTE-ACS at the 12-month follow-up.

Keywords: cardiac arrest; comorbidity; elderly; non-ST elevation - acute coronary syndrome; percutaneous coronary intervention.

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SAMMANFATTNING PÅ SVENSKA

Syftet med avhandlingen var att utvärdera

1) Överlevnaden och den uppskattade hjärnfunktionen hos överlevare bland de äldre som får hjärtstopp på sjukhus och där hjärt-lungräddning (HLR) påbörjas.
2) Förekomsten av samsjuklighet hos patienter som får hjärtstopp utanför sjukhus och där HLR påbörjas samt hur överlevnaden till 30 dagar påverkas av samsjukligheten.
3) Beskriva om samsjukligheten påverkar utfallet av tidig hjärt-lungräddning som påbörjas innan ambulansen kommer fram till patienten.
4) Att jämföra en invasiv strategi (kranskärlsröntgen och eventuell ballongdilatation) med en konservativ strategi bland patienter ≥80 år som drabbas av en hjärtinfarkt där det inte föreligger ST höjningar på EKG.

Metodologiskt var delarbetena I-III i denna avhandling baserade på registerdata från det svenska hjärt-lungräddningsregistret samt även från patientregistret i delarbete II-III. Delarbete IV är en randomiserad kontrollerad studie med två behandlingsarmar.

I delarbete I inkluderades patienter över 70 år som hade drabbats av hjärtstopp på sjukhus och där HLR påbörjats och delades in i tre åldersgrupper: 70-79, 80-89, ≥90 år. Med stigande ålder sjönk 30 dagars överlevnaden (28%, 20%, 14% i respektive grupp) och de flesta av överlevarna uppskattades ha en relativt god cerebral funktion.

I delarbete II studerades patienter som hade drabbats av hjärtstopp utanför sjukhus och där HLR påbörjats. I studien var hjärt-lungräddningsregistret samkört med patientregistret för att belysa förekomsten av samsjuklighet. Studien visade vilka sjukdomar som påverkade chansen att överleva 30 dagar. Med stigande samsjuklighet minskade chansen att överleva 30 dagar.

I delarbete III användes samma databas som i delarbete II. Här belystes skillnaden i samsjuklighet mellan de som hade drabbats av hjärtstopp utanför sjukhus och fick HLR innan ambulansen var framme hos patienten och de som inte fick tidig HLR. Patienter som fick tidig HLR var lite friskare men skillnaden i samsjuklighet påverkade inte den

positiva effekten av ett tidigt HLR-ingripande avseende 30 dagars överlevnaden.

Delarbete IV beskriver en randomiserad kontrollerad studie på patienter som var ≥80 år gamla och som drabbats av hjärtinfarkt där det inte förelåg ST höjningar på EKG. I studien lottades 186 patienter slumpvis (randomiserades) antigen till a) behandling med kranskärlsröntgen och eventuell efterföljande ballongdilatation samt läkemedel eller b) enbart behandling med läkemedel. Efter 12 månaders uppföljning sågs ingen statistiskt säkerställd skillnad i förekomsten av ogynnsamma hjärt-kärl händelser mellan de två behandlings grupperna. Det förelåg inte heller någon skillnad i överlevnad eller i förekomst av kärlkramp.

Slutsatsen är att överlevnaden sjunker med stigande ålder efter hjärtstopp på sjukhus där behandling har påbörjats men de flesta överlevarna förefaller att ha en relativt god neurologisk funktion. En ökande samsjuklighet begränsar överlevnaden efter hjärtstopp utanför sjukhus men förefaller inte att påverka överlevnads effekten av ett tidigt HLR ingripande. Det förelåg ingen statistiskt säkerställd skillnad i utfall mellan en invasiv strategi jämfört med en konservativ strategi vid instabil kranskärlsjukdom hos ≥ 80 år gamla patienter.

LIST OF STUDIES

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Hirlekar G, Karlsson T, Aune S, Ravn-Fischer A, Albertsson P, Herlitz J, Libungan B.

Survival and neurological outcome in the elderly after in-hospital cardiac arrest.

Resuscitation. 2017. Sep;118:101-106.

II. Hirlekar G, Jonsson M, Karlsson T, Hollenberg J, Albertsson P, Herlitz J.

Comorbidity and survival in out-of-hospital cardiac arrest.

Resuscitation. 2018. Dec;133:118-123.

III. Hirlekar G, Jonsson M, Karlsson T, Bäck M, Raswhani A, Hollenberg J, Albertsson P, Herlitz J.

Comorbidity and bystander cardiopulmonary resuscitation in out-of-hospital cardiac arrest.

Heart. (E-pub 2020 Jan 23).

IV. Hirlekar G, Libungan B, Karlsson T, Bäck M, Herlitz J, Albertsson P.

Percutaneous coronary intervention in the very elderly with NSTE-ACS: the randomized 80+ study

Submitted

TABLE OF CONTENTS

ABBREVIATIONS

ACE	Angiotensin converting enzyme
ACS	Acute coronary syndrome
AED	Automated external defibrillator
AHA	American heart association
ARB	Angiotensin II receptor blocker
CA	Cardiac arrest
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CCI	Charlson comorbidity index
CFS	Clinical frailty scale
CHF	Congestive heart failure
CI	Confidence interval
CK	Creatine kinase
COACT	Coronary angiography after cardiac arrest without ST-segment elevation
CPC	Cerebral performance category
CPR	Cardiopulmonary resuscitation
CRUSADE	Can rapid risk stratification of unstable angina patients suppress adverse outcomes with early implementation of the ACC/AHA guidelines
DAPT	Dual antiplatelet therapy
DNAR	Do not attempt resuscitation
ECG	Electrocardiography
EMS	Emergency medical service
ESC	European society of cardiology
FRISC	The Fragmin and fast revascularization during instability in coronary artery disease trial
GP	glycoprotein
GRACE	Global registry of acute coronary events
ICD-10	International classification of diseases-10
ICTUS	Invasive versus conservative treatment in unstable coronary syndromes
IHCA	In-hospital cardiac arrest
HR	Hazard ratio
LBBB	Left bundle branch block
MACCE	Major adverse cardiac and cerebrovascular event
MAR	Missing at random
MCAR	Missing completely at random
MI	Myocardial infarction
MNAR	Missing not at random
NPR	National patient registry
NSAID	Nonsteroidal anti-inflammatory drugs

NSTE-ACS	Non-ST elevation - acute coronary syndrome
NSTEMI	Non-ST elevation myocardial infarction
OASIS	the organization to assess strategies in ischemic syndromes
OHCA	Out-of hospital cardiac arrest
OR	Odds ratio
PCI	Percutaneous coronary intervention
PEA	Pulseless electrical activity
PLATO	Platelet inhibition and patient outcomes
RITA	Randomized trial of a conservative treatment strategy versus an interventional treatment strategy in patients with unstable angina
ROSC	Return of spontaneous circulation
SRCR	The Swedish registry for cardiopulmonary resuscitation
STEMI	ST elevation myocardial infarction
TACTIC-TIMI	Treat angina with aggrastat and determine cost of therapy with an invasive or conservative strategy-thrombolysis in myocardial infarction
TNT	Troponin T
TRITON-TIMI	Trial to assess improvement in therapeutic outcomes by optimizing platelet Inhibition with Prasugrel-thrombolysis in myocardial infarction
TTM	Targeted temperature management
UA	Unstable angina
VF	Ventricular fibrillation
VT	Ventricular tachycardia

1 INTRODUCTION

There is an increase in the number of elderly in the global population and the number of elderly patients will continue to increase as the prevalence of chronic diseases increases, particularly with advancing age. In Sweden, almost half of the population is afflicted with at least one chronic disease and 25% have more than one [1]. Comorbidity, as the total burden of medical conditions and old age, can possibly influence the effect of different interventions and the choice of treatment given. Old age is a major risk factor for coronary artery disease which can lead to myocardial infarction and sudden cardiac death. When treating the elderly with different other conditions, the treatment strategy can possibly be influenced by a patient's comorbidities. Therefore, when investigating and comparing two treatment strategies in an observational study, the two cohorts can possibly conceal one or several confounders that have influenced the choice of treatment and the effect of the treatment given. Comorbidity can possibly be such a confounder. Thus, the comorbidity burden may influence the choice of treatment strategy and how aggressively we choose to treat our patients.

The main purposes of this thesis are to 1) investigate the survival of the elderly after an in-hospital cardiac arrest (IHCA); 2) investigate the association between comorbidities and survival after out-of hospital cardiac arrest (OHCA); 3) investigate whether comorbidity impacts the effect of bystander cardiopulmonary resuscitation on survival after OHCA; and 4) compare two treatment strategies with a randomized clinical trial in very elderly patients who suffer from Non-ST elevation - acute coronary syndrome (NSTE-ACS).

1.1 CARDIAC ARREST

Previously, there have been different definitions of cardiac arrest (CA) and rather variable inclusion criteria in reports of cardiac arrest. In order to standardize the reporting of cardiac arrest, the Utstein Style consensus template was created in the Utstein Abby in Norway in 1990 for OHCA [2]; subsequently, templates for IHCA were also published in 1997 [3].

The Utstein style definition of a cardiac arrest is '*the cessation of cardiac mechanical activity as confirmed by the absence of signs of circulation'* [4]. Cardiac arrest can take place both within and outside a hospital. According to the Utstein report, a cardiac arrest is defined as IHCA if the patient had a pulse at the time of admission to hospital and that chest compression or defibrillation were delivered within the hospital walls [5].

1.1.1 EPIDEMIOLOGY

Out of hospital cardiac arrest is a common cause of death worldwide. However, there are global variations in reporting the incidence of treated OHCA. In Europe [6], there are at least 275,000 cases of OHCA that are annually treated by emergency medical services (EMS) and this number is 180,000 in the USA [7]. Globally, the incidence is estimated to be 62.3 cases/100,000 people [8]. Further, the mean incidence rate of initiated resuscitation was 56 per 100,000 inhabitants per year in Europe [9] and 47.3/100,000 per year in North America [8]. In Sweden, there are approximately 6000 cases of OHCA annually, which are treated by EMS, with an incidence of 52/100,000 inhabitants per year [10]. Most of the articles dealing with OHCA report on the number of cases in which resuscitation was attempted. However, in certain studies the given figure refers to the number of cases considered for resuscitation. The survival to discharge in patients for whom CPR was initiated was approximately 8% in Europe [9]. In Sweden, the survival to 30-day has doubled since 1992 and is currently around 11% [10].

The incidence of IHCA globally is not as well studied as that of OHCA. There are quite a few national and regional registries for IHCA. The incidence of IHCA can be calculated as the number of events per 1000 patient admissions or per 100 hospital beds. The number of cases with IHCA where resuscitation was attempted varies between states in the US, with approximately 200,000 cases annually in the entire country and six to seven cardiac arrests per 1000 admissions, with an overall survival-to-discharge rate of approximately 17%–23% [11,12]. There has been an increase in the survival rate in the USA in the previous decade and cases of reporting are increasing as well [12].

In the UK National Cardiac Arrest Audit database, the overall incidence of adult in-hospital cardiac arrest was 1.6 per 1000 hospital admissions, with a survival to discharge rate of 18.4%. Other studies have reported an incidence of 1–6 events per 1000 hospital admissions [13].

In Sweden, there are approximately 2500 cases of IHCA reported to the SRCR annually and the survival to 30-day is approximately 30%. The incidence has been reported to be 1.7 per 1000 hospital admissions [14].

A number of factors influence the incidence and the variability between countries in terms of both incidence and survival after IHCA. The degree of comorbidity, culture, and the composition of admitted patients as well as different systems surrounding the resuscitation team can potentially influence the incidence. When estimating the incidence of IHCA, CPR is initiated only in a minority of cases [15]. Thus, a large proportion of patients have a Do Not Attempt Resuscitation (DNAR) order explaining why CPR was not initiated. This is in contrast to the situation after OHCA, where CPR is initiated in a majority of cases, since there is often a lack of information regarding the patient's comorbidity at the time of cardiac arrest. Further, the number of cases reported can depend on whether such events took place in the intensive care unit or in the catheterization lab, since such units do not always activate the resuscitation team and, therefore, there is a risk of not reporting the event to the register.

1.1.2 AETIOLOGY OF CARDIAC ARREST

There are numerous conditions that can progress and, if untreated, lead to cardiac arrest and potentially to sudden death. In OHCA, the exact aetiology can be difficult to determine, as numerous patients die at the scene without an autopsy being performed. However, when patients collapse in hospitals, it is often not unexpected, since the cardiac arrest is often preceded by a deterioration of vital signs and is therefore often not as sudden as when they collapse outside hospital [16].

In the Utstein template, it has been recommended that—at least for OHCA—the causes of cardiac arrest must be classified as having a medical or a non-medical aetiology [17]. Medical aetiology can then be

further classified as cardiac or non-cardiac aetiology. Table 1 lists a few causes of cardiac arrest.

Cardiac arrest has been assumed to be of a cardiac aetiology when there is no other obvious cause of the cardiac arrest [18]. In certain studies, the EMS have estimated that cardiac aetiology is found in 50%–90% of all cases [19]. A cardiac aetiology can possibly be overestimated by EMS, as the presumable cause of OHCA in the prehospital setting can be uncertain. An autopsy is the golden standard to determine the definite aetiology of the cause of death [20]. An autopsy study showed that 74 of 100 patients who died from sudden cardiac death had a coronary thrombus and 21 had plaque fissuring [21]. Another study found that in 51 of 90 hearts, there were acute changes in a coronary lesion (thrombus and/or plaque disruption) [22]. In the SRCR, the aetiology is assumed to be cardiac in 60% of all cases of OHCA where CPR was attempted. The corresponding figure is approximately 70% among patients older than 65 years but only 10% among patients aged 16–40 years.

In the coronary angiography after cardiac arrest (COACT) study [23], patients with OHCA and initial shockable rhythm, and who did not have STEMI on the initial ECG, were randomized to immediate or delayed coronary angiography. The results revealed that only 5% of patients had a thrombotic occlusion of a coronary artery but coronary artery disease was present in 64.5% of the patients that performed coronary angiography.

The composition of aetiology can differ irrespective of whether the cardiac arrest occurs inside a hospital or outside. However, the most common aetiology of IHCA is a cardiac disease [24,25] and the second most common cause is a pulmonary condition [25,26].

Medical		Non-medical
Cardiac	**Non-cardiac**	
Acute myocardial infarction	Trauma	Trauma
Arrhythmia such as Brugada syndrome, and long QT syndrome	Malignancy	Overdose
Cardiomyopathy, such as myocarditis, dilated cardiomyopathy, hypertrophic CMP	Bleeding, such as gastrointestinal, cerebrovascular, and aorta dissection	Drowning
Valvular heart disease	Hypoxia, such as pneumonia, chronic obstructive pulmonary disease, pulmonary embolism	Electrocution
Congenital heart disease	Septic shock	Asphyxial

Table 1. Adopted from Lancet [27]*. The causes are not listed in order of frequency and the list is not complete.*

1.1.3 THE CHAIN OF SURVIVAL

When a patient collapses, it is often sudden and the likelihood of a positive outcome is influenced by how rapidly each link in the chain of survival is activated [10,28]. These links include the dispatch centre, a bystander, and the EMS team in OHCA and the hospital staff in IHCA. This concept was first introduced in 1991 [29] with four links in the **chain of survival**. Today, these links are defined as early recognition and call for help, early CPR, early defibrillation, and post-resuscitation care. All links are important to ensure that the patient survives with an intact neurological function.

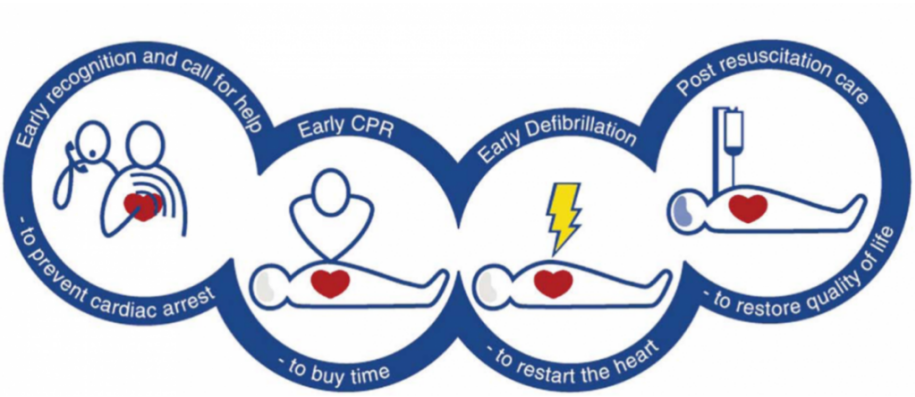

Figure 1. The chain of survival. Adapted from Nolan [30] *and reprinted with permission from Elsevier.*

1.1.4 FACTORS ASSOCIATED WITH SURVIVAL

There are numerous factors that are associated with outcome in cardiac arrest. The following are a few examples of factors that are associated with outcome:

Age

Age is an independent predictor of the risk of death after OHCA and the 30-day survival decreases with increasing age.

There is a similar association between age and the risk of death after IHCA, with a lower likelihood of survival with increasing age [13,24,31].

Comorbidity

Studies that have investigated the association between comorbidity and survival after OHCA have found conflicting results [32,33]. For OHCA, a few studies have found an association [34–37] while others have not [33,38–40]. A systematic review [41] of 29 observational studies found that prearrest comorbidity was, in general, associated with reduced survival and poorer neurological outcomes.

Studies on pre-arrest comorbidity in IHCA have found that increased comorbidity is associated with reduced survival [14,42]. Further, a meta-analysis [31] found that history of malignancy, chronic kidney disease, congestive heart failure, chronic obstructive pulmonary disease, diabetes mellitus, and acute coronary syndrome (ACS) were all associated with a lower survival rate after IHCA.

Witnessed event

The Utstein definition of a bystander-witnessed cardiac arrest is when the collapse is witnessed or heard by a person who is not a member of the EMS team or if the patient is being monitored on an ECG machine [17]. When the cardiac arrest is witnessed, the likelihood of survival is higher due to earlier recognition and earlier initiation of treatment. When the CA is unwitnessed, the survival is very poor.

Bystander CPR

Bystander CPR is defined as CPR performed by a person who is not part of the system that is activated by the dispatch centre [17]. The main effect of CPR is to maintain circulation and prolong the shockable phase of VF/VT by enhancing coronary perfusion [43,44]. Numerous studies have found that bystander CPR is associated with a two-to-threefold increase in 30-day survival rate in OHCA [45–47]. The effect of bystander CPR may be affected by the EMS response time. Thus, it has been suggested that when EMS delay is over 13 min, the effect of bystander CPR becomes less substantial [48]. The quality of CPR performed by the bystander is also important [47].

Studies have shown that bystander CPR is more often performed in younger patients, patients who collapse outside the home, and where the initial rhythm is shockable [45]. With these differences between the group that receives bystander CPR and the group that does not, it is possible that the actual effect of bystander CPR could be overestimated; therefore, differences in age and place of OHCA, in particular, must be adjusted for.

First monitored rhythm

The first monitored rhythm is the first cardiac rhythm that is recorded once the monitor or defibrillator is attached to the patient after collapse [17]. The rhythms are classified to shockable and non-shockable rhythms. Shockable rhythms include ventricular fibrillation (VF) or pulseless ventricular tachycardia (VT). Non-shockable rhythms include asystole or pulseless electrical activity (PEA).

Whether the first monitored rhythm is shockable or not is a major predictor for survival in both OHCA [46] and IHCA [14,31]. The 30-day survival of patients with VF/VT as initial rhythm is approximately 35% compared to 4% in patients with non-shockable rhythm in OHCA [49].

Shockable rhythms are more related to a cardiac aetiology, particularly myocardial ischemia. VF/VT can often be treated promptly with defibrillation in order to prevent it from deteriorating to non-shockable PEA/asystole.

Early defibrillation

Defibrillation can be applied when the monitored rhythm is shockable. In the OHCA setting, the 30-day survival is highest after the first defibrillation and decreases with each defibrillation attempt [50]. The time from collapse to defibrillation is important and strongly related to the likelihood of survival [51,52]. The time to the attachment of an automated external defibrillator (AED) and the time taken for the arrival of the rescue team/EMS must be as short as possible. AEDs are now available for public use and such a strategy has shown to improve survival in OHCA settings [53,54]. When an AED is unavailable, the time for EMS to arrive to perform defibrillation is particularly critical [55]. With a longer EMS response time, likelihood of survival decreases [48].

In the in-hospital setting, AEDs are often available in general wards and they can easily be applied in the case of shockable rhythm [56,57].

Location of cardiac arrest

The majority (65%) of OHCA occur in a patient's home with a lower likelihood of survival compared to OHCA in a public location [58]. Patients who collapse at home differ in certain aspects as compared to patients who collapse outside of the home; the former are older, more often women, less often have a witnessed arrest and less often receive bystander CPR. In addition, they are less often found in a shockable rhythm and with a longer delay to initiation of EMS treatment [58].

On the other hand, survival after IHCA is highly dependent on whether or not the cardiac arrest occurs in a monitored ward [59]. An IHCA that occurs in a monitored ward is highly associated with an increased likelihood of survival, as there is an earlier detection of cardiac arrest and immediate availability of advanced life support [31,60]. A large proportion of cardiac arrests occur in general wards without monitoring [61]. However, the association between the location of IHCA and survival is more complex in in-hospital settings than in out-of hospital settings, since patients who are critically ill are more often located in a ward that has more extensive monitoring and a more intensive care [62].

1.1.5 COMPARISON OF OHCA AND IHCA

In both OHCA and IHCA, there is a high risk of death. The reasons for a much higher survival after an IHCA than after an OHCA are numerous. A few of these are explained here: As previously mentioned, the deterioration of vital signs often precedes an IHCA, whereas OHCA often occurs suddenly and without early warning signs. Further, there are a few some major differences that contribute to the difference in 30-day survival between IHCA and OHCA [63]. In IHCA, the delay of initiating treatment is shorter and since these cases are more often witnessed and ECG monitored, the time to initiating CPR and defibrillation is shorter [64].

Further, there is a case selection in IHCA, since cases which are not suitable for further life support can be given a DNAR order, thereby resulting in a case selection where only patients with a reasonable likelihood of survival will receive resuscitation attempts.

1.2 CORONARY ARTERY DISEASE IN THE ELDERLY

''The physician should not treat the disease but the patient who is suffering from it'

– Moses Maimonides

Coronary artery disease (CAD) is the leading cause of morbidity and mortality worldwide and will continue to be so in the future as well [65]. Advanced age is one of the strongest predictors of mortality and morbidity in acute coronary syndrome.

The proportion of elderly in the population is increasing and will continue to increase in the next few years [66]. In Sweden, it is estimated that in the next decades, life expectancy will increase further to over 89 years for women and over 87 years for men [67].

There is no consensus on how to define the elderly. There is some agreement that people aged ≥ 75 years can be defined as elderly [68] and those aged ≥ 80 years as very elderly; however, the World Health Organization (WHO) has also applied an age cut-off of as low as 65 years to define the elderly [69].

What is coronary artery disease?

Coronary artery disease (CAD) occurs due to atherosclerosis in the coronary arteries. Atherosclerosis leads to the formation of an atherosclerotic plaque that can be initially asymptomatic but can then progress and lead to impaired blood flow and cause ischemia in the heart muscle. Stable angina pectoris is a condition when blood flow is sufficient at rest but the heart muscle becomes ischemic with exercise or stress [70]. The first clinical presentation of CAD can be stable angina pectoris or acute coronary syndrome (ACS).

1.3 ACUTE CORONARY SYNDROME

The clinical spectrum of ACS is caused by acute myocardial ischemia. Acute Coronary Syndrome can be classified in the following manner according to the electrocardiogram (ECG):

- ST-segment elevation myocardial infarction (STEMI)
- Non-ST elevation - acute coronary syndrome (NSTE-ACS)
    - Non-ST segment elevation myocardial infarction (NSTEMI)
    - Unstable angina (UA).

This classification has important therapeutic implications in that patients that present with STEMI should receive immediate reperfusion therapy, whereas patients with NSTE-ACS are risk stratified for invasive management. NSTEMI and UA represent a continuity and are clinically indistinguishable; therefore, both are grouped together as NSTE-ACS or unstable coronary artery disease. The difference between NSTEMI and UA is that in UA there is no elevation of cardiac biomarkers such as TNT, TNI, or CK-MB [71].

Epidemiology of NSTE-ACS in the elderly

The incidence rate of NSTEMI has increased only slightly in the previous decade [72–74]. The incidence of NSTE-ACS increases with age and is more frequent in the elderly than STEMI [75,76]. Overall, there are more patients with NSTE-ACS than patients with STEMI [77,78] and patients > 75 years of age constitute approximately one-third of all NSTEMI patients [76,79].

Register studies have shown that mortality increases with age in NSTE-ACS [80]. In the SWEDEHEART registry, the one year mortality among patients >80 years of age with NSTEMI was approximately 30% [74]. Additionally, mortality for patients >75 years of age is twice as high than in patients <75 years of age [81]. Other registries have shown that mortality is decreasing the last decade in patients older than 80 years of age with NSTEMI [82].

The reasons for the high mortality and morbidity in the elderly are multifactorial. Age is not only a risk factor for cardiovascular disease but

also a risk factor for adverse outcomes after cardiovascular events as well as for complications and side effects of pharmacological treatment.

The pathophysiology of acute coronary syndrome

The pathophysiological mechanism underlying ACS is the development of an atherosclerotic plaque rupture, ulceration, fissure, erosion or dissection that results in thrombus formation, low blood flow, and, consequently, myocardial necrosis. Other mechanisms that can cause elevation of cardiac biomarkers is a supply-demand mismatch (Type 2 myocardial infarction) [83]. Elderly patients are often admitted to hospital due to various concurrent conditions that can cause supply-demand mismatch, such as pneumonia, arrhythmia and chronic pulmonary disease [68].

1.3.1 CLINICAL PRESENTATION OF NSTE-ACS

The most common symptom of NSTE-ASC is chest pain, with a retrosternal sensation of pressure or the feeling of something heavy on the chest. The pain can also be located in the back, epigastrium, arms, or jaws. The pain may radiate to the left arm (right or both), neck, abdomen, or jaw. Other symptoms include sweating, nausea, pain in the abdomen, and dyspnoea.

Clinical presentation in the elderly

Recognition of NSTE-ACS can be difficult in older patients due to the atypical clinical presentation. Generally, symptoms are not completely different when compared with younger patients. The most typical symptom and presentation of an ACS is chest pain. However, the elderly can present with other symptoms than chest pain, which can possibly delay the time until a diagnosis is established or the diagnosis can occasionally be completely missed with harmful consequences. Common atypical symptoms for NSTE-ACS in the elderly can be isolated dyspnoea, nausea and vomiting, and diaphoresis [84]. Therefore, a high suspicion of NSTE-ACS must be checked for in elderly patients with such symptoms.

In the electrocardiogram (ECG) ST segment deviation is less frequently observed among the elderly with NSTE-ACS as compared to among younger patients [85], and the baseline ECG may display other patterns such as left bundle branch block (LBBB) or a pacemaker pattern, thereby making the diagnostic workup even more difficult [86].

A part of the workup is to measure cardiac biomarkers. The elderly can have a higher baseline troponin level due to chronic conditions, such as chronic renal failure or chronic heart failure rather than acute myocardial ischemia; this can further confuse the diagnostic workup, particularly in an atypical presentation.

The European Society of Cardiology (ESC) guidelines [71] recommend the assessment of ischemic risk by calculating the Global Registry of Acute Coronary Events (GRACE) risk score. The GRACE risk calculator can be used to estimate in-hospital mortality as well as mortality at one year and three years. The risk of death or MI at one year can also be estimated [87]. The variables used in the GRACE risk calculation include age, systolic blood pressure, heart rate, serum creatinine, Killip class at presentation, cardiac arrest at admission, elevated cardiac biomarkers, and ST deviation. The GRACE risk calculator can be predictive of in-hospital mortality in octogenarians [88]. Therefore, a high GRACE score can be suggestive for an invasive strategy. According to the 2015 ESC guidelines for the management of ACS in patients presenting without persistent ST-segment elevation, patients with a GRACE score >140 must undergo angiography within 24 hours [71].

1.3.2 TREATMENT OF NSTE-ACS IN THE ELDERLY

In clinical trials, the elderly are often not included either due to exclusion criteria or due to the fact that investigators tend to include only low-risk patients with low degree of comorbidity [89]. This causes a challenge for clinicians who are taking care of the elderly, since they rely on guidelines for guidance. In addition, the challenge with guidelines for one specific condition becomes a problem in the elderly as they often suffer from multiple chronic conditions, and each condition has a different pharmacological treatment. The lack of knowledge in how to

treat the elderly forced the American Heart Association (AHA) to publish a scientific statement in order to identify knowledge gaps in the evidence. This statement included the benefit and risks of pharmacologic treatment, invasive vs conservative strategy and risk stratification [90].

However, the very elderly is such a heterogeneous group that it is rather unlikely that an universal treatment strategy would work for them. A more tailored and personalized approach is needed to adjust for physical and cognitive function, comorbid diseases, and even drug metabolism that can vary in older adults and thereby change the course of ACS and potentially also alter the response to a given treatment.

Previous studies have shown that elderly patients do not receive aggressive evidence-based medical treatment to the same extent as younger patients do [75]. However, times are changing and recent studies have shown an increased use of PCI and evidence-based treatment in this patient population [91,92].

Initial management of NSTE-ACS is based on initial treatment with different medications with the goal of 1) relieving the symptoms, 2) relieving myocardial ischemia, 3) antithrombotic therapy, and 4) secondary prevention. This basic initial medical treatment is applicable to all patients [71].

Pharmacological treatment

Treating an older patient with medication may be challenging; it is important to consider dose adjustment as well as drug interaction with other prescribed medication. ESC guidelines recommend the adjustment of antithrombotic treatment in accordance with weight and renal function [71]. These challenges of antithrombotic treatment in the elderly was further addressed by an ESC expert position paper [93]. Thus, the treatment decision must balance the risk of myocardial ischemia versus the risk of bleeding, and with a more aggressive anti-thrombotic treatment, there is likely to be an increase in the risk of bleeding events.

Antiplatelet therapy

All patients with NSTE-ACS must be treated with aspirin regardless of their age unless there is a contraindication [71]. Aspirin must be administered at the time of the event and continued for long term. In a meta-analysis of RCTs, aspirin reduced major vascular events and the benefit was greater in older patients compared to younger patients [94]. However, increasing age is independently linked to increased bleeding risk according to the GRACE registry [95].

Current guidelines recommend using a dual antiplatelet therapy (DAPT) with aspirin and a P2Y12 receptor inhibitor at the time of the event and continuing such treatment for 12 months, regardless of treatment strategy [71,96]. The usage of more potent P2Y12 antiplatelet agents has raised questions regarding safety in the elderly with NSTE-ACS. Guidelines recommend the use of more potent agents like either ticagrelor or prasugrel in addition to aspirin as first-line P2Y12 inhibitors in all patients. However, according to real life registries across Europe, clopidogrel is the most commonly used P2Y12 receptor blocker in elderly patients with NSTE-ACS [97]. However, the utilisation of ticagrelor is becoming more common in recent years in ACS [98]. Clopidogrel is recommended when ticagrelor or prasugrel are not available. There are no restrictions on the use of ticagrelor in elderly patients, but clopidogrel is recommended in combination with oral anticoagulated medication [96].

The platelet inhibition and patient outcomes (PLATO) study revealed that ticagrelor, compared to clopidogrel, was associated with a significantly reduced rate of cardiovascular death, MI, or stroke without increase in major bleeding [99]. A subgroup analysis in PLATO of patients aged ≥75 years showed that the benefit of ticagrelor was not dependent on age but occurred at the expense of an increase in major bleeding among the elderly [100].

Trial to assess improvement in therapeutic outcomes by optimizing platelet inhibition with prasugrel-thrombolysis in myocardial infarction (TRITON-TIMI) 38 trial compared clopidogrel to standard dosage (10mg) prasugrel. A subgroup analysis in patients aged ≥75 years showed no benefit for prasugrel compared to clopidogrel, and there was even a higher rate of bleeding in the former group [101]. Thus, 10mg prasugrel is not recommended for elderly patients. In the targeted

platelet inhibition to clarify the optimal strategy to medically manage acute coronary syndromes (TRILOGY-ACS), patients aged ≥ 75 years were randomized to clopidogrel or a reduced dosage (5mg) of prasugrel. In the trial, there was no difference in ischemic or bleeding complications between the two groups [102]. Therefore, if it is necessary to use prasugrel in the elderly, 5 mg must be used but it is contraindicated if there is a history of prior stroke/transient ischemic attack (TIA) [93].

Anticoagulation

Treatment with anticoagulants is recommended in NSTE-ACS and the use of fondaparinux is recommended [71]. Fondaparinux is a factor Xa inhibitor and was associated with a lower bleeding risk and similar efficacy as enoxaparin in the organization to assess strategies in ischemic syndromes (OASIS)-5 trial [103].

Statin

The use of statins is recommended as a class IA, which implies that the treatment is recommended with good evidence. Statins must be initiated as early as possible to all patients without contraindications and maintained over the long term [71]. The elderly have been under-represented in statin studies. In a meta-analysis [104] of 186,854 participants in 28 trials, only 8% of the participants were over 75 years of age. However, the reduction in vascular events appears to be independent of age. Moreover, there was no statistical difference in coronary revascularization or stroke in patients >75 years of age, but treatment with statins reduced major coronary events among these patients. Statins may even be more beneficial among the elderly compared to younger patients in preventing myocardial infarction and death [105].

Further, there have been concerns that the use of statins in the elderly can cause memory and cognitive problems. However, this was not observed in a recent prospective observational study [106].

ACE or ARB inhibitor

In the ESC guidelines, an angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor blockers (ARB) are recommended for all patients with LVEF ≤40% to reduce the risk of death, recurrent MI,

and hospitalization for heart failure. In the elderly, the doses must be adjusted to each individual in order to prevent side effects [71].

Beta blocker

The documentation of a beneficial effect of beta blockers in NSTEMI is based on a meta-analysis of 27 studies and treatment with beta-blockers was associated with a 13% relative risk reduction of death after the first week following a myocardial infarction [107]. Another meta-analysis of 73,396 patients with ACS showed an 8% relative risk reduction for in-hospital mortality associated with betablockers, without any increased risk of cardiogenic shock [108]. Patient factors that are associated with risk for cardiogenic shock with early beta-blocker use are age >70 years, heart rate >110 beats/min, and systolic blood pressure <120 mmHg [109].

ESC guidelines [71] recommend the use of beta-blockers in the acute phase of NSTE-ACS without any contraindication, followed by long-term treatment regardless of age [110].

Invasive strategy with revascularization

To perform an angiography or not. What is the current evidence?

The elderly are a high risk population for adverse events after NSTE-ACS but, simultaneously, they have possibly the most benefit [111–114]. The elderly have been less likely to undergo a coronary angiography after NSTE-ACS [115]. However, there has been a temporal increase in the use of an invasive strategy among patients over 80 years of age [116,117].

The elderly have a more complex CAD with more extensive CAD with multivessel disease, calcification, and vessel tortuosity [118]. Thus, in Sweden, the approach to an invasive strategy among the very elderly (≥80 years) differs markedly between centres in the country, with 20%–70% of patients treated with an invasive strategy according to unpublished data from RIKS HIA for the period 2007–2018.

Current guidelines from the ESC for the management of ACS without ST-segment elevation recommend *that 'Elderly patients should be*

considered for an invasive strategy and, if appropriate, revascularized after careful evaluation of potential risks and benefits, estimated life expectancy, comorbidities, quality of life, frailty and patients values and preferences' [71]. The guidelines of the American Heart Association/American College of Cardiology for the management of patients without ST elevation (NSTE-ACS) recommend invasive treatment and revascularization if appropriate in patients who are older than 75 years of age [119].

However, there is no specific recommendation available regarding how to decide which treatment strategy must be selected and which patient factors or type of comorbidity must be considered. Frail patients are less likely to be treated with coronary angiography than non-frail patients [120].

Data from observational studies

There are numerous previously published observational studies and registry data. Overall, these studies suggest that invasive strategies are superior compared with conservative strategies regarding mortality at 12-month follow-up [79,115,116,121] and myocardial infarction at follow-up [79,116].

- Bauer et al. [79] analysed elderly patients aged ≥ 75 years with NSTEMI in the German Acute Coronary Syndrome registry from 2000 to 2002. A total of 1005 (51.9%) patients underwent coronary angiography and 931 (48.1%) underwent a conservative strategy. With propensity score analysis, the invasive strategy was superior for in-hospital death (OR 0.55, 95% CI 0.35-0.86), death and MI (OR 0.51, 95% CI 0.35-0.75), and death at 12 months (OR 0.56, 95% CI 0.38-0.81).

- Devlin et al. [122] analysed the GRACE registry from 1999 to 2006. A total of 620 patients were revascularized with PCI or CABG; 2,390 patients were treated with conservative treatment; revascularization was associated with reduced six-month mortality (OR 0.68, 95% CI 0.49–0.95) in very elderly patients (>80 years) with NSTE-ACS.

- Gierlotka et al. [116] analysed the Polish Registry of Acute Coronary Syndromes (PL-ACS) of 13,707 patients aged ≥80 years from 2003 to 2009. Treatment with an invasive strategy had lower rates of myocardial reinfarction, mortality at 30 days, 6 months, 12 months, and 24 months at the cost of a higher rate of major bleeding.

- Buber et al. [115] performed a study on 363 patients who were aged ≥80 years between 2004 to 2008 with NSTEMI. Early angiography was associated with a lower risk of death at 12 months, HR = 0.40 (p=0.04), and 30-day HR 0.38 (p = 0.02) compared with no angiography.

- Kolte et al. [123] studied patients aged ≥80 years in the Nationwide Inpatient Sample database from 2003 to 2010. A total of 968,542 patients were included; 83% were treated with an initially conservative approach and 17% had an early invasive strategy. An early invasive strategy was associated with a lower in-hospital mortality OR 0.76 (95% CI 0.74–0.78).

- Reinius et al. [121] studied 13,854 patients >80 years of age with NSTEMI from 2011 to 2014 from The Swedish Websystem for Enhancement and Development of Evidence-based Care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART) registry. Treatment with PCI was associated with a lower 12-month and 30-day mortality compared with conservative treatment (HR 0.49 (0.42–0.57) and adjusted HR 0.40 (0.25–0.63).

Data from randomized clinical trials and sub-studies from RCTs

Elderly patients are underrepresented in published RCTs of ACS. A review of 593 RCTs found that patients >75 years of age formed only 9% of the study cohort, and between the years 1991 and 2000, 40% of the trials excluded patients based on age. Therefore, it is problematic

to generalize data from RCTs to real-world practice [89]. Further, the patient's characteristics differ as well. Compared to real-life patients, those who participate in RCTs are healthier [68]. Thus, the evidence for optimal treatment is limited due to the underrepresentation of the elderly in ACS trials.

Further, subgroup analyses of RCTs that were not designed for elderly patients have revealed the following aspects:

- A subgroup analysis from the TACTICS-TIMI 18 trial [111] found that 278 patients who were >75 years with NSTE-ACS benefitted from an early invasive treatment strategy. This reduced the composite endpoint of death and MI at six months. However, there was a significantly higher rate of major bleeding with an invasive strategy.

- A subgroup analysis of five-year pooled data from the Fragmin and fast revascularization during instability in coronary artery disease (FRISC) trial, invasive versus conservative treatment in unstable coronary syndromes (ICTUS), and randomized trial of a conservative treatment strategy versus an interventional treatment strategy in patients with unstable angina (RITA-3) (FIR) found that with regard to a five-year composite endpoint of cardiovascular death or MI, the routine invasive strategy was associated with lower hazards in patient aged ≥75 (n = 839) as compared with a selective invasive strategy (HR 0.71, 95% CI 0.550.91) [114].

There are two RCTs that were specifically designed for the elderly.

- The **Italian Elderly ACS Study** [124] randomized 313 patients aged ≥75 years with NSTE-ACS within 48 hours from symptom onset to an early invasive strategy or an initially conservative strategy. The primary combined endpoint of death, MI, stroke, repeat cardiovascular hospitalization, or severe bleeding did not differ significantly between the two groups.
  However, a subgroup analysis among patients with high troponin values revealed a reduction in events among

patients randomized to an invasive strategy (22% vs 40%, p = 0.0004) without any difference in major bleeding between the two groups. Galasso et al. [125] performed a sub-analysis of the study and compared invasive treatment to conservative treatment during the index hospitalization and found that the primary endpoint composite of death, MI, disabling stroke, and repeat hospital stay for cardiovascular causes or bleeding within one year had an HR of 0.56 (95% CI 0.37–0.83). The invasive treatment group had lower rates of MI (HR 0.43 (95% CI 0.20–0.92) and a lower rate of the combined endpoint of death and MI with an HR of 0.48 (95% CI 0.29–0.81).

- **The After Eighty Study** [126] was a randomized multicentre controlled study including 457 NSTE-ACS patients aged ≥80 years. Patients were randomized to an invasive strategy that involved coronary angiography with revascularization and optimal medical treatment or to a conservative strategy with only optimal medical treatment. The primary combined endpoint included MI, need for urgent revascularization, stroke and death. The primary endpoint was significantly reduced (41% vs 61%, p = 0.0001) with an invasive treatment strategy at 1.5 years of follow-up. There was no difference in bleeding complications and no difference in health-related quality of life, measured by the SF-36 between the two groups [127].

The evidence from these two trials supports an invasive strategy in elderly patients with NSTE-ACS. However, the generalization of these cohorts is difficult since the patients involved were relatively healthy.

Data from meta-analysis

The following meta-analyses were conducted:

- Gnanenthira et al. [128] included four RCT and three observational studies of patients aged ≥75 years with NSTE-ACS. The analysis of both the RCTs and the observational studies showed that routine invasive treatment reduced mortality OR 0.67 (95% CI 0.61–0.74) and MI OR 0.56 (95% CI 0.45–0.70). A separate analysis of the four RCTs revealed a reduction of MI, OR 0.51 (95% CI 0.40–0.66) and revascularization, OR 0.27 (95% CI 0.13–0.56), but mortality was not significantly reduced ,OR 0.84 (95% CI 0.66–1.06). The risk for major bleeding was increased with an invasive strategy in the RCT with OR 2.19 (95% CI 1.12–4.28).

- Saraswat et al. [129] conducted a meta-analysis and included three RCTs and six observational studies with patients aged ≥75 years. OR for mortality at one month was 0.50 (95% 0.33-0.75) and 12 months was 0.45 (95% CI 0.34-0.59), with a higher frequency of major bleedings in the invasive cohort, OR 1.63 (95% CI 1.05–2.54). The mortality benefit was driven from data in the observational studies and not from the RCTs, thereby suggesting a selection bias in studies with an observational design.

Garg et al. [130] conducted a meta-analysis of six RCTs and compared a routine invasive strategy (RIS) with a selective invasive strategy (SIS). In the routine group, 63% were revascularized whereas 30% were revascularized in the selective group. Among patients in RIS, there was a significant decrease in the risk of a) composite endpoint of death or MI (OR 0.65, 95%CI 0.51–0.83), b) MI (OR 0.51, 95%CI 0.40–0.66), and c) need for revascularization (OR 0.31, 95% CI 0.11–0.91) compared with patients in SIS. There was no significant difference in cause of death, cardiovascular death, or major bleeding.

Jobs et al. [131] conducted a meta-analysis, comparing an early invasive treatment group with a delayed invasive group, including eight

RCT on the optimal timing of an invasive strategy. They found that an early invasive treatment might reduce the risk of death among patients who were aged ≥75 years (HR 0.65; 95% CI 0.46–0.93, p for interaction 0.006). Another meta-analysis [132] revealed that a routine early invasive strategy reduced the risk of rehospitalization and the combined endpoint of recurrent MI and death more in older patients (>65 years) than in the younger ones.

In order to summarize current evidence, it can be said that an invasive strategy reduces the risk for MI and urgent revascularization during follow-up but a significant mortality benefit can be observed in observational studies but not in RCTs, thereby suggesting that elderly patients must be selected carefully for an invasive treatment strategy, weighing in frailty and potential benefit.

1.3.3 ISSUES IN THE TREATMENT OF NSTE-ACS IN THE ELDERLY

In everyday practice, clinicians must consider the entire clinical picture and weigh the risks-benefit ratio before beginning a treatment. A large number of issues must be considered in the elderly—for example, frailty, chronic renal failure, and bleeding risk.

Frailty

According to the WHO, frailty is *'a clinically recognizable state in which the ability of older people to cope with every day or acute stressors is compromised by an increased vulnerability brought by age-associated declines in physiological reserve and function across multiple organ systems, such that the ability to cope with every day or acute stressors is compromised'* [133]. Moreover, it reflects better the biological age than chronological age. The prevalence of frailty increases with age and is approximately 16% among persons aged 80–84 years and 26% among patients aged >85 years [134]. Frailty can be recognized by a number of clinical instruments and scales. One such scale was developed by Rockwood et al. [135], which was a seven-point clinical frailty scale (CFS). The scale was subsequently revised and expanded to nine levels. Of all the available models to

measure frailty, ESC recommends the CFS [136]. Frailty is independently associated with both 30-day and one-year mortality [120,137]. An observational study suggested that invasive treatment is beneficial in the non-frail very elderly patients with NSTE-ACS; however, in frail patients, there may be no benefit of such a treatment [138]. Possible confounders in the studies may be that frail patients have a more complex CAD that may not be appropriate for PCI [139].

Further, a meta-analysis [140] of the prognostic value of frailty in ACS found that frailty was associated with a 2.6-fold higher risk of death, a 1.5-fold increased risk of any-type cardiovascular disease, a 1.5-fold increased risk of a major bleeding, and a 1.5-fold increased risk of readmission among elderly patients with ACS. Therefore, it is reasonable to reduce the bleeding risk in frail patients, such as by adding a proton pump inhibitor, avoiding nonsteroidal anti-inflammatory drugs (NSAID) and glycoprotein (GP) IIb/IIIa inhibitors, and using a radial access during a coronary angiography [141].

Chronic renal failure

With age, there is an increase in the prevalence of chronic renal failure (CRF) because of a progressive decline in the glomerular function as well as an increase in the prevalence of comorbidities that are associated with renal damage, such as hypertension and diabetes. Patients with chronic renal failure have an increased risk of morbidity and mortality when treated with PCI [142]. The PCI procedure is dependent on the use of contrast and patients with CRF have a higher bleeding risk. Therefore, clinicians tend to provide conservative treatment to patients with renal failure. In the SWEDEHEART registry, from 2003 to 2006, there was a trend of not treating patients with NSTEMI and declining renal function with coronary angiography [143]. However, in a post-hoc analysis of the Italian Elderly Study, PCI was associated with a lower mortality risk at 12 months compared with medical treatment in elderly patients with renal dysfunction [144]. Additionally, another post-hoc analysis of the Italian Elderly ACS study revealed that patients who underwent coronary angiography did not have a higher rate of acute kidney injury (AKI) compared to those who did not. Those that developed AKI had higher adverse clinical events and AKI was an independent predictor of one-year mortality [145]. Therefore, it is important to take a patient's renal function into consideration when deciding the treatment strategy and take

precautions for the elderly who are a high-risk group for contrast-induced nephropathy [146]. Dose adjustment of antithrombotic medication in accordance with renal function is important in the elderly, as is recommended by the ESC NSTE-ACS guidelines [71].

Bleeding risk

The elderly have an increased risk for bleeding events and major bleeding events are associated with increased mortality [122]. In a study of patients >75 years of age, bleeding post-PCI was an important prognostic factor; there was an increased risk of bleeding in women and in patients with chronic renal failure [147].

There are scores available to estimate the risk for bleeding. The rapid risk stratification of patients with unstable angina can suppress adverse outcomes with early implementation of the ACC/AHA guidelines; the can rapid risk stratification of unstable angina patients suppress adverse outcomes with early implementation of the ACC/AHA guidelines (CRUSADE) bleeding risk score identified eight predictors of in-hospital major bleeding [148]. The CRUSADE bleeding risk score considers patient characteristics that are associated with a high risk for bleeding, such as female gender, history of diabetes, peripheral vascular disease, and stroke and clinical variables at admission and laboratory values. The risk score estimates the risk for an in-hospital major bleeding event. However, the CRUSADE score was not predictive of bleeding, either in patients aged ≥75 years [149] or in patients aged ≥ 80 years with NSTE-ACS [88].

When coronary angiography is performed, the preferred access site should be the radial artery, since it reduces the risk of bleeding complications [150]. A recent meta-analysis showed that elderly patients aged ≥70 years with ACS had a reduced risk for stroke, vascular complications, and death when a transradial approach was used [151].

2 AIM

The **main aim** of the thesis was to determine the association between comorbidity and survival after cardiac arrest and to compare two treatment strategies in patients aged ≥80 with NSTE-ACS.

The following are the **specific aims** of this thesis:

I. To describe the characteristics of and the outcome among elderly who have suffered from IHCA, where resuscitation was attempted and to, in this subset, analyse the age-related differences in outcome.

II. To describe the comorbidity among patients who suffer from OHCA when resuscitation was attempted, as well as the association between comorbidity and outcome.

III. To determine the comorbidity among patients who received CPR before arrival of EMS compared to those who did not after OHCA, and to determine if there is an association between CPR before arrival of EMS and 30-day survival when adjusting for comorbidity.

IV. To compare an invasive treatment strategy to a conservative treatment strategy in the very elderly with NSTE-ACS with regard to risk of future cardiovascular events.

3 PATIENTS AND METHODS

Table 2. Overview of Studies I–IV.

	Study I	Study II	Study III	Study IV
Design	Observational cohort study	Observational cohort study	Observational cohort study	Randomized controlled study
Data source	SRCR	SRCR	SRCR	Study-CRF
Inclusion criteria	Aged ≥70 years IHCA	Aged ≥18 years with bystander witnessed OHCA	Aged ≥18 years with bystander witnessed OHCA	Aged ≥80 years with NSTE-ACS
Years	2007–2015	2011–2015	2011–2015	2009–2017
Number	N = 11,396	N = 12,012	N = 11,955	N = 186
Statistical methods	Multiple logistic regression Multiple imputation	Multiple logistic regression Multiple imputation	Multiple logistic regression Multiple imputation	Kaplan-Meier Cox proportional hazard regression
Outcome	30-day survival CPC score	30-day survival Any ROSC ROSC at hospital admission	30-day survival Any ROSC ROSC at hospital admission	MACCE at 12 months
Ethical approval	Dnr 246-15	Dnr 246-15	Dnr 246-15	Dnr 157-09

3.1 DATA SOURCE

3.1.1 THE SWEDISH REGISTRY FOR CARDIOPULMONARY RESUSCITATION

The Swedish Registry for Cardiopulmonary Resuscitation (SRCR) is one of over 100 national quality registers in Sweden [152] and represents a prospective quality control of the handling of patients who suffer from IHCA and OHCA, where resuscitation is attempted in the entire country. The objectives of SRCR is to expand the knowledge on CA cases and to measure how the chain of survival is executed. This provides the opportunity for quality improvement and for providing feedback to the EMS and to all those who are involved in the treatment of CA at the time of the event and during the follow-up of survivors.

The SRCR was initiated in 1990 and initially covered only patients suffering from OHCA. Collection of data from patients suffering from IHCA was initiated in 2005. From the beginning in 1990, all cases with OHCA were reported to the registry, but after a few years, only patients in whom resuscitation was attempted were reported.

The criteria for cardiac arrest being reported to the registry are defined as unconsciousness without any respiration and receiving CPR and/or defibrillation by the rescue team or a bystander. The reporting has increased with time and since 2008, all EMS systems have entered all OHCA data into a web-based form. In addition, there is complete coverage of all EMS organizations since 2010 and it is assumed that >90% of all individuals who have suffered an OHCA and where resuscitation was attempted are currently reported to the registry.

The validity of reported data of OHCA was checked for data from 2008 to 2010 and it was revealed that 25% of cases were not reported prospectively. Retrospectively reported cases were older, received bystander CPR less often but had a higher survival rate than those cases which were prospectively reported [153].

When a patient collapses in a hospital and CPR is initiated, the case is usually reported directly into the web-based form by the nurse or physician who attended the event. It is required to register time intervals

and variables regarding the IHCA into the web-based form. Similar to the situation after OHCA, data from the IHCA event have been reported from an increasing number of hospitals over the years.

Currently, all 74 hospitals in Sweden report to the SRCR, and it is estimated that approximately 80% of all IHCA patients are captured. Validation has taken place in 34 hospitals and the information on place and survival was accurate in 99% of the cases. Further, information on witness status was accurate in 96% of the cases and on first-recorded rhythm in 94% of the cases, respectively.

Annually, approximately 6000 cases with OHCA and 2500 cases with IHCA are reported in the registry. A majority of the cases are reported to the registry prospectively using the Utstein-based template [17]. The SRCR is funded by the Swedish Association of Local Authorities and Regions and has also received support by the Swedish Resuscitation Council, the Swedish Heart Foundation, and the Leardal Foundation.

3.1.2 THE NATIONAL PATIENT REGISTRY

The National Patient Registry (NPR) is run by the Swedish National Board of Health and Welfare. The NPR was established in 1964 and has expanded with time; since 1987, the coverage has been nationwide. The NPR includes data on diagnoses and surgical procedure codes from hospitals and specialist clinics. A validation of the NPR reveals that 85%–95% of all diagnoses are valid. Since 2001, the registry has also included out-patient visits from both private and public caregivers, but primary care or out-patient clinics without any physician involvement are not included in the NPR. The fact that primary care diagnoses are not included is a limitation. Diagnoses that can possibly be underestimated are diabetes mellitus and hypertension, which often are only treated in primary care. All hospital admissions (both in- and out-patients) in Sweden are reported to the registry with International Classification of Disease (ICD)-10 codes [154].

3.2 THE CHARLSON COMORBIDITY INDEX

In 1984, Charlson et al. defined the clinical conditions in the score and assessed the association of these comorbidities with one- year mortality risk. The Charlson comorbidity index (CCI) is the most extensively studied comorbidity index, which was published in 1987 [155]. The CCI is a method of categorizing comorbidities of patients based on ICD-10 diagnosis codes. Each condition category has a weighted score from one to six. The higher the number, the higher the risk for death or resource use. The scores for each category are added together to yield a total score, which is the CCI for that patient. A CCI of 0 implies that no comorbidity condition could be found. The index was tested to predict the risk of death from comorbid diseases—an increase in score implies an increase in the risk of death [156].

With the development of more advanced treatments in chronic conditions, the CCI has evolved and the condition categories have been modified. The original weight of each condition category has also been modified [157]. There are different versions of CCI that are used; the recent version of the CCI from the year 2011 included 12 condition categories compared to 17 categories from the year 2005 [156,158].

3.3 STUDY I

Study population

All patients with IHCA aged ≥70 years at the time of event during 1 January 2007 to 31 December 2015—which were reported to the SRCR were included in the study.

Hypothesis

1) The survival of elderly after IHCA decreases with increasing age.
2) The neurological outcome does not differ between the survivors after IHCA.

Outcome measures

The primary outcome was 30-day survival and Cerebral Performance Categories (CPC) score [159] among patients who were discharged alive from hospital. The secondary outcome was discharged alive.

Statistics

The patients were divided into three age groups for descriptive purposes: 70–79 years, 80–89 years, and ≥90 years. The Mann-Whitney U test was used to test for association between actual age and patient characteristics, neurological outcome, and 30-day survival. Due to missing data for certain variables, we used multiple imputation in the multivariable analysis. The missing data was assumed to be missing at random (MAR). Further, in order to identify independent predictors of 30-day survival, we used multiple logistic regression.

3.4 STUDY II

Study population

All patients aged ≥18 years with bystander-witnessed OHCA reported to the SRCR between 2011 and 2015 were included. Only bystander-witnessed cases were included. Thus, unwitnessed cases and cases witnessed by the EMS crew were excluded.

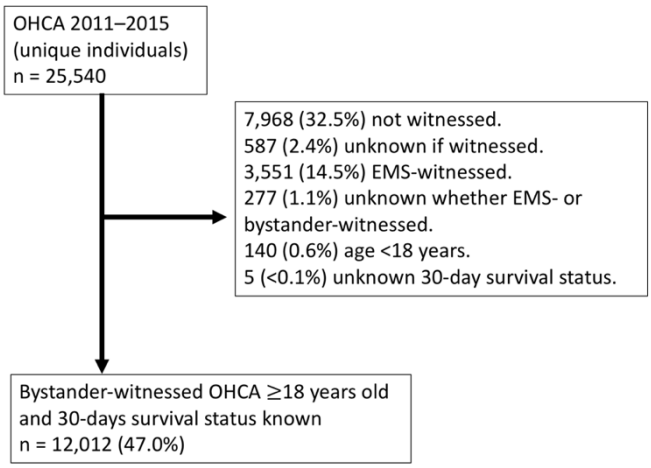

Figure 2. Flow chart of patient selection in Study II. Reprinted with permission from Elsevier.

Hypothesis

The primary hypothesis was that with increasing comorbidity, there would be a decreased likelihood of 30-day survival.

Outcome measures

The primary outcome measure was 30-day survival. Secondary outcome measures were any return of spontaneous circulation (ROSC) and ROSC at hospital admission.

Statistics

We used the Mann-Whitney U test for ordered/continuous variables and Fisher's exact test to test for difference in baseline characteristics and between the CCI groups. We used logistic regression for calculating odds ratios and adjusted for year of OHCA, age, sex, initial rhythm, location of OHCA, bystander CPR, mechanical chest compression, aetiology, treatment with adrenalin, intubation, use of anti-arrhythmics, time from collapse to CPR, and EMS response time.

Further, we utilised multiple imputation for the multivariable analysis due to missing data on the covariates. The assumption of MAR was indicated to be valid by an examination of the associations between the missingness of each variable with another and by comparing complete and incomplete cases.

In order to estimate how the predicting value of adding CCI to the model would change, we used area under the ROC curve (AUC) and the net reclassification improvement (NRI) index.

3.5 STUDY III

Study population

All patients aged ≥18 years with bystander-witnessed OHCA and reported to the SRCR between 2011 and 2015 were included. Unwitnessed cases and cases witnessed by the EMS crew were excluded.

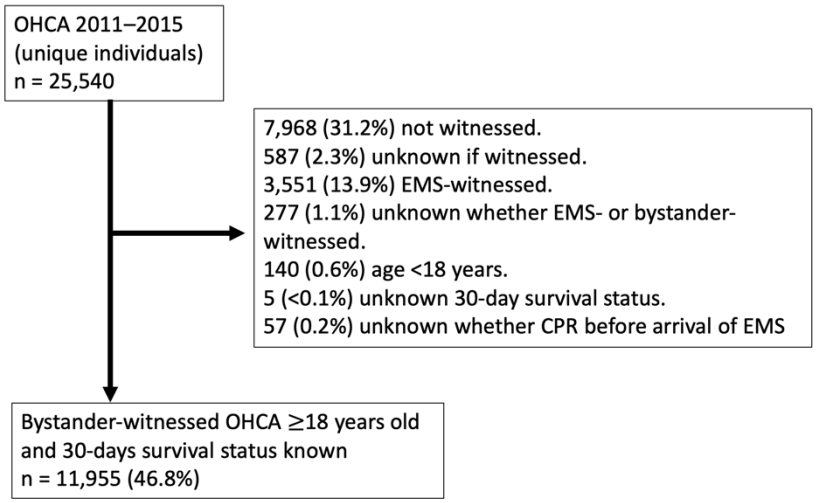

Figure 3. Flow chart of patient selection in Study III. Reprinted with permission from Heart.

Hypothesis

The primary hypothesis of this study was that patients with OHCA who receive CPR before the arrival of EMS had a lower comorbidity than those who do not receive bystander CPR.

When adjusting for the eventual difference in comorbidity between these two groups, the impact of comorbidity on the association between early (mainly bystander) CPR and 30-day survival was not markedly affected.

The positive survival effect of bystander CPR is associated with the patient's comorbidity—that is, the lower degree of comorbidity the higher the likelihood of survival.

Outcome measures

The primary outcome measure was 30-day survival. Secondary outcome measures were any ROSC and ROSC at hospital admission.

Statistics

We utilised standardized difference to assess the difference in baseline characteristics between those who received bystander CPR and those who did not. Fisher's exact test was used for unadjusted comparison of outcome. Fisher's exact test and the Mann Whitney U-test were used for a comparison of the conditions in CCI and CCI itself between those who received bystander CPR and those who did not.

Due to missing data in the adjustment factors, we used multiple imputation in the multivariable analysis. Missing data were assumed to be MAR, as was already observed in Study II.

We used logistic regression for calculating odds ratios and adjusted for age, sex, location, aetiology, and time from call to EMS to EMS arrival. We did not adjust for initial rhythm in the main analysis because it is believed to be a part of the effect of bystander CPR.

3.6 STUDY IV

Study population

The study was an open-label, randomized, controlled multicentre trial including patients aged ≥80 years with NSTE-ACS. Patients were recruited from three centres in Sweden. The inclusion and exclusion criteria are listed in Table 3.

Inclusion criteria	1) Aged ≥ 80 years 2) NSTE-ACS with ischemic symptoms (mainly chest pain) lasting over 10 minutes within the previous 72 hours, 3) Ischemic ST-segment depression ≥ 1 mm **and/or** elevated troponin I, troponin T, or CK-MB.
Exclusion criteria	1) PCI within 30 days prior to randomization 2) Suspected ongoing active internal bleeding 3) ST-segment elevation of ≥ 1 mm in two contiguous leads on ECG (electrocardiogram) 4) Enrolled in another study that has not completed the follow-up phase 5) Known allergy to aspirin or $P2Y_{12}$ antagonists 5) Severe dementia 6) Expected limited one-year survival due to another disease (s) 7) Unwillingness to participate in the trial or expected problems with compliance.

Table 3. Inclusion and exclusion criteria in the 80+ study.

After the patients had signed informed consent, they were randomized 1:1 to one of the two treatment strategies. The treatment strategy was either optimal medical treatment with coronary angiography and PCI if appropriate or an optimal medical treatment without coronary angiography.

Patients' frailty was assessed at the bedside by the study nurse, physician, or by the records in the patients' files, in accordance with the Canadian Study of Health and Aging Clinical Frailty Scale [135]. For details see table 4.

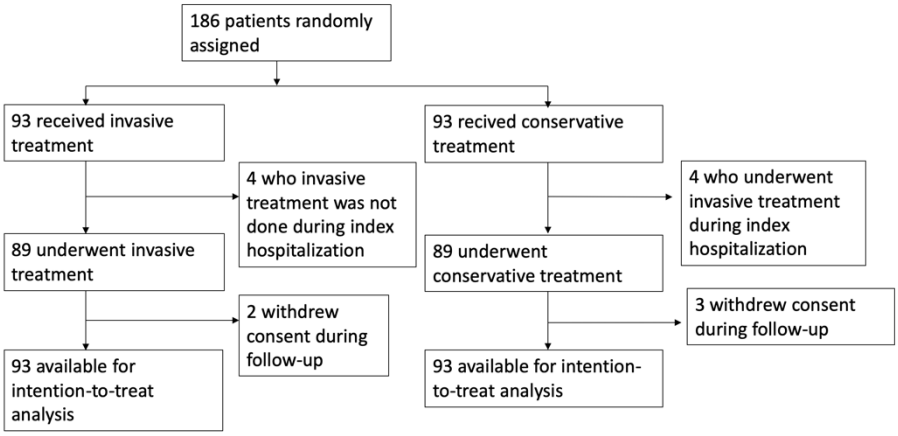

Figure 4. Trial profile of Study IV.

Table 4. The clinical frailty scale adopted from Rockwood et al. [135]

1 Very fit	Robust, active, energetic, well-motivated and fit; these people commonly exercise regularly and are in the most fit group for their age
2 Well	Without active disease, but less fit than people in category 1
3 Well, with treated comorbid disease	Disease symptoms are well controlled compared with those in category 4
4 Apparently vulnerable	Although not frankly dependent, these people commonly complain of being 'slow' or have disease symptoms
5 Mildly frail	With limited dependence on others for instrumental activities of daily living
6 Moderately frail	Help is needed with both instrumental and non-instrumental activities of daily living
7 Severely frail	Completely dependent on others for the activities of daily living, or terminally ill

Hypothesis

The primary hypothesis was that the invasive strategy was superior to the conservative strategy in reducing the combined endpoint of MACCE within 12 months. The secondary hypothesis was that the invasive strategy resulted in more bleeding, a lower mortality, and a lower degree of angina pectoris.

Outcome measures

The primary outcome was the first occurring event of the combined endpoint of MACCE within 12 months. This was defined as the composite of death, myocardial infarction, urgent revascularization, stroke, and recurrent hospitalization for a cardiac reason. A cardiac reason for recurrent hospitalization was defined as the new onset of atrial fibrillation or heart failure.

The secondary outcomes included MACCE within one month, all-cause mortality, myocardial infarction, death and/or myocardial infarction within 12 months, and major and minor bleeding [160] within one month.

Statistics

We used intention-to-treat analysis in which each patient remained in the treatment group that he/she was randomized to—that is, either invasive strategy group or conservative strategy group—irrespective of whether or not they underwent angiography. We also performed a per-protocol analysis. We constructed Kaplan-Meier curves for survival free from MACCE during the 12-month follow-up and compared the two groups using a log-rank test. The outcome rates were calculated as 100 - Kaplan-Meier estimates and Cox proportional hazard regression was used to calculate hazard ratios (HR) with 95% confidence intervals.

4 RESULTS

4.1 STUDY I

During the study period, 11,396 patients aged ≥70 years were reported to SRCR.

With increasing age, there were more comorbidities such as a history of heart failure, stroke, and renal dysfunction. However, a history of diabetes, respiratory insufficiency, and malignancy decreased with increasing age.

With increasing age, there was a reduction in the frequency of IHCA cases in monitored wards and the first recorded rhythm that was shockable decreased with increasing age.

The delay to treatment did not differ with age but the delay from collapse to first ECG recording increased with increasing age. Further, with increasing age, the treatment was less aggressive.

The 30-day survival was 28% for patients aged 70–79 years, 19% for patients aged 80–89 years, and 14% for patients aged ≥90 years.

The proportion of patients with a favourable neurological outcome (CPC 1-2) of those discharged alive from hospital were 92%, 93%, and 87% for the three age groups 70–79, 80–89, and ≥90 years, respectively.

The strongest predictors of 30-day survival in multivariable analysis were shockable first-recorded rhythm with OR 4.17 (95% CI 3.69–4.71), witnessed IHCA OR 2.86 (95% CI 2.38–3.44), if the aetiology of IHCA was arrhythmia OR 2.48 (95% CI 2.16–2.84), and if the IHCA was ECG-monitored OR 2.25 (95% CI 2.01–2.53).

4.2 STUDY II

This study included a total of 12,012 patients. Of these, 1598 (13%) patients survived up to 30 days.

The comorbidities that were associated with 30-day survival were a history of renal disease (OR 0.53; 95% CI 0.40–0.72), metastatic carcinoma (OR 0.61; 95% CI 0.40–0.93), diabetes without complications (OR 0.63; 95% CI 0.52–0.75), diabetes with complications (OR 0.65; 95% CI 0.49–0.84), and congestive heart failure (OR 0.84; 95% CI 0.71–0.99).

The 30-day survival decreased with increasing CCI, and after adjusting for baseline characteristics the OR for each CCI interval decreased with increasing CCI as compared to the CCI 0–2 group.

The inverse association between increasing severity of comorbidity and adjusted OR for 30-day survival was observed in patients with VF/VT as initial rhythm as well.

The relationship between comorbidity and any ROSC after adjustment was only significant in patients with CCI >6 in relation to CCI 0–2.

There was no significant association between comorbidity and ROSC at hospital admission.

4.3 STUDY III

During the study period, 25,540 OHCA cases were registered in the SRCR. After exclusion of cases, as described in the methods section, 11,955 cases of bystander-witnessed OHCA were included in the study.

CPR was initiated before the arrival of EMS in 71% of the cases. Comorbidity measured with CCI was slightly lower in those who received CPR before the arrival of EMS. The total points of CCI in those who received early CPR reached a mean ± SD of 2.2 ± 2.3 compared to 2.5 ± 2.4 among those who did not.

The adjusted OR for 30-day survival when comparing patients who received bystander CPR with those who did not was 2.34 (95% CI 2.01–2.74). We adjusted for age, sex, location, aetiology, and time delay between the emergency call and arrival of EMS. Adding CCI to the adjusted OR did not change with an adjusted OR of 2.32 (95% CI 1.98–2.71). The degree of comorbidity did not interact with the association between early CPR and 30-day survival.

The same relationship was observed for patients with shockable or non-shockable first-monitored rhythm—that is, including CCI as a covariate to the model did not alter the relationship between bystander CPR and 30-day survival.

The adjusted OR for bystander CPR in relation to no bystander CPR in terms of either ROSC at any time or ROSC at hospital admission was almost identical when CCI was included in the statistical model. However, the degree of comorbidity interacted significantly with the association between bystander CPR and any ROSC as well as ROSC at hospital admission.

4.4 STUDY IV

In the study period from 2009 to 2017, 186 patients were included in the study. Further, 93 patients were randomized to the invasive strategy group and 93 to the conservative strategy group. There was an imbalance between the groups in terms of a few aspects in the baseline characteristics.

The invasive group had a higher percentage of patients with frailty (5–7 on the scale) compared with the conservative group—21% vs 13%, respectively.

In the invasive group, 89 patients underwent coronary angiography, of which 57 underwent PCI, and one underwent a coronary artery bypass grafting (CABG) operation. In the conservative group, four patients crossed over during the index admission and underwent coronary angiography, of which three underwent PCI and one underwent CABG.

Primary outcome

At the 12-month follow-up, major adverse cardiac and cerebrovascular events (MACCE) had occurred in 31 patients in the invasive group and in 34 patients in the conservative group (HR 0.90 (95% CI 0.55–1.46; p = 0.66)). The HR value for urgent revascularization was 0.29 (95% CI 0.10-0.85; p = 0.02), whereas it was 0.56 (95% CI 0.27-1.18; p = 0.13) for myocardial infarction, 0.70 (95% CI 0.31-1.58; p = 0.40) for all-cause mortality, 1.35 (95% CI 0.23-7.98; p = 0.74) for stroke, and 1.62 (95% CI 0.67-3.90; p = 0.28) for recurrent hospitalization for cardiac reasons.

Secondary outcome

There was no significant difference in any secondary outcome between the invasive and conservative groups. Further, there was no difference in the severity of angina pectoris between the two groups either at the one-month follow-up or at the 12-month follow-up.

5 DISCUSSION

What are the main findings of this thesis?

The following are the main findings of this thesis: 1) The majority of elderly survivors of IHCA appear to have a relatively good neurological outcome after the event. 2) With increasing comorbidity, the likelihood of 30-day survival after OHCA decreases. 3) Comorbidity did not alter the effect of bystander CPR on 30-day survival after OHCA. 4) There was no significant difference in MACCE at 12 months follow-up between the invasive treatment group and conservative treatment group among patients aged ≥80 years with NSTE-ACS.

Should we resuscitate the elderly with IHCA?

In Study I, we found that increasing age was associated with a decreased likelihood of survival after IHCA. Other studies [161] found that increasing age is associated with a decreased likelihood of survival. However, survival was highly dependent on the initial recorded rhythm and whether or not the patient was ECG-monitored at the time of the event. Thus, a subgroup of patients aged ≥90 years with VF/VT as initial rhythm had an over 40% survival rate at 30 days.

In our opinion, patients must not be excluded from resuscitation only because they are old. We make this statement particularly since a relatively good neurological outcome can be achieved in both older and younger patients despite the fact that increasing age has been associated with fewer witnessed cases, a lower degree of monitoring at the time of the event, and a less aggressive treatment.

Excluding patients only because of high chronological age does not appear justified. Other clinical measurements such as frailty may be more appropriate to take into account when considering an eventual DNAR order [162–164].

Is it justified to treat the elderly with IHCA less aggressively?

In Study I, we found that there was no difference in the delay to treatment in the elderly, with the exception of the delay time from collapse until initial rhythm recording. This may be explained by the fact that the elderly are often admitted to a general ward without ECG

monitoring. Therefore, it will take a longer time for the resuscitation team to bring an AED or defibrillator on the scene and it will also take a longer time until the first ECG is recorded. There are numerous factors that can potentially influence the clinical decision to limit the advanced life support treatment that is associated with the resuscitation procedure in both the peri- and post-arrest phases. The comorbidity increases with age and can thus influence the efforts of the resuscitation teams as well as the willingness to perform post-resuscitation interventions, such as PCI and TTM.

Thus, it is important to discuss DNAR orders before cardiac arrest occurs and inform the patient when the likelihood of survival is low and thereby respect the patient's autonomy. Prearrest tools do guide clinicians—for example, the prediction of outcome for in-hospital cardiac arrest (PIHCA) score has been created and can possibly be used as a guidance in the DNAR process [165].

Other studies have indicated that older age and being dependent on assistance for activities of daily living is associated with a shorter duration of CPR [166]. One study found that the duration of CPR after IHCA was concordant with the predicted outcome—that is, the resuscitation teams performed CPR for a longer time among patients with a high predicted survival rate and vice versa [167].

In general, all those who do not have DNAR orders must be treated with advanced life support, just as anyone else; thus, advanced age alone must not be used to deny patients treatment. However, there could be unmeasured factors or medical reasons that the rescue team may have considered that have lead to the decision not to treat the patients aggressively. Survival is highly associated with the initial rhythm; therefore, restriction could possibly be to only defibrillate VF/VT.

Is cerebral performance category (CPC) score an optimal measurement of neurological outcome?

The CPC score is a scale from 1 to 5 and is used to classify neurologic outcome after cardiac arrest. Categories 1 and 2 are defined as a good outcome and categories 3 and 4 are defined as poor outcome. Category 5 is death. The CPC categories correlate with survival after cardiac arrest and the score is usually estimated from medical records at

discharge from hospital [168]. The Utstein report from 2004 [4] recommends documenting the patient's neurological status at discharge from the hospital but acknowledges that it can be difficult to measure CPC at hospital discharge. There is no consensus regarding which source that must be used to estimate CPC. A study from the UK found that CPC was most often reported from case note review (72.6%) and that there were variations in the CPC score according to source but this was not clinically important [169].

A simple neurological score such as CPC must be recorded, if available. The problem with recording the CPC score at discharge from hospital is that neurological outcome can change after discharge and patients can improve or deteriorate during a longer follow up [170].

The limitation of using CPC score is that it can possibly overestimate the neurological outcome, since it is often measured retrospectively from case records. Therefore, the utilisation of other measurements in the elderly, such as physical function, quality of life, independent living, and not having to be admitted to a nursing home are important alternatives.

Other measurements for neurological function have been recommended and include the modified Ranking Scale (mRS) [171]. This scale is a seven-score scale from 0 (no symptoms) to 6 (dead). An mRS score of 0 to 3 is defined as a good neurological outcome corresponding to a CPC score of 1–2. A recent statement from the International Liaison Committee on Resuscitation suggests using mRS rather than CPC to measure functional recovery after cardiac arrest [172]. The mRS must be measured with direct contact with the patient or through a telephone interview with the patient and his/her relatives [173].

Why is the frequency of 'missing data' so high for a few variables in Study I?

There are numerous reasons for missing data in different variables. Data information is entered directly in the SRCR after cardiac arrest. Variables associated with peri-arrest factors and treatments given during resuscitation are reported by a nurse or a physician who attends the event. Possible mechanisms behind missing variables are, for example, uncertainties around the time of the event. The circumstances

around IHCA are often very stressful and data can be missed or unknown when reported to the web-based registry. Moreover, variables regarding aetiology are often missing since the aetiology behind the cardiac arrest is often unknown. Thus, it is not surprising that there is a high rate of missing data in some of the variables associated with resuscitation. However, there are also variables where we expected a much lower frequency of missing information. One such variable is the first recorded arrhythmia.

There are different reasons for why data may be missing in data collection in healthcare research. The mechanisms explaining the missing data are 1) missing completely at random (MCAR), 2) missing at random (MAR), and 3) missing not at random (MNAR) [174]. We handled the missing values in the data analysis with multiple imputation in Studies I, II, and III. The mechanism underlying the missing values was assumed to be missing at random (MAR). MAR is '*any systematic difference between the missing values and the observed values can be explained by differences in observed data*' [175]. To explain this further, the missing data is related to other variables, but the actual value of the missing variables is not completely random. In MCAR, there is no relationship between the missing variables and the observed variables. MNAR is similar to MAR, but the actual value of missing variable is not as random as that in MAR.

In Study I, we assumed that the missing data was MAR. In Studies II and III, we used the same database and the assumption of MAR was indicated by checking for association between the missingness of each variable with others. We also performed sensitivity analysis by comparing patients with complete and incomplete data and found a few major differences which suggest that the missing data was MAR.

What is comorbidity and why could patient's comorbidity be a confounder in cardiac arrest studies?

There is no clear consensus on how comorbidity must be defined. Feinstein was the first to use the term and described it as '*an associated illness arising from other disease'* [176]. There are several other variations regarding the interpretation of the term comorbidity. One of the definitions is '*presence of additional diseases in relation to an index disease in one individual*' [177]. Another definition is '*comorbidity may be defined as the total burden of illnesses unrelated to the principal*

diagnosis' [178]. The term *multimorbidity* has subsequently evolved and is defined as '*the co-occurrence of multiple chronic or acute diseases and medical conditions within one person'* [179].

Comorbidity in observational studies

In general, patient's comorbidity is an important factor in research and it can possibly affect the outcome in different research designs. Comorbidity could possibly conceal the true treatment effect. In observational studies, co-existing comorbid conditions can possibly affect the outcome with a competitive mortality risk. With RCTs, the comorbidity can be balanced between the study groups.

Research activities and evidence for different treatment strategies in cardiac arrest are often based on an observational study design. The randomization between intervention and no intervention associated with resuscitation may be regarded as unethical based on the informed consent dilemma. As an example, it may not be regarded as ethical to randomize patients who suffer from cardiac arrest to either receive bystander CPR or no bystander CPR.

Thus, evidence for resuscitation research often comes from registry research. Then, there is a risk that confounders may create difficulties in the interpretation of the data. A recent review by Fouche et al. [180] indicates that comorbidity is often neglected in cardiac arrest research. Therefore, comorbidity could possibly become a confounder, a predictor, or an effect-modifying factor in cardiac arrest research. Hence, the comorbidity can be an important factor and must be included in cardiac arrest research to diminish bias and further increase our understanding of cardiac arrest epidemiology and treatment.

What is the best measurement of comorbidity?

There are a number of available methods to measure comorbidity in administrative patient data, and comorbidity indices are used to estimate the overall comorbidity burden. There are several indexes available and one of these is the CCI [181].

The index that is the most appropriate for use in administrative databases and register studies is a matter of discussion. The most important issue is transparency and demonstration of the version that was used. We used the 2005 version of CCI in Studies II and III because

we wanted to include more numbers of categories and the C-statistics differed minimally between version 2005 and 2011 (AUC 0.883 in the updated 2011 CCI and 0.881 in the 2005 CCI) [158].

The CCI is used to estimate comorbidity severity in administrative databases. Using only ICD-10 diagnosis codes generates a number of possible dilemmas. As an example, is the severity of each disease not graded in each CCI category.

Other measurements of the comorbidity burden are, for example, the Elixhauser Comorbidity index (ECI) [182].The ECI is a weighted index of 29 comorbid conditions.

However, the comorbidity index that is optimal for use in cardiac arrest research is unknown. Several studies have used the CCI and there are a few available versions of the CCI. In order to address which index and version that is most suitable, we suggest research to be conducted to compare these versions by using C-statistics, which could be informative. Other important issues include how comorbidity information was collected and the duration of the evaluation prior to the event that was assessed. Finally, one may argue whether there are any comorbidities that could possibly affect the outcome that are not included in CCI—for example, hypertension and psychological disorders.

Why were renal dysfunction, diabetes with and without complications, heart failure, and cancer with metastases associated with lower survival in OHCA in Study II?

When comparing the results with other studies, only the study by Andrew et. al [32] is comparable to our methodology. They found that increasing CCI was associated with a reduced likelihood of survival at 12 months. They described the risk of death in a subgroup of patients with OHCA who were found in VF/VT and observed a significant association between a history of heart failure, pulmonary disease, diabetes, renal disease and metastatic cancer on the one hand and survival to hospital discharge on the other. An analysis of patients with initial VF/VT in our study showed similar results but without a significant association between the risk of death and a history of heart failure or pulmonary disease but a significant association with dementia. We had 30-day survival as the endpoint instead of survival to discharge from

hospital. However, previous experiences suggest that these two endpoints yield similar results [183].

A meta-analysis of IHCA studies found that histories of malignancy, CHF, chronic kidney disease, diabetes, and chronic pulmonary disease were associated with reduced odds of survival [31].

Previous studies have described a history of diabetes as being associated with a lower likelihood of survival after OHCA [184,185] and IHCA [186]. One possible pathophysiologic explanation for this is that patients with diabetes have an overall more severe comorbidity, including a more frequent history of myocardial infarction, angina pectoris, hypertension, and heart failure [184]. Therefore, these disease conditions can possibly coexist in the same patients and reflect a more extensive atherosclerotic vascular disease with a smaller reserve for cerebral hypoperfusion in a low-flow or no-flow state during cardiac arrest.

Another possible mechanism is selection bias. This implies that people with a more severe comorbidity did not receive the same level of post-resuscitation care and the comorbidity could, thus, influence the extent of treatment in the post-resuscitations phase. Winther-Jensen et al. [40] suggested that patients with a lower degree of comorbidity were more likely to undergo coronary angiography during the first 24 hours after ROSC. A study from South Korea [187] on patients with OHCA showed that patients with a history of cancer affected the intensity of treatment in the post-resuscitation phase. They were less likely to undergo PCI and targeted temperature management (TTM). Therefore, the study suggested that patients with cancer had a lower probability of receiving optimal post-resuscitation care.

Does comorbidity increase the risk of death after OHCA and if so why?

When an association is observed from clinical research, the next step is to assess it is significance. A statistically significant association does not prove a causality in observational studies. In Study II, we found that patients with increasing comorbidity were older, had a lower frequency of VF/VT, received less CPR before the arrival of EMS, had a greater frequency of cardiac arrest at home and had a longer time from collapse to initiation of CPR. All these factors can be associated with a negative

impact on survival. When adjusted for confounders, an increased comorbidity was associated with reduced odds of survival. Using ROSC as an outcome endpoint, the association with comorbidity was not significant when using ROSC at hospital admission. When using any ROSC as an endpoint, there was only a significant association with comorbidity among patients with the most severe comorbidity status (CCI >6). This suggests that patients with higher comorbidity do not survive in the post-resuscitation phase. The following are the likely mechanisms for increased risk of death with increased comorbidity: 1) Selection bias in the hospital treatment where healthier patients are treated more aggressively. 2) The aetiology that led to cardiac arrest is different among patients with a more severe comorbidity. Even though such patients sustain ROSC they do not survive. 3) The comorbidity may influence the potential benefit of post-resuscitation care, such as PCI and TTM.

Who is a bystander?

According to the Utstein criteria, a bystander response is defined as CPR performed by a person who is not part of the team that has been alerted from the dispatch centre. Those who witness the patient's collapse and initiate CPR on scene are the 'true bystanders'. The first tier can be a police officer or a firefighter and they are not 'true bystanders'. There is some confusion regarding how to define bystander CPR that has recently been highlighted [188] due to the introduction of different actors in the first link of the chain of survival after OHCA. In order to avoid such confusion, it may be practical to use the broader term 'CPR initiated before the arrival of EMS'. However, it is important to emphasize that such a definition includes the 'true bystanders' as well as firemen, police officers, first responders, and 'text message life savers'.

In Study III, we did not have data on which type of bystander that performed CPR in SRCR until 2015. During 2015, only a minority of actors who performed CPR before the arrival of EMS were police officers or firefighters. Thus, the vast majority appear to have been bystanders according to the Utstein definition, thereby making the bystanders in our study relative comparable with bystanders in numerous other studies.

What is the rationale for the hypothesis that bystander CPR is possibly performed in more healthy patients?

The idea underlying Study III was that in Study II we observed that comorbidity was associated with 30-day survival. Further, we described that the proportion of patients who received bystander CPR decreased with increasing comorbidity. Thus, the lower survival rate among patients who did not receive bystander CPR may theoretically have been explained by an increased comorbidity rather than a lack of bystander CPR. Therefore, in theory we may have overestimated the true effect of bystander CPR.

Further, in 1994, it was already hypothesized that the observation of more patients being found in asystole among those who did not receive bystander CPR may have been explained by a greater number of cases with a terminal disease [189]. We still believe that it is reasonable to assume that a bystander is more likely to initiate CPR immediately when the individual who collapses is apparently healthy as compared with an individual who seems to suffer from a severe comorbidity. However, if the victim is a stranger, there is most likely a lack of knowledge regarding these issues.

Have we now eliminated all possible hidden confounders in our understanding about the association between bystander CPR and 30-day survival after OHCA?

We can only adjust for what we can measure. We have adjusted for those factors that may potentially affect the outcome. Eliminating all possible confounders is impossible. For example, we did not adjust for any in-hospital treatment factors such a TTM, PCI, or treatment with an Internal Cardioverter Defibrillator (ICD). Further, income and psychosocial factors, including ethnicity, may influence the association between bystander CPR and outcome [190–192] and these aspects were not considered in our analyses.

Finally, frailty may very well be a hidden confounder which may influence the observed association between bystander CPR and survival after OHCA.

How can we explain the small difference in comorbidity between those who received CPR before the arrival of EMS or those who did not in Study III?

It is known that patients that receive CPR before the arrival of EMS are younger and more often collapse outside home than those who do not [45]. In Study III, we hypothesized that patients who received bystander CPR before the arrival of EMS would be healthier and have a more positive effect of bystander CPR. They were somewhat healthier than those who did not receive bystander CPR but to a much lesser extent than we expected. An unadjusted analysis revealed a significant association of CCI points with bystander CPR—that is, patients with low CCI points were more likely to receive bystander CPR. A logistic regression analysis using CPR as an outcome showed OR 0.93 (95% CI 0.89–0.97; p = 0.002). This analysis indicates that comorbidity is associated with CPR.

The possible reasons underlying a small difference in comorbidity between those who received bystander CPR and those who did not is probably multifactorial:1) The severity of the comorbidity was unknown to the bystander and even among those with > 6 CCI where 68% received bystander CPR. 2) We only included bystander witnessed cases and those with the most severe comorbidity had cardiac arrest at home witnessed by family members who did not always know how to do CPR. 3) The person who witnessed the arrest may not have known how to do CPR, was reluctant to initiate CPR, or did not recognize the cardiac arrest. 4) Unclear recognition of cardiac arrest by the dispatch centre.

Why was there no significant difference in MACCE between the invasive strategy and the conservative strategy groups in Study IV?

In Study IV, we estimated the sample size based on the hypothesis that the primary endpoint would occur in 40% in the conservative strategy cases and in 20% of the invasive strategy cases, with a 50% reduction in invasive treatment, which might have been too optimistic. However, the event rate was 37.4% in the conservative strategy group and 34.4% in the invasive strategy group, with a 10% relative risk reduction (RRR). Therefore, the study was underpowered to reveal any statistically significant benefit when the difference in the event rate in the primary

endpoint was so low. In order to demonstrate a statistically significant difference with a 10% RRR, approximately 4000 patients in each group were required.

One factor that may have contributed to the lack of a confirmed effect of an invasive strategy was that patients included in the study were at a low risk for events and had a low ischemic burden. One of the exclusion criteria was 'hemodynamically unstable', since it would be unethical to withhold treatment with coronary angiography for these patients. Physician selection bias is another possible contributing factor since, occasionally, the treating physician had already decided the treatment modality (invasive strategy) among high-risk patients with high troponin levels and/or reduced left ventricle function revealed in echocardiography.

There is an increased awareness among physicians that the elderly must be treated with medication for secondary prevention, like statins, and that they must receive rehabilitation after NSTE-ACS; this may have even further reduced the event rate. Further, the follow-up time was shorter (12 months) compared to the After Eighty study (18 months) [126].

Another factor that may have created difficulties in the interpretation of the data was that a number of patients who were not suitable for revascularization were included in the study. Those patients who were not revascularized did not have NSTE-ACS but had elevated biochemical markers due other reasons. Examples were patients with myocarditis, atrial fibrillation, Takotsubo cardiomyopathy, and supply demand mismatch MI (type 2 MI). A meta-analysis of NSTEMI patients suggested that it is the revascularization with PCI or CABG which is the crucial beneficial factor for improving clinical outcome [193].

The only difference that could be observed was the likelihood of being revascularized, which was an expected finding in an open-labelled study.

We did not find that the risk of MI or the severity of angina pectoris differed between the two groups. The majority of patients were free from angina pectoris in both groups. The possible reasons for the lack of a difference in angina pectoris class may have been that in the invasive group, only 67% of eligible patients were treated with PCI and only 33%

were fully revascularized. Other possible mechanisms responsible for our findings were good medical management in both groups and eventually a low exercise capacity of the patients due to high age.

Why did we need eight years to enrol patients in Study IV and still needed to discontinue prematurely?

A slow recruitment of elderly patients in RCTs is a well-known problem. There were a number of reasons for the slow recruitment in our study. Examples were that patients were unable to decide whether or not to participate and very often had to discuss with relatives.

Other contributing factors were uncertainty regarding the diagnosis in the early phase and that the treating physician had already decided on the choice of strategy.

Further, a slow recruitment among the elderly has also been a problem in other RCTs, such as the Italian Elderly ACS study which only recruited 313 (62%) of the targeted 504 patients and an RCT with patients over 70 years of age with NSTEMI [194], which included 71% of the targeted 150 patients. The After Eighty Study attained its target recruitment of 457 patients. In addition, the After Eighty Study included only 23% of possible candidates for inclusion, and the Italian Elderly ACS study included 49% of possible candidates. In our study, we did not have a list of all screened patients in all centres, but we assume that the proportion of possible candidates who were included in the study was extremely low.

During the study period, more evidence evolved for the beneficial effect of an invasive strategy in the very elderly that may have made clinicians hesitate to include patients in the study. Clinical trial fatigue is another factor that develops with slow patient enrolment and a long study period. With slow enrolment in the study, investigators lose interest. Two centres stopped enrolling and one centre did not enrol any patient. Therefore, recruitment must perhaps not continue for longer than five years.

Should we perform RCTs in the elderly?

RCTs have been the golden standard for evaluating the effect of interventions, but when the enrolment is not very effective and continues for a very long time, the generalizability and utility of results

becomes questionable. It is obvious that there are problems associated with the performance of RCTs in the elderly, as we encountered in Study IV. However, more evidence is needed in the cardiovascular field on treatment in the elderly, and the elderly must not be excluded from clinical trials [90]. The cohort in clinical trials must be more representative of the real world with frail and comorbid elderly patients.

PREDICT (increasing the participation of the elderly in clinical trials) has published a document to reduce the gap between the cohort recruited in clinical trials and the real world [195]. The document outlines that older people have the right to be offered evidence-based treatment, clinical trials must be practical and safe, outcome variables must be relevant for older people, the values of older patients participating in clinical trials must be respected, and recruitment of older patients must be promoted to prevent discrimination.

Another approach may be cluster randomization. Then, patients are randomized to different treatment strategies in clusters. A final methodologic design is real-life observational registry studies that can include the more comorbid and frail patients who are usually excluded from RCTs. Observational studies from high-quality national registries are important complements to RCTs in terms of gaining external validity. Registry studies are cheaper but are potentially a subject for unmeasured confounders and selection bias.

What treatment strategy should we recommend for very elderly patients with NSTE-ACS?

According to the previous existing literature, for very elderly patients with NSTE-ACS, an invasive treatment strategy is superior to a conservative treatment strategy in reducing re-myocardial infarction and urgent revascularization compared to medical treatment alone [125,126].

Meta-analysis of RCTs [128,129] did not show any significant mortality benefit at follow-up due to lack of power. However, several observational studies [116,122,123] have revealed an association between an invasive strategy and an increased survival compared with a conservative strategy. However, an increased revascularization in this age group does not necessarily lead to a lower mortality rate [116,196]. Patients who are enrolled in an RCT are highly selected and patients

who are selected for an invasive strategy in observational studies represent confounding by indication.

Therefore, it is suggested that the decision of how to treat an elderly patient must always be individualized, weighing the risks against the benefits. Therefore, further studies must attempt to include frailty in order to attempt to guide clinicians regarding which elderly patients will benefit from an invasive treatment.

Overall, our result supports the current evidence for the use of an invasive strategy for very elderly in order to reduce the risk of the requirement of an urgent revascularization, but there was no significant reduction in the risk of MI or death, possibly due to the small sample size. We advise that the decision to perform a coronary angiography in very elderly patients with NSTE-ACS at high risk must be individualized.

Ethical considerations in the thesis

All the studies in the thesis have received ethical approval by regional boards of ethics in Gothenburg, and the Dnr numbers for each study are listed in Table 2.

When caring for the elderly, there are multiple ethical dilemmas in both cardiac arrest and when caring for elderly with challenging medical and psychosocial problems. With advanced care planning, healthcare preferences are identified by patients or by surrogate decision-makers in cases where the patient cannot make a healthcare decision independently. Advanced care planning includes patient-clinician discussion of future and end-of life care. In practice, the consent to CRP is presumed unless there is a DNAR order. The autonomy of the patients includes the right to refuse or request medical interventions. The patient also has the right to change his/her mind regarding treatment if his/her viewpoint alters. Survival of the elderly after cardiac arrest is often very poor, and patients can overestimate the success rate after cardiac arrest. However, after being informed about the likelihood of success, the patients may decline to be resuscitated [197].

Patients who were terminally ill and for whom CPR was not initiated were not included in the SCRC. Further, patients who survive resuscitation are informed about their participation in the registry.

In Study IV, there was an ethical challenge in determining the decision-making capacity of the patients and in ensuring that the information was understood. Providing patients information regarding randomization and treatment options can be challenging, as the elderly trust that the physician will treat the patient in the best possible manner. It is questionable to withhold invasive treatment that we expect may possibly reduce event rate by 50% and, therefore, withhold effective treatment modality for the sake of more evidence. During the study period, more evidence evolved with regard to the beneficial effect of invasive strategies, like the After Eighty study [126], which complicated the enrolment even further.

6 CONCLUSION

Study I

Increasing age among the elderly is associated with a lower 30-day survival after IHCA. Prerequisites such as more comorbidities, less shockable initial rhythm, and lower ECG monitoring at the time of the event and less aggressive treatment may have contributed to the findings. Among survivors of IHCA, the neurological outcome did not differ significantly between the three age groups among the elderly.

Study II

This large national study showed that increasing comorbidity was associated with a decreased likelihood of survival to 30 days after OHCA. This association remained after covariate adjustment.

Study III

Patients who undergo CPR before the arrival of EMS have a somewhat lower degree of comorbidity than those who do not. Taking this difference into account, bystander CPR was still associated with a marked increase in 30-day survival after OHCA.

Study IV

In the very elderly with NSTE-ACS, we did not find any significant difference in MACCE between the invasive and conservative treatment group at 12-month follow-up, possibly due to the small sample size.

7 FUTURE PERSPECTIVES

In this thesis, we discussed the outcome of IHCA in the elderly, the influence of comorbidity on survival and on the effect of bystander CPR, and the impact of an invasive strategy compared to a conservative strategy on outcome in a RCT.

There is a knowledge gap regarding how the association of in-hospital factors, such as PCI and TTM, can potentially impact the survival of elderly who have suffered from an IHCA and the long-term outcome of IHCA.

In Study II, we demonstrated that comorbidity influences the 30-day survival but in-hospital treatment could possible alter the association between comorbidity and survival. Hence, comorbidity must be included in the statistical analysis of future cardiac arrest research. National cardiac arrest registries could possibly further implement a web-based form of the most important comorbidity conditions.

In Study III, we further highlighted the importance of bystander CPR and that the positive effect of bystander CPR is not affected by the patient's comorbidity. Other potential factors including frailty are important to study in order to further identify barriers for the true bystander to initiate CPR in order to increase the possibilities of optimising the frequency and quality of CPR in the community.

In Study IV, we found that the observed treatment effect with an invasive strategy offered to very elderly patients with NSTE-ACS was lower than expected. Thus, there was no statistical difference in MACCE at 12 months between the two treatment modalities. Further research is required in order to optimize the use of an invasive strategy among these patients. Future clinical studies can possibly remove the upper age limit and include older patients, as the elderly have a high burden of cardiovascular diseases and possibly have the most to gain, particularly from new treatment modalities. Challenges of including a sufficient sample size of elderly patients would most likely require a multicentre international RCT. In Sweden, it could be possible to initiate a registry-based randomized controlled trial (RRCT) within the SWEDEHEART registry. Then, we could possibly obtain a larger sample size of patients in a shorter time period and further gain information regarding which patients are included and which patients

are not. Those patients who do not wish to participate could have a further follow-up in the registry. With such an approach, we could gain insight and further knowledge regarding elderly patients with NSTE-ACS and possibly identify which patients can benefit from revascularization.

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APPENDIX