

# ACUTE CORONARY SYNDROME AND CARDIAC ARREST IN THE ELDERLY

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Cover illustration: A little girl and elderly woman keeping a red heart in their palms together. Photo by Kosobu.

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*"Medicine is a science of uncertainty and an art of probability."*

William Osler

*To my family*

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## HIGHLIGHTS

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- The elderly are currently the fastest growing segment of clinical practice and data are needed to adequately counsel patients so that their expectations are aligned with their likely outcomes.
- Making the diagnosis acute coronary syndrome (ACS) in the elderly is not always a simple task
- The quality and quantity of the underlying scientific evidence is limited making it problematic for clinicians to evaluate benefit and risk from treatment in the elderly, but this fact alone should not result in treatment being withheld
- Elderly remain a challenging patient group in research and results from geriatric studies may be difficult to interpret.
- Aging seldom comes alone, often being accompanied by chronic diseases, comorbidity, disability, and frailty.
- The principal barrier in recommending medical or invasive therapy to elderly patients with ACS is their greater perceived risk, explaining an undertreatment compared to their younger counterparts.
- A universal, one-size-fits all, therapy approach is unlikely to be successful in the total cohort of elderly patients with ACS. A more reasonable treatment approach would be an individualized one, taking into consideration: life expectancy, risk, benefit and patient preferences.
- Future investigations should continue to challenge age-related discrimination, demanding rigorous investigation into the factors that impair quality and quantity of life.

## LIST OF PAPERS

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

- I. Libungan B, Karlsson T, Hirlekar G, Albertsson P, Herlitz J, Ravn-Fischer A. Delay and inequality in treatment of the elderly with suspected acute coronary syndrome. *International Journal of Cardiology*. 2014;176(3):946-950.
- II. Libungan B, Karlsson T, Albertsson P, Herlitz J. Elderly patients with myocardial infarction selected for conservative or invasive treatment strategy. *Clinical interventions in aging*. 2015;10:321-327.
- III. Velders MA, James SK, Libungan B, et al. Prognosis of elderly patients with ST-elevation myocardial infarction treated with primary percutaneous coronary intervention in 2001 to 2011: A report from the Swedish Coronary Angiography and Angioplasty Registry (SCAAR) registry. *American Heart Journal*. 2014;167(5):666-673.
- IV. Libungan B, Hirlekar G, Albertsson P. Coronary angioplasty in octogenarians with emergent coronary syndromes: Study protocol for a randomized controlled trial. *Trials*. 2014;15(1).
- V. Libungan B, Lindqvist J, Strömsöe A, Nordberg P, Hollenberg J, Albertsson P, Herlitz J. Out-of-hospital cardiac arrest in the elderly: A large-scale population-based study. *Submitted*

## ABBREVIATIONS

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ACS	Acute Coronary Syndrome
ACLS	Advanced Cardiac Life Support
CA	Cardiac Arrest
CABG	Coronary artery bypass grafting
CAD	Coronary Artery Disease
DNR	Do-not-resuscitate
ECG	Electrocardiogram
EMS	Emergency Medical Service
FDA	Food and Drug Administration
IHD	Ischemic heart disease
MI	Myocardial Infarction
NS	Non Significant
NSTEMI	Non ST-elevation myocardial infarction
OHCA	Out-of-hospital cardiac arrest
PCI	Percutaneous coronary intervention
QoL	Quality of Life
RCT	Randomized Controlled Trial
STEMI	ST-elevation myocardial infarction
UAP	Unstable angina pectoris
VF	Ventricular Fibrillation

## ABSTRACT

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The elderly are currently the fastest growing segment of clinical practice but the quality and quantity of the underlying scientific evidence to guide treatment is limited. In this thesis five individual studies investigating aspects of geriatric cardiac care are presented.

In Paper I, a study of age related differences in patients with symptoms suggestive of acute coronary syndrome (ACS) showed that elderly patients (>80 years) were more likely to receive a final diagnosis of ACS but were less often investigated with coronary angiogram or echocardiography than their younger counterparts. Elderly with ACS received less medical treatment with P2Y<sub>12</sub> antagonists and lipid lowering drugs. Elderly with chest pain could not be shown to have a delay to hospital admission compared to their younger counterparts. These findings underscore the substantially more complex comorbidities and worse outcome among elderly patients who were less likely to receive evidence based treatment.

In Paper II, the differences between elderly (>75years) patients with myocardial infarction selected for invasive or conservative treatment strategy were investigated. Heart failure, both previous history and at presentation, turned out to be more common in the conservative group compared to the invasive group. There was lower mortality in the invasive group (in-hospital 9% vs. 20%,  $p<0.0003$ ) compared to the conservative group. Although it is tempting to attribute the apparently lower mortality rate to the invasive treatment strategy such a causative assumption cannot be made due to the observational study design and should be confirmed by a randomized clinical trial (such as described in Paper IV).

In Paper III, elderly STEMI patients treated with PCI were investigated during a 10-year study period. During the study period, average age and co-morbidity increased, but the procedural success and prognosis remained constant. In addition, risk, in terms of bleeding, re-infarction, heart failure and stroke remained similar during the study period.

In Paper V, elderly patients (>70 years) who suffered OHCA were stratified in 3 different age groups: 70-79, 80-89 and  $\geq 90$  years of age. With increasing age the 30-day survival decreased. However, even in patients above 90 years of age, defined subsets with a survival rate of more than 10% exist. In survivors, age was not a key determinant for bad neurological outcome.

# AGING

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*"Old age is the most unexpected of all things that can happen to a man."*  
-Leon Trotsky

Aging is defined as the process of becoming older. It represents the changes in the human body with time. There occur multiple changes with time, both psychological and physiological.

Age is measured chronologically depending on a persons birthdate, but there exists a more physiological term, referred to as biological age. Although biological age is used in the clinical setting it turns out to be observer dependent. There have been evolved different methods to determine biological age, but these methods are not practical as they require measurements of multiple biomarkers<sup>1</sup> and/or genetic testing.<sup>2</sup>

Aging is individualized and multidimensional. There exists extreme heterogeneity among the group of aged. The medical, physiologic, psychological, and cognitive changes of aging are poorly reflected in chronologic age and can be best appreciated with a multidimensional assessment of the older person.

## **Elderly and life expectancy**

There exist various definitions of old age or elderly, which explains the inconsistency in the research setting. The term elderly is defined officially by the World Health Organization (WHO) as chronological age 65 years, but this applies for western countries. In the continent of Africa the age 50-55 years is sufficient to be considered elderly, due to the much lower life expectancy. The United Nations criterion for old age and elderly is 60 years.

In the scientific world, different definitions exist to describe the group of elderly. In the American Heart Association (AHA) guidelines from 2002 for management of ACS >75 years patients were categorized as a special at-risk group. In 2007, an AHA scientific statement<sup>3</sup> recommended the use of age cut

points based on the average population age, such as <65, 65-75, 75-85 and above 85 years for studies of the elderly in western countries.

Some other definitions exist such as Octogenarians describing those over 80 years old, Nonagenarians >90 years old and finally, Centenarians >100 years old.

Life expectancy varies in the different countries. Some African countries may have a life expectancy of only around 55 years of age, while in the developed countries the life expectancy is much higher and is on the increase.<sup>4</sup> In Sweden, the mean life expectancy at birth is around 84 years for women and 80 years for men but is increasing (figure 1). The main explanation for the temporal trend of increasing life expectancy in developed countries is medical innovations and advances leading to extended life.

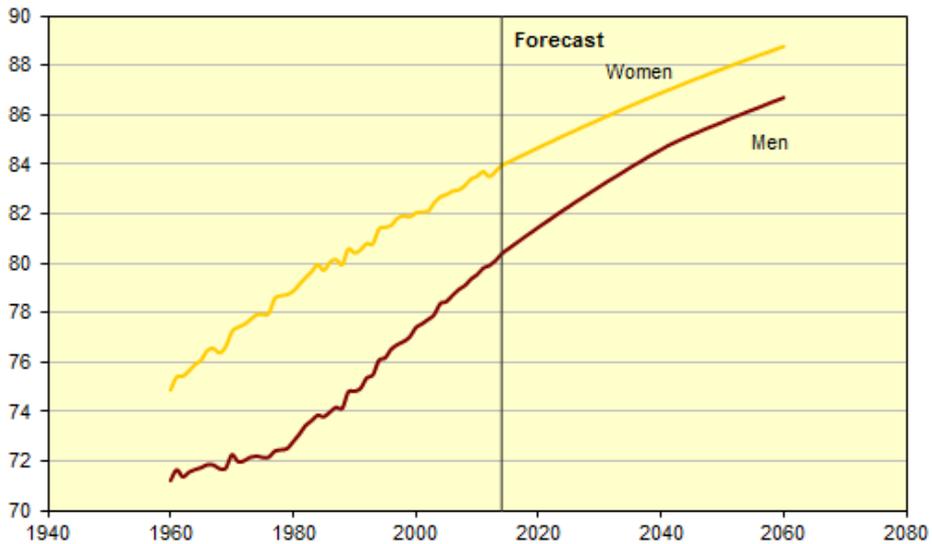


Figure 1. Life expectancy at birth by sex in 1960-2013 and forecast 2014-2060 in Sweden. Statistics Sweden. [www.scb.se](http://www.scb.se)

## THE OLD AGE PROBLEM

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*"All diseases run into one, old age."*

-Ralph Waldo Emerson

Population aging is the increase in the number and proportion of the elderly in a country. According to the United Nations World Population Report<sup>5</sup> globally, the number of older persons (aged 60 years or over) is expected to more than double, from 841 million people in 2013 to more than 2 billion in 2050. Population aging is primarily due to lower child and adult mortality in combination with lower fertility rates.

The problem of old age will not go away, it will only escalate. Problems related to aging, multimorbidity, and polypharmacy have become a prominent issue in global healthcare. Under the past years it has been realized that as the population ages, health care consumers also increase rapidly with major economic and social consequences. Another alarming fact is that the old-age support ratio (number of working-age adults per older person in a population) is declining meaning fewer individuals supporting social security systems with increasing demand for resources. Preparation and prioritizing is needed to meet these demands of elderly individuals in the future. In the most utopic sense this should be done by fulfilling the ethical principles of beneficence and non-maleficence, or do not harm, without any age-discrimination. But a strong evidence base will be needed in order to do so.

Policymakers face the challenge of understanding and managing future health care costs. In a systematic review of health care utilization in the elderly population, with each additional chronic condition a linear or near exponential relationship was found in the use and cost of health care.<sup>6</sup>

Medical advances have lead to some extremely expensive technologies in cardiology such as left ventricular assist devices and intraventricular cardioverter defibrillators. With the increasing number of elderly individuals there will be large populations with indications for such therapies in the future. Cost-effective analysis<sup>7</sup> in elderly individuals will probably reveal therapies with high cost and lower effectiveness compared to the younger population. The concept of Quality Adjusted Life Year (QALY) has been introduced in order to measure disease burden taking into consideration the quality and quantity of life lived.<sup>8</sup> One concern is that it does not take into account equity issues such as the overall distribution of health states - younger, healthier

cohorts have many times more QALYs than elderly individuals with co-morbid diseases. As a result, QALY analysis may undervalue treatments that benefit the elderly or others with a lower life expectancy.

Techniques that preserve life can prolong an inevitable death, at the risk of diminishing quality of life and personal dignity. As we add years of life we may be adding years with disabilities. The aging of global populations is the main reason for the increase in years lived in disability.<sup>9</sup> Saving patients from what before was a fatal disease, such as stroke, typically increases those with functional disabilities in the community. In qualitative studies of end-of-life decision making one of the most important issues for the elderly is being able to return to their valued daily activities.<sup>10,11</sup> The ultimate goal of the future should not only be prolonging life, but also prolonging health.



Figure 2. Elderly Common Diseases in word collage. Image by Mypokcik.  
<[www.shutterstock.com](http://www.shutterstock.com)>

## DIFFERENCES BETWEEN THE YOUNG AND OLD

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*"It is not our differences that divide us. It is our inability to recognize, accept, and celebrate those differences."*

-Audre Lorde



*Figure 3. With aging progressive physiological changes occur. Downloaded from [www.google.com](http://www.google.com) (reuse labeled).*

There exist important differences between the young and old. With age, progressive physiological changes occur that lead to decline in function of organ systems. Another term sometimes used is organ reserve decreases. As a result, the capacity of older adults to recover after an illness can be significantly affected. One example of decreased organ reserve would be renal function, which declines progressively with age, explaining why age is one of the values needed to calculate the estimated glomerular filtration rate.<sup>12</sup>

Also, there is increased prevalence of co-morbid diseases increasing the heterogeneity in the group of elderly. Increased co-morbidity commonly leads to polypharmacy.

*Frailty* is important from a clinical point of view, because it constitutes a condition of greater risk of adverse outcomes, such as less mobility, less independence, hospitalization, disability, and death.<sup>13</sup> Frailty is concept in the old, but unfortunately the exact definition is lacking<sup>14</sup> making it difficult to estimate the prevalence. There are multiple manifestations of frailty but no single manifestation is sufficient to be considered frail. Most authors agree that frailty can be defined as a physiologic state of increased vulnerability to stressors that results from decreased physiologic reserves. Physical frailty can be estimated with different scales, for example with the Fried Frailty Index (FFI) that requires the presence of three or more of the following five components: weight loss, exhaustion, weakness, slowness, and low physical activity. According to a systematic review<sup>15</sup> the prevalence of frailty in the community dwelling population of elderly (>65 years) turned out to be around 10% but in the hospital or nursing home setting the percentage is higher.

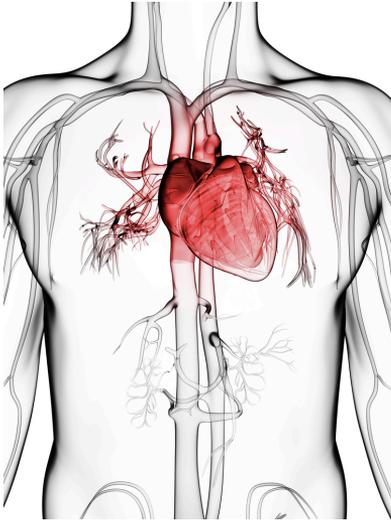
In a recent study investigating the prognostic value of geriatric conditions (frailty, physical disability, instrumental disability, cognitive impairment, and co-morbidity) frailty turned out to capture most of the prognostic information after ACS.<sup>16</sup>

Ethical values may change with increasing age. Studies show that younger patients prefer a more active stance in medical decision making than older patients or that medical preferences change with increased age. One survey showed that preferences for active involvement increased until 45 years of age, and then declined with age.<sup>17</sup>

In general, the same principles do not necessarily apply for the younger as do for the older. This is the main reason for why dedicated studies to the elderly are important in order to assess risk and benefit.

## THE AGING HEART

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*"Everyone is the age of their heart."*  
-Guatemalan Proverb

*Figure 4. 3D rendered illustration of the human vascular system. Image by Sebastian Kaulitzki.  
<www.shutterstock.com>*

Many physicians have very little formal training in geriatric medicine and find it difficult to distinguish between normal aging and disease states.

In the heart, there occur important physiological changes associated with age. The net effect of these changes result in decreased exercise tolerance and increased vascular resistance.<sup>18</sup> The more important changes associated with aging of the cardiovascular system are: Firstly, compliance in the cardiovascular system decreases with age leading to risk for higher blood-pressure and diastolic dysfunction of the left ventricle. Secondly, loss of myocytes occurs with age leading to hypertrophy of the remaining cells. Thirdly, calcification of the valves and conduction system occurs. Fourthly, due to changes in the sarcoplasmic reticulum  $\text{Ca}^{2+}$  ATP-ase pump myocardial relaxation slows, adding to the risk for diastolic dysfunction.

The etiology for cardiovascular aging is under study, but the proposed mechanisms have been; cumulative changes in gene expression, mitochondrial dysfunction, non-enzymatic glycation and inflammation. More recently, mitochondrial dysfunction is getting more central to theories of aging, because age-related changes of mitochondria are likely to impair a host of cellular physiological functions contributing to the development of age-related diseases.<sup>19,20</sup> In experimental rodent models several pharmacological and genetic manipulations related to mitochondria and aging are being studied,<sup>21,22</sup> but no such therapy has been approved in men.

# CORONARY ARTERY DISEASE IN THE ELDERLY

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## The impact of coronary artery disease

The prevalence of coronary artery disease (CAD) increases with age. ACS refers to a spectrum of clinical presentations ranging from those for ST-segment elevation myocardial infarction (STEMI) to presentations found in non-ST-segment elevation myocardial infarction (NSTEMI) or in unstable angina. It is almost always associated with rupture of an atherosclerotic plaque and partial or complete thrombosis of the infarct-related artery. With increasing age there is a shift to more patients presenting with NSTEMI and less with STEMI or unstable angina.<sup>23</sup>

The leading cause of mortality in developed countries is coronary artery disease and ACS.<sup>24,25</sup> Nevertheless, in most European countries, coronary heart disease mortality rates have continued to decrease in younger adults at similar or greater rates when compared with older age groups<sup>26</sup> and are now less than half what they were in the 1980s.<sup>27</sup> This reduction in mortality is due to several factors the most important ones being the reduction of modifiable risk factors, with the exception of diabetes and obesity, and advances that have occurred in treatment.

## ACS can manifest differently in the elderly

Elderly patients may not report symptoms that they consider to be part of normal aging, such as dyspnea, fatigue or functional decline.

Unusual manifestations of disorders, such as ACS, are common in the elderly. The diagnostic approach to suspected ACS includes three major components: 1. clinical profile or symptoms, 2. ECG and 3. cardiac biomarkers (most widely used Troponins). But all of these three factors can be difficult to evaluate in elderly patients.

Atypical symptoms (no chest pain) commonly occur in elderly with ACS, such as: dyspnea, diaphoresis, nausea or vomiting and syncope. With increasing age, the risk for atypical presentation increases and was found to be 43% in a group of patients >75 years of age.<sup>28</sup> Even in a group of STEMI patients, with most likely an occluded coronary artery, chest pain at presentation occurred in only 57% of those  $\geq 85$  years of age compared to 90% in the younger cohort (<65 years).<sup>29</sup> ACS patients that present without chest pain are at risk for delays in

seeking medical attention, receive less aggressive treatments and have high in-hospital mortality.<sup>30</sup>

In elderly patients, the ECG can be more difficult to interpret due to higher incidence of baseline ECG changes such as right or left bundle branch block, non-specific ST-deviations or pacemaker rhythm.<sup>31,32</sup>

The cardiac troponins are more often elevated in the elderly in the absence of ACS, which could add further to the uncertainty of whether or not the patient has myocardial infarction. The main reasons explaining the elevated troponins, in patients without myocardial infarction are: impairment of renal function, arrhythmias and diastolic and/or systolic heart failure. When assessing the high sensitive troponin (hsTnT) the optimal cut-off value to distinguish elderly patients (>70 years) with or without acute myocardial infarction turned out to be around 4-5 times higher than the cut-off value in a younger cohort.<sup>33</sup> Hence, the risk for a false positive result in elderly individuals would be higher if a general (for all age groups) cut-off value is used.

These aforementioned factors may cloud the clinical picture and prevent a timely diagnosis of ACS.

## **Age related inequalities in ACS care (Paper I)**

Realizing the difficulties in diagnosing ACS in the elderly population one would expect delay and undertreatment of elderly patients seeking with symptoms suggestive of ACS. To answer such a question, if inequality or delay exists, one would need a group of consecutively included patients, in all ages, captured early in the ambulance or hospital phase. Consecutive inclusion, during a defined time period, would eliminate the risk for selection bias and increase the external validity of the study, as all patients seeking during that period are included. Such a study is Paper I.<sup>34</sup>

The aim of Paper I was to explore the differences between elderly and younger patients seeking with symptoms suggestive of ACS. More specifically, time to treatment, admission and diagnostic tests were registered in order to evaluate delay time.

All patients with chest pain who were admitted to a hospital in the Gothenburg area were included consecutively over a 3-month period in year 2008. They were divided into an elderly group ( $\geq 80$  years) and a reference group ( $< 80$

years). Previous medical history, ECG findings, treatments, diagnostic tests, and delay times were registered.

The elderly group consisted of 478 patients presenting with chest pain with a mean age  $\pm$  SD of  $86 \pm 4$  years (range 80–103). The reference group consisted of 2110 patients with a mean age  $\pm$  SD of  $54 \pm 16$  years (range 16–79).

In table 1, showing comparison of hospitalized patients, there were no significant differences in delay time to hospital ward admission, to first medical therapy with aspirin, or to investigation with coronary angiography (CA) between the two groups (elderly and reference). The elderly patients had a significantly shorter median time from first medical contact to first ECG (12 vs. 14 minutes,  $p=0.002$ ) but after adjustment for confounding factors, especially mode of transport, the opposite was found to be the case ( $p=0.002$ ).

Elderly patients were more likely to receive a final diagnosis of ACS (17% vs. 8%) than their younger counterparts. Elderly hospitalized patients with ACS were less often investigated with CA (44% vs. 89%,  $p<0.0001$ ). Elderly with ACS received less medical treatment with P2Y<sub>12</sub> antagonists and lipid lowering drugs. One-year mortality in hospitalized patients was 26% in the elderly group, compared to 4% in the reference group.

The conclusions of Paper I are the following: Elderly individuals with symptoms suggestive of ACS could not be shown to have a delay to hospital admission compared to their younger counterparts, but elderly with ACS received less medical treatment and diagnostic investigations (coronary angiography and echocardiography). These findings underscore the substantially more complex comorbidities and worse outcome among elderly patients who were less likely to receive evidence based treatment.

*Table 1. Shown on the next page (20): Delay variables in patients above and below the age of 80 years, with symptoms suggestive of ACS*

All hospitalized patients: median (10th, 90th percentile; in minutes); odds ratio (OR) and corresponding 95% confidence interval (CI) for those  $\geq 80$  years old in relation to those  $< 80$  years old having a delay above median.

Delay variable	$< 80$ yrs (n = 1002)	$\geq 80$ yrs (n = 348)	$p^a$	OR <sup>b</sup> (95% CI)	$p^b$
Arrival in hospital to admission in PCI laboratory or ward (median = 215)	217 (77.537)	212 (80.473)	0.59	1.03 (0.76,1.38)	0.86
1st physical contact to 1st ECG (median = 13)	14 (0.76) <sup>d</sup>	12 (0.68) <sup>c</sup>	0.002	1.68 (1.21,2.35)	0.002
1st physical contact to 1st aspirin (median = 79)	94 (5.1289) <sup>c</sup>	26 (5.902) <sup>c</sup>	0.04	0.79 (0.39,1.61)	0.52
Arrival in hospital to coronary angiography (median = 1815)	2022 (25.8433) <sup>c</sup>	402 (19.7422) <sup>c</sup>	0.12	0.63 (0.27,1.48)	0.29

<sup>a</sup> Unadjusted.

<sup>b</sup> For having a delay above median, adjusted for all baseline variables with univariate  $p < 0.20$  for both association with age group and delay. Baseline variables used are as follows: for arrival in hospital to admission in PCI laboratory or ward: sex, previous angina pectoris, previous PCI, depression/psychiatric disease, need of interpreter, transported by ambulance and ST-depression; for 1st physical contact to first ECG: previous diabetes, previous hypertension, previous MI, previous angina pectoris, previous stroke, peripheral vascular disease, need of interpreter, transported by ambulance and ST-depression; for 1st physical contact to first aspirin: sex, previous diabetes, previous hypertension, previous heart failure, previous MI, previous angina pectoris, previous PCI, previous stroke and transported by ambulance; and for arrival in hospital to coronary angiography: sex, previous MI, previous PCI, peripheral vascular disease, transported by ambulance and ST-depression.

<sup>c</sup> 5–10% missing.

<sup>d</sup> 10–25% missing.

## MEDICAL TREATMENT FOR ACS

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*Figure 5. Many pills and tablets isolated on white background. Photo by Photostock 10.  
<www.shutterstock.com>*

The aims of therapy for coronary artery disease are to prevent further episodes of myocardial ischemia and doing so, controlling symptoms and decreasing morbidity and mortality.

In general, the evidence to support medical therapy in older adults is less robust than in their younger counterparts, especially in individuals >75 years of age.

The following medications are those most widely used in patients with ACS and are recommended in the guidelines,<sup>35</sup> in the absence of contraindications. In the elderly, a tailored approach to medical therapy might be needed due to polypharmacy and co-morbidity- risks and benefits must be balanced for each patient.

A troubling fact is that elderly patients with major cardiovascular diseases are denied from indicated medical treatments probably due to chronological age alone.<sup>36</sup> But, temporal trend analysis of prescribing patterns have shown improvements in prescribing evidence-based therapies to the elderly. In a study of very old patients (> 85 years), between 2003 and 2010 the rates of prescription of the following secondary prevention medications increased: clopidogrel (28-89%), statins (61-69%) and beta-blockers (49-56%).<sup>23</sup>

In another large study, medical therapy among the elderly with ACS increased with time (1998-2010), and with increasing age there was an increase in therapy until age 75 (statins) and 85 (anti-hypertensive therapy), then an age related decline in therapy rates occurred.<sup>37</sup>

Antithrombotic therapy or antiplatelet therapy is essential to modify the disease process in coronary disease. The oral antiplatelets used today are aspirin and the thienopyridines or P2Y<sub>12</sub> antagonists. The intensity of treatment is based on individual risk.

## Aspirin

Aspirin (ASA) irreversibly inhibits cyclooxygenase-1 within platelets and thus prevents the formation of thromboxane A<sub>2</sub>. As a result, platelet aggregation diminishes promoted by this pathway.

Aspirin is recommended for all elderly patients, in the absence of contraindications, without any dosage adjustment in the elderly. A meta-analysis has shown the benefit in high-risk groups, such as the elderly, to exceed the hazard.<sup>38</sup> Nevertheless, there exists a problem of aspirin undertreatment in elderly individuals.<sup>39</sup>

## Thienopyridines

The P2Y<sub>12</sub> receptor is the main platelet receptor responsible for adenosine diphosphate-induced platelet aggregation. P2Y<sub>12</sub> inhibitors common (in the past and present) in clinical use are: ticlopidine, prasugrel, clopidogrel, and ticagrelor.

Due to safety reasons, the first generation thienopyridine ticlopidine has been replaced with other drugs.

In the TRITON-TIMI 38 trial,<sup>40</sup> the potent P2Y<sub>12</sub> inhibitor prasugrel was associated with a reduction in ischemic events compared with clopidogrel in high-risk ACS patients undergoing PCI. Post-hoc analysis identified patients at higher risk in whom prasugrel was associated with harm, with no net clinical benefit as the ischemic benefit was offset by the risk of bleeding, including the elderly (age >75 years). Due to these findings, the use of prasugrel in patients >75 years of age is generally not recommended.

In the substudy of a randomized trial (PLATO) comparing two different age strata (younger or older than 75years),<sup>41</sup> the clinical benefit and overall safety

of ticagrelor compared with clopidogrel in ACS patients were not found to depend on age.

In this regard, the medications most commonly used today are ticagrelor and clopidogrel. Clopidogrel is more widely used in the cohort concomitantly treated with Vitamin K-antagonists (warfarin).

## **Beta-blockers**

Beta-blockers competitively block the effects of catecholamine on cell membrane beta-receptors. By doing so, they decrease the contractility and heart rate responses to chest pain, exertion and other stimuli. They also decrease blood pressure.

After myocardial infarction, patients with conditions that are often considered to be contraindications for beta-blockade, such as pulmonary disease and older age, benefit from beta-blocker therapy.<sup>42,43</sup>

In the elderly without contraindications, due to safety reasons, a reasonable approach would be to start with low dose of beta-blocker and titrate slowly especially in those with conduction abnormalities, peripheral artery disease or obstructive lung disease.

## **ACE-I**

Angiotensin-Converting Enzyme Inhibitors (ACE-I) inhibit one step in the renin-angiotensin pathway. ACE-I has been shown to reduce mortality rates in patients with myocardial infarction.

Even though there is benefit of treatment with ACE-I, particularly in patients with reduced left ventricular function, the side effects of ACE-I treatment may outweigh benefit in elderly patients. The American Geriatric Society has published a list of medications that are potentially inappropriate for older adults (also known as the Beers criteria).<sup>44</sup> ACE-I is included on this list due to risk for orthostatic hypotension and syncope. Other examples of common medications that may be inappropriate for older adults, mentioned in the Beers criteria, are: Digoxin, Spironolactone, Prasugrel and NSAIDs.

Due to the risk for adverse effects, ACE-I should be tested in low dose among elderly ACS patients without contraindications to therapy, and titrated carefully with monitoring of renal function, potassium and blood pressure.

## Statins

Statins have been shown to be beneficial in prevention of subsequent MI and death, primarily by lipid-lowering effects. Hyperlipidemia is a significantly modifiable risk factor for coronary heart disease, but approaches to such modification must be considered in light of the individual's life expectancy and risk for side effects.

In the ACC/AHA Lipid guidelines<sup>45</sup> high-intensity statins, such as Atorvastatin 80 mg, has been recommended for patients below 75 years of age, but in those above 75 years moderate intensity statins are recommended instead. These recommendations have been based on low evidence for benefit and higher risk with high-intensity statins based on age. In contrast, the European guidelines<sup>46</sup> state a universal statin treatment regimen without any treatment modification in regards to age.

Statin-associated muscle effects (SAME) is an umbrella term for muscle related symptoms in patients on statin drugs, such as: myopathy, rhabdomyolysis and myalgia. Even in the absence of statin therapy, the elderly often have complaints of pain from the musculoskeletal system, so determining if the complaint is an adverse drug effect may be challenging. Even though some patients with SAME require drug discontinuation, many patients can tolerate a switch to a different statin or lower dose.

Cognitive dysfunction has been recognized as an adverse effect of statins, based on cases reported in the FDA's Adverse Event Reporting System.<sup>47</sup> This serious side effect would be especially important in the elderly, based on the higher prevalence of dementia with increasing age - one reason why statin therapy may be withheld. Observational studies have reported reversibility of the cognitive changes after a few weeks of discontinuation of the drug.<sup>48</sup>

When treating older adults, care must be given to life expectancy and the time to perceived benefit of the intervention or drug therapy. Regarding statins, the time to see full benefit from statins can be 2-3 years<sup>49</sup> but it has been shown to be shorter among those on a statin for secondary prevention.

## CONSERVATIVE OR INVASIVE TREATMENT

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Initial therapy for ACS should focus on stabilizing the patient's condition. In addition, relieving chest pain, providing antithrombotic therapy, and revascularization when appropriate to reduce myocardial damage. Medical treatment would commonly include a low-molecular-weight heparin (LMWH) in addition to the aforementioned therapy, if no contraindications exist.

Invasive treatment (coronary angiography and intervention if feasible) of patients with (ACS) has been shown to lead to better outcomes than medical therapy alone,<sup>35</sup> but the elderly have been under-represented in many of the studies. The benefit and risk of ACS treatment is discussed in more detail in a later chapter.

### **Selection of treatment method in the elderly (Paper II)**

In order to describe the differences between elderly MI patients who are selected for conservative or invasive therapy, one must have a database that includes all patients regardless of the admitting department in hospital. In Paper II, elderly patients admitted to all departments in a Swedish hospital were included, for example those who were admitted to a surgical department and had a periprocedural MI.

There are limited data on very elderly patients with MI especially those conservatively treated. Conservatively treated patients often get excluded from studies, even observational studies, due to the fact that study design includes only those admitted to specialized cardiology departments or those undergoing an intervention.

The aim of Paper II<sup>50</sup> was to explore differences between elderly MI patients selected for invasive or conservative treatment strategy. The characteristics describing the group of conservatively treated patients were of high interest.

The clinical characteristics and outcome was compared in 1413 elderly patients (>75 years old) admitted to Sahlgrenska University Hospital (Gothenburg, Sweden) with a final diagnosis of acute myocardial infarction in 2001 and 2007. The group was stratified into patients receiving a conservative treatment strategy (conservative group=CG) and those patients who underwent coronary angiography and were revascularized if indicated (invasive group=IG). The decision whether to treat the patient with the invasive treatment strategy or not

was made by the treating physicians, who were not aware of this study (retrospective data collection).

The results of Paper II is that other than higher age in the CG, traditional risk factors like hypertension, diabetes and smoking did not turn out to differ between those in the CG and IG. Heart failure, both as previous history and at presentation, and cerebrovascular disease turned out to be higher in the CG. Table 2 shows the characteristics of elderly patients with MI at presentation to hospital.

	2001		2007		2001+2007		P*	P**
	Cons (n=706)	Inv (n=97)	Cons (n=463)	Inv (n=147)	Cons (n=1,169)	Inv (n=244)		
Symptoms								
Chest pain/pressure/discomfort	81 <sup>a</sup>	98	68 <sup>a</sup>	90	76 <sup>a</sup>	93	<0.0001	0.18
Loss of consciousness	7 <sup>a</sup>	5	9	5	8 <sup>a</sup>	5	0.13	0.79
Pulmonary edema or cardiogenic shock	7	5	10	8	8	7	0.24	0.81
Other at presentation								
Cardiogenic shock	1 <sup>a</sup>	0	<1 <sup>a</sup>	3	1 <sup>a</sup>	2	0.27	0.15
Congestive heart failure	45	15	52 <sup>a</sup>	27 <sup>a</sup>	48 <sup>a</sup>	22 <sup>a</sup>	<0.0001	0.28
ECG recording available <sup>#</sup>								
ST elevation	9	23	7	28	8	26	<0.0001	0.15
Location								
Anterior	8	20	6	19	7	19	<0.0001	0.55
Inferior	2	9	2	15	2	13	<0.0001	0.26
Lateral	0	3	0	2	0	3	0.0005	1.00
ST-depression	27	31	25	35	26	33	0.008	0.45
LBBB	15	8	15	8	15	8	0.005	0.96
Other pathological ECG changes	50	59	44	49	46	53	0.09	0.74
Normal ECG	23	20	27	19	25	20	0.10	0.54
Sinus rhythm	67	81	68	76	68	78	0.07	0.45

**Notes:** \*For difference between conservative and invasive treatment strategy groups (age adjusted); \*\*for time period by treatment interaction; <sup>#</sup>percentages below refer to patients with available ECG recordings; <sup>a</sup>1%–5% missing.

**Abbreviations:** Cons, conservative; Inv, invasive; ECG, electrocardiogram; LBBB, left bundle branch block.

*Table 2. Characteristics of elderly patients with MI, at presentation (%)*

Overall, among the elderly with MI the proportion undergoing an invasive treatment strategy doubled from 12% in year 2001 to 24% in year 2007, despite a slightly higher mean age.

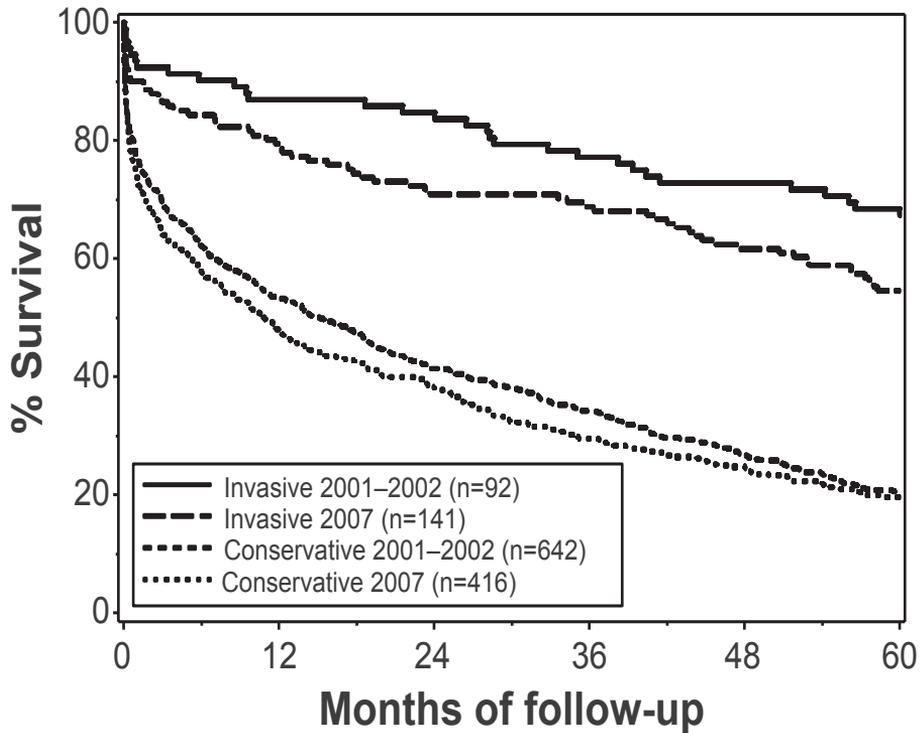


Figure 6. Kaplan-Meier curve describing survival in elderly patients with MI related to year and treatment strategy group.

The conclusions of Paper II are that elderly patients with MI in the conservative treatment strategy group are older and have more chronic diseases, such as congestive heart failure and cerebrovascular disease. Although it is tempting to attribute the apparently lower mortality rate to the invasive treatment strategy, as shown in figure 6, a causative assumption cannot be made due to risk for bias (confounding by indication). Such a conclusion must be confirmed by a randomized clinical trial. One randomized trial has been started in Sweden and is still recruiting (Paper IV); this trial is designed to evaluate the treatment effect of conservative and invasive treatment strategy in the elderly with ACS.

## UNTANGLING CLINICAL COMPLEXITY

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*"For every complex problem there is an answer that is clear, simple, and wrong."*

-H.N. Mencken

There must be done a careful weighing up of benefit and risk in the elderly population. But, as explained in this chapter, this task might turn out to be challenging. In addition, the life quality and life expectancy of the individual should be taken into consideration. These factors, risk, benefit, quality of life and life expectancy should be the base for a discussion with the patient and their family regarding treatment strategy.



*Figure 7. Factors that should be taken into consideration during clinical decision making, in complex elderly patients. Illustration by the author*

In patients with high risk for complications and in some cases unclear benefit from active treatment - a shared decision making with the patient, medical caregivers and family would be the most reasonable approach. Having conversations about the goal of care earlier in the course of illness often affects satisfaction and choices patients make. A patient-doctor relationship with continuity is the ideal context for a stepwise approach to discussing the goals of care. But unfortunately, in the era of the escalating productivity requirements currently characterizing medical practice many physicians may feel that they

lack time to manage complex symptoms, emotional, practical and social needs in their patients. Also, physicians may feel lack of competence and training dealing with complex situations and as a consequence, a tempting approach may be simply treating the disease within the field of expertise- instead of tackling complexity.

Dealing with patients with emptied treatment options, or unfixable problems, can be a difficult situation for caregivers. Doctors are taught to fight disease, and shifting treatment goal from curative to palliative care can be regarded as abandoning the patient and taking away patients' hope. Interestingly, a randomized study of cancer patients showed the opposite, that palliative care increased survival, quality of life and mood compared to standard care.<sup>51</sup> Moreover, there may exist unclear responsibility to who should initiate end-of-life decisions: The primary care physician, geriatric specialist at the nursing home, nursing staff or the hospital specialist treating the patient during acute illness?

## **Prognosis and life expectancy**

To better target services to those who may benefit from treatment, many guidelines recommend incorporating life expectancy into clinical decisions. This may be a difficult task, prone to subjectivity, but many prognostic indices have been described in order to guide clinicians. The quality of these have been evaluated in a systematic review<sup>52</sup> and some are available online, such as ePrognosis (<http://eprognosis.ucsf.edu>). They are designed to complement, not replace, the relationship between a patient and the medical provider. The clinician can estimate the patient's mortality by answering a series of questions included in each index. The risk score is correlated with an absolute risk of mortality for a specified time period. One must though add clinical judgment to decide if the estimated mortality risk seems reasonable. Prognostic indices offer a potential role for moving beyond age-based cutoffs in clinical decision-making.

In order to define patients who need different treatment than guidelines advocate due to complexity and risk, methods have been evolved in order to define the minimum elapsed time until the cumulative incremental benefits of a guideline exceeds its cumulative incremental harm, such as the payoff model.<sup>53</sup> If the payoff time of a guideline exceeds a patient's comorbidity-adjusted life expectancy, then the guideline is unlikely to benefit the patient and should be modified. Whether or not this approach helps patients is unclear, but it can be regarded as an additional tool in the assessment of the patient.

## EVALUATING RISK IN THE ELDERLY

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*Figure 8. Risk in the elderly may be due to different factors; all contribute to the total individual risk. Illustration by the author*

Overtreating the elderly may do more harm than benefit due to adverse events. When treatments are more complex and risky, it gets more important to know the patients risk factors for bad outcome. The accurate risk stratification of older adults would allow targeting of medications and interventions to those who benefit from treatment without taking unnecessary risk.

Even though time-consuming, a comprehensive assessment of the older person to address individual problems that may compromise the safety and effectiveness of treatment is necessary. The elements of this assessment would be: function, co-morbid diseases, cognition and psychological conditions, socioeconomic conditions, medications, nutrition and finally, geriatric syndromes, such as frailty.

In general, there are four different types of risk for bad outcome that can occur simultaneously in the same individual. Firstly, age-related risk, secondly competing risk, thirdly disease related risk and finally, treatment related risk (figure 8).

## Age related risk

Chronological age is a strong independent factor increasing risk for mortality in acute coronary syndrome,<sup>54</sup> even after adjusting for differences in baseline risk (competing risk) and therapeutic differences. Obviously, chronological age is a non-modifiable risk factor.

As previously mentioned, organ reserve capacity decreases with age. Due to physiological changes, age is usually found to be an independent predictor for bad outcome, such as increased mortality and morbidity. Chronological age is a variable in some of the popular risk calculators in cardiology, such as the Framingham risk score<sup>55</sup> and the GRACE risk score.<sup>56</sup>

## Competing risk

Comorbid diseases are other diseases the patient has simultaneously to one condition. The risk for adverse events (morbidity and mortality) increases with comorbid diseases and therefore in research and in the clinical setting this is sometimes described as competing risk.

The causes of two or more diseases co-existing can be: genetic (mutation of a gene causing 2 different diseases), single pathogenic mechanism causing a number of diseases, anatomic proximity of diseased organs, cause-effect relation between diseases, one disease resulting from complications of another or of course simply by chance.

In average, elderly patients have multiple disorders.<sup>57</sup> A disorder in one organ system can weaken another, leading to deterioration of both with risk for disability, dependence and mortality. In patients with many comorbid diseases, treatments must be well integrated. Treating one disorder without taking into consideration co-morbidity may lead to clinical deterioration.

In order to capture the value of comorbid conditions, there have been evolved tests or indices to consolidate each individual comorbid condition into a single, predictive variable that measures outcome, such as mortality. No one test is as yet recognized as a standard but experts have validated such tests because of their predictive value. In research, such indices have been used to adjust for heterogeneity in study groups, in order to decrease bias.

One more popular index used today to capture the increased risk of comorbidity is the Charlson index<sup>58</sup> but many other indices do exist.<sup>59</sup> After

adding the points in the Charlson comorbidity index (table 3) both from the comorbidity score and age score, one can calculate the estimated 10-year mortality risk by using a mathematical formula.

Score	Condition
<b>1 point for each</b>	Myocardial infarction (history, not ECG changes only), congestive heart failure, Peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, peptic ulcer disease, mild liver disease, diabetes without end-organ damage (excludes diet-controlled alone)
<b>2 points for each</b>	Hemiplegia, moderate or severe renal disease, diabetes with end-organ damage, tumor without metastasis (exclude if > 5years from diagnosis), Leukemia (acute or chronic), Lymphoma
<b>3 points for each</b>	Moderate or severe liver disease
<b>6 points for each</b>	Metastatic solid tumor, AIDS (not just HIV positive)

*Table 3. The Charlson comorbidity index. For age >40 years, for each decade 1 point is added.*

Although helpful, the different indexes are far from perfect. No single generally accepted method exists. When using different international comorbidity assessment scales, a clinician would come across totally different evaluations due to their inconsistency. The uncertainty of the result might complicate the doctor’s judgment about the level of severity of the patient’s condition. These tools are proven to be helpful in research of elderly patients, due to the high risk of competing risks and therefore bias. One example would be using the Charlson comorbidity index in the statistical analysis, in order to adjust for comorbidity.

The current paradigm of care for the elderly is based on extrapolation from conventional evidence-based guidelines for each of the multiple diseases these patients often suffer. However, there is no evidence that the evidence-based therapeutic approach to a single disease is also applicable to multiple diseases and the corresponding use of multiple medications, due to non-existing studies of polypharmacy in patients with multiple diseases. Not only is evidence-based knowledge on the efficacy of polypharmacy lacking but also there is no information about the safety of polypharmacy.

Subspecialists sometimes find it difficult to tackle all the different diseases, which are unlikely to be seen concomitantly in the younger patients they are more accustomed to caring for.

Among some ACS patients the balance of co-morbidity may be such that revascularization may not offer an acceptable level of periprocedural risk.

## **Disease related risk**

When diagnosed with a disease the patient will have increased risk for mortality or morbidity associated with his/her new diagnosis. In the population of ACS patients, examples of patients with high risk for death would be those presenting after cardiac arrest, with cardiogenic shock or STEMI.

Age is a prognostic marker in the majority of the ACS risk scores, negatively effecting survival. There has been observed an inverse relationship between the rate of PCI (or the rate of angiography) and risk status (myocardial infarction or mortality) of the patient<sup>60</sup> indicating that referral to PCI is more likely to be based on referral practice or angiographic findings- rather than validated risk scores. Even though this finding is disturbing, as guidelines advocate revascularization in patients with moderate or high risk for mortality- unacceptable procedural risk might be the reason for procedures being withheld.

## **Treatment related risk**

Among the elderly, there is risk associated with both medical treatment and invasive procedures. Interventions can have life-altering effects extending beyond that of the original diagnosis for which the intervention was indicated.

In particular elderly patients with lower homeostatic threshold the stress associated with surgery can lead to imbalance in autonomic, endocrine, metabolic, and immune factors.

The significance of activation of the autonomic sympathetic response, related to surgery, could have negative effects in elders due to hypertension, tachycardia and possibly arrhythmias. The net effect can result in increased oxygen demand, which can add to ischemia in vulnerable patients with preexisting coronary heart disease. In addition, circulating catecholamines may contribute to a hypercoagulable state and trigger coronary vasoconstriction- all factors that can add to risk for myocardial ischemia associated with treatment.

There exist many potential problem domains with prescribing drugs to the elderly. The high prevalence of polypharmacy with aging may lead to an increased risk of inappropriate drug use, underuse of effective treatments, medication errors, poor adherence, drug-disease and drug-drug interactions and, most importantly, adverse drug reactions.

Toxicity of medical therapy is a problem with higher prevalence among the elderly. This is due to impairment of homeostatic mechanisms (such as delayed gastric emptying, less intestinal motility, decrease in lean body mass and lower serum albumin), increase of co-existing diseases (such as renal and liver failure), and the fact that older patients are often taking several medications concurrently. When prescribing for the elderly these factors should be kept in mind, in order to minimize the risk for unwanted effects. In many cases the dose should be reduced or the dose interval increased. One problem is that randomized trials, that provide the base for medical therapy, include few elderly study individuals, so the safety of drugs tends to be overrated. Clinicians should be aware of these problems and review drugs frequently in elderly individuals in order to avoid adverse events.

In a systematic review<sup>61</sup> examining the adverse drug reactions (ADR) among hospitalized elderly, one in ten elderly patients will experience an ADR leading to, or during their hospitalization. Older female patients and those with multiple comorbidities and multiple medications were more likely to experience an ADR.

In the elderly with coronary disease, there exists higher risk for bleeding but also a higher risk for ischemia and hence, higher presumed benefit from treatment with antithrombotic therapy- which can make treatment choice difficult.

Age is a predictor for greater rate of all PCI-related complications.<sup>62</sup> Bleeding after PCI has been associated with increased mortality and the reasons can be multiple. Firstly, cessation of evidence-based therapy such as antithrombotic therapy, secondly, anemia itself that may drive myocardial ischemia, thirdly,

unwanted effects of blood products transfused and finally, greater prevalence of co-morbidities in those who bleed. In addition, making things even more complicated: With increasing age the prevalence of atrial fibrillation (AF) increases and the risk for stroke. Accordingly, there will be a higher rate of elderly patients on anti-coagulant drugs further adding to the risk for bleeding associated with anti-platelet drugs or PCI. The use of verified risk assessment scores for bleeding, such as CRUSADE,<sup>63</sup> which does not include age, may enable more objective assessment to evaluate bleeding risk.

The group of patients over 80 years of age that experience periprocedural complications are at particular risk.<sup>64</sup>

Due to the aforementioned therapy related risk, interventions, such as PCI for ACS should be kept as simple, swift and safe as possible.

### **Risk related to therapy in STEMI patients (Paper III)**

In order to evaluate risk related to therapy in a population of patients, one would need a database that captures hopefully all patients undergoing the procedure, during a defined time period. In Paper III,<sup>65</sup> the Swedish Coronary Angiography and Angioplasty Registry (SCAAR) was used to study elderly patients undergoing PCI for STEMI.

The SCAAR registry is a population-based quality registry in Sweden, sponsored by the Swedish Health Authorities. All consecutive coronary angiographies and PCI procedures performed in Sweden are documented. In total 30 hospitals with a catheterization laboratory enroll patients. Only during the first years, a few PCI procedures may have been performed outside of the SCAAR registry. The data are collected prospectively. During the over 20 years the registry has existed, temporal trends show that the mean age of patients has increased, PCI indication has shifted to be more frequently ACS instead of stable coronary disease and the complexity of the coronary pathology has increased with more multivessel and left main disease being treated with PCI.<sup>66</sup> In Paper III, consecutive patients with STEMI, 80 years or older undergoing primary PCI during a 10-year period (2001-2010) were identified. Temporal trends in care and outcome were investigated, and long-term outcome was compared with a reference group of patients with STEMI aged 70 to 79 years.

	<b>2001-2004 (n = 814)</b>	<b>2005-2006 (n = 1222)</b>	<b>2007-2008 (n = 1427)</b>	<b>2009-2010 (n = 1413)</b>	<b>P for trend</b>
Age (y), mean ± SD	83.1 ± 2.7	83.7 ± 3.1	84.0 ± 3.2	84.0 ± 3.3	<.001
Age ≥90 y	23 (2.8)	61 (5.0)	92 (6.4)	98 (6.9)	<.001
Male gender	449 (55.2)	641 (52.5)	720 (50.5)	716 (50.7)	.130
Diabetes mellitus	114 (14.3)	170 (13.9)	187 (13.1)	205 (14.5)	.813
Hypertension	291 (36.1)	514 (42.1)	628 (44.0)	746 (52.8)	<.001
Hyperlipidemia	91 (11.7)	138 (11.3)	192 (13.5)	243 (17.2)	<.001
Current smoker	53 (6.6)	76 (6.2)	94 (6.6)	102 (7.2)	.775
History of					
Myocardial infarction	189 (23.4)	222 (18.2)	190 (13.3)	189 (13.4)	<.001
Coronary artery bypass grafting	17 (2.1)	28 (2.3)	37 (2.6)	41 (2.9)	.010
Peripheral vascular disease	38 (4.7)	51 (4.2)	53 (3.7)	60 (4.2)	.737
Stroke	99 (12.2)	182 (14.9)	184 (12.9)	180 (12.7)	.241
Kidney failure	9 (1.1)	17 (1.4)	29 (2.0)	42 (3.0)	.006
Cancer in the last 3 y	31 (3.8)	45 (3.7)	47 (3.3)	70 (5.0)	.131
Onset symptoms to PCI (min), median (IQR)	317 (169-865)	255 (163-485)	230 (148-451)	235 (145-450)	.003
First ECG to PCI (min), median (IQR)	82 (37-173)	84 (50-148)	77 (49-131)	78 (50-120)	.074
Cardiogenic shock	65 (9.7)	87 (7.3)	106 (7.4)	64 (4.5)	<.001
Follow-up duration (y), median (IQR)	7.1 (6.4-8.2)	4.9 (4.4-5.4)	2.9 (2.5-3.4)	1.0 (0.5-1.5)	–

*Table 4. Baseline characteristics of elderly patients, treated with primary PCI*

	<b>2001-2004 (n = 814)</b>	<b>2005-2006 (n = 1222)</b>	<b>2007-2008 (n = 1427)</b>	<b>2009-2010 (n = 1413)</b>	<b>P for trend</b>
Vascular access					<.001
Femoral access	610 (94.3)	1056 (86.4)	1103 (77.3)	820 (58.1)	
Radial access	37 (5.7)	163 (13.3)	320 (22.4)	588 (41.6)	
Angiographic findings					<.001
Single-vessel disease	274 (37.4)	393 (32.8)	533 (37.4)	512 (36.3)	
Dual-vessel disease	192 (26.2)	346 (28.9)	403 (28.2)	405 (28.7)	
Triple-vessel disease	185 (25.2)	341 (28.4)	369 (25.9)	343 (24.3)	
Left main disease	80 (10.9)	109 (9.1)	104 (7.3)	114 (8.1)	
Treatment technique					<.001
Only balloon angioplasty	80 (9.9)	116 (9.5)	175 (12.3)	169 (12.0)	
Bare-metal stenting	650 (80.0)	816 (66.7)	1175 (82.5)	1106 (78.4)	
Drug-eluting stenting	82 (10.1)	290 (23.8)	74 (5.2)	135 (9.6)	
Stent length (mm), mean ± SD	17.1 ± 6.1	18.0 ± 6.2	17.6 ± 5.8	17.8 ± 5.8	.003
Stent diameter (mm), mean ± SD	3.1 ± 0.5	3.0 ± 0.5	3.0 ± 0.5	3.0 ± 0.5	.041
Procedural success	725 (92.6)	1110 (91.0)	1303 (91.5)	1287 (91.4)	.651
Medication					
Any antithrombotic treatment prior to PCI	505 (62.7)	1054 (87.5)	1227 (86.2)	1235 (87.7)	<.001
Aspirin before PCI	482 (59.4)	1015 (83.2)	1152 (80.9)	1167 (82.9)	<.001
P2Y12 inhibitor before PCI	192 (23.8)	636 (52.3)	956 (67.1)	1030 (73.2)	<.001
Thrombolysis prior to PCI	95 (11.8)	43 (3.6)	17 (1.2)	17 (1.2)	<.001
Glycoprotein IIb/IIIa inhibitor during PCI	400 (49.3)	657 (53.8)	570 (40.0)	334 (23.7)	<.001
Bivalirudin during PCI	–	166 (15.7)	485 (34.1)	779 (55.3)	<.001

*Table 5. Angiographic and procedural characteristics of elderly patients treated with primary PCI for STEMI*

In total, 4,876 elderly patients with STEMI were included. As shown in table 4 and 5, during the study period, average age and presence of comorbidity increased, as well as the use of antithrombotic therapy. The percentage of patients over 90 years old increased during the study period (2,8 % - 6,9 %). Procedural success remained constant. One-year mortality was exclusively reduced between the most recent vs. the earliest cohort, whereas the risk of reinfarction, heart failure, stroke, and bleeding remained similar. The risk of

death was higher for elderly patients early after PCI, after which the prognosis was slightly better, compared with the general population. Long-term risk of adverse events increased markedly with age.

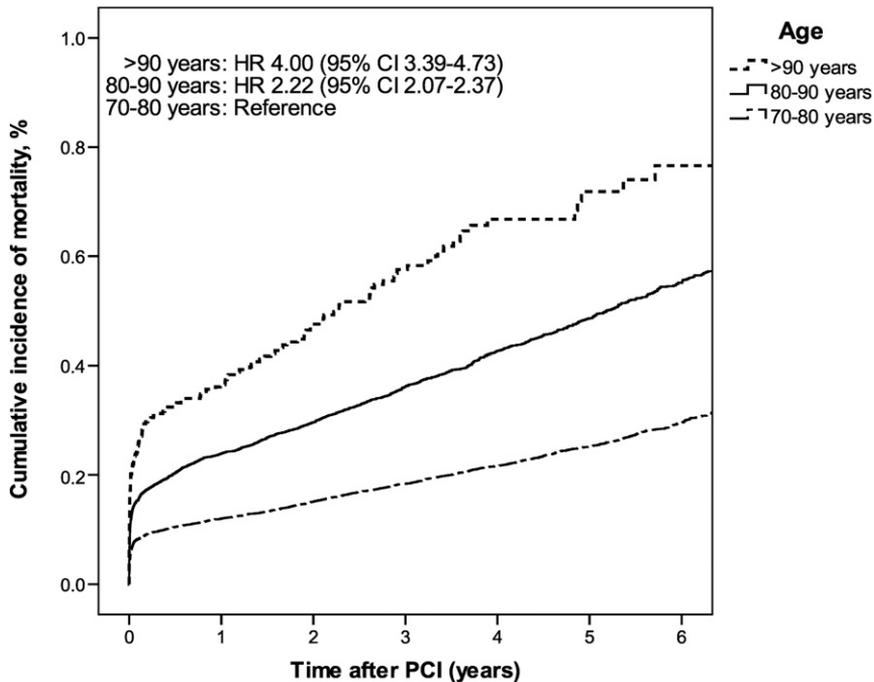


Figure 9. Mortality during long-term follow-up in three different age cohorts: 70-80 years, 80-90 years and >90 years.

The conclusions of Paper III is that the prognosis of patients older than 80 years treated with primary PCI for STEMI was relatively unchanged during the 10-year inclusion period, despite changes in patient characteristics and treatment. Advanced age increased the risk of adverse events and death (figure 9), but survivors of the early phase after PCI had a slightly improved prognosis compared with the general population.

These results cannot be generalized to all patients over 80 years of age with STEMI, as only patients who received PCI were included in the analysis. Other studies<sup>23,67,68</sup> have shown the rate of revascularization for the total octogenarian STEMI population to be approximately 20-30%. Hence, in Paper III one can assume a rather large exclusion rate. Assumably, frail patients or those with serious co-morbidities were more likely to be treated conservatively.

## EVALUATING BENEFIT TO THE ELDERLY POPULATION

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In general, treatment should only be provided when it is effective. Effective meaning that treatment can prolong life (prognostic indication) and/or decrease symptoms (symptom indication).

### Prognostic indication

Underrepresentation in clinical trials and probably fear of complications in older patients has led to a suspected underutilization of invasive treatment in the elderly compared to that in younger individuals. Two main reasons are for the underrepresentation of elderly patients in studies, firstly, elderly patients simply meeting upper age criteria predefined in trials and secondly, elderly having higher rate of co-morbidity - and therefore have a higher risk of being excluded due to predefined exclusion criteria being met. Among trials conducted in patients with ACS published in the period 1996 to 2000, more than half failed to include at least one patient >75 years of age.<sup>69</sup>

A substudy from a large randomized trial<sup>70</sup> showed that the oldest patients appeared to benefit the most from the invasive treatment approach in ACS. In 2007, the American Heart Association published a statement<sup>3</sup> in order to highlight the problem of possible undertreatment in the elderly.

The available data on efficacy of revascularization with CABG or PCI in the aged population with coronary artery disease mostly consist from subset analysis of randomized trials or non-randomized retrospective analysis, but during the past years two studies have been presented that are randomized dedicated trials to the elderly with ACS. These two studies have opposing results. The Italian elderly ACS study<sup>71</sup> and the recently presented, but unpublished, After eighty study.

In the *Italian elderly ACS study* a total of 313 ACS patients >75 years, excluding STEMI patients, were randomized to conservative therapy or early invasive therapy. This study was negative, i.e. there was no difference in the primary outcome (composite of death, myocardial infarction, disabling stroke, and repeat hospital stay for cardiovascular causes or severe bleeding) between the two groups. The crossover rate (from conservative to revascularization) turned out to be approximately 30%. But in a subgroup with elevated troponins, a benefit was seen with invasive strategy.

The slightly larger (n=458) *After eighty study* (ClinicalTrials.gov Identifier: NCT01255540) has been presented at the American College of Cardiology Scientific Session conference in 2015. Among elderly patients (>80 years) with NSTEMI-ACS (ACS excluding STEMI), invasive therapy was beneficial at reducing adverse cardiovascular events compared with conservative therapy. This was mainly due to a reduction in recurrent MI and urgent revascularization procedures. The primary outcome of death, MI, stroke, or urgent revascularization occurred in 41% of the invasive group versus 61% of the conservative group ( $p < 0.0001$ ). There were no statistical differences between the groups regarding death (25% vs. 27%, NS) or stroke (3% vs. 6%, NS).

The authors of this study have concluded: "Elderly are at high risk for adverse events after a NSTEMI-ACS, and invasive therapy remains the optimal treatment to reduce this risk."

Only through repeated research can certainties emerge. Interpreting and implementing these different study results in clinical practice can be challenging. In addition, the results of these trials are probably not generalizable to the total cohort of elderly because of the high rate of excluded patients.

Currently, the clinical guidelines for the management of the elderly with ACS are the same as for their younger counterparts<sup>72</sup> but with the condition that treatment should be individualized. These recommendations stress the importance of a balance between treatment risk and benefit in elderly patients.

## Symptom indication

The invasive treatment strategy may provide unclear benefit in reducing death (prognostic indication) in some cohorts, the more important indication for some patients would be to decrease symptoms due to myocardial ischemia and thus increase quality of life. Failure of the conservative strategy to be successful due to intolerable angina symptoms is a known problem worth mentioning, to some extent explaining the high crossover rate from conservative therapy to invasive therapy in randomized trials. In addition, cost-effective analysis for elderly with stable coronary artery disease has shown that early increased costs of revascularization in invasive patients were balanced after one year by increased medical charges and symptom-driven late revascularizations in medical patients. Therefore, the invasive strategy had improved clinical effectiveness (in stable coronary disease) at only marginally higher cost compared to medical management.<sup>73</sup>

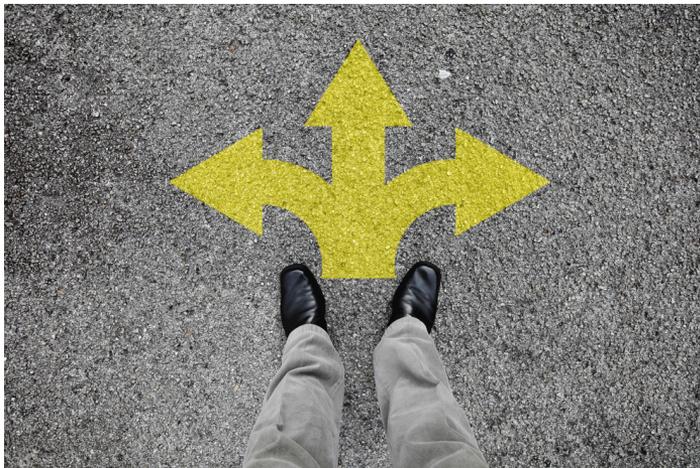
Among elderly individuals, the generally lower level of physical activity results in less myocardial oxygen demand and hence, one would expect less angina symptoms. In elderly patients with presumed high-risk for periprocedural PCI complications and unclear benefit, initiating conservative therapy with the possibility of shifting the treatment strategy based on the patients symptoms, would be a reasonable approach.

## SHARED DECISION MAKING

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*"Medicine is not only a science; it is also an art. It does not consist of compounding pills and plasters; it deals with the very processes of life, which must be understood before they may be guided."*

-Paracelsus



*Figure 10. A pair of feet standing on a tarmac road with yellow arrow print pointing in three different directions for the concept of making decision at the crossroad. Photo by Gwoeii.*

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Patients should be able to make choices in their care that best fit their individual circumstances. Health care providers should have the time and communication skills to elicit their patients' wishes, needs and concerns. Breakdowns in the patient-doctor relationship can occur when the patient feels that he/she has received too little information and the physician has rushed through the encounter. Communicating effectively in challenging situations like helping patients make complex choices in circumstances of medical uncertainty or breaking bad news should be regarded as a part of continuing professional development. Unfortunately, opportunities rarely exist for practicing physicians to develop new communication skills or to receive systematic feedback. Communication skills are a learned expertise; that allows clinicians to fulfill their clinical and moral responsibilities to patients. Physicians usually acknowledge acquiring new technical skills or information about different

treatments as a part of professional career involvement, but frequently fail to recognize communication skills as such. We must change our thinking about this fundamental obligation. The importance of incorporating the patient in a shared decision making process must be stressed, and if done effectively-success in terms of increased patient satisfaction and trust will be the outcome, even in patients with limited treatment options.

Treatment outcome is a strong determinant of patients' preferences. In one study, of seriously ill older patients, the burden of treatment, its outcomes, all influenced the treatment preferences.<sup>74</sup> Almost all study participants chose a low-burden therapy (short hospital time, less diagnostic testing and less invasive interventions) that would restore their current health. However, for a low-burden treatment with less chance for good functional or cognitive outcome, almost all of the participants stated that they would not wish to receive such a therapy.

Life expectancy and treatment outcomes play a dominant role in the final decision making process among elderly patients. The outcome of such discussions may be having comfort care as the treatment goal, instead of continuing with treatment with potential harm, and unknown benefit.

Previous research has indicated that many hospital admissions in the elderly can be avoided and may be inappropriate.<sup>75,76</sup> A series of complex reasons, including factors associated to the physician, the patient and the family, are usually given for this. Denial about prognosis can lead to predictable crises and potentially avoidable emergency visits. Underlying reasons for unnecessary admissions often being the failure to recognize approaching death at the appropriate time and thus to shift treatment towards maintaining comfort or palliative care. Knowing our patients' priorities, and acting to fulfill these, will lead to a better quality of life, or among those beyond cure - quality of death.

## **Too risky or simply too old?**

Unfortunately, in the absence of sound evidence, clinical decisions can be strongly influenced by the stereotypic and often negative perception of physicians who have previously treated elderly patients with complications. Some would argue this to be good clinical judgment based on "experience". But these stigmas can result in deleterious consequences for people in normal aging- with risk for discrimination based on chronological age. The perception of aging among health professionals has been found to be negative but physicians and nurses with experience and interest in geriatric care, more senior

in position, and those with elderly social contacts were found to have a more positive attitude towards the elderly.<sup>77-79</sup>

There is no simple solution to counter ageism among health professionals, but gerontology education and training has been shown to enhance positive attitudes toward elderly patients.<sup>80,81</sup>

In the ideal world, all health care providers will have the training and team support to manage the expanding elderly population with complex diseases and treatment.

## Upcoming studies

There are some studies of the elderly with ACS in the pipeline, trials designed to try to answer the question of benefit and risks with each treatment strategy (conservative or invasive), two trials are discussed below.

The *Revascularization or Medical Therapy in Elderly Patients With Acute Angina Syndromes (RINCAL)* (ClinicalTrials.gov Identifier: NCT02086019) is a randomized controlled trial in patients >80 years of age with NSTEMI, with both elevated Troponins and ECG with ischemic changes. The estimated number of study participants is 750 and they will be randomized to invasive or conservative therapy. The primary outcome measure is 1-year mortality and 1-year non-fatal myocardial infarction. The study was initiated by the Brighton and Sussex University Hospitals and started to recruit patients in May 2014 with estimated completion year 2019.

## The Octogenarians study (Paper IV)

Another upcoming study is described in Paper IV,<sup>82</sup> *the Octogenarians study* (ClinicalTrials.gov Identifier: NCT02126202). This study is a multicenter; investigator initiated randomized controlled trial of patients  $\geq 80$  years old with two parallel treatment arms, a medical group and an invasive group. Participating hospitals are: Sahlgrenska University Hospital in Gothenburg, Norra Älvsborg Regional Hospital in Trollhättan, Skåne University Hospital in Lund, and Skaraborg Hospital in Skövde. In total, 200 patients with non-ST-elevation myocardial infarction or unstable angina will be randomized to medical or invasive treatment strategy. Due to risk for unbalanced treatment arms regarding age, two different predefined strata (80-84 and  $\geq 85$  years of age) will be used for random assignment.

	STUDY PERIOD						
	Enrollment	allocation		Post-allocation			Close-out
Time point**		0	day 1	in-hospital	at discharge	day 30	1 year
<b>Enrollment:</b>							
Eligibility screen	X						
Informed consent	X						
History and ECG	X						
Allocation		X					
<b>Interventions:</b>							
Medical treatment*			X				
Invasive treatment strategy				X			
<b>Assessments:</b>							
Echocardiography and frailty score	X						
QoL and angina questionnaire	X						X
Adverse events				X	X	X	X
If symptoms, additional assessments**					X	X	X
<b>Outcome:</b>							
MACCE***						X	X <sup>§</sup>
Myocardial infarction							X
All-cause mortality							X
<b>Safety measure: bleeding</b>				X	X	X	X

\*Medical treatment will be given to all study participants regardless of treatment allocation, provided that there are no contraindications.

\*\*If symptoms of ischemia: ECG, CK-MB, and cardiac troponins. If symptoms of bleeding: hemoglobin and platelet count.

\*\*\*Combined endpoint: MACCE: major adverse cardiac or cerebral event.

§Primary endpoint of the study.

QoL: Quality of life, ECG: Electrocardiogram.

*Table 6. Schedule of enrollment, interventions, assessments, and outcome/safety measures for the Octogenarian study*

According to power calculations, with  $\alpha$  level  $<0.05$ , 80% power and expected major adverse cardiac or cerebrovascular event (MACCE) rate according to the TACTICS-TIMI 18 study<sup>70</sup> there will be required 82 individuals in each group. Due to possible dropout, a total of 200 patients will be included. The study started in 2009 and is still recruiting patients. The schedule of enrollment, interventions, assessments, and outcome/safety measures for the study are shown in table 6. The primary outcome measure is the combined endpoint MACCE within 1 year. Other outcome and safety measures are grade of angina, quality of life, frailty and bleeding.

This study seeks to determine the efficacy and safety of invasive and medical treatment strategies in the elderly with ACS. Our hypothesis is that invasive treatment of elderly patients with ACS will lead to better outcome in terms of survival and quality of life than medical therapy alone, with acceptable risk.

## HIGH RISK GROUPS

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### Cardiogenic shock

Acute coronary syndrome accounts for approximately 75% of those with cardiogenic shock (CS). The incidence of 6-8% within the ACS population has been relatively unchanged during the past years,<sup>35</sup> but is higher among the elderly as they turn out to have poor organ reserve and can have difficulties in tolerating stress. In Paper III, among elderly patients with STEMI treated with PCI the incidence of CS was 9,7% years 2001-2004 but decreased to 4,5% years 2009-2010.

The mortality is high, especially in elderly patients, 65-80%.<sup>83,84</sup> The most common cardiac etiology for CS is left ventricular failure, but other causes are papillary muscle rupture, severe mitral valve insufficiency, ventricular septal defect, and free wall rupture.

Because revascularization is the cornerstone of the treatment in patients with cardiogenic shock complicating ACS, emergency coronary angiography is indicated according to the guidelines.<sup>35</sup> But, there have been conflicting results regarding the benefit of early revascularization of elderly patients with CS. In the SHOCK study<sup>85</sup> subgroup analysis showed no benefit from early revascularization in patients >75years, but this result was only based on 56 elderly patients, with unbalanced treatment groups in regards to congestive heart failure, thus there was risk for underpowered and biased study results. Observational studies have shown that the early revascularization is associated with better outcome compared to conservative therapy, but observational studies carry risk for selection bias.<sup>86,87</sup>

There are no existing registered (Clinical trials.gov) dedicated trials of cardiogenic shock in the elderly.

## Cardiac arrest (Paper V)

Another important group with very high mortality among ACS patients are patients with cardiac arrest. Approximately 70% of those with out-of-hospital cardiac arrest have coronary artery disease with acute coronary occlusion observed in 50%.<sup>88</sup>

In resuscitated cardiac arrest patients, neurological recovery is the most critical issue. In case of cardiac arrest, qualitative reports<sup>10,89</sup> have shown that elderly people are mainly concerned about loss of autonomy, and about whether they would be able to return to their valued life activities. This is why, in studies of elderly patients, one should not only concentrate on survival rates but also on inclusion of other outcome measures—such as neurological outcome, which is one factor that really matters for patients and their families.

Earlier studies on hospitalized elderly victims of cardiac arrest have shown poor prognosis.<sup>90-92</sup> These data were unfortunately extrapolated to all elderly patients by medical professionals and also by the lay press. They included sudden death victims in the community, leading to the incorrect assumption that efforts to resuscitate elderly people were futile and should be withheld. More recent studies have shown that the prognosis for the elderly with OHCA is improving as time goes by, with higher survival rates.<sup>93-95</sup>

The aim Paper V was to evaluate an elderly population of OHCA victims, to analyze temporal trends, and to determine whether there were age-related differences in outcome (30-day survival and cerebral performance category score).

Elderly OHCA patients ( $\geq 70$  years), who were registered in the Swedish Cardiopulmonary Resuscitation Register, between 1990 and 2013 were included and divided into three age categories (70–79, 80–89, and  $\geq 90$  years). Their baseline characteristics are shown in table 7 and the factors associated with 30-day survival are shown in table 8.

	<b>Age (years)</b>			p
	70-79 (n=19422)	80-89 (n=14710)	≥ 90 (n=2473)	
<b>Age (median; years)</b>	75	83	92	
<b>Gender (%) (3, 2, 2)*</b>				
Women	30	38	56	<0.0001
<b>Etiology (%) (6, 7, 7) *</b>				
Cardiac	77	78	71	0.20
<b>Place (%) (0.8, 0.7, 0.7) *</b>				
At home	69	68	70	0.78
<b>Witnessed (%) (6, 6, 5) *</b>				<0.0001
By crew	14	18	22	
By a bystander	57	55	54	
Non witnessed	29	27	24	
<b>Initial arrhythmia (%) (9, 10, 10)*</b>				
Ventricular fibrillation	31	25	16	<0.0001
<b>Bystander CPR (%) (2, 1, 1)*</b>				
Yes	45	42	45	<0.0001
<b>30-day survival (%) (0.4, 0.5, 0.6)*</b>				
All patients	6.6	4.4	2.3	<0.0001
Witnessed, cardiac etiology found in VF†	19.8	14.8	11.0	<0.0001
<b>Delay times (min) (2, 0.3, 1)*</b>				
Call for – Arrival of EMS†† (13,14,17)*	7 (9.5)**	7 (9.1)	7 (9.2)	<0.0001
Collapse – Call for EMS (21,23,27)*	3 (5.0)	3 (4.8)	3 (4.5)	0.0001
Collapse – Start of CPR# (18,19,20)*	9 (10.7)	8 (10.1)	7.5 (9.1)	<0.0001

\* Proportion of patients with missing information

\*\* Median and mean within brackets

† VF = Ventricular fibrillation †† EMS = Emergency Medical Service

# CPR = Cardiopulmonary resuscitation

*Table 7. Baseline characteristics of elderly OHCA patients*

## Factors associated with 30-day survival

	OR	Adjusted OR*
<b>Age (years; continuous)</b>	0.95 (0.94 – 0.96)	0.94 (0.93 – 0.96)
<b>SEX</b>		
Women/ men	0.75 (0.68 – 0.83)	---
<b>PLACE</b>		
At home (yes/no)	0.28 (0.25 – 0.30)	0.40 (0.34 – 0.46)
<b>Witnessed</b>		
Yes/no	5.05 (4.26 – 6.03)	2.20 (1.79 – 2.72)
<b>Bystander CPR*</b>		
Yes/no	2.87 (2.54 – 3.25)	1.84 (1.58 – 2.14)
<b>First recorded rhythm</b>		
Ventricular fibrillation (yes/no)	10.04 (8.97 – 11.25)	5.86 (5.00 – 6.88)
<b>Delay Call for – arrival of EMS*</b>		
Continuous, logaritmised	0.38 (0.34 – 0.42)	0.38 (0.33 – 0.43)

\* Crew witnessed cases were excluded

Adjusted OR for age, gender, cardiac etiology, place, witnessed status, bystander CPR, initial rhythm and EMS response time.

*Table 8. Factors associated with 30-day survival*

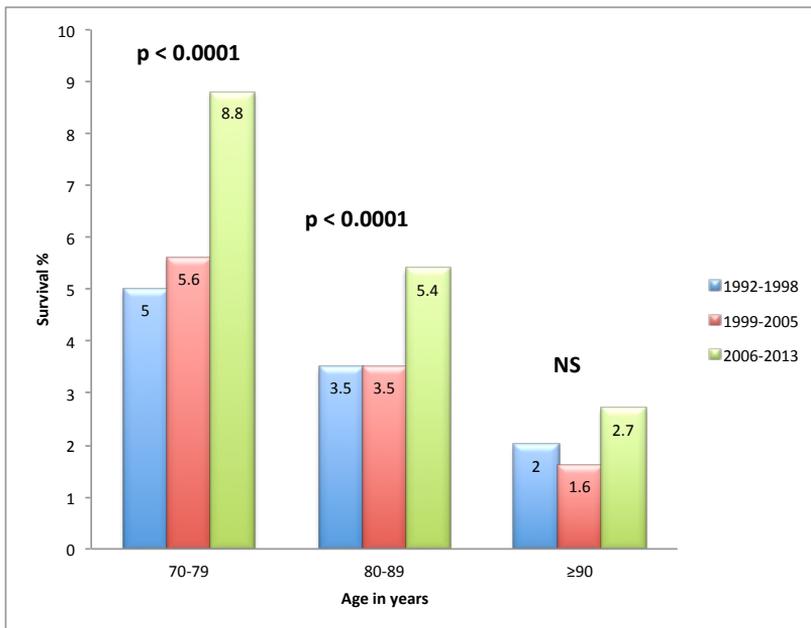


Figure 11. Changes in survival in relation to age from 1992 to 2013

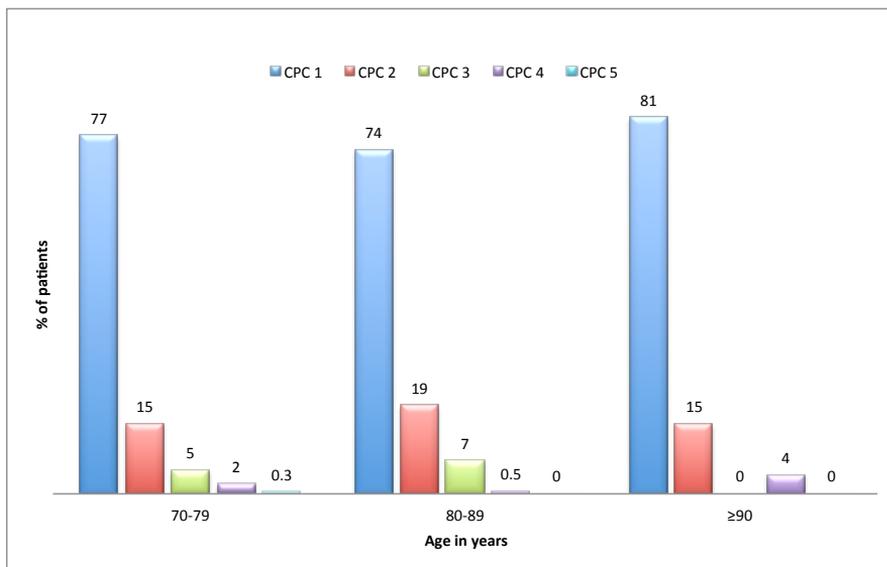


Figure 12. Estimated cerebral function according to CPC score among survivors of OHCA in relation to age. Missing rate and the number of evaluated cases were: 70-79 years 28%, n=339, 80-89 years 25%, n=192 and ≥90 years 27%, n=27

Altogether, 36,605 cases were included in the study. The 30-day survival was 6.6% in patients aged 70–79 years, 4.4% in patients aged 80–89 years, and 2.3% in those over 90 years. The results depending on different time periods are shown in figure 11. In 30-day survivors, the distribution according to the cerebral performance categories (CPC) score at discharge from hospital was similar in the three age groups (figure 12). The following conclusions were reached in Paper V, advanced age turned out to be an independent predictor of mortality in OHCA patients over 70 years of age. However, even in patients above 90 years of age, defined subsets with a survival rate of more than 10% existed. In survivors, the neurological outcome remained similar regardless of age.

Regarding CPR for cardiac arrest, therapy must be applied promptly and without hesitation, in order to have any chance of success. It would be unfair to put a difficult ethical decision burden on rescuers regarding whether or not to start CPR in the case of sick or frail elderly patients. Even though discussions regarding the end of life are challenging and emotionally charged, clinicians should take time to discuss them with patients. The preferences of patients and their proxies in combination with information about expected outcome should form the basis of end-of-life decisions. DNR (Do-not-resuscitate) orders should not be regarded as markers of death, but rather the result of informed discussion about end-of-life care.

In Paper V, the survival rates for the elderly with OHCA were determined according to age and, the cardiac arrest characteristics that predicted survival. We did not have information about pre-arrest diseases in our analysis. In order to guide DNR decisions, other factors that poorly affect outcome—such as pre-arrest co-morbidity—should be taken into consideration. This has proven to be a difficult task. A meta-analysis failed to do so, mainly due to the heterogeneity of the studies included.<sup>96</sup> A step-by-step approach as previously described, taking into consideration life expectancy, risk, benefit and patient or their proxies' preferences would also be possible to apply during end-of-life decision-making.

# CHALLENGES IN GERIATRIC RESEARCH

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*Figure 13. There exist different challenges in research of the elderly population. Illustration by the author*

## **Patient selection and risk for bias**

The effect of a treatment strategy in heterogenic patient groups is very difficult to evaluate. One cannot eliminate the possibility of the difference in outcome being simply due to differences in baseline characteristics within the study population. When examining treatment effects, comparing interventions head to head within subpopulations, such as the elderly, heterogeneity among patients with multiple chronic conditions complicates research. Heterogeneity of study participants would be especially problematic in observational studies. This is called different names such as: selection bias, bias by indication, confounding by indication or poor internal validity. Even though adjustments can be made for known confounding factors -unknown confounding factors are more difficult to tackle, one important, but not always accounted for is frailty.

Frailty could turn out to be useful for risk stratification of the elderly population, thus being a valuable tool to compensate for the heterogeneity in the group of elderly, and in doing so, correct for potential confounding or bias.

Unfortunately, information about frailty is lacking in many databases, analysis and published studies, but has on the other hand been gaining more acknowledgements in the recent years.

But this complexity of elderly patients in studies argues for adapting research designs to the important study questions. This fastest growing segment of complex patients within health care should not be ignored.

## **Patient recruitment**

Even though the population of elderly patients is large and constantly growing, randomized controlled clinical trials are very difficult to perform in the elderly population, although this research design is considered the most valuable.

One of the common problems encountered by research teams are geriatric patient recruitment and retention issues. Major barriers to recruitment of older adults in research relate to their co-morbidity, limited life expectancy, frequent hospitalizations, polypharmacy, social barriers, and potentially impaired capacity to provide informed consent. Researchers, often appropriately, may be concerned about the safety or risk of study procedures. Elderly individuals are likelier to be excluded from clinical trials explaining the lower average age in study participants compared to real life patients. Some reasons that may justify this approach are: avoiding attrition (high mortality, risk for general health decompensation, cognitive impairment, impaired mobility), minimizing confounding due to competing risks, avoiding longer study visits due to hearing or sight impairments. In addition, many randomized studies have upper age limits or long lists of exclusion criteria making it impossible for elderly patients to enter. But if the aim of the study is to generalize results to older adults with complex health problems, the inclusion and exclusion criteria must be designed to allow their participation.

Because elderly hospitalized patients may have complex situations, family members or friends are often involved as a substitute decision-maker during enrollment in studies. Proxies may understandably be protective and skeptical about any research project that might add burden to an already difficult situation.

The problem, in general, with dedicated randomized studies in the elderly has been recruiting issues, slow and difficult enrollment. Unfortunately, this has resulted in study centers simply giving up and some studies terminating early without results.

Some of these challenges can be overcome with some practical approaches: eliminating upper age limits in studies, minimizing exclusion criteria, timely screening, keeping interest and cooperation of study sites, ensuring a favorable risk: benefit ratio of study participants, choosing an adequate but not too large sample size, and addressing problems of study participants who consider to dropout (such as need for assistance or travel cost).

## **Challenging data analysis and interpretation of results**

Most clinical research projects in medicine focus on the disease-oriented approach, which does not take account of the complexity of the typical elderly patient. In most of the randomized clinical trials, sample size, duration, and co-prescribed drug therapies are often tailored to the target disease but issues in the elderly such as quality of life; short life expectancy, polypharmacy, and multimorbidity are not accounted for.

Randomization and the intention-to-treat analysis of data, if successful, would divide confounding factors equally in both groups being studied thus eliminating most bias. But, if treatment groups are unbalanced by chance, study participants are misclassified (for example without the studied disease) or if there is large crossover to the other parallel treatment group, then the results can be very difficult or impossible to interpret.

Non-adherence to study protocols such as in phase 3 drug trials, due to limited tolerability of treatment, is a problem commonly encountered among the elderly. This would lead to loss of study participants that might be difficult to account for.

Some of the larger randomized trials also have results from post-hoc subgroup analysis of the elderly within the study population. Interpretations of results from secondary and subgroup analyses are useful for hypothesis generation, but are usually underpowered, too often misleading, and may be based on chance findings alone.

Crossover to the other treatment arm, such as in studies of invasive or conservative treatment for ACS, is another known potential problem. Observational data in elderly patients support the power of clinical judgment compared with unselective use of invasive treatment. The reality may be that the randomization cannot account for the importance of clinical judgment in achieving best outcomes in the complex elderly.

## AGE IS OPPORTUNITY

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*"Age is opportunity no less,  
Than youth itself, though in another dress  
And as the evening twilight fades away,  
The sky is filled with stars, invisible by day."  
-Henry Longfellow*



*Figure 14. A beautiful green and red aurora dancing over the Jökulsárlón lagoon, Iceland.  
Photo by Krissanapong Wongsawarnng. <[www.shutterstock.com](http://www.shutterstock.com)>*

Despite risk associated with treatment in complex elderly patients, these individuals have the greatest potential for clinical benefit due to high risk for mortality and morbidity - compared to younger, healthier subjects.

We should not assume that age is a non-modifiable risk for worse outcomes. We need to understand the biological and social factors that result in poor outcomes for our elderly and develop systems of care capable of addressing these issues. Our perception of what constitutes “old” is continually changing. This has been exemplified by the progress we have achieved in providing cardiovascular care to this growing and constantly older set of patients.

In cardiology, our services could be provided with reasonable risks and with potentially much gain to the elderly. Advancements in the delivery of care have permitted us to apply valuable, life-preserving techniques to the geriatric population. Future investigations should continue to challenge age-related discrimination against treating patients, demanding rigorous investigation into the factors that impair quality and quantity of life.

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Professor *Johan Herlitz*, my co-supervisor, with a highly successful research career, whom has guided so many physicians and nurses to a PhD degree. Now I understand how you do it. Thank you for all kindness, warmth and supportive comments. Some e-mailed positive comments I read more than twenty times. It was easy to find genuine joy in working with research.

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## SWEDISH SUMMARY

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Den äldre patientgruppen är snabbt växande inom sjukvården. Hur denna grupp skall behandlas är ofta ett kliniskt dilemma då denna patientgrupp är dåligt studerad och såväl kvaliteten som kvantiteten av underliggande vetenskapliga bevis är begränsad.

I denna avhandling presenteras fem olika studier som undersöker olika aspekter av hjärtsjukvård avseende patienter av hög ålder.

I delarbete I beskrivs skillnader mellan äldre och yngre patienter med symtom (framförallt bröstsmärta) tydande på akut kranskärlssjukdom. Studien visar att trots att äldre patienter (> 80 år) oftare får en slutlig diagnos av akut koronart syndrom (17 % vs 8 %), blir de mer sällan undersökta med kranskärlsröntgen (44 % vs 89 %,  $p < 0,0001$ ) och ekokardiografi än de yngre patienterna. De äldre patienterna får dessutom i lägre utsträckning medicinsk behandling med blodförtunnande och blodfettsänkande läkemedel. Däremot påvisas ingen fördröjning till sjukhusinläggning jämfört med yngre. Att äldre patienter i lägre grad får evidensbaserad behandling kan sannolikt förklaras att man värderar att risken ofta överväger nyttan för denna patientgrupp, även om detta inte är verifierat i studier.

I delarbete II studeras äldre (>75år) patienter med hjärtinfarkt. De som valts ut för invasiv strategi (kranskärlsröntgen eventuellt följt av intervention) jämförs med den grupp som behandlats konservativt (medicinsk behandling). Det var en högre andel patienter med hjärtsvikt, både i anamnesen och vid ankomsten, i den konservativa gruppen jämfört med den invasiva gruppen. Det var lägre sjukhusdödlighet i den invasiva gruppen (9 % vs 20 %,  $p < 0,0003$ ). Man kan inte dra slutsatsen att invasiv strategi generellt är bättre då det var stora skillnader i bakgrundsvariabler mellan grupperna. En randomiserad studie behövs för att man skall kunna dra en slutsats vilken strategi som är bäst för de äldre patienterna. Ett protokoll för en sådan pågående studie diskuteras i delarbete IV.

I delarbete III, studeras äldre (> 80 år) patienter med STEMI som behandlats med PCI under en 10-års studieperiod. Medelålder och co-morbiditet ökade successivt under åren men trots detta var utgången oförändrad. Dessutom var komplikationsrisken i form av blödning, hjärtinfarkt, hjärtsvikt och stroke oförändrad under studieperioden.

I delarbete V, stratifierades patienter över 70 år som drabbats av hjärtstopp utanför sjukhus, i tre olika åldersgrupper: 70-79, 80-89 och  $\geq 90$  år. Med stigande ålder minskade chansen för 30-dagars överlevnad. Däremot var ålder var inte en avgörande faktor för dåligt neurologisk resultat efter hjärtstopp. Samma faktorer (t.ex. bevittnat hjärtstopp och defibrillerbar första rytm) som visat sig vara associerad med bättre prognos i yngre kohorter, var även gynnsamma för de äldre grupperna.

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