Prognostic Prediction and Treatment of Cardiac Diseases in the Elderly

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ABSTRACT

Aim The overall aim of this thesis was to study the prognostic prediction and its association with treatment strategies in the elderly patients presenting with acute coronary syndrome (ACS) and left ventricular systolic heart failure (HF).

Methods: A total 353 octogenarians with ACS, 182 patients treated with percutaneous coronary intervention (PCI) and 171 treated without PCI, were consecutively included and retrospectively studied for prognostic predictors of long-term all-cause mortality. Moreover, 140 patients ≥70 years were prospectively studied for prognostic predictors for major adverse cardiovascular events (MACE) in patients with ACS referred for coronary angiography. In case of heart failure, 182 octogenarians with left ventricular systolic HF were consecutively included and retrospectively studied for impact of different dose levels of guideline recommended neurohormonal blockades, beta-blockers (BBs) and angiotensin converting enzyme inhibitors (ACEIs)/ angiotensin receptor blockers (ARBs), on long-term mortality.

Results: In ACS-cohorts: Cox-regression analysis of octogenarian patients with ACS treated with PCI showed following factors as independent predictors of 5-year all-cause mortality: atrial fibrillation, mitral regurgitation (MR), tricuspid regurgitation (TR), estimated glomerular filtration rate (eGFR) ≤30 ml/min and dependency in activities of daily living. Furthermore, in the overall cohort of octogenarians with ACS, both PCI-treated and non-PCI-treated, PCI was associated with lower 5-year all-cause mortality. At least mild grade MR was associated with higher 5-year all-cause mortality and PCI was associated with improved prognosis even in patients with MR compared with patients with MR treated without PCI. Finally, in a prospective cohort of ACS patients ≥70 years referred for coronary angiography, during an average follow-up of 39±11 months, 41% of the patients had one or more MACE and 24% developed post-ACS heart failure. The study cohort had as good quality of life as an age-matched reference population from Swedish normative SF-36 database in both physical health subscales (physical functioning, role physical, bodily pain and general health) and mental health subscales (Vitality, social functioning, role emotional and mental health). The all-cause mortality rate was 10%.

In heart failure cohort: In octogenarians with left ventricular systolic HF treated with highest tolerable doses of neurohormonal blockades, target dose of ACEIs/ARBs were associated with improved 5-year survival rate, despite that this was achievable in only about half of the patients. No significant differences in survival were found between the different doses of BBs; however the heart rate was comparable between the different dose groups.

Conclusion: In elderly patients with ACS**,** PCI was associated with improved long-term survival despite high age. Several prognostic predictors including MR were identified. Moreover, in the modern era of reperfusion therapy, despite improved quality of life and low mortality rate MACE occurred frequently in elderly patients after ACS indicating further need of tailored care. In octogenarian patients with systolic HF, target dose of ACEIs/ ARBs was associated with reduced five-year all-cause mortality, but this dose survival relationship did not find in case of the beta-blockers.

Keywords: acute coronary syndrome, heart failure, percutaneous coronary intervention, elderly, octogenarians, beta-blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, quality of life, major adverse cardiovascular events.

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LIST OF PAPERS

This thesis is based on the following papers.

I Barywani SB, Lindh M, Ekelund J, Petzold M, Albertsson P, Schaufelberger M, Lund LH, Fu M. Predictors of long-term outcome of percutaneous coronary intervention in octogenarians with acute coronary syndrome.
IJC Heart and Vessels. 2014; 4: 138-144.

II Barywani SB, Li S, Lindh M, Ekelund J, Petzold M, Albertsson P, Lund LH, Fu M. Acute coronary syndrome in octogenarians: association between percutaneous coronary intervention and long-term mortality.
Clinical Interventions in Aging. 2015; 10:1547-1553.

III Li S, Barywani SB, Fu M. Prognostic significance of mitral regurgitation in long-term all-cause mortality in patients aged ≥80 years with acute coronary syndrome.
Int J Cardiol. 2014; 176: 340-345.

IV Barywani SB, Ergatoudes C, Schaufelberger M, Petzold M, Fu M. Does the target dose of neurohormonal blockade matter for outcome in Systolic heart failure in octogenarians?
Int J Cardiol. 2015; 187: 666-672.

V Sigurjonsdottir R, Barywani SB, Albertsson P, Fu M. Acute coronary syndrome aged ≥70 years in the modern era of reperfusion therapy – major adverse cardiovascular events and quality of life after 2 years of follow-up.
Submitted

CONTENTS

ABBREVIATIONS

ACS	Acute coronary syndrome
PCI	Percutaneous coronary intervention
MI	Myocardial infarction
STEMI	ST-segment elevation myocardial infarction
NSTEMI	Non-ST-segment elevation myocardial infarction
HF	Heart Failure
HFrEF	Heart failure with reduced ejection fraction
HFpEF	Heart failure with preserved ejection fraction
eGFR	Estimated glomerular filtration rate.
MR	Mitral regurgitation.
ACEIs	Angiotensin converting enzyme inhibitors
ARBs	Angiotensin receptor blockers
BBs	Beta-blockers
MACE	Major adverse cardiovascular events
PS	Propensity score
ESC	European Society of Cardiology
S-HFR	Swedish Heart Failure Registry

INTRODUCTION

Definition of the elderly

In developed world it is generally accepted to use the age of 65 years as a definition of 'elderly' or older person. This has however not been adopted in developing countries where their citizens receive pension benefits earlier, usually at 60 years old. The definition is therefore more arbitrary. World Health Organization (WHO) has accepted 60+ years as a cutoff to refer to the older population.

In different studies in the elderly different age limits were used, mostly ≥70 years[1], while patients older than 85 years were often classified as 'very elderly'[2].

An aged population worldwide

The elderly are a growing group in western world and other developed countries[3]. According to data from the United Nations Department of Economic and Social Affairs approximately 8% of the world's population were 60 years and older in 1950. This number had increased to 10 percent by 2000; it is expected to reach 21 percent by 2050. The leading causes of death in developed countries are still cardiovascular diseases[4]. Moreover, according to data from the Swedish Central Statistical Bureau people ≥65 years constituted 20% (n, 1 912 884) of Swedish population (2014) and the population ≥80 years was 499 408 persons constituting 5% of the Swedish population.

Ageing and cardiovascular system

There are several specific changes in cardiac structure and function associated with ageing like; myocyte loss with reactive cellular hypertrophy and alterations in the function of myocytes including impaired calcium metabolism and regulation, which reflects an alteration of processes of contraction and relaxation[5,6]. In addition, contractile proteins change with age and adenosine triphosphate (ATP) utilization is less efficient in the ageing heart[6]. Another potential mechanism associated with the higher risk of development of heart failure (HF) in advancing age is the shortening of telomeres, which has been suggested as a marker of biological and cellular ageing and associated with development of HF with a subsequent detrimental increase in myocardial collagen content and development of fibrosis[7]. These abnormalities may provide the substrate for worsening cardiac function in the setting of exacerbating conditions[6].

Moreover, age-associated changes affect the entire vascular system, causing arterial vascular wall fibrosis, thickening and stiffening with endothelial damage and advanced atherosclerosis[8]. These mechanisms may culminate not only in the development of clinically evident heart failure with preserved ejection fraction (HFpEF), but also in the development of arterial hypertension, atrial fibrillation, coronary artery disease and cerebrovascular diseases[9].

Acute coronary syndrome in the elderly

Definition

According to European Society of Cardiology (ESC) guidelines 2015, acute coronary syndrome (ACS) consists of ST elevation ACS (ST-ACS) and Non-ST-segment elevation ACS (NSTE-ACS). ST-elevation ACS is defined as persisted ST-segment elevation >20 minutes combined with symptoms of acute myocardial ischemia. This generally reflects an acute total coronary occlusion and most patients develop an ST-elevation myocardial infarction (STEMI). NSTE-ACS is defined as no persistent ST-segment elevation, but either other ischemic ECG changes or no ECG changes, combined with symptoms of acute myocardial ischemia. The pathological correlate at the myocardial level is either cardiomyocyte necrosis (NSTEMI) or, less frequently, myocardial ischemia without cell loss (unstable angina)[10,11].

According to ESC guidelines 2015 acute myocardial infarction (MI) is defined as cardiomyocyte necrosis in a clinical setting consistent with acute myocardial ischemia[11,12].

A combination of criteria is required to meet the diagnosis of acute MI, the detection of an increase and/or decrease of a myocardial necrosis biomarker, with at least one value above the 99th percentile of the upper reference limit and at least one of the following:

- Symptoms of ischaemia.
- New or presumed new significant ST-T wave changes or left bundle branch block on 12-lead ECG.
- Development of pathological Q waves on ECG.
- Imaging evidence of new or presumed new loss of viable myocardium or regional wall motion abnormality.
- Intracoronary thrombus detected on angiography or autopsy.

Pathophysiology

Coronary artery atherosclerosis with consequent plaque formation is the pathology underlying the coronary artery disease. Plaque growth is dependent on the burden of atherogenic risk factors. A growing plaque under certain circumstances may become unstable (vulnerable); a plaque with thin fibrous cap and a lipid rich core infiltrated with inflammatory cells and sometimes with intra plaque hemorrhage. Vulnerable plaque is the direct pathology causing acute coronary syndrome via plaque rupture with a subsequent intra luminal thrombosis as the final common pathway leading to coronary instability[13]. Moreover, with aging coronary arteries become more tortuous with more medial calcification and further impaired endothelial dysfunction. Definitely with ageing the degree of atherosclerosis continues to increase and it becomes more extensive with high prevalence of multivessel coronary disease[14].

Characteristics

Compared with younger patients, older patients (≥65 years) have more often NSTEMI, but less STEMI and unstable angina (UA) with higher proportion of female[15-24]. The available data demonstrates an increase of proportion of unstable angina (UA) with age showing a peak in the ages 65-74 yeras and thereafter declining[15,16,18,19]. Elderly ACS-patients had higher prevalence of all conventional risk factors except cigarette smoking which was more prevalent in the younger groups[16]. Elderly patients were more likely to have comorbidities such as diabetes mellitus, renal insufficiency, cerebrovascular disease, and heart failure. Limited functional capacity and dementia are also more common[16]. Older patients are less likely to present with chest pain, but more likely to present with breathlessness or collapse with cardiogenic chock. Silent ischemia is more common in the elderly, especially in very old patients [17].

According to the annual report of SWEDEHEART (2014), characteristics of ACS patients have markedly changed during the last decades; the average age of MI patients increased in the 1990s but has been stable since 2000; between 75–76 years for women and 69–70 years for men.

Prevalence and incidence

According to data from Global Registry of Acute Coronary Events (GRACE, n=24165), elderly patients constitute 53% of all patients with ACS; 28% in 65-74 years, 20% in 75-84 years and 6% in patients ≥85 years. Concerning type of ACS, 31%, 29% and 31% of patients had STEMI in age groups 65-74 years, 75-84 years and ≥85 years, respectively. In case of NSTEMI, 30%, 36% and 41% in age groups 65-74 years, 75-84 years and ≥85 years, respectively[15]. According to data from the annual report of SWEDEHART 2014, 44 089 care episodes were registered, 61% of all hospitalizations were due to ACS. Acute MI was present in 42% and unstable angina in 7%. Data from Swedish National Board of Health and Welfare 2013 showed that the incidence rate of acute MI/ 100000 residents in younger age groups 50-54, 54-59 and 60-64 were 179, 293 and 419 respectively. While the incidence rate was much higher in the older age groups 571, 853, 1219, 1759 and 3126 in age groups 65-69, 70-74, 75-79, 80-84 and 85+, respectively.

Guideline recommended management

Management of ACS is divided into pharmacological and reperfusion therapy (PCI or CABG). The indication for an invasive approach, the timing for myocardial revascularization and the selection of the revascularization modality depend on numerous factors, including clinical presentation, comorbidities, risk stratification, presence of high-risk features specific for a revascularization modality, frailty, cognitive status, estimated life expectancy and functional and anatomic severity as well as pattern of coronary artery disease (CAD)[10,11]. Immediate reperfusion is recommended for all ST-ACS patients (class 1, evidence A). In NSTE-ACS patients, the reperfusion strategies are quite different. It depends on the risk stratification.Very high risk patients with ongoing ischemia and signs of hemodynamic instability or life threatening arrhyth-

mias should be managed according to immediate invasive strategy (<2 hours). High risk patients (myocardial infarction, dynamic ST-segment or T-wave changes or Grace Score ≥140) should be managed according to early invasive strategy (<24 hours) and intermediate risk patients (Grace score 109-140, renal insufficiency, left ventricular ejection fraction <40%) should be managed according to early invasive strategy (<72 hours)[25-28]. Pharmacological therapies with class 1 recommendation are dual platelet inhibitors, beta-blockers and anticoagulant (Fundaparinox) in the acute phase[10,29-33]. Secondary prevention of CV events, including optimal medical therapy, risk factor modification and lifestyle changes such as diet, exercise and smoking cessation, is very essential because after an ACS episode patients remain at high risk for recurrent ischemic events[34-36].

Secondary prevention has been shown to have a major impact on long-term outcome[35-37]. Secondary pharmacological therapy consists of high intensity Statins[38], beta-blockers, ACEIs or ARBs[39,40], and aldosterone receptor antagonists[41,42].

However, elderly patients should be treated with caution[11]. Antithrombotic treatment should be tailored according to body weight and renal function. Adjusted dosing regimens of beta-blockers, ACE inhibitors, ARBs and statins should be considered to prevent side effects. Elderly patients should be considered for an invasive strategy and, if appropriate, revascularization after careful evaluation of potential risks and benefits, estimated life expectancy, comorbidities, quality of life, frailty (class IIa recommendation)[11,43,44].

Evidence level

ESC and other international guidelines are based on clinical trials from patient cohorts with mean age generally <70 years, Table 1. This means that elderly patients are in general underrepresented in the major randomized clinical trials in this important field and the use of the guidelines in this age group is an extrapolation of the results of these studies. Moreover, patients ≥ 80 years are often excluded from the clinical trials, not only due to the higher age but also due to the high prevalence of comorbidities. It is therefore very essential to study different medical and invasive therapies specifically in this patient group to obtain evidence needed to ensure safety in the management of this patient population.

Table 1. Major randomized clinical trials in the management of ACS

Study and comparators	No. of patients	Mean age (years)
RITA-3, PCI vs conservative treatment in ACS, 2002	1810	62
ICTUS, early PCI vs selective PCI in ACS, 2004	1200	61
FRISC-II, PCI vs conservative treatment in NSTEMI, 2006	2457	64
PLATO, Ticagrelor vs Clopidogrel in ACS, 2009	18624	Median 62, 15% ≥75
IMPROVE-IT, Simvastatin 40 mg vs Simvastatin 40 mg + Ezetimibe 10 mg, 2015	18144	63

Prognosis

Despite the advances in the management of ACS, elderly patients with ACS still have high mortality rate and high rates of major adverse cardiovascular events, probably as a consequence of the higher prevalence of multivessel coronary artery disease and depressed left ventricular function[14]. The complication rates of PCI, anticoagulation and antiplatelet therapies exceed that observed in younger patients. Despite old age is a well-known powerful predictor of mortality in patients with acute MI, elderly patients have been considerably less often treated by cardiologists, less extensively investigated, and, when presenting with ST-elevation ACS, less likely to be treated with reperfusion[14]. However, elderly ACS patients are also more likely to benefit from appropriate therapies[16]. For instance, data from the Myocardial Ischemia National Audit Project (MINAP) showed reductions in in-hospital mortality in those over 85 years from 2003 to 2010 (STEMI: 30–19%, and NSTEMI: 31–20%)[45]. Short term (30 days) data from the last mentioned registry showed sustained improvement in mortality rate also in those over 80 years with NSTEMI (18.9–15.0% from 2004 to 2009)[45].

According to data from the Swedish National Board of Health and Welfare 2013, 1-year mortality after acute MI was 24%, 28%, 34%, 43% and 60% in age groups 65-69, 70-74, 75-79, 80-84 and 85+ respectively. There were no substantial differences between males and females. Data from the last mentioned institute have shown a dramatic decrease in both the incidence of, and mortality from, acute MI in the past two decades. Over this period, the associated 30-day mortality fell from 44% to 28% for all patients and from 27% to 12% for hospitalized patients.

Prognostic prediction

According to ESC Guidelines for the management of ACS (2015), short term risk assessment by means of scores is superior to the clinical assessment alone. The GRACE risk score provides the most accurate stratification of risk both on admission and at discharge[10,11,46,47]. The association between age and mortality was weakened significantly when corrected for other biological factors, such as comorbidity, cognition, social and functional status, which suggests that other factors, distinct from age, have impact on prognosis[48]. Traditionally, the prognostic prediction in the elderly is based on age and co-morbid conditions. Many scores based on age and grade of comorbidities have been developed to identify patients with high risk for adverse outcome, such as Charlson score that was based on 17 comorbid conditions[49]. More recently developed scores are based on functional capacity. For instance frailty assessment has emerged as a measure of biological age and it may help to predict adverse events in elderly population. Frailty has been shown to predict postoperative complications and mortality in elderly patients[50-54].

A recently published study demonstrated that the Canadian Study of Health and Aging Clinical Frailty Scale can help to predict adverse outcome after PCI, including mortality and length of stay in hospital[55]. However, prognostic prediction regarding long-term survival is still inadequately studied in elderly patients with ACS.

Heart failure in the elderly

Definition

According to the ESC guideline, heart failure can be defined as an abnormality of cardiac structure or function leading to failure of the heart to deliver oxygen at a rate coincident with the requirements of the metabolizing tissues[56]. For clinical purposes, diagnostic criteria of HF are typical symptoms (e.g. breathlessness, ankle swelling, and fatigue) and signs (e.g. elevated jugular venous pressure, pulmonary crackles, and displaced apex beat) resulting from an abnormality of cardiac structure or function.

Pathophysiology

Elderly HF patients demonstrate distinctive pathophysiological features and complex co-morbidity profiles. The etiology of heart failure in the elderly is more likely to be multifactorial. In the elderly, hypertension and coronary artery disease account for more than 40% of the cases[57.] Importantly, hypertension results in predominantly HF with preserved systolic function (HFpEF), whereas myocardial infarction results in predominantly HF with reduced systolic ejection fraction (HFrEF)[58]. Longer exposure to risk factors and age-related changes may also make the elderly more prone to develop HF[58].

Characteristics

The majority of patients with heart failure are elderly. For instance according to the annual report (2014) from the Swedish Heart Failure Registry (S-HFR) mean age of patients with heart failure was 75 years, with 26% and 54% women in patients <65 years and >85 years, respectively. Epidemiological studies in the general population have showed that the mean age at first diagnosis of HF has increased over the last years, now being 80 years[57-62].

A large Swedish study based on data from S-HFR demonstrated that, compared with patients ≤65 years (n, 8347) elderly HF patients ≥85 years (n, 15899) were characterized by higher proportion of women, higher systolic blood pressure, lower body-mass index, more than twice as many patients with preserved left ventricular ejection fraction, higher incidence of ischemic heart disease, hypertension, atrial fibrillation, stroke and non-cardiovascular comorbidities except diabetes mellitus which was more prevalent in younger patients[63].

Prevalence and incidence

Heart failure (HF) is a major health problem worldwide, with an estimated prevalence of ~2% in the Western world[64-66]. The incidence and prevalence of HF increase steeply with the increasing age of the population. The incidence of HF increases with age; 65-74 years (8-10/1000), 75-84 years (14-19/1000) and 85-94years (26-28/1000)[67]. According to a cross sectional study conducted in Stockholm, the prevalence of heart failure was 2.2% (both women and men) and the incidence was 3.8/1000 person-years (both women and men). The mean age for HF patients in 2010 was 77 years (women

80 years, men 74years). More than 90% of the patients were 60 years and older[68]. According to the annual report (2014) from S-HFR 9304 new patients were registered with a HF diagnosis with a mean age of 75 years. A recent published study based on data from the Swedish National Board of Health and Welfare's statistical database revealed that the prevalence of patients who have been hospitalized with HF in Sweden was 1.70% in men and 1.77% in women 1990. The prevalence in both sexes increased to 2.13% in men and 2.14% in women around 1998–2000. Then, the prevalence decreased to 2.03% in men and 1.93% in women 2007. The prevalence has increased predominantly in the elderly and youngest age groups during 1990-2007[64].

Guideline recommended management

According to ESC guidelines systolic HF management consists of pharmacological treatment, cardiac device treatment, coronary reperfusion therapies, mechanical circulatory support, heart transplantation and holistic management, including exercise training and multidisciplinary management programs, patient monitoring, and palliative care in end stage heart failure[69].

Pharmacologically; neurohormonal blockers, ACEIs/ARBs, beta-blockers, and mineralocorticoid receptor antagonists are fundamentally important in modifying the course of systolic HF and should at least be considered in every patient. They are commonly used in conjunction with a diuretic given to relieve the symptoms and signs of congestion.

Implantable cardiac defibrillator (ICD) is recommended in patients with symptomatic HF (NYHA class II–III) and an EF ≤35% despite ≥3 months of treatment with optimal pharmacological therapy, who are expected to survive for >1 year with good functional status, to reduce the risk of sudden death[70].

Cardiac resynchronization therapy with or without ICD (CRT-P/CRT-D) is recommended in patients in sinus rhythm with a QRS duration of ≥120 ms, LBBB QRS morphology, and an EF ≤35%, who are expected to survive with good functional status for >1 year, to reduce the risk of HF hospitalization and the risk of premature death[71-73].

Evidence level

ESC and other international guidelines are based on clinical trials from patient cohorts with mean age < 70 years. For instance, the mean age in the major randomized clinical trials in systolic heart failure management has been around 65 years (Table 2).

This means that elderly patients in general are underrepresented in the major randomized clinical trials and the use of the guidelines directed medical therapy (GDMT) in elderly patients is an extrapolation of the results of these clinical trials. Moreover, patients ≥80 years have more often been excluded from the clinical trials, not only due to the higher age but also due to the high prevalence of comorbidities. It is therefore essential to study efficacy and safety of GDMT specifically in this aged patient group.

Table 2. Major randomized clinical trials in the management of systolic heart failure

Study	No. of patients	Mean age, years
SOLVD, Enalapril, 1991	2569	61
CIBIS-II, Bisoprolol, 1999.	2647	61
MERIT-HF, Metoprolol , 1999	3001	63.8
CHARM, Candesartan, 2003	7601	62.9
SHIFT, Ivabradine, 2010.	6558	60
CIBIS-eld II, Bisoprolol, 2010-2014.	728	73
PARADIGM, angiotensin receptor–neprilysin inhibitor LCZ696, 2014	8442	63

Prognosis

Prognosis is poor with a 5-year survival rate of ~50%[62]. An epidemiological cross sectional study conducted in Sweden (2006-2010) revealed that five-year survival rate was 48%. The mean age for death for HF patients in 2010 was 85±10 years (women 87±9 years, men 83±10 years). Mortality decreased by 0.5/1000 person-years between 2006 and 2010, in both sexes[68]. Although overall survival after onset of HF has substantially improved with contemporary therapies[62], this benefit is less evident in older age groups[74]. According to the annual (2014) report from S-HFR 1-year mortality in all HF patients was in average 19.5%, and for those <65 years 5%, for those 65-74 years 11%, for 75-84 years 21% and for those >85 years 39%.

Prognostic prediction

Numerous prognostic markers have been identified in heart failure patients including; etiologic, comorbidities, clinical, radiological, hemodynamic, echocardiographic and biochemical parameters. Based on different prognostic markers a large number of prognostic models and scores have been developed[75,76]. One of the most developed HF risk scores is MAGGIC, proven to be able to categorize patients in separate risk strata[75]. MAGGIC predictive score is based on data (n, 39 372) derived from 30 cohort studies and the score is based on 13 highly significant independent predictors of mortality.

Alba and co-workers, via a systematic review, could only identify 5 HF predicative risk models which were validated in independent cohorts; the Heart Failure Survival Score, the Seattle Heart Failure Model, the PACE risk score, a model by Frankenstein et al, and the SHOCKED predictors. The Heart Failure Survival Score was validated in 8 cohorts (2240 patients), showing poor-to-modest discrimination. The Seattle Heart Failure Model was validated in 14 cohorts (16 057 patients), describing poor-to-acceptable discrimination. The other 3 models were validated in one cohort each, reporting poor-to-modest discrimination. Thus, externally validated heart failure models showed inconsistent performance[77].

A systematic review of the factors affecting prognosis in chronic and acute heart failure patients was published recently[78]. The authors identified 117 models in 55 papers. These models used 249 different variables. Mortality was most accurately predicted by prospective registry studies using large number of clinical predictor variables. There was no significant difference in discriminating value of models between patients with chronic and acute heart failure. Prediction of mortality and in particular heart failure hospitalization in patients with heart failure remains only moderately successful, with best predication value in the setting of short-term mortality. However, the predictive scores developed in younger HF patients might not predict successfully in elderly HF patients, for instance Bjurman and co-workers demonstrated that risk assessment in elderly HF patients required significantly higher levels of NTproBNP than younger patients[79].

AIMS

Overall objectives

The overall aim of this thesis was to study the prognostic prediction and its association with treatment strategies in elderly patients presenting with ACS and systolic HF.

Specific objectives

- To investigate predictors of long-term all-cause mortality among octogenarians who had undergone PCI due to ACS (Paper I).
- To assess probable association between PCI and long-term mortality in octogenarians with ACS (Paper II).
- To determine the impact of MR on long-term all-cause mortality and to further reveal whether PCI could influence the prognosis in octogenarian ACS patients with MR (Paper III).
- To investigate whether the highest tolerated and ≥50% of BBs' or ACEIs'/ARBs' target dose outperforms the highest tolerated and <50% target dose, and whether target dose outperforms all other doses in a representative elderly population with heart failure with reduced ejection fraction (Paper IV).
- To study health related quality of life and major adverse cardiovascular events in ACS patients ≥70 years referred for coronary angiography (Paper V).

SUBJECTS AND METHODS

Study population in outline

This dissertation is based on two very old patient cohorts (≥80 years) and a relatively younger old patient cohort (≥70 years): (1) The first cohort consists of 353 patients presenting with ACS, (2) The second cohort consists of 208 patients who have undergone coronary angiography for any reasons, of them 140 patients had ACS, (3) The third cohort consists of 185 patients ≥80 years with HFrEF (EF ≤40%) who have undergone up-titration of BBs and ACEIs/ARBs.

ACS cohorts

Three hundred fifty three patients aged ≥80 years (mean age 85±4 years) who were hospitalized due to ACS during 2006-2007 at two University hospitals (Sahlgrenska and Östra) were included from January 2 to May 30, 2012. Among them, 182 (mean age 83.7±2.8) were treated with PCI, whereas 171(mean age 87±4) were not. Follow-up was at least five years. The only exclusion criterion was if the patient did not belong to catchment area of Sahlgrenska University Hospital (SU), since medical records from other hospitals were not accessible. All together 145 parameters covering social, functional and medical domains were entered into a database. Papers I, II and III are based on this cohort, Figure1.

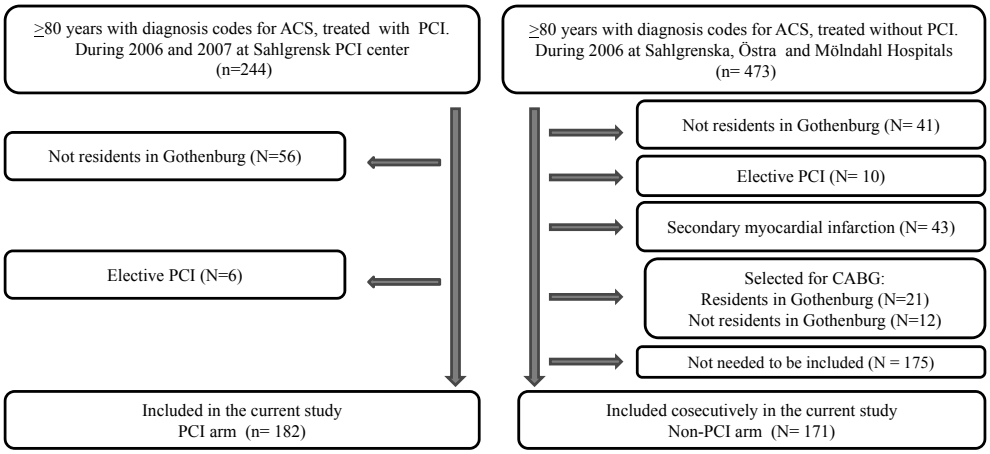

Figure 1. Enrollment flowchart for ACS cohort, Paper 1, II and III.

The second cohort consists of 208 patients ≥70 years, referred for coronary angiography for any reasons at Sahlgrenska University Hospital's Cath lab, were included consecutively between October 2010 and February 2013 during normal office hours only. One of the criteria for inclusion into the study was that blood tests must be taken no later than 24 hours after the angiography. No exclusion criteria were applied except for time >24 hours after angiography and not being willing or able to sign a written consent. All patients gave written consent. For the purpose of the current thesis only patients with ACS were included in analysis (n=140). Patients were followed up prospectively in a minimum period of 2 years. Paper V is based on this cohort, Figure 2.

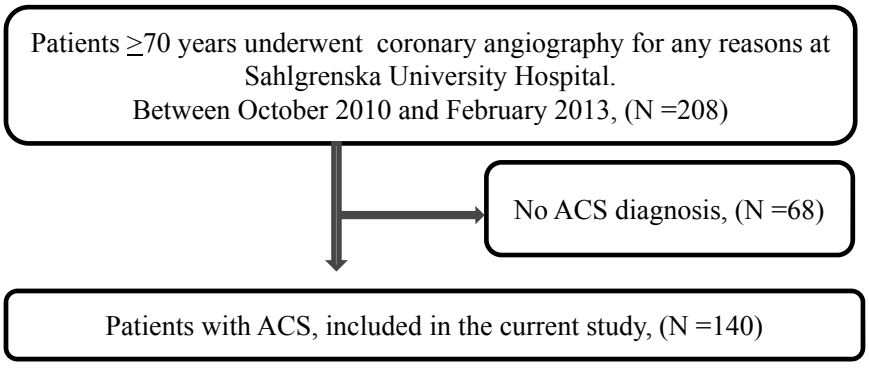

Figure 2. Enrollment flowchart for prospective ACS cohort, Paper V.

HFrEF-study cohort

Patients aged ≥80 years (n =185, mean age 83±2.8) with HFrEF (EF ≤40%), referred to the heart failure (HF) outpatient clinics at Sahlgrenska University Hospital (SU), SU/Sahlgrenska and SU/Östra, were consecutively included between January 2000 and January 2008, and retrospectively studied from January 2 to May 30, 2013, figure 3. Follow-up was at least five years. All patients underwent up-titration of HF medication; BBs and ACEIs/ARBs. Up-titration was stopped after reaching the target dose, or otherwise the highest tolerable dose. Determination of the highest tolerable dose was first determined by a HF specialized nurse then confirmed by a HF specialist responsible for the patient. After a final control after the last up-titration, patients were followed as usual at the outpatient clinic or referred to the primary care units. Paper IV is based on this cohort, Figure 3.

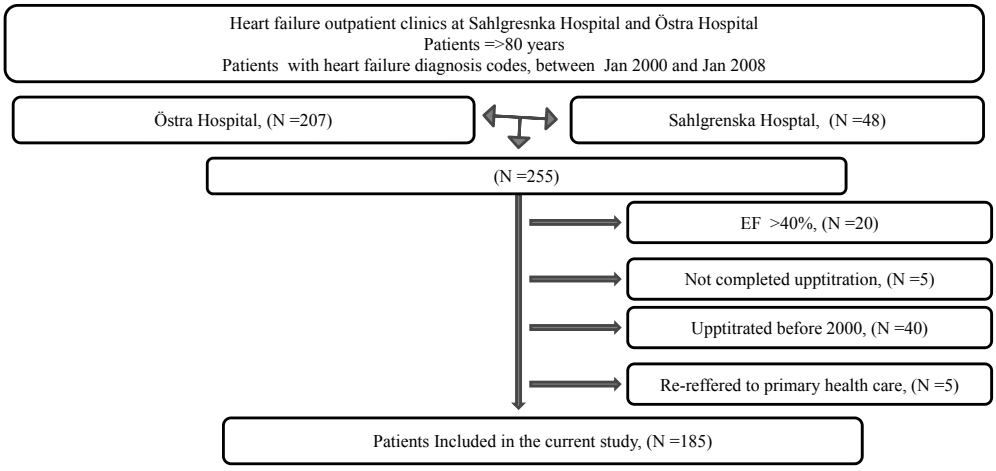

Figure 3. Enrollment flowchart for HFrEF cohort, Paper IV.

Ethics

All study protocols in this thesis were approved by the Ethical Committee at the University of Gothenburg and conformed to the principles outlined in the 1964 Declaration of Helsinki. Moreover, all patients gave written consent in prospective study.

OUTCOME

The primary outcome in paper I, II and III was five-year all-cause mortality. In paper IV, the primary outcome was five-year all-cause mortality and the secondary outcomes were five-year cardiac mortality or hospitalization due to worsening heart failure. In paper V the Primary endpoint was major adverse cardiovascular events consisting of all-cause death or re-admission due to heart failure, onset of atrial fibrillation, recurrent ACS, new PCI and stroke. The secondary endpoint in paper V was health related quality of life in those surviving ACS in the end of study. Data regarding causes of death were obtained from the death registry of the National Board of Health and Welfare in Sweden. The Automated Classification of Medical Entities system was used to select the underlying cause of death. Data about readmissions were obtained from hospital records.

STATISTICS

Overall statistics

Statistical Package for Social Sciences (PASW Statistics 18) was used for data analyses. Categorical variables are expressed as percentages and continuous variables are expressed as mean ± SD. In the case of continuous variables that visual inspection for their histograms, normal Q-Q plots and box-plots showed that the variables were approximately normally distributed, statistical analysis was performed using Student's unpaired t-test. Mann-Whitney test were used for non-normally distributed continuous variables. One way ANOVA with F-test was used in case of comparing more than two groups. For categorical variables, the chi-square test was used. Cox proportional-hazard survival models were used for survival analysis. The multivariable Cox models used in paper I and V to determine prognostic predictors and to adjuste for baseline parameters in evaluating impact of PCI on survival in paper II and III, and impact of neurohormonal blockade doses on survival in paper IV. In paper II and III, propensity score matching has been used to build matched groups and Kaplan-Meier estimate with log-rank test were used to compare survival between patients treated with PCI and patients treated without PCI in propensity score matched groups. Concerning quality of life, licensed Quality Metric Health Outcomes Scoring Software 4.0 were used for scoring and the results were analyzed with SPSS, paper V. Cox models were assessed for proportional hazard assumption for covariates, graphically with Cox adjusted log minus log curves and statically using Schoenfeld global test. All models were tested for co-linearity. Hazard ratios with confidence intervals and p-values were presented. A value of $P<0.05$ was regarded as statistically significant.

Specific statistics

Paper I

Parameters with high clinical relevance and low percentage data missing (<17%) as well as statistical significance from univariable analysis were further tested in multivariable models. Parameters with statistical significance from multivariable models were further tested with Kaplan–Meier estimate, both in separate and in combinations, to demonstrate if patients with more than one risk factor had worse prognosis than those with only one risk factor.

Paper II

Propensity score (PS) matching with 1:1 nearest neighbour matching was employed, stratified by intervention with PCI or not; the matched variables were chosen based on clinical relevance. The matched cohort was tested with Kaplan–Meier estimate with log-rank test to compare survival between patients treated with PCI and patients treated without PCI. Both the overall cohort and the PS matched cohort were analysed by Cox proportional-hazards regression models for probable association between intervention with PCI and long-term mortality.

Paper III

A PS matching was employed to develop a matched cohort, stratified by mitral regurgitation (MR) or no MR; the matched variables were chosen based on clinical relevance. The matched cohort was also tested with Kaplan–Meier estimate with log-rank test to compare survival between patients with at least mild MR and patients without MR.

Cox proportional-hazard regression models, adjusted for baseline parameters were used to evaluate any association between MR and all-cause mortality in both the overall and the matched cohort. Cox proportional-hazard regression analysis was also applied in the subgroup of patients with MR to evaluate any association between intervention with PCI and all-cause mortality.

Paper IV

To adjust for the underlying clinical parameters and to analyze for probable association between any of the three different doses of each agent and the outcome, the cohort was analyzed using Cox proportional-hazards regression multivariable models built individually for the three doses of each agent; BBs and ACEIs/ARBs.

Paper V

Cox proportional-hazard regression analysis was used to identify independent predictors for major cardiovascular adverse events. Health related quality of life was assessed using the Swedish version of the medical outcomes study short form 36 health survey (SF-36). Scores were calculated for each scale. The results were compared with age matched reference values from the Swedish SF-36 normative population, not gender matched due to only 25% female gender in the whole sample.

RESULTS

Predictors of long-term outcome of PCI in octogenarians with ACS

Five-year all-cause mortality in a cohort of ACS patients ≥80 years treated with PCI was 46%. Multivariable Cox regression analysis identified atrial fibrillation, estimated glomerular filtration rate ≤30 ml/min, at least mild mitral valve regurgitation, at least moderate tricuspid valve regurgitation and dependency in activities of daily living as independent predictors of all-cause mortality, Table 3.

Table 3. Independent predictors of 5-year all-cause mortality assessed by Cox-regression multivariable models

Predictors	HR	95% CI	P-Value
Estimated glomerular filtration rate ≤30 ml/min	4.0	1.8–10	0.003
Atrial fibrillation	2.4	1.4–4.2	0.002
Mitral valve regurgitation grade ≥1 (scale, 0.5–4)	1.9	1.1–3.3	0.013
Tricuspid valve regurgitation grade >2 (scale, 0.5–4)	3.9	1.6–9.6	0.002
Dependency in activities of daily living	2.5	1.1–5.6	0.029

Notes: HR, hazard ratio; CI, confidence interval.

Kaplan-Meier estimate with log-rank test showed statistically significant lower survival rate in patients who had the risk predictors, with worst prognosis in patients who had more than one of these risk predictors, Figure 4.

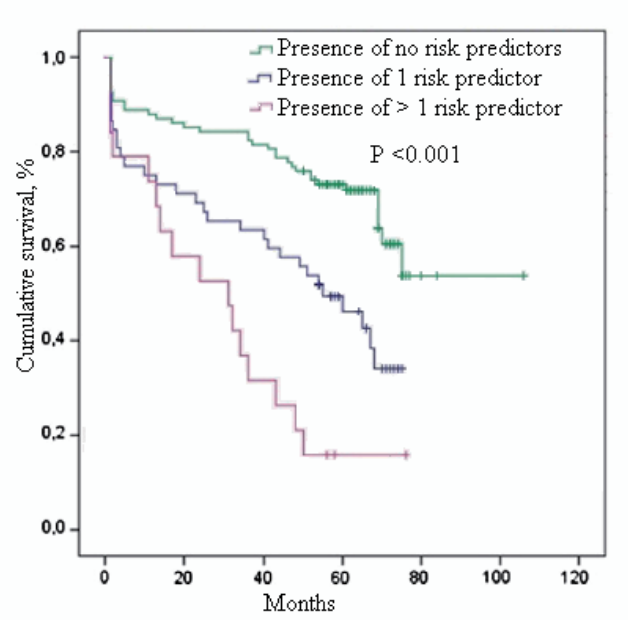

Figure 4. Impact of accumulation of prognostic predictors on 5-year all-cause mortality.

Association between PCI and long-term mortality

Kaplan Meier analyses of propensity score (PS) matched patients demonstrated significantly improved survival of 67 months (95%CI, 60-74) for PCI-treated patients *versus* 26 months (95%CI, 22-31) for non-PCI-treated patients, Figure 5.

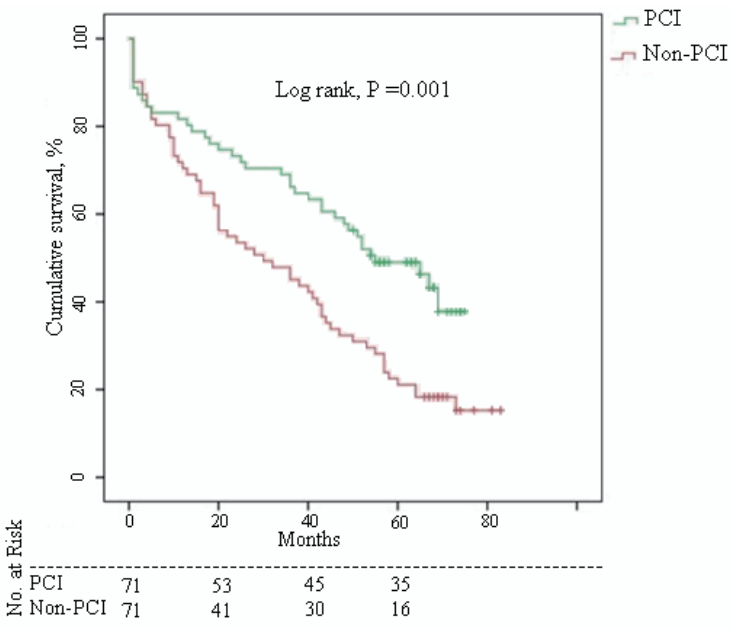

Figure 5. Kaplan Meier survival curves for all-cause mortality for patients treated with PCI versus non-PCI treated in propensity matched cohort.

Cox proportional-hazard regression analysis, adjusted for PS and confounders in PS matched cohort and the overall cohort, demonstrated that PCI was an independent predictor of long-term mortality (HR 0.5, 95%CI 0.2–0.9, *P*=0.020; HR 0.4, 95% CI 0.2–0.5, *P*<0.001) in PS matched and overall cohort (Figure 6), respectively.

Prognostic significance of mitral regurgitation in long-term all-cause mortality in patients aged ≥80 years with ACS.

Compared with ACS patients without mitral regurgitation (MR), patients with MR were older, more frequently women (53% vs 39%) and had higher proportion of ejection fraction <50%, lower hemoglobin level and estimated glomerular filtration rate. Prevalence of MR in each age-group was 35.3% (80-85 years), 53.2% (86-90 years) and 80% (>90 years), Figure 7.

Cox proportional-hazard regression analysis demonstrated that MR was independently associated with long-term all-cause mortality in the overall and matched cohorts (HR 1.58, 95%CI 1.01–2.47, *P*=0.043; HR 1.90, 95% CI 1.15–3.13, *P*=0.013), respectively.

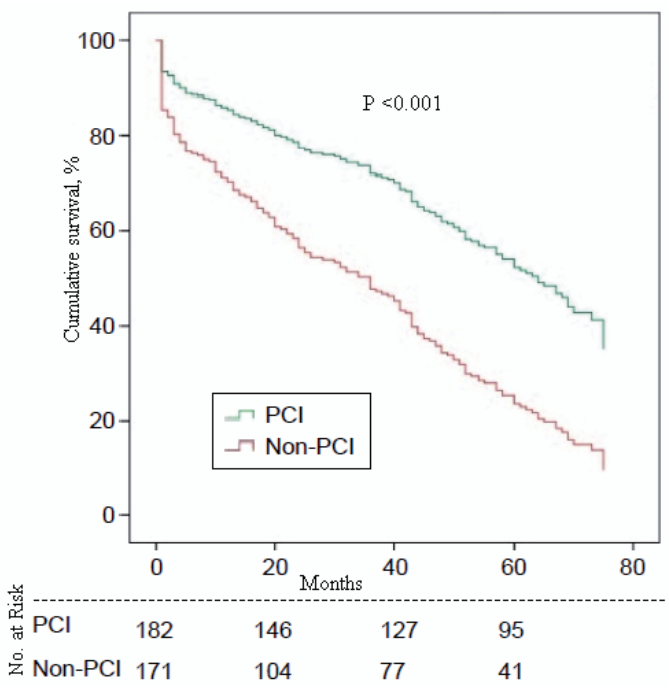

Figure 6. Cox regression survival curves of all-cause mortality for patients treated with PCI versus non-PCI treated in the overall cohort. Adjusted for confounders.

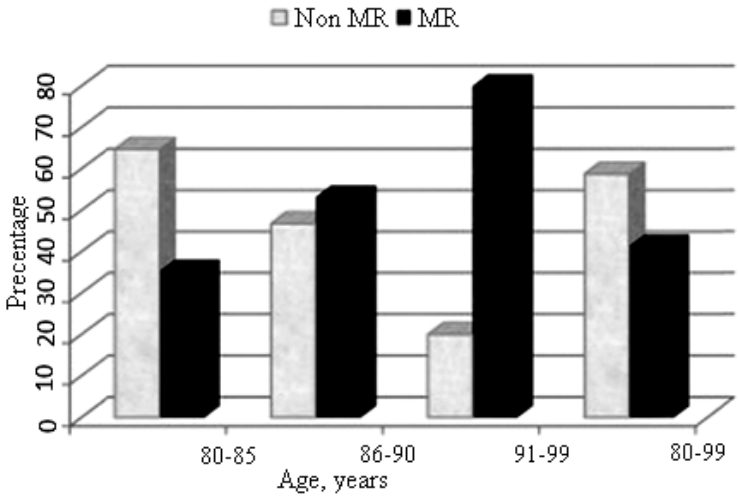

Figure 7. Prevalence of MR in each age group in overall cohort.

In the matched cohort (n, 138), Kaplan-Meier estimate with log rank test demonstrated that patients with at least mild MR had significantly higher mortality rate compared with patients without MR (*P*=0.001), Figure 8.

In the subgroup with MR (n, 92), PCI had still significant association with lower 5-year mortality (HR 0.54, 95% CI 0.33-0.87, *P*=0.011).

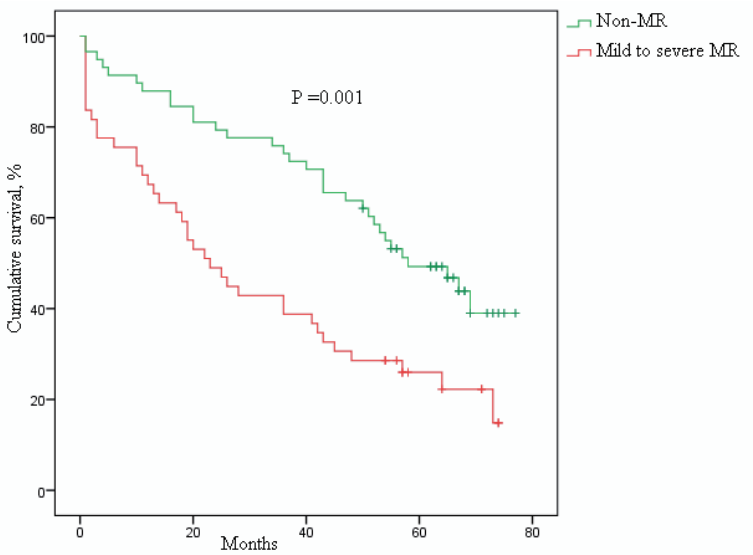

Figure 8. Kaplan–Meier curves to assess relationship between occurrence of MR and long-term all-cause mortality in the propensity matched cohort.

Does the target dose of neurohormonal blockade matter for outcome in systolic heart failure in octogenarians?

In an octogenarian patient cohort (n, 185) with HFrEF, five-year all-cause mortality and cardiac mortality were 76% and 60%, respectively. Of the study population, half received <50% of the target dose of BBs and 21% received the target dose. Moreover, 26% received <50% of the target dose of ACEIs/ARBs and 53% received the target dose.

Cox proportional-hazard regression demonstrated that patients who received the target dose of ACEIs/ARBs had higher survival (Figures 9 and 10) compared with those receiving <50% of the target dose, but this dose-survival relationship was not the case for BBs.

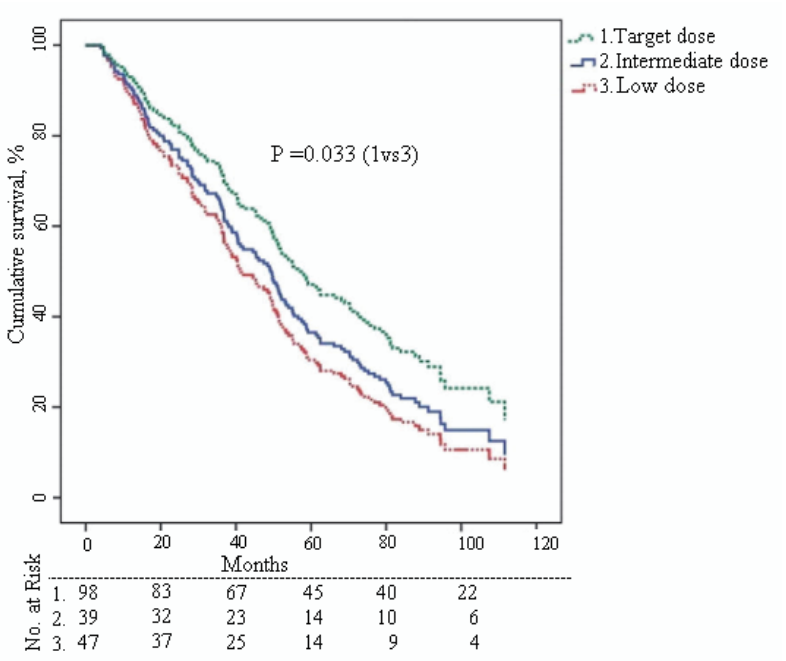

Figure 9. Adjusted Cox regression survival curves for the 3 different doses of ACEIs/ARBs. Endpoint: all-cause mortality.

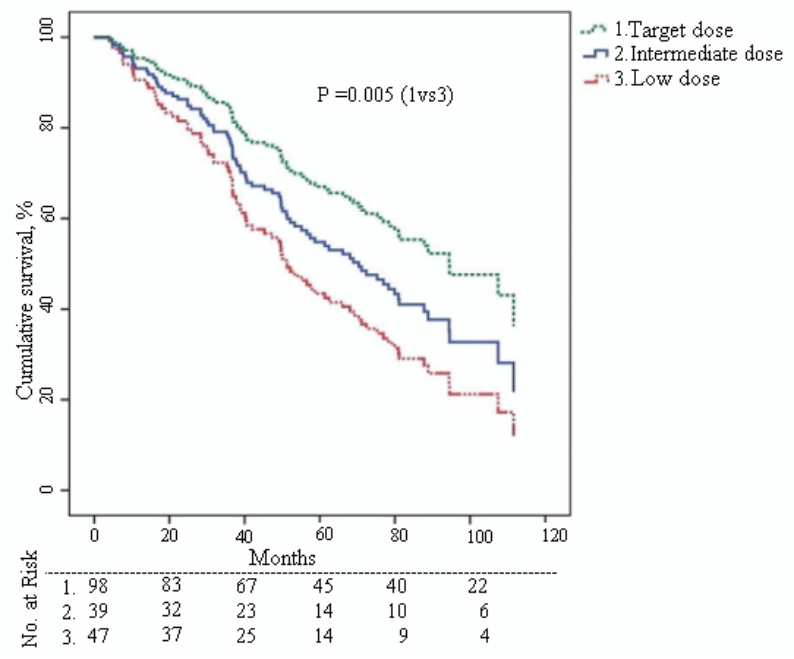

Figure 10. Adjusted Cox regression survival curves for the 3 different doses ACEIs/ARBs. Endpoint: cardiac mortality.

ACS aged ≥70 years in the modern era of reperfusion therapy – major adverse cardiovascular events and quality of life after 2 years of follow-up.

In an ACS patient cohort ≥70 years with 25% women (n, 140), all-cause death was 10% after a mean follow-up of 39±11 months. A total of 58 patients (41%) had one or more MACE and 24% developed post ACS heart failure. The distribution of ACS was; STEMI 46%, NSTEMI 40% and unstable angina 14%. Of the whole population, 74% were successfully treated with PCI and 13.6% of the patients had CABG during admittance or within 1 month after discharge.

Cox proportional hazard regression survival analysis showed that post ACS heart failure, left bundle branch block, left ventricular ejection fraction (LVEF) <50%, at least moderate MR and age were independent predictors of MACE, Figure 11. According to logistic regression analysis LVEF<50% and hsTNT >500 nmol/L were negative predictors for post ACS heart failure, whereas treatment with PCI was a favorable predictor.

The study cohort had as good quality of life as an age-matched population from the normative Swedish SF-36 database in both physical health subscales (physical functioning, role physical, bodily pain and general health) and mental health subscales (Vitality, social functioning, role emotional and mental health).

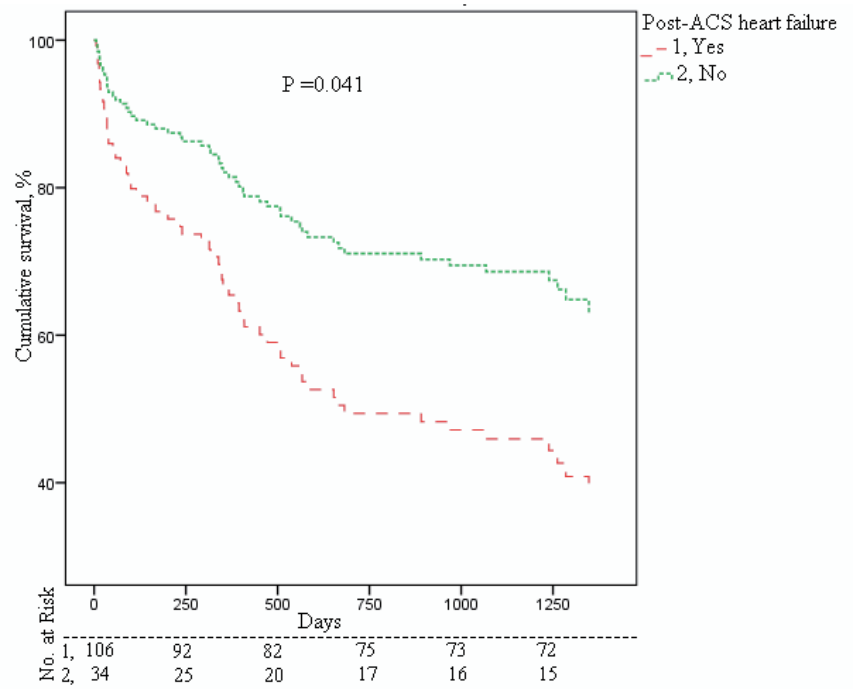

Figure 11. Impact of post-ACS heart failure on survival.

DISCUSSION

Impact of co-morbidity on prognosis in elderly patients with ACS

Elderly patients in general and those with CAD and other cardiovascular diseases in particular suffer from multiple comorbidities[80]. In a cohort of elderly patients ≥80 years presented with ACS and treated with PCI, we identified five independent risk factors (comorbidities) for poor survival despite treatment with PCI. This indicates that comorbidities have an important impact on survival in elderly patients with ACS and it is important to take co-morbidities in consideration in revascularization decision-making. In this cohort all-cause mortality five years after PCI was 46% which is not high in a population with a mean age of 83 years. However, there were substantial differences in mortality rate between those with more than one risk predictor (16% of patient population with 5-year mortality rate, ~80%) and those without the risk predictors (83% of patient population with 5-year mortality rate, ~39%). This indicates that the majority of patients in this old cohort had a good survival after PCI. However, ACS patients (n, 171) not treated with PCI were older (mean age 85 years) with more co-morbidities and had higher five-year all-cause mortality rate, 89%.

Atrial fibrillation and eGFR ≤30 ml/min were highly significant predictors for all-cause death despite treatment with PCI. It is well known that atrial fibrillation is usually combined with severe cardiovascular co-morbidity such as HF[81-85]. The increased risk of AF in patients with ACS could reflect the influence of several factors including; atrial dysfunction and ischemia, HF due to myocardial ischemia, and sympathetic stimulation[86-88]. AF might deteriorate the outcome by increasing oxygen consumption, loss of atrial contraction and atrioventricular asynchrony[89]. Estimated GFR ≤30 indicates severe renal failure which has itself poor prognosis, and is also usually combined with cardiovascular co-morbidities[90]. Dependency in activities of daily living (ADL) was also an independent risk factor for poor survival. This is in line with previous studies and might be explained by the fact that patients with ADL dependency usually suffer from significant co-morbidities[91-93]. Other risk factors for poor survival were Tricuspid and mitral valve regurgitation. The last one will be discussed separately. In case of tricuspid valve regurgitation (TR), its association with poor survival is not completely unknown. Some studies have identified an association between TR and increased mortality[94,95]. But the exact mechanism is not completely defined. However, TR might be regarded as a better marker for right ventricular dysfunction.

Accordingly, our study implies that among patients ≥80 years a substantial subgroup of patients who had only few risk factors for poor survival had a relatively excellent survival rate five years after PCI.

Impact of PCI on prognosis in octogenarians with ACS

As shown in this thesis, in an octogenarian patient cohort presenting with ACS from daily clinical practice, there was an association between PCI and reduced all-cause death over five years of follow-up.

In the overall cohort, there was a significant association between reduction of five-year all-cause mortality and PCI. But due to differences in baseline characteristics between the two groups a propensity score (PS) based matching was performed. In the PS matched cohort, both Kaplan Meier estimate with log rank test and Cox regression analysis with adjustment for the baseline risk factors and PS demonstrated significant association between intervention with PCI and lower five-year all-cause mortality rate. Therefore, our study implies that among patients aged ≥80 years, there is a potential prognostic benefit for intervention with PCI in patients presenting with ACS. This is in line with previous observational studies which have been in favour of PCI in elderly ACS patients, but randomised clinical trials in this field are very limited and moreover with uncertain results. Savonitto and co-workers demonstrated that in ACS patients ≥75 years an early aggressive approach (coronary angiography and, when indicated, revascularization within 72 h) resulted in a significant reduction in the primary endpoint (the composite of death, myocardial infarction, disabling stroke, and repeated hospital admission for cardiovascular causes or severe bleeding within 1 year) in elderly patients with NSTEMI. However, in this study, this positive outcome was observed only in those with elevated troponin on admission[44]. In another multicentre study by dr Tegn et al, elderly ACS patients who underwent an invasive strategy had a decrease in the primary composite endpoint (myocardial infarction, need for urgent revascularization, stroke, and death) as compared with a conservative approach[96]. However, it is noteworthy to mention that in above studies it is an early invasive approach that was studied, i.e. PCI only in case of indication, in comparison with conservative strategy, rather than head to head comparison between PCI and non-PCI treatment which is the case in our observational study.

Furthermore, in paper I, 83% of patient population had a relatively very good prognosis after PCI with a 5-year all-cause mortality rate about 39%, but these patients were healthier with less comorbidity than the remaining patients (16%) who had worse prognosis despite PCI with 5-year all-cause mortality about 80%. In addition, in paper III, PCI was associated with improved long-term survival in elderly ACS patients with MR, although MR was associated with increased mortality rate in this patient group.

Impact of mitral valve regurgitation on prognosis in octogenarians with ACS

MR is common after myocardial infarction with significant negative impact on long-term survival[97-105]. Moreover, even increasing degree of MR has been associated with higher mortality rate[97-99]. However, all the circumstances surrounding the development of ischaemic MR are still not well clarified. The known causal mechanisms comprise annulus dilatation, ischaemia or a scar at the level of the papillary muscles, papillary muscle rupture, and most commonly, a change in the ventricular geometry disturbing the function of the mitral leaflets[99-103]. It is well-known that prevalence of MR increases greatly with age and up to 40% of elderly >70 years have at least mild degree MR[102,105]. The prevalence of MR in our overall cohort was 41%, but kept increasing with aging (35% in 80-85 years, 53% in 86-90 years and 80% in >90 years).

In this thesis we have demonstrated that patients with MR had worse survival rate compared with those without MR, and treatment with PCI improved survival even in

patients with MR. Impact of MR on survival might be explained by the fact that MR might be a better marker of left ventricular dysfunction than low ejection fraction. In our cohort there was no tendency to lower ejection fraction in patients with MR. Furthermore, there are data showing association between MR and high prevalence of atrial fibrillation and HF, both of which are well-known predictors for worse outcome[99,102-105].

Impact of modern management of ACS on prognosis in the elderly: MACE and quality of life

In our prospective study of elderly ACS patients (paper V) we found that despite advanced treatment according to the current guidelines, MACE still occurs in 41% of patients and post ACS heart failure in 24% of cases, after a mean follow-up period of 39 months. All patients underwent primary coronary angiography and received reperfusion therapy if needed, with modern medication and secondary prevention. However, the mortality rate was only 10% and patients had health related quality of life (QoL) as good as an age-matched reference group from the Swedish SF36 normative database. Low mortality rate might be explained by the fact that the incidence of sudden cardiac death after acute MI have declined after the introduction of modern treatment with optimal medical therapy (β-blockers, aspirin, statins and ACE inhibitors) and revascularization[106-110]. With the exception of age which is a well-known risk factor for MACE, we identified other risk factors such as left bundle branch block, reduced left ventricular ejection fraction, mitral valve regurgitation and post MI heart failure. All these factors have associations with left ventricular dysfunction[89,99-105,111,112]. It is therefore reasonable to assume that their significance in our study cohort is due to their association with heart failure.

Post MI heart failure has previously been shown to significantly affect mortality but was inadequately studied in the elderly. It is important to note that after 2 years only 82% had BB (only 42% ≥50% of target dose) and 75% hade ACEI or ARB (only 40% ≥50% of target dose). It is well-known that neurohormonal blockade reverse pathological remodeling and thereby prevent heart failure and probably atrial fibrillation. Therefore, there are still potential to further improve the outcome by improvement of secondary prevention with neurohormonal blockade.

Neurohormonal blockers: dose-survival relationship in HFrEF

By studying a representative elderly HF population (paper IV), we demonstrated in this thesis that target dose of ACEIs/ARBs is associated with reduced all-cause and cardiac mortality in very old patients with systolic heart failure, despite that this was achievable in only about half of the patients. However, the clinical outcome of BB therapy was independent of BB dose. Despite up-titration in dedicated heart failure specialized outpatient clinics, only 21% of patients reached the target dose of BBs and 53% reached the target dose of ACEIs/ARBs. It is important to mention that all patients were up-titrated to the target dose or the highest tolerated doses of both, BBs and ACEIs/ARBs. It is difficult to compare our results with results from previous studies since previous results are either from data from registries or up-titration performed at clinics not specialized in HF where the dose might not be optimally up-ti-

trated. For instance, in the SIGNAL-HF study the up-titration was done in the primary care[113]. Lower percentage of patients reached target dose of BBs could be explained by the fact that elderly with heart failure are more characterized with chronotropic insufficiency, compared with younger patients[114]. Moreover, age and co-morbidities are known to affect up-titration of BBs or ACEIs/ARBs. In general our dose levels are comparable to those of previous studies in which highly tolerated doses were achieved[115-117]. In terms of all-cause mortality, target dose of ACEIs/ARBs had a significantly higher survival rate than those receiving <50% of the target dose. This is in line with previous randomized clinical trials suggesting a greater effect with higher doses[118-121]. In a recently published Norwegian study based on data from Norwegian Heart Failure Registry, patients on ACEI-doses ≥50% of the target dose had lower mortality rate, and the authors concluded that the guideline recommended target doses of ACEIs may have a crucial role in survival improvement, however ARBs had no significant association with decreased all-cause mortality rate[122]. Several studies have demonstrated an association between ACEI-therapy and reduction in the risk of sudden cardiac death, arrhythmic death or appropriate chock in patients with ICD[123-124]. The reduction of ICD shock or sudden cardiac death could be secondary to the role of ACEIs/ARBs in reducing circulating angiotensin II and noradrenalin with subsequent reduced interstitial fibrosis and scar formation and subsequent remodeling[123, 125].

In case of BBs, 21% of our patients reached the target dose. This is only slightly lower than in the previous studies[126]. In the CIBIS-ELD study 32% received the target dose of BBs, but the study population was slightly younger (71±5 years)[127]. We did not find any difference in mortality between the three different doses of BBs, regardless of all-cause or cardiac death. This might be because BBs were optimally up-titrated based on heart rate and the heart rates among the three dose levels after up-titration was comparable. Our results are in accordance with results from several studies demonstrating that the resting heart rate independently indicated prognosis, but BB dose did not[128-130]. However, a recently accepted study in JACC based on data derived from HF-ACTION trial, demonstrated that BB-dose, but not HR, was associated with improved outcomes in unadjusted analysis, but did not remain significant when adjusted for other predictors of outcome in the cohort[131]. The authors concluded that, there were more associated improvements in outcomes with higher BB dose than reduced HR suggesting that titrating BB-doses may confer a greater benefit than reducing HR in such patients. This study was however not designed for up-titration of BBs and patients had probably not undergone an optimal uptitration as they did in our cohort. As long as dose of BBs is not optimally uptitrated individually it is impossible to compare effect of BBs between individuals. It had been difficult to identify if the positive impact of beta-blockers on survival was only due to rate lowering effect or due to other effects of BBs. But, SHIFT trial of the drug Ivabradine, a selective heart rate lowering agent, showed strong evidence for lower heart rate as predictor for improved survival[129, 130]. In our study, we found no differences in re-hospitalization among different dose levels. This may be because all patients received the highest tolerable doses of both agents (BBs or ACEIs/ARBs), which was effective in relieving symptoms for the individual patients.

Limitations

- The thesis is based on observational studies that the clinical decisions made of attending clinicians and their judgment might be influenced by own experiences.
- The PCI cohort was selected, which however is the main stream in our daily clinical practice and such selection bias is difficult to be avoided in the view of limited evidence available in the elderly.
- Despite propensity matching and adjustment with Cox-regression models, it is still impossible to rule out residual confounding from unmeasured variables.
- The underlying cause of MR is not determined, and whether or not it existed before ACS is unclear.
- Only HF patents in our specialized HF clinics were studied. This must be taken in consideration in generalizing our results, especially to HF patients at primary care units.
- In the prospective study patients were included only during normal office hours and therefore the inclusion has not been entirely consecutively.

Strengths

- All data were validated by access to medical journals.
- All cohorts were from daily clinical practice, with selection at the discretion of attending clinicians, not investigators.
- The two most common diseases in the elderly have been studied: ACS and HF.
- Impact of PCI on long term survival was studied by head to head comparison between PCI and non-PCI, not comparing invasive strategy with conservative strategy.
- Impact of dose effect of BBs and ACEIs/ARBs in octogenarians on long term survival was studied after optimal dose uptitrations in dedicated HF outpatient clinics.

CONCLUSIONS

- In an octogenarian patient cohort who suffered from ACS undergone PCI in daily clinical practice, we have identified five prognostic predictors for all-cause death after five years' follow-up and found that a substantial subgroup of patients who had only few risk factors had a relatively excellent survival rate.

- In the overall octogenarian ACS cohort, PCI was significantly associated with reduced all-cause death after five years of follow-up.

- In subgroup analyses of the overall octogenarian ACS cohort, MR was independently associated with higher long-term all-cause mortality rate, and PCI was an independent determinant for improving the long-term survival rate even in patients with MR.

- Despite low mortality rate and improved quality of life, MACE still occurred frequently among ACS patients ≥70 years, suggesting need of improved tailored care in this elderly population, probably by optimizing the secondary preventive therapy.

- Target dose of ACEIs/ARBs was associated with reduced five-year all-cause mortality, despite that this was achievable in only about half of the patients. However, the clinical outcome of BB therapy was independent of BB dose.

CLINICAL IMPLICATIONS

- Intervention with PCI in elderly ACS patients is probably of prognostic benefit. It should be considered in all patients, but with caution, because patients with high rate of comorbidities had worse prognosis despite PCI.

- Despite modern management of ACS in elderly with reperfusion strategy and secondary prevention there are still potential for further improvement to prevent the incidence of MACE and post ACS heart failure.

- In elderly patients with systolic heart failure, ACEI/ARB doses should be up-titrated to the target doses when possible. In case of BBs, target heart rate is probably a better predictor for improved survival.

SAMMANFATTNING PÅ SVENSKA

Bakgrund

Majoriteten av patienter med hjärtsvikt och akut koronart syndrom (AKS) är äldre. Både internationella och europeiska riktlinjer angående handläggning av hjärtsvikt och AKS är baserade på studier där deltagande patienter huvudsakligen varit <70 år. Detta medför att den äldre patientpopulation inte är tillräckligt studerad och effekten av riktlinje-rekommenderade behandlingar är osäker i denna patientgrupp.

Syfte

Syftet med avhandlingen var att studera prognostisk prediktion och dess association med handläggning av äldre patienter med hjärtsvikt och AKS.

Resultat

I en patientpopulation av 182 patienter ≥80 år som genomgått behandling med ballongvidgning av förträngningar i hjärtats kranskärl (PCI) på grund av AKS identifierade vi 5 riskfaktorer för ökad dödlighet efter 5 år. Dessa riskfaktorer var förekomst av förmaksflimmer, kraftigt nedsatt njurfunktion, minst lindrig grad av läckage i mitralisklaffen, minst måttlig grad av läckage i trikuspidalisklaffen och beroende i allmän daglig livsföring.

I en AKS-kohort ≥80 år (n, 353) var överlevnaden bättre efter PCI än utan PCI. I samma kohort hade patienter med minst lindrig grad av läckage i mitralisklaffen lägre överlevnad, men effekten av behandling med PCI var också här associerad med högre överlevnad. Läckage i mitralisklaffen var mycket vanlig i denna patientgrupp och förekomsten steg med stigande ålder.

I en patientkohort ≥80 år (n, 182) med nedsatt pumpförmåga i vänster hjärtkammare (systolisk hjärtsvikt) var överlevnaden högre om man uppnått måldos av något av läkemedlen ”angiotensin converting enzyme inhibitor» (ACEI)/angiotensin receptor blockerare (ARB) jämfört med behandling med lägre doser. Beträffande betablockerare fann vi ingen association mellan olika doser och överlevnad trots att hjärtfrekvensen var jämförbar mellan olika dosgrupper. Av 140 patienter som genomgått koronarangiografi på grund av AKS och erhållit rekommenderad förebyggande behandling enligt gällande riktlinjer avled 10%, 41% utvecklade allvarliga kardiovaskulära händelser och 24% utvecklade hjärtsvikt inom 2 år efter insjuknandet. Patienter som överlevde hade lika bra livskvalitet som normalpopulationen.

Slutsatser

Vi har identifierat 5 riskfaktorer för ökad dödlighet 5 år efter PCI hos äldre patienter med AKS.

PCI är associerad med sänkt mortalitet även i en äldre patientpopulation.

Läckage i mitralisklaffen är vanligt förekommande bland äldre AKS-patienter och är associerat med sämre överlevnad.

Hos patienter med hjärtsvikt på grund av nedsatt vänster kammarens pumpförmåga var måldos ACEI/ARB associerad med högre överlevnad jämfört med lägre doser.

Trots låg mortalitet och bra livskvalitet efter AKS hos äldre patienter som behandlats enligt gällande riktlinjer med PCI och modern läkemedelsbehandling förekommer fortfarande allvarliga kardiovaskulära händelser och hjärtsvikt i hög frekvens.

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REFERENCES

1. Manzano L, Babalis D, Roughton M, Shibata M, Anker SD, et al. Predictors of clinical outcomes in elderly patients with heart failure. Eur J Heart Fail. 2011; 13: 528–536.

2. Mogensen UM, Ersboll M, Andersen M, Andersson C, Hassager C, et al. Clinical characteristics and major comorbidities in heart failure patients more than 85 years of age compared with younger age groups. Eur J Heart Fail. 2011; 13:1216–1223.

3. Jugdutt BI. Aging and heart failure: changing demographics and implications for therapy in the elderly. Heart Fail Rev. 2010; 15: 401–405.

4. United Nations Department of Economic and Social Affairs Population Division. World population ageing: 1950–2050. http :// www.nu .org/esa/population /publications/ worldageing19502050/ Accessed March 26, 2008.

5. Olivetti G, Melissari M, Capasso JM, Anversa P. Cardiomyopathy of the aging human heart. Circ Res 1991; 68: 1560–1568.

6. Lakatta EG, Levy D. Arterial and cardiac aging: major shareholders in cardiovascular disease enterprises: Part II: the aging heart in health: links to heart disease. Circulation. 2003; 107: 346–354.

7. Haver VG, Mateo Leach I, Kjekshus J, Fox JC, Wedel H, et al. Telomere length and outcomes in ischaemic heart failure: data from the COntrolled ROsuvastatin multiNAtional Trial in Heart Failure (CORONA). Eur J Heart Fail. 2015; 17: 313-9.

8. Chen W, Frangogiannis NG. The role of inflammatory and fibrogenic pathways in heart failure associated with aging. Heart Fail Rev. 2010;15:415–422

9. Mogensen UM, Ersboll M, Andersen M, Andersson C, Hassager C, et al. Clinical characteristics and major comorbidities in heart failure patients more than 85 years of age compared with younger age groups. Eur J Heart Fail. 2011; 13: 1216–1223.

10. Steg PG, James SK, Atar D, Badano LP, Blomstrom-Lundqvist C, et al. ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J. 2012; 33: 2569.

11. Marco Roffi, Carlo Patrono, Jean-Philippe Collet, Christian Mueller, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J. 2015; pii: ehv320.

12. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR,Third universal definition of myocardial infarction. Eur Heart J. 2012; 33: 2551–2567.

13. Filippo Crea and Giovanna Liuzzo. Pathogenesis of Acute Coronary Syndromes. J AM Coll Cardiol. 2013: 61: 1-11.

14. Juan C , Munoz J.J, Alonso J.M, Duran, Federico G, et al. Coronary stent implantation in patients older than 75 years of age: clinical profile and initial and long-term (3 years) outcome. Am Heart J. 2002; 143: 620–626.

15. Avezum A, Makdisse M, Spencer F, Gore JM, Fox KA, et al. Impact of age on management and outcome of acute coronary syndrome: observations from the Global Registry of Acute Coronary Events (GRACE). Am Heart J. 2005; 149: 67–73.

16. Michelle M. Graham, William A. Ghali, Peter D. Faris, et al. Survival after Coronary Revascularization in the Elderly (APPROACH). Circulation. 2002; 105: 2378-2384.

17. Soiza RL, Leslie SJ, Harrild K, Peden NR, Hargreaves AD. Age-dependent differences in presentation, risk factor profile, and outcome of suspected acute coronary syndrome. J Am Geriatr Soc. 2005; 53: 1961-5.

18. Rosengren A, Spetz CL, Koster M, Hammar N, Alfredsson L, Rosen M. Sex differences in survival after myocardial infarction in Sweden; data from the Swedish National Acute Myocardial Infarction Register. Eur Heart J. 2001; 22: 314–322.

19. Eagle KA, Lim MJ, Dabbous OH, Pieper KS, Goldberg RJ, et al. A validated prediction model for all forms of acute coronary syndromes: estimating the risk of 6–month post discharge death in an international registry. J Am Med Assoc. 2004; 291: 2727–33.

20. Graham M, Galbraith P, O'Neill D, Rolfson D, Dando C, Norris C. Frailty and outcome in elderly patients with acute coronary syndrome. Can J Cardiol 2013; 29: 1610–5.

21. Fleg J, Forman D, Berra K, Bittner V, Blumenthal JA, et al. Secondary prevention of atherosclerotic cardiovascular disease in older adults: a scientific statement from the American Heart Association. Circulation 2013; 128: 2422–46.

22. Yan A, Yan R, Huynh T, Casanova A, Raimondo FE, et al. Registry data highlight temporal improvements in mortality from AMI that are age dependent (Understanding physicians› risk stratification of acute coronary syndromes: insights from the Canadian ACS 2 Registry. Arch Intern Med. 2009; 169: 372–8.

23. Marschner IC, Colquhoun D, Simes RJ, Glasziou P, Harris P, et al. Long-term risk stratification for survivors of acute coronary syndromes. Results from the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) Study. J Am Coll Cardiol. 2001; 38: 56.

24. Gale CP, Cattle BA, Woolston A, Baxter PD, West TH, et al. Resolving inequalities in care? Reduced mortality in the elderly after acute coronary syndromes. The Myocardial Ischaemia National Audit Project 2003-2010. Eur Heart J. 2012; 33: 630-9.

25. Donoghue M, Boden WE, Braunwald E, Cannon CP, Clayton TC, et al. Early invasive vs conservative treatment strategies in women and men with unstable angina and non-ST-segment elevation myocardial infarction: a meta-analysis. JAMA. 2008; 300: 71–80.

26. Fox KA, Clayton TC, Damman P, Pocock SJ, Wallentin L, et al. Long-term outcome of a routine versus selective invasive strategy in patients with non-ST-segment elevation acute coronary syndrome a meta-analysis of individual patient data. J Am Coll Cardiol. 2010; 55: 2435–2445.

27. Noc M, Fajadet J, Lassen JF, Kala P, MacCarthy P, et al . Invasive coronary treatment strategies for out-of-hospital cardiac arrest: a consensus statement from the European Association for Percutaneous Cardiovascular Interventions (EAPCI)/Stent For Life (SFL) groups. EuroIntervention. 2014; 10: 31–37.

28. Navarese EP, Gurbel PA, Andreotti F, Tantry U, Jeong YH. Optimal timing of coronary invasive strategy in non-ST-segment elevation acute coronary syndromes: a systematic review and meta-analysis. Ann Intern Med. 2013; 158: 261–270.

29. Chatterjee S, Chaudhuri D, Vedanthan R, Fuster V. Early intravenous beta-blockers in patients with acute coronary syndrome—a meta-analysis of randomized trials. Int J Cardiol. 2013; 168: 915–921.

30. Patrono C, Andreotti F, Arnesen H, Badimon L, Baigent C, et al . Antiplatelet agents for the treatment and prevention of atherothrombosis. Eur Heart J. 2011; 32: 2922–2932.

31. Gurbel PA, Bliden KP, Butler K, Tantry US, Gesheff. Randomized double-blind assessment of the onset and offset of the antiplatelet effects of ticagrelor versus clopidogrel in patients with stable coronary artery disease: the Onset/Offset study. Circulation. 2009; 120: 2577–2585.

32. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2009; 361: 1045–1057.

33. Yusuf S, Mehta SR, Chrolavicius S, Afzal R, Pogue J, et al . Comparison of fondaparinux and enoxaparin in acute coronary syndromes. N Engl J Med. 2006; 354: 1464–1476.

34. Skolnick AH, Alexander KP, Chen AY, Roe MT, Pollack CV Jr, et al. Characteristics, management, and outcomes of 5,557 patients age ≥90 years with acute coronary syndromes: results from the CRUSADE initiative. J Am Coll Cardiol. 2007; 49: 1790–1797.

35. Chow CK, Jolly S, Rao-Melacini P, Fox KA, Anand SS, Yusuf S. Association of diet, exercise, and smoking modification with risk of early cardiovascular events after acute coronary syndrome. Circulation. 2010; 121: 750–758.

36. Pfeffer MA, McMurray JJ, Velazquez EJ, Rouleau JL, Swedberg K, et al. Valsartan, Captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. N Engl J Med. 2003; 349: 1893–1906.

37. Le Corvoisier P, Bastuji-Garin S, Renaud B, Mahé I, Bergmann JF, et al. Functional status and co-morbidities are associated with in-hospital mortality among older patients with acute decompensated heart failure: a multicentre prospective cohort study. Age Ageing. 2015; 44: 225-31.

38. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med. 2015; 372: 2387–97.

39. Yusuf S, Teo KK, Pogue J, Dyal L, Copland I, et al. Telmisartan, ramipril, or both in patients at high risk for vascular events. N Engl J Med. 2008; 358: 1547–1559.

40. Flather MD, Shibata MC, Coats AJ, Van Veldhuisen DJ, Parkhomenko A, et al. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). Eur Heart J. 2005; 26: 215–225.

41. Zannad F, McMurray JJ, Krum H, Veldhuisen DJ, Swedberg K, et al. Eplerenone in patients with systolic heart failure and mild symptoms. N Engl J Med. 2011; 364: 11–21.

42. Pitt B, Remme W, Zannad F, Neaton J, Martinez F, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med. 2003; 348: 1309–1321.

43. Malkin CJ, Prakash R, Chew DP. The impact of increased age on outcome from a strategy of early invasive management and revascularisation in patients with acute coronary syndromes: retrospective analysis study from the ACACIA registry. BMJ Open. 2012; 2: e000540.

44. Savonitto S, Cavallini C, Petronio AS, Murena E, Antonicelli R, et al. Early aggressive versus initially conservative treatment in elderly patients with non-ST-segment elevation acute coronary syndrome: a randomized controlled trial. JACC Cardiovasc Interv. 2012; 5: 906–916.

45. Emily Herrett, Liam Smeeth, Lynne Walker, Clive Weston, on behalf of the MINAP Academic Group. The Myocardial Ischaemia National Audit Project (MINAP). Heart. 2010; 96: 1264-1267.

46. Aragam KG, Tamhane UU, Kline-Rogers E, Li J, Fox KA, et al. Does simplicity compromise accuracy in ACS risk prediction? A retrospective analysis of the TIMI and GRACE risk scores. *PLoS One.* 2009*;* 4*:* e7947.

47. De Araujo Goncalves P, Ferreira J, Aguiar C, Seabra-Gomes R. TIMI, PURSUIT, and GRACE risk scores: sustained prognostic value and interaction with revascularization in NSTE-ACS. *Eur Heart J* 2005*;* 26: 865–872.

48. Singh M, Alexander K, Roger VL, Rihal CS, Whitson HE, et al. Frailty and its potential relevance to cardiovascular care. Mayo Clinic Proc. 2008; 83: 1146–53.

49. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987; 40: 373-383.

50. Clegg A, Young J, Life S, Iliffe S, Rikkert MO, Rockwood Ket. Frailty in elderly people. Lancet 2013; 381: 752–62.

51. Lee DH, Buth KJ, Martin BJ, Yip AM, Hirsch GM. Frail patients are at increased risk for mortality and prolonged institutional care after cardiac surgery. Circulation. 2010; 121: 973–8.

52. Masel MC, Graham JE, Reistetter TA, Markides KS, Ottenbacher KJ. Reistetter TA, et al. Frailty and health related quality of life in older Mexican Americans. Health Qual Life Outcomes. 2009; 7: 70.

53. Mitnitski AB, Graham JE, Mogilner AJ, Rockwood K. Frailty, fitness and late-life mortality in relation to chronological and biological age. BMC Geriatr. 2002; 2: 1.

54. Rockwood K, Song X, Macknight C, Bergman H, Hogan DB, et al. A global clinical measure of fitness and frailty in elderly people. CMAJ. 2005; 173: 489–95.

55. Rachel Murali-Krishnan, Javaid Iqbal, Rebecca Rowe, Emer Hatem, Yasir Parviz, et al. Impact of frailty on outcomes after percutaneous coronary intervention: a prospective cohort study. Open Heart. 2015; 2: e000294.

56. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ and Swedberg K. et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. Eur J Heart Fail. 2008; 10:933–989.

57. Ho KKL, Pinsky JL, Kannel WB, Levy D. The Framingham Study. J AM Coll Cardiol. 1993; 22: 6a±13a.

58. Jugdutt BI. Prevention of heart failure in the elderly: when, where and how to begin? Heart Fail Rev. 2012; 17: 5s31–544.

59. M. Komajda, O. Hanon, M. Hochadel, Lopez-Sendon JL, Follath F, et al. Contemporary

management of octogenarians hospitalized for heart failure in Europe: Euro Heart Failure Survey IIEur Heart J. 2009; 30:478–486.

60. Miani D, Fresco C, Lucci D, Albanese MC, Gonzini L, et al. Clinical characteristics, management, and prognosis of octogenarians with acute heart failure admitted to cardiology wards: results from the Italian Survey on Acute Heart Failure Am Heart J. 2009; 158: 126–132.

61. Mogensen M, Ersbøll M, Andersen M, Andersson C, Hassager C, et al. Clinical characteristics and major comorbidities in heart failure patients more than 85 years of age compared with younger age. Eur J Heart Fail. 2011; 13: 1216–1223.

62. Levy D, Kenchaiah S, Larson MG, Benjamin EJ, Kupka MJ, et al. Long-term trends in the incidence of and survival with heart failure. N Engl J Med. 2002; 347: 1397–1402.

63. Holmström A, Sigurjonsdottir R, Edner M, Jonsson A, Dahlström U, Fu ML. Increased comorbidities in heart failure patients ≥ 85 years but declined from >90 years: data from the Swedish Heart Failure Registry. Int J Cardiol. 2013; 167:2747-52.

64. Parén P, Schaufelberger M, Björck L, Lappas G, Fu M, Rosengren A. Trends in prevalence from 1990 to 2007 of patients hospitalized with heart failure in Sweden. Eur J Heart Fail. 2014; 16: 737-42.

65. Ho KK, Pinsky JL, Kannel WB, Levy D. The epidemiology of heart failure: the Framingham Study. J Am Coll Card. 1993; 22:6A–13A.

66. Schocken DD, Arrieta MI, Leaverton PE, Ross EA. Prevalence and mortality rate of congestive heart failure in the United States. J Am Coll Card. 1992; 20: 301–306.

67. Kannel WB. Incidence and epidemiology of heart failure. Heart Fail Rev. 2000; 5:167–173.

68. Zarrinkoub R, Wettermark B, Wändell P, Mejhert M, Szulkin R, et al. The epidemiology of heart failure, based on data for 2.1 million inhabitants in Sweden. Eur J Heart Fail. 2013; 15:995-1002.

69. Michele Brignole, Angelo Auricchio, Gonzalo Baron-Esquivias, Pierre Bordachar, Giuseppe Boriani, et al. 2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy The Task Force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). European Heart Journal. 2013; 34: 2281–2329.

70. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med. 200; 352:225–237.

71. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, Tavazzi L. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med. 2005; 352: 1539–1549.

72. Al-Majed NS, McAlister FA, Bakal JA, Ezekowitz JA. Meta-analysis: cardiac resynchronization therapy for patients with less symptomatic heart failure. Ann Intern Med. 2011; 154: 401–412

73. Sipahi I, Carrigan TP, Rowland DY, Stambler BS, Fang JC. Impact of QRS duration on clinical event reduction with cardiac resynchronization therapy: meta-analysis of randomized controlled trials. Arch Intern Med. 2011; 171: 1454–1462.

74. Goldberg RJ, Glatfelter K, Burbank-Schmidt E, Farmer C, Spencer FA, et al. Trends in mortality attributed to heart failure in Worcester, Massachusetts, 1992 to 2001. Am J Cardiol. 2005; 95: 1324–1328.

75. Sartipy U, Dahlström U, Edner M, Lund LH. Predicting survival in heart failure: Validation of the MAGGIC heart failure risk score in 51 043 patients from the Swedish Heart Failure Registry. Eur J Heart Fail. 2014; 16: 173-9.

76. Pocock SJ, Ariti CA, McMurray JJ, Maggioni A, Swedberg K, et al. Predicting survival in heart failure: a risk score based on 39 372 patients from 30 studies. Eur Heart J. 2013; 34: 1404–1413.

77. Ana C. Alba, Thomas Agoritsas, Milosz Jankowski, Delphine Courvoisier, Stephen D. Walter, et al. Risk Prediction Models for Mortality in Ambulatory Patients With Heart Failure. Circ Heart Fail. 2013; 6: 881-889.

78. Wouter Ouwerkerk, Adriaan A. Voors, Aeilko H. Zwinderman. Factors Influencing the Predictive Power of Models for Predicting Mortality and/or Heart Failure Hospitalization in Patients with Heart Failure. JCHF. 2014; 2: 429-436.

79. Christian Bjurman, Juliana Jensen, Max Petzold, Ola Hammarsten, Michael L X Fu. Assessment of a multimarker strategy for prediction of mortality in older heart failure patients: a cohort study. BMJ Open. 2013; 3: e002254.

80. Mary C. Spalding, and Sean C. Sebesta, Texas Tech Univ. ersity Health Sciences Center at El Paso, El Paso, Texas. Geriatric Screening and Preventive Care. Am Fam Physician. 2008; 78: 206-215.

81. Kober L, Swedberg K, McMurray JJ, Pfeffer MA, Velazquez EJ, et al. Previously known and newly diagnosed atrial fibrillation: a major risk indicator after a myocardial infarction complicated by heart failure or left ventricular dysfunction. Eur J Heart Fail. 2006; 8: 591-598.

82. Madias JE, Patel DC, Singh D. Atrial fibrillation in acute myocardial infarction: a prospective study based on data from a consecutive series of patients admitted to the coronary care unit. Clin Cardiol. 1996; 19: 180-186.

83. Almendro-Delia M, Valle-Caballero MJ, Garcia-Rubira JC, Muñoz-Calero B, Garcia-Alcantara A. Prognostic impact of atrial fibrillation in acute coronary syndromes: results from the ARIAM registry. Eur Heart J Acute Cardiovasc Care. 2014; 3: 141-8.

84. Galvão Braga C, Ramos V, Vieira C, Martins J, Ribeiro S, et al. New-onset atrial fibrillation during acute coronary syndromes: predictors and prognosis. Rev Port Cardiol. 2014; 33: 281-7.

85. Wendy A. Wattigney, George A. Mensah, Janet B. Croft. Increased atrial fibrillation mortality: United States, 1980–1998. Am J Epidemiol. 2002; 155: 819–826.

86. Zicha S, Tsuji Y, Shiroshita-Takeshita A, Nattel S. Beta-blockers as antiarrhythmic agents. Handb Exp Pharmacol. 2006; 171: 235–66.

87. Crenshaw BS, Ward SR, Granger CB, Stebbins AL, Topol EJ, Califf RM. Atrial fibrillation in the setting of acute myocardial infarction: the GUSTO-I experience. Global utilization of streptokinase and TPA for occluded coronary arteries. J Am Coll Cardiol. 1997; 30: 406–13.

88. Rathore SS, Berger AK, Weinfurt KP, Schulman KA, Oetgen WJ, Gersh BJ. Acute myocardial infarction complicated by atrial fibrillation in the elderly: prevalence and outcomes. Circulation. 2000; 101: 969–74.

89. Pizzetti F, Turazza FM, Franzosi MG, S Barlera, A Ledda, et al. Incidence and prognostic significance of atrial fibrillation in acute myocardial infarction: the GISSI-3 data. Heart. 2001; 86: 527–532.

90. R. Vanholder1, Z. Massy, A. Argiles, G. Spasovski, F. Verbeke1, N. Lameire1.Chronic kidney disease as cause of cardiovascular morbidity and mortality. Nephrol Dial Transplant. 2005; 20: 1048–1056.

91. Hiroyuki N. Importance of activities of daily living in elderly patients with acute myocardial infarction undergoing primary coronary intervention. J Am Coll Cardiol. 2015; 65 :(10_S).

92. Juan Sanchis, Clara Bonanad, Vicente Ruiz, Julio Fernández, Sergio García-Blas, et al. Frailty and other geriatric conditions for risk stratification of older patients with acute coronary syndrome. Ahj. 2014; 168: 784–791.e2.

93. Inouye SK, Peduzzi PN, Robison JT, Hughes JS, Horwitz RI, Concato J. Importance of functional measures in predicting mortality among older hospitalized patients. JAMA. 1998; 279: 1187–1193.

94. Nath J, Foster E, Heidenreich PA. Impact of tricuspid regurgitation on long-term survival. J Am Coll Cardiol. 2004; 43: 405.

95. Santas E, Chorro FJ, Miñana G, Méndez J, Muñoz J, et al. Tricuspid Regurgitation and Mortality Risk Across Left Ventricular Systolic Function in Acute Heart Failure. Circ J. 2015; 79: 1526-33.

96. Invasive vs. Conservative Strategy in Patients Over 80 Years with Non–ST-Elevation Myocardial Infarction or Unstable Angina Pectoris: Clinical Trial - After Eighty Study. American College of Cardiology website. http://www.acc.org/latest-in-cardiology/clinical-trials/2015/03/15.

97. Pastorius CA, Henry TD, Harris KM. Long-term outcomes of patients with mitral regurgitation undergoing percutaneous coronary intervention. Am J Cardiol. 2007; 100: 1218–3.

98. Annemrie E. Engster M , Marje M, Berto J and Bouma, et al. Mitral regurgitation is an independent predictor of 1-year mortality in ST-elevation myocardial infarction patients presenting in cardiogenic shock on admission. Acute Cardiac Care. 2010; 12: 51–57.

99. Núñez-Gil IJ, Estrada I, Pérez de Isla L , Feltes G, De Agustín JA, Vivas D, et al. Functional mitral regurgitation after a first non-ST segment elevation acute coronary syndrome: very-long-term follow-up, prognosis and contribution to left ventricular enlargement and atrial fibrillation development. Heart. 2013; 99: 1502-8.

100. Perez de Isla L, Zamorano J, Quezada M, Almería C, Rodrigo JL, Serra V, et al. Prognostic significance of functional mitral regurgitation after a first non-ST-segment elevation acute coronary syndrome. Eur Heart J. 2006; 27: 2655–60.

101. Perez de Isla L, Zamorano J, Martinez Quesada M, Corros C, Ortiz P, et al. Prognostic significance of ischemic mitral regurgitation after non-Q-wave acute myocardial infarction. J Heart Valve Dis. 2005; 14: 742–8.

102. Persson A, Hartford M, Herlitz J, Karlsson T, Omland T, Caidahl K. Long-term prognostic value of mitral regurgitation in acute coronary syndromes. *Heart.* 2010; 96: 1803-1808.

103. Tcheng JE, Jackman JD Jr, Nelson CL, Gardner LH, Smith LR, RankinJS, Califf RM, Stack RS. Outcome of patients sustaining acute ischemic mitral regurgitation during myocardial infarction. Ann Intern Med. 1992; 117: 18 –24.

104. Lehman KG, Francis CK, Dodge HT. Mitral regurgitation in early myocardial infarction. Incidence, clinical detection, and prognostic implications. TIMI Study Group. Ann Intern Med. 1992; 117: 10–17.

105. Bursi F, Enriquez-Sarano M, Nkomo VT, Jacobsen SJ, Weston SA, et al. Heart failure and death after myocardial infarction in the community: the emerging role of mitral regurgitation. Circulation. 2005; 111: 295–301.

106. Fan X, Hua W, Xu Y, Ding L, Niu H, Chen K, Xu B, Zhang S. Incidence and predictors of sudden cardiac death in patients with reduced left ventricular ejection fraction after myocardial infarction in an era of revascularisation. Heart. 2014; 100: 1242-9.

107. Derek Chew; Rosza Sas; Katherine Kavanagh, Margaret Morck, et al. Factors associated with left ventricular remodeling post myocardial infarction. J Am Coll Cardiol. 2015; 65(10_S).

108. Makikallio TH, Barthel P, Schneider R, Raphael S, Axel B, Jari MT. Frequency of sudden cardiac death among acute myocardial infarction survivors with optimized medical and revascularization therapy. Am J Cardiol. 2006; 97: 480–4.

109. Charlotte A, David S, Alan S. Go, Tara I. C, Dhruv K, et al. Beta-Blocker Therapy and Cardiac Events Among Patients With Newly Diagnosed Coronary Heart Disease. J Am Coll Cardiol. 2014; 64: 247-252.

110. Yong Liu; Yingying Wang; Xiaoning Zhao; Lihui Ren. Stress echocardiography predicts major adverse cardiovascular event after percutaneous coronary intervention in patients with acute myocardial infarction. J Am Coll Cardiol. 2015; 66(16_S).

111. Liyew Desta, Tomas Jernberg, Ida Löfman, Claes Hofman-Bang, Inger Hagerman, et al. Incidence, Temporal Trends, and Prognostic Impact of Heart Failure Complicating Acute Myocardial Infarction. The SWEDEHEART Registry. JCHF. 2015; 3: 234-242.

112. Mircea Petrina, Shaun G. Goodman, Kim A. Eagle. The 12-lead electrocardiogram as a predictive tool of mortality after acute myocardial infarction: Current status in an era of revascularization and reperfusion. Am Heart J. 2006; 152: 11-8.

113. Persson H, Erntell H, Eriksson B, Johansson G, Swedberg K, Dahlström U. Improved pharmacological therapy of chronic heart failure in primary care- SIGNAL-HF. Eur J Heart Fail. 2010; 12: 1300-1308.

114. Brubaker PH, Kitzman DW. Chronotropic Incompetence Causes, Consequences, and Management. Circulation. 2011; 123: 1010-1020.

115. Maggioni AP, Dahlström U, Filippatos G, Chioncel O, Leiro MC, et al. The Heart Failure Pilot Survey (ESC-HF Pilot). Eur J Heart Fail. 2010; 12: 1076-84.

116. Gheorghiade M, Albert NM, Curtis AB, Thomas Heywood J, McBride ML, et al. Medication Dosing in Outpatients with Heart Failure after Implementation of a Practice-Based

Performance Improvement: Findings from IMPROVE HF. Congest Heart Fail. 2012; 18: 9-17

117. Fiuzat M, Wojdyla D, Kitzman D, Fleg J, Keteyian SJ, et al. Relationship of beta-blocker dose with outcomes in ambulatory heart failure patients with systolic dysfunction: results from the HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training) trial. J Am Coll Cardiol. 2012; 17; 60: 208-15.

118. Konstam MA, Neaton JD, Dickstein K, Drexler H, Komajda M, et al. Effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure (HEAAL study): a randomized, double-blind trial. Lancet. 2009; 374: 1840–1848.

119. Swedberg K, Kjekshus J, Snapinn S. Long-term survival in severe heart failure in patients treated with enalapril. Ten year follow-up of CONSENSUS I. Eur Heart J. 1999; 20: 136-9.

120. Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, et al. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. Lancet. 2003; 362: 759-66.

121. Packer M, Poole-Wilson PA, Armstrong PW, Cleland JG, Horowitz JD, Massie BM, Rydén L, et al. Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. Circulation. 1999; 100: 2312–2318.

122. Jonathan De B, Morten F, Morten G, Anne S, Lars G, et al. ESC guidelines adherence is associated with improved survival in patients from the Norwegian Heart Failure Registry. Eur Heart J. 2015; 1: 31-36.

123. AlJaroudi WA, Refaat MM, Habib RH, Al-Shaar L, Singh M, et al. Effect of angiotensin converting enzyme inhibitors and receptor blockers on appropriate implantable cardiac defibrillator shock in patients with severe systolic heart failure failure (from the GRADE Multicenter Study) Am J Cardiol. 2015; 115: 924-31.

124. Schnee J.M, Hsueh W.A. Angiotensin II, adhesion, and cardiac fibrosis. Cardiovasc Res. 2000; 46: 264-8.

125. Scott P.A, Rosengarten J.A, Murday D.C, Peebles C.R, Harden S.P. Left ventricular scar burden specifies the potential for ventricular arrhythmogenesis: a LGE-CMR study. J Cardiovasc Electrophysiol. 2013; 24: 430–436.

126. Franke J, Wolter JS, Meme L, Keppler J, Tschierschke R, et al. Optimization of pharmacotherapy in chronic heart failure: is heart rate adequately addressed? Clin Res Cardiol. 2013; 102: 23-31.

127. Gelbrich G, Edelmann F, Inkrot S, Lainscak M, Apostolovic S, Waagstein F; CIBIS-ELD investigators. Is target dose the treatment target? Uptitrating beta-blockers for heart failure in the elderly. Int J Cardiol. 2012; 155: 160-6.

128. Düngen HD, Musial-Bright L, Inkrot S, Apostolović S. Heart rate following short-term beta-blocker titration predicts all-cause mortality in elderly chronic heart failure patients: insights from the CIBIS-ELD trial. Eur J Heart Fail. 2014; 16: 907-14.

129. Böhm M, Swedberg K, Komajda M, Borer JS, Ford I, et al. Heart rate as a risk factor in chronic heart failure (SHIFT): the association between heart rate and outcomes in a randomized placebo-controlled trial. Lancet. 2010; 376: 886-94.

130. Swedberg K, Komajda M, Böhm M, Borer JS, Ford I, Dubost-Brama A, Lerebours G, Tavazzi L; SHIFT Investigators. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. Lancet. 2010; 376: 875-85.

131. Mona F, Pharm D, Daniel W, Ileana P, Adams K, et al. Heart Rate or Beta-blocker Dose? Association with Outcomes in Ambulatory Heart Failure Patients with Systolic Dysfunction: Results from the HF-ACTION Trial. JACC, accepted Sep 14, 2015. Reference: JCHF 370. DOI: 10.1016/j.jchf.2015.09.002.