2012

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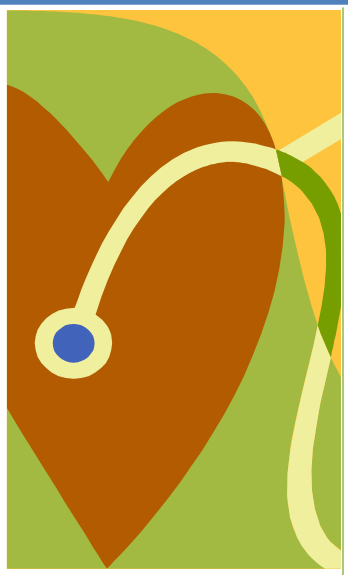

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Master thesis, Programme in Medicine

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Gothenburg, Sweden 2012

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ABSTRACT

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INSTITUTION, CITY, COUNTRY: Section of Cardiology, Department of Medicine, Sahlgrenska University Hospital/Östra Hospital, Gothenburg, Sweden

BACKGROUND: Elderly patients constitute the majority of patients with acute coronary syndrome. Nevertheless, due to a paucity of data, decision-making on the use of percutaneous coronary intervention in this patient group is mainly empirical. Old age is associated with higher risk of adverse outcome of PCI. It is however not well-known what other factors than age that are of prognostic significance. Likely, considering the heterogeneity of the patient group, there is a subgroup of elderly patients for which the prospects of gaining from intervention are greater than for others. By studying and evaluating factors that may be of prognostic significance this subgroup of elderly patients may be identified and so a more optimal use of PCI could be attained.

OBJECTIVE: To evaluate the prognosis of elderly patients undergoing PCI in the setting of ACS. More specifically, to retrospectively identify predictors of all-cause long-term mortality among patients ≥ 80 years, i.e. the "oldest" old.

METHODS: Data on 64 patients ≥80 years undergoing PCI with the indication ACS at the Sahlgrenska University Hospital in Gothenburg, Sweden, were retrospectively collected in a database. In order to identify predictors of long-term mortality multivariate regression analysis was performed. Kaplan-Meier curves were constructed to illustrate the relation between factors of prognostic significance and survival over time.

RESULTS: 4-year all-cause mortality in the current study population was about 40%. Age, heart rate, glomerular filtration rate and prior CABG were identified as independent predictors of long-term mortality.

CONCLUSIONS: In an elderly patient population patients with an age of >85 years, increased heart rate, renal insufficiency and prior CABG are at higher risk of adverse long-term outcome of PCI and so potentially have less to gain from intervention. However, further studies, in particular prospective ones, are needed to validate these results.

KEY WORDS: percutaneous coronary intervention; acute coronary syndrome; elderly; predictors; long-term mortality

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ABBREVIATIONS

ACS	acute coronary syndrome
BMI	body mass index
CABG	coronary artery bypass grafting
CAD	coronary artery disease
CVD	cardiovascular disease
ECG	electrocardiogram
GFR	glomerular filtration rate
LVEF	left-ventricular ejection fraction
MACE	major adverse cardiac events
MI	myocardial infarction
NSTE-ACS	non-ST-elevation acute coronary syndromes
NSTEMI	non-ST-elevation myocardial infarction
PCI	percutaneous coronary intervention
RCT	randomised clinical trial
STEMI	ST-elevation myocardial infarction
UAP	unstable angina pectoris
WHO	World Health Organization

INTRODUCTION

BACKGROUND

Cardiovascular diseases (CVDs), defined as diseases of the heart, vascular diseases of the brain and diseases of blood vessels, are the leading cause of death and disability globally (1). Even though CVDs to a large extent are preventable mortality and morbidity keep rising from a global perspective. According to the World Health Organization (WHO) this is a result of an increase in the prevalence of cardiovascular risk factors caused by the aging of populations and the globalisation of unhealthy behaviours.

The major categories of CVDs are cerebrovascular disease and coronary artery disease (CAD) (1). Out of these, the latter category causes most death and disability, both among men and women. The main underlying pathogenesis of CAD, as well of cerebrovascular disease, is the process of atherosclerosis (1, 2). This refers to a chronic inflammation of the arterial wall which leads to the formation of atheromatous plaques with subsequent obstruction of the arterial lumen and reduction of blood flow. The development of atherosclerotic plaques is a slow process influenced by a number of risk factors such as smoking, high blood pressure and high cholesterol levels (3).

Atherosclerosis is considered as a chronic disease with stable and unstable periods depending on variations in inflammatory activity (4, 5). In the heart, reduced coronary blood flow with subsequent myocardial ischemia typically manifests itself clinically as diffuse pain or discomfort in the chest and changes in the ECG. However, atypical manifestations are not uncommon and myocardial ischemia may also exist in the absence of clinical symptoms and signs (2). In stable CAD the characteristic clinical manifestation, known as stable angina pectoris, is a radiating chest pain elicited by physical exercise and relieved by rest or the administration of nitroglycerin (2, 6). The pathophysiology of stable CAD is an inability of

stenosed coronary arteries to increase blood flow, and thereby the delivery of oxygen, sufficiently to meet an increase in myocardial demand for oxygen, e.g. during physical exercise. During unstable periods CAD may manifest itself clinically as acute coronary syndrome (ACS). ACS is a generic term comprising the conditions of unstable angina pectoris (UAP), myocardial infarction (MI) and sudden coronary death (5, 6). These conditions are, in contrast to stable CAD, usually caused by an abrupt reduction in coronary blood flow due to plaque disruption with subsequent thrombus formation and potential artery occlusion. The extension of myocardial injury in ACS is determined by the degree of ischemia which in turn is determined by several factors (4-6). Belonging to these factors are the duration and totality of artery occlusion and the extent to which there is collateral blood flow to the myocardium distal to the occlusion. In contrast to UAP, in which vessel occlusion of short duration causes transient myocardial ischemic injury, ischemia in MI persists long enough to cause myocardial cell death or necrosis. Myocardial necrosis develops 15-30 minutes after the onset of ischemia and is detected via the release of specific proteins, e.g. cardiac troponin, into the blood by damaged myocytes. Based on changes in the ECG MI is clinically classified as either non-ST-elevation myocardial infarction (NSTEMI) or ST-elevation myocardial infarction (STEMI) (7, 8). In NSTEMI necrosis is limited to the inner, or subendocardial, part of the myocardial wall. In STEMI, due to more severe ischemia usually caused by occlusion of a major coronary artery, necrosis comprises the entire myocardial wall.

The treatment of coronary artery disease aims at relieving symptoms as well as preventing the progression of atherosclerosis, thereby reducing the risk of the development of acute coronary syndrome (2, 5). In ACS the principal objective of treatment, apart from symptom relief, is the upheaval of myocardial ischemia by the restoration of coronary blood flow (5). Treatment also aims at reducing the risk of heart failure and arrhythmia secondary to myocardial

ischemic damage. Furthermore, an important objective of treatment in ACS is the prevention of recurrent thromboembolic events.

The principal treatment modalities for CAD are lifestyle changes, pharmacological treatment and myocardial revascularisation (2, 5, 9). Myocardial revascularisation refers to invasive strategies to restore blood flow in stenosed or occluded coronary arteries and comprises coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) (10). In contrast to CABG, PCI aims at restoring the blood flow of the native coronary artery or arteries by balloon dilatation and stent implantation in stenosed or occluded sections.

According to established guidelines revascularisation therapy is indicated in all patients presenting with symptoms of myocardial ischemia of duration shorter than 12 hours, and in some patients with symptoms of longer duration, and signs of STEMI in the ECG (8). In this context PCI, if performed within 1.5-2 hours from the first medical contact, is the preferred strategy of reperfusion (8, 9). The benefits of so called primary PCI, which is defined as PCI without prior or simultaneous fibrinolysis, compared to pharmacological reperfusion include a decrease in the risk of reinfarction, stroke and death (provided it is performed within the time limit mentioned above) (5). In UAP and NSTEMI, together referred to as non-ST-elevation acute coronary syndromes (NSTE-ACS), an invasive strategy of reperfusion is recommended in patients at high risk for cardiovascular events and death and in patients presenting with either recurrent symptoms or stress-inducible ischemia (5, 7, 10). Indicators of high risk e.g. include relevant changes in troponin-levels, dynamic ST- or T-wave-changes in the ECG, diabetes mellitus, renal insufficiency and old age. The choice of invasive reperfusion strategy, PCI or CABG, in NSTE-ACS is based on the clinical status of the patient in combination with the severity and distribution of CAD. PCI is suitable in most cases of single-vessel disease whereas in multi-vessel disease the choice between PCI and CABG is more complex.

The guidelines on the use of reperfusion therapy in ACS described above are based on data derived from randomised clinical trials (RCTs) or meta-analyses (7, 8, 10). PCI has been the subject of more RCTs than any other intervention. However, data regarding PCI in certain patient subgroups such as the elderly is still limited (9). One reason for this is that elderly patients are often excluded from trials because of their generally high rates of co-morbidities (11). Furthermore, old age in itself is frequently used as an exclusion criterion in RCTs (12, 13).

Despite that evidence on the use of PCI in elderly patients remains limited there are data available indicating that PCI is beneficial in elderly patients with ACS. A recently published review of RCTs and retrospective studies, in which persons ≥ 65 years were defined as elderly, concluded that primary PCI compared to fibrinolysis significantly reduced short-term morbidity (recurrent MI and stroke) and mortality in elderly patients presenting with STEMI (13). Furthermore, another analysis of 22 RCTs showed that the size of the reduction in short-term (30 days) morbidity and mortality with PCI compared to fibrinolysis in STEMI is independent of the patient's age (14). In NSTE-ACS the advantages of PCI over conservative medical therapy have been less clear than in STEMI as shown by either an increased risk with PCI or no difference between the two treatment options (13). However, more recent studies, conducted after stent implantation became routine in PCI, have demonstrated significant reductions in short-term mortality and morbidity among elderly patients who receive invasive treatment.

Concerning outcomes of PCI in elderly patients compared to younger patients observational studies have demonstrated that old age is associated with both higher in-hospital mortality rates and frequent PCI-related complications such as renal failure and bleedings (13, 15-17). Results from studies on mid- and long-term outcomes of PCI are more ambiguous. For example, incidence rates among elderly patients of major adverse cardiac events (MACE),

defined as the combined events of deaths, revascularization and myocardial infarction, have been found to be both higher and similar to rates among younger patients (18-21). Moreover, higher mortality rates were observed among elderly patients at 12 and 36 months follow-up.

The paucity and inconsistency of data on the use of PCI in the elderly has several implications. The underrepresentation of elderly patients in RCTs restricts the applicability of prevailing guidelines in clinical practice (7, 12). In the present situation, it is difficult for physicians to make well-founded decisions on the use of PCI in the elderly. Elderly patients have been found to be less likely than younger patients to undergo PCI, partly because some of the existing data suggest that age is associated with negative outcomes (22-24).

The finding that elderly patients undergo PCI to a lesser extent than younger patients holds even after adjusting for contraindications and co-morbidities that may be of relevance (22-24). The suggestion that elderly patients are sometimes withheld PCI solely because of their age is contrary to prevailing ethical principles (9). Even if age itself has in some studies been found to be a predictor of death and other adverse outcomes of PCI (13, 15, 20, 25) the elderly constitute a heterogeneous group. The term ‘elderly’ is a broad term comprising the “young” old (65-74 years), the “older” old (75-84 years) and the “oldest” old (≥85 years) (26). Moreover, the elderly have considerable individual variation in co-morbidities and physical capabilities (15). In view of the heterogeneity of the elderly patient group it is likely that some elderly patients have better prospects of gaining from PCI in the setting of ACS than others. However, identifying this subgroup of elderly patients for which the advantages of PCI exceed the risks requires data on which factors other than age that are of prognostic significance. Studies aiming at identifying predictors of negative outcome of PCI among elderly patients have been conducted (13, 15, 16, 18, 20, 21, 25, 27-31). However, those studies are mainly retrospective observational cohort studies with a follow-up period of one

year or less. Further studies, in particular prospective ones, are needed to allow for physicians to make well-founded decisions and so optimizing the use of PCI in elderly patients with ACS.

OBJECTIVE OF STUDY

Provided that the subgroup of elderly patients for whom the benefits of undergoing PCI exceed the risk can be identified a more optimal use of the procedure in this patient population may be attained. Identification of patients who have the potential of benefiting from intervention can be made possible by studying and evaluating factors that may be of prognostic significance. The objective of this master thesis is to evaluate the prognosis of elderly patients undergoing PCI in the setting of ACS. More specifically, the objective is to retrospectively evaluate predictors of long-term mortality among patients ≥ 80 years, i.e. the "oldest" old. The thesis constitutes part of a larger research project aiming at, by both retrospective and prospective studies, elaborating a predictive model that can be used in clinical practice for identifying elderly patients who, in terms of risks related to benefits, are suitable candidates for PCI.

SIGNIFICANCE OF THE STUDY

Despite the fact that the elderly constitute the majority of patients with ACS prevailing guidelines, by being based on studies mainly including younger patients, are of limited use in decision-making on PCI in this patient group. This master thesis, and the research project of which it is part, may contribute to an increased knowledge of what factors are of prognostic relevance concerning PCI in the elderly with ACS. Such increased knowledge could in turn facilitate clinical decision-making to the benefit of patients.

METHODS

STUDY POPULATION

The study population of this master thesis is composed of patients ≥ 80 years who underwent PCI at the Sahlgrenska University Hospital in Gothenburg, Sweden, during 2006-2007. The time-period 2006-2007 was chosen to allow for a follow-up period of 4-5 years. Performed PCI procedures for the specified age group and time period were identified from medical records. Within the framework of this study 125 out of the identified procedures were assessed. A number of exclusion criteria were applied to identify the procedures that were to be included in the study. Firstly, since the catchment area of the Sahlgrenska University Hospital for performing PCI during emergency hours is larger than during office hours a substantial amount of the procedures were performed in individuals who are not normally patients of the hospital. These procedures (n=33) were excluded from the study since medical records from before and after the procedure were not accessible for these patients. Secondly, in some cases (n=16) two or more PCI procedures were performed in the same patient. In these cases only the first PCI the individual patient underwent after the age of ≥ 80 years were included. Thirdly, since the objective of the study is to evaluate prognosis after PCI in ACS, elective PCI procedures with the indication of stable angina pectoris (n=9) were excluded. Finally, a few procedures (n=3) involved only coronary angiography without balloon dilatation and stent implantation. These procedures, incorrectly labeled as PCI, were also excluded. After excluding PCI procedures according to the criteria described above 64 procedures in 64 individual patients remained. These procedures and patients constitute the study population of this thesis.

DATA COLLECTION

A thorough survey of the medical records of each individual patient was conducted. Medical records at the Sahlgrenska University Hospital are electronically stored since the middle of the 1990s. All electronically stored information, from all clinical departments of the hospital, concerning the time period before the PCI and up until 4-5 years[1] after the procedure was surveyed. Data on a total number of about 170 variables and 6 outcome measures were, when available, registered in a database. The registered variables could be summarized in 12 principal categories: basic demographics (age, sex), social conditions (e.g. marital status and level of education), functional status (e.g. level of physical exercise and independence in ADL), basic clinical parameters (e.g. BMI, blood pressure at admission and discharge), changes in the ECG, PCI-related variables (e.g. type and number of stents used), UCG-related variables, prior cardiovascular interventions, cardiovascular risk factors and diseases, other co-morbidities (somatic and psychiatric), laboratory parameters (admission and discharge) and medications (admission and discharge). Registered outcome measures included mortality, cardiovascular events and symptoms, hospital readmissions and functional status (level of independence in ADL and physical capabilities).

ETHICAL CONSIDERATIONS

This master thesis, and the research project it is part of, involved the collection of sensitive personal data concerning the health status of living persons. In accordance with the Personal Data Act (1998:204) and the Act Concerning the Ethical Review of Research Involving Humans (2003:460) a permission from the Regional Ethical Review Board, Gothenburg, was obtained before data collection was initiated.

[1] For patients undergoing PCI during April-December 2007 the retrospective follow-up period was between 4 and 5 years. Patients undergoing PCI in 2006 and between January-March 2007 were retrospectively followed-up for 5 years.

STATISTICAL METHODS

Statistical analysis was, due to the limited scope of this master thesis, performed on a selection of 48 of the variables on which data was completed. Variables assumed to be independent of each other and of particular prognostic significance were selected[2]. Moreover, variables for which sufficient data was available were selected. All-cause mortality at 4 years was used as the outcome measure of the analyses. All statistical analyses were made using SPSS® software (version 20, SPSS Inc., Chicago, IL, USA). A p-value of <0.05 was considered significant.

Patients were divided into two groups: those who died during the follow-up period and those who were still alive 4 years after undergoing PCI. Baseline characteristics of the two patient groups are presented as percentages for categorical (or discrete) variables and as means and standard deviations for numerical (or continuous) variables. Values for troponin T and I, which are not normally distributed variables, are presented as medians and quartiles. P-values were calculated in order to determine if there were any significant differences between the patient groups (‘dead’ and ‘alive’) at baseline. The Pearson’s chi-square test was used to calculate p-values for categorical variables. For normally distributed numerical variables the t-test was used while for troponin T and I the Mann-Whitney test was used. Normality of the distribution of the variables was tested by means of histograms.

Univariate regression analysis was performed to determine whether there was any statistically significant relation between each single variable and mortality over time. For troponin T and I logarithmic values were used to adjust for their abnormal distribution. Results of the univariate analysis are presented as hazard ratios (HR). Confidential intervals of 95% were calculated for HRs.

[2] Selected variables are listed in table 1.

In order to determine which variables that were independently related to mortality multivariate Cox regression analysis was performed on variables which were found to be of significance in the univariate analysis. Multivariate regression analysis including all significant variables was conducted. However, since the study population and number of events (i.e. deaths) was relatively small, multivariate analyses were also conducted on a smaller number of covariates at a time. In this way, the applicability of the results to the general population was increased.

Survival analysis was performed to illustrate how different variables were related to survival over time. Kaplan-Meier curves, showing the fraction of patients being alive at different points of time after PCI, were constructed for all variables found to be significantly connected to mortality in the univariate regression analysis. For numerical variables patients were grouped into categories using clinically relevant limit values. The Logrank test was used to establish whether there were any significant differences between patient groups with regard to survival curves.

RESULTS

BASELINE CHARACTERISTICS

Baseline demographic and clinical characteristics of the total study cohort as well as of the two patient groups ‘dead’ and ‘alive’ are presented in Table 1. 26 patients, about 40%, out of the total number of 64 patients died during follow-up. The mean age of the total study cohort was 83.9±3.2 years. The patients who died during follow-up were slightly older than the patients who were still alive 4 years after the PCI procedure. However, the difference in mean age was not significant. Additionally, with 65.4% of the patients who died and 60.5% of the patients who were still alive at 4 years being male, there was no significant difference in the proportion of men between the two patient groups.

Patients who died were living alone to a greater extent than those who survived follow-up. Moreover, they were more dependent in ADL. However, the differences in social conditions and functional status between the patient groups at admission were not significant.

With the exception of glomerular filtration rate (GFR) and congestive heart failure there were no significant differences between the two patient groups concerning basic clinical parameters, laboratory parameters, cardiovascular risk factors and diseases, interventions, co-morbidities and medication (Table 1). Patients who died during follow-up had significantly lower mean GFR at admission than patients being alive at 4 years follow-up (46.4±16.4 compared to 59.0±17.3 ml/min, $p<0.01$). When GFR at admission was further divided into categories of <60 and <30 ml/min both were significantly more frequent in patients who died. The proportion of patients with a history of symptomatic congestive heart failure was 23.1% among patients who died during follow-up compared to 5.3% among patients who still lived at 4 years after the PCI. A left-ventricular ejection fraction (LVEF) of less than 40% was more common among patients who died during follow-up, but not significantly so.

FOLLOW-UP

Results of the univariate and multivariate regression analyses are presented in Table 2 and 3 respectively. 6 of the 48 variables were found to be significantly related to mortality over time in the univariate regression analysis; age, heart rate, haemoglobin levels, glomerular filtration rate, congestive heart failure and prior CABG. Furthermore, as already mentioned, multivariate regression analysis was performed in different multivariate models. Firstly, all significant variables (Table 2) were included. Secondly, considering the limited number of events, only 3 significant variables were included in 4 different multivariate models (Table 3). When all significant variables from the univariate regression analysis were entered into multivariate analysis 2 of the 6 variables, heart rate and prior CABG, were revealed to be independently predictive of mortality over time. As seen in Table 2, heart rate had a HR of 1.022 (95% CI 1.01-1.04, $p<0.05$) and prior CABG a HR of 4.278 (95% CI 1.04-17.68, $p<0.05$) in this analysis. Results of the additional 4 multivariate models, including only 3 significant variables, are presented in Table 3. As seen in this table heart rate remained an independent predictor of mortality in all of these models while prior CABG was significantly related to mortality in only two of the models. Age and GFR were, in contrast to the results of the multivariate regression analysis including all significant variables from the univariate analysis, also found to be significantly related to mortality. However, haemoglobin levels and congestive heart failure were not.

Kaplan-Meier survival curves are shown in Figure 1-6. Figure 1 illustrates that cumulative survival was significantly lower for patients with an age of ≥85 years compared to patients with an age of 80-84 years. Concerning heart rate a trend towards lower survival rates with increasing heart rate is illustrated in Figure 2.A-D. However, a significant difference in survival between patient groups was only seen when a heart rate of > 100 beats/min was used

as limit value (Figure 2-D). However, as seen in Figure 2-D, only 3 out of the patients who died during follow-up had a heart rate of > 100 beats/min at admission. All of these patients died during the first year after the PCI procedure. Survival rates according to haemoglobin levels are shown in Figure 3. A haemoglobin level of < 120 g/L, which is the WHO definition of anemia for men, did not entail significantly lower survival rates (Figure 3-A). Severe anemia, defined as haemoglobin levels of < 110 g/L, was however related to significantly lower survival (Figure 3-B). In regard to glomerular filtration rate Kaplan-Meier survival curves were constructed with limit values of 60 ml/min, equivalent to a moderate reduction of renal function, and 30 ml/min, equivalent to a severe reduction of renal function (Figure 4.A-B). Survival rates were, as seen in Figure 4.A, significantly lower even for a moderately reduced renal function. Kaplan-Meier survival curves for the categorical variables congestive heart failure and prior CABG are presented in Figure 5 and 6 respectively. Concerning prior CABG curves cross at about 4 months after the PCI indicating that the HR for this variable was not proportional over time.

DISCUSSION

The primary findings of this study were that age, heart rate, glomerular filtration rate and prior CABG were independent predictors of all-cause mortality among those aged ≥ 80 years having undergone PCI at 4 years follow-up.

This retrospective study was conducted in a study population of 64 patients ≥ 80 years with ACS undergoing PCI during 2006-2007. As shown in Table 1, this was a highly selected patient group. Indications of selection include well-controlled blood pressure, a majority in sinus rhythm and proportions of only 15% with a reduced LVEF and 13% with symptomatic heart failure. This reflects the reality of daily clinical practice in the elderly patient population where evidence is lacking and decision-making is often empiric. However, despite this selection, and allowing for this pilot study of predictive modeling among elderly patients undergoing PCI, 4 year all-cause mortality was still more than 40%.

Among the variables found to be independent predictors of 4 year all-cause mortality in the current study age, with a HR of 1.167, was one of the strongest. This variable has previously been demonstrated to be an independent predictor of mortality after PCI among patients ≥ 80 years (15, 16, 18, 20, 25). However, there are also studies with conflicting results concerning the prognostic effect of age (21, 27, 31). For example, Kamiya et al. (27) found that among patients ≥ 80 years an age of ≥ 85 years was not predictive of 5-year mortality. This might be due to differences in sample size and study design. Similar inconsistency, indicating that findings from patients ≥ 80 years are not necessarily comparable to those from patients >85 years, has been found concerning the prognostic effects of renal insufficiency on mortality (27, 31). In accordance with previous results (3), heart rate was shown to be a predictor of long-term mortality in this study. Moreover, renal insufficiency and prior CABG were demonstrated to be of negative prognostic significance in the current study population.

Concerning renal insufficiency it has been shown to constantly worsen prognosis in a continuum of cardiovascular disease. Prior CABG was found to be an independent predictor of mortality possibly because it indicates advanced coronary artery disease.

The finding of this study that age is one among several factors of prognostic significance concerning patients ≥ 80 years undergoing PCI supports the hypothesis that there is a subgroup of elderly patients with better prospects of gaining from intervention than others. This thesis may have added to prior knowledge on which variables that are of relevance in the identification of this patient subgroup. The current study clearly indicates that a high heart rate, reduced glomerular filtration rate and prior CABG are of negative prognostic significance implying that patients with the above-mentioned factors probably have less to gain from PCI in the setting of ACS. Still, these results need to be validated in a prospective manner and further studies are needed to test the hypothesis. This study mainly focused on the prognostic significance of clinical characteristics such as laboratory parameters, cardiovascular risk factors, co-morbidities and medications. Even if clinical characteristics have been shown to be more prognostically important among patients ≥ 80 years (18) the evaluation of variables related to e.g. the PCI procedure would be valuable. As described in the methods section, data on 170 variables, including additional clinical as well as PCI-related ones, and 6 outcome measures were collected for this master thesis creating opportunities for further analyses. A more comprehensive retrospective study is performed within the framework of the larger research project of which this thesis constitutes part. This extended study, which also comprises a larger study population (n=200), among other things aims at evaluating predictors of long-term symptom relief and functional outcome. These outcome measures, which in turn are related to quality of life, are of great interest concerning elderly patients for whom the remaining expected length of life may be limited. Furthermore, within

the framework of an extended retrospective study, it would be interesting to evaluate predictors of long-term outcome for the different PCI indications (UAP, NSTEMI and STEMI) separately. Patients presenting with NSTE-ACS constitute a more heterogeneous population in terms of risks and prognosis than patients presenting with STEMI(7). A separate analysis of elderly patients presenting with NSTE-ACS would, as decision-making in this patient group may be particularly complicated, therefore be interesting. Apart from extended retrospective analysis further prospective randomised studies are also needed to allow for the identification of the subgroup of elderly patients who have prospects of benefiting from PCI. A prospective study of patients ≥ 80 years undergoing PCI in the setting of ACS is currently conducted at the Sahlgrenska University Hospital. This study includes a control group of patients who are randomised to either PCI or conservative treatment and will, together with the retrospective analysis described above, form the basis for the elaboration of a predictive model that can be used in clinical decision-making.

STUDY LIMITATIONS

One of the main limitations of this study is its retrospective design. For some of the variables and outcome measures data were scarce. Another main limitation is the lack of a control group, e.g. patients ≥ 80 years who underwent other treatment than PCI. The fact that the study is not randomized and only includes patients undergoing PCI poses a risk of a selection bias. As discussed above, it is likely that the elderly patients who have been considered as suitable candidates for PCI are healthier than the general population of patients ≥ 80 years with ACS. Furthermore, an important limitation of this study is that the study population is relatively small. In particular, the number of events (i.e. deaths) in relation to the variables included in the multivariate regression analysis is limited, calling for caution when

interpreting the results. Finally, this was a single-center study and so the possibilities for extrapolation of results to other centers are limited.

CONCLUSIONS

In summary, this study showed that age, heart rate, glomerular filtration rate and prior CABG were independent predictors of all-cause mortality among patients aged ≥ 80 years undergone PCI upon 4 years follow-up. In order to establish with greater certainty what factors other than age that are of prognostic significance, and their relative importance, further studies are however required. Such studies would facilitate decision-making on the use of PCI in a patient group that, in view of the aging of populations, constitutes an increasing part of the general patient population. This in turn would, both by decreasing the risk of use in patients for whom risks exceed benefits and increasing the probability of use in patients for whom benefits exceed risks, lead to a more optimal use of PCI and so in the end gain patients

POPULÄRVETENSKAPLIG SAMMANFATTNING

Hjärt-kärlsjukdomar är den kategori av sjukdomar som orsakar mest sjuklighet och flest dödsfall i världen. Den vanligaste typen av hjärt-kärlsjukdom är kranskärlssjukdom, det vill säga sjukdom i de artärer som försörjer hjärtat med blod. Kranskärlssjukdom orsakas av en process som kallas för ateroskleros och som innebär att blodfetter lagras in i kärlväggen och bildar så kallade plack. Utvecklingen av plack sker långsamt och påverkas av ett antal riskfaktorer som till exempel rökning, högt blodtryck och höga blodfetter.

Kärl där plack har bildats blir trängre och blodflödet i kärlet försämras därmed. När detta sker i hjärtats kranskärl kan syrebrist uppstå i hjärtmuskeln. Det vanligaste symtomet på syrebrist i hjärtmuskeln är kärlkramp, det vill säga bröstsmärta som framför allt kommer vid fysisk ansträngning då syrebehovet i hjärtmuskeln ökar. Kranskärlssjukdom kan också orsaka hjärtinfarkt. Det som händer vid hjärtinfarkt är att ett plack plötsligt går sönder så att kroppens koagulationssystem aktiveras och en blodpropp bildas. Blodproppen täpper i sin tur helt eller delvis till kärlet. Syrebristen i den del av hjärtmuskeln som försörjs av det kärl som täppts igen blir då så stor att hjärtmuskelceller dör. En hjärtinfarkt ger ofta kraftigare bröstsmärta än kärlkramp och diagnostiseras med hjälp av EKG och blodprov som mäter ett protein, troponin, som läcker ut i blodet från skadade hjärtmuskelceller.

Ett av de viktigaste målen med behandling av kranskärlssjukdom är att förhindra att aterosklerosen, eller åderförfettningen, förvärras och därmed minska risken för hjärtinfarkt. Detta gör man bland annat med hjälp av livsstilsförändringar som ökad fysisk aktivitet och rökstopp och med hjälp av läkemedel mot högt blodtryck och höga blodfetter. När en hjärtinfarkt väl utvecklats är det viktigt att, för att minska risken för att hjärtmuskelceller dör och begränsa skadan på hjärtmuskeln, öppna upp det kärl som täppts till. På så sätt minskar

risken för att hjärtsvikt, det vill säga en minskad förmåga för hjärtat att pumpa ut blod, och rytmrubbningar utvecklas som komplikation till hjärtinfarkten.

En propp som bildats i ett kranskärl kan lösas upp med läkemedel. I de flesta fall föredrar man dock att behandla en akut hjärtinfarkt med ballongvidgning, eller perkutan koronar intervention (PCI). Denna behandling ska ges så fort som möjligt efter att diagnosen hjärtinfarkt ställts. En ballongvidgning inleds med att man går in med en smal slang, eller kateter, i ett kärl i handleden eller ljumsken och, via kroppspulsådern, till hjärtats kranskärl. Via denna kateter sprutas kontrastmedel in samtidigt som röntgenbilder tas. Genom att titta på hur kontrastmedlet sprids i hjärtats kranskärl kan man identifiera det kärl som är tilltäppt. Detta kärl kan sedan öppnas upp med hjälp av en ballong som förs in genom samma kateter som använts för att spruta in kontrastmedel och som blåses upp vid det ställe där kärlet är tilltäppt. Efter att ballongen blåsts upp läggs vanligtvis ett litet metallnät, eller stent, in för att förhindra nya förträngningar.

Nyttan med ballongvidgning vid hjärtinfarkt är välstuderad. När det gäller äldre människor är dock kunskapen om behandlingen, trots att äldre utgör den största delen av patienter med hjärtinfarkt, fortfarande begränsad. Studier har visat att äldre patienter generellt har större risk att drabbas av komplikationer och att avlida i samband med ballongvidgning än yngre patienter. Hög ålder i sig verkar vara en faktor som påverkar prognosen vid ballongvidgning negativt. Äldre utgör dock en brokig grupp när det gäller bland annat samsjuklighet och vitalitet. Sannolikt är det därmed också så att det bland äldre personer finns en stor variation både i risken av att drabbas av komplikationer av ballongvidgning och chansen att dra nytta av behandlingen. Problemet idag är att man inte med tillräcklig stor säkerhet vet vilka andra faktorer än den höga åldern som påverkar prognosen. Detta gör det svårt för läkare att fatta välgrundade beslut om behandling av äldre personer med hjärtinfarkt. I sin tur leder detta till

en risk för att äldre patienter som skulle dra nytta av ballongvidgning undanhålls behandling, och tvärtom, att patienter där riskerna med ballongvidgning egentligen kan anses vara för stora i förhållande till de möjliga vinsterna ändå genomgår behandling.

Syftet med detta examensarbete har varit att studera och identifiera faktorer som påverkar prognosen efter ballongvidgning hos äldre personer med hjärtinfarkt. Arbetet ingår i ett större forskningsprojekt som har som slutgiltigt mål att, utifrån en ökad kunskap om prognostiska faktorer, utarbeta en modell som läkare ska kunna använda som beslutsstöd när det gäller ballongvidgning hos äldre patienter. Som underlag för examensarbetet har information som samlats in från journaler för 64 patienter ≥80 år som genomgått ballongvidgning på Sahlgrenska Universitetssjukhuset i Göteborg under 2006-2007 använts. Från journalerna har bland annat information om vilka sjukdomar förutom hjärtinfarkt patienterna hade, vilka läkemedel de använde, hur fysiskt aktiva de var och vad blodprover i samband med ballongvidgningen visade inhämtats. Journalerna har också gåtts igenom för att se hur det gått för patienterna till och med 4-5 år efter ballongvidgningen. Det visade sig att cirka 40 % av patienterna avlidit under uppföljningsperioden på 4-5 år. Med hjälp av statistiska analyser kunde det konstateras att en ålder över 85 år, en hjärtfrekvens på mer än 100 slag i minuten vid ankomsten till sjukhuset, nedsatt njurfunktion och att tidigare ha genomgått en bypass-operation på hjärtats kranskärl var faktorer som påverkade prognosen efter ballongvidgningen negativt. Av detta kan man dra slutsatsen att, i gruppen 80 år eller äldre, är patienter med de faktorer som beskrivits ovan troligen mindre lämpliga att genomgå ballongvidgning.

Resultaten från den här studien behöver kompletteras med ytterligare studier. Med hjälp av fler studier skulle läkare med större säkerhet kunna avgöra vilka äldre patienter som bör genomgå ballongvidgning vid hjärtinfarkt. Genom att minska risken för både över- och underbehandling skulle detta i slutändan främja patienterna.

ACKNOWLEDGEMENTS

I wish to thank the following people: Michael Fu and Salim Barywani for guidance and for including me in their research project; Josefin Ekelund for great collaboration and company; Alexandra Holmström for helping out with the statistics and the staff of the Research Unit at the Sahlgrenska University Hospital/Östra Hospital for lending me a work-place. Also, a special thanks to my friend and future colleague Daniella Isaksén for rewarding exchanges of thoughts and ideas.

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APPENDIX: TABLES AND FIGURES

Table 2. Univariate and multivariate regression analyses of 4-year all-cause mortality in total study cohort

	Univariate			**Multivariate**		
Total study cohort	**HR**	**95% CI**	**P-value**	**HR**	**95% CI**	**P-value**
Age	1.135	1.02-1.27	0.025*	1.074	0.92-1.25	0.369
Heart rate	1.016	1.00-1.03	0.018*	1.022	1.01-1.04	0.014*
Haemoglobin levels	0.973	0.95-1.00	0.026*	0.991	0.96-1.02	0.532
Glomerular filtration rate	0.963	0.94-0.99	0.007**	0.973	0.94-1.00	0.074
Congestive heart failure	3.043	1.21-7.63	0.018*	1.200	0.28-5.20	0.807
Prior CABG	3.281	1.11-9.67	0.031*	4.278	1.04-17.68	0.045*

Table 3. Different models for multivariate regression analysis of 4-year all-cause mortality in total study cohort

Model 1	**HR**	**95% CI**	**P-value**
Age	1.167	1.03-1.33	0.019*
Heart rate	1.019	1.00-1.04	0.017*
Prior CABG	4.772	1.46-15.60	0.010*
Model 2			
Haemoglobin levels	0.990	0.96-1.02	0.491
Heart rate	1.016	1.00-1.03	0.040*
Prior CABG	2.753	0.84-9.02	0.094
Model 3			
Glomerular filtration rate	0.965	0.94-0.99	0.011*
Heart rate	1.024	1.01-1.04	0.008**
Prior CABG	4.204	1.33-13.25	0.014*
Model 4			

Congestive heart failure	2.796	0.94-8.40	0.066
Heart rate	1.016	1.00-1.03	0.031*
Prior CABG	2.147	0.65-7.11	0.211

Table 1. Baseline demographic and clinical characteristics of patients

	Total study cohort	**Dead**	**Alive**
	n=64	n=26	n=38
Age (years) (mean±SD)	83.9±3.2	84.8±3.7	83.2±2.7
Male (%)	62.5	65.4	60.5
Social Conditions and Functional Status			
Living alone (%)	35.5	41.7	31.6
Dependent in ADL (%)	3.1	7.7	0.0
Basic Clinical Parameters[1]			
BMI (kg/m^2) (mean±SD)	25.4±3.9	25.5±4.7	25.2±3.4
Systolic BP (mmHg) (mean±SD)	150.7±26.8	148.8±27.3	152.1±26.8
Diastolic BP (mmHg) (mean±SD)	83.0±15.2	81.0±12.0	84.4±17.3
Heart rate (beats/min) (mean±SD)	79.0±25.2	85.6±35.5	74.5±13.0
Sinus rhythm (%)	86.2	79.2	91.2
LVEF <40% (%)	14.8	17.4	12.9
Time onset of symptoms-PCI (hours) (mean±SD)	111.1±153.2	112.0±135.1	110.4±167.7
PCI indication			
Unstable angina pectoris (%)	12.5	7.7	15.8
NSTEMI (%)	35.9	42.3	31.6
STEMI (%)	51.6	50.0	52.6
Laboratory Parameters[2]			
Haemoglobin (g/L)(mean±SD)	133.3±17.3	128.2±17.0	136.8±16.8
Sodium (mmol/L) (mean±SD)	138.7±3.1	138.4±3.4	138.9±3.0
Potassium (mmol/L) (mean±SD)	4.1±0,5	4.1±0.6	4.0±0.4
GFR (ml/min) (mean±SD)[3]	53.9±17.9	46.4±16.4**	59.0±17.3
Leukocyte count (x10^9/L) (mean±SD)	9.3±2.9	9.6±3.7	9.1±2.1
PT(INR) (mean±SD)	1.3±0.5	1.3±0.6	1.2±0.4
Total cholesterol (mmol/L) (mean±SD)	4.5±1.1	4.6±1.2	4.4±1.0
Troponin T (µg/L) (median(25th-75th percentile))	1.01(0.25-4.66)	1.79(0.25-4.72)	0.98(0.25-4.57)
Troponin I (µg/L) (median(25th-75th percentile))	4.0(1.3-7.0)	1.67(0.10-1.67)	4.0(1.42-10.00)
Cardiovascular Risk Factors			
Current smoker (%)	6.7	8.0	5.7
Ever smoker (%)[4]	71.7	81.3	66.7
Hypertension (%)	65.6	73.1	60.5
Diabetes mellitus (%)	23.4	34.6	15.8
Hypercholesterolemia (%)	30.2	34.6	27.0
Cardiovascular Diseases			
Prior MI (%)	29.7	42.3	21.1
Angina pectoris (%)	45.3	50.0	42.1
Atrial fibrillation (%)	20.3	23.1	18.4
Congestive heart failure (%)	12.5	23.1*	5.3
Peripheral arterial disease (%)	9.4	11.5	7.9
Interventions			
Prior CABG (%)	7.8	15.4	2.6
Prior PCI (%)	10.9	11.5	10.5
Co-morbidities			
Stroke/TIA (%)	17.2	15.4	18.4
Pulmonary disease (%)	18.8	23.1	15.8
Psychiatric disorder (%)	15.6	19.2	13.2
GFR <60 ml/min (%)	64.5	80.0*	54.1
GFR<30 ml/min (%)	6.5	16.0*	0.0
Medication[5]			
Aspirin (%)	54.8	69.2	44.4
Clopidogrel (%)	9.8	8.0	11.1
Warfarin (%)	6.3	7.7	5.4
Beta-blocker (%)	56.5	61.5	52.8
ACEi/Angiotensin receptor II blocker (%)	31.1	44.0	22.2
Calcium antagonist (%)	32.8	40.0	27.8
Diuretics (%)	32.8	42.3	25.0
Digoxin (%)	9.7	8.3	10.5

[1]BMI, systolic BP, diastolic BP, heart rate and sinus rhythm: values at admission. LVEF >40%: during hospitalization. [2]Troponin T and I: maximum value during hospitalization. All other laboratory parameters: value at admission. [3]GFR according to Cockcroft-Gault. [4]Current or former smoker. [5]Digoxin at admission or during hospitalization. All other

medications at admission only. *p<0.05 dead compared with alive, **p<0.01 dead compared with alive

Figure 1. Long-term survival according to age

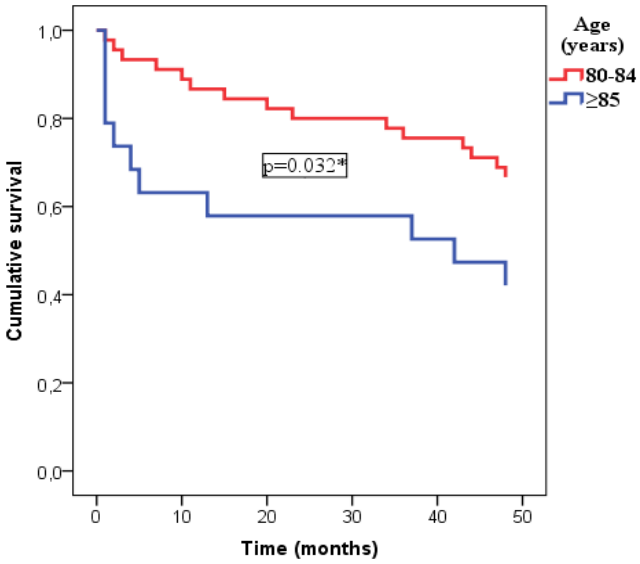
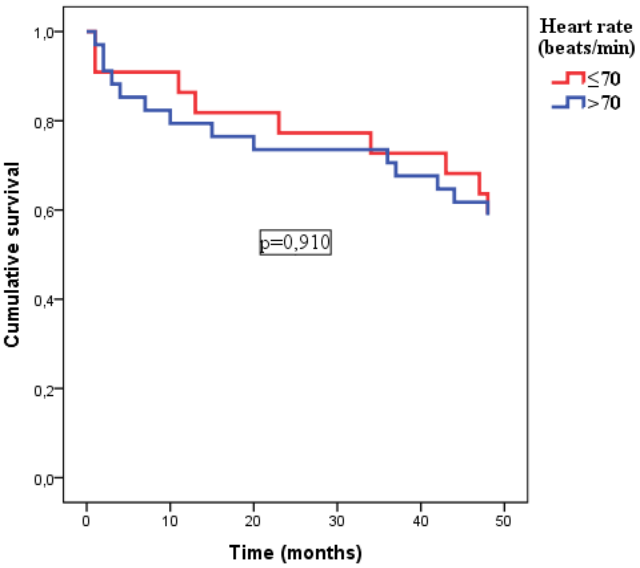
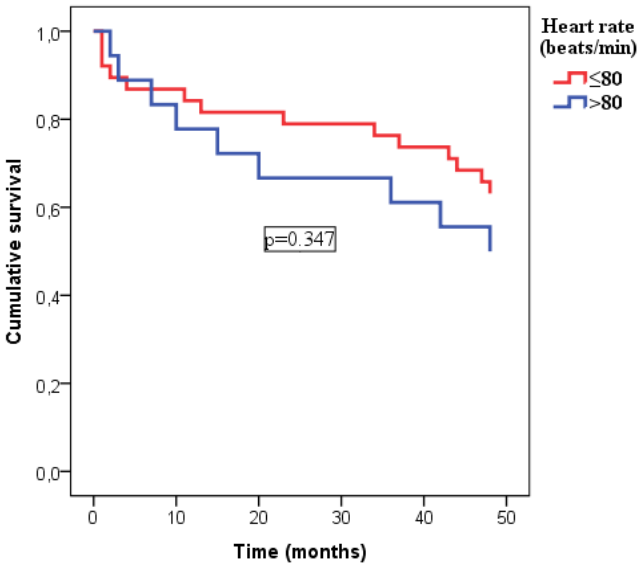


Figure 2. Long-term survival according to heart rate

A **B**





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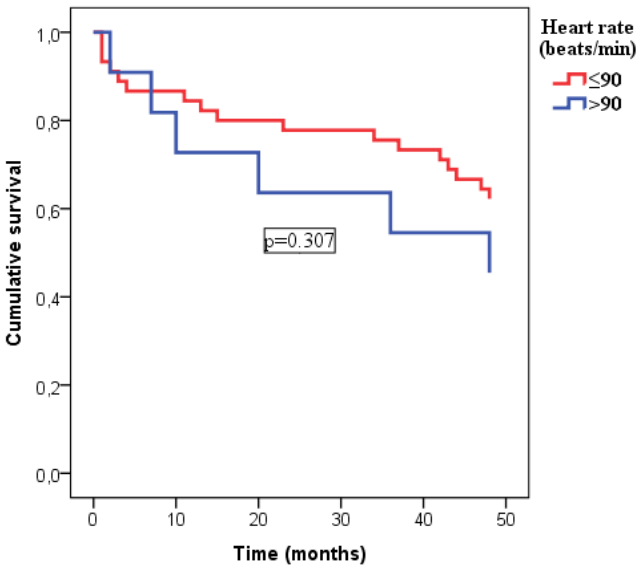


D

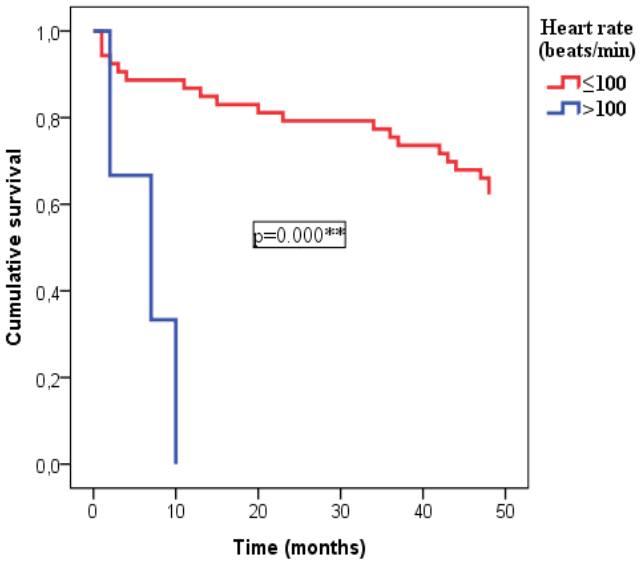
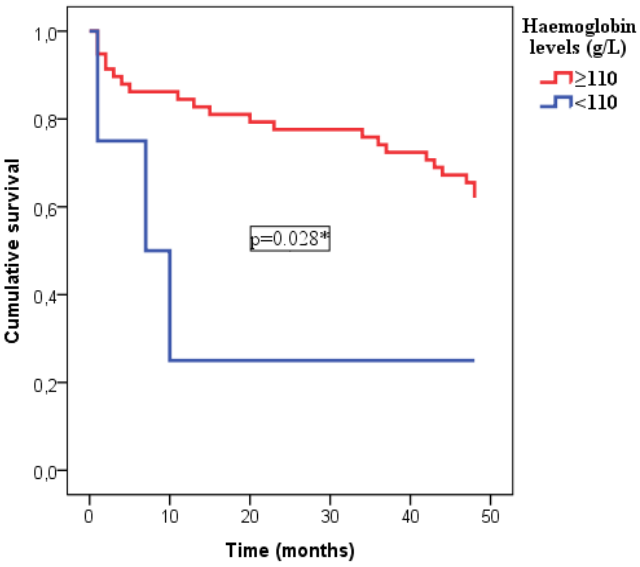


Figure 3. Long-term survival according to haemoglobin levels

A **B**


Cumulative survival
1,0
0,8
0,6
0,4
0,2
0,0
0
10
20
30
40
50
Time (months)
p=0.028*
Haemoglobin levels (g/L)
≥110
<110

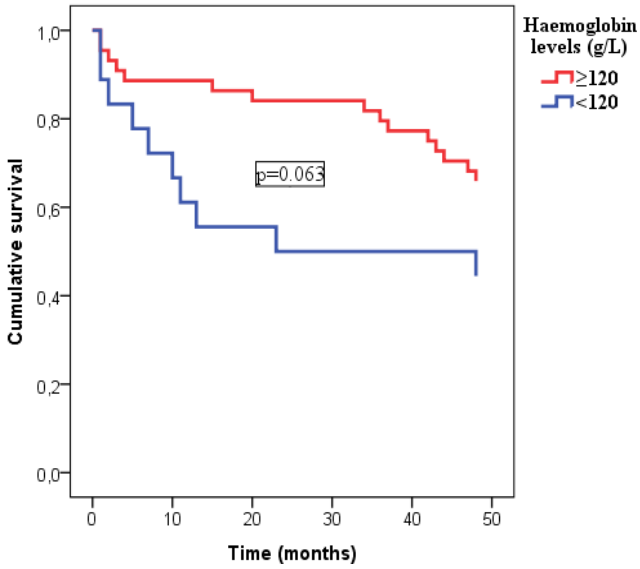

Cumulative survival
1,0
0,8
0,6
0,4
0,2
0,0
0
10
20
30
40
50
Time (months)
p=0.063
Haemoglobin levels (g/L)
≥120
<120

Figure 4. Long-term survival according to glomerular filtration rate

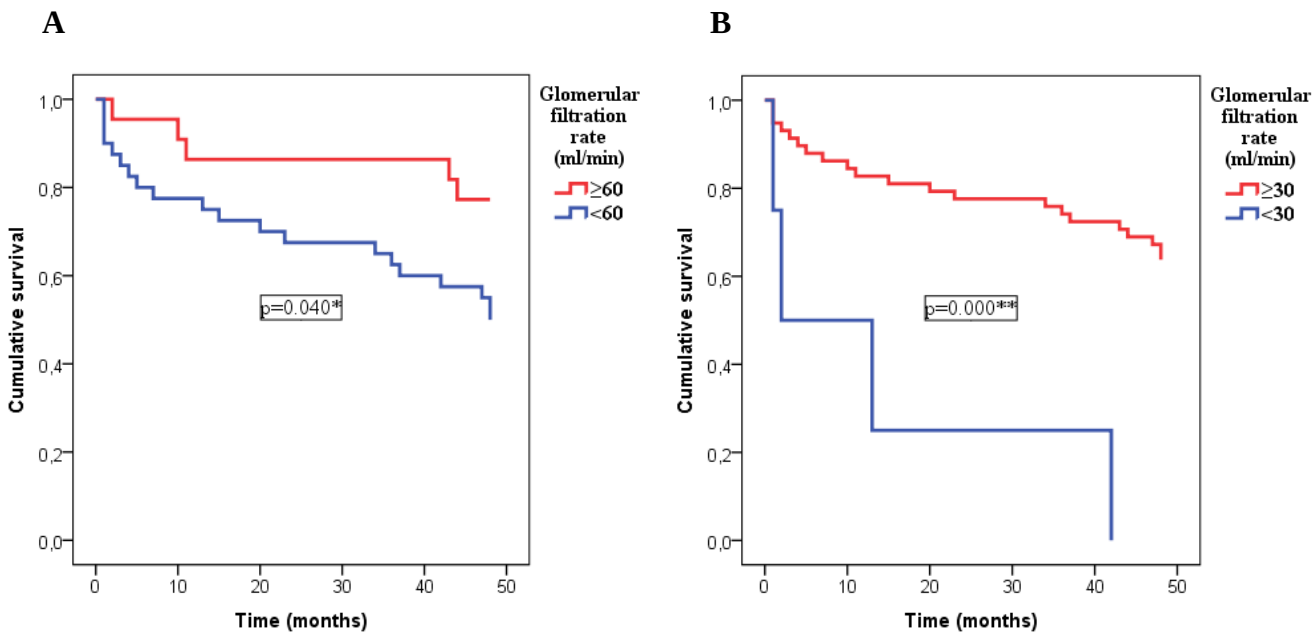


Figure 5. Long-term survival according to congestive heart failure

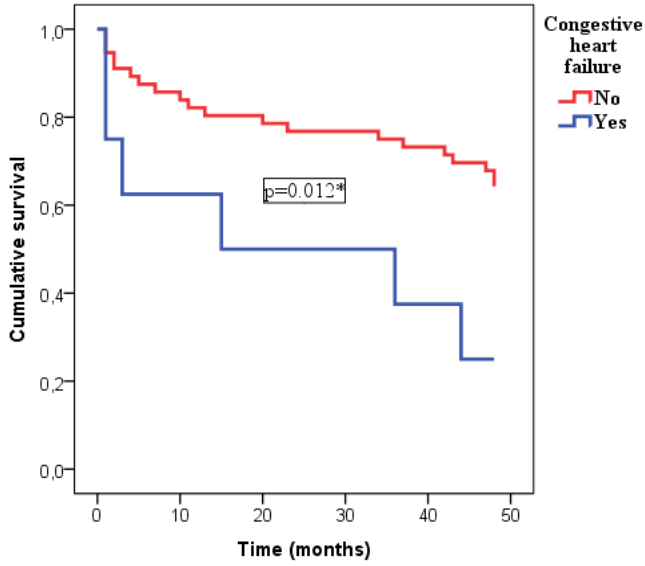


Figure 6. Long-term survival according to prior CABG