Beyond Randomized Clinical Trials

Multi-morbidity, Age and Gender Impact on the Treatment of Coronary Artery Disease

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Thesis for the degree of Philosophiae Doctor

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Þegar slembirannsóknum sleppir

Áhrif fjölveikinda, aldurs og kyns á meðferð kransæðasjúkdóma

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Ágrip

Tilgangur: Konur og fjölveikir aldraðir með kransæðasjúkdóma bera oft skarðan hlut frá borði við framkvæmd slembirannsókna. Tilgangur þessarar doktorsrannsóknar er að rannsaka þessa hópa með gögnum úr gæðaskránni SWEDEHEART. Nánari markmið eru: i) að bera saman árangur kransæða–þræðinga (KÞ) og kransæðavíkkana (KV) á Íslandi og í Svíþjóð; ii) að bera saman líkur kvenna og karla með brátt kransæðaheilkenni (BKH) á að fara í KV og skoða hvort munur er á fylgikvillum og dánartíðni eftir kyni; iii) að bera saman afdrif fjölveikra aldraðra sem fengu ífarandi meðferð við BKH við afdrif þeirra sem fengu eingöngu lyfjameðferð og iv) að skoða árangur og fylgikvilla KÞ og KV hjá einstaklingum á tíræðisaldri.

Aðferðir: Öll gögn komu úr SWEDEHEART sem er safn nokkurra gæðaskráa yfir hjartasjúkdóma. i) Í grein eitt var gerður samanburður á öllum KÞ og KV sem voru framkvæmdar á Íslandi og í Svíþjóð árið 2007. ii) Í grein tvö voru skoðaðar allar KÞ á Íslandi og í Svíþjóð framkvæmdar á árunum 2007-2011. Tilvísanir kvenna í KV og opna kransæðaaðgerð voru bornar saman við tilvísanir karla. Fylgikvillar og 30 daga dánartíðni kynjanna voru borin saman. iii) Í grein þrjú og óbirtu efni var ífarandi meðferð borin saman við lyfjameðferð hjá fjölveikum einstaklingum sem voru sjötugir eða eldri og fengu BKH á árunum 2006-2013 í Svíþjóð og voru skráðir í SWEDEHEART. iv) Í grein fjögur var metinn fjöldi, ábendingar, árangur og fylgikvillar eftir KÞ og KV hjá öllum einstaklingum á tíræðisaldri sem fóru í slíkar aðgerðir á árunum 2006-2014 í Svíþjóð.

Niðurstöður: i) Fjöldi KÞ á mann var hærri á Íslandi en í Svíþjóð en fjöldi KV var sá sami. Stöðug hjartaöng var algengari sem ábending á Íslandi en í Svíþjóð. Munur var á áhættuþáttum og ábendingum sjúklinga á Íslandi og í Svíþjóð. KV voru framkvæmdar á nokkuð svipaðan hátt. Einn munur var að þrætt var í gegnum úlnliðsslagæð í 1% tilvika á Íslandi en í 33% tilvika í Svíþjóð ($p<0.001$). Fylgikvillar eftir kransæðavíkkanir KV voru 6% á móti 3% á þræðingarstofu og 8% á móti 5% á hjartadeild, á Íslandi borið saman við Svíþjóð (bæði $p<0.01$).

ii) Alls voru 34,120 KÞ ± KV framkvæmdar í konum en 72,761 í körlum. Hjá 27% kvenna og 12% karla fundust ekki marktækar þrengingar við KÞ. Fylgikvillar eftir KV voru algengari hjá konum (leiðrétt hlutfallslíkuhlutfall [HLH] með 95% öryggisbili 1.58 [1.47-1.70]). Konur með þrengingu í einni kransæð fóru síður í KV en karlar. Í hópnum með hjartavöðvadrep með ST hækkun á

hjartarafriti (STEMI) fóru 94% kvenna og 97% karla í KV en í hópnum með BKH án ST hækkunar (NSTE-ACS) fóru 82% kvenna og 86% karla í KV. Í hópnum með þrengingar í þremur kransæðum og/eða í höfuðstofni og NSTE-ACS, fóru konur oftar í KV (leiðrétt HLH 1.12 [1.05-1.20]) en var sjaldnar vísað í opna kransæðaaðgerð (leiðrétt HLH 0.83 [0.77-0.90]). Enginn kynjamunur var á þrjátíu daga dánartíðni hjá öllum hópnum (3% hjá konum og 2%, leiðrétt HLH 0.97 [0.84-1.05]). Hvorki var kynjamunur á dánartíðni í hópnum með þrengingu í einni kransæð, né í hópnum með þrengingar í þremur kransæðum og/eða höfuðstofni.

iii) Alls voru rannsakaðir 10,825 fjölveikir einstaklingar sem voru sjötugir eða eldri með BKH (2004 höfðu STEMI og 8821 NSTE-ACS). Sjúklingar með STEMI sem fengu ífarandi meðferð fengu síður samsettan klínískan endapunkt, 31% miðað við 55% af þeim sem fengu lyfjameðferð (leiðrétt áhættuhlutfall [95% öryggisbil] 0.73 [0.63-0.80]). Ekki var hægt para hópinn með NSTE-ACS sem fékk ífarandi meðferð og þann sem fékk lyfjameðferð með áhættuskora-pörun (propensity score).

iv) Alls fóru 1,692 einstaklingar á tíræðisaldri í KÞ og KV í Svíþjóð á níu árum. Af þeim höfðu 87% einhver kransæðaþrengsli og 62% þrengsli í tveimur eða fleiri kransæðum. KV höfðu bráðar ábendingar hjá 94% einstaklinga á tíræðisaldri og 8% þeirra fengu fylgikvilla; dánartíðni þeirra á spítala var 8%.

Ályktanir: Hægt er að rannsaka ýmsa minnihlutahópa með gögnum úr SWEDEHEART gæðaskránni. Konur fóru síður í KV og opna kransæðaaðgerð en karlar en sá munur á meðhöndlun hafði ekki áhrif á dánartíðni þeirra. Þegar fjölveikir aldraðir fá STEMI leiðir ífarandi meðferð til lækkunar samsetts endapunkts án þess að auka tíðni endurinnlagna vegna blæðinga. Kransæðasjúkdómur er útbreiddur meðal einstaklinga á tíræðisaldri og fara þeir aðallega í KV vegna bráðra ábendinga. Þetta ásamt hárri tíðni fylgisjúkdóma á líklega þátt í að útskýra tíðni fylgikvilla og dánartíðni.

Lykilorð: Kyn, fjölveikir aldraðir sem þurfa á margs konar heilbrigðisþjónustu að halda, SWEDEHEART, kransæðavíkkun, ífarandi meðferð.

Abstract

Aims: The purpose of this doctoral research is to investigate the treatment of coronary artery disease in groups that are underrepresented in randomized clinical trials using the SWEDEHEART registry. The more specific aims are: i) to compare the outcomes of coronary angiographies (CA) and percutaneous coronary interventions (PCI) in Iceland, with the outcomes in Sweden; ii) to compare the revascularization rate and complication rate in women and men with acute coronary syndromes (ACS); iii) to compare the outcomes of an invasive strategy to that of a non-invasive strategy in older people with multi-morbidity, complex health needs and ACS; and finally, iv) to study catheterizations in nonagenarians.

Methods: Data originated from SWEDEHEART, a collection of cardiology registries used in Iceland and Sweden. i) In Paper I, all CA and PCI performed in Iceland and Sweden in 2007 were compared. ii) Paper II analyzed all consecutive CA between 2007-2011 due to ACS to explore gender differences in revascularization, in-hospital complications and 30-day mortality. iii) Paper III and unpublished data compared one-year outcome following invasive strategy in patients ≥ 70 years with multi-morbidity and complex health needs that were admitted in 2006-2013, due to ACS, to the outcome of a non-invasive strategy. iv) Paper IV enrolled all consecutive nonagenarians undergoing CA or PCI during 2006-2014 and examined indications, treatment decisions and outcomes.

Results: i) More CA were performed per capita in Iceland in 2007 than in Sweden, but the overall PCI rate was similar. Stable coronary artery disease was more common as an indication for both CA and PCI in Iceland than in Sweden. The practice of PCI was largely similar in the two countries. One of the differences was the use of radial access; it was used in 1% of catheterizations in Iceland compared to 33% in Sweden. After PCI, the complication rate in the coronary care unit was 8% and 5%, in Iceland and Sweden respectively.

ii) In total 34,120 CAs ±PCIs were performed in women and 72,761 in men during the study period. No significant stenosis was found in 27% of women and 12% of men. Women with one-vessel disease were less likely to undergo PCI compared to men, 94% and 97% for those with ST-elevation myocardial infarction (STEMI) and 82 and 86% respectively for those with non-ST elevation ACS (NSTE-ACS). Amongst patients with three-vessel

disease or left main stem disease and NSTE-ACS, women were more likely to undergo PCI, (adjusted OR 1.12 ([1.05-1.20]) but less likely to undergo coronary artery bypass graft (adjusted OR 0.83 [0.77-0.90]). There was no gender difference in 30-day mortality (3% vs. 2%, adjusted OR 0.97 [0.84-1.05]), with similar results in those with one-vessel disease and those with three-vessel diseases and/or left main stem stenosis.

iii) Multi-morbid patients with complex health needs and ACS registered in SWEDEHEART were 10,825 (2,004 with STEMI and 8,821 with NSTE-ACS). After STEMI, patients in the invasive group had a significantly lower risk of one-year primary event (death, ACS, stroke or transient ischemic attack [TIA]), compared to those who were in the non-invasive group, 31% and 55%, (risk-adjusted hazards ratio [HR] 0.73 [95% CI 0.63-0.80]). The risk of readmissions due to bleeding events was not increased. Patients with NSTE-ACS could not be matched with propensity scores.

iv) A total of 1,692 nonagenarians underwent catheterizations, of whom 87% had at least one significant stenosis and 62% had multi-vessel disease. The indication for PCI vas ACS in 94%. Both in-hospital complication rate after PCI and in-hospital mortality were 8%.

Conclusion: Groups that are underrepresented in randomized clinical trials can be studied using SWEDEHEART. Women are less often treated invasively compared to men, but this does not affect their mortality. Multi-morbid older people with complex health needs and STEMI have a high risk of new ischemic events and, in concordance with randomized studies in younger healthier patients, benefit from an invasive strategy. Most nonagenarians undergoing CAs have multi-vessel disease and a high level of lesion complexity, which, along with multi-morbidity and mainly acute indications, might partly explain both the in-hospital mortality and complication rate.

Keywords: Gender, multi-morbid older people with complex health needs, revascularizations, SWEDEHEART, invasive strategy.

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Three statisticians contributed to this thesis. Henrik Renlund at UCR consulted on the design of logistic regression models and handling of missing cases in Paper II. Bodil Svennblad at UCR designed the forest plot in figure 16. Bodil also merged the databases for Paper III and unpublished data. Aldina Pivodic, statistician at Statistiska Konsultgruppen in Gothenburg, performed the survival analyses in Paper III and Paper IV. I would like to thank them all for their contributions.

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Content

List of abbreviations

ACE-I	Angiotensin-converting enzyme inhibitors
ACS	Acute coronary syndromes
ADL	Activities of daily living
ADP	Adenosine diphosphate
AIRE study	The Acute Infarction Ramipril Efficacy Study
AMI	Acute myocardial infarction
ARB	Angiotensin II receptor blockers
ASA	Acetylsalicylic acid
ATP	Adenosine triphosphate
BARI 2D	The Bypass Angioplasty Revascularization Investigation 2 Diabetes
BMS	Bare metal stents
CA	Coronary angiography
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CGA	Comprehensive geriatric assessment
CI	Confidence interval
CKMB	Creatine kinase MB isoenzyme
COPD	Chronic obstructive pulmonary disease
The COURAGE trial	The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation trial
CVD	Cardiovascular disease
DAPT	Dual antiplatelet therapy

DES	Drug-eluting stents
ECG	Electrocardiogram
ESC	European Society of Cardiology
eGFR	Estimated glomerular filtration rate
GRACE-risk score	The Global Registry of Acute Coronary Events-risk score
HbA1c	Glycosylated hemoglobin
HR	Hazard ratio
ICD-10	Statistical Classification of Diseases, 10th revision
IQR	Interquartile range
LDL	Low-density lipoprotein
LMWH	Low-molecular-weight heparin
The LONGEVI-SCA registry	Impacto de la Fragilidad y Otros Síndromes Geriatricos en el Manejo y Pronóstico Vital del Anciano con Síndrome Coronario Agudo sin Elevación de Segmento ST
NSTEMI	Non-ST-elevation myocardial infarction
NSTE-ACS	Non-ST-elevation acute coronary syndromes
OR	Odds ratio
PCI	Percutaneous coronary intervention
PET	Positron emission tomography
PVD	Peripheral vascular disease
RIKS-HIA	The Register of Information and Knowledge About Swedish Heart Intensive Care Admissions
SCAAR	The Swedish Coronary Angiography and Angioplasty Registry

SD	Standard deviation
Senior PAMI	Primary Angioplasty Versus Thrombolytic Therapy for Acute Myocardial Infarction in the Elderly
SEPHIA	The National Registry of Secondary Prevention
SPECT	Single photon emission computed tomography
STEMI	ST-elevation myocardial infarction
SWEDEHEART	The Swedish Web-system for Enhancement and Development of Evidence-based care in Heart Disease Evaluated According to Recommended Therapies
TIA	Transient ischemic attack
TRIANA	TRatamiento del Infarto Agudo de miocardio eN Ancianos
UAP	Unstable angina pectoris

List of figures

List of tables

List of original papers

This thesis is based on the following original publications, which are referred to in the text by their Roman numerals:

Paper I: Gudnason T, Gudnadottir GS, Lagerqvist B, Eyjolfsson K, Nilsson T, Thorgeirsson G, Thorgeirsson G, Andersen K, James S. (2013). Comparison of interventional cardiology in two European countries: A nationwide internet-based registry study. *Int J Cardiol*. 168(2):1237-42.

Paper II: Gudnadottir GS, Andersen K, Thrainsdottir IS, James S, Lagerqvist B, Gudnason Th. (2017). Gender differences in coronary angiography, subsequent interventions and outcomes among patients with acute coronary syndromes. *Am. Heart J*. 191: 65-74.

Paper III: Gudnadottir GS, Andersen K, James S, Lagerqvist B, Thrainsdottir IS, Ravn-Fischer A, Varenhorst C, Gudnason Th. (2017). Invasive strategy in STEMI provides benefits to multi-morbid older people with complex health needs. Manuscript.

Paper IV: Gudnadottir GS, Andersen K, Thrainsdottir IS, James S, Lagerqvist B, Libungan B, Gudnason Th. (2017). Age comes to PCI—Cardiac catheterizations in nonagenarians during 2006-2014. Manuscript.

Declaration of contribution

Paper I: I took part in planning this study. I performed all statistical analyses. I wrote the manuscript draft and participated in all subsequent revisions.

Paper II: I planned this study. I analyzed all data and interpreted the results. I made the graphics except figure 2. I wrote the manuscript draft and participated in all subsequent revisions.

Paper III: I planned this study. I participated in the statistical analyses. A statistician performed the survival analyses, but I interpreted the results. I wrote the manuscript draft.

Paper IV: I planned this study. I performed all analyses except the survival analysis. I interpreted the results. I made the graphics. I wrote the manuscript and participated in all subsequent revisions.

1 Introduction

1.1 General introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide, causing 17.3 million deaths per year. CVD-related deaths are estimated to continue to increase and to reach over 23.6 million in 2030 (Laslett et al., 2012). Coronary artery disease (CAD) was the single disease that most men and women died from in 2015, 4.6 million men and 4.2 million women ("Health statistics and information systems. Estimates for 2000-2015. Cause specific mortality.," 2017). Every day clinicians are faced with decisions in treating groups with CAD that are not well represented in most clinical trials. Those include women and older people, especially multi-morbid older people (Bourgeois et al., 2017)(Mehta et al., 2016). Considering the aging of the western population those clinical day to day issues are only going to increase.

The terms coronary heart disease and ischemic heart disease are often used interchangeably with CAD. Some investigators use ischemic heart disease for all disease that cause ischemia within the myocardium, for example, obstruction of the coronary arteries, obstruction in the microcirculation and imbalance in supply/demand of oxygen. In those cases, CAD refers to disease in the major coronary arteries (The EUGenMed Cardiovascular Clinical Study Group 2016). In this thesis, the term CAD will be used for all the above.

1.1.1 Atherosclerosis

The most common cause of CAD is atherosclerosis that can either fully or partially occlude the coronary arteries. Atherosclerosis is an accumulation of cholesterol deposits, which may start in adolescence. Chronic inflammation commonly plays a role. The endothelium gradually changes when it is subjected to hemodynamic disturbances, inflammation, oxidative stressors or other stimuli. The endothelium becomes more permeable to inflammatory cells such as monocytes as well as low-density lipoprotein cholesterol (LDL) (Nabel & Braunwald, 2012). Monocytes enter the arterial wall and mature into macrophages. The macrophages accumulate oxidized and glycosylated LDL and become foam cells that produce cytokines and attract more inflammatory cells. The inflammatory response in atherosclerosis is complicated, some cells and cytokines increase atherosclerosis while others inhibit the process (Libby, 2012). Both the smooth muscle cells and endothelial cells proliferate and extracellular matrix is formed (figure 1). This leads to a fibrous cap over a developing atheromatous plaque (Nabel & Braunwald, 2012).

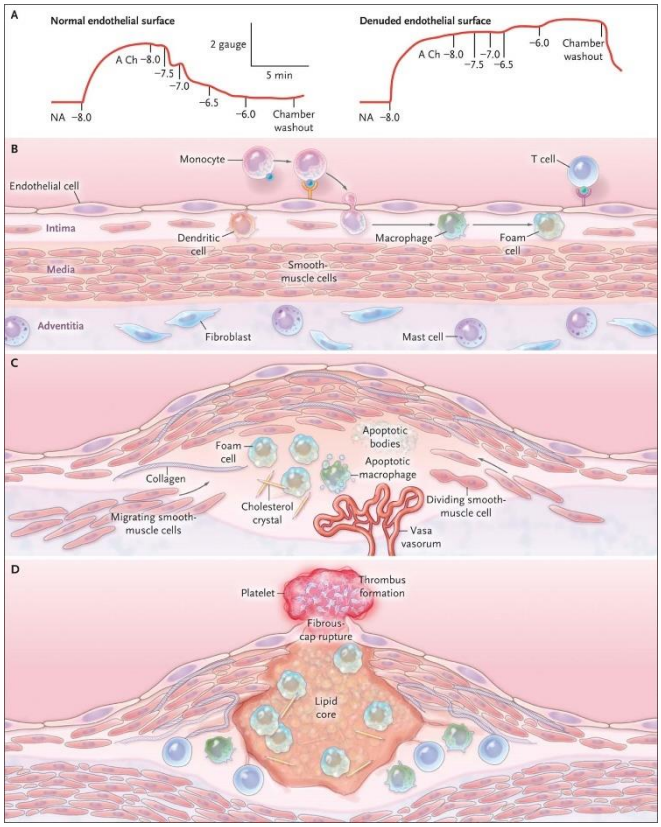

Figure 1. Atherosclerosis.

Panel A shows how arterial smooth muscle with endothelium responds to acetylcholine by producing vasodilating nitric oxide. On the right, endothelial cells were denuded and nitric oxide was not released, leading to vasoconstriction. Panels B through D show the development of atherosclerosis. The initial steps include adhesion of blood leukocytes to activated endothelial cells, migration of leukocytes into the intima, maturation of monocytes into macrophages and their uptake of lipid, yielding foam cells (Panel B). Lesions progress as smooth muscle cells migrate from the media to the intima, the resident intimal and media-derived cells proliferate and extracellular matrix macromolecules are synthesized. Lipid, cholesterol crystals and micro vessels accumulate in the central region of the plaque, forming a necrotic core (Panel C). Thrombosis complicates physical disruption of the atherosclerotic plaque. Fracture of the cap exposes blood coagulant components to tissue factors in the plaque, triggering occlusive thrombus formation that limits blood flow (Panel D). Adapted from reference (Nabel & Braunwald, 2012) with permission.

1.1.2 Pathology and forms of CAD

Genetic and lifestyle factors both contribute to the development of atherosclerosis and CAD. Smoking, hypertension, diabetes, waist/hip ratio, dietary patterns, physical activity, alcohol consumption, blood apolipoproteins and psychosocial factors have collectively been shown to account for around 90% of the risk for acute myocardial infarction (AMI) (Yusuf et al., 2004). CAD has a strong genetic component (Lloyd-Jones et al., 2004) and during the last 12 years, the use of genome-wide association studies has led to the discoveries of dozens of loci that increase the risk of CAD (Khera et al., 2016; Roberts, 2014). Several risk factors also have a genetic predisposition, such as high cholesterol and central obesity.

Atherosclerosis can progress to the point that the lumen of the coronary artery narrows enough to limit the blood flow to the heart under exertion or in a stress situation. Thus, the patient experiences symptoms under exertion. This form of CAD is called stable CAD or stable angina. CAD can also present abruptly as an acute coronary syndrome (ACS), where plaque rupture and thrombosis most often play a role in the pathogenesis. ACS includes four different syndromes; unstable angina (UAP), myocardial infarction without ST-elevation on electrocardiogram (ECG) (non-ST-elevation myocardial infarction [NSTEMI]), myocardial infarction with ST-elevation (ST-elevation myocardial infarction [STEMI]) and cardiac arrest (Roffi et al., 2016). UAP and NSTEMI are collectively called non-ST-elevation acute coronary syndromes (NSTE-ACS); STEMI and NSTEMI are collectively called AMI.

The most common cause of ACS is plaque rupture. When the fibrous cap of the plaque is disrupted the procoagulant core is exposed resulting in platelet adhesion and activation. Activated platelets release, among other substances, adenosine diphosphate (ADP) and thromboxane A2. There is activation of the coagulation cascade. Thrombin converses fibrinogen to fibrin; there is further platelet activation and a platelet plug is formed (figure 1d and figure 2) (Furie & Furie, 2008; Nabel & Braunwald, 2012). Other types of atheromatous plaques and different mechanisms can cause thrombus formation, but this discussion will be featured later. If the interruption of the blood flow is temporary and does not lead to myocardial cell death, the plaque rupture causes UAP. If the blood flow disturbance leads to prolonged ischemia and death of myocardial cells in the parts of the heart closest to the heart chamber, it is called sub endocardial infarction or NSTEMI. When the ischemia results in transmural necrosis, STEMI evolves. The death of the myocardial cells increases the amount of various proteins that can, in turn, be used in diagnosing AMI (Thygesen et al., 2007).

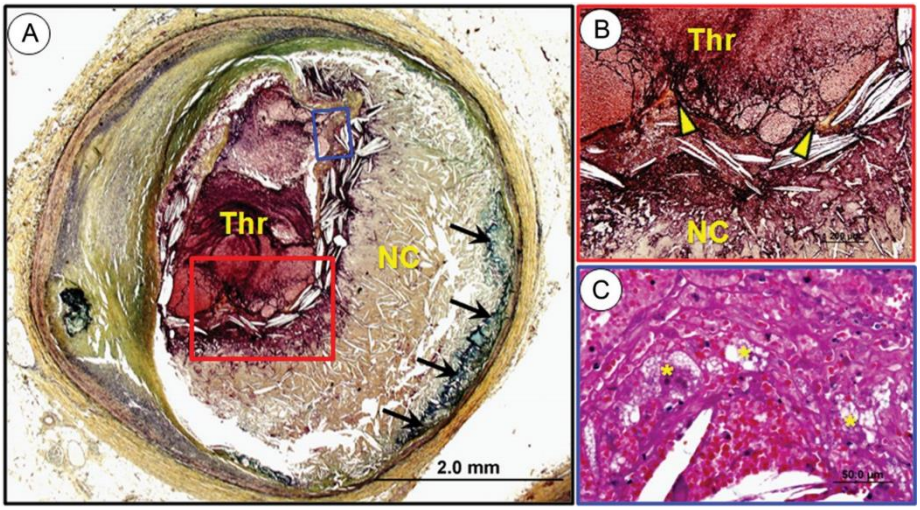

Figure 2. Plaque rupture.

Cross-sectional photomicrograph of a coronary artery showing plaque rupture. (A) Note the presence of an acute occlusive luminal thrombus (Thr) with an underlying large necrotic core (NC) and almost total absence of a fibrous cap. The medial wall is destroyed and near the base of the NC note the presence of calcification (arrows). (B) Higher-magnification image of the rupture site (red box in A). Thin fibrous cap is disrupted (arrowheads). (C) Higher-magnification of thrombus with cholesterol clefts, (blue box in A), red cells and foamy macrophages (asterisks). Adapted from (Falk et al., 2013) with permission.

1.1.3 Symptoms and diagnosis of CAD

CAD can present with various symptoms and signs. The cornerstone of diagnosing CAD is a good medical history and physical examination (Haasenritter et al., 2012). Then, various non-invasive, as well as invasive tests, can be used to confirm the diagnosis.

1.1.3.1 Stable CAD

The most common symptom of CAD is substernal discomfort, often described as heaviness, which can radiate to the jaw, shoulders or the arm. Other common symptoms that can accompany chest pain are diaphoresis, dyspnea and nausea. CAD may present with only one of these symptoms (Chun & McGee, 2004). It helps to divide chest pain into typical angina, atypical angina and non-anginal chest pain. Typical angina meets three characteristics: a) It is located post sternal, b) provoked with exercise or emotional distress, and c) relieved by nitroglycerin or rest within minutes. When chest pain meets two out of three characteristics, it is called atypical

angina and when it meets one or lacks all it is called non-anginal chest pain (Montalescot et al., 2013). Some patients may present with no symptoms of their CAD or only have vague general symptoms such as dizziness, irregular heartbeat and fatigue; this is especially common in older people and patients with diabetes (Kawano et al., 2016).

A thorough physical examination of the heart, lungs and vascular system should be performed in all patients and resting ECG taken (Chun & McGee, 2004). Even in severe stable CAD a normal ECG is not uncommon and does not exclude CAD. ECG can show signs of CAD, for example old AMIs, and it provides a reference point for future events. In most cases an echocardiography, also called ultrasound, of the heart, should be performed. It does not confirm or deny the presence of CAD but it adds valuable information about the overall capacity of the heart to pump, the ejection fraction. The ejection fraction is an important prognostic indicator in all forms of CAD. Echocardiography can also reveal other diseases that can give symptoms similar to CAD, such as valvular diseases. Chest x-ray is appropriate in selected patients to exclude other causes of chest pain (Montalescot et al., 2013).

To confirm the diagnosis of stable CAD, several non-invasive tests are available. The most common and least expensive of these is an ECG-based stress test utilizing a treadmill or stationary bicycle. Stress tests may even be performed with medications that induce stress on the heart. Various types of imaging-based stress tests are available, including stress-echocardiogram, two types of myocardial perfusion scintigraphs (single photon emission computed tomography and positron emission tomography) and cardiac magnetic resonance stress testing. In younger patients with low and intermediate pre-test probability, a coronary computed tomography angiography is sometimes performed. It examines the anatomy of the coronary arteries and a normal study in low-risk individuals is highly suggestive of the absence of obstructive coronary disease. The type of test that is most appropriate depends on pre-test probability, individual risk assessment and pre-existing conditions of the patient. Pre-test probability is different in different age groups and between men and women (figure 3 and figure 4). When individuals with stable CAD have severe angina or a very high-risk profile, an invasive investigation with coronary angiography (CA) to confirm CAD is recommended (Montalescot et al., 2013). CA is a procedure where the coronary arteries are catheterized, injected with a contrast dye and the vessels are then visualized with x-ray imaging. Access to the arterial system is usually either through radial artery or the femoral artery (figure 5) (Grech, 2003).

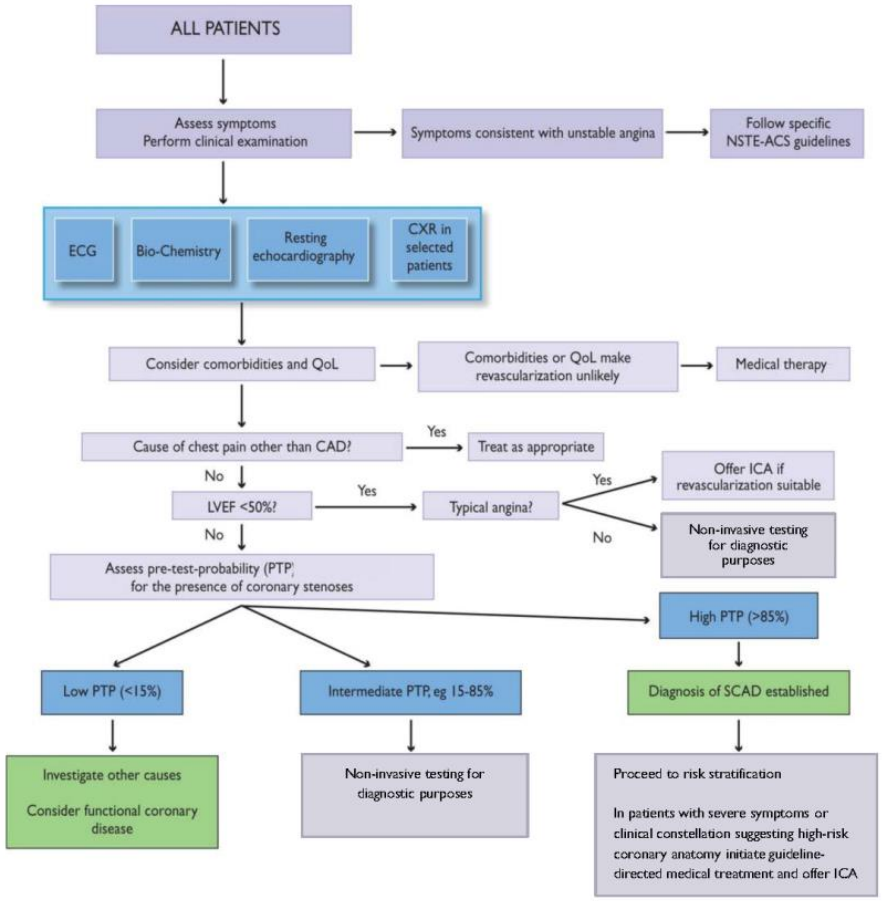

Figure 3. Initial diagnostic management of patients with suspected stable coronary artery disease.

CAD: coronary artery disease; CTA: computed tomography angiography; CXR: chest X-ray; ECG: electrocardiogram; NSTE-ACS: non-ST-elevation acute coronary syndromes; ICA: invasive coronary angiography; LVEF: left ventricular ejection fraction; PTP pre-test probability; SCAD: stable coronary artery disease; QoL: quality of life. Adapted from the guidelines of the European Society of Cardiology with permission (Montalescot et al., 2013)

	Typical angina		Atypical angina		Non-anginal pain	
Age	Men	Women	Men	Women	Men	Women
30–39	59	28	29	10	18	5
40–49	69	37	38	14	25	8
50–59	77	47	49	20	34	12
60–69	84	58	59	28	44	17
70–79	89	68	69	37	54	24
>80	93	76	78	47	65	32

Figure 4. Clinical pre-test probability of stable coronary artery disease.

Blue groups have a pre-test probability of 15-65% and could have either an electrocardiogram (ECG)-based stress test as the initial test or non-invasive imaging-based tests. Groups in light red boxes have a probability of 66-85% and should have non-invasive imaging-based tests. The groups in the red box have a pre-test probability over 85% and stable coronary artery disease can be assumed. Adapted from the guidelines of the European Society of Cardiology with permission (Montalescot et al., 2013).

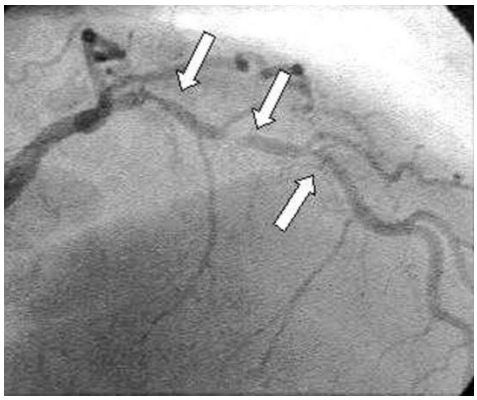

Figure 5. Coronary angiography.

A catheter tube is inserted into the coronary arteries; access is usually through the radial artery or the femoral artery. The coronary arteries are injected with contrast dye and visualized with x-ray imaging. The photo illustrated three lesions in left anterior descending artery. Adapted from (Grech, 2003) with permission.

1.1.3.2 ACS

Chest pain that does not subside with rest or comes with minimal exertion is suggestive of ACS, either UAP or AMI. In diagnosing ACS, the medical

history and physical examination continue to be important, alongside taking an ECG and cardiac biomarkers as soon as possible. Changes on ECG that are suggestive of ACS are new ST-segment elevations or bundle branch block as well as new ST-segment depressions or Q waves (Chun & McGee, 2004); a normal ECG, however, does not exclude ACS (Thygesen et al., 2007). When myocardial cells die, various proteins appear in the blood that can be measured and used to diagnose AMI. The proteins are called cardiac biomarkers and the most common are myoglobin, cardiac troponin T, cardiac troponin I and creatine kinase MB isoenzyme (CKMB). Troponin T or I are almost myocardial tissue-specific as well as highly sensitive in diagnosing AMI and are the preferred biomarker (figure 6) (Thygesen et al., 2012).

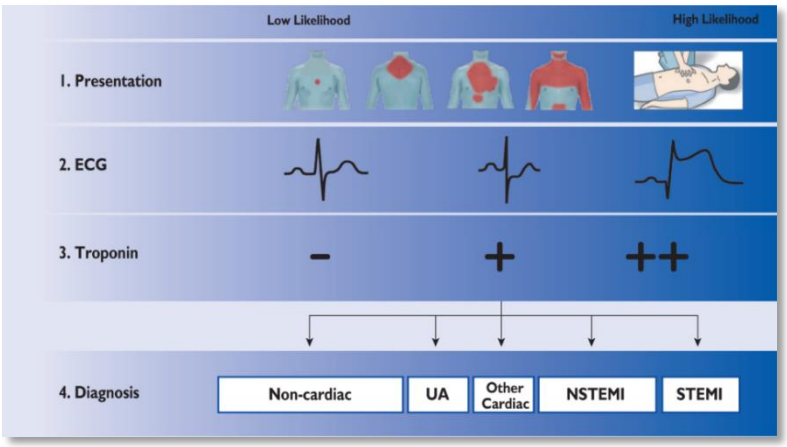

Figure 6. Initial assessment of patients with suspected acute coronary syndromes.

The initial assessment is based on the integration of low-likelihood and/or high-likelihood features derived from clinical presentation, 12-lead ECG and cardiac biomarkers. UAP: unstable angina pectoris; NSTEMI: non-ST-elevation myocardial infarction; STEMI: ST-elevation myocardial infarction. Adapted from the guidelines of the European Society of Cardiology with permission (Roffi et al., 2016).

Chest x-rays can aid in excluding other causes of acute chest pain such as pneumonia and pneumothorax (Thomas et al., 2002). Echocardiography can be of help if the diagnosis is uncertain and spiral computer tomography should be performed if pulmonary embolus or dissections of the aorta are suspected, which can both present with chest pain and/or dyspnea (Roffi et al., 2016).

The continuing investigation of ACS is intermingled with the treatment of ACS. The next steps depend on whether ST elevations on ECG are present or not, as well as the individual risk. The individual risk includes the risk for cardiac arrhythmias and ischemic events, as well as the risk for complications of invasive investigations or antithrombotic medical treatment (Ibanez et al., 2017; Roffi et al., 2016). Current guidelines do not recommend a different approach for women or older patients, but there are specific considerations for both groups that will be discussed later.

1.1.4 Treatment of ACS

The treatment of ACS is aimed at relieving the symptoms of angina and preventing or reducing as much as possible myocardial damage and necrosis. Furthermore, treatment is aimed at decreasing the risk of sudden cardiac death associated with ACS.

1.1.4.1 STEMI

When patients present with STEMI, they should be transported quickly to a hospital and receive antiplatelet therapy with 300 mg loading dose of Acetylsalicylic acid (ASA). Pain and anxiety should be relieved and oxygen delivered to those who are hypoxic or have heart failure, with the goal of keeping saturation slightly over 90%.

Reperfusion therapy is indicated in almost all patients with STEMI and symptoms of <12 h duration (figure 7). Reperfusion means that blood flow is restored with either thrombolytic therapy or an immediate percutaneous coronary intervention (PCI) most often called a primary PCI. First a CA is performed and if an occlusion or stenosis is found a guide wire is introduced through the stenosis or occlusion. A balloon catheter is introduced on to the guidewire and advanced to the level of the stenosis or occlusion, where it is inflated and consequently dilates the lumen. Then, a stent is most often deployed to keep the vessel open (figure 8). The preferred reperfusion therapy of STEMI is PCI, but if transportation to a catheterization lab exceeds 90-120 minutes, thrombolytic therapy is given instead (figure 7). Patients with STEMI should receive a second antiplatelet medication, such as clopidogrel or ticagrelor, as well as an anticoagulation drug. They also receive medications that lower the risk of new ischemic events or progression of heart failure (Ibanez et al., 2017). These medications are discussed more in the following chapter about treatment of NSTE-ACS.

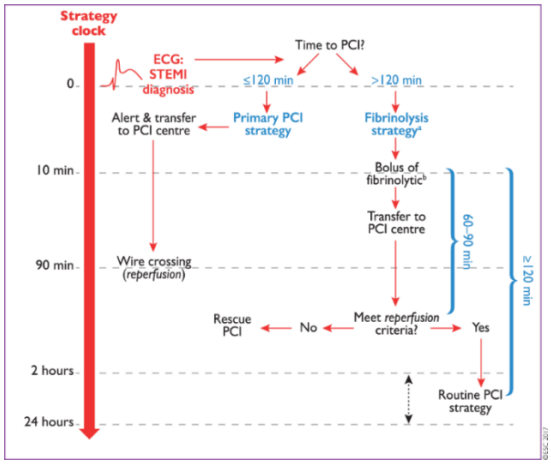

Figure 7. Reperfusion therapy in patients with ST-elevation myocardial infarction.

Treatment aims at restoring blood flow as soon as possible with reperfusion therapy, preferably with primary percutaneous coronary intervention (PCI), but if primary PCI is not available within 120 minutes, fibrinolysis is given. ECG: electrocardiogram; STEMI: ST-elevation myocardial infarction; PCI: percutaneous coronary intervention. The figure is adapted from the guidelines of the European Society of Cardiology with permission (Ibanez et al., 2017).

1.1.4.2 Medical treatment of NSTE-ACS

The first-line treatment in NSTE-ACS is medical therapy with two types of antiplatelet drugs as well as anticoagulant drugs to reduce thrombus formation, decrease myocardial cell death and lower mortality (figure 9) (Wallentin et al., 2009; Yusuf et al., 2001). The first antiplatelet drug is ASA which irreversibly inactivates cyclooxygenase-1 and suppresses thromboxane A_2 activity in platelets. The second antiplatelet drug that is given is usually a P2Y12 receptor antagonist. They inhibit ADP from binding to its P2Y12 receptors and thus inhibit ADP-induced platelet aggregation in the forming of hemostatic plugs and thrombi. The most common ones are clopidogrel, prasugrel and ticagrelor (Roffi et al., 2002). A third group of platelet inhibitors in use are the glycoprotein IIb/IIIa antagonists that inhibit glycoprotein IIb/IIIa integrin complexes on two adjacent platelets. They were more widely used before the start of routine use and pretreatment with P2Y12 receptor antagonist but are still in use during and after PCI in certain patients. Anticoagulant drugs which inhibit either factor Xa or thrombin are given in addition to the antiplatelet drugs. These include unfractionated heparin, low-molecular-weight heparin (LMWH), fondaparinux and bivalirudin (figure 9) (Roffi et al., 2016).

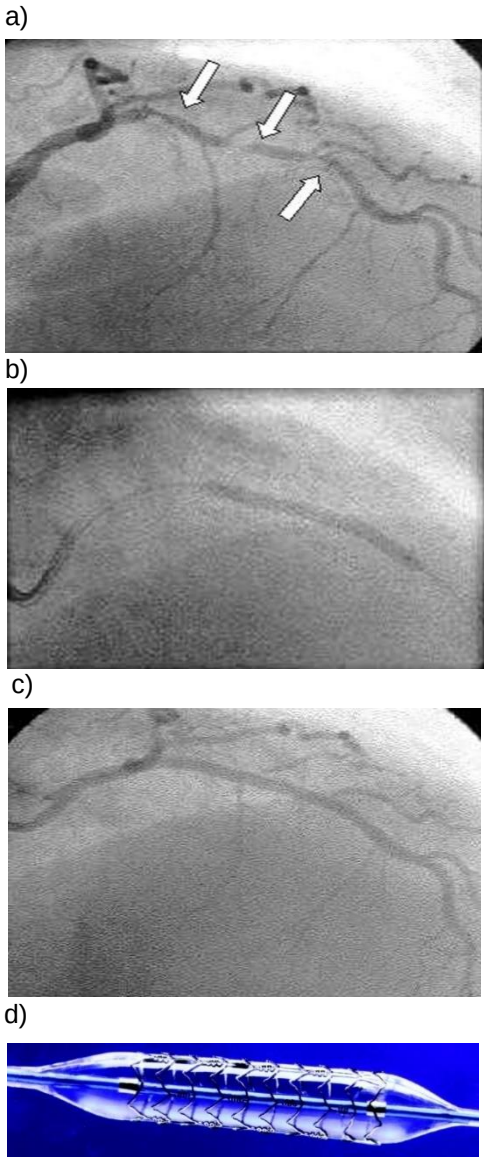

Figure 8. Percutaneous coronary intervention

Panel a) shows the same artery as in figure 5, b) shows a stenosis being stented, c) shows the artery after stenting and d) shows a stent that can be inserted into a coronary artery. Adapted from reference (Grech, 2003) with permission.

Anti-ischemic drugs are used during ACS. Beta-blockers inhibit the effects of catecholamines and thereby lower heart rate, blood pressure and myocardial contractibility. Their early administration decreases mortality after both STEMI and NSTEMI and they can reduce the size of the AMI (Yusuf et al., 1988). Nitrates dilate the arteries, increase blood flow to the myocardium and lower blood pressure. Nitrates provide symptom relief but do not affect prognosis (Borzak et al., 1998). Nitrates are especially important when there is a spasm of the coronary arteries (Roffi et al., 2016).

Angiotensin-converting enzyme inhibitors (ACE-I) are recommended in both NSTE-ASC and STEMI patients with reduced cardiac ejection fraction, diabetes or high blood pressure. ACE-I inhibit a step in the renin-angiotensin system and have been shown to reduce mortality in the settings of AMI and reduce cardiac remodeling and progression of heart failure. If the ACE-I is not tolerated, angiotensin II receptor blockers (ARB) can be used instead (The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators, 1993; Roffi et al., 2016).

Statins reduce blood cholesterol by blocking a HMG-CoA reductase, a liver enzyme which plays a central role in the production of cholesterol. They have other less known pleiotropic effects, for example, suppression of vascular inflammation and vascular dilation. Statins decrease atherosclerosis and decrease the likelihood of new thrombotic events and deaths. European Society of Cardiology (ESC) guidelines recommend high-intensity statins such as atorvastatin in patients with ACS. They should be started within 1-4 days from index ACS (Catapano et al., 2016).

1.1.4.3 Revascularization in NSTE-ACS

The decision to proceed with CA and, when appropriate, revascularization with PCI or coronary artery bypass graft (CABG) in patients with NSTE-ACS is called invasive strategy (figure 10). When done in patients within 24-72 hours, it is called early invasive strategy. Selectively invasive strategy or conservative strategy means that patients are invasively investigated only if they continue to have symptoms despite optimal medical treatment. The decision to adapt an invasive strategy and its timing is based on risk stratification, both the risk for further ischemic events and the individual risk associated with invasive procedures. Risk stratification is based on clinical history and symptoms, vital signs and findings from physical examination as well as ECG and laboratory results (Roffi et al., 2016).

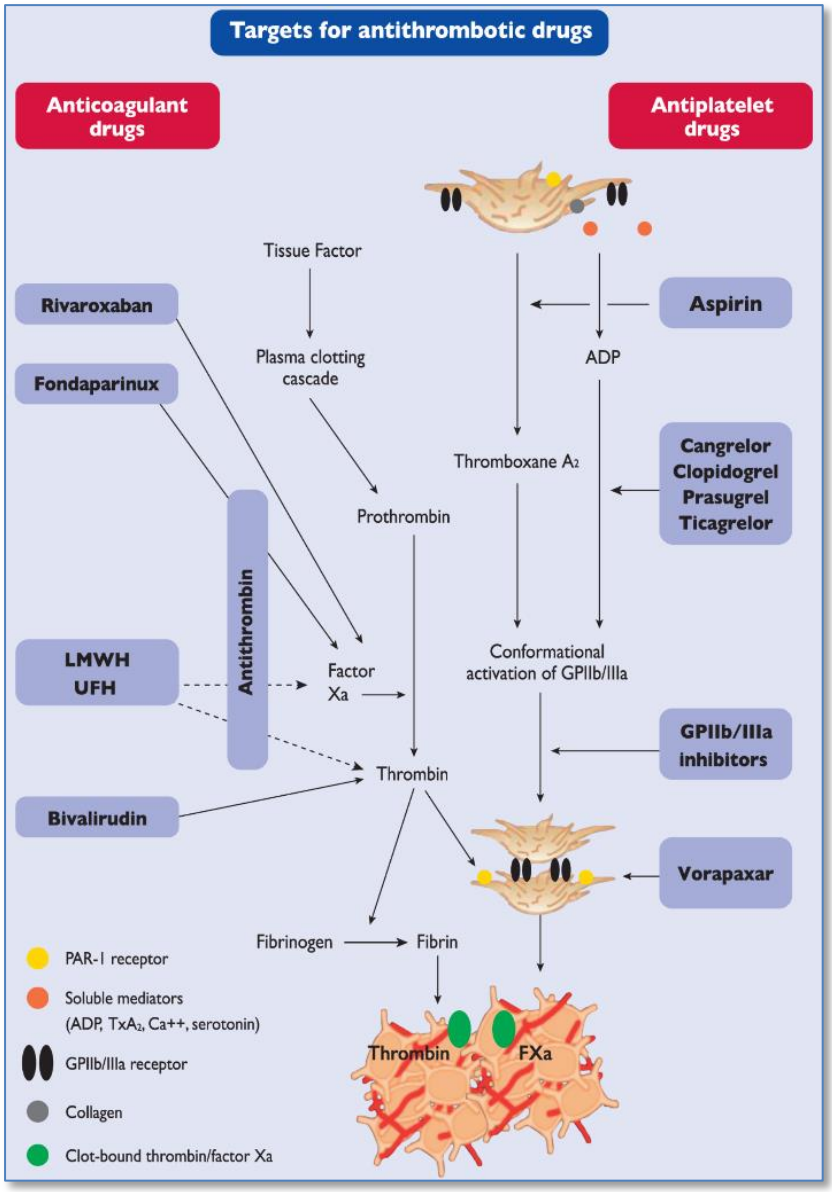

Figure 9. Antithrombotic drugs.

The figure depicts the targets of available antithrombotic drugs that can be used to inhibit blood coagulation and platelet aggregation during and after thrombus. The figure is adapted from the guidelines of the European Society of Cardiology with permission (Roffi et al., 2016). Aspirin: Acetylsalicylic acid. ADP: adenosine diphosphate. AT: antithrombin. GP: glycoprotein. LMWH: low-molecular-weight heparin. Tx: thromboxane. UFH: unfractionated heparin. Vorapaxar is a protease-activated receptor I (PAR I) blocker.

The Global Registry of Acute Coronary Events risk score (GRACE-risk score) gives a quantitative assessment of the risk of a new AMI or other ischemic events, as well as the short- and long-term mortality risk. This risk score should be applied to all NSTE-ACS patients (K. A. Fox et al., 2014). Compared to conservative or selective invasive strategy based on symptoms, a routine invasive strategy in NSTE-ACS has been shown to reduce rehospitalizations and mortality (Alfredsson et al., 2011; Bavry et al., 2006).

In modern practice of PCI, stents are used to keep the coronary arteries open after a balloon has been inflated in the stenotic part (figure 8c). The first stents used were bare metal stents with restenosis rates up to 40%. During the last 15 years' various drug-eluting stents have been introduced, which has reduced restenosis to below 5%. The drugs in the stents inhibit proliferation and migration of vascular smooth muscle cells that form the extracellular matrix which causes restenosis. After the placement of stents, two platelet inhibitors are usually administered for 6-12 months, often referred to as dual antiplatelet therapy (DAPT) (Grech, 2003; Stefanini & Holmes, 2013). If the initial CA in the acute phase of NSTE-ACS identifies the vessel that is suspected to have caused the event, a culprit vessel, it is usually treated with PCI during the same procedure. It is still a matter of debate whether or not other vessels with significant stenosis discovered at that time should also be treated during the index procedure or the hospital stay in the case of multi-vessel disease.

Revascularization of patients with NSTE-ACS and multi-vessel disease can also be achieved, and sometimes preferably so, with CABG. CABG is customarily performed through a midline sternotomy. The left internal mammary artery is usually used as a graft to bypass the stenosis in the left anterior descending artery and veins harvested from the legs of the patient are used to bypass stenosis in other coronary arteries. The most commonly used is the greater saphenous vein of the leg (J. H. Alexander & Smith, 2016). The timing for myocardial revascularization and the selection of revascularization method, namely PCI or CABG, depends on various factors such as clinical presentation, risk stratification, diabetes and other comorbidities, frailty, cognitive status, whether the ejection fraction is lower than normal and the anatomic severity and pattern of CAD (Roffi et al., 2016).

1.1.4.4 Long-term care after ACS

Patients who smoke should be encouraged to quit smoking immediately. All patients should aim for a healthy diet and after the acute phase they should be encouraged to exercise regularly. DAPT is recommended for up to 12

months, but the period can be shortened or lengthened depending on individual risk for bleeding and ischemic events. Beta-blockers and statins are given during the acute phase and recommended long-term unless contraindications are present. Blood pressure, diabetes and other risk factors should be well managed in both patients during and after ACS (Ibanez et al., 2017; Roffi et al., 2016).

1.1.5 Treatment of stable CAD

In patients with stable CAD, medical therapy aims at improving symptoms such as angina, hindering progression of atherosclerosis and preventing thrombotic events like ACS. Antiplatelet therapy is recommended. ASA is the therapy of choice for most patients. In patients with prior AMI, prior stroke or peripheral vascular disease (PVD), clopidogrel, a P2Y12 receptor antagonist, is recommended. Statins should also be used in patients with stable CAD to lower cholesterol and decrease the risk of AMIs as well as mortality. ACE-I reduce AMI risk as well mortality in a subgroup of patients with stable CAD, namely those with heart failure, prior AMIs, as well as high-risk diabetes. Beta blockers are indicated in patients with lowered ejection fraction to attenuate progression of heart failure, but have not been shown to reduce mortality. Short- and long-acting nitrites are used for symptom relief (Montalescot et al., 2013).

Revascularization with either PCI or CABG in patients with stable CAD can be an option, especially if the patient does not respond to medical therapy or tolerates it poorly. In a group of patients with stable CAD, where the coronary anatomy was known and patients with left main stem stenosis had been excluded, The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial in 2007 demonstrated that performing PCI in patients without severe angina on optimal medical therapy did not reduce death or nonfatal MI. However, invasive treatment improved the symptoms of angina. Two-third of the patients in the COURAGE trial had one- or two-vessel disease and around 40% had low angina burden (Boden et al., 2007). In some groups with a high likelihood of ischemic events, for example, people over 75, PCI reduces mortality in patients with stable CAD (Pfisterer, 2004). Some studies have shown PCI to improve functional capacity in older people (Chait et al., 2011; Figueiredo Neto et al., 2015). The ESC guidelines recommend that the clinician should consider whether the patient has symptoms despite optimal medical therapy and make a risk assessment for future thrombotic events based on the patient age and risk factor profile, the burden of CAD shown at CA and the left ventricular ejection fraction. Revascularization with either PCI or CABG is recommended in the patients at high risk for thrombotic events or death (Montalescot et al., 2013).

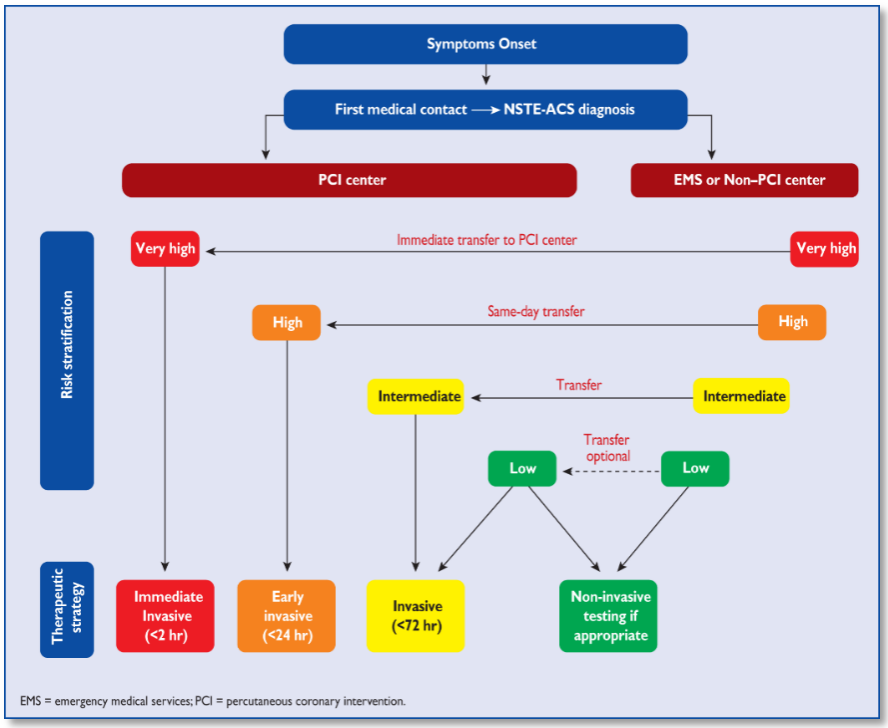

Figure 10. Selection of treatment strategy in patients with non-ST-elevation acute coronary syndrome.

Very high-risk group includes patients with hemodynamic instability or recurrent or ongoing chest pain refractory, life-threatening arrhythmias or cardiac arrest, recurrent ST-T wave changes as well as mechanical complications of MI. High-risk group includes patients with positive cardiac biomarker, dynamic ST- or T-wave changes or the Global Registry of Acute Coronary Events (GRACE) risk score >140. Intermediate risk group constitutes individuals with GRACE-risk score 109-140, diabetes, ejection fracture of the left ventricle under 40% and prior history of cardiac interventions. Adapted from guidelines of European Society of Cardiology with permission (Roffi et al., 2016).

CAD costs countries in the European Union around €59 billion a year in direct health-care costs, productivity losses and informal care of people (Wilkins et al., 2017). It is therefore essential to create platforms to make sure that as many as possible suffering from CAD receive optimal evidence-based care. One way is to collect information from quality registries for CAD and use them to give feedback to patient care centers, as well as to conduct scientific studies. Quality registries in cardiovascular care are numerous and we will explore some of them in the next section.

1.2 SWEDEHEART and other quality registries in Sweden

“When you need to innovate, you need collaboration”

Marissa Mayer

CVD is the leading cause of death in Sweden in both men and women and CAD caused around 42% of those deaths ("Swedeheart, background and history," 2017). To improve the quality of care of patients with CAD, a national quality registry called SWEDEHEART started in 2009. It was created by merging four existing quality registries and is the largest of its kind in Sweden.

Sweden has 108 government-funded quality registries in health care ("All Swedish Quality Registries," 2016). Their completeness and the quality of data varies greatly, with 60% of them covering over 80% of their target population. Many registries are considered important for research in their field as well as for the development of evidence-based care (Emilsson et al., 2015).

SWEDEHEART stands for The Swedish Web-system for Enhancement and Development of Evidence-based care in Heart Disease Evaluated Per Recommended Therapies. SWEDEHEART collects information on patients hospitalized for ACS, patients undergoing coronary or valvular interventions and surgery. There is also a follow-up and prevention aspect of the registry. SWEDEHEART was formed by merging the Register of Information and Knowledge About Swedish Heart, Intensive Care Admissions (RIKS-HIA), the Swedish Coronary Angiography and Angioplasty Registry (SCAAR), the Swedish Heart Surgery Registry and the National Registry of Secondary Prevention (SEPHIA). There are a couple of hundred variables in SWEDEHEART; among them are variables for patient demographics and comorbidities, treatment, complications and outcomes. The registry is web-based. Data is registered online directly by the caregiver and immediately encrypted. SWEDEHEART provides users with real-time online interactive reports where each hospital can compare its outcome over time and with other hospitals. Using the unique personal identification number that every citizen has in Sweden, SWEDEHEART can be merged with the National Cause of Death Register, the National Patient Registry and with the National Registry of Drug Prescriptions recording all drug prescriptions in Sweden (Jernberg et al., 2010).

RIKSHIA contains 106 variables about patients admitted with ACS. Those include variables for patient demographics and medical history, ECG changes, biochemical markers, other clinical features and clinical investigations, medical treatment in hospital, interventions, hospital outcomes, discharge diagnoses and discharge medications (Jernberg et al., 2010). The degree of patient coverage was 68-98% in 2011 in patients younger than 80, with the median around 85%. The degree of coverage for older patients was considerably lower, varying from 24% to 96%, with median around 60% (SWEDEHEART 2011 Annual Report, 2012).

SCAAR has almost 100% coverage of all patients undergoing CA and/or PCI. Beside baseline patient demographics, the registry includes a detailed description of angiographic findings, procedures, type of stenosis, type of stents used, which antithrombotic treatment is given and complications both in the catheterization lab and the coronary care unit (Jernberg et al., 2010).

The Swedish National Patient Register contains diagnoses at discharge for all hospital stays in Sweden and outpatient hospital based specialist care. Most of the diagnoses in the registry have around 85-95% positive predictive value. The sensitivity, however, varies greatly. For diagnoses that require hospitalization, like AMI and stroke, the sensitivity is over 90%, but for diseases that do not necessarily require hospitalization, it is much lower. An example is chronic obstructive pulmonary disease (COPD), where the sensitivity is only around 26% (Ludvigsson et al., 2011). A study in 2016 examined how good the combined use of the National Patient Register and the Swedish Cause of Death Register were in identifying bleeding events in patients with atrial fibrillation receiving anticoagulation. The combined use of the registries yielded 99.5% sensitivity and 94.0% specificity in diagnosing major bleeding events, when counting fatal bleeding events as the first or second cause of death and all hospitalizations with bleeding diagnoses in any position (Friberg & Skeppholm, 2016).

Quality registries in Sweden have been used to improve clinical practice Many pediatric diabetic centers reduced the glycosylated hemoglobin (HbA1c) in their patient population using a quality registry. Those centers also observed reduced frequency of severe hypoglycemia and/or ketoacidosis (Peterson et al., 2014). A project on quality improvement in the treatment of AMI used RIKS-HIA as a platform. Each participating hospital team locally decided what their problem in treating AMI was and came up with improvement strategies. The outcome was improvement in adherence to five different recommended therapies (Peterson et al., 2007).

1.3 Women with ACS

“Share our similarities, celebrate our differences.”

M. Scott Pegg

Quality registries like SWEDEHEART can be used to examine groups that often are not present in adequate numbers in clinical trials. One such group is women with ACS (Mehta et al., 2016). There are both similarities and differences in ACS in men and women. ACS develops a decade later in life in women than in men and they have more multi-morbidity when they are diagnosed. The incidence and prevalence of ACS are higher in men than in women, but as women generally become older than men, they catch up in absolute numbers at around eighty years of age (Blomkalns et al., 2005; Rosengren et al., 2006). Causes of ACS other than obstruction of epicardial coronary arteries, such as microvascular disease and vasospasm, are also more common in women. Confusion of the terms sex and gender differences often complicate the discussion. Sex differences refer to biological differences between men and women; for example, obstructive epicardial CAD is less common in women than in men. Gender disparity includes broader social, environmental and community influences (Mehta et al., 2016).

An example of gender disparity is the lack of enrolment of women in clinical trials and the paucity of reports on sex-specific data. In an extensive review of the medical literature from 1999-2011 performed to assess the effectiveness of major treatment options of ACS in women, 65% of the omitted articles were excluded because they failed to report sex-specific data (Dolor et al., 2012). The treatment options examined were primary PCI vs. fibrinolysis in STEMI, routine early invasive therapy vs. initially conservative in NSTE-ACS and CABG vs. PCI. In most studies of treatment options for ACS, women constitute less than 1/3 of patients (Dolor et al., 2012; Kragholm et al., 2015; Vaina et al., 2009).

1.3.1 Pathology

The classical risk factors for CAD discussed previously affect both genders, but their impact can vary. Smoking and diabetes are, for example, more hazardous for women. Disorders that are unique for women increase their risk for CAD. Examples of this are gestational hypertension, gestational diabetes, as well as polycystic ovary syndrome (Appelman et al., 2015).

Studies on the effects of estrogen with regard to atherosclerosis and thrombosis have been conflicting; however, it is known that estrogen can affect various proteins in coagulation and fibrinolytic pathways and there are various estrogen receptors on platelets. Estrogen improves vascular endothelial function by increasing nitric oxide synthase and inhibiting thromboxane A2 generation (Braunstein et al., 2002; Khetawat et al., 2000). Despite estrogen having positive effects on vascular endothelium, estrogen substitution therapy after menopause increases the risk for thrombotic events such as AMI and stroke (Rossouw et al., 2007).

As in men, the most common pathological process behind ACS in women is the formation of atheromatous plaques, which over time become unstable, rupture and a thrombus is formed on top of the plaques. Ruptured plaques cause 55% of AMIs in women but 75% in men. Plaque erosions are another mechanism that can cause ACS, these are more common in women than in men. In plaque erosions, there is no ruptured plaque and the thrombosed arterial segment of the endothelium is typically missing at the erosion site and the intima exposed. The intima is pathologically thickened with intact media, whereas the media is typically destroyed in ruptured plaques (figure 11). There is usually little or no inflammation in plaques that erode and they do not necessarily cause a significant stenosis of the coronary arteries (Falk et al., 2013).

Women with ACS commonly have no significant stenosis within the coronary arteries. A study of patients with UAP found no significant stenosis in the coronary arteries in 30% of women and in 7% of men (Chaitman et al., 1981). There are unusual pathophysiological mechanisms of ACS that are more common in women than men, such as spontaneous coronary artery dissections, coronary artery spasms, microvascular heart disease and Takotsubo cardiomyopathy (Chen et al., 2016; Komamura et al., 2014; Sharkey & Maron, 2014; Yip & Saw, 2015).

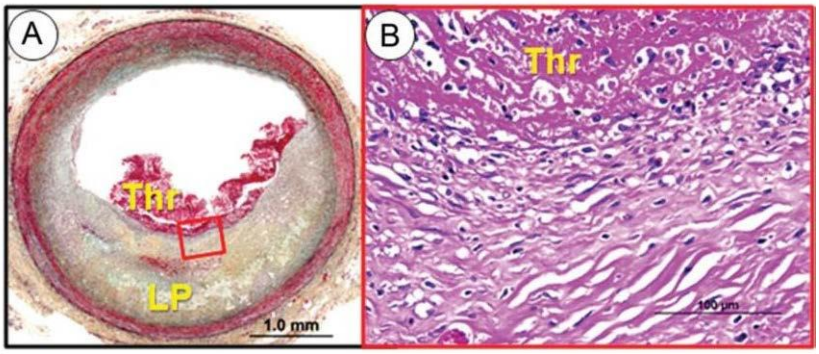

Figure 11. Plaque erosions.

The photos show a cross-section of a coronary artery. In (A), a non-occlusive thrombus (Thr) is present on the surface of a plaque with pathological intimal thickening. The media is intact and no connection between thrombus and the lipid pool (LP). (B) shows a higher-magnification image of the red box in (A). The thrombus lies on an underlying plaque which consists of smooth muscle cells in a proteoglycan and collagen matrix and there is an absence of inflammation. Adapted from (Falk et al., 2013) with permission

1.3.2 Symptoms and diagnosis

Classical angina is the most common symptom of CAD in women. Additionally, women are more likely than men to experience atypical angina or symptoms other than chest pain (Mehta et al., 2016). These symptoms may involve dyspnea, nausea, heart rhythm disturbances, worsening endurance and general malaise.

In women ECG-based stress test on a treadmill or a bicycle has a sensitivity of only 61% and specificity of 70%, as opposed to 70% and 72% in men (Gibbons et al., 2002). Women have lower pre-test probability (figure 4) and this affects the sensitivity and specificity. Women are less likely than men to reach the recommended 85% of the predicted maximum heart rate. Additional reasons leading to a diminished accuracy of ECG-based stress tests in women include ST-segment abnormalities due to menstrual cycle or other hormonal changes and lower QRS voltage form (Shaw et al., 2006). Other imaging-based non-invasive stress tests such as stress echocardiography or myocardial perfusion scintigraphs have higher sensitivity and specificity in women and should be used when local expertise allows (Coelho-Filho et al., 2011; Petix et al., 2005; Shaw et al., 2005).

ACS in women is diagnosed in the same manner as in men. Women under 65, compared to men in the same age group, more commonly present

with NSTE-ACS than STEMI. In older patients, there is no sex difference in the likelihood of ACS presenting as STEMI (Hochman et al., 1999; Rosengren et al., 2004). Women with NSTEMI are less likely than men to have an initially elevated troponin. The sensitivity and positive predictive value of troponin are lower in women and can lead to underdiagnoses of AMI (Slagman et al., 2015). The ECG in NSTE-ACS is also less likely to be clinically diagnostic in women, making the diagnosis even more complicated (Hochman et al., 1999).

Women with NSTE-ACS are 30% less likely than men to be referred to CA, even after considering their multi-morbidity at presentation and higher age (Poon et al., 2012; Worrall-Carter et al., 2016). Some studies show that the gender disparity in referral to CA attenuates in older cohorts (Thang et al., 2016). Other studies do not confirm this (Redfors et al., 2015). The guidelines for invasively investigating and treating NSTE-ACS do not suggest a different approach in women and men with NSTE-ACS. Intermediate- and high-risk patients should be treated with an invasive strategy (Roffi et al., 2016). There are, however, conflicting results for this approach in women, as we will explore in the following chapter.

1.3.3 Treatment of women with ACS

Data on sex differences for the efficacy of antithrombotic drug therapies in ACS does not support less efficacy in women. Some trials have shown a higher bleeding risk for women than men, but guidelines for antithrombotic therapy ACS do not recommend a different approach in women (Baigent et al., 2009; Ibanez et al., 2017; Roffi et al., 2016; Verdoia et al., 2016). Despite this, various studies show that women are less likely to receive ASA and P2Y12 receptor antagonists than men (El-Menyar et al., 2009 1468; Johnston et al., 2011; Lin et al., 2014). Meta-analyses of ACE-I in patients with heart failure and statin therapy after AMI have not demonstrated sex differences in efficacy (Baigent et al., 2005; Flather et al., 2000). I am not aware of specific analyses on sex differences in efficacy of beta-blockers after ACS. Despite this, women with AMI are less likely to be discharged with statins, ACE-I and beta blockers (Redfors et al., 2015).

To study whether gender disparities are found in referrals to revascularization with PCI or CABG, one needs to consider that women less often have obstruction of coronary arteries on CA, are older and have more comorbidity burden. Some studies show that women are less likely to undergo subsequent revascularization (Alfredsson et al., 2007; Dey et al., 2009; Hvelplund et al., 2010; Watson et al., 2001). Others do not show

gender differences in subsequent revascularization after confirming obstructive epicardial disease or claim that those differences disappear once comorbidities and confounders are accounted for (Anand et al., 2005; Blomkalns et al., 2005; Nguyen et al., 2008).

Studies have consistently shown that routine early invasive strategy benefits men with NSTE-ACS (Alfredsson et al., 2014) above a selectively invasive strategy. This is not the case for women. Although some studies support this (Alfredsson et al., 2011), others do not (Alfredsson et al., 2014; Swahn et al., 2012).

1.3.4 Gender differences in outcomes

Data on gender differences in in-hospital mortality and short-term mortality after ACS is conflicting (El-Menyar et al., 2009). Some studies show higher mortality in women compared to men, but others show no differences or contribute the higher mortality to age and comorbidity differences (Bufe et al., 2010; Worrall-Carter et al., 2016). Female sex has not been proven to be an indicator of increased one-year or long-term mortality (Bufe et al., 2010; Perl et al., 2015; Singh et al., 2008; Y. Wang et al., 2017). Interestingly, some studies that have not found increased mortality overall in women with ACS have demonstrated higher in-hospital mortality in women under 60 with STEMI compared to men of the same age (Heer et al., 2015; Redfors et al., 2015).

Women make up around one-quarter of the patients undergoing CABG. There is also contradicting data on the effects of female sex on outcomes after CABG; some show more complications and higher short-term mortality (Alam et al., 2013; Filardo et al., 2016); other studies indicate that these differences are caused by higher age and more comorbidities (Saxena et al., 2012; Toumpoulis et al., 2006). Mortality 30 days or more after CABG seems to be the same in men and women after adjusting for confounders (Arif et al., 2016) and one study found female sex to be predictive of lower five-year mortality (Toumpoulis et al., 2006).

Women are older than men when they present with CAD and ACS. The discussion about gender and sex differences in treatment and outcomes is therefore also a discussion of age-related differences.

1.4 CAD in older people

**“How old would you be,
if you didn’t know how old you are?”**

Satchel Paige

Older people are another group that has been underrepresented in clinical trials and can be studied in SWEDEHEART. Over a 10-year period, 1990 to 2000, the proportion of patients over 75 years old with ACS included in trials was 9%, despite them constituting 40% of the ACS population. Half of the trials did not include anyone over 75 years of age (Lee et al., 2001). Even today, the older patients are underrepresented in trials and the ones who are included tend to be less frail and have less comorbidity than the general elderly population (Hutchinson-Jaffe et al., 2010).

It is expected that the number of people over 65 years of age in Europe will double from 88 million to 153 million in 2030. This means that the proportion of the European population 65 years old and older will increase to 26% in 2030 and to 30% in 2060. At the same time, the proportion of those aged 80 years or more is estimated to rise from 5% to 12% (*Population ageing in Europe. Facts, implications and policies*, 2014). The prevalence and incidence of CAD increase with advancing age. This demographic shift toward an older population will have clinical and economic challenges for the European nations.

In Western nations the term older people is generally reserved for those over 65 years of age, relating mainly to the age of retirement. In nations where life expectancy is shorter those as young as 50 years old are considered old ("Health statistics and information systems. Proposed working definition of an older person in Africa for the MDS Project.," 2012). The American Heart Associations suggested in 2007 in their guidelines that those 75 years old and older should be considered a special at-risk group due to more frailty and complications (K. P. Alexander et al., 2007). They also recommended dividing older people further into groups for example under 65, 65 to 75, 75 to 85 and above 85 years for studies in Western countries.

1.4.1 The aging heart

With increasing age, the heart stiffens and becomes more hypertrophic. The cardiomyocytes enlarge but decrease in number and there is more collagen linking and fibrosis. The heart's response to sympathetic stimulation decreases but not to parasympathetic stimulation. The sarcoplasmic reticulum changes and CA^{2+} ATP pump relaxation slows. This decrase in compliance leads to diastolic dysfunction. With advancing age people become more reliant on atrial contraction for ventricular filling (Ferrari et al., 2003).

The intima and media in arterial walls thicken and there is more disposition of collagen and elastin. This leads to less distensibility in major arteries and they elongate and stiffen. With age, the permeability of the endothelium increases and there are changes in endothelial signaling and inflammatory mediators. The response to β-adrenergic-mediated vasodilation decreases and the peripheral resistance in the vascular system increases (Ferrari et al., 2003).

Alongside changes in the heart and cardiovascular system, which accompany aging, atherosclerosis and other diseases become more common (Cheitlin, 2003). Sometimes differentiating what is aging and what is disease can be difficult. The accumulation of deficits that accompany aging leads to a disease. The speed of aging and the burden of disease is a highly individual process leading to a wide range of interpersonal variability in physiological functions in older people (Ferrari et al., 2003; Mitnitski et al., 2006). The chronological age alone is not sufficient to determine a person's vulnerability to diseases and procedures. The term biological age is sometimes used more appropriately, but even the interpretation of biological age is troublesome and has been shown to be observer-dependent (Hochschild, 1989).

1.4.2 Age does not come alone: Frailty, multi-morbidity and disability

With advances in medical care and public health, a greater number of older people are living with incurable chronic disease. When a person has two or more chronic conditions, they are considered to have multi-morbidity. Multi-morbidity is present in at least 64% of individuals between 65 and 84 years old and in 81% of those who are 85 years and older. The average number of diseases in the former group is 2.6 and in the latter 3.6 (Barnett et al., 2012). When treating older people with CAD, physicians cannot avoid considering multi-morbidity and its consequences.

Multi-morbidity can refer only to the number of diseases, but in some cases, the term refers to the number and severity of diseases and sometimes all the above along with concurrent limitations in functional status. Studies have shown that multi-morbidity is associated with longer hospital stays, more complications after procedures, lower quality of life and increased mortality (Gijsen et al., 2001). Comorbidity can be defined as the existence of any additional disease alongside the index disease. The use of this term puts more focus on a specific disease and other diseases are adjuvants, while multi-morbidity puts more focus on all the diseases together (Ording & Sorensen, 2013).

Bearing in mind the consequences of multi-morbidity in older people, the question arises of how to measure this burden. A commonly used index is the Charlson Comorbidity Index. It is used to predict the relative risk of dying within 10 years. Any concomitant disease receives a score on the scale 1-6, depending on the risk of dying associated with it. It has been translated into International Statistical Classification of Diseases, 10th revision (ICD-10) codes and has good reliability (de Groot et al., 2003). A CAD-specific index was derived from the Charlson comorbidity index, looking at a large sample of patients undergoing CA. This index omits some diseases, adds others and changes the weight of some (table 1) (Sachdev et al., 2004) depending on the impacts on mortality in the population with CAD. One of the arguments of using a CAD-specific index is that AMI and chronic heart failure very often are manifestations of CAD rather than comorbidities. A CAD-specific index adds smoking and hypertension as risk factors and adds weight to peripheral artery disease, diabetes and chronic pulmonary disease as those conditions had more impact on the mortality in this population with CAD.

Frailty is a separate clinical condition from multi-morbidity and disability. It describes a state of reduced physical and cognitive reserve, which causes an individual to have reduced resistance to stressors. There is no gold standard for the definition of frailty, but the most widely known criteria were defined by Fried in 2001 as meeting three out of five parameters: unintentional weight loss, self-reported exhaustion, weakness (decreased grip strength), slow walking speed and low physical activity (Fried et al., 2001). The risk of frailty increases with advancing age. Frailty is three to four times more common in older people with CVD than those without (Afilalo et al., 2009). This correlation is not surprising as atherosclerosis and frailty share a common biopathology. Factors associated with inflammation and thrombosis have been shown to underlie the biopathology of frailty. This includes a rise in interleukin-6, C-reactive protein, leukocytes, factor VIII, D-dimer and

fibrinogen (Barzilay et al., 2007; Leng et al., 2005; Soysal et al., 2016; Walston et al., 2002). Frail patients experience more complications after PCI and have longer hospital stays (Murali-Krishnan et al., 2015) and frailty is a strong prognostic factor for mortality in patients with CAD. Frail patients over 75 with NSTEMI had a one-year mortality of 49% as opposed to 13% in the non-frail (Ekerstad et al., 2013). Already in 2007, the American Heart Association emphasized understanding and reporting geriatric syndromes such as frailty and cognitive impairment, as they overlap with CADs and help to estimate procedural risk in older people (K. P. Alexander et al., 2007). The 2015 ESC guidelines on NSTE-ACS include a chapter on older people. They recommend careful dosing of antithrombotic medications according to renal function as well as considering frailty and other geriatric syndromes (Roffi et al., 2016).

Disability is often used interchangeably with frailty and comorbidity, but that is not correct. Disability is any condition that restricts everyday activities necessary to independent living, such as tasks needed for self-care, taking care of a household and activities important to one´s quality of life. In health care, these tasks are called activities of daily living (ADL). Restrictions on performing ADL are often diagnosed by self-reports, but there are objective screening instruments available, for example, the Barthel index (Fried et al., 2004). Disability overlaps with both frailty and multi-morbidity (figure 12).

Table 1. CAD-specific index and Charlson comorbidity index. The table shows the different weight each disease has on mortality risk in the two indexes.

Disease or condition	**CAD-specific index[c] weighing**	**Charlson index weighing**
Current smoker	1	0
Hypertension	1	0
AMI	0	1
Dementia	-	1
Peptic ulcer disease	-	1
Chronic heart failure	0	1
Connective tissue disease	-	1
Mild liver disease	-	1
Cerebrovascular disease	1	1
Diabetes mellitus	2	1
Chronic pulmonary disease	2	1
Peripheral vascular disease	2	1
Hemiplegia	-	2
Leukemia	-	2
Any tumor	2	2
Diabetes with end-organ damage	3	2
Moderate or severe renal disease[a]	7	2
Lymphoma	-	2
Moderate or severe liver disease	-	3
AIDS[a]	-	6
Metastatic solid tumor	5	6

[a]Moderate renal failure: 30≤ estimated glomerular filtration rate (eGFR) <60 ml/min//1.73m^2, severe renal failure: eGFR <30 ml/min//1.73m^2; [b]AIDS: immunodeficiency syndrome; [c]CAD: coronary artery disease.

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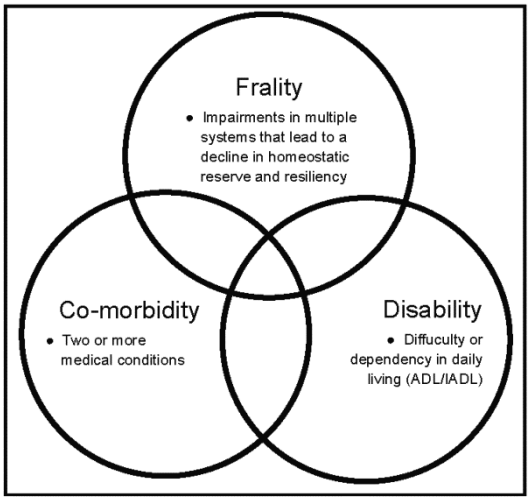

Figure 12.The overlap between frailty, comorbidity and disability.

ADL: activities of daily living. IADL: instrumental activities of daily living. The figure is adapted from reference (Afilalo et al., 2009) with permission.

1.4.3 Multi-morbid older people in Sweden

Multi-morbidity and frailty are often associated with abundant utilization of health-care and social-care services. The Swedish National Board of Health and Welfares has defined a group of older people with extensive use of these services. This group is called in Swedish “mest sjuka äldre”, but unfortunately, there is no official international term. Possible English phrases are: “multi-morbid older people with abundant utilization of health and social care” or “older people with complex health problems and severe needs”. This group is defined using three Swedish registries: the National Patient Registry, Registry for Social Care of Older People and Persons with Impairment (registret över socialtjänstinsatser till äldre och personer med funktionsnedsättning) as well as the Registry for Services for the Functionally Impaired (registret över insatser enligt lagen om stöd och service till vissa funktionshindrade (*De mest sjuka äldre. Avgränsning av gruppen*, 2011).

To be defined as having multi-morbidity per the Swedish National Board of Health and Welfares, an individual must meet criteria a-c): a) be at least 65 years old, b) be hospitalized at least three times with main diagnoses from at least two different ICD-10 chapters, and c) at least one hospitalization must be within 12 months prior to index date. The group that uses a lot of health care services can be called in English “multi-morbid older people with complex health needs”. These individuals meet criteria a) and one of b-d):

a) Meet the criteria for the definition of multi-morbidity, see above,
b) History of more than 19 days of hospitalization or outpatient visits to specialist clinics during the last 12 months before index date,
c) History of more than three hospitalizations during the last 12 months before index hospitalization,
d) History of more than seven visits to a specialist in outpatient care during the last 12 months before index date (*De mest sjuka äldre. Avgränsning av gruppen*, 2011).

A recent study showed that almost 90% of patients who fit the definition of multi-morbid older people with complex health needs are frail or pre-frail (Mazya et al., 2017). This gives us an opportunity to study frail patients using combined registry data from SWEDEHEART and the National Patient Register.

1.4.4 Presentation and diagnosis of CAD in older people

Older people often have an atypical presentation of their CAD, both stable CAD and ACS. Those symptoms include nausea, syncope, diaphoresis and dyspnea as well as confusion and functional decline (Brieger et al., 2004).

Older people are more likely to have baseline changes in their ECG such as left bundle branch block or nonspecific changes (Molander et al., 2003) (Rosengren et al., 2006). This makes ECG-based stress tests in patients with suspected stable CAD difficult to interpret. Due to deconditioning, attenuated sympathetic response and muscle weakness, older people often have a hard time reaching 85% of maximal heart rate, which makes stress tests less reliable. The higher prevalence of CAD in older people can also give rise to false negative stress tests (Shaw et al., 2008; Shaw et al., 2000).

In a group of 75 years old and older, 43% did not have chest pain as a presentation of their ACS compared to 29% of those who were under 65 years of age (Brieger et al., 2004). ACS patients that present without chest pain are at risk for delay in seeking medical attention, receive less aggressive treatments and have high in-hospital mortality (Canto et al., 2000). The baseline ECG changes make the ECG harder to interpret in the settings of ACS. High-sensitivity troponin T is less specific in older people and mild elevations are common in non-ACS patients. The main causes of elevated troponins in patients without AMI are impairment of renal function, arrhythmias and heart failure (Reiter et al., 2011).

1.4.5 Special aspect of medical treatment of ACS in older people

As patients age, renal function worsens and many medications require adjustments in dosage. In a cohort study of patients with NSTE-ACS, 42% received at least one antithrombotic agent outside the recommended dose range. Dosing errors most commonly occur in older people, women, those with low body weight and patients with renal insufficiency or diabetes (K. P. Alexander et al., 2005).

When older people have multi-morbidity and/or polypharmacy, their pharmacokinetics and pharmacodynamics are altered, rendering them more susceptible to side effects. For example, muscle-related adverse effects of statins become more common with increasing age. The ESC guidelines recommend starting at lower doses in multi-morbid patients and titrating them (Catapano et al., 2016).

ACE-I are among the medications listed as potentially inappropriate per the American Geriatrics Society 2015 Beers Criteria due to a risk for adverse events such as syncope and hypotension ("American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults," 2015). At the same time, older people are more likely than younger patients to have diabetes and congestive heart failure, which makes the ACE-I beneficial to them. Many studies have shown that ASA, beta blockers, ACE-I, P2Y12 receptor antagonists and statins are withheld in patients over 75 years old with ACS (Libungan, Karlsson, et al., 2014; Rathore et al., 2003). Older people with ACS benefit from these medications just like younger patients and medications should not be withheld from them due to advanced age. The risk-benefit ratio should be considered for each individual and the approach tailored according to their renal function, frailty status and polypharmacy.

1.4.6 Treatment of STEMI in older people

Primary PCI is the preferred reperfusion strategy in older people and old age is not considered a contraindication for PCI (Ibanez et al., 2017). Despite this, old age has been reported as the most common cause of reperfusion therapies not being given to elderly patients with STEMI (Gharacholou et al., 2010).

There are three randomized trials dedicated to individuals aged 70 or 75 years and older with STEMI, randomizing them to either fibrinolysis or PCI. The largest one is the unpublished Senior PAMI trial randomizing 481 patients ("Senior PAMI: Primary Angioplasty Versus Thrombolytic Therapy

for Acute Myocardial Infarction in the Elderly,"). A smaller trial in 2002 and 2003 randomized 81 patients with STEMI and found PCI superior in reducing composite endpoints of death, reinfarction or stroke at 30 days and 6 months, respectively (M. J. de Boer et al., 2002). The TRIANA trial in 2011 was terminated early due to slow enrolment (TRIANA: TRatamiento del Infarto Agudo de miocardio eN Ancianos). There was not a significant difference between outcomes in the fibrinolysis and primary PCI arm. In a pooled analysis with the Senior PAMI trial as well as De Boer et al., the TRIANA group found primary PCI superior to fibrinolysis in reducing the composite endpoint of death, reinfarction or stroke (Bueno et al., 2011).

Randomized data is even more sparse for those who are over 85 or 90 years old. In recent years, some registry studies have reported results for patients over 85 or 90 years old undergoing PCI. Procedural success is 84-98% and major in-hospital bleeding events around 4% and stroke less than 1% (Danzi et al., 2010; Petroni et al., 2016). A large registry study comparing mortality in nonagenarians with STEMI found the mortality of those who did not undergo PCI to be almost double compared to those who did (Mandawat et al., 2013). The conclusion of the American Heart Association in 2007 for reperfusion in those who are over 85 years old with STEMI still holds. It says: “A one-size-fits-all approach to care in the oldest old is not feasible and ethical issues will remain even in the presence of adequate evidence. Nevertheless, if the contributors to treatment benefits and risks are understood, guideline-recommended care may be applied in a patient-centered manner in the oldest subset of patients” (K.P. Alexander et al., 2007).

1.4.7 Treatment of NSTE-ACS in older people

Invasive treatment with CA and, if feasible, revascularization is recommended in older patients with NSTE-ACS and intermediate- to high-risk features, just like in younger patients. The ESC guidelines have a separate chapter about treating patients over 75 years old. They recommend invasive strategy if appropriate and revascularization after considering carefully the life expectancy, comorbidity, quality of life, frailty and both cognitive and functional impairment (Roffi et al., 2016).

In recent years, two randomized trials have been performed specifically in older people with NSTE-ACS. The Italian Elderly ACS trial randomized 75-year-old and older individuals with NSTE-ACS to initial conservative medical treatment and initial early invasive angiography within 24 to 72 hours and, if appropriate, revascularization. They found that revascularization improved the combined endpoint of death, MI, stroke, repeat hospitalizations and

bleedings at one year if the patients had raised cardiac troponin but not in the group without positive cardiac biomarkers (Savonitto et al., 2012). In the After Eighty study, octogenarians with NSTE-ACS were randomized to either initially conservative treatment with optimal medical treatment or invasive treatment and, if appropriate, revascularization with either PCI or CABG. The absolute reduction in composite endpoints over one and half years by the invasive treatment was 20% (Tegn et al., 2016). A third randomized trial in octogenarians with NSTE-ACS is ongoing (Libungan, Hirlekar, et al., 2014). In this study, the patients are, among other conditions, screened for frailty status which might add valuable information regarding the efficacy and risks of invasive treatment.

Randomized data for nonagenarians with NSTE-ACS is very limited. In the After Eighty study they concluded that somewhere around 92 years of age the scale tipped over to more risk than benefits; however, only 33 persons over 90 years of age were included in the study. Therefore, the interpretation of risks and benefits in that age category should be done carefully. Registry studies in nonagenarians with NSTE-ACS suggest adherence to clinical guidelines increases survival (Skolnick et al., 2007), but more studies in this group are needed.

1.4.8 PCI, multi-morbidity and frailty

Clinical decision making is complicated in many older people with CAD due to multi-morbidity and frailty. In the After Eighty study mentioned above, 53% of the originally screened octogenarians met exclusion criteria, highlighting the clinical complexity of patients in this age group. The exclusion criteria included being clinically unstable with cardiogenic shock or ongoing ischemic signs or symptoms, continuing bleeding problems and life expectancy under 12 months due to serious comorbidities (Tegn et al., 2016). Despite multi-morbid patients being largely excluded in clinical trials, cohort studies show an increasing number of multi-morbid patients are undergoing PCI (Bromage et al., 2016).

Comorbidities, like renal failure, increase the bleeding risk from antithrombotic medical therapy and the risk of bleeding events after PCI. However, at the same time, multi-morbidity and frailty tend to go hand in hand with more burden of CAD. Those suffering from multi-morbidity or frailty simultaneously with CAD could possible benefit more from invasive procedures (Palau et al., 2012). It can be challenging to predict the effects of numerous diseases and frailty coinciding on the effects of following treatment guidelines for a single disease. It is important to see how invasive strategy in treating ACS affects the outcomes in those who have multi-morbidity and complex health needs.

2 Aims

The general aim of this thesis, using the quality registry SWEDEHEART, is to study the treatment of groups with CAD who are underrepresented in randomized controlled clinical trials. The specific aims are enumerated below.

1) To study and compare all CA and PCI performed in two European countries in a nationwide registry, SCAAR, during the first year it was in use in Iceland (**Paper I**).

2) To investigate whether gender disparities exist in referral of women with ACS for revascularization with PCI or CABG. Furthermore, to study the subsequent complication rate and 30-day mortality (**Paper II**).

3) To compare one-year outcomes of invasive strategy to non-invasive in older people with ACS, multi-morbidity and complex health needs (**Paper III** and unpublished data).

4) To evaluate indications and outcomes of CA and PCI in nonagenarians; furthermore, to describe temporal changes in practice during nine years of cardiac catheterizations in nonagenarians (**Paper IV**).

3 Materials and methods

Appropriate ethical approvals were obtained for the studies in this thesis in accordance with the Declaration of Helsinki. Permissions were obtained from the Data Protection Authority in Iceland and the National Bioethics Committee in Iceland, permission numbers 2008040331 and 08-087; as well as the Ethical Committee in Uppsala, Sweden, permission number Dnr 2015/272 (with later amendments). Patient consent is not required for entering data into SWEDEHEART, but participants are informed of their participation and have the right to deny participation or have data removed later, in accordance with Swedish and Icelandic legislations.

3.1 Patients and data collection

Patient groups, inclusion periods and data sources in each paper are described in table 2. Patient characteristics and previous diseases from each data source are described in table 3. Data sources for outcomes are in table 4. The ICD-10 codes for each disease collected from the National Patient Register are shown in Appendix 1 and ICD-10 codes for one-year outcomes collected from the National Patient Register are shown in Appendix 2.

3.2 Methods

In Paper I, comparisons were made between Iceland and Sweden for the following: indications, patient's characteristics, numbers of CA and PCI, procedural characteristics of PCI, as well as results of CA and treatment decisions. The in-hospital complications and mortality after CA respectively PCI were calculated for each country and compared between them. The number of CA and PCI/1,000,000 in each country was calculated.

In Paper II, revascularization rate with PCI or CABG in women was compared to the rate in men. The in-hospital complication rate in women was compared to the rate in men, after CA only or CA followed by PCI. The 30-day mortality of women was compared to men.

Unpublished data for all patients 70 years old and older admitted due to ACS has so far been analyzed for patient characteristics, comorbidity burden and crude one-year events.

Table 2. Patient groups, inclusion periods and data sources for each paper and unpublished data.

Paper	I	II	Unpublished data	III and unpublished data	IV
Patients	Patients ≥ 18 undergoing CA[b] and/or PCI[c] in Iceland and Sweden	Patients ≥ 18 undergoing CA ± PCI in Iceland and Sweden	Patients ≥ 70 admitted to coronary care units in Sweden and registered in RIKS-HIA[f]	Patients ≥ 70 admitted to coronary care units in Sweden who meet the criteria for the definition of older people with multi-morbidity and extensive use of health care[g]	Patients ≥ 90 undergoing CA±PCI in Sweden
Forms of CAD[a]	Any CAD	ACS[e]	ACS	STEMI, NSTE-ACS	Any CAD
Inclusion periods	Jan. 2007 – Dec. 2007	Jan. 2007 – Dec. 2011	Jan. 2006 – Dec. 2013	Jan. 2006 – Dec. 2013	Jan. 2006 – Dec. 2014
Data sources	SCAAR[d]	SCAAR	RIKS-HIA, SCAAR, National Patient Register	RIKS-HIA, SCAAR, National Patient Register	SCAAR, RIKS-HIA[f]

[a]CAD: coronary artery disease; [b]CA: coronary angiography; [c]PCI: percutaneous coronary intervention; [d]SCAAR: the Swedish Coronary Angiography and Angioplasty Registry; [e]ACS: acute coronary syndromes; [f]RIKS-HIA: The Register of Information and Knowledge About Swedish Heart, Intensive Care Admissions; [g]older people with multi-morbidity and complex health needs are defined by the Swedish National Board of Health and Welfare as following: They meet criteria a)-c) and either d), e) or f): a)are ≥ 65 years old, b) hospitalized at least three times with main diagnoses from at least two different International Statistical Classification of Diseases, 10th revision (ICD-10) chapters and c) at least one hospitalization must be within 12 months prior to index date, d) have more than 19 days of hospitalization or outpatient's visits to specialist clinics during the last 12 months before index date, e) more than three hospitalizations during the last 12 months before index hospitalization or f) more than seven visits to specialist in outpatient care during the last 12 months before index date.

Table 3. Data sources for patient characteristics and burden of diseases.

Paper	I	II	III and unpublished data	IV
SCAAR[a]	Age, sex, diabetes, hypertension, smoking status, hyperlipidemia, prior PCI[d] or CABG[e] or AMI[f], cardiogenic shock, indications for CA[g] or PCI	Same as for Paper I, weight, creatinine	Weight, creatinine	Same as for Paper II
RIKS-HIA[b]	NA[h]	NA	Age, sex, weight, diabetes, hypertension, smoking status, hyperlipidemia, prior PCI, prior CABG, prior AMI, [i]BMI, indication for admission, creatinine, prior stroke, medications at admission & discharge	Weight, creatinine, height, blood pressure, heart rate
National Patient Registry[c]	NA	NA	Hypertension, heart failure, renal failure, stroke, [j]TIA, stroke, [k]COPD, [l]PVD, cancer, anemia, dementia, atrial fibrillation, rheumatological disease, diabetes, hyperlipidemia, [m]older people with multi-morbidity & complex health needs	NA

[a]SCAAR: the Swedish Coronary Angiography and Angioplasty Registry; [b]RIKS-HIA: The Register of Information and Knowledge About Swedish Heart, Intensive Care Admissions; [c]International Statistical Classification of Diseases, 10th revision (ICD-10) codes can be found in Appendix I; [d]PCI: percutaneous coronary intervention; [e]CABG: coronary artery bypass graft; [f]AMI: acute myocardial infarction; [g]CA: coronary angiography; [h]NA: not applicable; [i]BMI: body mass index; [j]TIA: transient ischemic attack; [k]COPD: chronic obstructive pulmonary disease; [l]PVD: peripheral vascular disease; [m]they are defined by the Swedish National Board of Health and Welfare as following: They meet criteria a)-c) and either d), e) or f): a)are ≥ 65 years old, b) hospitalized at least three times with main diagnoses from at least two different ICD-10 chapters and c) at least one hospitalization must be within 12 months prior to index date, d) have more than 19 days of hospitalization or outpatient's visits to specialist clinics during the last 12 months before index date, e) more than three hospitalizations during the last 12 months before index hospitalization or f) more than seven visits to specialist in outpatient care during the last 12 months before index date.

Table 4. Data sources for procedural characteristics and outcomes.

Paper	I	II	III and unpublished data	IV
[a]**SCAAR**	Outcomes of CA[c], number of catheterizations (CA and PCI[d]), treated lesions, procedural characteristics, treatment decisions, complications in the catheterization laboratory, in-hospital complications, in-hospital mortality	Same as I	Number and timing of catheterizations (CA and PCI), outcomes of CA, treatment decisions	Same as I
[b]**RIKS-HIA**	NA[e]	NA	Readmission due to ACS[f]	NA
National Patient Registry	NA	NA	Any readmission Readmission due to ACS[g] Readmission due to stroke or TIA[h] Readmission due to a bleeding event Readmission due to heart failure	NA
Statistics Sweden, Statistics Iceland	Number of people alive in each country	30-day mortality	One-year mortality	One-year mortality Number of alive nonagenarians

[a]SCAAR: the Swedish Coronary Angiography and Angioplasty Registry; [b]RIKS-HIA: The Register of Information and Knowledge About Swedish Heart, Intensive Care Admissions; [c]CA: coronary angiography; [d]PCI: percutaneous coronary intervention; [e]NA: not applicable; [f]ACS: acute coronary syndromes; [g] [c]International Statistical Classification of Diseases, 10th revision (ICD10) codes for diagnosis of outcomes from National Patient Registry are in appendix; [h]TIA: transient ischemic attack.

In Paper III, one-year outcomes for multi-morbid older people with STEMI who were examined and treated with invasive strategy were compared to those who were not. Invasive strategy was defined as the performance of any CA ≤14 days of admission (Alfredsson et al., 2011). Primary event was combined one-year mortality, readmission due to ACS, readmission due to stroke or TIA; secondary events were one-year readmission due to bleeding events, any single component of primary outcome, one-year readmissions due to heart failure, one-year readmission due to any cause. Patients who were referred to CA after 14 days or not at all constituted the non-invasive group.

Unpublished data for multi-morbid older people with complex health needs and NSTE-ACS were analyzed similarly to data in Paper III.

In Paper IV, indications for CA and PCI were assessed, as were the number of procedures, outcomes of CA and treatment decisions after CA. The in-hospital complications after CA and PCI, as well as one-year mortality, were examined. Finally, the temporal changes in practice and outcomes of catheterizations in nonagenarians during 2006-2014 were evaluated.

3.3 Data analyses and statistics

In all papers and unpublished data for patients 70 years or older with ACS, patient characteristics and comorbidities were shown with descriptive statistics. Categorical variables were reported as frequency values; and continuous variables were presented as mean (±standard deviation [SD]) or median (±interquartile range [IQR]), where appropriate. When groups were compared, categorical values were tested with Chi-square test; continuous variables were tested with a Student t-test or Mann-Whitney test depending on the normality of the distribution.

Glomerular filtration rate was calculated in Papers II-IV using the Cockcroft-Gault formula and presented as estimated glomerular filtration rate (eGFR) in milliliters/min.

In Paper I, the same methods for presenting data and testing the difference between Iceland and Sweden were used as described above for patient characteristics.

In Paper II, outcome variables were revascularization with PCI, revascularization with CABG, any in-hospital complication, any in-hospital bleeding event, serious in-hospital bleeding events and 30-day mortality. Mortality was further examined per revascularization status and severity of

CAD. Women were compared to men using unadjusted logistic regression for each outcome. Multivariable logistic regression models were designed for each outcome to adjust for clinically relevant covariates (table 5). The method for entering covariates in the logistic regression was enter. In examining the gender differences in referral to PCI or CABG, only patients with obstruction of at least one coronary artery were included. In all logistic regression models, the interaction between sex and each covariate was examined. When the interactions were positive, subclass calculations were performed. All multivariable logistic regression models were performed on datasets with multiply-imputed data and 20 datasets. Missing data was imputed using the monotone method, as the missing data pattern was clustered.

In Paper III, the one-year events were evaluated in patients who were alive at discharge. The reason was to avoid bias caused by including patients in the non-invasive group who were so severely ill that it precluded them from being referred to CA. However, in-hospital mortality in invasively treated patients was compared to those who received a conservative approach.

To compare the results of invasive and non-invasive strategy, a propensity score method was used to compensate for the non-randomized study design. It included characteristics and comorbidity burden that differentiated between the invasive and non-invasive group. Variables tested for difference between the groups were: age (continuous variable), sex, smoking status, year of index date, hypertension, stroke, diabetes, COPD, PVD, a tumor, tumor with metastases, history of congestive heart failure, anemia, atrial fibrillation, AMI or renal disease, prior PCI, eGFR, CAD-specific index, as well as medical treatment on admission. Medications on admission were ACE-I, ARB, ASA, P2Y12 receptor antagonists, oral anticoagulants, beta blockers, lipid-lowering drugs, diuretics, digitalis, long-acting nitroglycerin and calcium antagonists.

For each outcome, Cox regression survival analyses were performed to compare the effects of invasive vs. non-invasive strategy. Three Cox regression analyses were performed: Model 1 included age, sex, eGFR and propensity scores. Model 2 included all covariates in model 1 and additionally adjusted for medications at discharge that differed between the groups (ACE-I or ARB, ASA, clopidogrel, beta blockers, statins, diuretics, digitalis, long-acting nitroglycerin and calcium antagonists). Model 3 included all covariates in model 2 and additionally adjusted for variables included in propensity scores for which balance between the groups was not achieved. Unless otherwise stated, adjusted HRs presented in this thesis are for model 3.

Unknown and missing values were kept as an additional level of the categorical covariates.

When the proportional hazards assumption was violated in the Cox regression, data were further analyzed with flexible parametric survival analyses, Royston-Parmer model (Royston & Parmar, 2002) and continuous HR were presented. Interactions were tested between age and treatment, sex and treatment and eGFR group and treatment. Subgroup analyses were performed in those groups.

In Paper IV, descriptive statistics were used as outlined for patient characteristics. Success and complications of catheterizations were evaluated for the whole group, as well as separately in nonagenarians with stable and acute indications. Relative survival of the nonagenarian population undergoing catheterizations was compared to the survival of the general nonagenarian population in Sweden for years 2006-2014. Age, sex and intervention-year mortality rates for the general population were obtained from life tables of Statistics Sweden. The relative survival was estimated for start to one-month, one-month to one-year, one-year to two-year and two-year to three-year intervals.

Most analyses in Papers I, II and IV were performed using IBM SPSS version 18-25. The forest plot shown in figure 16 (figure 2 in Paper II) was made with the statistical software R version 64 3.2.5. Survival analyses in paper IV were performed using SAS version 9.4. Survival analyses and other analyses in Paper III as well as in unpublished data for patients with NSTE-ACS were performed using SAS version 9.4.

Table 5. Covariates included in logistic regression models in Paper II.

	Revascularization with PCI[a], revascularization with CABG[b]	**In-hospital bleeding events, in-hospital complications, 30-day mortality**	**After PCI: In-hospital bleeding events, in-hospital complications, 30-day mortality**
Covariates	Age[c], sex (men, women), age, eGFR[d], indication (STEMI/NSTE-ACS[e]), extent of coronary artery disease, diabetes (one vessel, two vessels, three vessels or left main stem), hypertension (yes/no), hyperlipidemia (yes/no), prior PCI (yes/no), prior acute myocardial infarction (yes/no), prior CABG (yes/no), smoking status (never smoked, prior smoker, current smoker), country (Iceland, Sweden) and year (2007/2008/2009/2010/2011)	Same as in column two, vascular approach (femoral, radial)	Same as in column three, treatment of left main stem (yes/no), complete revascularization (yes/no), P2Y12 receptor antagonists (yes/no), acetylsalicylic acid (yes/no), glycoprotein IIb/IIIa inhibitors (yes/no), anticoagulation before PCI (yes/no), thrombolysis before PCI (yes/no), type of stents (BMS/DES[f]), treatment of chronic total occlusion (yes/no), treatment of bifurcations (yes/no), whether the patient was in a cardiogenic shock (yes/no)

[a]PCI: percutaneous coronary intervention; [b]CABG: coronary artery bypass graft; [c]age and glomerular filtration rate are continuous variables, others are categorical; [d]eGFR: estimated glomerular filtration rate, calculated with Cockcroft Gault (µmol/L); [e]STEMI: ST-elevation myocardial infarction, NSTE-ACS: non-ST elevation acute coronary syndrome; [f]BMS: bare-metal stents, DES: drug-eluting stents.

4 Results

4.1 Using SWEDEHEART in Iceland (Paper I)

There were more CA performed per capita in Iceland in 2007 than in Sweden, 5,437/million and 4,022/million (p<0.001). The overall PCI rate was similar in both countries, 2,139 patients/million vs. 2,036/million (p=ns). Indications differed with a higher proportion of both CAs and PCIs in Iceland being performed due to stable CAD, than in Sweden (table 6). When indications were calculated per million inhabitants, the rate for CA due to stable CAD was double in Iceland and the rate for PCI 50% higher (figure 13).

Table 6. Indications for catheterizations in Iceland and Sweden in 2007.

	All CA[c]		All PCI[e]	
Indication	Iceland N=1693 %	Sweden N=36904 %	Iceland N=666 %	Sweden N=18680 %
Stable CAD	39.0[d]	23.1	40.1[d]	23.5
UAP/NSTEMI[a]	29.0	39.4	36.2	45.3
STEMI[b]	9.0	16.2	20.0	27.4
Other	23.0	21.3	3.8	3.8

[a]UAP: unstable angina pectoris, NSTEMI: non-ST-elevation myocardial infarction; [b]ST-elevation myocardial infarction; [c]CA: coronary angiography; [d]difference between indications was tested with Chi-square and all p were < 0.001; table modified from (Gudnason et al., 2013) with permission.

The risk factors varied between countries with Swedish patients being older, more likely to have diabetes and prior AMI than Icelandic patients. In Iceland, the patients were more likely to have hypertension and current treatment with lipid-lowering drugs than in Sweden. Smoking was more common in Iceland than Sweden (table 7).

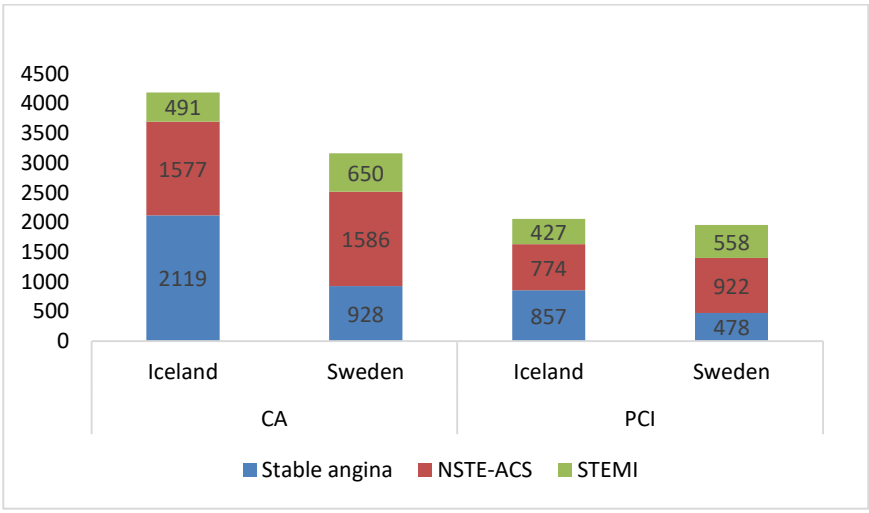

Figure 13. Indications for catheterization/1,000,000 in Iceland and Sweden.

In comparing the rate between the countries, all p< 0.01, except for CAs due to NSTE-ACS, where there was no difference; CA: coronary angiography; PCI: percutaneous coronary intervention; STEMI: ST-elevation myocardial infarction; NSTE-ACS: non-ST-elevation acute coronary syndromes

Table 7. Patient demographics in Iceland and Sweden in patients undergoing percutaneous coronary interventions.

	Iceland n=666 %	**Sweden n=18,680** %	**p**
Mean age-years[a]	63.7 (±11.7)	66.2 (±10.9)	<0.001
Female sex	21.0	28.3	<0.01
Hypertension	61.9	52.4	<0.01
Diabetes	15.6	18.8	ns
Smoking	28.7	19.1	<0.001
Hyperlipidemia	61.3	53.3	<0.05
Cardiogenic shock	1.8	1.4	ns
Prior PCI[b]	30.2	26.5	ns
Prior CABG[c]	11.7	10.3	ns
Prior AMI[d]	24.6	27.7	ns

[a]Age is shown as mean (±standard deviation), other variables are percentages; [b]PCI: percutaneous coronary intervention; [c]CABG: coronary artery bypass graft; [d]AMI: acute myocardial infarction. Table modified from (Gudnason et al., 2013) with permission.

No significant stenosis was found in 30.6% of CA in Iceland and 29.1% in Sweden (p=ns), one-vessel disease in 23.0% vs 27.7% (p<0.01), two-vessel disease in 18.4% vs 17.9% (p=ns), three-vessel disease in 18.0% vs. 17.3% (p=ns) and left main stem stenosis in 9.8% vs. 7.6% (p<0.01).

After CA, the complication rate in the catheterization laboratory was 0.9% (10) in Iceland and 0.7% (135) in Sweden (p=ns). Complications in the coronary care unit were 2.7% (29) in Iceland and 1.5% (304) in Sweden (p<0.01). In-hospital mortality in patients undergoing CA was 0.8% (9) in Iceland and 0.4% (74) in Sweden (p<0.01).

The radial access was used in 0.6% (6) of CAs in Iceland and 32.8% (6621) in Sweden, (p<0.001) with similar results for the approach in PCIs. The fluoroscopy time during PCI was longer in Iceland 11.06 min (IQR: 7.30-18.31) vs. 10.33 min (IQR: 6.47-17.18) in Sweden (p<0.05). Contrast use during PCI was also higher in Iceland, 220 ml (IQR: 140-220) vs. 150 ml (IQR: 114-200) (p<0.05).

The success of PCI was similar in the two countries, 87.5% in Iceland and 93.2% in Sweden (p=ns). Overall stent use was 87.6% in Iceland and 83.9% in Sweden (p=ns). Drug-eluting stent use was higher in Iceland 23.1% vs. 18.8% in Sweden (p<0.01). Thrombolysis was given before acute PCI in 1.3% (9) in Iceland and 0.9% (149) in Sweden (p=ns).

After PCI, complication rate in the catheterization laboratory was 5.7% (38) in Iceland and 3.1% (577) in Sweden (p<0.001). Complications in the coronary care unit were 7.5% (50) in Iceland and 4.9% (920) in Sweden (p<0.01). In-hospital mortality did not differ between the two countries, 1.7% (11) in Iceland and 1.2% (218) in Sweden (p=ns).

Since 2007, the use of the radial approach has increased in both Iceland and Sweden (figure 14). During 2011, it was used in 44.1% of PCIs in Iceland and 67.5% in Sweden. During 2012, it had increased to 73.4% in Iceland and 73.1% in Sweden. Complications during those two years after PCI were 1.9% in Iceland vs. 1.8% in Sweden in the catheterization laboratory. Complications in the coronary care unit were 3.1% in Iceland vs. 4.1% in Sweden, both p=ns. This data is unpublished. New equipment for the catheterization lab in Iceland was bought in December 2008 (Þórarinn Guðnason, written communications) and there was a decrease in contrast use the following months (figure 15).

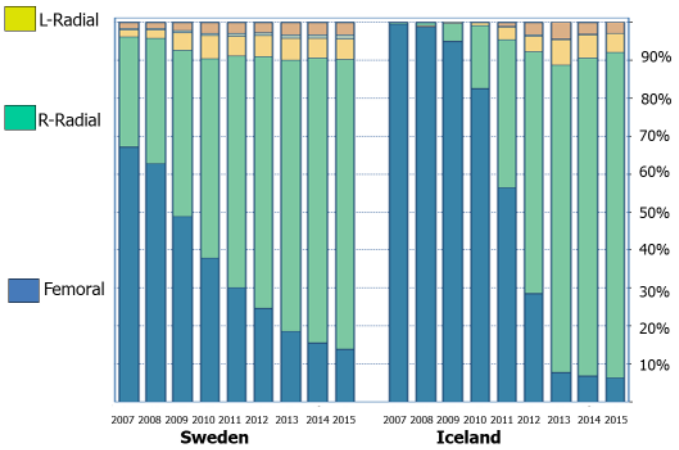

Figure 14. Access site during coronary angiography 2007-2015.

This data is unpublished and is from the Swedish Coronary Angiography and Angioplasty Registry. The figure is created by Þórarinn Guðnason. L: left; R: right.

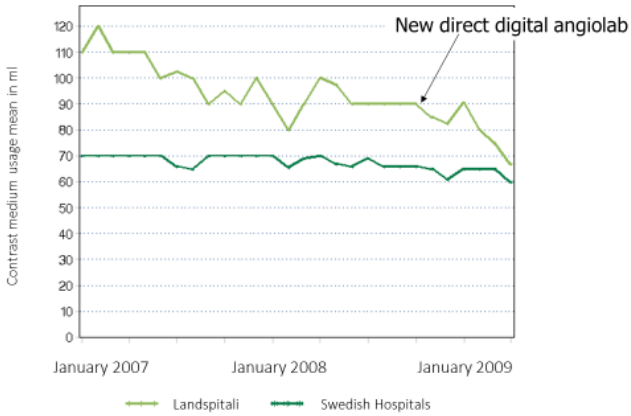

Figure 15. Contrast use in Iceland and Sweden 2007-2009.

This data is unpublished and is from the Swedish Coronary Angiography and Angioplasty Registry. The figure is created by Þórarinn Guðnason.

4.2 Women with ACS (Paper II)

Women undergoing CA due to ACS were four years older and had a higher comorbidity burden than men. The proportion of patients presenting with STEMI was 24.6% in women and 27.6% in men (p<0.001) (table 8). Similar results for comorbidities and risk factors were recorded in patients undergoing PCI. Women had less extensive CAD than men and 27.4% of women with ACS had no significant stenosis (table 9).

Table 8. Comorbidity burden in women and men undergoing coronary angiography due to acute coronary syndromes.

	Women N=34,120 %	**Men N=72,761** %
Percentage of patient population	31.9 [g]	68.1
Age (mean, ± 1SD; years)[a]	69.5 (11.3)	65.7 (11.3)
Percentage 80 years old and older	20.3	11.7
Diabetes	20.4	19.1
Hypertension	59.3	51.9
Hyperlipidemia	46.9	48.0
Ongoing smoking	19.2	20.8
Prior acute myocardial infarction	23.0	28.5
eGFR (mean, ±SD; ml/min/1.72m^2)[b]	77.0 (33.0)	93.7 (35.7)
Prior PCI[c]	17.3	22.8
Prior CABG[d]	6.1	11.1
STEMI[e]	24.6	27.6
NSTE-ACS[f]	75.4	72.4
Radial access	49.5	47.8

[a]Age and glomerular filtration rate are presented as mean ± standard deviation (SD), other results are percentages; [b]eGFR: Glomerular filtration rate, calculated with Cockcroft Gault (µmol/L); [c]PCI: percutaneous coronary intervention; [d]CABG: coronary artery bypass graft; [e]STEMI: ST-elevation myocardial infarction; [f]NSTE-ACS: non-ST elevation acute coronary syndrome; [g]differences between men and women were tested with a Student t-test for age and eGFR, other variables were tested with Chi-square, all p were < 0.001. Table modified from (Gudnadottir et al., 2017) with permission.

After excluding individuals without significant stenosis in at least one coronary artery, 77.6% of women and 77.0% of men underwent PCI; unadjusted odds ratio (OR) with 95% confidence interval (CI) was 1.04 (1.00-1.07) for women compared to men. After adjustment for age and various comorbidities, the OR for women to undergo PCI compared to men was 0.95 (0.92-0.99) (figure 16). There were positive interactions between sex and age, smoking status, extent of CAD and indication. In patients with one-vessel disease and STEMI, women were less likely to undergo PCI; 94.1% vs. 96.9% of men, adjusted OR 0.52 (0.43-0.64). Women with one-vessel

disease and NSTE-ACS were also less likely to undergo PCI, adjusted OR 0.78 (0.72-0.85). In patients with three-vessel disease or left main stem disease and NSTE-ACS, women were more likely to undergo PCI, adjusted OR was 1.12 (1.05-1.20) (figure 16).

Table 9. Extent of coronary artery disease in women and men with acute coronary syndromes.

Diseased vessels	**Women (n=34,120) %**	**Men (n=72,761) %**	**p[c]**
Inconclusive[a]	0.3	0.2	<0.001
Normal/atheromatous	27.4	12.0	<0.001
One-vessel disease	32.8	34.3	<0.001
Two-vessel disease	18.7	23.1	<0.001
Three-vessel disease/LM[b]	20.9	30.4	<0.001

[a]Includes missing; [b]LM=left main stem stenosis; [c]Significance was tested with Chi-square test. Table modified from (Gudnadottir et al., 2017) with permission.

Women were less likely to undergo CABG; unadjusted OR 0.76 (0.72-0.80). Even after adjustments for higher age and more comorbidities, the adjusted OR for women intended for revascularization with CABG was 0.81 (0.76-0.87) (figure 16). There were positive interactions between sex and age, indication, prior PCI, extent of CAD and prior CABG. In the subgroup of patients with NSTE-ACS and three-vessel disease or left main stem disease, the adjusted OR for referral to CABG in women was 0.83 (0.77-0.88) compared to men (figure 16).

In-hospital complications after PCI were more common in women than in men, adjusted OR 1.55 (1.44-1.66). Bleeding events were twice as common in women and serious bleeding events four times as common (table 10).

Women had higher crude 30-day mortality than men, 3.0% (1024) vs. 2.4% (1746), unadjusted OR 1.25 (1.16-1.35). After adjusting for age and comorbidities, the differences disappeared, adjusted OR 0.97 (0.84-1.05). Interactions between sex and each covariate were negative.

Due to the difference in referral to revascularization, mortality was examined in patients with a different extent of CAD. After adjusting for age and comorbidities, the mortality in women was similar to men, in patients with one-vessel, two-vessels disease as well as either three-vessels or left main stem disease (table 11).

Mortality in different age groups is shown in table 12.

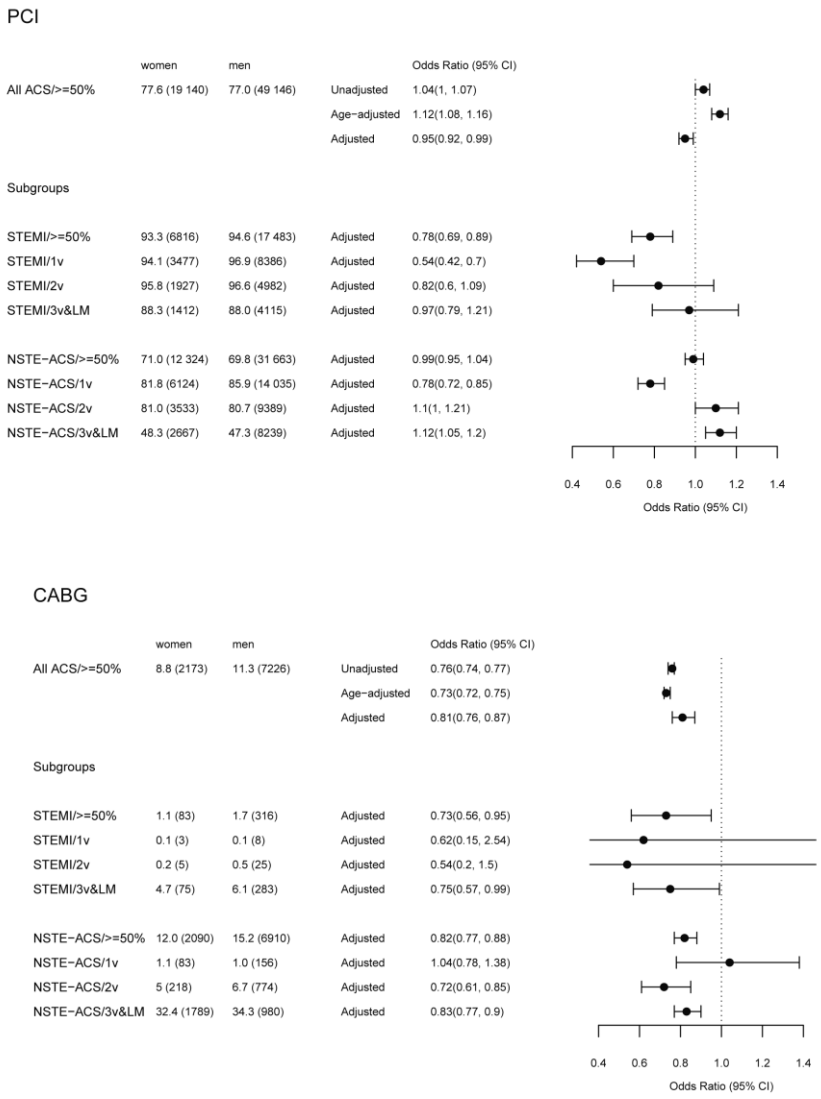

Figure 16. Referral for women and men with acute coronary syndromes to revascularization in patients with significant obstruction in the coronary arteries.

The figure shows the odds ratio from logistic regression for women compared to men adjusted for age, extent of coronary disease, indication, diabetes, hypertension, smoking, hyperlipidemia, prior coronary artery bypass graft, prior percutaneous coronary intervention, prior acute myocardial infarction, country, glomerular filtration rate and calendar year. Imputed data. ACS: acute coronary syndromes. NSTE-ACS: non-ST elevation acute coronary syndrome, STEMI: ST elevation myocardial infarction, LM: left main stem stenosis. Figure modified from (Gudnadottir et al., 2017) with permission.

Table 10. In-hospital complications in women and men after percutaneous coronary interventions due to acute coronary syndromes.

	Women 19,991 %	**Men 50,492 %**	**Unadjusted OR (95% CI)[a]**	**Adjusted OR (95% CI)[b]**	**Adjusted OR (95% CI)[c]**
Any in-hospital complications	8.4	5.4	1.61 (1.52-1.72)	1.55 (1.44-1.66)	1.58 (1.47-1.70)
Any in-hospital bleeding event	4.2	2.2	1.90 (1.73-2.09)	1.75 (1.59-1.94)	1.77 (1.60-1.97)
Serious in-hospital bleeding events	0.7	0.2	4.92 (3.70-6.55)	4.17 (3.07-5.66)	4.41 (3.22-6.05)

[a]Logistic regression, unadjusted odds ratio (OR) for women compared to men with 95% confidence intervals (CI); [b]logistic regression, OR for women compared to men, adjusted for age, extent of coronary disease, indication (ST-elevation myocardial infarction/non-ST-elevation acute coronary syndromes), diabetes, hypertension, smoking, hyperlipidemia, prior coronary artery bypass graft, prior percutaneous coronary intervention (PCI), prior acute myocardial infarction, vascular access, country, estimated glomerular filtration rate and calendar year, imputed data; [c]logistic regression, OR for women compared to men, adjusted for the same as in [b], as well as: treatment of left main stem, complete revascularization, P2Y12 receptor antagonists, acetylsalicylic acid, glycoprotein IIb/IIIa inhibitors, anticoagulation before PCI, thrombolysis before PCI, type of stents, treatment of chronic total occlusion or bifurcations and whether the patient was in a cardiogenic shock, imputed data; table modified from (Gudnadottir et al., 2017) with permission.

Table 11. 30-day mortality in women and men with acute coronary syndromes.

		Women %	Men %	Unadjusted OR (95% CI)[e]	Adjusted OR (95% CI)[f]
STEMI[a]	W=8,385[d] M=20,067	7.8	5.3	1.50 (1.36-1.66)	0.97 (0.87-1.08)
One-vessel	W=3,694 M=8,654	5.8	3.1	1.93 (1.60-2.33)	1.08 (0.88-1.33)
Two-vessel	W=2,012 M=5,158	7.8	4.9	1.67 (1.35-2.05)	0.95 (0.75-1.20)
Three vessel/LM[b]	W=1,600 M=4,677	14.6	10.5	1.60 (1.36-1.89)	0.93 (0.77-1.12)
NSTE-ACS[c]	W=25,735 M=52,694	1.5	1.4	1.11 (0.98-1.26)	0.94 (0.88-1.08)
One-vessel	W= 7,482 M=16,330	0.8	0.6	1.28 (0.93-1.75)	0.94 (0.67-1.32)
Two-vessel	W= 4,361 M=11,629	1.2	1.0	1.26 (0.91-1.76)	0.84 (0.59-1.20)
Three-vessel/LM	W= 5,520 M=17,412	4.1	2.6	1.46 (1.24-1.74)	1.04 (0.87-1.14)

[a]STEMI: ST-elevation myocardial infarction; [b]LM: left main stem stenosis; [c]NSTE-ACS: non-ST-elevation acute coronary syndromes; [d]W: women, M: men [e]logistic regression, unadjusted odds ratio (OR) for women compared to men with 95% confidence intervals (CI); [f]logistic regression, OR for women compared to men, adjusted for: age, extent of coronary disease, indication (STEMI/NSTE-ACS), diabetes, hypertension, smoking, country, hyperlipidemia, prior coronary artery bypass graft, prior percutaneous coronary intervention, prior acute myocardial infarction, vascular access, estimated glomerular filtration rate, access site and calendar year, imputed data. This data is unpublished.

Table 12. Effects of female sex on 30-day mortality in different age groups in patients with ST-elevation myocardial infarction undergoing percutaneous coronary interventions.

Age groups	Women %	Men %	Unadjusted OR (95% CI)[b]	Adjusted OR (95% CI)[c]
<60 years old W= 1,168 M=5,705	2.9	2.2	1.43 (0.93-2.04)	1.18 (0.79-1.79)
60-69 years old W=1,739 M=5,704	4.2	3.6	1.10 (0.86-1.40)	0.95 (0.72-1.27)
70-79 years old W=2,047 M=4,102	7.6	6.8	1.08 (0.89-1.30)	1.03 (0.83-1.28)
80 years and older W=1,970 M=2,154	14.5	14.2	0.97 (0.83-1.15)	0.89 (0.74-1.09)

[a]W: women, M: men; [b]logistic regression, odds ratio (OR) with 95% confidence interval(CI) for women compared to men; [c]logistic regression, OR for women compared to men adjusted for: extent of coronary disease, diabetes, hypertension, smoking, hyperlipidemia, prior coronary artery bypass graft, prior percutaneous coronary intervention, prior acute myocardial infarction, radial access, country, estimated glomerular filtration rate and calendar year, imputed data. Table modified from (Gudnadottir et al., 2017) with permission.

4.3 Older people with ACS (Unpublished data)

During 2006-2013, 80,386 people 70 years old or older (range: 70 to 103) were admitted due to ACS in Sweden and registered in RIKS-HIA. Only index admissions during the period were included. The mean age was 79.8 years (SD±6.4); 50.2% were 70 to 79 years old, 42.3% were 80 to 89 years old and 7.5% were 90 years old and older. Women were 43.4%. Patients 70 years old and older admitted due to ACS had multiple comorbidities; 64.2% had hypertension, 16.2% had atrial fibrillation, 16.3% had prior stroke and 9.9% had anemia. In total, 63.7% had a high burden of comorbidities according to CAD-specific index and 13.3% belonged to the group elderly with multi-morbidity and complex health needs. The mean eGFR was 58.8ml/min/1.73 m^2; and 47.4% had eGFR < 60 ml/min/1.73 m^2 (table 13).

In total, 21.0% died within a year of admission. Of those surviving to discharge 59.5% were readmitted the following year due to any cause. Readmissions due to cardiovascular causes and bleeding events are shown in table 14.

Table 13. Comorbidity burden in people 70 years old or older admitted due to acute coronary syndromes.

Disease	**N=80,386** **%**
Smoking status[a]	
Current smoker	9.3
Prior smoker	31.8
Prior AMI[b]	28.1
Prior PCI[c]	11.8
Prior stroke	16.3
TIA[d]	6.7
Diabetes	26.0
Heart failure	17.4
Hypertension	64.2
Renal failure	4.8
Peripheral vascular disease	5.0
COPD[e]	6.9
Tumor	7.3
Metastases	0.7
Anemia	9.9
Dementia	2.2
Atrial fibrillation	16.2
Rheumatological disease	10.2
CAD-specific index[f]	
Low burden	23.7
Moderate burden	7.5
High burden	63.7
eGFR, ml/min/1.73 m^2, mean (±SD)[g]	58.8 (±24.2)
90≥	8.6
60≤ but <90	29.7
30≤ but <60	38.2
<30	9.2
Multi-morbid older people with complex health needs	13.3

[a]Information about smoking status and estimated glomerular filtration rate (eGFR) are collected from The Register of Information and Knowledge About Swedish Heart Intensive Care Admissions (RIKS-HIA). Information regarding stroke, hypertension, diabetes and prior coronary artery disease are collected from both RIKS-HIA and National Patient Register. Other variables are from National Patient Register. Missing values are not included in the denominator. Missing variables for smoking are 3.6% and for eGFR 14.4% and CAD index 13.5%. Other have less than 0.5% missing; [b]AMI: acute myocardial infarction; [c]PCI: percutaneous coronary intervention; [d]TIA: transient ischemic attack; [e]COPD: chronic obstructive pulmonary disease; [f]CAD: coronary artery disease; [g]eGFR was calculated with Cockcroft Gault formula, SD: standard deviation.

Table 14. One-year events in people 70 years old or older with acute coronary syndromes.

	N=74,589[c] **%**
Readmissions due to any cause	59.5
Readmission due to ACS[a]	15.2
Readmission due to heart failure	9.4
Readmission due to stroke	2.7
Readmission due to a bleeding event[b]	6.6

[a]All events are for patients who survived to be discharged, ACS: acute coronary syndromes; [b] International Statistical Classification of Diseases, 10th revision (ICD-10) codes for bleeding events are in appendix 3; [c]readmission due to ACS are from The Register of Information and Knowledge About Swedish Heart Intensive Care Admissions and National Patient Register, other events are from National Patient Register.

4.4 Multi-morbid older people with complex health needs and ACS

People 70 years old and older admitted due to ACS and registered in RIKS-HIA who belonged to the group older people with multi-morbidity and complex health needs during 2006-2013 were 10,825. Of those, 47.0% were women and mean age was 80.5 years (±6.4). STEMI was the discharge diagnosis in 18.5% and NSTE-ACS in 81.5%. In-hospital mortality was 15.6% in patients with STEMI and 7.1% in patients with NSTE-ACS, leaving 1,659 in the STEMI study population and 8,179 in NSTE-ACS population (figure 17).

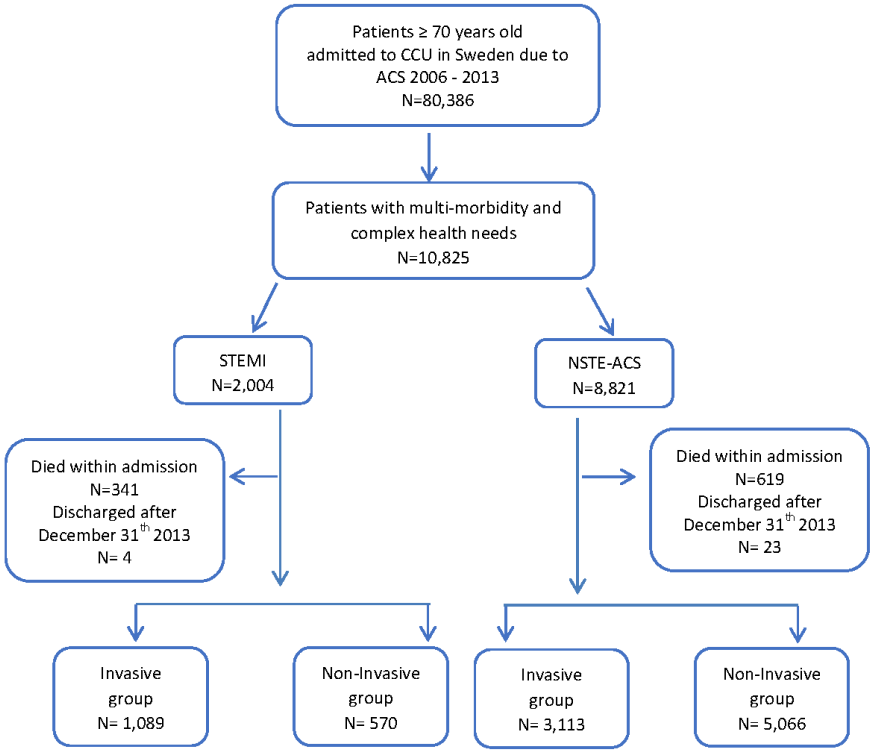

Figure 17. Patient selection in Paper III and unpublished data.

STEMI: ST-elevation myocardial infarction: NSTEMI: non-ST elevation myocardial infarction; UAP: unstable angina pectoris; invasive group: all patients who underwent coronary angiography (CA) ≤14 days. Non-invasive group: patients who did not undergo CA or did so after 14 days.

4.4.1 Invasive strategy in patients with STEMI (Paper III)

Invasive strategy was the choice in 1,089 (65.6%) of included patients with STEMI. Of those, 85.0% underwent CA and when possible primary PCI the first day. The invasive group was younger and had a lower comorbidity burden; 71.0% of them had a severe burden of comorbidities but 91.0% of the non-invasive group. In the invasive group, 21.9% had atrial fibrillation and 33.2% in the non-invasive group (table 15). The invasive group had fewer medications upon admission (table 16).

Medical treatment during admission varied; 83.8% of the invasive group had statins at discharge, 89.8% had P2Y12 receptor antagonist and 78.5% had ACE-I or ARB. For the invasive group, these numbers were 47.2%, 37.1% and 58.5% (table 17).

Balance between the groups was reached in a propensity score for all baseline characteristics and medications at admission except ARB ($p < 0.049$), see table in appendix 3.

One-year primary event (death, new ACS or stroke/TIA) was reached in 30.9% in the invasive group and 54.6% in the non-invasive group, adjusted hazard ratio (HR) 0.67 (0.54-0.83). The one-year mortality in the invasive group was 17.7% and 44.9% in the non-invasive group, adjusted HR 0.51 (0.39-0.65). Readmissions due to bleeding events did not differ between the two groups (table 18).

To be included in our analyses, patients had to be alive at discharge. Mortality during hospitalization was analyzed to exclude biases in favor of invasively treated patients. New propensity scores were built for the whole group of STEMI patients. The groups were well balanced for all baseline characteristics and all medications at admission in a propensity score. The adjusted HR for in-hospital mortality in the invasive group was 12.5% and in the non-invasive 24.4%, adjusted HR 0.74 (0.57-0.94).

Table 15. Patient characteristics in multi-morbid people 70 years old or older with ST-elevation myocardial infarction.

	Invasive group[f] (N=1,089) %	**Non-invasive group (N=570)** %	**p-value[g]**
Age, years (±SD)[a]	78.7 (5.7)	83.4 (6.2)	<.0001
70-<80 years	55.9	26.0	
80-<90 years	40.7	58.2	<.0001
≥90 years	3.4	15.8	
Women	45.1	55.1	0.0001
Not an active smoker	87.6	90.5	
Active smoker	12.4	9.5	0.14
Missing smoking status	n=95	n=130	
Year of index date			
2006-2008	28.3	43.9	
2009-2011	12.9	40.5	<.0001
2011-2013	16.2	26.5	
Hypertension	58.6	61.9	0.21
Stroke	16.3	23.5	0.0006
Diabetes	25.2	29.1	0.094
COPD[b]	12.6	13.9	0.51
PVD[c]	6.8	12.3	0.0003
Cancer during the last three years	21.9	24.2	0.30
Heart failure	19.9	35.8	<.0001
Anemia	16.6	29.5	<.0001
Atrial fibrillation	21.9	33.2	<.0001
Acute myocardial infarction	25.5	35.2	<.0001
eGFR ml/min/1.73m^2 (±SD)[d]	25.1	22.4	0.0004
≥90	9.9	4.7	
60≤eGFR<90	32.3	17.2	
30≤eGFR<60	45.3	54.9	
eGFR<30	12.5	23.2	
Missing eGFR, number	n=71	n=122	<.0001
CAD-specific indexes			
Low burden	16.7	3.3	
Moderate burden	12.2	5.6	
High burden	71.0	91.0	
Missing CAD index, number	n=68	n=90	<.0001

[a]SD: standard deviation; [b]COPD: chronic obstructive pulmonary disease; [c]PVD: peripheral vascular disease; [d]eGFR: estimated glomerular filtration rate, calculated with Cockcroft Gault formula; [e]CAD: coronary artery disease; [f]invasive strategy: patients who underwent coronary angiography ≤14 days; [g]for comparison between groups Fisher´s Exact test was used for dichotomous variables, the Mantel-Haenszel Chi-square test was used for ordered categorical variables, Chi-square was used for non-ordered categorical variables and Mann-Whitney U-test was used for continuous variables.

Table 16. Medications at admission in multi-morbid people 70 years old or older and ST-elevation myocardial infarction.

	Invasive group[a] (n=1,089) %	**Non-invasive group (n=570) %**	**p-value[b]**
ACE-I[c]	22.5	28.6	0.0084
ARB[d]	17.0	13.1	0.046
Calcium antagonists	24.1	21.7	0.30
Beta blockers	45.5	52.4	0.0090
Statins	31.3	30.6	0.81
Acetylsalicylic acid	40.0	49.4	0.0003
P2Y12 receptor antagonist	7.5	8.5	0.56
Oral anticoagulants	8.1	11.3	0.042
Digitalis	4.2	9.2	0.0001
Long-acting nitroglycerin	13.1	22.2	<.0001

[a]Invasive group: Patients underwent coronary angiography ≤14 days; [b]for comparison between groups, Fisher´s Exact test was used for dichotomous variables, the Mantel-Haenszel Chi-square test was used for ordered categorical variables, Chi-square was used for non-ordered categorical variables and Mann-Whitney U-test was used for continuous variables; [c]ACE: Angiotensin-Converting Enzyme; [d]ARB: Angiotensin II receptor blockers.

Table 17. Medications at discharge in multi-morbid people 70 years old or older with ST-elevation myocardial infarction.

	Invasive group[a] (n=1,089) %	**Non-invasive group (n=570)** %	**p-value[b]**
ACE-I[c]	60.9	45.1	<.0001
ARB[d]	17.6	13.4	0.031
Calcium antagonists	16.4	15.5	0.69
Beta-blockers	88.2	79.6	<.0001
Statins	83.8	47.2	<.0001
Acetylsalicylic acid	91.6	78.5	<.0001
P2Y12 receptor antagonist	89.8	37.1	<.0001
Oral anticoagulants	10.3	10.4	1.00
Digitalis	6.2	7.4	0.40
Aldosterone blockers	10.0	10.2	1.00
Long-acting nitroglycerin	15.3	32.5	<.0001

[a]Invasive group: Patients underwent coronary angiography ≤14 days; [b]for comparison between groups, Fisher´s Exact test was used for dichotomous variables, the Mantel-Haenszel Chi-square test was used for ordered categorical variables, Chi-square was used for non- ordered categorical variables and Mann-Whitney U-test was used for continuous variables; [c]ACE-I: Angiotensin-Converting Enzyme; [d]ARB: Angiotensin II receptor blockers.

Table 18. Events in invasive and non-invasive groups in multi-morbid people 70 years old or older with ST-elevation myocardial infarction.

	Invasive group[b] (n=1,089) %	**Non-invasive group (n=570)** %	**Invasive and non-invasive group HR (95% CI) Model1**	**Model 2**	**Model 3**
One-year primary event (death, ACS, stroke, TIA)[a]	30.9	54.6	0.56 (0.47 - 0.68)	0.67 (0.54 - 0.83)	0.67 (0.54 - 0.83)
One-year secondary events					
Readmission due to a bleeding event	8.3	11.2	0.67 (0.45 - 0.97)	0.66 (0.43 - 1.02)	0.66 (0.43 - 1.02)
Death	17.7	44.9	0.42 (0.33 - 0.52)	0.51 (0.40 - 0.66)	0.51 (0.39 - 0.65)
Readmission due to ACS	12.9	16.1	0.76 (0.55 - 1.03)	0.76 (0.53 - 1.09)	0.76 (0.54 - 1.09)
Readmission due to stroke/TIA	4.3	5.1	0.91 (0.53 - 1.57)	0.74 (0.40 - 1.37)	0.74 (0.40 - 1.37)
Readmission due to heart failure	11.8	15.3	0.80 (0.58 - 1.10)	0.88 (0.61 - 1.26)	0.88 (0.61 - 1.26)
Any readmission	70.8	69.8	0.86 (0.75 - 0.99)	0.88 (0.75 - 1.03)	0.88 (0.75 - 1.03)

[a]ACS: acute coronary syndromes, TIA: transient ischemic attack; [b]invasive group: patients underwent coronary angiography ≤14 days; [c]shows hazard ratios (HR) with 95% confidence intervals (CI) from Cox regression, adjusted for age, sex and propensity scores; model 2: model 1, additionally adjusted for medications at discharge that significantly differed between the treatments (angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers (ARB), diuretics, statins, acetylsalicylic acid, P2Y12 receptor antagonist and long-acting nitrates); model 3: Model 2 additionally adjusted for variables included in propensity score for which balance between the groups was not achieved (ARB).

For the primary event as well as readmission due to a bleeding event and death, there were positive interactions between treatment group and both age and eGFR. In those who were 90 years old and older, the adjusted HR for the primary event was 1.57 (0.93-2.64), for death it was 1.39 (0.78-2.47) and for readmission due to bleeding events 1.51 (0.59-3.86) (table 19). There were 37 nonagenarians in the invasive group and 90 in the non-invasive group (table 15).

In the group with severe renal failure (eGFR<30ml/min/1.73m^2), the adjusted HR for the primary event in the invasive group compared to non-invasive was 0.84 (0.58-1.22), for death 0.88 (0.58-1.32) and for readmission due to bleeding events 1.50 (0.66-3.39) (table 19). In the non-invasive group, there were 109 individuals and the invasive group included 127.

Women and men receiving invasive strategy both had lower risk for reaching the primary event than those who did not. The adjusted HR for women for invasive strategy compared to non-invasive was 0.76 (0.59-0.99) but in men 0.57 (0.44-0.75); p for interaction was 0.07 (table 19).

For the event death during one-year after discharge in the STEMI group, the assumptions of proportional hazards in the Cox regression were not met. Continuous HRs are shown in figure 18. The risk reduction was highest during the first three months and decreased after that. The HR remained under zero the whole year, but the difference between the groups was not significant after nine months.

Table 19. Events in invasive and non-invasive groups in different subgroups of multi-morbid people 70 years old or older with ST-elevation myocardial infarction.

	Subgroup	**Invasive & non-invasive group HR (95% CI)[b]**	**p-value for interaction[c]**
One-year primary event (death, ACS, Stroke, TIA)[a]	70-79 years	0.61 (0.45-0.97)	
	80-89 years	0.62 (0.48-0.80)	.012
	≥90 years	1.57 (0.93-2.64)	
	Men	0.57 (0.44-0.75)	
	Women	0.76 (0.59-0.99)	.07
	eGFR, min/1.73m^2	0.62 (0.30-1.29)	
	≥90ml		
	60≤ eGFR <90	0.41 (0.28-0.62)	
	30≤ eGFR <60	0.73 (0.56-0.96)	.049
	eGFR < 30	0.84 (0.58-1.22)	
	eGFR unknown	0.50 (0.29-0.84)	
Readmission due to a bleeding event	70-79 years	0.42 (0.23-0.77)	
	80-89 years	0.73 (0.42-1.25)	.048
	≥90 years	1.51 (0.59-3.86)	
	Men	0.77 (0.44-1.35)	.39
	Women	0.58 (0.34-0.98)	
	eGFR ml/min/1.73m^2		
	≥90	0.40 (0.23-0.77)	
	60≤ eGFR <90	0.30 (0.14-0.66)	
	30≤ eGFR <60	0.75 (0.43-1.32)	.018
	eGFR < 30	1.50 (0.66-3.39)	
	eGFR unknown	0.20 (0.04-0.90)	
Death	70-79 years	0.34 (0.23-0.48)	
	80-89 years	0.55 (0.40-0.74)	.0022
	≥90 years	1.39 (0.78-2.47)	
	Men	0.36 (0.26-0.50)	
	Women	0.67 (0.49-0.90)	.0016
	eGFR, ml/min/1.73m		
	≥90	0.21 (0.08-0.51)	
	60≤ eGFR <90	0.23 (0.14-0.38)	
	30≤ eGFR <60	0.56 (0.40-0.78)	<.0001
	eGFR < 30	0.88 (0.58-1.32)	
	eGFR unknown	0.31 (0.15-0.61)	

[a]ACS: acute coronary syndromes, TIA: transient ischemic attack; [b]Patients who underwent coronary angiography ≤14 days constituted the invasive group, they were compared to those who did not with Cox regression, shown are hazard ratios (HR) with 95% confidence intervals (CI) adjusted for age, sex, propensity score, medications at discharge (angiotensin-converting enzyme inhibitors at admission, medication angiotensin II receptor blockers, diuretics, statins, acetylsalicylic acid, P2Y12 receptor antagonist and long-acting nitrates) and for variables included in propensity score for which balance between the groups was not achieved (angiotensin II receptor blockers at admission). [c]Interactions between treatment group and subgroup.

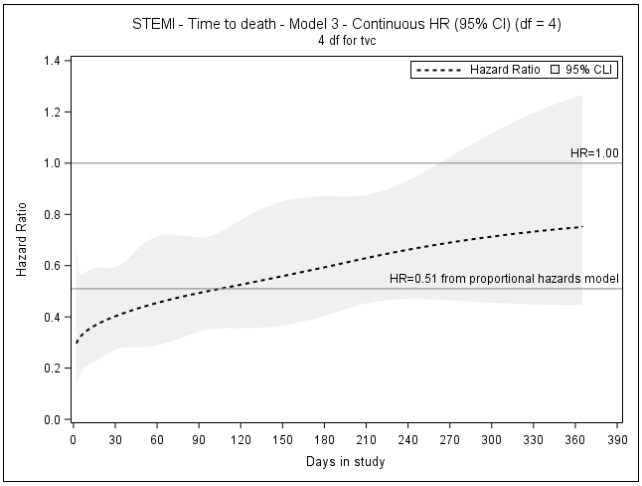

Figure 18. Continuous hazard ratio for mortality during one-year in multi-morbid people 70 years old or older with ST-elevation myocardial infarction.

The figure shows the continuous hazard ratio (HR) for invasive group compared to non-invasive group during one-year obtained from flexible parametric survival analyses, Royston-Parmer model. HR (95% confidence interval) are as following: day 10: 0.35 (0.21-0.58); day 30: 0.40 (0.27-0.59); day 60: 0.45 (0.29-0.71); day 90: 0.49 (0.34-0.71); 6 months: 0.59 (0.41-0.87); 9 months 0.69 (0.46-1.03); and one-year: 0.75 (0.45-1.27).

4.4.2 Invasive strategy in patients with NSTE-ACS (Unpublished data)

In patients with NSTE-ACS, the invasive group was five years younger and had a lower comorbidity burden than the non-invasive group. In the invasive group, 68.1% of the patients had a severe burden of comorbidities per CAD-specific index and 89.5% in the non-invasive group. Atrial fibrillation was present in 26.2% of patients in the invasive group and 35.7% in the non-invasive. The proportion of UAP was 18.1% in the invasive group and 8.9% in the non-invasive group (table 20). The non-invasive group had more medications at admission (table 21).

Medical treatment during admission was higher in the invasive group; 86.5% had statins at discharge, 78.2% had P2Y12 receptor antagonist and 74.5% had ACE-I or ARB. For the non-invasive group, these numbers were 54.7%, 42.3% and 58.7%. The percentage receiving anticoagulants was the same in both groups (table 22).

The primary event (composite of death, stroke or TIA) was reached in 30.3% in the invasive group and 54.0% in the non-invasive group. One-year mortality after discharge was 12.5% in the invasive group and 37.8% in the non-invasive group (table 23).

Balance between the groups was not reached in a propensity score for baseline characteristics and medications at admission. Differences persisted in year of index date, age, eGFR groups and many medications at admission (beta-blockers, statins, P2Y12 receptor antagonist and long-acting nitrates), see table in appendix 3. As many of these characteristics have a strong impact on prognosis in patients with NSTE-ACS, the differences between the groups are likely to be influenced strongly by selection bias and additional Cox regression analyses were not performed.

Table 20. Patient characteristics in multi-morbid people 70 years old or older with non-ST-elevation acute coronary syndromes.

	Invasive group[f] (n=3,113) %	**Non-invasive group (n=5,066) %**	**p-value[g]**
Age, years (±SD)[a]	77.1 (4.9)	82.2 (6.3)	<.0001
70-<80 years	67.7	32.8	
80-<90 years	31.3	54.6	<.0001
≥90 years	1.0	12.7	
Women	42.3	49.7	<.0001
Not an active smoker	90.8	91.4	
Active smoker	9.2	8.6	.39
Missing smoking status, number	n=268	n=929	
Year of index date			
2006-2009	40.5	55.9	<.0001
2010-2013	59.5	44.1	
Hypertension	65.5	68.1	0.019
Stroke	15.3	25.5	<.0001
Diabetes	33.8	35.8	.068
COPD[b]	12.8	17.2	<.0001
PVD[c]	10.6	13.8	<.0001
Cancer during the last three years	19.7	21.3	.085
Heart failure	25.5	49.6	<.0001
Anemia	16.4	30.4	<.0001
Atrial fibrillation	26.2	35.7	<.0001
Acute myocardial infarction	39.6	49.1	<.0001
eGFR ml/min/1.73m^2 (±SD)[d]	25.2	22.7	<.0001
≥90	11.4	4.3	
60≤eGFR<90	38.9	18.5	
30≤eGFR<60	41.0	51.4	
eGFR<30	8.8	25.8	<.0001
Missing eGFR, number	n=84	n=912	
CAD-specific indexes[e]			
Low burden	16.0	4.4	
Moderate burden	15.4	6.0	
High burden	68.1	89.5	<.0001
Missing CAD index, number	n=136	n=650	
NSTEMI	81.9	91.1	
UAP	18.1	8.9	<.0001

[a]SD: standard deviation; [b]COPD: chronic obstructive pulmonary disease; [c]PVD: peripheral vascular disease; [d]eGFR: estimated glomerular filtration rate, calculated with Cockcroft Gault formula; [e]CAD: coronary artery disease; [f]patient underwent coronary angiography ≤14 days; [g]for comparison between groups Fisher´s Exact test was used for dichotomous variables and the Mantel-Haenszel Chi-square test for ordered categorical variables, Chi-square was used for non-ordered categorical variables and Mann-Whitney U-test was used for continuous variables.

Table 21. Medications at admission in multi-morbid people 70 years old or older patients and with non-ST-elevation acute coronary syndromes.

	Invasive group[a] (N=5,066) %	**Non-invasive group (N=3,113)** %	**p-value[b]**
ACE-I[c]	31.4	32.0	0.61
ARB[d]	21.6	17.3	<.0001
Calcium antagonists	26.5	22.4	<.0001
Beta-blockers	59.0	61.6	0.024
Statins	51.0	39.4	<.0001
Acetylsalicylic acid	59.7	60.4	0.58
P2Y12 receptor antagonist	15.5	12.9	0.0012
Oral anticoagulants	13.3	13.9	0.47
Digitalis	5.0	7.9	<.0001
Long-acting nitroglycerin	28.2	35.2	<.0001

[a]Invasive strategy: Patients underwent coronary angiography ≤14 days; [b]for comparison between groups Fisher´s Exact test was used for dichotomous variables, the Mantel-Haenszel Chi-square test was used for ordered categorical variables, Chi-square was used for non-ordered categorical variables and Mann-Whitney U-test was used for continuous variables; [c]ACE-I: Angiotensin-Converting Enzyme; [d]ARB: Angiotensin II receptor blockers.

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Table 22. Medications at discharge in multi-morbid people 70 years old or older and with non-ST-elevation acute coronary syndromes.

	Invasive group[a] (N=3,113) %	**Non-invasive group (N=5,066)** %	**p-value[b]**
ACE-I[c]	50.0	41.7	<.0001
ARB[d]	24.5	17.0	<.0001
Calcium antagonists	26.3	22.3	<.0001
Diuretics	46.7	68.1	<.0001
Beta-blockers	87.8	81.0	<.0001
Statins	86.5	54.7	<.0001
Acetylsalicylic acid	90.9	77.8	<.0001
P2Y12 receptor antagonist	78.2	42.3	<.0001
Oral anticoagulants	12.9	14.0	0.17
Digitalis	4.6	8.2	<.0001
Aldosterone blockers	8.6	10.5	0.18
Long-acting nitroglycerin	32.7	45.2	<.0001

[a]Invasive strategy: Patients underwent coronary angiography ≤14 days; [b]for comparison between groups Fisher´s Exact test was used for dichotomous variables; the Mantel-Haenszel Chi-square test was used for ordered categorical variables, Chi-square was used for non-ordered categorical variables and Mann-Whitney U-test was used for continuous variables; [c]ACE-I: Angiotensin-Converting Enzyme; [d]ARB: Angiotensin II receptor blockers.

Table 23. Events in invasive treatment and non-invasive groups in people 70 years old or older with non-ST-elevation acute coronary syndromes.

	Invasive group[a] (N=3,113) %	**Non-invasive group (N=5,066)** %
One-year primary event: (death, ACS[a], Stroke, TIA[b])	30.3	54.0
One-year secondary events:		
Readmission due to a bleeding event	9.4	9.9
Death	12.5	37.8
Readmission due to ACS	18.5	23.7
Readmission due to stroke/TIA	3.7	4.5
Readmission due to heart failure	10.6	18.3
Any readmission	75.3	79.4

[a]ACS: acute coronary syndromes; [b]TIA: transient ischemic attack; [c]invasive strategy: patients underwent coronary angiography ≤14 days.

4.5 Nonagenarians undergoing catheterizations (Paper IV)

There were 1,692 nonagenarians that underwent 1,874 catheterizations in Sweden during 2006-2014. Results are presented for catheterizations during index admissions. Women constituted 56.9% of the nonagenarians. In total, 65.1% had treated hypertension and 13.1% had diabetes (table 24). The mean eGFR for nonagenarians was 40.0 ml/min/1.73 m^2 (±13.2). Of 1,692 nonagenarians, 93.3% had eGFR ≤ 60 ml/min/1.73 m^2.

ACS was the indication for CA in 79.5% of nonagenarians (STEMI 45.5% and NSTE-AS 34.0%) (table 25) Multi-vessel disease was found in 62.2% of nonagenarians and 86.9% had a significant CAD.

During the index catheterization, 65.6% nonagenarians underwent PCI directly after CA, 2.0% underwent PCI later during the admission and another 2.0% were referred to PCI after discharge. Of 1,692 nonagenarians, 19 were referred to CABG.

Table 24. Clinical characteristics in nonagenarians.

	N=1,692 %
Age, years: median (range)[a]	91.0 (90-100)
Age ≥95	6.8
Women	56.9
Diabetes	13.5
Hypertension	65.1
Hyperlipidemia	30.4
Ongoing smoking	2.1
Prior smoking	24.2
Prior AMI[b]	32.8
Prior PCI[c]	6.3
In cardiogenic shock	4.7
Prior CABG[d]	11.1
eGFR in ml/min/1.73 m^2, mean (±SD)[e]	
<30	21.0
30-60	60.4
> 60	7.3

[a]All variables except age are shown as %; missing values were none for age and sex, 13.7% for smoking status, 11.2% for eGFR. For all other variables, they were 4-5%. Missing values are not in the denominator; [b]AMI: acute myocardial infarction; [c]PCI: percutaneous coronary intervention; [d]CABG: coronary artery bypass graft; [e]eGFR: Glomerular filtration rate, calculated with Cockcroft Gault (µmol/L), SD: standard deviation.

Table 25. Indications and outcomes of coronary angiographies in nonagenarians.

		N=1,692 %
Indications	STEMI[a]	45.5
	NSTE-ACS[b]	34.0
	Stable CAD	4.7
	Other[c]	15.8
Outcomes	Normal/atheromatous	13.1
	One-vessel disease	24.7
	Two-vessel disease	22.3
	Three-vessel disease	26.2
	Left main stem stenosis	13.7

[a]STEMI: ST-elevation myocardial infarction; [b]NSTE-ACS: Non-ST-elevation acute coronary syndromes; [c]of other indications, 86.0% were investigations due to valvular disease, planned to be operated by trans-catheter aortic valve implantation or in some cases an open-heart surgery.

STEMI was the indication in 58.9% of 1,141 PCIs in nonagenarians during index admission, NSTE-ACS in 35.5%, stable CAD in 4.1% and other indications in 1.5%. The lesions were complex in 63.3% of PCIs. Of these PCIs, 15.6% were multi-vessel and in 1.8% of PCIs another segment was treated during another catheterization. Stents were used in 87.5% and drug-eluting stents (DES) in 32.2% (table 26).

After PCI, 8.1% of nonagenarians had some complications in the hospital. Serious bleeding events and neurological complications were rare, 0.7% and 0.6% respectively**.** The in-hospital mortality in the PCI group was 7.7%. No nonagenarian had a reported renal failure after PCI and one had renal failure after CA (table 27).

For the 499 nonagenarians who did not undergo revascularization, one-year mortality was 29.9%. The one-year mortality for the 1,193 nonagenarians, who did undergo revascularization with either PCI or CABG, was 33.0%. Mortality/1,000 nonagenarians, who underwent catheterizations, was higher than in the general nonagenarian population in Sweden during the study period (figure 19).

Table 26. Procedural characteristics of percutaneous coronary interventions in nonagenarians

	N=1,141 %
Lesion complexity B2 or C[a]	63.0
Multi-vessel PCI[b]	15.6
Another segment treated with PCI within 31 days	1.8
Target vessel was LAD[c]	43.6
Target vessel was left main stem	7.0
Stent use	87.5
Drug-eluting stents	32.2
Number of stents placed 2 or more	33.6
Procedural success	89.8
Complete revascularization	36.4
Acetylsalicylic acid	91.7
Glycoprotein IIb/IIIa inhibitors	10.5
Any P2Y12 receptor antagonist	92.1
Ticagrelor	25.1
Radial approach	52.9

[a]Classification is per (Ryan et al., 1988), see description in appendix 4; [b]PCI: percutaneous coronary interventions. Multi-vessel PCI: at least two segments were treated. [c]LAD: left anterior descending artery. Missing values are less than 2.5% and are not included in denominator.

Table 27. In-hospital complications in nonagenarians.

	PCI[b] N=1,141 %	CA[c] N=551 %
Any complication	8.1	4.1
Any bleeding event	3.7	2.6
Serious bleeding events	0.7	0.2
Any neurological complication	0.6	0.2
Cath-lab hemodynamic complications[a]	1.4	0.2
Treated arrhythmias in the cath-lab	1.1	0.2
Pseudo aneurysm	0.3	0.0
Renal failure	0.0	0.2
Mortality	7.7	2.4

[a]Cath-lab: catheterizations laboratory: [b]PCI: percutaneous coronary intervention. Of those 1,141, 33 PCIs were performed during another session during index admission; [c]CA: coronary angiography.

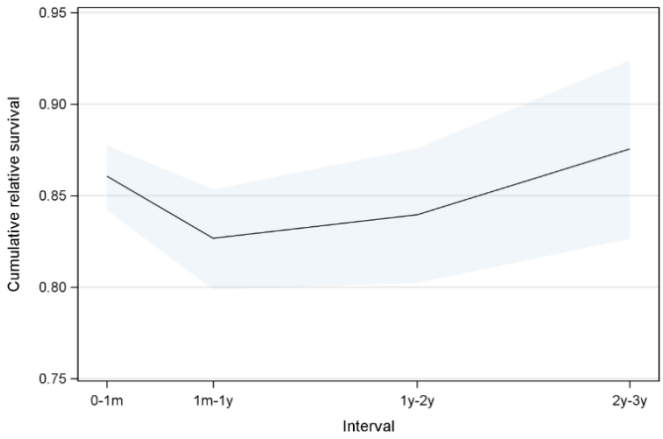

Figure 19. Relative survival of nonagenarians undergoing catheterizations compared to the nonagenarian population in Sweden.

STEMI: ST-elevation myocardial infarction; NSTE-ACS: Non-ST-elevation acute coronary syndromes; of other indications, 86.0% were investigations due to valvular disease

4.5.1 Temporal changes in practice of catheterizations

During 2006-2014, catheterizations in nonagenarians increased from 98/100,000 to 343/100,000 alive nonagenarians in Sweden (figure 20). The proportion of stable indications for catheterizations remained the same for the nine years, but the proportion of catheterizations due to other indications increased from 6.3% to 19.8% (figure 21).

Procedural methods changed during the nine years; the radial access became more common and was used in 62.9% of PCIs in 2014; Ticagrelor was first given to nonagenarians undergoing PCI in 2011 and was given to 62.9% in 2014. The use of GP IIb/IIIa inhibitors decreased during the nine years. Stents use remained around 84% during the nine years. DES use first declined from 21.3% in 2006 to 5.0% in 2007 but started to increase after 2009 and in 2014 DES was used in 68.5% of PCIs (figure 22).

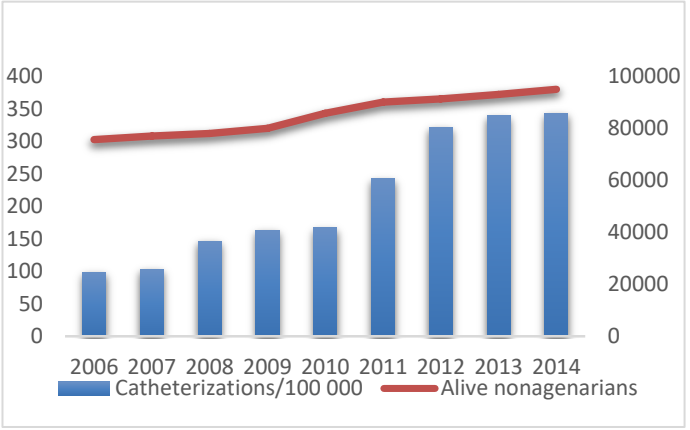

Figure 20. Number of cardiac catheterizations per year and 100,000 alive nonagenarians in Sweden.

Catheterizations in the figure are the index catheterizations, coronary angiography ± percutaneous coronary intervention.

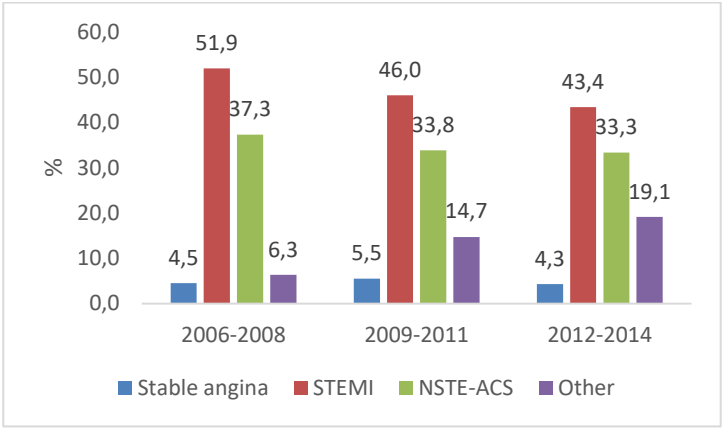

Figure 21. Indications for catheterizations in nonagenarians during 2006-2014.

STEMI: ST-elevation myocardial infarction; NSTE-ACS: Non-ST-elevation acute coronary syndromes; of other indications, 86.0% were investigations due to valvular disease.

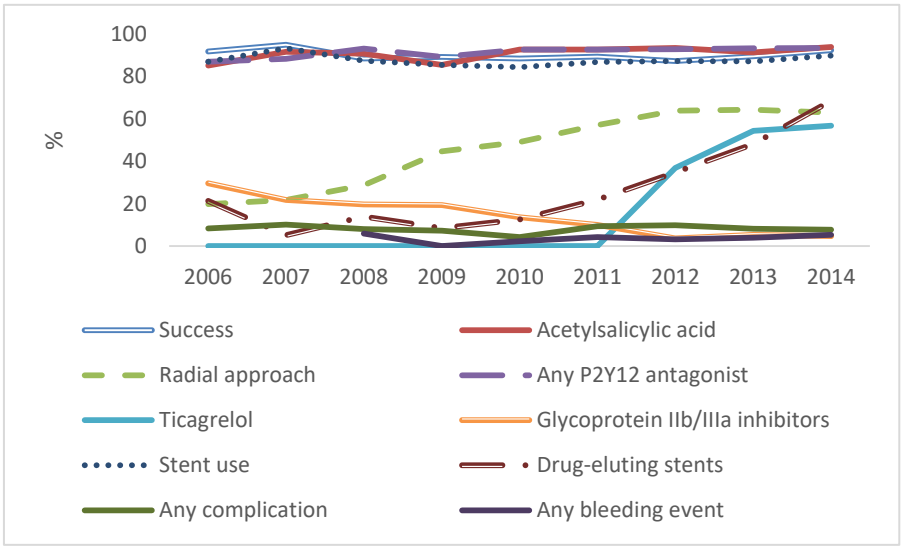

Figure 22. Temporal changes in procedural characteristics in nonagenarians undergoing percutaneous coronary interventions.

Bleeding events in hospital were redefined 2008 and are not available for 2006 and 2007.

4.5.2 Complications and stable CAD (Unpublished data)

The 37 nonagenarians with stable CAD who underwent CA experienced no in-hospital complications. After PCI, two patients (4.7%) experienced in-hospital complications, both of which were bleeding events (table 28).

Table 28. In-hospital complications in nonagenarians with stable CAD.

		STEMI[c] N=97 %	**NSTE-ACS[d] N=173** %	**Stable CAD N=37** %
CA[a]	Any complication	4.1	4.0	0.0
	Any bleeding event	1.2	3.2	0.0
	Serious bleeding	1.1	0.0	0.0
	Neurological complications	0.0	0.6	0.0
		STEMI N=673 %	**NSTE-ACS N=404** %	**Stable CAD N=42** %
PCI[b]	Any complication	8.5	8.1	4.7
	Any bleeding event	3.6	4.0	4.7
	Serious bleeding	0.8	0.7	0.0
	Neurological complications	0.5	0.2	0.0

[a]CA: coronary angiography; [b]PCI: percutaneous coronary interventions; [c]STEMI: ST-elevation myocardial infarction, Missing values are less than 2.5% for each variable and are not included in the denominator; [d]NSTE-ACS: Non-ST-elevation acute coronary syndromes.

5 Discussion

In this thesis, different minority groups with CAD were studied using the SWEDEHEART registry. The practice and outcomes of catheterizations in a small country were compared to the practice and outcomes in a larger country, women were compared to men, the benefits of invasive strategy in STEMI in multi-morbid older people with complex health needs were evaluated and finally, catheterizations in nonagenarians were studied.

The practice and success of performing CA and PCI in Iceland and Sweden were largely similar. However, some differences existed between the countries, namely in risk factors and indications. The use of radial access during catheterizations was more frequent in Sweden but procedural times, contrast use and subsequent complication rates were higher in Iceland. After the research period concluded procedural changes were implemented in Iceland such as contrast use and radial access. The rate of complications also improved. These positive changes are presumably in part related to the comparison with Sweden enabled through participation in SWEDEHEART.

Women were treated differently than men. Women with one-vessel disease were less likely than men to undergo PCI and women with three-vessel disease or left main stem stenosis were less likely to be referred to CABG but more likely to undergo PCI. Women had twice as many in-hospital bleeding events compared to men and a fourfold higher rate of serious bleeding events. Despite these differences, women did not have a higher 30-day mortality.

Individuals 70 years of age and older who experienced ACS had a high burden of comorbidities and 60% of them were readmitted the following year. When multi-morbid older patients with complex health needs had STEMI, an invasive strategy decreased the mortality risk the following year without increasing the risk of serious bleeding events. This is in accordance with randomized clinical trials in less sick patients with STEMI.

The number of nonagenarians undergoing catheterizations increased over nine years; they had a high level of multi-morbidity and almost all of them had coronary pathology. Most lesions were complex and multi-vessel disease was demonstrated in most patients. Also, after PCI, many still had significant stenosis. The major indications for PCI in nonagenarians were ACS (STEMI in 59% and NSTE-ACS in 36%), which along with the features mentioned above explains the in-hospital complication rate of 8% as well as in-hospital mortality rate of 8%.

5.1 Using the SWEDEHEART registry in Iceland (Paper I)

**"Do the best you can until you know better.
Then when you know better, do better."**

Maya Angelou

Randomized clinical trials are the gold standard when studying the efficacy of a treatment. They minimize selection bias by blind randomization of patients to different groups and are considered the most rigorous method to determine if there is a cause-effect relationship between an intervention and an outcome. However, such trials are both costly and time-consuming. Randomized clinical trials can lose external validation through rigorous patient selection. Thus, the results may not be generalizable to the entire patient population. Randomized clinical trials often don't have sufficient study periods or population sizes to identify rare diseases or rare but serious adverse effects of treatment (Frieden, 2017).

Even if efficacy is very important when evaluating an intervention, the effectiveness often needs to be measured in other types of studies than RCT. Effectiveness refers to how the intervention performs in real-world situations and broader groups than the efficacy was measured in (Singal et al., 2014). Quality registries are one type of data that can be used to look at various outcomes and to study complex situations not suitable for randomized clinical trials. They can provide information on rare diseases when it is difficult to find enough participants to perform a randomized clinical trial (Psoter & Rosenfeld, 2013). Quality registries can provide insights into everyday clinical practice and when they are online like SWEDEHEART, they can provide continuous feedback to participating clinics that can be used to improve treatments locally; as was demonstrated in Iceland after using SWEDEHEART for one year.

There are numerous pitfalls when performing studies using registry data. Maintaining a good quality registration requires efforts that can take time from clinical practice. Registries often have missing data and coding errors and it is often the case that the sicker the patients are, the more likely they are to have missing data. This gives rise to information bias. When different registry populations are compared, they are not randomized and it can cause selection bias. All those various biases need to be addressed when studies of populations in registries are planned. The researcher conducting registry-based studies needs to be familiar with the registries and as in any scientific

study, a clear question or a hypothesis should be provided at the beginning (Psoter & Rosenfeld, 2013).

The number of CA per capita was higher in Iceland 5,436/1,000,000 inhabitants compared to 4,022 in Sweden. The number of PCI per capita was the same in the two countries, around 2,100 per 1,000,000. The reasons for this difference in the use of diagnostic CA are not clear but they might reflect differences in access to non-invasive testing for CAD in the two countries or an easy access to CA in Iceland where 2/3 of the population live in the Reykjavik area where the catheterization laboratory is located.

The rate for CA due to stable CAD was double in Iceland compared to Sweden and the rate for PCI 50% higher. These differences likely reflect both easy access to CA in Iceland and differences in local traditions in practice of diagnosing stable CAD. The ESC guidelines from 2006 recommended non-invasive stress testing before CA (K. Fox et al., 2006). Even if the COURAGE trial and the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) study did not show decrease in death or new cardiovascular events after revascularization in patients with stable CAD (Boden et al., 2007; Frye et al., 2009), both trials randomized patients after performing CA and excluded those with left main stem disease. In the COURAGE trial, over 40% had no or little angina and both trials had relatively low mortality rates in both groups and therefore probably represented low risk groups. In 2014, The American College of Cardiology and American Heart Association has pointed out the lack of trials randomizing patients with stable CAD to diagnostic CA or not (Stephan et al., 2014). This is still an ongoing debate (Stone et al., 2016).

There were more CA and PCI performed per 1,000,000 inhabitants with STEMI as the indication in Sweden. The incidence of STEMI in Iceland is somewhat lower than in Sweden, 560/1,000,000 and 660/1,000,000 (Snorrason, 2015; Steg et al., 2012) and probably explains this difference. Only 1%, in both countries, received thrombolysis before PCI, indicating that most patients with STEMI receive primary PCI. In 2013, 75% of patients in Sweden with STEMI received primary PCI and 5% received thrombolysis (*Swedeheart Annual Report 2013*, 2014). The percentages in Iceland were similar (Þórarinn Guðnason, written communication). Both countries are sparsely populated with challenging geography making it impressive that most STEMI patients receive primary PCI.

There were more complications after PCI in Iceland than Sweden in 2007. The low use of radial access in Iceland during 2007 might be the cause of this. The use of radial access has consistently been shown to reduce access

site complications and in high-risk patients to reduce mortality. It is easier to compress the radial artery than the femoral artery, there is an absence of major veins and nerves nearby; and patients can be ambulated sooner and discharged earlier than after a femoral approach (Del Furia et al., 2016; Jolly et al., 2011; Romagnoli et al., 2012). The fluoroscopy time was longer and contrast volume use was higher in Iceland. This might indicate older equipment in the catheterization laboratory and that, in turn, could have caused more complications in Iceland.

Iceland was the first country besides Sweden to start registering all its CAs and PCIs in SCAAR in 2007 (Tomas Jernberg 2017, written communication). A few years later, other parts of SWEDEHEART came into use in Iceland. Centers in other countries can register in SWEDEHEART (Jernberg et al., 2010), but there are yet no other countries besides Iceland and Sweden that register all procedures. The comparison between Sweden and Iceland is to the best of my knowledge the first nationwide comparison of all CA and PCI in two countries during a whole year using the same quality registry. It can be used as an example model for other European countries to offer registration and quality control in similar manner for their interventional cardiology. There is now a possibility to use SWEDEHEART to perform randomization, thereby enabling performance of cheap randomized studies. An example is the TASTE study that looked at routine thrombus aspiration during PCI in patients with STEMI (Frobert et al., 2013). Two other randomized studies from SWEDEHEART were recently published in the New England Journal of Medicine (Erlinge et al., 2017; Hofmann et al., 2017). Ongoing is the international multi-center FULL-REVASC trial where patients are recruited in nine countries, including Australia (Böhm, 2016).

5.2 Women with ACS (Paper II)

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

Audre Lorde

In 27% of women with ACS in Paper II, no significant obstruction of the epicardial coronary arteries was found. This was almost three times higher than in the men with ACS. AMI without obstruction in the coronary arteries is not a benign condition. One analysis found those patients to have a higher adjusted risk of one-year mortality than NSTEMI patients with obstruction in coronary arteries (Planer et al., 2014). There are various reasons why AMI without obstruction in coronary arteries is more common in women. Sometimes, the CA underestimates the atheromatous burden of a lesion. During atherosclerosis, the artery can partly remodel expansively and attenuate the obstruction. The underlying plaque is still vulnerable to rupture or erosions with a following ACS (Falk et al., 2013). Intravascular ultrasound can help in better identifying the extent of coronary atherosclerosis in this setting. One study found plaque erosions in 38% of cases with AMI without obstruction (Reynolds et al., 2011), plaque erosions being more common in women. Coronary artery spasm is one mechanism that can cause ACS without an underlying obstruction and is more common in women than men. It usually causes recurrent episodes of chest pain with associated transient ST-segment changes, but on rare occasions, it can cause AMI. The pathogenesis is multifactorial and includes vascular smooth muscle hyperactivity, endothelial dysfunction and an imbalance of the autonomic nervous system. Cigarette smoking is a major risk factor for coronary artery spasm, as is other nicotine use (Lanza et al., 2007). Dysfunction of the microvascular circulation is another mechanism that can cause angina or ACS in patients with only minimal atherosclerosis (Lanza et al., 2014). Takotsubo cardiomyopathy is a condition characterized as a transient left ventricle dysfunction with rapid recovery generally induced by a stressful emotional or physical event. It is most common in postmenopausal women. Recent studies suggest microvascular dysfunction is a plausible pathophysiological mechanism (Galiuto et al., 2010). Microvascular disease, coronary artery spasm, as well as spontaneous dissections of a coronary artery, are all conditions that are more common in women with ACS than in men. The best treatment for these conditions is not well established and the American Heart Association recently gave a scientific statement encouraging

more studies about these conditions to improve the treatment of women with ACS (Mehta et al., 2016).

Our results showed slightly less referral to PCI among women than men are in concordance with other studies (Dey et al., 2009; Hansen et al., 2015; Nguyen et al., 2008; Redfors et al., 2015). The finding of less referral of women with one-vessel disease was in Paper II was similar to findings in a Danish registry study (Hansen et al., 2015). There are some possible explanations as to why women with one-vessel disease were less likely to undergo PCI. The increased risk of complication in women after PCI might affect the clinical decisions, as well as the fact that not all studies of NSTE-ACS patients show benefits with early invasive approach in women. The above-mentioned conditions that can cause ACS without obstruction in coronary arteries could have coexisted with an obstruction in one coronary artery. An estimated 8% of ACS in women are caused by Takotsubo cardiomyopathy vs. less than 1% in men (Komamura et al., 2014). Up to 10% of patients with Takotsubo cardiomyopathy have a significant stenosis in at least one coronary artery that was not considered to cause the ACS (Lyon et al., 2016).

Many studies show less referral of women to CABG compared to men. (Alfredsson et al., 2007; Hansen et al., 2015; Nguyen et al., 2008) and some show increased likelihood of women with three-vessel disease being referred to PCI, similar to the results in Paper II (Heer et al., 2015). Women have smaller coronary arteries, which makes the CABG procedure technically more challenging (Swaminathan et al., 2016) and women undergoing CABG are older and have more comorbidities compared to men. A systematic review of 23 CABG studies that reported sex-stratified data, as well as a large registry study with 40,000 CABG patients, showed that, after adjusting for baseline differences, women have an increased risk of in-hospital complications and mortality (Bukkapatnam et al., 2010; Kim et al., 2007). Long-term survival in women is comparable to the survival of men, but women are more likely to be readmitted with congestive heart failure and AMI after CABG than men (den Ruijter et al., 2015; Guru et al., 2006; Nicolini et al., 2016). The worse short-term survival of women after CABG as well as higher long-term readmission rates might cause greater hesitation in referring women with multi-vessel disease and/or left main stem disease to CABG.

The differences between men and women in revascularization in this study did not lead to increased mortality, neither in the whole group nor in those who had one-vessel disease, two-vessel disease or three-vessel

and/or left main stem disease. This was irrespective of revascularization status and extended to both women with STEMI as well as women with NSTE-ACS. Other studies have not found higher 30-day or 60-day mortality in women with either STEMI or NSTE-ACS (Berger et al., 2009; Hansen et al., 2015; Redfors et al., 2015). We did not examine long-term mortality, but a recent meta-analysis of 358,827 patients with NSTE-ACS found no difference in long-term mortality in women compared to men after adjustment for baseline cardiovascular risk factors, clinical differences and angiography data (Y. Wang et al., 2017).

Women under 60 years of age with STEMI have been shown to have worse outcome than men in the same age group (Lawesson et al., 2010; Otten et al., 2013; Redfors et al., 2015). This was not the case in Paper II, but there were few women under 60 with STEMI in the research group, so the study might be underpowered to observe increased mortality in that group. Some of the studies showing higher mortality also showed gender disparities in referral to CA (Redfors et al., 2015). All the patients in our study underwent CA, it is therefore plausible that some of the high mortality in young women with STEMI might be caused by disparities in referral to CA. The VIRGO study enrolled patients under 55 years of age with STEMI and NSTEMI. Women had more delays in presentation, lower peak biomarker levels and fewer diagnostic findings on ECG. This demonstrates the more complex diagnosis process in women. Those young women had more stress and a poorer mental health status than men and stress might have negative effects on prognosis after AMI. The young women in the VIRGO study more commonly had three or more cardiovascular risk factors than the young men; the CAD that presents in young women might, therefore, be an especially aggressive form (Bucholz et al., 2016).

Women had a two-fold increased rate of bleeding events after PCI and four-fold risk of serious bleeding events. The increased rate of bleeding events in women compared to men after PCI has been confirmed in many studies (Fuchs et al., 2009; Ndrepepa et al., 2015). This is concerning, as bleeding events have been associated with increased mortality after ACS and PCI (Eikelboom et al., 2006; Mehran et al., 2010; Ndrepepa et al., 2008). Bleeding events and mortality might simply have shared risk factors instead of cause-and-effect relationship, but there are many possible causal mechanisms. If a bleeding event occurs, the antithrombotic medications are often discontinued, which may cause in-stent thrombosis; low blood pressure due to bleeding events could lead to discontinuation of beta-blockers. The location of the bleeding can be hazardous, for example, intracranial or

retroperitoneal bleedings. Anemia can cause systemic amplification of the coagulation cascade as well as secondary erythropoietin production. Erythropoietin can cause a systemic prothrombotic state long after the acute phase of a bleeding event (Doyle et al., 2009). The combination of amplified prothrombotic state as well as discontinuing antithrombotic medications could cause ischemic events such as stroke or a new AMI. The transfusion of red blood cells carries its own risks. There is a risk of allergic reaction to blood parts. There can be problems related to the storage of blood and contamination, as well as immunological, inflammatory and thrombotic reactions to the residual leukocytes and platelets in the stored blood (Y. Wang et al., 2016). The risk for patients with CAD associated with bleeding events empathizes the importance of lowering women's excess risk for bleeding events after CA and PCI.

The reason women have increased bleeding risk is multifactorial. Their higher age and greater comorbidity burden put them at risk, but even after correcting for those factors, their increased risk prevails (Ahmed et al., 2009). Their smaller body size and lower muscle mass compared to men results in lower serum creatinine; that, in turn, causes their renal function to be overestimated. This increases the risk of overdosing as demonstrated in a study where women were four times as likely to receive excessive doses of Glycoprotein IIa/IIIb inhibitors (K. P. Alexander et al., 2006). There are sex-related differences in pharmacokinetics and pharmacodynamics of drugs. Women have greater proportion of body fat and lower water content in the body, causing difference in distribution volumes and plasma levels compared to men (Rosano et al., 2015). As women are not included in adequate numbers in randomized trials, their dosing is often based on tests performed largely on men and this decreases the knowledge of efficacy and safety of drugs in women. In a report about drugs pulled from the market in the United States, eight out of 10 drugs had more side effects in women (*Drug Safety: Most Drugs Withdrawn in Recent Years Had Greater Health Risks for Women*, 2001).

The evidence for sex-based differences in platelet reactivity as well as in the coagulation-fibrinolytic pathways is somewhat contradictory. Many studies show higher in vivo platelet reactivity to agonists among women compared with men, implying that the female sex has more at risk for ischemic events than bleeding events (Becker et al., 2006; Zuern et al., 2009). Female platelets bind more fibrinogen and have higher plasma thromboxane levels (Khetawat et al., 2000). This should also make women more prone to platelet aggregation than bleeding events. Studies have not

shown increased platelet suppression in response to antiplatelet therapy in women compared to men (Gremmel et al., 2014; Silvain et al., 2012). Again, this should lead to a lower, rather than increased bleeding risk. Thus, we still do not understand these mechanisms and their complexity with regards to sex differences.

There are anatomical factors regarding access site that make coronary catheterizations in women more difficult than in men and increase the risk of complications as the femoral artery is smaller in diameter in women than in men. It is generally considered safest to perform the puncture between the lower border of the inferior epigastric artery and above the common femoral artery bifurcation. Women have a smaller and shorter common femoral artery bifurcation compared with men, making this more challenging (Schnyder et al., 2001). Women also have smaller radial arteries, which are more tortuous and prone to radial artery spasm (Pandie et al., 2015). These factors might explain part of the increased complication rate in women.

There are several bleeding avoidance strategies that can be applied when performing PCI. The use of radial access has been shown to decrease access site bleeding events in both men and women (Joyal et al., 2012; Kwok et al., 2015; Pandie et al., 2015). It is therefore positive that its use has increased in both Iceland and Sweden. The use of smaller catheters (5/F) when performing PCI through radial access decreases complications in women (Pandie et al., 2015). The use of alternative anticoagulants to heparin decreases the risk of bleeding events in both men and women. Fondaparinux has been shown to be associated with lower rate of bleeding events than heparin (Bundhun et al., 2017); as has bivalirudin (Daugherty et al., 2013). Vascular closure devices applied when femoral access is used to decrease risk. The use of any bleeding avoidance strategy or combination of them, is associated with significant reduction in bleeding risk in both men and women. The absolute benefits, however, are substantially higher in women making them especially important for them (Daugherty et al., 2013; Pandie et al., 2015).

5.3 Older people with ACS (Papers III and IV)

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

William Osler

The care of older people with ACS is complex. Among other things, it requires thinking about geriatric syndromes like multi-morbidity and frailty as well as weighing the risks and benefits of treatment in their presence. There are several tools to assist clinicians in improving the care of older people. It is likely that the most important tool is good communication skills where the patient should decide what risks he or she is willing to take and what burden of treatment or disease is acceptable to them. Communication skills are a learned expertise; and just as most clinicians strive to acquire the new technical skills and gather new information, they should strive to improve this skill as well.

The benefit of any treatment can be measured in its effect on prognosis and whether or not it decreases symptoms or increases well-being. The risk of treatments includes age-related risk, competing risk of concomitant diseases and treatment-related risk. The age-related risk is the lowering of organ reserve capacity that increases with higher age. Frailty is the hallmark of this process. Multiple diseases and conditions can compete and change the balance of the risks and benefits of a treatment for one of the diseases. Many comorbid diseases, like anemia and chronic renal disease, increase the risk for adverse events with the antithrombotic therapies used in treating ACS (Mehran et al., 2010; Melloni et al., 2016). Life expectancy must be taken into consideration, as the absolute impact of treatments and the time it takes for them to have effects varies. The patient must live long enough to gain positively from the treatment for any risk arising from it to be acceptable.

The baseline risk for mortality and morbidity a disease carries varies. STEMI carries higher baseline risk than NSTE-ACS, an example of different disease-related risk. The Italian Elderly ACS study found an invasive strategy to reduce the combined event of mortality and AMI only in the patients with positive biomarkers, but not those without (Savonitto et al., 2012). Patients with positive biomarkers are from the beginning at more risk of thrombotic events than those without. This might explain mortality benefits in the former

group with invasive treatment, their disease-related risk for new events was higher from the beginning.

Both randomized trials in older people with NSTE-ACS showed symptom relief with invasive treatment, demonstrated by the increased need of revascularization in conservatively treated patients (Savonitto et al., 2012; Tegn et al., 2016). A follow-up of the After Eighty trial did not find improvements in the health-related quality of life in patients treated with invasive strategy in other domains than bodily pain. One-third of the patients in each treatment arm dropped out and this high drop-out might have affected the outcomes (Tegn et al., 2017). A systematic review of over 700 octogenarians in 11 cohort studies showed improvements in quality of life (Johnman et al., 2013). Other non-randomized studies have shown improved quality of life in those who are over 70 years old after PCI due to both stable and acute indications (Chait et al., 2011; Shan et al., 2014). An upcoming randomized clinical trial in octogenarians with NSTE-ACS will among other endpoints examine the effects of invasive treatment on quality of life and angina symptoms (Libungan, Hirlekar, et al., 2014).

The risk of thrombotic events is double in patients with chronic stable CAD and coexisting diabetes and chronic renal disease compared to those without those comorbidities (Glynn et al., 2008). Some comorbidities share a common pathophysiological pathway with ACS, like stroke and PVD. Some, like diabetes, are risk factors for ACS (Piette & Kerr, 2006). Comorbidities in patients with ACS can increase the risk for both future thrombotic events and the risk for bleeding events at the same time, similar to stacking rocks on both sides of a scale weighing the risks and benefits of treatment in older people (figure 23). Chronic renal disease is an example of this, where the risk for thrombotic events as well as bleeding events increases in almost a continuous inverse function of the eGFR (Melloni et al., 2016).

Figure 23: Weighing risks and benefits of treatment.

This photo is marked with a free copyright. Adjustments were done by Mariska Groen.

In this thesis, the risk of reaching the primary event in multi-morbid older people with complex health needs and STEMI was lower in the invasive group than in the non-invasive group. The risk of one-year mortality was also lower. This is in accordance to randomized controlled clinical trials in younger patients with less comorbidity burden. The positive effects of primary PCI on prognosis in STEMI for patients up to 75 or 80 years old are well documented in randomized trials (Boersma, 2006; S. P. de Boer et al., 2010), but to the best of my knowledge there are no randomized trials in patients with multi-morbidity and complex health needs and STEMI. A cohort study of 1,000 octogenarians with STEMI undergoing primary PCI during 2005-2011 showed an increasing multi-morbidity burden in those who underwent PCI, but at the same time, the long-term mortality did not increase (Bromage et al., 2016). Another cohort study in patients over 70 years of age in Switzerland with AMI during the period of 2001-2012 showed a higher age and higher comorbidity burden during the last four years compared to the first four years. At the same time, the use of primary PCI in STEMI increased in all age groups and the in-hospital outcomes improved (Schoenenberger et al., 2016). These results suggest that effects of primary PCI on prognosis in patients with STEMI are not limited by multi-morbidity. Revascularization decreased the risk for new AMI or death in patients with NSTE-ACS and at

least two comorbidities but not in those with one or none (Palau et al., 2012). Patients with frailty and NSTE-ACS had lower mortality if they underwent PCI, but this was not the case in those who were not frail in a recent prospective cohort study (Nunez et al., 2017). This might be the paradox of risk and gains; more frailty and more multi-morbidity can mean both larger gains with revascularization and increased risk of bleeding events. The coexistence of more thrombotic risk in those with multi-morbidity makes the absolute impact of invasive treatment higher and might offset the increased complication risk.

The effects of invasive treatment were highest in the first months after STEMI in multi-morbid patients with complex health needs in this thesis, demonstrated by the lower HR during the first months than during the last months. During the last three months, the difference between the groups was not significant. The non-invasive group had 44.9% one-year mortality after discharge, meaning that 314 people remained alive at the end of the year. This caused widening of the confidence intervals during the year as the number remaining alive decreased over time.

The effects of invasive treatment differed, not only between age groups but also according to renal function. Using the Cox regression analysis, this difference was shown with positive interactions between the abovementioned variable and treatment. The impacts on the primary event were seen in octogenarians and people between 70 and 80 years old. The invasive treatment seems to have a trend to increase risk of reaching primary event in nonagenarians. Nonagenarians receiving invasive strategy numbered only 37, making all generalization for that age group difficult.

Patients with eGFR less than 30ml/min/m^3 did not have a significant reduction in the risk for primary event or death with invasive treatment and there was a trend for increased risk of bleeding events. The likelihood of post procedural renal failure as well as increased bleeding risk increases with worse renal function (Melloni et al., 2016; Tsai et al., 2014), so, the risk associated with invasive treatment might start to outweigh the benefits with the worst baseline renal function.

After NSTE-ACS, the older patients with complex health needs in the invasive group were younger than the ones in the non-invasive group and had a lower comorbidity burden. Among the variables that could not be matched with propensity scores were age and eGFR. Both are important prognostic factors and therefore additional calculations were not performed as the effects of inclusion bias would limit the interpretation. The published

randomized clinical trials in older patients with NSTE-ACS included patients with less comorbidity burden than the present study. The Italian ACS study demonstrated that in patients 75 years old and older with NSTE-ACS, an early invasive therapy decreased mortality and new AMI only in those with positive biomarkers (Savonitto et al., 2012). The After Eighty study found an invasive strategy to decrease the risk for new AMI and revascularization but not mortality (Tegn et al., 2016). During the inclusion process in the After Eighty study, over half of older people were excluded due to clinical risk factors or multi-morbidity. To study whether an invasive strategy should be used in NSTE-ACS in multi-morbid older people with complex health needs, a randomized clinical trial is needed. This could be done using the randomization feature of SWEDEHEART.

The success of PCI in nonagenarians was 90%, same as the success in other cohort studies of nonagenarians (Hendler et al., 2011; LeBude et al., 2012; Teplitsky et al., 2007). With 94% of nonagenarians having acute indications for their PCI and 63% of lesions intervened upon being complex, the in-hospital complication rate was 8% and in-hospital mortality was 8%. Other cohort studies have shown complication rate from 8-17% (LeBude et al., 2012; Ma et al., 2008; Ohlow et al., 2012; Teplitsky et al., 2007); and in-hospital mortality rate of 7%-27% (Koutouzis et al., 2010; Mandawat et al., 2013; Petroni et al., 2016; Skolnick et al., 2007). The comorbidity burden, the proportion of nonagenarians in cardiogenic shock or with STEMI varies between these studies and largely explains the discrepancy. Importantly our study is an all-comer study, including all nonagenarians undergoing CA with or without PCI. Taking this into consideration the 8% complication rate and and 8% in-hostpial mortality rate are important figures to have in mind when considering a very old patient. In fact they are surprisingly low compared to the complication rates and mortality in much younger patients and considering these patients high age and clinical situation.

One nonagenarian was diagnosed with renal failure after a catheterization in this study. Other studies of nonagenarians with ACS undergoing PCI found renal failure to be over 20% in those with baseline eGFR less than 60ml/min and up to 40% in those with less than 30ml/min (Gayed et al., 2017; Toso et al., 2015). It seems likely that renal failure in SWEDEHEART is underreported; and as renal failure is an important prognostic indicator in patients with ACS (Reinecke et al., 2003; Tsai et al., 2014) this warrants improved registration of renal function before and after PCI in SWEDEHEART.

The mortality of nonagenarians undergoing catheterizations was higher than the mortality of the general nonagenarian population. Possible causes are the burden of CAD in the study population, the high percentage of patients with ACS and the level of renal disease. In one study, the mean eGFR of community-dwelling older people over 85 was 55 ml/min/m^2 and 41% had eGFR over 60ml/min/m^2 (Lopes et al., 2013). In this study, mean eGFR was 40 and 7% had eGFR over 60. The mortality in nonagenarians who underwent revascularization was higher than those who did not. From the data in this study, it is not possible to conclude whether revascularization has any effect on the mortality. It is of note that in the After Eighty study of patients with NSTE-ACS, invasive strategy did not lower mortality at one year (Tegn et al., 2016).

The changes in the practice of PCI in nonagenarians followed the changes in practice in younger patients during the study period with a switch to radial access from femoral access, the use of DES instead of bare-metal stents (BMS) and changes in the choice of antithrombotic medical therapy. For some procedural techniques, there is randomized data in 80-year-olds and older. There are at least two randomized trials comparing DES and bare-metal BMS in 75- to 80-year-olds and older showing increased efficacy of DES over BMS (de Belder et al., 2014; Kurz et al., 2015) and one of them showed decreased mortality (Kurz et al., 2015). There is no randomized data for nonagenarians, but one cohort study of over 40,000 patients 85 years and older undergoing PCI found DES use to be associated with lower mortality risk than BMS use and that the bleeding risk was similar between DES and BMS (T. Y. Wang et al., 2012). People over 75 years with ACS have increased bleeding risk with GP IIb/IIIa inhibitors and are often overdosed with them (K. P. Alexander et al., 2007). The use of this treatment in nonagenarians decreased during the nine-year study period. Ticagrelor was compared to clopidogrel in the PLATO trial and it proved successful in reducing ischemic events and mortality in a sub analysis of 75-year-olds and older (Husted et al., 2012). One of the conclusions was that ticagrelor was more effective than clopidogrel in reducing primary end points and mortality over the full age range up to 95 years old. The absolute number of 85-90-year-olds and 90-95-year-olds in PLATO was not published (Husted et al., 2012). A small randomized study of 200 ACS patients with a mean age of 79 years compared ticagrelor with clopidogrel. They found significantly lower risk of cardiovascular death in ticagrelor group as well as lower risk of AMI. At the same time ticagrelor did not increase the risk of bleeding events (H. Wang & Wang, 2016). The radial approach has been shown to decrease major

access site complications in patients who are 75 years old and older (Cantor et al., 2015). At the same time there were no significant differences in the primary outcome of death, AMI or stroke. The cross over from radial to femoral approach is 10-12% (Alnasser et al., 2017; Cantor et al., 2015). One trial examined the safety of the radial approach in an observational trial of 228 octogenarians with either stable CAD or ACS. The decision whether to go radial or femoral was left to the operator with almost 50% using the radial approach. The trans-radial approach was associated with shorter procedure times, less contrast volume being used, fewer vascular access complications and shorter time to ambulation (Jaffe et al., 2007). Even if there is no randomized data for the radial approach in those who are over 85 years old and over 90 years old, the decrease in complications associated with this approach supports its use whenever it is possible.

The proportion of nonagenarians undergoing PCI due to stable CAD remained at 5% during the nine-year study period. The in-hospital complication rate after PCI due to stable CAD was 4%, half of the rate of complications in nonagenarians with acute indications. Even if invasive treatment has not been proven to increase survival in all patients with stable CAD (Boden et al., 2007) the main goal of any therapy in very aged individuals is to maximize quality of life and maintain independence. Studies have shown improvement of quality of life after PCI with both acute and stable indications, especially in those with severe angina (Chait et al., 2011) and some have shown improved functional capacity (Figueiredo Neto et al., 2015). The low complication rate in nonagenarians after PCI due to stable CAD and the effects it can have on quality of life indicates that PCI should be considered in vital nonagenarians with stable CAD who do not respond to medical treatment. The individual bleeding risk should be assessed first and DAPT kept as short as possible.

A recently published trial by Costa et al. used eight multi-center randomized trials to develop a new tool which enables identification of patients who have a high risk of out-of-hospital bleeding in the year after PCI. It is called the PRECISE-DAPT score; it examined short therapy (3-6 months) vs. long-term therapy (12-24 months) DAPT. The benefits of ischemic events with longer treatment with DAPT was found only in the group with a low-risk bleeding score, not in the one with a high-risk score. The risk of bleeding events was elevated in individuals with a high-risk score, not in those with low scores (Costa et al., 2017). The PRECISE-DAPT score gives points for the following patient characteristics: age, creatinine clearance, hemoglobin, white blood cell count and previous spontaneous bleeding. It is an example of how

a risk score can help identify the patients who have the most benefits of longer DAPT and to avoid using longer DAPT in those who do not.

The annual risk of major bleeding events was over 4% in those who were over 85 years old, compared to 1.2% in those who were 70 to 74 years old in a study of bleeding events in older people receiving ASA as a secondary prevention for ten years. Importantly, over half of the bleeding events in those who were 85 years old and older were life-threatening or fatal. Most of the bleeding events were gastrointestinal. The concomitant prescription of proton pump inhibitors reduced the major bleeding events 70-90% and the number needed to treat to prevent one bleeding event was 338 for patients younger than 65 years but 25 for patients aged 85 years or older (Li et al., 2017). There have been concerns with proton pump inhibitors diminishing the effects of clopidogrel. Clinical cohort studies have not confirmed increased thrombotic event rates in those who do receive them alongside DAPT (Gargiulo et al., 2016; Zhu et al., 2017). When patients of this high age receive antithrombotic therapy, the prescription of proton pump inhibitors should be strongly considered. Other medications should also be reviewed and all medications that contribute to the risk of bleeding events should be stopped if possible.

Older people with frailty and multi-morbidity have been demonstrated to carry a high CAD burden, thus it can be argued that as a result this patient groups might have much to gain from interventions. There is probably a tipping point though, where the risk from multi-morbidity and frailty starts to cause too high a complication rate which outweighs the benefits. One way to personalize the care of older patients is a more specific screening for frailty and other geriatric syndromes. There is an upcoming study, the LONGEVI-SCA registry (Impacto de la Fragilidad y Otros Síndromes Geriatricos en el Manejo y Pronóstico Vital del Anciano con Síndrome Coronario Agudo sin Elevación de Segmento ST), which will include 500 consecutive octogenarian patients with NSTE-ACS. The study will include an assessment of functional status, frailty, comorbidity burden and quality of life. The primary outcome is a 6-month mortality, but secondary outcomes will be changes in functional status and quality of life (Alegre et al., 2016). Hopefully, this study will answer important questions about making an individual judgment of risks and gains and further assist in tailoring the treatment.

The steering committee of SWEDEHEART has decided to test screening for frailty in patients admitted to coronary care in seven centers this winter ("Meeting of The Steering Group of Swedeheart 21 of october 2016. ," 2016).

The screening tool that will be used is called Canadian Clinical Frailty Scale (CFS) and was developed by Rockwood et al. CFS measures the degree of frailty from very healthy through pre-frail, frail and to those who are at the end of their life (Rockwood et al., 2005).

When frailty is present in older people admitted due to general internal medical problems, their outcomes can be improved with care in geriatric units using Comprehensive Geriatric Assessment (CGA) (Ekerstad et al., 2017). CGA is a multidisciplinary approach in which the medical, psychosocial and functional capabilities of older adults are evaluated. Then, a coordinated plan is built to maximize overall health. Within hospital admission, CGA is used to minimize the hazardous effects of hospital admissions for frail older people and to decrease the progression of frailty to disability (Pilotto et al., 2016). CGA has mainly been shown to be effective in the settings of geriatric units and home-based programs. The evidence for using it in inpatient geriatric consultation services is conflicting.

Frail older people with ACS should continue to be treated in coronary care units where they can receive the specialized care they need. With the integration of frailty screening planned in RIKS-HIA this winter, the possibility opens to incorporate some aspects of CGA into the care in coronary care units.

Even if more frailty and comorbidity burden in older people with ACS does often come alongside more gains with guideline indication therapies due to increased disease burden, their additional risk for adverse events requires more rigorous follow up than in younger less frail patients. The SPRINT study found the effects of intensive blood pressure lowering therapy to decrease mortality in high-risk patients. This effect extended to those older patients who were frail. The follow up in that study was rigorous, with each patient having their blood pressure measured on three occasions after any change in treatment (Williamson et al., 2016). Those patients were all able to ambulate and come to the doctor’s office. The patients were therefore not the most severely frail in their age group. This study demonstrates the importance of intensive follow-up when treating those at high risk. The same should apply to older patients with ACS.

5.4 Limitations and confounders

SWEDEHEART, like all registries, has missing data and there is a risk for errors in registration and coding. Even if almost every person that undergoes CA or PCI in Sweden and Iceland is included in SCAAR, the coverage of

RIKS-HIA is 80%. For people over 80, the coverage drops to 60%. Older people who are not registered in RIKS-HIA are more likely not to be in a coronary care unit and they have worse prognosis than those who are included in the registry. This is a limitation when using SWEDEHEART to study the treatment of older people. The National Patient Registry has good sensitivity when it comes to diseases that generally lead to an admission, such as AMI and stroke. It does not, however, have good sensitivity for diagnoses that do not cause admissions in most cases, such as COPD or dementia.

In Paper I, the small number of the Icelandic population gives rise to fluctuations in numbers between years. This could have caused the differences in complication rate that would not have been present with larger samples, a type I error. The definitions of bleeding events after CA and PCI changed during 2008, so during the study year, they were more inaccurate, giving rise to possible type I error again.

When studying gender disparity in referral to PCI in Paper II, the knowledge of other reasons for ACS than obstructive CAD might have decreased the absolute difference between the genders, for example, spontaneous coronary artery dissections and Takotsubo cardiomyopathy. Another limitation is not knowing if the lesions found on CA are proximal or distal. Small distal lesions may not be amiable to PCI and stenting and could have caused type I error. We could not differentiate between NSTEMI and UAP and the former group carries more risk from the beginning. Separating the two groups of NSTE-ACS might have given different numbers for 30-day mortality. Data was missing for some variables but the numbers of missing data were however small and we performed imputations to correct for this.

The non-randomized design was the main limitation of the study in multi-morbid older people with STEMI. The sickest patients were probably not selected for invasive strategy. Even if we excluded the patients who died within the admission and extensively adjusted for confounding variables with a propensity score method, some selection bias is likely to remain. The definition of multi-morbid older people with complex health needs does not include all older people with frailty and multi-morbidity. An example of older patients who might be missing are the ones who are in nursing homes.

Due to the diversity within the group with NSTE-ACS, the invasive and non-invasive groups could not be matched on important prognostic variables for mortality such as eGFR and age. This meant that a large part of the

difference in outcomes could be affected by selection bias and we could not continue the analysis using the chosen method.

Many of the nonagenarians in Paper IV had multi-morbidity. It is known though that in this high-age group there is a selection bias where healthier individuals are more likely to be chosen for catheterizations. This limits the generalization of those results to the whole nonagenarian population. We did not know the ratio of conservatively treated versus those who underwent CA for the whole nonagenarian population during those nine years. The rate of missing values in the nonagenarian population was higher than it is in SCAAR in general. There are outcome variables that are very common in older people during hospitalizations that are not registered in SCAAR and other cardiac catheterization registries. Those include delirium and hospital infections.

6 Conclusions and future tasks

Groups that are underrepresented in randomized clinical trials need to be studied using various data forms. Some of these groups were looked at in this thesis using data from SWEDEHEART, even if those with NSTE-ACS and complex health needs could not be studied. Implementation of this registry might have contributed to improvements in the local practice of cardiac catheterizations in Iceland.

It was shown through this doctoral research that women were less frequently chosen for invasive ACS treatment compared to men, while at the same time it did not show increased short-term mortality in women. The focus of equal treatment of women and men should perhaps not be treating women the same as men. Women have numerous reasons for their ACS than epicardial CAD. The focus should be to better study and address the specific problems of women and to make sure enough women are included in clinical trials so that their specific risks and benefits of procedures and therapies are documented. The double rate of bleeding events after PCI in women demonstrated in this thesis is worrying and measures should be taken to decrease this risk when possible.

The results of this thesis showed the complicated nature of treating CAD in older people. The majority of older people with ACS had multi-morbidity and they had a high readmission rates the following year. Multi-morbid older people with complex health needs and STEMI had a high risk of new ischemic events and death. Invasive strategy lowered the risk for new thrombotic events and mortality; in concordance with the results of randomized clinical trials in younger and healthier patients.

This thesis provides important information about the success and complication rate in nonagenarians undergoing CA and PCI, an age group that is largely ignored. Most nonagenarians undergoing CA had multi-vessel disease and a high level of lesion complexity, which along with multi-morbidity and mainly acute indications, might partly explain both in-hospital mortality and complication rate.

Older people with ACS need multifactorial care to address their other medical problems and decrease readmission due to any cause. They also need strategies to decrease the complications of invasive treatments and antiplatelet therapies. The frailty screening in SWEDEHEART, that will start

this winter, gives rise to the opportunity to find ACS patients who are pre-frail or frail. Interventions to prevent the progression to more frailty, disability and dependence can then be tested. An example is to use a consulting platform where a geriatrician could work in liaisons with personnel in the coronary care units, in a constructed platform several times a week. They can assist in further risk screening of those with medium or high scores on CFS, address polypharmacy during admission and determine the best available follow-up strategy. The pre-frail and the ones who are mildly frail when they have ACS can gain from a few visits from a hospital-based specialized team of nurses and doctors after discharge. The ones who are severely frail might need another approach, for example, hybrid teams of primary care doctors, geriatricians and home nursing care. The outcomes of frail older people with ACS can be measured before and after the beginning of such interventions, using the follow-up that the secondary prevention part of SWEDEHEART allows. Effort should be made to increase the registration of older people in SWEDEHEART and to decrease the missing values. Registration of renal function after interventions in all patients with decreased function on baseline should be improved. Older people should also be included in the secondary prevention part of SWEDEHEART, as that would enable better follow-up of their quality of life and further improve the necessary comprehensive care older people with ACS need.

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Paper I

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Comparison of interventional cardiology in two European countries: A nationwide internet based registry study

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ABSTRACT

Background: The practice of interventional cardiology differs between countries and regions. In this study we report the results of the first nation-wide long-term comparison of interventional cardiology in two countries using a common web-based registry.
Methods: The Swedish Coronary Angiography and Angioplasty Registry (SCAAR) was used to prospectively and continuously collect background-, quality-, and outcome parameters for all coronary angiographies (CA) and percutaneous coronary interventions (PCI) performed in Iceland and Sweden during one year.
Results: The rate of CA per million inhabitants was higher in Iceland than in Sweden. A higher proportion of patients had CA for stable angina in Iceland than in Sweden, while the opposite was true for ST elevation myocardial infarction. Left main stem stenosis was more commonly found in Iceland than in Sweden. The PCI rate was similar in the two countries as was the general success rate of PCI, achievement of complete revascularisation and the overall stent use. Drug eluting stents were more commonly used in Iceland (23% vs. 19%). The use of fractional flow reserve (0.2% vs. 10%) and the radial approach (0.6% vs. 33%) was more frequent in Sweden than in Iceland. Serious complications and death were very rare in both countries.
Conclusion: By prospectively comparing interventional cardiology in two countries, using a common web based registry online, we have discovered important differences in technique and indications. A discovery such as this can lead to a change in clinical practice and inspire prospective multinational randomised registry trials in unselected, real world populations.

1. Introduction

Although comprehensive clinical guidelines have been issued in interventional cardiology, considerable variation persists between different centres in Europe, in the performance and outcome of procedures [1,2]. These differences may be due to economic constraints, differences in the incidence of cardiovascular disease, local expertise, demographics or traditions, but to a large extent they remain unexplained. In recent years there has been a marked increase in both primary percutaneous coronary interventions (PCI) for acute ST elevation myocardial infarction (STEMI), as well as of ad hoc PCI, in Europe [1]. The Euro Heart Survey and the on-going PCI Registry based on the Cardiology Audit and Registration Data Standards (CARDS) dataset facilitate comparisons between countries but are limited by a short observation period and the selected populations studied [3,4]. The participation in these registries is voluntary; they do not compare whole populations and are therefore subject to a selection bias. Earlier results from the Swedish Coronary Angiography and Angioplasty registry (SCAAR) have shown that there are considerable differences regarding invasive treatment between regions and hospitals in Sweden. Thus, it is more common that patients in the middle and southern regions of Sweden undergo coronary angiography (CA) than patients in the northern part. The use of drug eluting stents has also varied considerably between, hospitals and over time [5].

In this study we report the results of the first nation-wide comparison of all CA and PCI performed in two European countries during a whole year, by prospective collection of data in a common web-based registry.

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2. Materials and methods

2.1. The SCAAR database

The SCAAR database holds data on all CA and PCI in Iceland (single centre, 8 interventionalists) and Sweden (30 centres, around 150 interventionalists). It has been internet based since 2001, thus enabling direct data entry in the catheterisation laboratory on patient demographics, clinical and procedural data, complications and mortality. The SCAAR data is collected in line with CARDS and is transferred in an encrypted format to a central server in Uppsala University Clinical Research Centre (UCR) in Uppsala, Sweden. The SCAAR system provides each centre with immediate and continuous feedback on procedures and quality of care measures. Monitoring and source-data verification of registry data have been performed regularly and the overall correspondence is over 95% [5,6]. A complete list of variables in SCAAR has been presented previously [7]. The experience of the interventionalists in the two countries varies; from being in-training, to having decades of experience in interventional cardiology.

Since the introduction of PCI in Iceland in 1987, a PCI-registry has been kept, including comparable variables as those registered in SCAAR [8]. Since January 2007 Iceland has registered all CA and PCI in the SCAAR registry, through a cooperation between Landspitali the University Hospital of Iceland and UCR. Legal obstacles were overcome in accordance with laws in both countries and the European Union Directive 95/46/EC.

The current study is nationwide in both countries and included all patients who underwent CA or PCI in Iceland and Sweden from the 1st of January to the 31st of December 2007. The data was prospectively registered and the registration was 98–100% complete in both countries during the study time, with a miniscule variation between parameters.

Frequencies of CA and PCI were calculated from the registry data and official population data were calculated from the national population registries in the countries, Statistics Iceland (Hagstofa Íslands) and Statistics Sweden, SCB (Statistiska centralbyrån).

2.2. Statistical analysis

In this study we compare the whole populations of two nations and not samples from them. Therefore, analysis of statistical significance is in fact not necessary to evaluate whether the sample represents the population from which it is selected. Nevertheless, we treated the dataset from each country as a sample of two different regions within the Nordic area and used simple statistical methods to illustrate our findings. Discrete variables are presented as frequencies and percentages that were compared with a Chi square test. Continuous variables with a near symmetrical distribution are presented as mean (+/− standard deviation (SD)) and compared with Students t-test. Continuous variables without appropriately near-symmetrical distributions are presented as medians (interquartile range (IQR)) and compared with Mann–Whitney U-test. A significance level $p<0.05$ was selected and all tests were two sided. Calculations were made using Windows Excel and SPSS 11.0 for Windows.

For most variables (n = 1693 in Iceland, and n = 36904 in Sweden) the results for CA are presented for all CA, whether followed by a PCI or not. However, for; fluoroscopy time, complications, puncture site, hospital mortality and contrast media volume, the results refer to cases where only a CA (and no PCI) was performed (n = 1076 in Iceland and, n = 20,184 in Sweden).

2.3. Ethics

This study conforms to the ethical guidelines of the current version of the Declaration of Helsinki [9]. The Data Protection authority in Iceland and the National Bioethics committee in Iceland approved the study, permission numbers 2008040331 and 08-087. A written informed consent for entering patient data into SCAAR is not required in Iceland or Sweden, but patients are made aware of the database and its use and can decline participation.

3. Results

3.1. Coronary angiographies

In Iceland more CA were performed overall per capita, 5437/million compared to 4022/million in Sweden ($p<0.001$). Patient demographics are shown in Table 1, for all CA, indicating certain risk factor, gender, and age differences between the countries. Stable angina was a more usual indication for CA in Iceland while NSTEACS (non-ST elevation acute coronary syndrome), and STEMI were more frequent indications for CA in Sweden (Table 2). Other indications were proportionally similar in the countries, the most common being atypical chest pain, arrhythmias, valvular disease, and heart failure. The indications for CA calculated per capita (Table 3) differed only for stable angina and STEMI but not for NSTEACS.

The median fluoroscopy time was the same in both countries, in Iceland, 2.4 min (IQR: 1.5–4.3) vs. 2.5 min in Sweden (IQR: 1.4–5.0) (p = ns) but contrast use was higher in Iceland 100 ml (IQR: 90–130) vs. 70 ml in Sweden (IQR: 50–95) ($p<0.05$). The radial approach was applied in 0.6% of the patients in Iceland and 32.8% in Sweden, ($p<0.001$).

The findings on CA are presented in Table 4. The treatment decisions made in the cath-lab after CA were the following: No intervention or only medical treatment in 50.1% in Iceland and 34.4% in Sweden ($p<0.001$), PCI in 36.6% in Iceland compared to 47.3% in Sweden ($p<0.001$) and coronary artery bypass grafting (CABG) in 12.9% in Iceland and 15.8% in Sweden ($p<0.01$). The decision to perform a PCI was made for 1988/million inhabitants in Iceland and 1904/million in Sweden (p = ns). Referral to CABG took place in 700/million in Iceland compared to 634/million in Sweden (p = ns). The decision not to intervene was made in 2723/million inhabitants in Iceland and 1383/million in Sweden ($p<0.001$). Complications in the cath-lab for CA without PCI were 0.9% (10 patients) in Iceland and 0.7% (135 patients) in Sweden (p = ns). Total complications in the coronary care unit were 2.7% (29 patients) in Iceland and 1.5% (304 patients) in Sweden ($p<0.01$).

No patient died in Iceland due to a CA procedure during the study year, but one in Sweden. Total mortality in the cath-lab during CA without performing PCI, for any indication was 0.09% (1) in Iceland and 0.06% (12) in Sweden (p = ns). Total hospital mortality after any CA was 0.8% (9) in Iceland and 0.4% (74) in Sweden ($p<0.01$).

3.2. Percutaneous coronary interventions

The overall PCI rate (planned and ad hoc PCI) was similar in the two countries 2139 patients/million in Iceland and 2036/million in Sweden (p = ns). Patient demographics are given in Table 1 for all PCI performed. The indications for PCI differed between the countries

Table 1
Patient demographics for all coronary angiographies and percutaneous coronary interventions in Iceland and Sweden 2007.

Demographics %	All CA			All PCI		
	Iceland n = 1693	Sweden n = 36904	p	Iceland n = 666	Sweden n = 18680	p
Mean age—years[a]	63.8 (11.2)	65.7 (11.6)	<0.001	63.7 (11.7)	66.2 (10.9)	<0.001
Female sex	29.3	33.5	<0.001	21.0	28.3	<0.01
Hypertension	62.7	52.8	<0.001	61.9	52.4	<0.01
Diabetes	13.8	18.2	<0.001	15.6	18.8	ns
Smoking	22.0	16.2	<0.001	28.7	19.1	<0.001
Lipid lowering treatment	62.9	53.0	<0.001	61.3	53.3	<0.05
In cardiogenic shock	1.1	0.8	ns	1.8	1.4	ns
Earlier PCI**	22.2	20.2	ns	30.2	26.5	ns
Earlier CABG**	10.5	9.5	ns	11.7	10.3	ns
Earlier MI**	19.4	24.4	<0.001	24.6	27.7	ns
Earlier thrombolysis	0.4	0.6	ns	0.9	1.1	ns

CA: coronary angiography, PCI: percutaneous coronary intervention, CABG: coronary artery bypass grafting, MI: myocardial infarction.
[a] Mean age is presented as number (+/− SD), other variables as %.

Table 2
Indications for coronary angiographies and percutaneous coronary interventions in Iceland and Sweden 2007.

Indication %	All CA			All PCI		
	Iceland n = 1693	Sweden n = 36904	p	Iceland n = 666	Sweden n = 18680	p
Stable CAD	39.0	23.1	<0.001	40.1	23.5	<0.001
NSTEACS	29.0	39.4	<0.001	36.2	45.3	<0.01
STEMI	9.0	16.2	<0.001	20.0	27.4	<0.001
Other indications	23.0	21.3	ns	3.8	3.8	ns

CAD: coronary artery disease, CA: coronary angiography, PCI: percutaneous coronary intervention; NSTEACS: non-ST elevation acute coronary syndrome, STEMI: ST elevation myocardial infarction.

whether they were calculated as simple rates (Table 2) or per capita (Table 3).

The median fluoroscopy time for PCI was 11.1 min (IQR: 7.3–18.3) in Iceland vs. 10.3 min (IQR: 6.5–17.2) in Sweden ($p<0.05$). The median contrast volume used during PCI was 220 ml (IQR: 140–220) in Iceland vs.150 ml (IQR: 114–200) in Sweden ($p<0.05$). The arterial puncture site differed between countries similarly as for CA's.

In 93.2% of PCI carried out in Iceland and in 87.5% in Sweden the procedure was considered successful by the operator (p = ns). Complete revascularisation was achieved in 56.9% in Iceland and 55.8% in Sweden (p = ns). A mean of 1.5 stent was used per procedure in both countries. Overall stent use was 87.6% in Iceland and 83.9% in Sweden (p = ns). Drug eluting stent use was higher in Iceland 23.1% vs. 18.8% in Sweden ($p<0.01$). Sub-acute stent thrombosis during 2007 was found in 0.8% (5) and 1.1% (211) of patients in Iceland and Sweden, respectively (p = ns). The coronary distribution of lesions treated was identical (Table 5). Thrombolysis was given prior to acute and sub-acute PCI in 1.3% (9) in Iceland and 0.9% (149) in Sweden (p = ns). The use of adjuvant devices during PCI differed and is presented in Table 6.

Complications in the cath-lab during any PCI were 5.7% (38) in Iceland and 3.1% (577) in Sweden ($p<0.001$). Complications in the coronary care unit for all PCI patients were 7.5% in Iceland and 4.9% in Sweden ($p<0.01$). No patient died in Iceland due to a PCI procedure but 13 died in Sweden (p = ns). Total hospital mortality after any PCI was 1.7% and 1.2% in Iceland and Sweden, respectively (p = ns).

4. Discussion

This is, to our knowledge, the first all-comer, nationwide comparison of all CA and PCI in two countries during a whole year and using the same data registry. The uniqueness of our study is the totally unselected nature of the study population which consecutively encompasses all coronary investigations and procedures performed in all invasive centres of two countries.

Large similarities were found between the two countries. However, considerable differences were found in some aspects such as the rate of CA per capita, the indications for CA and PCI, DES use, and patient demographics. The radial approach was more commonly used in Sweden possibly explaining somewhat fewer complications in Sweden. In spite of these differences in complications the hospital mortality was similar. The value of this kind of benchmarking is to provide countries, centres and regions with a tool to improve techniques and to optimise patient outcomes and safety. For example, by demonstrating differences in contrast use, vascular access and complications between Iceland and Sweden, steps have been taken to encourage less contrast use, upgrading cath-lab equipment and to increase the number of procedures where the radial approach is used in Iceland.

SCAAR or a similar unified data management system may serve as a model for more European countries to register and quality control their interventional cardiology in the future. This will have the potential to minimise errors due to a different use of clinical parameters locally or nationally. This methodology might support and enhance the Euro PCI survey conducted by the European Society of Cardiology, for example by controlling the estimates done by the survey. Such a system may be used to further improve quality control in interventional cardiology in Europe and to build a platform for prospective multinational randomised registry trials.

Differences were apparent in the cardiovascular risk factors for patients undergoing CA in the two countries. Smoking was more prevalent in Iceland and diabetes was more common in Sweden. This probably merely reflects the fact that there was a higher percentage of smokers in 2007 in the general population in Iceland than in Sweden, over 20% compared to 16% [10]. Similarly, there was a higher prevalence of diabetes in Sweden, 7.3% vs. 4.7% in Iceland [11]. More patients in Iceland were medically treated for high blood pressure and hyperlipidaemia. Blood pressure has been shown to be lower in Iceland than in Sweden [12,13] while cholesterol levels in the two countries seem to be similar [14,15]. The difference in treatment of these risk factors at the index CA or PCI in the two countries is unexplained, and should be further investigated.

The number of CA per capita was higher in Iceland 5436/million inhabitants compared to 4022 in Sweden. However, the finding of no significant stenosis was equally common in both countries (around one third). Also, in spite of this, a higher proportion of the patients in Iceland had a left main stenosis, a serious form of coronary artery disease.

Some countries have already reported the number for CA/million inhabitants in 2007, i.e. Spain 2725 [16] and Germany 10,100 [17] but complete data for Europe in 2007 has not been available. In 2008 an estimate of 5346 CA per million was published based on

Table 3
Indications for coronary angiographies and percutaneous coronary interventions in Iceland and Sweden 2007 per million inhabitants.

Indications/million, n	All CA			All PCI		
	Iceland	Sweden	p	Iceland	Sweden	p
Stable CAD	2119	928	<0.001	857	478	<0.001
NSTEACS	1577	1586	ns	774	922	<0.01
STEMI	491	650	<0.001	427	558	<0.01

CAD: coronary artery disease, CA: coronary angiography, PCI: percutaneous coronary intervention, NSTEACS: non-ST elevation acute coronary syndrome, STEMI: ST elevation myocardial infarction.

Table 4
Outcome of all coronary angiographies in Iceland and Sweden 2007.

Outcome of CA %	Iceland n = 1693	Sweden n = 36904	p
No significant stenosis	30.6	29.1	ns
Single vessel disease	23.0	27.7	<0.01
Two vessel disease	18.4	17.9	ns
Triple vessel disease	18.0	17.3	ns
Left main stenosis	9.8	7.6	<0.01
Restenosis after prior PCI	5.1	6.9	<0.01
Stenosed CABG grafts	6.3	6.2	ns
Inconclusive	0.1	0.2	ns

CA: coronary angiography; PCI: percutaneous coronary intervention, CABG: coronary artery bypass grafting.

Table 5
Coronary distribution of treated lesions with a percutaneous coronary intervention in Iceland and Sweden 2007.

Treated lesion %	Iceland n = 973	Sweden n = 27210	p
Left anterior descending artery	40.1	42.2	ns
Right coronary artery	33.8	30.7	ns
Circumflex artery	21.0	20.7	ns
Intermedius	0.7	1.4	ns
Left main stem	1.8	2.0	ns
Venous graft	2.3	2.6	ns
Arterial graft	0.2	0.2	ns
Unknown	0.1	0.2	ns

older reports from each country. According to this estimate Germany performed 12,290 CA /million inhabitants, Finland 8939/million and Austria was in third place with 7940/million. In Sweden the estimated number was 5573 which is an overestimation according to our data, and Iceland 5243 which is close to the actual Icelandic figures [18]. The numbers of CA performed in Europe in 2005 range from 675/million in Romania to 8632/million in Germany with an average of about 4030/million in Europe. Iceland was in the seventh place with 5347 and Sweden in the 15th place with 3896 [19].

In this study the 4022 CA per million represents the average for all centres in Sweden. However, SCAAR reveals a considerable regional difference within Sweden, ranging in 2006 from 3220 to 5330 between different regions [20] and in 2008 from 3000 to 5600 [5]. The rate of CA in Iceland is therefore similar to the rate in the highest Swedish regions and close to the average in Europe.

Both STEMI and NSTEACS were more common indications for CA in Sweden than in Iceland, 16.2% and 39.4% in Sweden compared to 9.0% and 29.0% in Iceland, respectively. In the Euro Heart Survey on coronary revascularisation, STEMI was the indication in 16% and NSTEACS for 30% of the patients [3], right in-between the Icelandic and Swedish figures.

Stable angina was a more common indication for CA in Iceland (39%) than in Sweden (23%). The reason for this difference is not clear. One explanation could be a difference in the use of non-invasive stress tests and imaging methods, but reliable data on this is not available. Another explanation could be the relatively high density of practicing cardiologists (90 per million inhabitants) in the great Reykjavik area with geographically easy access to the only invasive centre, for the two thirds of the population living in the south-west corner of Iceland. On the other hand, the use of CA for stable angina in Europe is on average higher than in Iceland. In the Euro Heart Survey study on coronary revascularisation, stable angina accounted for 53% of the indications for CA [3] and for 52% in a recent Danish study [21]. Thus, Iceland seems more conservative than many other European countries in performing CA for stable angina and Sweden even more so, and the debate on when it is appropriate to perform CA for stable angina is ongoing.

In one half of CA in Iceland the angiography was not followed by revascularisation while this applied for only one third of the CA in Sweden. This is most likely explained by stable angina being a more common indication in Iceland. Detection of a ruptured plaque or a thrombus in patients with STEMI or NSTEACS almost without exception leads to revascularisation, while the finding of a stable plaque may often appropriately lead to a treatment with intensified medical treatment [22] or further investigations.

Table 6
Adjuvant therapy and diagnostic procedures used during percutaneous coronary interventions in Iceland and Sweden 2007.

Therapy/procedure %	Iceland n = 666	Sweden n = 18680	p
Thrombectomy	3.3	3.6	ns
Aorta balloon pump	1.1	1.5	ns
Pacemakers	0.5	0.6	ns
Distal protection device	0.2	0.5	ns
IVUS	0.5	2.9	<0.001
FFR measurements	0.2	9.5	<0.001

IVUS: intravascular ultrasound, FFR: fractional flow reserve.

No significant coronary artery disease was found in 31% and 29% of cases in Iceland and Sweden, respectively. This may seem high since in the Euro Heart Survey no significant stenosis was found in 24% of cases [3]. However, the Euro Heart Survey centres were to a large extent tertiary referral hospitals with a proportion of patients already having confirmed coronary artery disease upon referral. Therefore one would expect a higher proportion in a nationwide population based registry. In a recent registry study on 663 American hospitals no significant coronary artery disease was reported in 39% of cases [23]. Another American study on elective CA's showed that hospitals varied greatly in their rate of finding no significant coronary artery disease, 0%–77% with median of 55% [24].

The two countries did not differ in the number of PCI performed per million inhabitants, roughly 2100 procedures in both countries. The rate of PCI in Europe has been increasing. In 2001 the average was 990 PCI /million inhabitants, reaching 1601/million in 2005. Then the rate was lowest in Romania, 189/million and the highest in Germany, 3017/ million. Iceland was in the 5th place with 2120 per million and Sweden in the 8th place with 1964 [1,2,19]. Some countries have reported actual numbers for PCI per million in 2007, i.e. Spain with 1347 [16] and Germany with 3630 [17]. The estimated rate of PCI overall in Europe in 2007 was 1600 PCI/million. Israel held the highest estimate 2862 followed by Germany 2492. Iceland was sixth with 1588 and Sweden in the eleventh place with 1130 [18]. Both Iceland and Sweden are above the estimated average of PCI performed per million inhabitants in Europe. It is important to point out that for Germany, Iceland and Sweden these estimates are lower than the actual numbers reported. This may point out a systematic error in such estimations that should be considered in the future.

NSTEACS was the indication in 40% of PCI in both countries. This can be compared to 30% in the Euro Heart Survey on PCI (Euro PCI) that included 130 hospitals from 31 European countries. STEMI was the indication for 20% of PCI in Iceland and 27% in Sweden compared to 25% in the Euro PCI [10]. Stable angina was the indication for PCI in 40% and 23% in Iceland and Sweden, respectively. In comparison, stable angina was found to be the indication for 40% of PCI in the Euro PCI [10], which is comparable to the Icelandic figures. The optimal PCI rate for stable angina has been debated and is still uncertain despite the results of the Courage trial, which had limitations i.e. that all the treatment decisions in that study depended on the results of a CA [22,25,26].

In both countries the overwhelming majority of patients with STEMI that receive reperfusion therapy, undergo primary PCI. This can be estimated from SCAAR where only around 1% of patients undergoing PCI have received thrombolytic-therapy prior to the PCI. It is therefore likely that the difference in the rate of PCI due to STEMI in the two countries is due to a higher incidence of STEMI in Sweden and not due to different treatment strategies. Notable is the extremely high proportion of STEMI patients undergoing primary PCI in both countries since both countries have challenging geography and are sparsely populated. In spite of this both countries seem to have been able to offer almost all patients' access to primary PCI for STEMI.

The complication rate, both in the cath-lab and the coronary care unit, seemed somewhat higher in Iceland, but hospital mortality did not differ between the countries. This difference could be explained by that the radial approach was less commonly used in Iceland than in Sweden. A recent randomised multicentre trial demonstrated a higher local vascular complication rate with the femoral approach compared to the radial approach. Specifically, the radial approach was better for STEMI patients and high volume radial approach

centres [27]. Furthermore, in 2007 bleeding complications in SCAAR were less accurately defined than they are today, after redefinitions were instituted in SCAAR aimed at improved accuracy in the reporting of bleeding complications. Therefore some of the difference may be due to different definitions on bleeding complications between centres in Iceland and Sweden. Since the complications are few this difference may also simply be due to chance and may disappear with longer observation.

Some differences between the countries were detected in the use of devices. Intravascular ultrasound (IVUS) and Fractional flow reserve (FFR) measurements were more commonly used in Sweden. The Fame study showed that routine measurement of FFR in patients with multi-vessel coronary artery disease, which are undergoing PCI with DES, significantly reduced the rate of the composite end point of death, nonfatal myocardial infarction, and repeat revascularisation at 1 year [28]. The use of FFR in association with PCI should probably be encouraged in both countries and especially in Iceland.

The use of drug eluting stents (DES) was somewhat higher in Iceland than in Sweden, 23% compared to 19%, respectively. In 2005 DES use in Europe was 26% [19]. DES use has varied considerably over time since a debate was ongoing on their safety [6,7,29]. In Sweden the use of DES decreased from over 60% in January 2006 to 19% in 2007 but increased again in 2008 to 29% [5]. In Iceland the DES rate was fairly stable between 20 and 25% from 2004 to 2007 [1,19].

In our investigation restenosis was found in only 5–7% of performed angiographies so the clinical restenosis rate in the real world practice in both these countries seems to be very low. Similar results were seen in the SCAAR population in Sweden where restenosis occurred in 5.5% for BMS and 4.5% for DES from 2004 to 2008 [7].

The value of large multicentre registries in cardiology has long been recognised, and they are considered effective tools to monitor quality of clinical care especially if the groups analyzed are from unselected populations. Such registries allow a cross sectional view of diseases, patient demographics, treatment, morbidity and mortality. They allow monitoring the adherence to clinical guidelines and allow comparison of local therapeutic practice and patient outcomes to national or international standards. They may also facilitate the comparison of the effectiveness and health economics of procedures and practices. Furthermore, registry data may help clinical investigators in designing clinical trials [30–32].

Various registries exist in Europe and worldwide for coronary interventions. Several national registries exist other than SCAAR, for example in Spain [33], Germany [34], Britain [35] and in Denmark [36]. Other registries contain information from several centres throughout Europe such as the Euro Heart Survey on Coronary Revascularization [3], the Euro Heart Survey on Acute Coronary Syndromes [37], and the Global Registry of Acute Coronary Events (GRACE) which contains information from 95 hospitals in 14 countries around the world [38]. The ESC has recognised the inefficiency of different countries, and even different hospitals in each country, collecting similar but not identical data on coronary interventions. Therefore the ESC in collaboration with the Irish Department of Health and Children and the European Commission developed the CARDS project to achieve data standards for use in Europe in, among others, data gathering in PCI registries [39,40]. The trend therefore goes in the direction of a unified registry on interventional cardiology. Our study shows that comparison using the same web based data managing system across borders in Europe is not only possible but also very feasible.

A further important result of this study is to present a way that can enable multinational research using an on-line quality registry. Such a platform may enable scientists to initiate and conduct multi-centre and multi-national randomised clinical registry trials in the participating countries, very cost effectively. One such study, the TASTE study, on thrombus aspiration in STEMI, has already been described based on SCAAR and inclusion of patients in that study has already begun in 3 countries [41].

5. Conclusions

By using the same internet-based database for quality control of interventional cardiology in two European countries we have discovered differences in indications, demographics, procedural technique and complications. A discovery such as this can lead to an important change in clinical practice and inspire prospective multinational randomised registry trials with unselected populations. We encourage the use of a pan-European registry for the purpose of facilitating cross-reference between countries and regions. This could be achieved through SCAAR or another comparable high quality registry.

Conflicts of interest

The SCAAR registry does not have any commercial funding. The Swedish Association of Local Authorities and Regions funds SCAAR and UCR. This work was supported by Landspitali University Hospital Research Fund and The Bent Scheving Thorsteinsson fund for Cardiology and Thoracic surgery in Iceland. Dr James has received research grants and honoraria from Terumo Inc., Boston Scientific, Medtronic Inc., Vascular Solutions, Abbot Vascular, Eli Lilly, Astra Zeneca, BMS and Merck.

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Paper II

Gender differences in coronary angiography, subsequent interventions, and outcomes among patients with acute coronary syndromes

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Background The objective was to investigate whether gender disparities are found in referrals of patients with acute coronary syndromes to percutaneous coronary interventions (PCIs) or coronary artery bypass grafting (CABG) and, furthermore, to study gender differences in complications and mortality.

Methods All consecutive coronary angiographies (CAs) and PCIs performed in Sweden and Iceland are prospectively registered in the Swedish Coronary Angiography and Angioplasty Registry. For the present analysis, data of patients with acute coronary syndromes, enrolled in 2007-2011, were used to analyze gender differences in revascularization, in-hospital complications, and 30-day mortality.

Results A total of 106,881 CAs were performed during the study period. In patients with significant coronary artery disease, the adjusted odds ratio (OR) for women to undergo PCI compared with men was 0.95 (95% CI 0.92-0.99) and 0.81 (0.76-0.87) for referrals to CABG. In patients with 1-vessel disease, women were less likely to undergo PCI than men, but women with 2- or 3-vessel or left main stem disease were more likely to undergo PCI. All in-hospital complications after CA followed by PCI were more frequent among women (adjusted OR 1.58 [1.47-1.70]). There was no gender difference in adjusted 30-day mortality after PCI (1.02 [0.92-1.12]) and after CABG (0.97 [0.72-1.31]).

Conclusions After CA showing 1-vessel disease, women as compared with men were less likely to undergo PCI. In the group with 2- or 3-vessel disease or left main stem stenosis, women were more likely to undergo PCI but less likely to undergo CABG. However, there was no gender difference in 30-day mortality. (Am Heart J 2017;191:65-74.)

Coronary artery disease (CAD) is the leading cause of death in both men and women. In 2012, 20% of men and 21% of women in Europe died from CAD.[1] Women are on average 5 years older than men when they are diagnosed with acute coronary syndrome (ACS), and they have more comorbidities at presentation.[2-4] Although at least as many women die from CAD as men, women are underrepresented in both randomized controlled clinical trials and cohort studies addressing CAD.[4] There are some differences in the presentation of ACS between men and women. Although chest pain is the most common symptom of ACS in both genders,[5,6] women are more likely to report non–chest pain symptoms such as weakness, nausea, and right arm pain.[5] When a coronary angiography (CA) is performed, men have significantly more obstructions of the coronary arteries than women.[7,8] Conflicting results are found regarding whether women receive revascularization with either percutaneous coronary interventions (PCIs) or coronary artery bypass grafting (CABG) to the same extent as men after confirming obstructive CAD. Some studies show that women are less likely to undergo subsequent revascularization.[6,9-11] Others do not show gender differences in subsequent revascularization.[12,13] Women with ACS have also been shown to have more adverse outcomes than men after PCI, that is, bleeding, stroke, and pseudoaneurysms.[14]

The purpose of this study was to investigate whether gender disparities are found in referrals of women with ACS to revascularization with PCI or CABG. Furthermore,

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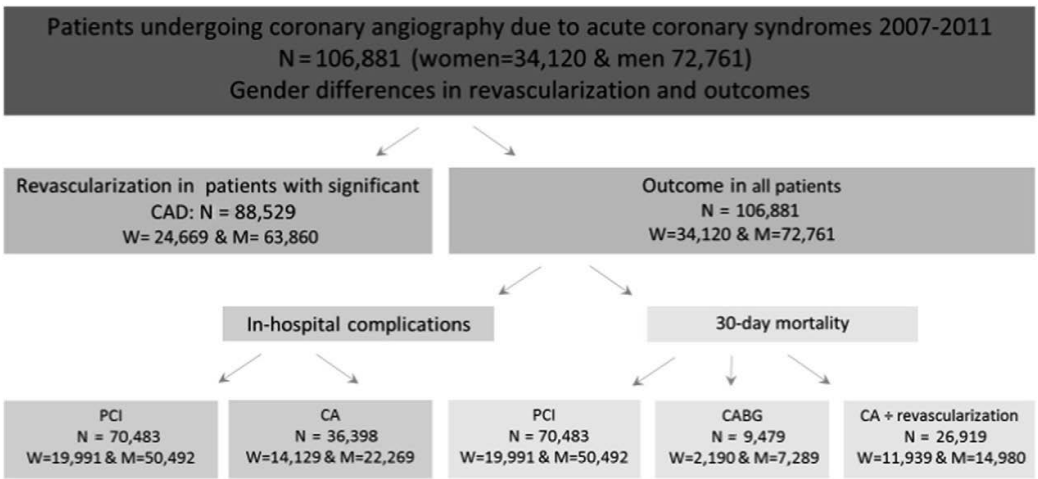
Figure 1



Flowchart: patient groups.Complications after CABG are not registered in SCAAR because patients are moved to a surgical ward.

we studied the subsequent in-hospital complication rate and 30-day mortality in a nationwide all-comer's registry in 2 countries during 5 years.

Methods

This is a prospective cohort study on gender differences in consecutive patients that underwent CA with the indication of ACS in Iceland and Sweden from January 1, 2007, to December 31, 2011 (Figure 1).

The Swedish Coronary Angiography and Angioplasty Registry

The Swedish Coronary Angiography and Angioplasty Registry (SCAAR) is a nationwide Internet-based continuous registry in Sweden and Iceland recording all patients that undergo CA and/or PCI in all 30 invasive centers in Sweden and the only invasive center in Iceland. SCAAR holds data on presentation, comorbidities, indications, procedural data, in-hospital outcomes, and follow-up in accordance with The Cardiology Audit and Registration Data Standards and European data standards for clinical cardiology practice.[15,16] All citizens in both countries have a unique 10-digit personal identification number. Based on this number, the SCAAR registry was merged with the national population registries in both countries to obtain the date of death of the participants.[15]

Definitions

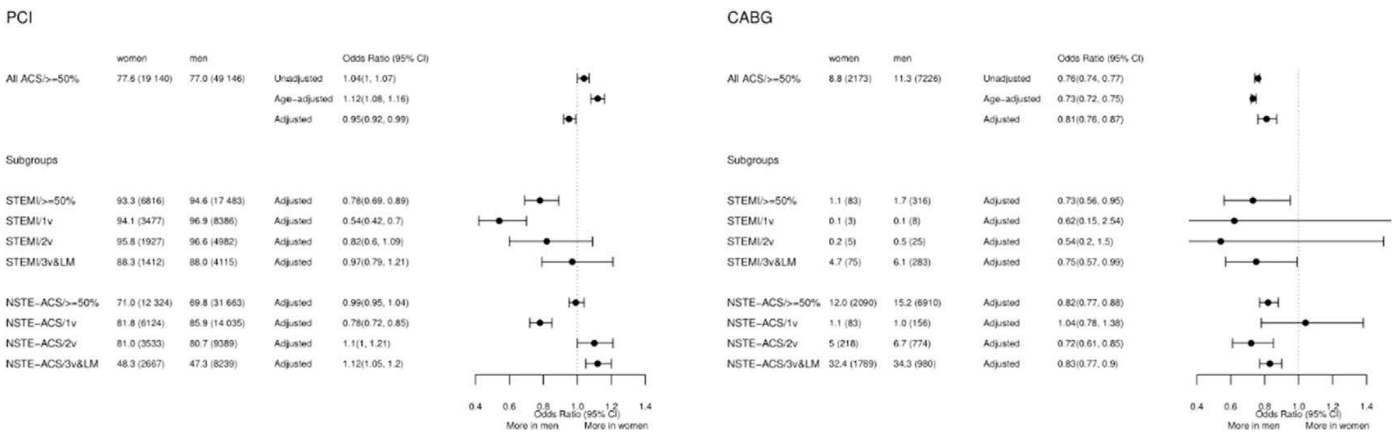
A *significant stenosis* was defined as at least 50% diameter stenosis in a major epicardial artery or a CABG graft. In-hospital complications were all complications, both in the catheterization laboratory and in the coronary care unit; see list in online data supplements. *In-hospital serious bleeding events* were defined as any bleeding event before discharge associated with a hemoglobin drop of $\geq$5 g/dL, intracranial bleeding, or the need for blood transfusion. Glomerular filtration rate (GFR) was calculated using Cockcroft-Gault (mL/min/1.73 m^2). ACS included both ST-elevation myocardial infarction (STEMI) and non–ST elevation ACS (NSTE-ACS). NSTE-ACS included both patients with unstable angina pectoris and those with non–ST elevation myocardial infarction, as we could not differentiate between these because cardiac enzymes are not routinely registered in SCAAR.

Statistics

In describing patient characteristics, extent of CAD, and treatment choices, categorical variables were reported as frequency values and proportions and tested by the χ^2 test. Continuous variables with a near-symmetrical distribution were presented as mean ± SD and tested with a Student *t* test.

Outcome variables were as follows: revascularization with PCI, revascularization with CABG, any in-hospital complication, any in-hospital bleeding event, serious in-hospital bleeding event, and 30-day mortality. Unadjusted odds ratios (ORs) from logistic regression, comparing women to men, were calculated for each outcome. Multivariable logistic regression models were designed to evaluate gender differences for each outcome adjusting for clinically relevant covariates.

Figure 2



Revascularization in women compared with men in patients with ACSs and significant CAD (coronary artery stenosis ≥50%)The figure shows the OR from logistic regression for women compared with men adjusted for age, extent of coronary disease, indication, diabetes, hypertension, smoking, hyperlipidemia, previous CABG, previous PCI, previous myocardial infarction, country, GFR, and calendar year. Imputed data. *LM*, left main stem stenosis.

Table I. Patient characteristics

	Women n = 34,120 %	Men n = 72,761 %	P*
Percentage of patient population %	31.9	68.1	
Age (mean ± 1 SD; y)	69.5 (11.3)	65.7 (11.3)	<.001
Percentage 80 y old and older	20.3	11.7	<.001
Comorbidity, %			
Diabetes	20.4	19.1	<.001
Hypertension	59.3	51.9	<.001
Hyperlipidemia	46.9	48.0	<.001
Ongoing smoking	19.2	20.8	<.001
Previous myocardial infarction	23.0	28.5	<.001
GFR (mean ± 1 SD; mL/min/ 1.72 m^2)†	77.0 (33.0)	93.7 (35.7)	<.001
Previous PCI	17.3	22.8	<.001
Previous CABG	6.1	11.1	<.001
Indication, %			
STEMI	24.6	27.6	<.001
NSTE-ACS	75.4	72.4	<.001
Radial access	49.5	47.8	<.001

* Age and GFR were tested with Student *t* test; other variables, with the χ^2 test.
† Calculated with Cockcroft-Gault (μmol/L).

Table II. Extent of coronary disease at CA

Diseased vessels	Women (n = 34,120) %	Men (n = 72,761) %	P*
Inconclusive†	0.3	0.2	<.001
Normal/atheromatosis	27.4	12.0	<.001
1-Vessel disease	32.8	34.3	<.001
2-Vessel disease	18.7	23.1	<.001
3-Vessel disease/LM	20.9	30.4	<.001

LM, left main stem stenosis.
* Significance was tested with χ^2.
† Includes missing results.

Patients who underwent PCI after CA were found by identifying all PCIs performed directly after the index CA or PCIs that were performed during the 30 days after the index CA. Patients assigned to CABG by the angiographer at the time of CA subtracting those who underwent PCI within 30 days were defined as the CABG group. In evaluating the referral to PCI or CABG with multivariable logistic regression, patients with no significant coronary obstruction were excluded. In the multivariable logistic regression models, age and GFR were continuous variables. Other variables were categorical: indication (NSTE-ACS/STEMI), extent of CAD (1-vessel, 2-vessel, 3-vessel disease or left main stem disease), diabetes (no/yes), hypertension (no/yes), hyperlipidemia (no/yes), previous PCI (no/yes), previous myocardial infarction (no/yes), previous CABG (no/yes), smoking status (never/previous/current), country (Sweden/Iceland), gender (man/woman), and year (2007/2008/2009/2010/2011).

To examine the gender differences in in-hospital complications, the group was divided into 2 categories, firstly patients undergoing CA and secondly patients undergoing CA followed directly by PCI. This categorization was done because the PCI procedure is associated with a higher risk for adverse events than CA only. There is more radiation during PCI, more contrast is used, and there is more use of antithrombotic therapy and antiplatelet therapy. The nature of the procedure is more invasive with wires, balloons, and stents being maneuvered in the coronary arteries, increasing risk for, for example, dissections, perforations, and thrombosis compared with CA only. Part of the group who did not undergo PCI was assigned to CABG. Complications after CABG are not registered in SCAAR but in another registry, The Swedish Heart Surgery Registry, which we did not have access to. A multivariable logistic model was designed to look at gender differences in in-hospital complications using the same variables as in the one for revascularization but adding vascular access site as a categorical value (femoral/radial access). As for the patients who underwent PCI, a second logistic regression model was developed using the previous 15 variables but adding variables for pharmacological therapy and procedural data. Many were categorical no/yes variables: left main stem was treated, acetylsalicylic acid prior to PCI, any P2Y12 receptor antagonist before PCI, glycoprotein IIb/IIIa inhibitor used before PCI, thrombolysis before PCI, patient on warfarin before PCI, complete revascularization, chronic total occlusion treated, bifurcation treated, and whether the patient was in shock before the procedure or not. Other categorical variables were which anticoagulant was used before PCI (unfractionated heparin/low–molecular weight heparin/bivalirudin/other), stent use (no stent/bare metal stent/drug-eluting stent), and number of stents (1/2/3 or more).

To examine gender differences in 30-day mortality, we examined the whole group irrespective of revascularization strategy. The group was then divided into the ones who underwent PCI within 30 days, the ones who were assigned to CABG, and the ones who underwent CA without revascularization. A multivariable logistic model was designed to look at gender differences in 30-day mortality using the same variables as for in-hospital complications, with a second model for the PCI patients as described before.

For most variables in the SCAAR registry, the missing data were less than 2.5% with an exception for smoking with 6.1% missing. GFR was calculated from other variables and had a total of 15.8% missing values. The pattern of missing values was not random; the missing values tended to be in cluster, with the same individuals having more than one missing. To decrease bias, missing data were imputed using the monotone method for 20 data sets. All multivariable logistic regression models were performed on data sets with multiply-imputed data. All analyses were performed using IBM SPSS version 24 except the forest plot in Figure 2 which was performed using R version 3.2.5.

Table III. Treatment and extent of CAD

	Medical treatment			PCI			CABG		
	Women %	Men %	P^*	Women %	Men %	P^*	Women %	Men %	P^*
Significant CAD W = 24,669, M = 63,860	13.6	11.7	<.001	77.6	76.9	NS	8.8	11.3	<.001
1-Vessel disease W = 11,176, M = 24,984	13.3	9.5	<.001	85.9	89.7	.001	0.8	0.7	NS
2-Vessel disease W = 6373, M = 16,787	9.6	10.6	<.01	85.7	85.6	NS	3.5	4.8	<.001
3-Vessel disease/LM W = 7120, M = 22,089	16.5	15.7	NS	57.3	55.9	NS	26.2	28.4	<.001

* Significance was tested with χ^2.

Ethics

This study conforms to the ethical guidelines of the current version of the Declaration of Helsinki.[17] Approval for the study was provided by the Data Protection Authority in Iceland and the National Bioethics Committee in Iceland, permission numbers 2008040331 and 08-087, as well as the Ethical Committee in Uppsala Sweden, permission number Dnr 2015/272. A written informed consent for entering patient data into SCAAR is not required in Iceland or Sweden, but patients are made aware of the database and its use and can decline participation.

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Results

Baseline characteristics and results of CA

From January 1, 2007, to December 31, 2011, 106,881 CAs were performed with ACS as an indication (Figure 1), whereof 31.9% were performed in women (Table I). Women were 4 years older and more commonly had hypertension and diabetes. They less often had hyperlipidemia or a previous history of MI, PCI, or CABG. STEMI was a less common indication in women (Table I). Patient characteristics for those undergoing CA and those undergoing CA followed by PCI are in online data supplements.

Women had less extensive CAD, with no significant stenosis found in 27.4% of CAs versus 12.0% in men ($P < .001$) (Table II). Both left main stem stenosis and 3-vessel disease were more common in men (Table III).

Revascularization

After CA, revascularization with PCI was performed in 58.6% (19,991) of women versus 69.4% (50,492) of men ($P < .001$), unadjusted OR 0.62 (95% CI 0.61-0.64). CABG was performed in 6.4% of women (2,190) versus 10.0% (7,289) of men. When individuals without significant stenosis (≥50% in at least 1 coronary artery) were excluded, there was no gender difference in performing PCI, which was done in 77.6% of women and 76.9.0% of men (P = not significant), unadjusted OR 1.04 (1.00-1.07). On the other hand, CABG was performed to a lesser extent in women, 8.8% (2,173) versus 11.3% of the men (7,726) ($P < .001$), OR 0.76 (0.72-0.80) (Table III).

After adjusting for comorbidities and age, the OR for women compared with men to undergo PCI in patients with significant CAD was 0.95 (0.92-0.99). There were positive interactions in the logistic regression model between gender and age, gender and smoking status, gender and extent of CAD, and finally gender and indication (all $P < .001$). In the subgroup of patients with 1-vessel disease and STEMI, women were referred to PCI in 94.1% of cases but men in 96.9% of cases, adjusted OR 0.52 (0.43-0.64). In the subgroup with 1-vessel disease and NSTE-ACS, women were referred to PCI in 81.8% of cases but men in 85.9%, adjusted OR 0.78 (0.72-0.85) (Figure 2). In patients with 3-vessel disease or left main stem disease and NSTE-ACS, women were more likely to be referred to PCI, OR 1.12 (1.06-1.20), compared with men. In the subgroup of patients with 2-vessel disease and NSTE-ACS, women were more likely than men to undergo PCI and less likely to be assigned to CABG. The effects of gender on referral to PCI in patients with STEMI were most profound in patients <60 years and in patients ≥80 years of age (Table IV). In patients with NSTE-ACS, the effects were most profound in patients <60 years old. Other

Table IV. Effects of age on revascularization in women compared with men in patients with ACSs and significant CAD (coronary stenosis ≥50%)

	<60 y old Adjusted OR*	60-69 y old Adjusted OR*	70-79 y old Adjusted OR*	>80 y old Adjusted OR*
PCI 50% stenosis/all ACS	0.71 (0.64-0.79)	0.95 (0.88-1.13)	1.03 (0.96-1.10)	1.07 (0.97-1.17)
PCI 50% stenosis/STEMI	0.45 (0.33-0.60)	0.94 (0.73-1.22)	1.00 (0.81-1.23)	0.86 (0.67-1.10)
PCI 1-VD/STEMI	0.37 (0.26-0.54)	0.68 (0.46-1.02)	0.65 (0.44-0.95)	0.43 (0.25-0.72)
PCI 2-VD/STEMI	0.83 (0.32-2.14)	0.84 (0.48-1.48)	1.09 (1.00-1.20)	0.66 (0.38-1.18)
PCI 3-VD or LM/STEMI	0.59 (0.33-1.05)	1.40 (0.90-2.24)	1.11 (0.81-1.52)	1.18 (0.82-1.68)
PCI 50% stenosis/NSTE-ACS	0.96 (0.87-1.07)	1.20 (1.11-1.29)	1.23 (1.15-1.32)	1.19 (1.08-1.32)
PCI 1-VD/NSTE-ACS	0.55 (0.47-0.65)	0.81 (0.70-0.93)	0.88 (0.77-1.01)	0.98 (0.79-1.23)
PCI 2-VD/NSTE-ACS	0.98 (0.76-1.25)	1.15 (0.96-1.38)	1.10 (0.95-1.28)	1.03 (0.81-1.31)
PCI 3-VD or LM/NTE-ACS	1.05 (0.86-1.28)	1.00 (0.87-1.15)	1.14 (1.03-1.27)	1.13 (0.99-1.30)
CABG 3-VD or LM/all ACS	0.93 (0.76-1.15)	0.98 (0.85-1.15)	0.79 (0.70-0.88)	0.79 (0.67-0.94)
CABG 50% stenosis/NSTE-ACS	0.82 (0.69-0.99)	0.95 (0.83-1.08)	0.81 (0.73-0.91)	0.82 (0.69-0.97)
CABG 2-VD/NSTE ACS	0.64 (0.43-0.97)	0.72 (0.54-0.97)	0.83 (0.65-1.06)	1.64 (0.35-1.16)
CABG 3-VD or LM/NSTE-ACS	0.88 (0.70-1.09)	1.00 (0.86-1.18)	0.80 (0.71-0.91)	0.81 (0.69-0.97)

VD, vessel disease.
* Logistic regression, OR for women compared with men, adjusted for diabetes, hypertension, smoking status, hyperlipidemia, previous CABG, previous PCI, previous myocardial infarction, country, calendar year and GFR. Imputed data.

subgroup analyses due to positive interactions are shown in online data supplements.

After adjusting for age and comorbidities and excluding patients that did not have significant coronary artery stenosis, the adjusted OR for women intended for revascularization with CABG was 0.81 (0.76-0.87) (Figure 2). There were positive interactions between gender and age, gender and indication, gender and previous PCI, gender and extent of CAD, and finally gender and previous CABG (all $P < .001$). In the subgroup of patients with 3-vessel disease or left main stem disease, the adjusted OR for referral to CABG in women was 0.83 (0.77-0.88) (Figure 2). Subgroup analyses for age groups showed that the effects of gender were more prominent in patients >70 years (Table IV). Other subgroups analyses due to positive interactions are shown in online data supplements.

In-hospital complications and 30-day mortality

All in-hospital complications after CA followed by PCI were more common in women than men, 8.4% versus 5.4% ($P < .001$), adjusted OR 1.58 (1.47-1.70). Bleeding events in hospital were almost 2-fold higher in women. Serious bleeding events were rare in both genders but 4-fold higher in women than in men (Table V).

After CA without PCI, in-hospital complications were less common than after CA followed by PCI (Table V). However, the risk of any in-hospital complication or bleeding event was still 2-fold higher in women compared with men. Serious bleeding events were rare in both genders (Table V). Analyses due to positive interactions are shown in online data supplements.

In the whole group, unadjusted 30-day mortality was higher in women. Adjusted mortality did not differ between men and women (Table VI). We did not find any gender differences in adjusted mortality in any subgroup irrespective of revascularization strategy. Interactions between gender and age and gender and each covariate were negative in the whole group and in all subgroups.

Discussion

Our study shows that, in patients with significant CAD, there are small but significant gender differences in revascularization and the effects of gender vary between subgroups. In the group with 1-vessel disease, women are less likely to undergo PCI, but in the group with 3-vessel disease or left main stem disease and NSTE-ACS, women were more likely to undergo PCI. At the same time, women were less likely to be referred to CABG, even in the group with NSTE-ACS as an indication combined with 3-vessel disease or left main stem disease. Another major result is that women undergoing invasive investigations with or without PCI for ACS have more in-hospital complications but, despite this, they do not have higher short-term mortality.

A recent registry study of ACS patients in Denmark showed that, after adjusting for age, comorbidity, and the extent of CAD, the adjusted OR for women to undergo PCI compared with men was 0.96,[18] in concordance with our results. However, this study did not differ between STEMI and NSTE-ACS. There are other studies in ACS populations that show that even after adjusting for the extent of CAD and comorbidity, a slight gender difference in referrals to PCI remains.[6,19] A recent study from the Swedish Registry of Information and Knowledge about Swedish Heart Intensive Care also found women with STEMI to be less likely to undergo PCI.[20] Heer et al[21] did not find gender differences in referral to PCI in

Table V. Rate of in-hospital complications in women compared with men after CA with or without PCI in patients with ACSs

		Women %	Men %	Unadjusted* OR (95% CI)	Adjusted† OR (95% CI)	Adjusted‡ OR (95% CI)
PCI	Any in-hospital complications	8.4	5.4	1.61 (1.52-1.72)	1.55 (1.44-1.66)	1.58 (1.47-1.70)
W = 19,991, M = 50,492	Any in-hospital bleeding event	4.2	2.2	1.90 (1.73-2.09)	1.75 (1.59-1.94)	1.77 (1.60-1.97)
	Serious in-hospital bleeding events	0.72	0.15	4.92 (3.70-6.55)	4.17 (3.07-5.66)	4.41 (3.22-6.05)
CA§	Any in-hospital complications	2.5	1.7	1.48 (1.29-1.71)	1.56 (1.33-1.83)	Not applicable
W = 14,129, M = 22,269	Any in-hospital bleeding event	1.8	1.0	1.79 (1.50-2.15)	1.72 (1.42-2.10)	
	Serious in-hospital bleeding events	0.26	0.05	5.14 (2.68-9.85)	5.29 (2.65-10.58)	

* Logistic regression, unadjusted OR for women compared with men.
† Logistic regression, OR for women compared with men, adjusted for age, extent of coronary disease, indication (STEMI/NSTE-ACS), diabetes, hypertension, smoking, hyperlipidemia, previous CABG, previous PCI, previous myocardial infarction, vascular access, country, GFR, and calendar year. Imputed data.
‡ Logistic regression, OR for women compared with men, adjusted for the same as in † as well as treatment of left main stem, complete revascularization, P2Y12 receptor antagonists, acetylsalicylic acid, glycoprotein IIb/IIIa inhibitors, anticoagulation before PCI, thrombolysis before PCI, type of stents, treatment of chronic total occlusion or bifurcations, and whether the patient was in a cardiogenic shock. Imputed data.
§ Patients assigned to CABG are included in the CA group because complications after CABG are not registered in SCAAR.

patients with at least 50% stenosis and either STEMI or NSTE-ACS, and the age-adjusted ORs for undergoing PCI were 1.02 and 1.07. They did find that women with 3-vessel disease or left main stem disease were more likely to undergo PCI as we did, but separate results were not shown for patients with 1-vessel disease. In the Danish study, the main difference in referral to PCI was found in patients with 1-vessel disease as well as those without any significant stenosis,[18] similar to our results.

Our findings of a gender disparity in referral to PCI in patients with 1-vessel disease and NSTE-ACS can be explained by the fact that whereas men with NSTE-ACS have consistently been shown to have a lower mortality rate when routine early invasive approach is used, women have not been shown to benefit from this approach.[22,23] Women do have more in-hospital complications after PCI[13,14] that may contribute to treatment decisions leading to a less invasive approach in women with NSTE-ACS.

There are a few possible explanations of gender differences in the group with 1-vessel disease and STEMI. Women have smaller coronary arteries, making them more difficult to intervene upon.[24,25] In very small vessels, that is, <2.0 mm, the use of stents is prohibited. Other causes of ACSs than atheromatous plaques such as microvascular disease, stress-induced cardiomyopathy (Takotsubo syndrome), spontaneous coronary artery dissections, and coronary artery spasm are more common in women.[26,27] Some patients might have had spontaneous coronary artery dissection, which most commonly affects a single vessel.[28] Around 10% of patients with stress-induced cardiomyopathy have concomitant epicardial obstruction,[29] and this might be the case with some patients in our study.

There was a positive interaction between gender and age. The largest difference between women and men in referral to PCI was in those who were <60 years old. There is some evidence of gender difference in plaque morphology in patients <65 years of age, with women exhibiting less necrotic core and less dense calcium than men, but this difference is attenuated after 65 years.[30] A recent study looking at histopathological differences in thrombus aspirate from STEMI patients did not find any gender difference, but in that study, there may have been too few young women to identify a difference.[31] Coronary artery dissections are more common in younger than older women,[27] as are microvascular spasm and myocarditis.[26] These differences might contribute to a different clinical approach in younger women presenting with ACS.

Our results showing that women are less likely to be referred to CABG are in concordance with the previously mentioned Danish study where adjusted OR for women was almost identical to our results (0.8).[18] Most studies show some gender bias in referrals to CABG.[9,11,12,18] Women who undergo CABG are older and have more comorbidities than men. Furthermore, women have poorer surgical outcomes and higher mortality after CABG.[32-34] The surgical grafting of smaller coronary arteries in women is more challenging and might contribute to this difference in outcomes.[34] Taking increased complication rates and mortality into consideration, some gender disparity in referral to CABG is to be expected.

Most studies show increased in-hospital complication rates in women after CA and PCI[13,14,35,36] and especially high rates of bleeding events,[14,37-39] as we have shown. There are probably many different explanations to increased bleeding in women. On average, women have lower body weight and lower GFR than men. This fact in addition to their underrepresentation in cardiovascular trials may lead to overdosing of antithrombotic medications.[4,40] Anatomical factors can contribute; for example, women with smaller femoral arteries have a higher complication rate than women with larger arteries, and women tend to have smaller arteries than men.[24] There might be some gender differences in platelet activity as well as coagulation that could

Table VI. Thirty-day mortality in women undergoing CA with or without revascularization in patients with ACSs

	Women %	Men %	Unadjusted* OR (95% CI)	Adjusted† OR (95% CI)
All patients, W = 34,120 M = 72,761	3.0	2.4	1.25 (1.16-1.35)	0.97 (0.84-1.05)
PCI/all ACS, W = 19,991 M = 50,492	3.8	2.6	1.48 (1.35-1.62)	1.02 (0.92-1.12)
PCI/STEMI, W = 6959 M = 17,794	7.9	5.2	1.56 (1.40-1.75)	0.97 (0.86-1.10)
PCI/NSTE-ACS, W = 13,032 M = 32,698	1.6	1.2	1.37 (1.15-1.62)	1.03 (0.86-1.23)
CABG/all ACS, W = 2190 M = 7289	3.4	2.3	1.47 (1.11-1.95)	0.97 (0.72-1.31)
CABG/STEMI, W = 85, M = 318	10.6	7.7	1.41 (0.63-3.16)	0.93 (0.36-2.41)
CABG/NSTE-ACS, W = 2105 M = 6971	3.1	2.1	1.50 (1.11-2.02)	0.99 (0.72-1.36)
CA without revascularization, W = 11,939 M = 14,980	1.7	2.0	0.85 (0.71-1.01)	0.83 (0.67-1.01)

* Logistic regression, unadjusted OR for women compared with men.
† Logistic regression, OR for women compared with men, adjusted for age, extent of coronary disease, indication, diabetes, hypertension, smoking, hyperlipidemia, previous CABG, previous PCI, previous myocardial infarction, vascular access, country, GFR and calendar year. Imputed data. A second logistic regression model was designed for patients undergoing PCI; covariates included previous covariates as well as treatment of left main stem, complete revascularization, P2Y12 receptor antagonists, acetylsalicylic acid, glycoprotein IIb/IIIa inhibitors, anticoagulation before PCI, thrombolysis before PCI, type of stents, treatment of chronic total occlusion or bifurcations, and whether the patient was in a cardiogenic shock. Imputed data were used, and the results were the same as in the other adjusted models for each subgroup.

contribute to the increased bleeding risk observed. Estrogen can affect various proteins in the coagulation and fibrinolytic pathways.[41] There are various estrogen and androgen receptors on platelets, and estrogen affects both nitric oxide synthase release as well as thromboxane A2 generation.[42] Female glycoprotein IIb/IIIa receptors on platelets respond more to various agonists.[43] The higher bleeding rate in women is of concern. Many studies have shown that bleeding events, and especially serious bleeding events after CA and PCI, are associated with higher long-term mortality.[44,45] The mechanisms underlying the effects of bleeding on mortality might be direct negative effects of blood transfusion in ACS patients[46] or due to cessation of evidence-based treatment such as β-blockers and antiplatelet therapies.[47] To reduce bleeding events and other complications in women after CA and PCI, it is important that cardiovascular trials are designed with enough statistical power to obtain results for women as well as men.[48,49]

After adjusting for age, comorbidities, vascular access, GFR, and the extent of CAD, we found no gender disparity in 30-day mortality after CA with or without PCI for ACS, in concordance with numerous studies.[6,18,50-53] Other studies have indicated higher short-term mortality in women, especially younger women.[54-56] In many studies, the comorbidities that are included are the ones that usually are registered in CA/PCI databases: diabetes, hypertension, age, high cholesterol, previous myocardial infarction, previous PCI, previous CABG, and extent of CAD. When studies include more comorbidities that tend to be more common in women with CAD, such as worse kidney function, chronic obstructive pulmonary disease, cardiogenic shock, and heart failure, gender difference in 30-day mortality tends to be absent.[6,9,51,52,57] Many studies have found higher short-term mortality after PCI due to STEMI in women to be especially high in the youngest group, under 50 or 60 years old.[54-56] We did not find positive interactions between age and gender when we looked at 30-day mortality in the PCI group, indicating that the effects of gender were not different in different age groups, but this might be because few patients were in the youngest age group. The lower 30-day mortality in patients not undergoing revascularization is probably because those individuals did not have any significant CAD.

This study presents nationwide and contemporary data in a large unselected cohort from 2 countries during a 5-years period. All patients who undergo CA due to ACS in both countries are included, and therefore, the risk for selection bias is minimized. The design of the study is prospective and observational because data are collected continuously. There may be factors that explain the gender differences that are not included in our registry. The lack of knowledge of other reasons for ACS than atherosclerotic plaque rupture and thrombus formation is a limitation, for example, spontaneous coronary artery dissections and arterial spasms. Another limitation is not knowing if the lesions found on CA are proximal or distal as well as not knowing the cardiac enzyme levels and ejection fraction. As in all registries, a proportion of the patients had missing data, even if this proportion in SCAAR is very low. We did, however, perform imputation to compensate for this.

Conclusion

There were no gender differences in 30-day mortality in patients undergoing PCI for ACS or in patients undergoing CABG due to ACS, yet women had more in-hospital complications than men. Serious in-hospital bleeding events were rare in both genders but 4 times higher in women. After CA showing 1-vessel disease, women as compared with men were less likely to undergo PCI. However, in the group with 2-vessel, 3-vessel, or left main

stem disease, women were more likely to undergo PCI. At the same time, women with 2-vessel, 3-vessel, or left main stem disease underwent CABG to a lesser extent than men. As these gender differences in revascularization did not lead to higher 30-day mortality, they may be appropriate, bearing in mind more complications in women. Future studies should focus on reducing the in-hospital complications in women after PCI and examining whether this difference in revascularization leads to worse long-term outcomes.

Contributors

Two statisticians contributed to this work. Henrik Renlund at UCR consulted on design of logistic regression models and how to handle missing cases, but the analyses were performed by the first author. Bodil Svennblad at UCR designed a forest plot in the statistical software R. Otherwise, the authors are responsible for the design and conduct of this study, the study analyses, the drafting and editing of the paper, and its final content.

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The authors report no relationships that could be construed as a conflict of interest.

Appendix. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ahj.2017.06.014.

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Paper III

Invasive strategy in STEMI provides benefits to multimorbid older people with complex health needs

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Abstract

Aims: To compare one-year outcomes of invasive strategy to non-invasive strategy in multimorbid older people with complex health needs and STEMI.

Methods: This was an observational study using prospectively collected data from the nation-wide SWEDEHEART registry and the Swedish National Patient Registry. Included patients were seventy years old or older, had ST-elevation myocardial infarction (STEMI), were registered in SWEDEHEART between 2006 and 2013, had multi-morbidity and high use of health care services. The one-year outcomes of patients who received invasive treatment (examined with coronary angiography ≤14 days) were compared to those who did not. The primary event was a composite of all-cause death, admission due to new ACS, stroke or transient ischemic attack.

Results: Multimorbid patients with complex health needs admitted due to acute coronary syndrome were 10 825, of which 2004 had STEMI. After excluding the patients who died during admission, 1089 patients were in the invasive group and 570 in the non-invasive group. The primary event was reached in 31% of patients in the invasive group and 55% in the non-invasive group, propensity score adjusted hazard ratio (95% confidence intervals): 0.67 (0.54-0.83). One-year mortality was 18% in the invasive group and 45% in the non-invasive group, adjusted hazard ratio 0.51 (0.39-0.65). In the invasive group, 8% were readmitted due to bleeding events the following year and 11 % in the non-invasive group, adjusted hazard ratio 0.66 (0.43-1.02). In both treatment groups, readmission rate due to any cause was 70%.

Conclusions: Multimorbid older people with complex health needs and STEMI have a high rate of new ischemic events and death. This study suggests that an invasive strategy decreases the event rate in this complex group. This is consistent with results from randomized trials in younger and healthier patients.

Introduction

The Western population is aging. Among patients with acute coronary syndromes, around 35% are 75 years old or older (1). Age is not an isolated condition and at least 64% of patients between 65 and 84 old, and 81% of those who are 85 years old and older, have two or more chronic conditions, also known as multi-morbidity (2). Primary percutaneous coronary interventions (PCI) has proven to reduce mortality and recurrent ischemia in older people with ST-elevation myocardial infarction (STEMI) (3) and modern guidelines do not exclude patients from primary PCI due to advanced age (4).

Most randomized trials exclude older people with extensive multi-morbidity (5). The presence of other conditions alongside STEMI can affect the benefits of the invasive strategy. For example, if comorbid conditions increase the risk of bleeding events in a patient that receives a coronary stent, requiring dual antiplatelet therapy for several months. There is concern that strict adherence to guidelines may cause harm in treating those with multi-morbidity (6).

Non-selected registries provide an opportunity to do observational studies on patients who are not included in most trials. The Swedish National Board of Health and Welfare has defined a group of older people with complex health needs. These patients have multi-morbidity and large consumption of health care (7). Almost 90% of them are frail or pre-frail (8). They can be identified with the Swedish quality registries.

Our objective in this study was to compare the one-year outcomes of multimorbid older people with complex health needs and STEMI who received invasive treatment to those who treated with a non-invasive treatment.

Methods

Endpoints:

Primary event was one-year composite of all-cause mortality, readmission due to ischemic stroke or transient ischemic attack (TIA) or readmission due to acute coronary syndromes (ACS). ACS included STEMI, non-ST-elevation myocardial infarction and unstable angina. Secondary events were one-year readmission due to bleeding events, any single component of the primary event, one-year readmissions due to heart failure, and one-year readmission due to any cause.

Patients and data sources:

This was an observational study of prospectively collected data from the SWEDEHEART registry (Swedish Web-system for Enhancement and Development of Evidence-based care in Heart Disease Evaluated According to Recommended Therapies) and the Swedish National Patient Registry. The SWEDEHEART registry contains RIKS-HIA (The Register of Information and Knowledge about Swedish Heart, Intensive Care Admissions) as well as SCAAR (Swedish Coronary Angiography and Angioplasty Registry) together with registries for thoracic surgery and secondary prevention. RIKS-HIA collects data for all patients admitted to Swedish coronary care units and includes over 100 variables for patients' medical history, strategy before admission, clinical conditions, management during hospital stay, treatment at discharge, and diagnosis. SCAAR collects angiographic data, procedural data, demographic data and treatment decisions for all patients who are investigated with coronary angiography and/or revascularized with percutaneous coronary interventions at every Swedish center

performing these procedures. Data is registered online and source data verification is performed annually in randomly selected patients from about 20 different hospitals (9). SWEDEHEART is merged regularly with the Swedish National Cause of Death Registry to obtain date of death and cause of death.

The Swedish National Patient Registry collects information about diagnoses at discharge from all hospital stays in Sweden, as well as diagnoses from outpatient hospital specialist care (10). Using information from the Swedish National Patient Registry, the Swedish National Board of Health and Welfares has defined a group of older people with multi-morbidity and complex health needs. An individual must meet criteria a-c) and either d), e) or f) at index date; a) be at least 65 years old b) be hospitalized at least three times with main diagnoses from at least two different the International Classification of Diseases, version 10 (ICD 10) chapters, c) at least one hospitalization must be within 12 months prior to index date, d) have more than 19 days of hospitalization or outpatient's visits to specialist clinics during the last 12 months before index date, e) have more than 3 hospitalizations during the last 12 months before index hospitalization or f) have more than 7 visits to specialist in outpatient care during the last 12 months before index date (7).

Patients hospitalized due to STEMI during January 1th 2006 – December 31th 2013 were included in the study. They all met the criteria for having multi-morbidity and complex health needs at admission. Only index admissions were included. Patients who died during admission were excluded to avoid bias caused by including patients in the non-invasive group who were so severely ill that it precluded them from being referred to coronary angiography (CA) (figure 1).

Date of death was obtained from the Swedish National Cause of Death Registry. Patient characteristics and new episodes of ACS were identified from both by RIKS-HIA and the Swedish National Patient Registry. Other endpoints were identified from the Swedish National Patients Registry. The ICD 10 codes for both patient characteristics and endpoints can be found in supplementary data.

Definitions:

Invasive strategy was defined as the performance of coronary angiography ≤14 days of admission. Patients who were referred to CA after 14 days or not at all constituted the non-invasive group (11). Bleeding events were defined as all hospitalizations with diagnoses of hemorrhage without regard to type or anatomical location implied by the diagnose code, as well as fatal bleeds with the bleeding diagnosis as a first or a second cause of death. ICD-10 codes for bleeding events can be found in supplementary data (12). The standards of the European Society of Cardiology for definition of myocardial infarctions and ACS are used in Swedish hospitals and RIKS-HIA (13). The treating physician sets the final diagnosis. STEMI is defined as the presence of ST-elevation on electrocardiogram (ECG) or new left bundle-branch block on electrocardiogram (ECG)

in addition to suspicion of ongoing ischemia. Renal function was measured by estimated glomerular filtration rate (eGFR), calculated with Cockcroft Gault formula. Normal renal function was defined as eGFR ≥ 90 ml/min/1.73 m^3, mild renal disease: 60 ≤ eGFR < 90 ml/min/1.73 moderate renal disease: 30 ≤ eGFR < 60 ml/min/1.73 m^3, and severe renal disease: eGFR ≤ 30ml/min/1.73 m^3. Comorbidity burden was measured by CAD specific index, which was described by Sachdev et al in 2004 (14), a description can be found in supplementary data.

Statistical analyses:

To compare patient characteristics in the group who did not undergo invasive strategy to the group who did, Fisher´s Exact test was used for dichotomous variables, the Mantel-Haenszel Chi square test for ordered categorical variables, Chi square test was used for non-ordered categorical variables and Mann-Whitney U-test was used for continuous variables.

A propensity score method was used to compare the results of invasive and non-invasive strategy to compensate for the non-randomized study design. It included all the patient characteristics that differed between the invasive and non-invasive group as well as comorbidity burden. Variables tested for difference between the groups were: age, gender, smoking status, year of index date, hypertension, stroke, diabetes, chronic obstructive pulmonary disease (COPD), peripheral vascular disease (PVD), a tumor or lymphoma, tumor with metastases, history of congestive heart failure, anemia, atrial fibrillation, prior myocardial infarction or renal (groups: normal, moderate, severe, eGFR unknown) disease, previous PCI, eGFR, CAD specific index, as well as medications on admission. Medications on admission were: angiotensin converting enzyme inhibitors (ACE-I), angiotensin receptor blockers (ARB), ASA, P2y12 receptor antagonists, oral anticoagulants, beta blockers, lipid-lowering drugs, diuretics, digitalis, long-acting nitroglycerin, and calcium antagonists).

For each outcome, Cox's regression survival analyses were performed to compare the effects of invasive vs not-invasive strategy. Three Cox regression analyses were performed for each outcome: Model 1 included age, sex, eGFR and propensity scores. Model 2 included all covariates in model 1 and additionally adjusted for medications at discharge that differed between the groups (ACE-I or ARB, ASA, P2y12 receptor antagonists, beta-blockers, statins, diuretics, digitalis, long-acting nitroglycerin, and calcium antagonists). Model 3 included all covariates in model 2 and additionally adjusted for variables included in propensity scores for which balance between the groups was not achieved. Unknown and missing values were kept as an additional level of the categorical covariates. For one-year mortality the criteria for proportional hazards during one year were not fulfilled, data was further analyzed with a flexible parametric survival model (Royston-Parmer model) (15). Thus, the interaction between the treatment group and time in study could be studied and described by continuous hazard ratios (HR). Interactions in the Cox regression analysis were tested between age

and strategy, gender and strategy, eGFR group and strategy. Subgroup analyses were performed in those groups.

Mortality during admission in the invasive group was compared to mortality in the non-invasive group using new propensity scores built in the same manner for the entire group and the method described for model 3. Mortality during various time periods from admission was compared between the two groups in the same manner.

Results

There were 80 386 individuals aged 70-103 years old admitted due to ACS to coronary care units in Sweden during 2006-2013 and registered in RIKS-HIA. Of those 10 825 had multi-morbidity and complex health needs; 2004 had STEMI. After excluding those who died during the admission period, 570 constituted the non-invasive group and 1089 the invasive group (figure 1). In the invasive group, 926 (85.0%) underwent coronary angiography the first day, of which 829 (89.5%) underwent primary PCI.

The non-invasive group was 4.7 years older than the invasive group, had higher comorbidity burden and more medications at admission (table 1 and table 2). The differences in clinical characteristics and medications at admission were well balanced after adjustment with a propensity score for all variables except ARB at admission (table 3). Medications at discharge were significantly different between the groups and were included in the adjusted models for outcomes.

The primary event was reached in 30.9% of the invasive group and 54.6% in the non-invasive, unadjusted HR 0.56 (95% confidence interval: 0.47-0.68). After adjustment with propensity scores, medications at discharge and the one variable that could not be adjusted in the propensity score (ARB at admission), the risk of the primary event was 33% lower in the invasive group, adjusted HR 0.67 (0.54-0.83) (table 4). Bleeding events occurred in 8.3% of the invasively treated patients and 11.2% in the non-invasive group, adjusted HR 0.66 (0.43-1.02) (table 4).

Readmissions due to any cause were 69.8% in the invasive group and 70.8% in the non-invasive group, adjusted HR 0.88 (0.75-1.03).

One-year mortality after discharge was 17.7% in the invasive group and 44.9% in the non-invasive group, adjusted HR 0.51 (0.39 - 0.65) (table 5). The flexible parametric survival model showed relative risk reduction between 65% and 47% during the first 120 days, adjusted HR 0.35 (0.21-0.58) to 0.53 0.53 (0.36-0.78). At nine months adjusted HR was 0.69 (0.46-1.03) and at one-year: 0.75 (0.45-1.27) (figure 2).

Those who were 90 years old and older in the invasive group had adjusted HR 1.57 (0.93-2.64) for the primary event compared to those in the non-invasive group, adjusted HR 1.51 (0.59-3.86) for readmissions due to bleeding events and HR 1.39

(0.78-2.47) for death (table 5). There were 37 nonagenarians in the invasive group and 109 in the non-invasive group (table 2). In the group with severe renal failure (eGFR<30ml/min/1.73m^2), the invasive group had adjusted HR 0.84 (0.58-1.22) for the primary endpoint compared to those in the non-invasive group, adjusted HR 1.50 (0.66-3.39) for readmissions due to bleeding events and HR 0.88 (0.58-1.32) for death (table 5).

In the main analyses, patients had to be alive at discharge. The in-hospital mortality was 12.5% in the invasive group and 24.4% in the non-invasive group, adjusted HR 0.74 (0.57 - 0.94). Mortality during other time periods from admissions are in supplementary data. In all cases the mortality rate was lower in the invasive group.

Discussion

In this cohort study, we have shown that multimorbid older people with complex health needs and STEMI have high risk of new ischemic events and death during one-year after discharge. Invasive strategy lowered the risk for the primary endpoint of death and new ischemic events and did not increased risk of readmissions due to bleeding events. This is consistent with the results of randomized clinical trials in younger and healthier patients, and suggests that the results from those trials can be referred to this complex older patient population. The benefits of invasive strategy were neither found in the small group nonagenarians in this study nor in the group with severe renal failure.

Primary PCI in patients over 70 years old with STEMI decreases the risk of death, stroke and a new myocardial infarction compared to fibrinolysis (3, 16, 17). The patients in those trials did not have as much multi-morbidity as the patients in the current cohort study. We are not aware of randomized trials in patients with multi-morbidity, complex health needs and STEMI. A cohort study of 698 ACS patients, where 25% had STEMI, found PCI to increase survival relatively more in those who had more multi-morbidity and had been admitted the year before ACS. In the group with the highest risk score the mortality risk reduction was 74% (18). A cohort study in patients over 70 years of age in Switzerland with acute myocardial infarction during the period of 2001 - 2012, showed increasing age and more multi-morbidity during the last four years compared to the first four years. At the same time the use of primary PCI in STEMI increased in all age groups and the in-hospital outcomes improved (19). Another cohort study in octogenarians with STEMI from 2005 to 2011 also found increased multi-morbidity the last years without increase in mortality rates (20). In concordance with our results, those results suggest that increased multi-morbidity and complexity of patients do not attenuate the benefits of PCI in increasing survival and decreasing new ischemic events. Advancing age, frailty and multi-morbidity increase the risk for

bleeding events and other complications after PCI (20, 21). At the same time those conditions coexist with more CAD burden and higher baseline risk for new ischemic events and death (22-24). The higher baseline risk for new events and death causes the efficacy of invasive strategy in those with multi-morbidity to be relatively higher than in those without, and probably offsets the risk associated with the treatment.

The mortality rate after STEMI is highest during the first months, especially the first thirty days (25), in concordance with our results where the impact of invasive strategy was relatively highest during the first months. After nine months, the risk difference was not significant between the groups even if the hazard ratios from nine to twelve months remained the same. The widening of the confidence intervals is probably caused by the non-invasive group constituting only 570 patients with 45% one-year mortality. As the months went by, fewer patients remained alive in the non-invasive group for comparison.

Readmissions due to bleeding events were close to 10% in both groups, this is not considering the patients who experienced bleeding events during the index admission. A randomized trial in octogenarians with NSTE-ACS, showed similar rate of one-year bleeding events as the current study (26). The risk for bleeding events should be estimated for each older patient and the duration of dual antiplatelet therapy adjusted to the risk. In a trial of patients with mixed diagnoses of coronary artery disease, duration of dual antiplatelet therapy over one year was not superior to short duration of 3-6 months in those at high risk for bleeding events (27). The risk was measured using age, hemoglobin level, history of prior bleeding events, white cell blood count and eGFR. Another bleeding risk score used the same conditions but added female sex and STEMI/NSTE-ACS as a component. The risk for bleeding events for 30 days varied from 1-40% (28). In older people with high risk of bleeding events a concomitant use of proton pump inhibitors to reduce gastrointestinal bleeding events might be appropriate (29).

The annual risk for bleeding events requiring hospital admissions rises sharply in the oldest patient group. A study in patients receiving only ASA as secondary prevention found more than three-fold rate of bleeding events requiring hospital admissions in patients over 85 years old compared to 65-74 years old, and over half of the bleeding events were disabling (29). This is in concordance with our results showing a trend for increased risk of bleeding events in the nonagenarians. There was also a trend toward increased risk of death and the composite endpoint. All the confidence intervals are very wide, and there were only 37 nonagenarians in the current study in the invasive group which limits the interpretations of their results. These nonagenarians are not necessarily the average nonagenarians but those with complex health needs already at admission, further adding to their age- related high risk for bleeding events. With increasing renal failure, the incidence of bleeding events as well as ischemic events rises (30). In the current study, the patients with severe renal failure showed a trend

toward increased risk for readmission due to bleeding events, but at the same time they had a small trend toward lower risk for primary endpoint and death.

Multi-morbidity and prior hospitalizations are both predictors of readmissions in older people (31) which partly explains the high readmission rate in this study. Readmissions during one year in older patients with myocardial infarction have been reported over 40% (32), and in those with multi-morbidity up to 60% (33, 34). In a cohort of NSTE-ACS patients, revascularization did not decrease all cause readmissions, in concordance to our results for STEMI patients (34). We are not aware of randomized trials looking specifically at reducing readmissions in older patients with STEMI and complex health needs. Some studies in patients with frailty and/or complex health needs suggest that admitting them to acute elderly care units who use interdisciplinary based geriatric care reduce mortality, improve quality of life and possibly reduce the frequency of readmissions (35). Patients with STEMI and complex health needs need to be treated in specialized coronary care units, but a possible way to address their multiple problems is to develop an ambulatory geriatric consulting unit that sees the patients during admission and continues follow-up after discharge as has been tried in patients with complex health needs and general internal medicine problems (36).

Strength and limitations

This study provides information about a group that is rarely examined in clinical trials but often encountered in clinical practice. The main limitation is the non-randomized design; as the allocation to invasive or non-invasive strategy was based on clinical decisions and not randomization. The individuals with the highest risk for complications were probably not assigned to invasive strategy. We excluded the patients that died within the admission to compensate for this and extensively adjusted for confounding variables with a propensity score method. This decreases the selection bias but does not erase it. There are likely some clinical conditions that are not available in the registries and were therefore not corrected for. An example of this is the severity of frailty.

Conclusion:

Consistent with studies in younger and healthier patients, this observational study using data from Swedish Quality registries suggests that invasive strategy decreases the risk for new ischemic events and death in multimorbid older people with complex health needs. Future studies should focus on individual assessment of risk for bleeding events and how to decrease the high readmission rate. The treatment and risk stratification of the nonagenarians with complex health needs as well as older people with severe renal failure need to be studied in larger studies.

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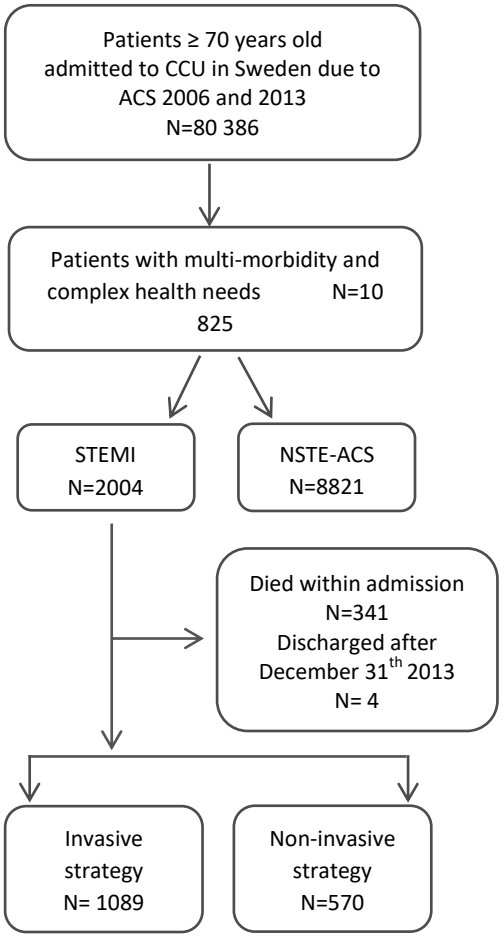
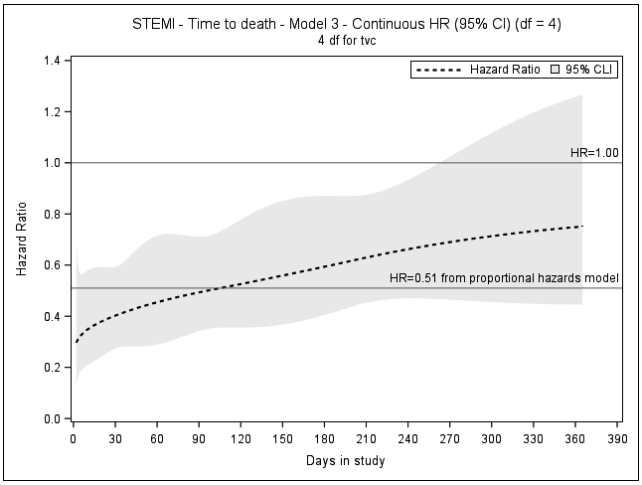
Figures and tables

Figure 1: Patient selection



Multimorbid older patient with complex health needs are defined by the Swedish National Board of Health and Welfares, using The Swedish National Inpatient Registry. An individual must meet criteria a-c) and either d), e) or f) at index date; a) be at least 65 years old b) be hospitalized at least three times with main diagnoses from at least two different ICD 10 chapters, c) at least one hospitalization must be within 12 months prior to index date, d) have more than 19 days of hospitalization or outpatient's visits to specialist clinics during the last 12 months before index date, e) have more than 3 hospitalizations during the last 12 months before index hospitalization or f) have more than 7 visits to specialist in outpatient care during the last 12 months before index date; ACS: acute coronary syndromes; CCU: coronary care unit; STEMI: ST-elevation myocardial infarction; NSTEMI: non-ST elevation myocardial infarction; UAP unstable angina pectoris; invasive strategy: coronary angiography performed ≤ 14 days of admission.

Figure 2: Continuous hazard ratio during one-year in multimorbid patients with STEMI



The figure shows the continuous hazard ratio (HR) for invasive strategy compared to non-invasive strategy during one-year obtained from flexible parametric survival analyses, Royston-Parmer model. HR (95% confidence interval) are as following: Day 10: 0.35 (0.21-0.58), day 60; 0.45 (0.29-0.71) day 90: 0.49 (0.34-0.71); day 120: 0.53 (0.36-0.78); six months: 0.59 (0.41-0.87); nine months 0.69 (0.46-1.03); and one-year: 0.75 (0.45-1.27).

Table 1. Patient characteristics in multimorbid older people with complex health needs and STEMI.

	Invasive group[g] (n=1089) **%**	**Non-invasive group** (n=570) %	**p-value**[i]
Age, years (±SD)[a]	5.7	6.2	<.0001
70-<80 years	55.9	26.0	
80-<90 years	40.7	58.2	<.0001
≥90 years	3.4	15.8	
Women	45.1	55.1	0.0001
Smoking status			
Not an active smoker	87.6	90.5	
Active smoker	12.4	9.5	0.14
Missing	n=95	n=130[b]	
Year of index date			
2006-2008	28.3	43.9	
2009-2011	12.9	40.5	<.0001
2011-2013	16.2	26.5	
Hypertension	58.6	61.9	0.21
Stroke	16.3	23.5	0.0006
Diabetes	25.2	29.1	0.094
COPD[c]	12.6	13.9	0.51
PVD[d]	6.8	12.3	0.0003
Cancer during the last year	21.9	24.2	0.30
Heart failure	19.9	35.8	<.0001
Anemia	16.6	29.5	<.0001
Atrial fibrillation	21.9	33.2	<.0001
Myocardial infarction	25.5	35.2	<.0001
eGFR ml/min/1.73m^2 (±SD)[e]	25.1	22.4	0.0004
≥90	9.9	4.7	
60≤eGFR<90	32.3	17.2	
30≤eGFR<60	45.3	54.9	
eGFR<30	12.5	23.2	
Missing	n=71	n=122	<.0001
CAD specific indexes[h]			
Low burden	16.7	3.3	
Moderate burden	12.2	5.6	
High burden	71.0	91.0	
Missing	n=68	n=90	<.0001

[a] SD: standard deviation; [b] missing values are not included in the denominator, if no value is given then there are no missing values; [c] COPD: chronic obstructive pulmonary disease; [d] PVD: peripheral vascular disease; [e] eGFR: estimated glomerular filtration rate, calculated with Cockcroft Gault formula; [f] CAD: coronary artery disease; [g] invasive strategy: patients who underwent coronary angiography ≤14 days; [h] CAD specific index: coronary artery disease specific index, see supplementary data; [i] for comparison between groups Fisher´s Exact test was used for dichotomous variables, the Mantel-Haenszel Chi square test was used for ordered categorical variables, Chi square was used for non-ordered categorical variables and Mann-Whitney U-test was used for continuous variables.

Table 2: Medications at admission and at discharge.

	Invasive group[a] (n=1089) %	**Non-invasive group** (n=570) %	p-value[b]
Admission			
ACE inhibitors[c]	22.5	28.6	0.0084
ARB[d]	17.0	13.1	0.046
Calcium antagonists	24.1	21.7	0.30
Beta-blockers	45.5	52.4	0.0090
Statins	31.3	30.6	0.81
Acetylsalicylic acid	40.0	49.4	0.0003
$P2Y_{12}$ receptor antagonist	7.5	8.5	0.56
Oral anticoagulants	8.1	11.3	0.042
Digitalis	4.2	9.2	0.0001
Long acting nitroglycerin	13.1	22.2	<.0001
Discharge			
ACE inhibitors	60.9	45.1	<.0001
ARB	17.6	13.4	0.031
Calcium antagonists	16.4	15.5	0.69
Beta-blockers	88.2	79.6	<.0001
Statins	83.8	47.2	<.0001
Acetylsalicylic acid	91.6	78.5	<.0001
$P2Y_{12}$ receptor antagonist	89.8	37.1	<.0001
Oral anticoagulants	10.3	10.4	1.00
Digitalis	6.2	7.4	0.40
Aldosterone blockers	10.0	10.2	1.00
Long acting nitroglycerin	15.3	32.5	<.0001

[a] Invasive strategy: patients underwent coronary angiography ≤14 days; [b] for comparison between groups Fisher´s Exact test was used for dichotomous variables, the Mantel-Haenszel Chi square test was used for ordered categorical variables, Chi square was used for non- ordered categorical variables and Mann-Whitney U-test was used for continuous variables; [c] ACE: angiotensin converting enzyme. Missing numbers are not included in the denominator, for other medications than aldodsteron blockers at discharge there were less than 20 missing in each group, for aldosterone blockers 482 were missing in non-invasive group and 759 in invasive group ; [d] ARB: angiotensin II receptor blockers.

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Table 3: Test between invasive vs non-invasive strategy with respect to variables included in the propensity score model.

Variable from the propensity score model	Invasive[a] vs non-invasive strategy adjusted p-value
Age	0.95
Gender	0.46
Year of index date	0.69
Heart failure	0.79
Anemia	0.34
Atrial fibrillation	0.66
Prior myocardial infarction	0.41
Prior PCI[b]	0.11
Renal disease[c]	0.84
CAD specific index[d]	0.37
Medications at admission	
ACE inhibitors[e]	0.41
ARB[f]	0.049
Beta-blockers	0.19
ASA[g]	0.55
Oral anticoagulants	0.74
Digitalis	0.28
Long-acting nitroglycerin	0.49

[a] Invasive strategy: patients underwent coronary angiography ≤14 days, continuous variables are tested by using t-test and categorical variables by using Chi-square test weighting the individuals by the inverse probability of receiving the treatment that they actually received; [b] PCI: percutaneous coronary intervention; [c] Renal disease was estimated glomerular filtration rate (eGFR), calculated with Cockcorft Gault formula in ml/min/1.73 m^2, groups were eGFR≥ 90, 30≤eGFR<60, eGFR≤30 and eGFR=unknown [d] CAD specific index: coronary artery disease specific index; [e] ACE: angiotensin converting enzyme; [f] ARB: angiotensin receptor blockers; [g] ASA: acetylsalicylic acid.

Table 4: Invasive strategy compared to non-invasive strategy in multimorbid older patients with complex health needs and STEMI.

	Invasive group[a] (n=1089) %	Non-invasive group (n=570) %	Invasive vs non-invasive strategy HR (95% CI)[b] Model 1[c]	Model 2[c]	Model 3[c]
Primary event					
Primary endpoint (death, ACS, Stroke or TIA)[d]	30.9	54.6	0.56 (0.47 - 0.68)	0.67 (0.54 - 0.83)	0.67 (0.54 - 0.83)
Secondary events:					
Readmission due to a bleeding event	8.3	11.2	0.67 (0.45 - 0.97)	0.66 (0.43 - 1.02)	0.66 (0.43 - 1.02)
Death[e]	17.7	44.9	0.42 (0.33 - 0.52)	0.51 (0.40 - 0.66)	0.51 (0.39 - 0.65)
Readmission due to ACS	12.9	16.1	0.76 (0.55 - 1.03)	0.76 (0.53 - 1.09)	0.76 (0.54 - 1.09)
Readmission due to stroke/TIA	4.3	5.1	0.91 (0.53 - 1.57)	0.74 (0.40 - 1.37)	0.74 (0.40 - 1.37)
Readmission due to heart failure	11.8	15.3	0.80 (0.58 - 1.10)	0.88 (0.61 - 1.26)	0.88 (0.61 - 1.26)
Any readmission	69.8	70.8	0.86 (0.75 - 0.99)	0.88 (0.75 - 1.03)	0.88 (0.75 - 1.03)

[a] Invasive strategy: patients underwent coronary angiography ≤14 days; [b] HR: hazards ratio, CI: confidence interval; [c] model 1: Cox regression, adjusted for age, sex and propensity scores; model 2: model 1, additionally adjusted for medications at discharge that significantly differed between the treatments (angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, diuretics, statins, Acetylsalicylic acid, $P2Y_{12}$ antagonist and long acting nitrates), model 3: model 2 additionally adjusted for variables included in propensity score for which balance between the groups was not achieved; [d] ACS: acute coronary syndromes, TIA: transient ischemic attacks; [e] The criterias for proportional hazards assumption in Cox regression were not met for this endpoint, the endpoint was further analyzed in flexible parametric survival analyses to look at continuous HR, see figure 2.

Table 5: The effects of invasive versus non-invasive strategy in different subgroups of patients with STEMI

	Subgroup	Invasive vs non-invasive strategy HR (95% CI)[b]	p-value for interaction[c]
Primary event (death, ACS, Stroke, TIA)[a]	70-79 years	0.61 (0.45-0.97)	
	80-89 years	0.62 (0.48-0.80)	.012
	≥90 years	1.57 (0.93-2.64)	
	Men	0.57 (0.44-0.75)	
	Women	0.76 (0.59-0.99)	.07
	eGFR ≥90ml/min/1.73m^2	0.62 (0.30-1.29)	
	60≤ eGFR <90	0.41 (0.28-0.62)	
	30≤ eGFR <60	0.73 (0.56-0.96)	.049
	eGFR < 30	0.84 (0.58-1.22)	
	eGFR unknown	0.50 (0.29-0.84)	
Readmission due to a bleeding event	70-79 years	0.42 (0.23-0.77)	
	80-89 years	0.73 (0.42-1.25)	.048
	≥90 years	1.51 (0.59-3.86)	
	Men	0.77 (0.44-1.35)	.39
	Women	0.58 (0.34-0.98)	
	eGFR ≥90 ml/min/1.73m^2	0.40 (0.23-0.77)	
	60≤ eGFR <90	0.30 (0.14-0.66)	
	30≤ eGFR <60	0.75 (0.43-1.32)	.018
	eGFR < 30	1.50 (0.66-3.39	
	eGFR unknown	0.20 (0.04-0.90)	
Death	70-79 years	0.34 (0.23-0.48)	
	80-89 years	0.55 (0.40-0.74)	.0022
	≥90 years	1.39 (0.78-2.47)	
	Men	0.36 (0.26-0.50)	
	Women	0.67 (0.49-0.90)	.0016
	eGFR ≥90 ml/min/1.73m^2	0.21 (0.08-0.51)	
	60≤ eGFR <90	0.23 (0.14-0.38)	
	30≤ eGFR <60	0.56 (0.40-0.78)	<.0001
	eGFR < 30	0.88 (0.58-1.32)	
	eGFR unknown	0.31 (0.15-0.61)	

Patients who underwent coronary angiography ≤14 days constituted the invasive strategy; [a] ACS: acute coronary syndromes, TIA: transient ischemic attack; [b] Cox regression, adjusted for age, sex, propensity score, medications at discharge (angiotensin-converting enzyme inhibitors at admission, medication angiotensin receptor blockers, diuretics, statins, Acetylsalicylic acid, $P2Y_{12}$ antagonist and long acting nitrates) and for variables included in propensity score for which balance between the groups was not achieved (angiotensin receptor blockers at admission). [c] Interactions between treatment group and subgroup. For following outcomes, the interactions between the subgroups and treatment group were not positive (lowest p was .21) admission due to heart failure, ACS, stroke/TIA or any cause. Those results can be found in supplementary data.

Paper IV

Age Comes to PCI – Cardiac Catheterizations in Nonagenarians during 2006-2014

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MeSH terms: Aged, 80 and over; coronary angiography; percutaneous coronary intervention; registries.

Keywords: nonagenarians, CA, PCI, complications, temporal changes

Structured abstract

Background: The Western nonagenarian population is growing and more coronary angiographies (CA) and percutaneous coronary interventions (PCI) are being performed on these aged individuals. The objective of this study is to analyze the indications, treatment decisions and outcomes of all cardiac catheterization in nonagenarians in Sweden over the course of nine years; and to describe the temporal changes in practice.
Methods and results: All consecutive CA and PCI performed in Sweden are prospectively registered in the Swedish Coronary Angiography and Angioplasty Registry (SCAAR). The database was used to analyze indications, treatment decisions and outcomes among all patients 90 years or older between 2006-2014. A total of 1692 nonagenarians underwent 1874 catheterizations over the study period. Acute coronary syndrome was the indication for 80% of CAs and 95% of PCIs. Mean estimated glomerular filtration rate (eGFR) in nonagenarians was 40.0 ml/min/1.73m^2 (SD+/- 13.2) and 93% had eGFR <60ml/min/m^2. Significant stenosis was found in 87% of nonagenarians and 62% had multi-vessel disease. The lesion complexity was B2 or C in 63%, multi-vessel PCI was performed in 16% and complete revascularization achieved in 37%. The PCI was considered successful in 90%. In-hospital complications after PCI were reported in 8% of nonagenarians and in-hospital mortality was 8%. In-hospital complications after CA were reported in 4%. Renal failure was reported in one nonagenarian, after CA.

Conclusions: Almost all nonagenarians who underwent CA had coronary pathology; where they had a high level of multi-vessel disease and high lesion complexity. This, along with acute indications and multimorbidity, might explain partly the complication rate. Future studies should focus on finding prognostic factors to help clinicians select patients for invasive investigations and procedures, who will gain the most at the least possible risk.

Introduction

The western population is aging and it is estimated that 19 million Americans will be 90 years and older in 2050, the equivalent of about 10% of the population (1). In 2008 a Dutch cardiologist named Waltenberger wrote: “PCI comes to age as age increasingly comes to PCI” (2). This has been apparent in Sweden where the age of patients undergoing cardiac catheterizations has been steadily rising; and in 2011 around 15% of the patients being invasively investigated and treated with coronary angiographies (CA) and percutaneous coronary interventions (PCI) were over 80 years old (3).
In the trials comparing PCI and fibrinolysis in patients with ST-elevation myocardial infarction (STEMI), three trials specifically included patients 75 years old and older. Using pooled data from those trials, the conclusion was that PCI outperformed fibrinolysis in older people (4-6). There are recent trials of patients over 75 years or 80 years old with non-ST-elevation acute coronary syndromes (NSTE-ACS) comparing early invasive therapy to conservative therapy (7-9). The After Eighty study is the only randomized trial in older people so far that has published separate data for nonagenarians. They concluded that the effects of invasive therapy could not be determined in those over 90 years of age, due to how few patients of that age were included (n=34) (8). Some cohort studies have studied the feasibility and safety of PCI in STEMI and NSTE-ACS in selected nonagenarian populations (10-14), but more data is needed.

The aim of this study is firstly to analyze indications, treatment decisions and outcomes of cardiac catheterization in nonagenarians; secondly to describe the temporal changes in practice during the nine years.

Methods

This is a nationwide prospective cohort study in all patients 90 years of age and older which underwent CA with or without PCI in Sweden between January 1st 2006 and December 31st 2014. Patients were identified through the national Swedish Coronary Angiography and Angioplasty Registry (SCAAR). SCAAR is a part of the

Swedish Web-system for Enhancement and Development of Evidence-based care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART). SCAAR holds data on all patients that undergo CA and/or PCI in all 31 invasive centers in Sweden. The registry includes demographic, clinical, angiographic and procedural data. It also records in-hospital outcomes. The data is in accordance with The Cardiology Audit and Registration Data Standards for clinical cardiology practice. Based on the unique 10-digit personal identification that all Swedish citizens have the SCAAR database is merged with the national population registry to obtain the date of death of the participants (15). For patients in the coronary care unit (CCU) additional information regarding weight, height and creatinine and vital parameters was collected from another registry in SWEDEHEART.

Definitions

A significant stenosis was defined as at least 50% diameter reduction in cross sectional diameter in a major epicardial artery or a graft from coronary artery bypass grafting (CABG). Multi-vessel PCI is defined as PCI where at least two segments were treated. Procedural success after PCI treatment of the coronary lesion is defined as residual stenosis <50%, decreased grade of stenosis after intervention by at least 20%, normal blood flow and no serious complications. Glomerular filtration rate (GFR) was calculated with Cockcroft Gault formula and is presented as estimated GFR (eGFR). Total complications included complications reported directly from the Catheterization laboratory and complications reported from the CCU (see complete list in online data supplements). In-hospital major bleeding events were defined as any bleeding event before discharge associated with a hemoglobin drop of ≥5 g/dL, intracranial bleeding, or the need for blood transfusion. Any bleeding event is a combined variable of: an access site hematoma >5cm, hemoglobin fall >2g/L, prolonged compression time, prolonged stay in hospital over 1 day, ultrasound performed due to a bleeding event, a bleeding event requiring surgical treatment and major bleeding events. ACS included both STEMI and NSTE-ACS. NSTE-ACS included both unstable angina pectoris and non-ST-elevation myocardial infarctions. Lesion complexity was defined according to the American College of Cardiology/American Heart Association as A, B1, B2 or C, see description in appendix (16). Treatment decision of PCI was defined as patient assigned to PCI by angiographer at the time of CA plus one of the following: PCI was performed during the index catheterization, PCI was performed during another catheterization but within index admission, PCI was performed during another admission within 30 days after index catheterization with an acute indication or PCI was performed within 90 days after index catheterization with stable angina as an indication. All PCIs other than the ones performed directly after CA were manually reviewed to exclude that they were due to new acute episodes. The CABG group was defined as patients assigned to CABG by the angiographer at the time of CA subtracting those with ACS who underwent PCI.

Statistical analyses

Descriptive statistics were used to show comorbidities, clinical characteristics, treatment decisions and outcomes. Categorical variables are displayed as frequency and percentages. Continuous variables are displayed as mean (+/- standard deviation) for variables with near normal distribution. Continuous variables that do not have normal distribution are shown as median (interquartile range). Relative survival of the nonagenarian population undergoing catheterizations was compared to the survival of the general nonagenarian population in Sweden for years 2006-2014. Age, gender, and intervention year mortality rates for the general population were obtained from life tables of Statistics Sweden. The relative survival was estimated from start to 1 month, 1 month to 1 year, 1-2 years and 2-3 years intervals. Analyses were performed using IBM SPSS version 25, except for age standardization which was performed in SAS version 9.4.

Ethics

A written informed consent for entering patient data into SCAAR is not required in Iceland or Sweden, but patients are made aware of the database and its use and can decline participation. The Data Protection authority in Iceland and the National Bioethics committee in Iceland approved the study, permission numbers 2008040331 and 08-087 as did the Ethical Committee in Uppsala Sweden, permission number Dnr 2015/272.

Results

During the study period, 1692 nonagenarians underwent a total of 1874 catheterizations (CA +/-PCI). During index admission, 551 underwent CA only and 1141 underwent both CA and PCI (figure 1). The results shown in this article are for catheterizations and decisions that were made during index admission.

Clinical characteristics, indications and results of index angiography

The median age during the index catheterization was 91.0 years (Interquartile range (IQR) 90-92). Out of 1692 patients, 24.0% were 93-100 years old (figure 2). Majority of patients, 56.9% were women, 2.1% were active smokers, but the majority was treated for hypertension. Over a third of the patients had previously had a myocardial infarction. The mean eGFR was 40.0 ml/min/1.73m^2 and 93.0% had eGFR under 60 ml/min/1.73m^2 (table 1).

In 79.5% of nonagenarians ACS was the indications for CA; 4.7% of nonagenarians had stable angina as an indication and 15.8% had other indications. Most nonagenarians, 86.9%, had significant stenosis in at least one coronary artery, and 62.2% had multi-vessel disease (table 2).

Treatment decisions

Of 1692 nonagenarians, 65.5% underwent PCI during the same catheterization as CA, and 2.0% underwent PCI later during the admission. Other treatment decisions were CABG in 1.1%, PCI during another admission in 2.0% and no invasive treatment in 28.9% (figure 1).

Procedural characteristics of PCI

Indications for the 1141 index PCIs were STEMI in 58.9%, NSTE-ACS in 35.5%, stable angina in 4.1% and other indications in 1.5%. The PCI was considered successful in 89.9% of cases and complete vascularization was achieved in 36.6%. Multi-vessel PCI was performed in 15.6% of patients and in 63.0% the lesion complexity was B2 or C (16). Complete revascularization was achieved in 36.7%. Stents were used in 87.5% of PCIs in nonagenarians and drug-eluting stents (DES) in 32.2% (table 3).

In-hospital outcomes and mortality

In-hospital complications after PCI were 7.7%. Serious bleeding events and neurological complications were rare, 0.7% and 0.6% respectively. In-hospital complications after CA were 4.1%. Renal failure was only reported in one out of 1692 nonagenarians. In-hospital mortality was higher in the group that underwent PCI than the group who underwent CA (table 4).

One-year mortality among the 1193 nonagenarians who underwent revascularization with either PCI or CABG was 32.6%. One-year mortality in the 499 nonagenarians who did not undergo revascularization was 29.9%. Compared to Swedish nonagenarian population, mortality was higher in the nonagenarians undergoing catheterization (figure 3).

Temporal trends in catheterizations

The number of catheterizations per 100 000 nonagenarians increased from 98/100 000 in 2006 to 343/100 000 in 2014 (figure 4). The proportion of catheterizations due to stable angina remained the same. Other indications were 6.3% during 2006-2009, and 19.8% during 2012-2014 (figure 5).

The success of PCI remained the same during the study period (figure 6). Use of any $P2Y_{12}$ antagonists increased and has remained over 92.7% since 2012. Use of radial access increased and was over 60% during the last four years. Ticagrelor was first given to nonagenarians undergoing PCI in 2011 and was given to 62.9% in 2014. Use of Glycoprotein IIb/IIIa inhibitors (GP IIb/IIIa inhibitors) decreased over the course of the study. Stents use remained unchanged over 84% during the nine years. DES use first declined from 21.3% in 2006 to 5.0% in 2007 but started to increase after 2009 and in 2014, DES were used in 68.5% of PCIs. Temporal trends for other procedural characteristics as well as clinical characteristics and outcomes are shown in online data supplements.

Discussion

Nonagenarians undergoing catheterizations are increasing in numbers, the reason may be widening of indications and operators feeling comfortable accepting patients at this high age. Almost all nonagenarians who underwent CA had coronary pathology, and they had high level of multi-vessel disease and lesion complexity. Many still had a significant stenosis after PCI. The main indications for PCI in nonagenarians were ACS (STEMI: 59% and NSTE-ACS:36%), which alongside the comorbidity burden and extent of CAD might partly explain in-hospital complication rate of 8% and mortality rate of 8%.

ACS was the most common indication for CA and PCI in all age groups in Sweden in 2007, but the proportion of acute indications was still lower than in nonagenarians in the present study. ACS was the indication for 56% of CAs and 73% of PCIs. One third of the patients did not have significant stenosis and 43% had multi-vessel disease (17). The burden of coronary artery disease (CAD) was considerably higher in the nonagenarians in this study.

We found the complication rate, in this very elderly cohort, after CA or PCI to be acceptable. The high age itself is a marker for high mortality and a more complex hospitalization. Our finding of 8% in-hospital complications after PCI is in concordance with some studies of nonagenarians (18). Many studies have shown a higher rate of in-hospital complications in nonagenarians undergoing PCI, around 13-17% (19-21). The comorbidity burden and the proportions of patients in cardiogenic shock varies between these studies and largely explains the discrepancy.

Studies of octogenarians and nonagenarians with ACS, have found the frequency of renal failure to vary from 2% to 23% (22-24), which is much higher than in the present study. The frequency of renal failure after PCI is mostly dependent on baseline eGFR and comorbidities. In a randomized trial of 75 years old and older with NSTE-ACS, creatinine increased in 21% of patients with baseline eGFR 30-60ml/min/m^2 and in 40% of those who had eGFR under 30ml/min/m^2 (23). Even a small absolute increase in creatinine after myocardial infarction has been associated with worse prognosis (25). As 93% of the nonagenarians had eGFR under 60ml/min/m^2, it can be assumed that the renal failure reported in SCAAR only refers to the most serious cases and is under-reported.

The mortality in nonagenarians undergoing catheterizations varies immensely between studies; in-hospital mortality from 7% -27% (12, 22, 26, 27), and one-year mortality 20%-47% (19, 22, 27, 28). Mortality in our study falls within this range. The proportion of nonagenarians in cardiogenic shock varies from 1-21%, and alongside with the different proportion of patients with STEMI probably explains these differences (13, 22, 26).

During the period of 2006 - 2014 there were advancements in medical and invasive treatment for coronary heart disease. The use of DES increased to 69%, radial access increased to 63% and ticagrelor generally replaced clopidogrel. There are at least two randomized trials comparing DES and bare-metal stents in 75-80 years old and older, showing lower rates of nonfatal myocardial infarction, in stent thrombosis and target vessel revascularization (29, 30) and decreased mortality (29). One large cohort study of the very elderly found the benefits associated with DES use to be present in this group without an increase in bleeding events (31). Ticagrelor was compared to clopidogrel in the PLATO trial and reduced ischemic outcomes and mortality in a sub analysis of 75 years old and older (32). One of the conclusions was that ticagrelor was more effective in the full age range up to 95 years old. In all age groups, there was a small non-significant trend for increased risk of bleeding. The absolute number of 85-90 years old and older was not published (32), which diminishes the strength of evidence in the oldest group. The radial approach has been shown to decrease major access site complications in patients who are 75 years old and older (33). There are no randomized trials of nonagenarians but the lower rate of complications with the radial approach supports its use in this population.

In nonagenarians with CAD, clinicians need to carefully weigh the benefits and risk of invasive procedures and medical treatments. The approach should be individualized and focused on improving quality of life. Risk scores can help in tailoring treatment and are now part of the European Society of Cardiology guidelines for NSTE-ACS (34). The individual life expectancy should be considered, along with renal function, frailty, comorbidity burden and both cognitive and functional impairment (34, 35).

Strengths and limitations:

This study presents contemporary data for a large cohort of nonagenarians in which all patients undergoing catheterizations from all centers in Sweden during nine years are included. The study has several limitations. There were missing variables. The current study only included invasively treated patients, which limits the generalizability of our results. We did not know the ratio of invasively investigated nonagenarians to those who were conservatively treated. A bias regarding selective referral of "healthier" older people is probable. Nevertheless, real world registry studies remain important to study clinical outcomes and practices in populations under-represented in clinical trials.

Conclusions

Almost all nonagenarians who underwent CA had coronary pathology, and they had high level of multi-vessel disease and lesion complexity. This, along with acute indications and multimorbidity, might explain partly the complication rate. Future studies should focus on finding prognostic factors to help clinicians select patients for invasive investigations and procedures, who will gain the most at the least possible risk. Furthermore, renal failure after catheterizations in older people need to be better registered in SCAAR.

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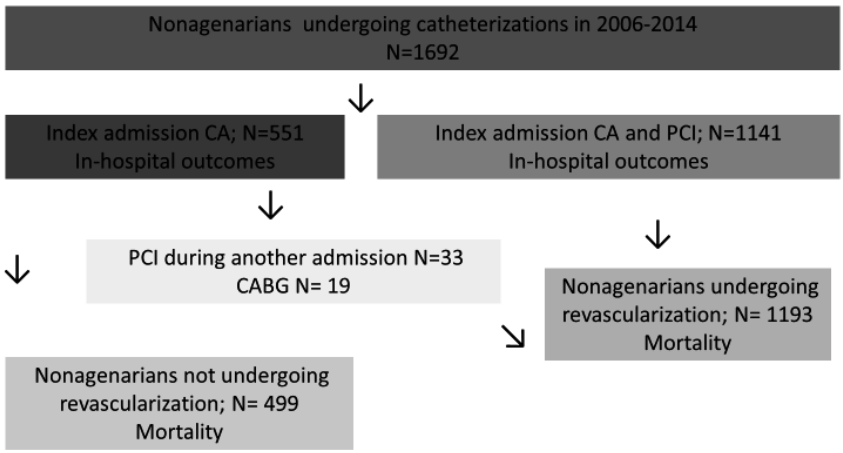
Figures

Figure 1: Nonagenarians undergoing cardiac catheterizations during 2006-2014 in Sweden.



CA: coronary angiography, PCI: percutaneous coronary intervention. Of the 1141 PCI's performed during index admission 33 were performed during another catheterization.

Figure 2: Age distribution at index catheterization (coronary angiography +/- percutaneous coronary intervention).

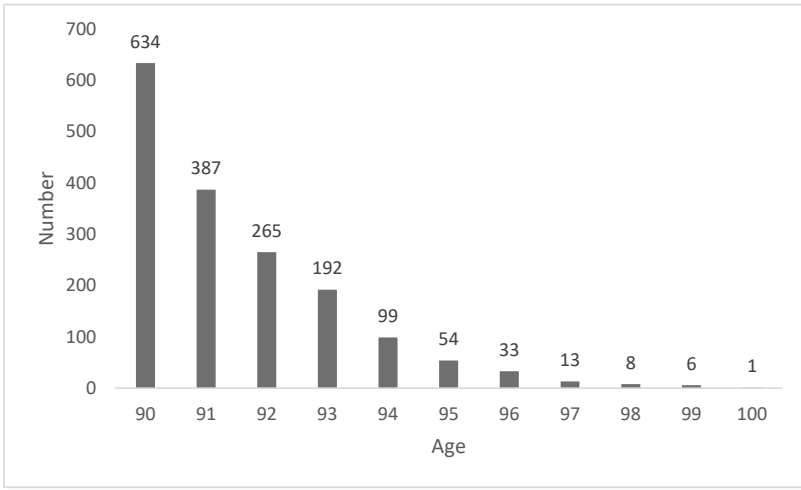


Figure 3: Relative survival of the nonagenarian population undergoing catheterizations compared to the survival of the general nonagenarian population in Sweden for years 2006-2014.

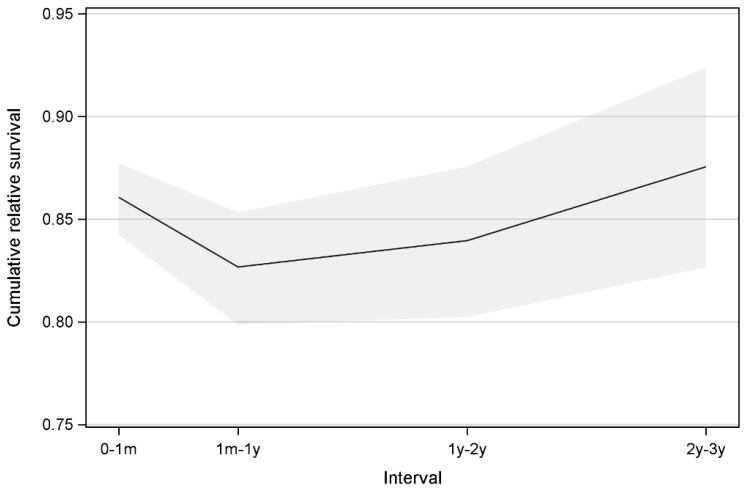


Figure 4: Number of cardiac catheterizations per year and 100.000 alive nonagenarians in Sweden and the number of nonagenarians each year. Index catheterization.

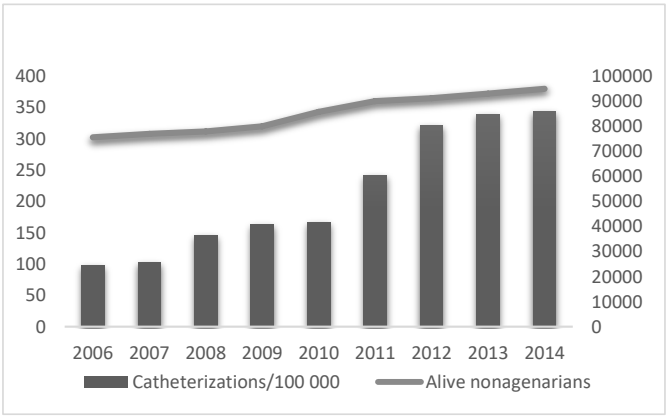
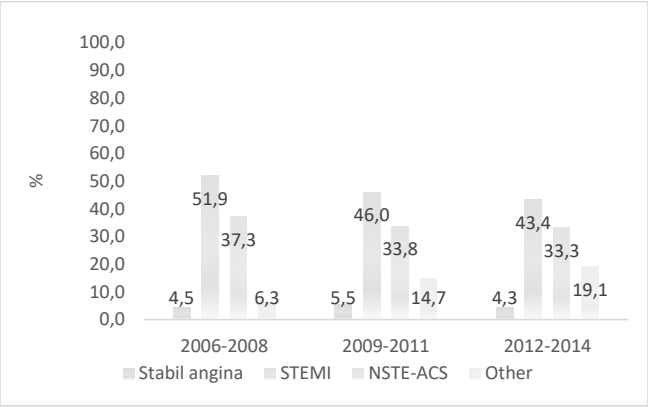
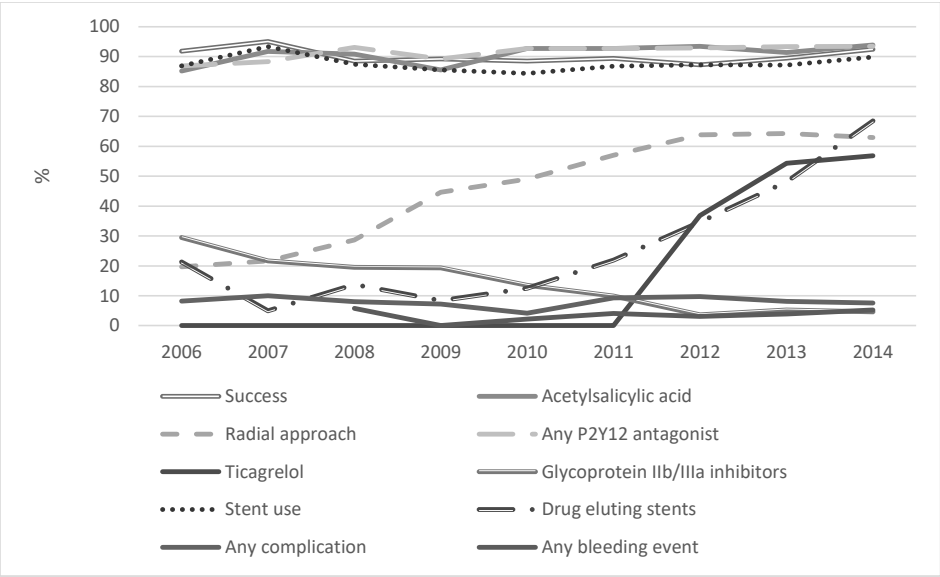


Figure 5: Indications for catheterizations in nonagenarians during 2006-2014.



STEMI: ST-elevation myocardial infarction. NSTE-ACS: Non-ST elevation acute coronary syndromes. Of other indications 86% are investigation of valvular disease and the rest are: atypical chest pain, cardiomyopathy, arrhythmias and cardiac arrest.

Figure 6: Temporal changes in procedural characteristics in nonagenarians undergoing percutaneous coronary interventions during 2006-2014, index PCI.



Bleeding events in hospital were redefined 2008 and are not available for 2006 and 2007.

Tables

Table 1: Clinical characteristics at first cardiac catheterization.

	N=1692 %	Missing %
Age, median (range)	91.0 (90-100)	0
Female gender	56.9	0
Diabetes	13.5	1.1
Treated hypertension	65.1	4.1
Lipid lowering therapy	30.4	5.4
Known coronary artery disease		
Previous MI[*]	32.8	4-1
Previous CABG[†]	6.3	0
Previous PCI[‡]	11.1	0
Smoking status		
Ex-smoker	24.2	13.7
Current smoker	2.1	
Cardiogenic shock	4.7	10.9
Body mass index, kg/m^2, mean (SD)[§]	23.9 (+/- 3.4)	
≤18.5	3.8	
18.6-24.9	83.9	12.3
25≥	12.3	
eGFR, ml/min/1.73 m^2, mean (SD)[‖]	40.0 (+/- 13.2)	
<30	21.0	11.2
30-60	60.4	
> 60	7.3	
Not staying in a coronary care unit	23.1	0
Index catheterization		
CA only[¶]	32.5	0
CA and PCI[#]	67.5	

[*]MI: myocardial infarction. [†]CABG: coronary artery bypass grafting. [‡]PCI: percutaneous coronary intervention. [§]BMI: body mass index, SD: standard deviation. [‖]eGFR: glomerular filtration rate, calculated with Cockcroft Gault formula. [¶]CA: coronary angiography. [#]Of those 33 PCI were performed during another catheterization within index admission.

Table 2: Indication and outcomes of index coronary angiography.

		N=1692 %
Indications	STEMI*	45.5
	NSTE-ACS†	34.0
	Stable angina	4.7
	Other‡	15.8
Outcomes	Normal/atheromatous	13.1
	One-vessel disease	24.7
	Two-vessel disease	22.3
	Three-vessel disease	26.2
	Left main stem stenosis	13.7

*STEMI: ST-elevation myocardial infarction, †NSTE-ACS: non-ST elevation acute coronary syndromes. ‡Of other indications, 86.0% were investigations due to valvular disease planned to be operated by trans-catheter aortic valve implantation, or in some cases an open-heart surgery.

Table 3: Procedural characteristics.

	N=1141 %
Lesion complexity B2 or C	63.0
Multi-vessel PCI*	15.6
Another segment treated with second PCI†	1.8
Complete revascularization	36.7
Target vessel was LAD‡	43.6
Target vessel was left main stem	7.0
Stent use	87.5
Drug eluting stents	32.2
Number of stents placed 2 or more	33.6
Procedural success	89.8
Complete revascularization	36.4
Acetylsalicylic acid	91.7
Glycoprotein IIb/IIIa inhibitors	10.5
Any P2Y12 antagonist before PCI	92.1
Ticagrelor	25.1
Radial approach	52.9

*PCI: percutaneous coronary interventions. Multi-vessel PCI: at least two segments were treated. †There was a second PCI performed on another segment within 31 days from index PCI. ‡LAD: left anterior descending artery. Missing values are less than 2.5% and are not included in denominator.

Table 4: In-hospital complications.

	PCI* N=1141 %	CA† N=551 %
Any complication‡	8.1	4.1
Any bleeding event	3.7	2.6
Serious bleeding events	0.7	0.2
Any neurological complication	0.6	0.2
Hemodynamic complication in the Cath-lab	1.4	0.2
Treated arrhythmias in the Cath-lab	1.1	0.2
Pseudo aneurysm	0.3	0.0
Renal failure	0.0	0.2
Mortality	7.7	2.4

*PCI: percutaneous coronary intervention. †CA: coronary angiography, Of the 1141 PCIs 33 were not performed directly after CA but during another catheterization within index admission. ‡Except for in-hospital mortality, missing values are less than 2.5% and are not included in denominator. Missing values for in-hospital mortality were 2.9%.

Appendix 1

Previous diseases collected from the Swedish National Patient Registry

Disease	ICD-10	ICD-9
Hypertension	I10- I14	401-405
Heart failure	I50	428
Renal disease	N17-N19	585-587
Stroke	I63, I64	433, 434
Transient ischemic attack	G45	435
COPD[a]	J43, J44	490-492
PVD	I70.2, I73.9	440.2, 443.9
Cancer and lymphoma	C00-C75, C81-C97, D00-D48	140-189, 200-239
Cancer with metastases	C76-C80	190-197
Anemia	D50-D64	280-285
Dementia	F00-F03, G30, G31, F10.7	290, 331
Atrial fibrillation	I48	427.3
Rheumatological disease	M00-M14, M30-M36, M45, M46, M49	710-714, 720, 725
Rheumatic fever	I01	391
Rheumatic heart disease	I05-109	393-298
Heart disease	I20-I25	410-414
DM type 1 without sequele	E11.9	250.00, 250.02
DM type 2 without sequele	E10.9	250.03, 250.01
DM type 1 with sequele	E11.1-E11.8	250.11, 250.13, 250.21, 250.23, 250.31, 250.33, 250.41, 250.43, 250.51, 250.91
DM type 2 with sequele	E10.1-E10.8	250.10, 250.12, 250.20, 250.22, 250.30, 250.32, 250.40, 250.42, 250.50, 250.90
DM other	E12-E14	249
Hyperlipidemia	E78	272

In unpublished data for older people with ACS, Paper III and unpublished data for multi-morbid older people with complex health needs and NSTE-ACS, previous diseases which were collected from the National Patient Registry were defined as hospitalizations with following International Statistical Classification of Diseases, 10th revision (ICD-10) or ICD-9 codes as main or secondary diagnoses. Cancer, leukemia and lymphoma were collected within three years before index admission and other diagnoses as far back as the registry goes. [a]COPD: chronic obstructive pulmonary disease; [b]PVD: peripheral vascular disease; [c]DM: diabetes mellitus.

Appendix 2
One-year outcomes in Paper III and unpublished data

In unpublished data for older people with ACS, Paper III and unpublished data for multi-morbid older people with complex health needs and non-ST-elevation acute coronary syndromes, one-year outcomes were collected both from the Swedish National Patient Registry and from RIKSH-HIA.

The following diagnose codes were collected from the National Patient Registry

Outcome	ICD-10
Readmission due to ACS[a]	I21, I22, I23, I20.0, I20.1
Readmission due heart failure	I50
Readmission due to ischemic stroke	I63, I64
Readmission due to TIA[b]	G45
Readmission due to bleeding events[c]	D62.9, D50.0, H11.3, H31.3, H35.6, H43.1, H45.0, H92.2, I60, I61, I62, I85.0, I98.3, J94.2, K22.6, K250, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.2, K27.4, K27.6, K28.0, K28.2, K28.4, K28.6, K29.0, K62.5, K66.1, K92.0, K92.1, K92.2, M25.0, N02, N50.1A, N93.9, N95.0, R04.1, R042, R04.8, R04.9, R319, R58, S063, S064, S065, S066, T810[c]

[a]ACS: acute coronary syndromes; [b]TIA: transient ischemic attack, [c]International Statistical Classification of Diseases, 10th revision (ICD-10) codes for bleeding events are according to Friberg et al. (2016).

Appendix 3
Matching with propensity scores in Paper III and unpublished data

Patients with ST-elevation myocardial infarction receiving invasive strategy matched with those who did not in Paper III. Test between invasive vs. non-invasive strategy with respect to variables included in the propensity score model by weighting the individuals by the inverse probability of receiving the treatment that they received.

Variable from the Propensity score model	Invasive vs. non-invasive group[h] adjusted p-value
Age	0.95
Gender	0.46
Year of index date	0.69
Heart failure	0.79
Anemia	0.34
Atrial fibrillation	0.66
Prior AMI[a]	0.41
Prior PCI[b]	0.11
Renal disease[c]	0.84
CAD-specific index[d]	0.37
Medications at admission	
ACE-I[e]	0.41
ARB[f]	0.049
Beta-blockers	0.19
ASA[g]	0.55
Oral anticoagulants	0.74
Digitalis	0.28
Long-acting nitroglycerin	0.49

[a]AMI: acute myocardial infraction; PCI: percutaneous coronary intervention; [c]renal disease was estimated glomerular filtration rate (eGFR), calculated with Cockcroft Gault formula in ml/min/1.73 m^2, groups were eGFR≥ 90, 30≤eGFR<60, eGFR≤30 and eGFR=unknown [d]CAD-specific index: coronary artery disease specific index; [e]ACE-I: angiotensin-converting enzyme; [f]ARB: angiotensin II receptor blockers; [g]ASA: acetylsalicylic acid; [h]Invasive strategy: patients underwent coronary angiography ≤14 days, continuous variables are tested by using t-test and categorical variables by using Chi-square test weighting the individuals by the inverse probability of receiving the treatment that they actually received.

Patients with non-ST-elevation acute coronary syndromes receiving invasive strategy matched with those who did not, unpublished data.

Variable from the Propensity score model	Invasive[h] vs. non-invasive group adjusted p-value
Age	0.0048
Gender	0.57
NSTEMI/UAP[a]	0.38
Year of index date	<.0001
Heart failure	0.70
Anemia	0.11
Atrial fibrillation	0.52
Prior AMI[b]	0.11
Previous PCI[c]	0.72
Renal disease[d]	0.042
CAD-specific index[e]	0.91
Medications at admission	
ARB[f]	0.62
Beta-blockers at admission	0.060
ASA[g]	0.
Statins at admission	0.0002
Other antiplatelet inhibitors	0.013
Digitalis at admission	0.16
Long-acting nitroglycerin	0.011

[b]NSTEMI: non-ST-elevation myocardial infarction, UAP: unstable angina pectoris; [b]AMI: acute myocardial infraction; [c]PCI: percutaneous coronary intervention; [d]renal disease was estimated glomerular filtration rate (eGFR), calculated with Cockcroft Gault formula in ml/min/1.73 m^2, groups were eGFR≥ 90, 30≤eGFR<60, eGFR≤30 and eGFR=unknown, [e]CAD-specific index: coronary artery disease specific index; [e]ARB: angiotensin II receptor blockers; [g]ASA: acetylsalisyclic acid; [h]Invasive strategy: patients underwent coronary angiography ≤14 days, continuous variables are tested by using t-test and categorical variables by using Chi-square test weighting the individuals by the inverse probability of receiving the treatment that they actually received.

Appendix 4
Lesion classification in Paper IV

Per Ryan T.J. et al. (1988):

Type A: <10mm, discrete, concentric readily accessible, <45-degree angle smooth contour, little or no calcification, less than totally occluded, not ostial, no major side branch involvement, absence of thrombus.

Type B1: One of the following characteristics: 10-20mm, eccentric, moderate tortuosity of proximal segment, irregular contour, presence of any thrombus grade, moderate or heavy calcification, total occlusion <3 months old, ostial lesion or bifurcation lesion requiring two guidewires.

Type B2: Two or more of the following characteristics: 10-20mm, eccentric, moderate tortuosity or proximal segment, irregular contour, presence of any thrombus grade, moderate or heavy calcification, total occlusion <3 months old, ostial lesion or bifurcation lesion requiring two guidewires.

Type C: >20 mm diffuse, excessive tortuosity of proximal segment, total occlusion >3 months old and/or bridging collaterals inability to protect major side branches, degenerated vein graft with friable lesions.