Diploma Thesis

Non-invasive ischemia evidence in stable invasive clarified coronary patients

Submitted by

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Affidavit

I declare that I have authored this thesis independently, that I have not used other than the declared sources, and that I have explicitly marked all material which has been quoted either literally or by content from the used sources.

Graz, 06.08.2017 Lisa-Marie Sandra Dollmann eh

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"An investment in knowledge pays the best interest"

Benjamin Franklin

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List of abbreviations

SPECT	single photon emission computed tomography
MRI	magnet resonance imaging
CCTA	coronary computed tomography angiography
LM	left main coronary artery
LAD	left anterior descending
LCx	left circumflex artery
RCA	right coronary artery
MI	myocardial infarction
ACS	acute coronary syndrome
SCAD	stable coronary artery disease
LDL	low density lipoprotein
HDL	high density lipoprotein
LVEF	left ventricular ejection fraction
STEMI	ST- segment elevation myocardial infarction
NSTEMI	non ST-segment elevation myocardial infarction
PCI	percutaneous coronary intervention
BMI	body mass index
CABG	coronary artery bypass grafting
OMT	optimal medical therapy
MPS	myocardial perfusion scintigraphy
MPI	myocardial perfusion imaging
OHCM	obstructive hypertrophic cardiomyopathy
LBBB	left bundle branch block
WPW	Wolff-Parkinson-White syndrome
EF	ejection fraction
SSFP	steady state free precession imaging
MRA	magnet resonance angiography
DE	drug eluting
DES	drug eluting stent
ASA	acetylsalicylic acid
PTP	pretest probability

CAD	coronary artery disease
FFR	fractional flow reserve

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Zusammenfassung

Hintergrund: Die ischämische Herzkrankheit ist in den Industrieländern die häufigste Todesursache. PatientInnen, die sich klinisch mit Symptomen präsentieren, die verdächtig für eine stabile koronare Herzkrankheit (KHK) sind, unterziehen sich zuerst nichtinvasiven kardialen Untersuchungen. Die invasive Herzkatheteruntersuchung wird zumeist an PatientInnen mit positiven Voruntersuchungen durchgeführt. Diese Studie soll die Frage beantworten, welche nichtinvasive Untersuchungsmethode für stabile KoronarpatientInnen die beste ist und die obstruktive KHK zuverlässig diagnostiziert.

Methoden: Diese Datenanalyse ist eine retrospektive Studie mit 587 eingeschlossenen PatientInnen. Alle PatientInnen, die sich im Jahr 2015 (01.01.2015-31.12.2015) sowohl einer elektiven invasiven Koronarangiographie im Herzkatheterlabor der Universitätsklinik in Graz als auch einer nicht invasiven kardialen Voruntersuchung unterzogen haben, wurden in diese Studie eingeschlossen. In das nichtinvasive Management wurden Ergometrie, Myokardszintigraphie, Koronarcomputertomographie (Koronar-CT) und Magnetresonanztomographie (MRT) eingeschlossen.

Ergebnisse: 569 PatientInnen hatten mindestens eine positive Voruntersuchung, davon zeigten 265 in der Koronarangiographie das Bild einer obstruktiven KHK. Das MRT zeigte in dieser Studienpopulation die höchste Genauigkeit (63%) mit 10 von 16 PatientInnen, die sowohl ein positives präprozedurales MRT als auch eine Koronarangiographie mit der Diagnose obstruktive KHK aufwiesen. Die Ergometrie zeigte die zweithöchste Genauigkeit (53%) gefolgt von Koronar-CT (47%) und Myokardszintigraphie (45%). Die diagnostische Koronarangiographie führte in 277 Fällen zu einer Intervention und 208 von diesen Patienten unterzogen sich einer perkutanen Koronarintervention.

Schlussfolgerung: Diese Analyse rückt das MRT als attraktive Alternative im nichtinvasiven Setting ins Zentrum. Des Weiteren ergeben die Evaluierungen dieser Studie, dass die Ergometrie eine höhere Genauigkeit aufweist, verglichen mit Koronar-CT und Myokardszintigraphie.

Schlagwörter: stabile KHK, Ergometrie, Myokardszintigraphie, Koronar-CT, Magnetresonanztomographie, invasive Koronarangiographie

Abstract

Background: Ischemic heart disease causes the highest number of deaths in industrialized countries. Patients who present with symptoms suspicious of stable coronary artery disease undergo non-invasive testing before an invasive coronary angiography (CA). The aim of this study was to evaluate which non-invasive test is the best method, in order to diagnose obstructive coronary artery disease (CAD) reliably in stable coronary patients.

Methods: This data analysis is a retrospective study with 587 included patients. All patients, who underwent both an elective CA in 2015 (01.01.2015-31.12.2015) at the cath lab at the University Clinic in Graz and have got at least one non-invasive cardiac investigation before invasive CA, were included in this trial. The non-invasive tests implicated ergometry, myocardial perfusion imaging (MPI), coronary computed tomography angiography (CCTA) and magnet resonance imaging (MRI).

Results: 569 participants were tested positive in their previous non-invasive procedure and 265 of these (47%) were diagnosed with obstructive CAD in CA. MRI demonstrated the highest accuracy (63%) in the study population with 10 patients out of 16 who presented with obstructive CAD in CA and a previous positive MRI. Ergometry reached the second highest accuracy (53%) followed by CCTA (47%) and MPI (45%). Diagnostic CA required an intervention in 277 patients of the study population (n=587) and of these 208 patients underwent percutaneous coronary intervention.

Conclusion: In conclusion, this study suggests that MRI could be an attractive alternative in non-invasive testing and that MRI is an effective gatekeeper for invasive CA. Furthermore, this study evaluates that ergometry has a higher accuracy compared to CCTA and MPI.

Keywords: stable coronary artery disease, ergometry, myocardial perfusion imaging, coronary computed tomography angiography, magnet resonance imaging, invasive coronary angiography

1 Background

1.1 Introduction

Cardiovascular diseases cause the highest number of deaths worldwide including low- and middle-income countries. In industrial countries a steady decline of death rates, according to primary and secondary prevention including identification and early treatment of cardiovascular risk factors, has been achieved (5).

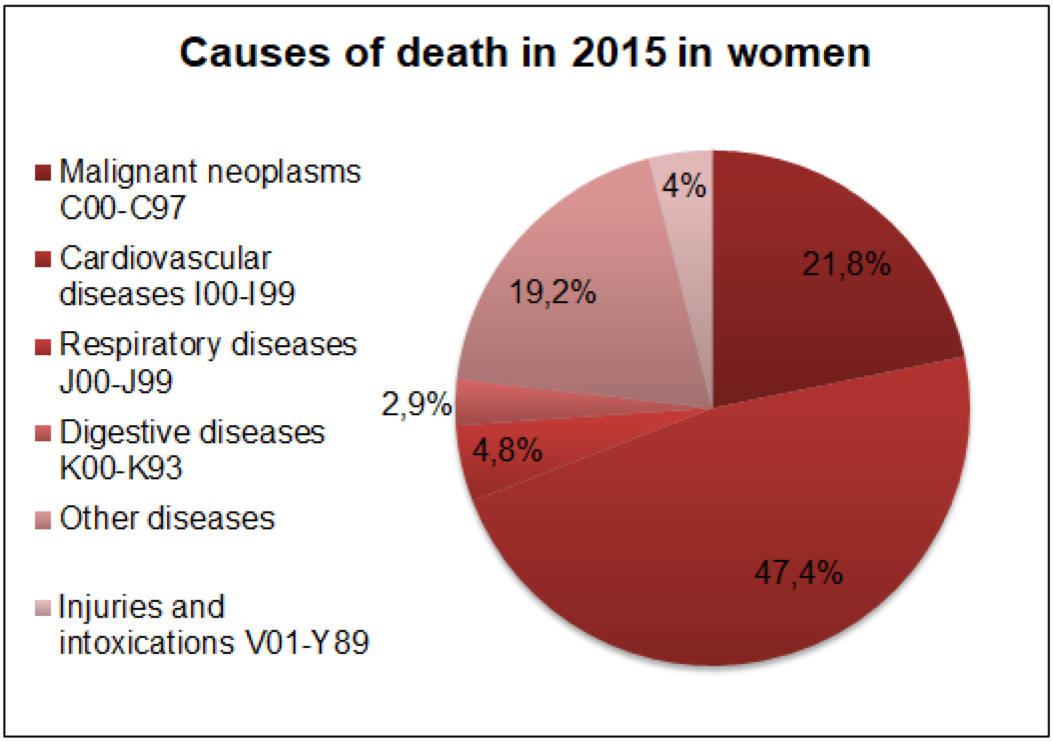

Figure 1: Statistics Austria causes of death in 2015 in women (1)

The leading cause of death in Austria, which represents a wealthy industrialized country, is cardiovascular disease (6). Figure 1 and 2 show the causes of death in Austria in 2015. Cardiovascular disease holds the highest percentage both in men (37,8%) and women (47,4%). In total 35.537 (42,8%) people in Austria died because of cardiovascular diseases in 2015.

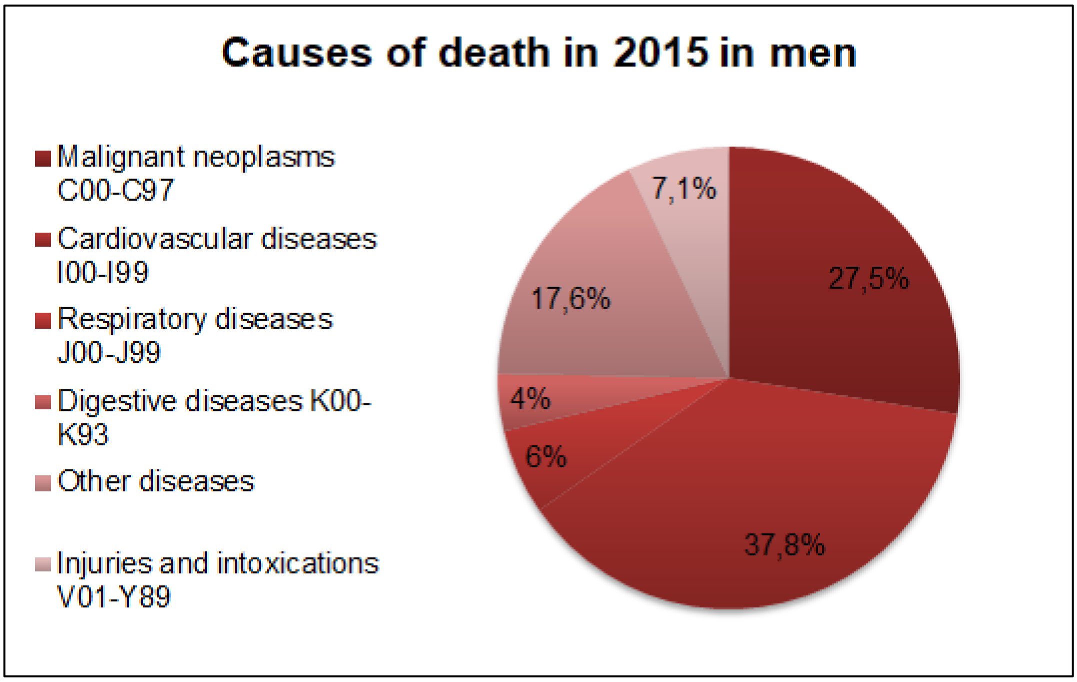

Figure 2: Statistics Austria causes of death in 2015 in men (1)

1.2 Coronary artery disease

The manifestation of atherosclerotic disease in the coronary artery is called coronary artery disease. The origin of CAD is the loss of defense mechanisms of the vascular endothelium including local control of vessel tone, presence of antithrombotic surface, to interfere inflammatory cell adhesion and diapedesis.
The loss of these normal functions causes luminal thrombus formation and "abnormal" interactions between blood leukocytes, especially monocytes and platelets. The formation of a thrombus containing platelet aggregates and fibrin strands with retained red blood cells causes a reduction of coronary blood flow. This reduction induces the clinical manifestations of myocardial ischemia.
The severity of clinical symptoms depends on the location of the coronary blood flow reduction. The coronary artery lesions cause a critical balance between myocardial oxygen demand and supply. Clinical manifestations, which are induced by myocardial ischemia, include stable angina pectoris, acute coronary syndrome, ischemic myocardial damage, arrhythmias and sudden cardiac death (7, 8).

1.2.1 Stable CAD

Stable coronary artery disease is defined as reversible episodes of myocardial demand/supply mismatch. These clinical symptoms occur usually during exercise, emotional stress or other forms of stress. The myocardial ischemia in SCAD is caused by fixed or dynamic stenosis of epicardial coronary arteries, microvascular dysfunction and focal or diffuse epicardial coronary spasm. The clinical symptoms of patients with SCAD range from stress induced angina to rest angina, totally asymptomatic patients and patients with a history of ischemic cardiomyopathy.

The results from episodes of myocardial ischemia are an increased concentration of hydrogen and potassium ions in the venous blood, abnormal wall motion abnormalities, development of ST-T changes and cardiac ischemic pain called angina. Angina, which represents the main clinical symptom, is caused by the release of ischemic metabolites which further stimulate sensitive nerve endings.

The treatment of SCAD includes lifestyle modification, patient education, control of cardiovascular risk factors, medical therapy and revascularization in selected cases. Revascularization in SCAD patients is indicated if the coronary lesions are flow limiting. In one vessel disease, non-invasive techniques determine the functional severity of coronary lesions reliably. In patients presenting with multivessel disease the hemodynamic effectivity can be assessed by measuring coronary artery pressure by fractional flow reserve. The optimal treatment goals of SCAD are both the reduction of symptoms and the prevention of future cardiovascular events (2, 9).

1.2.2 Cardiovascular risk factors

The risk factors for cardiovascular diseases are divided in both metabolic and behavioral risk factors. Initially a major metabolic risk factor is hyperlipidemia, especially high low-density lipoprotein cholesterol levels and low high-density lipoprotein levels. Additionally, hypertension has been identified as a major risk factor and is classified in mild (140-159 and /or 90-99) moderate and severe (≥180 and/or ≥110) hypertension. Obesity (BMI≥ 30kg/m²) represents an important CV risk factor and furthermore general obesity and abdominal obesity are associated with the risk of death (10). In patients with a history of diabetes mellitus cardiovascular disease represents the leading cause of morbidity and mortality. The main purpose in the treatment is the improved glycemic control in order to prevent microvascular complications. In terms of lifestyle behaviors smoking, unhealthy nutrition and physical inactivity are associated with a high risk for cardiovascular diseases. Smoking associates an increased risk for all types of CVD and the 10-year risk for CV events is doubled in smokers (7, 11, 12). Finally, coronary artery disease or myocardial infarction with early onset in close family members, male gender and an age ≥ 45 years in male gender and ≥55 years in women cause an increased risk for CVD.

Another study evaluated if increased genetic risk for CVD can be offset by a healthy lifestyle. Genetic risk was quantified by using a polygenic score of DNA sequence polymorphisms. The healthy lifestyle was defined by a scoring system consisting of four factors: no current smoking, no obesity, regular physical activity and a healthy diet. The three lifestyle risk categories included favorable (at least three of the four healthy lifestyle factors), intermediate (two of the healthy lifestyle factors) or unfavorable (no or only one healthy lifestyle factor). Among patients at high genetic risk of CAD a favorable lifestyle was associated with a nearly 50% lower relative risk for developing coronary artery disease than an unfavorable lifestyle (13).

1.2.3 Epidemiology and prognosis

The lifetime prevalence of CAD amounts 30% in men and 15% in women.
Both the prevalence for CAD and for angina increases within the age in male and female gender. Currently the prevalence of diagnosed CAD is increasing which may be contributed to the improved sensitivity of diagnostic tools.

In general the prognosis for patients with diagnosed CAD is worse in those with reduced left ventricular ejection fraction and heart failure, a greater number of affected vessels, stenosis in the main LCA, greater severity of lesions, older age and more severe angina (2, 8).

1.3 Non-invasive cardiac investigations

Non-invasive testing is recommended for patients who presented with symptoms suspicious of stable coronary artery disease and a pretest likelihood of 15-85% before elective invasive procedures are considered. Non-invasive procedures for cardiac ischemia are based on either reduced perfusion or induction of ischemic wall motion abnormalities during exercise or pharmacological stress. The most established non-invasive tests for ischemia are electrocardiogram exercise testing, stress echocardiography, myocardial perfusion scintigraphy, coronary computed tomography angiography and magnetic resonance imaging (14).

	Diagnosis of CAD	
	Sensitivity (%)	Specificity (%)
Exercise ECG [a, 91, 94, 95]	45–50	85–90
Exercise stress echocardiography[96]	80–85	80–88
Exercise stress SPECT[96-99]	73–92	63–87
Dobutamine stress echocardiography[96]	79–83	82–86
Dobutamine stress MRI[b,100]	79–88	81–91
Vasodilator stress echocardiography[96]	72–79	92–95
Vasodilator stress SPECT[96, 99]	90–91	75–84
Vasodilator stress MRI[b,98, 100-102]	67–94	61–85
Coronary CTA[c,103-105]	95–99	64–83
Vasodilator stress PET[97, 99, 106]	81–97	74–91

Table 1: Sensitivities and specificities of non-invasive tests used to diagnose CAD (2)

In table 1 commonly used non-invasive tests for the detection of coronary artery disease are presented. These non-invasive tests have sensitivities and specificities of approximately 85%. The exercise ECG has a low sensitivity of 50% which depends on the high number of false tests in patients with a positive predictive value >65%. The positive predictive value is composed of the prevalence of the disease in the population observed and clinical components including cardiovascular risk factors of a patient.

As a result, exercise stress test should not be performed in populations already on high risk to diagnose the presence of CAD. The highest sensitivity is accomplished by the coronary CTA (99%), while the exercise ECG has the lowest sensitivity (50%). In terms of specificity the vasodilator stress echocardiography obtains the highest specificity (95%) and the coronary CTA shows the lowest specificity (83%) (2).

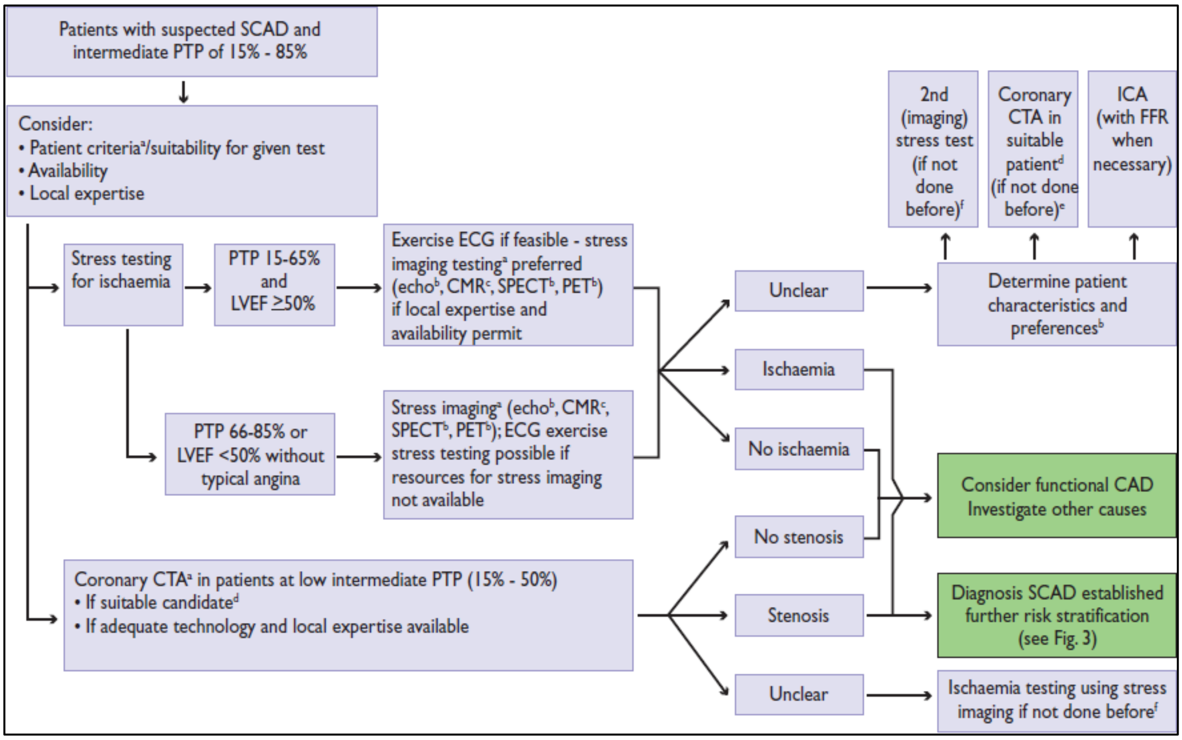

Figure 3: Non-invasive testing algorithm in patients with intermediate pretest probability (2)

Figure 3 shows the algorithm for the different possibilities of non-invasive cardiac testing in patients with suspected coronary artery disease. In this algorithm patients with a pretest probability of 15%-85% are presented. The reason for this inclusion is that the non-invasive tests for cardial ischemia reach approximately sensitivities and specificities of 85%. As a consequence, tests for patients with a PTP over 85% and fewer than 15% will cause more false results compared with no testing in these individuals. In conclusion patients with a PTP over 85% are diagnosed with obstructive CAD and the ones presenting with a PTP below 15% are diagnosed with non-obstructive CAD.

On patients with a PTP of 15-85% further non-invasive testing is recommended. Patients presenting with a PTP ≥15-65% and a left ventricular ejection fraction of ≥50% should basically undergo exercise ECG as non-invasive stress testing. Patients who have a PTP above 66% should have stress imaging by echocardiography, cardiac MR, SPECT or PET. Finally, CCTA is indicated in patients diagnosed with a low intermediate PTP (15-50%), under the condition that a meaningful CCTA can be performed in these patients, taking into account radiation exposure and the possibility of an unclear result in patients with diffuse, severe or focal coronary calcifications.

Patients presenting with no significant stenosis in CCTA should receive medication without further non-invasive cardiac investigations, because of the high negative predictive value of CCTA. Hence CCTA is a useful procedure to exclude coronary artery disease for patients with a low or intermediate pretest probability (2).

1.3.1 Ergometry

Ergometry or also called electrocardiogram exercise testing is performed on patients suffering from stable angina without ischemia signs at rest to identify myocardial ischemia while exercise. The electrocardiogram exercise testing is performed by using bicycle exercise testing and a 12–lead ECG monitoring. The maximum heart rate during the procedure is calculated for every patient separately (220 minus patient age). The physical load increases every 2-3 minutes until the maximal load is achieved. The test has to be stopped if the workout is achieved or symptoms, like progressive angina pectoris, severe dyspnea or dizziness, ST-elevation > 0,1 mV or ST- segment depression > 0,1 mV appear. Additionally, ergometry provides information such as blood pressure, heart rate and workload achieved, which has importance for further diagnostics and prognosis of SCAD. This ECG exercise test is a useful option for patients with suspected stable coronary artery disease (stable angina pectoris) or asymptomatic patients with cardiovascular risk factors. Furthermore, patients with a history of coronary artery disease and increasing symptoms have an indication for ergometry.

The ergometry is contraindicated in patients with severe aortic stenosis, unstable blood pressure, acute coronary syndrome, unstable angina pectoris, obstructive hypertrophic cardiomyopathy and symptoms according to NYHA 3-4.
The exercise ECG shows an inconclusive result in patients with limited capacity due to orthopedic or other non-cardiac problems.

Furthermore, concomitant medication with digitalis and anti-ischemic drugs can falsify the result. For patients with a pacemaker and the ones, who are diagnosed with left bundle branch block or Wolff-Parkinson-White syndrome the ECG testing is not of diagnostic value, because the ECG changes are not interpretable. For female participants, the ergometry has a lower sensitivity and specificity, than in the male ones. The exercise ECG reveals an indication of cardiac ischemia, if a horizontal or descending ST- segment depression ≥0.1 mV, which insists for at least 0,06-0,08s after the J-point in one or more ECG leads, is diagnosed (2, 15).

1.3.2 Myocardial perfusion scintigraphy

The myocardial perfusion scintigraphy with SPECT provides images of the myocardial perfusion at rest and during stress. Stress can be induced using a bicycle ergometry. As an alternative to exercise stress pharmacological stress is indicated in patients who are not able to exercise adequately. Adenosine, dobutamine and regadenoson can be used as pharmaceutical stressors. The most frequently applied tracers are Technetium-99m (99mTc) and Thallium 201 (201Tl). During the procedure, the tracer is injected 1 minute prior to terminating the exercise part, followed by the resting part with a second tracer injection. SPECT employs a gamma camera head which rotates around the patient to provide sectional images. For the procedure evaluation, all sectional images were reconstructed in parallel levels to the main axes of the left ventricle (transversal and sagittal). The tracer activity depends on the myocardial blood flow pattern and is shown in the scintigraphy.

The main diagnostic abnormality is the reduced tracer uptake, which equates to myocardial hypoperfusion. The main diagnostic value is to differentiate between reversible and fixed malperfusion evidence. The ischemia is reversible and stress induced if the myocardial hypoperfusion appears only during stress, in comparison with the uptake at rest. Fixed malperfusion is characterized by reduced tracer uptake during stress and at rest so called myocardial scar. Predictors of severe coronary artery disease are transient ischemic dilatation and reduced post-stress ejection fraction.

Myocardial perfusion scintigraphy is indicated in patients with intermediate risk for coronary artery disease for ischemia evidence and for patients with an inconclusive exercise ECG. Furthermore, patients with a history of CAD undergo myocardial perfusion scintigraphy to reevaluate the functional relevance of plaque. Finally, patients scheduled for elective myocardial revascularization have an indication for perfusion scintigraphy in order to detect myocardial viability (2, 15).

Myocardial perfusion imaging is not recommended in patients with low pretest likelihood for CAD. An advantage of myocardial perfusion scintigraphy with SPECT is its extensive availability. However, SPECT has limitations including the exposure to radiation, comparably long acquisition time and the relative shortage of 99mTc. In addition, a disadvantage is the frequently appearance of attenuation artifacts created by respiratory motion or surrounding tissue particularly in women and obese patients (16, 17).

1.3.3 Computed tomography

CT imaging of the coronary arteries can detect and quantify the calcification in the coronary arteries (calcium scoring) and the coronary computed tomography angiography visualizes the coronary artery lumen. The investigation can be performed without contrast injection while coronary calcium scoring or after intravenous injection of iodinated contrast in CCTA (2).

1.3.3.1 Calcium scoring

Calcification in the coronary arteries is a sensitive marker to diagnose coronary atherosclerosis. Before the clinical manifestation of coronary artery disease, it is possible to detect calcified coronary artery plaque with calcium scoring CT. As a consequence, asymptomatic patients with an increased risk factor for myocardial infarction are identified earlier in order to prevent MI or sudden cardiac death, independent of conventional cardiovascular risk factors. CT calcium scoring and quantifying the amount of calcified coronary artery plaque has been widely accepted as a non-invasive procedure for screening risk of future cardiac events.

The procedure is performed using unenhanced low dose CT and coronary calcification is identified as hyperdense area along the coronary arteries. In CCTA, structures with enhanced density are highlighted visually and are verified as coronary artery plaques by an evaluator. By default, enhanced density from 130 Hounsfield units are considered as coronary calcification excluding coronary stents or metal clips. The quantification of coronary artery plaque is accomplished using the Agatston score or scores such as the volume score or calcium mass. Coronary calcification reveals the presence of atherosclerotic plaque in coronary arteries. Conversely the deficiency of coronary calcification does not rule out coronary plaques, because the prevalence of significant stenosis caused by non-calcified plaques in patients with negative calcium scoring amounts 3-5% (18).

1.3.3.2 Coronary computed tomography angiography

Coronary computed tomography angiography is a non-invasive technique to assess coronary anatomy. The procedure should be performed with at least 64 slice CT and local expertise. Patients who undergo CCTA should be capable of breath holding, have a sinus rhythm and a heart rate of 65 beats per minute or less and should not suffer from obesity. The Agatston score, which usually quantifies calcified lesions in the coronary arteries, should be under 400 for the CCTA, because of decreasing specificity with higher Agatston scores.

CCTA reaches a sensitivity of 95-99% and a specificity of 64-83% including patients with suspected coronary artery disease with at least one vessel disease in coronary angiography. The sensitivity of CCTA which is performed on patients with previous PCI, previous MI or a history of CAD is lower (85%), while specificity is higher (90%) in those patients. Previous PCI causes artifacts in CCTA procedure, because of metal in the coronary stents.

The investigation is indicated in both patients with low to intermediate pretest probability (15-50%) and suitable clinical criteria. The procedure finding could be unclear in candidates with severe, diffuse or focal calcification. Furthermore, CCTA is performed on patients with positive previous non-invasive stress testing for coronary ischemia, but negative clinical judgment, especially if coronary angiography would be the other possibility to rule out significant stenosis.

One of the strengths of CCTA is the high negative predictive value (>99%), which excludes significant CAD reliably in a negative finding. As a consequence, CCTA can be used as an adequate gatekeeper for invasive heart catheterization. If CCTA is performed on patients with low or intermediate pretest probability the following procedures will be restricted to those with a positive CCTA finding.(19) CCTA provides detailed anatomical information on patients with suspected CAD including existence, composition and position of both obstructive and non-obstructive plaques (20) .

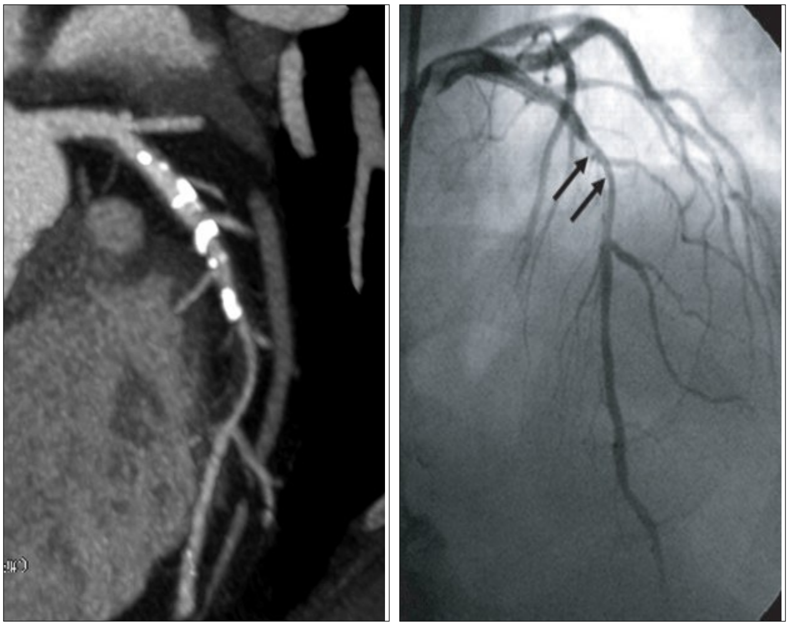

Figure 4: Coronary CT angiography versus coronary angiography finding (3)

The CCTA in figure 4 shows extensive calcified plaques in the proximal and middle segments of the LAD and the following CA confirms the significant stenosis. Disadvantages of the coronary CT angiography are the ionizing radiation, the utilization of nephrotoxic contrast media and that the procedure cannot provide information about the functional effect of a stenosis (17).

The decision-making for CCTA is based on careful deliberation if the benefit expected from the CT examinations is greater than the radiation risk (3).

1.3.4 Magnet resonance imaging

Coronary MR angiography is a non-invasive procedure to visualize the coronary arteries without the use of ionizing radiation. MRI is a reliable procedure to evaluate patients with suspected or known CAD. The ventricular function and wall motion are determined both at rest and during infusion of inotropic agents.
At first a bolus of Gadolinium contrast medium is injected followed by a MRI scan of the heart. The myocardial perfusion can be assessed while Gadolinium passes through the heart chambers and into the myocardium.
The areas of low signal intensity in the myocardium present relative perfusion deficits. Pharmacologic stress can be induced using vasodilators during perfusion imaging to detect physiologically significant coronary artery lesions (7).

The whole heart coronary MR angiography performed by using a free breathing 3D steady state free precession imaging (SSFP) is the most frequently used MRI method. The reasons therefore are the simplicity of this access in prescribing image location and the reduced imaging time compared to earlier procedures. Various techniques of coronary MR angiography are available, starting with 1,5 Tesla coronary MRA, which can be gathered using SSFP MRA sequences without injection of Gadolinium based contrast medium and offers an intrinsically high blood signal intensity. Whole heart coronary MRA at 3.0 Tesla used with contrast medium improves the contrast-to-noise ratio compared with non-contrast enhanced 1.5 Tesla whole heart coronary MRA. The image quality improves, nevertheless the use of contrast medium is associated with potential side effects especially in patients with impaired renal function (21).
The advantages of coronary MRA are the high sensitivity (88%) for the detection of significant CAD and a negative predictive value of 88%, which presents an important method to rule out CAD in patients with chest pain. Furthermore, coronary MRA has a high negative predictive value (99%) in patients with LM stenosis or three vessel disease using 1.5 Tesla whole heart coronary MRA(21).

Another strength of coronary MRA is the possible combination with cine MR imaging, stress perfusion MR or late Gadolinium enhanced MRI, which offers a complete assessment for patients with a history of CAD or the ones who are suspicious of CAD (22). As a cause coronary MRA provides evaluation of overall cardiac anatomy and function in the same examination (2). In addition coronary MRA presents the lumen of the coronary artery reliably including segments with heavily coronary calcification. Nonetheless there are also limitations using coronary MRA, which include long image time, operator dependency and lower spatial resolution compared to CCTA (22).

1.3.5 Stress echocardiography

The main indication for stress echocardiography is to diagnose ischemic heart disease and to figure out its severity. The patients undergo stress echocardiography both at baseline and immediately after exercise. Stress echocardiography is performed with exercise (bicycle) or with pharmacological agents. For patients, who are able to exercise adequately, the procedure offers extra physiological data like exercise time and workload, changes of the heart rate, blood pressure and ECG. The stress echocardiography shows positive signs of ischemia if new regional wall motion abnormalities, a decline in ejection fraction or an increase in end systolic volume occur while stress imaging. The diagnostic patterns for stress echocardiography are as follows: an unsuspicious stress echo at rest and during stress is considered as “normal”, a stress echo “within normal limits” at rest and abnormal during stress is suspicious for ischemic heart disease and an atypical stress echo during rest and stress is a sign for a necrotic area in the myocardium.

Stress imaging with pharmacological agent is achieved administering an infusion of Dobutamine in order to increase myocardial oxygen demand.

Patients, who underwent exercise ECG and got a less informative and/or interpretable exercise ECG either caused by anatomic abnormalities or further investigations (pacemaker) have an indication for stress echocardiography.

In these patients presenting with a known or suspected CAD stress echo should not be the first line imaging for diagnostic and prognostic functions. The main advantages of stress echocardiography include low cost, wide availability and most importantly it is a radiation free procedure (7, 23).

1.4 Coronary angiography

Diagnostic heart catheterization and coronary angiography are used as a gold standard in terms of the valuation of the anatomy and physiology of the heart and its associated vessels. In 1958 Dr. F. Mason Sones unintentionally performed the first selective “coronary arteriogram” of the right coronary artery. He examined a patient with rheumatic aortic valve disease and placed the closed-end catheter in the ascending aorta just above the aortic valve in order to obtain an aortogram, but he catheterized the right coronary and most of the contrast agent was delivered there. From this moment on the visualization of coronary arteries had become possible (24).

The main indication for coronary angiography is the evaluation of the extent and severity of coronary artery disease in symptomatic patients and to decide either medical, catheter based or surgical interventions are indicated (4). Coronary angiography is basically performed in patients with increasing symptoms of cardiac dysfunction, which may include acute coronary syndromes such as unstable angina or acute myocardial infarction. Furthermore, a reason for CA is a previous proof of myocardium at risk for ischemia (exercise ECG or exercise MPS) or echocardiography, which suggests that the patient has findings that signal for progressing to functional failure or myocardial infarction.

According to elective CA the risks are relatively low such as 0,05% for myocardial infarction, 0,07% for stroke and 0,08%-0,14% for death. In cases of emergencies, for example acute myocardial infarction or in hemodynamically unstable patients, these risks increase extensively. One possible risk after CA is acute renal failure according to the use of contrast agent. Another risk after CA is vascular catheter insertion site bleeding, which occurs in 1,5-2% of patients and presents the most common complication. Especially patients with a history of baseline renal dysfunction or proteinuria may develop a decrease of renal function after CA. In order to prevent renal dysfunction in those patients an adequate prehydration is indicated. Patients, who undergo diagnostic CA and are suspected for CAD, receive oral acetylsalicylic acid (325mg) before the procedure to have the possibility to perform PCI in the cath lab.

The coronary angiography is performed with awake but sometimes lightly sedated patients using diazepam (5-10 mg) or midazolam (1mg).
The coronary angiography begins with the needle puncture either of the femoral or the radial artery. After the arterial puncture, a flexible guidewire is inserted through this needle in order to support the insertion of a vascular access sheat. Through this vascular access sheat, which is invested within Seldinger-technique, the chosen catheters can be pushed forward retrograde to the heart. The common techniques for the probing of the coronary arteries are the Judkings- technique using a Judkings-catheter with the femoral arterial access and the Sones-technique with use of Sones-catheter with the brachial arterial access. The tips of specially shaped catheters are placed into the left and then the right coronary artery and any surgical bypass grafts under fluoroscopic guidance. While the procedure contrast agent is injected through the coronary catheter in order to evaluate their lumina. Every coronary artery is shown in several projections to locate and stage any stenosis related to the adjacent “normal” artery segment (15).

Furthermore, the CA offers information about the rapidity of coronary flow and possible collateral pathways which subserve myocardial territories normally supplied by an occluded vessel. The stage of stenosis is evaluated visually of percent diameter stenosis of each lesion relative to the “normal” adjacent reference segment. 50% stenosis represents the lowest significant lesion (7).
The clinical importance of coronary angiography is based on the opportunity to assess a patient´s risk of death or future cardiac events through CA of the presence. In addition, an advantage of CA is the assessment of the extent of obstructive CAD and the feasibility of catheter based or surgical intervention. Finally, the CA also shows limitations for example the interobserver reliability and the provision of only anatomic data of the coronary arteries without the functional significance of proven coronary lesions. Lastly it is not possible to distinguish between vulnerable plaque, thin fibrous cap and increased macrophages and stable plaque in this procedure (25).

1.4.1 PCI, PTCA revascularization

The PCI procedure begins after the assessment of the extent, location and severity of at least one coronary artery lesion by diagnostic coronary angiography, which should be treated by catheter based intervention. Anticoagulation is achieved using either unfractionated heparin (50-70 IU/kg) or a direct thrombin inhibitor for example bivalirudin. Basically, acetylsalicylic acid pretreatment is performed (150-325mg/d) before the CA and the loading with clopidogrel (300-600mg) follows, if a PCI is needed.

First a guiding catheter (6 F=2mm), which has a larger inner lumen than a diagnostic coronary angiography catheter in order to permit balloon and stent advancement, is placed in the affected coronary artery. Afterwards a steerable guidewire (0,4mm) is advanced in the vessel distal beyond the treated lesion in order to permit the advancement of a predilating balloon. This balloon is placed across the target lesion and is inflated with dilute radiographic contrast to 6-16 atm to partially relive the target stenosis under fluoroscopic guidance. This is followed by the advancement of a drug eluting stent of both appropriate size and length to cover the diseased segment plus a 5mm margin on either side of the stenosis. Then the DE-stent is placed by the inflation (14-16 atm) of an angioplasty balloon on which the stent is mounted. The steps of the PCI procedure are depicted in figure 5. Furthermore, the stent can be expanded by a postdilating balloon as needed.

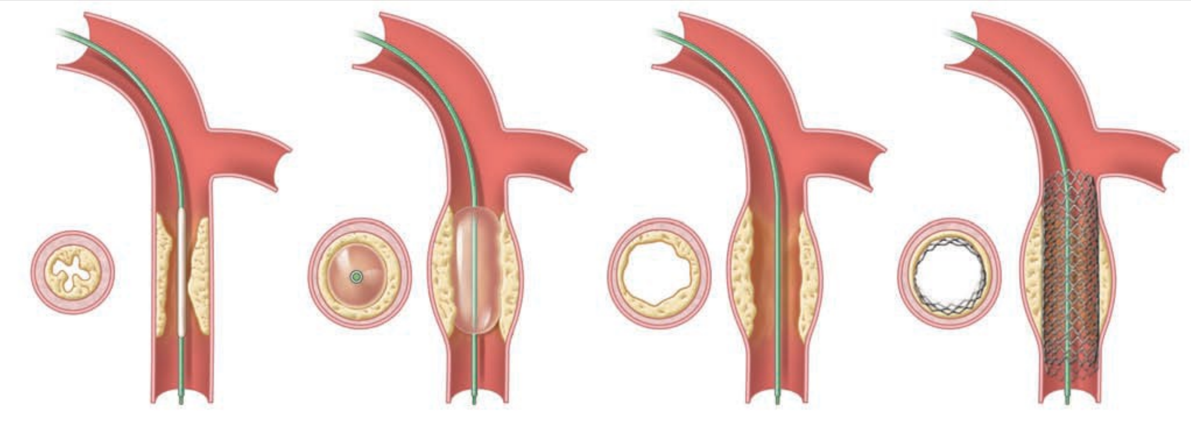

Figure 5: Balloon angioplasty and stenting procedure (4)

Finally the result of the PCI procedure is assessed by a repeat angiography (7). Revascularizations by PCI or CABG for patients with a history of stable coronary artery disease are indicated if the symptoms persist even with optimal medical treatment and/or revascularization improves the prognosis. In addition PCI or CABG may be indicated in patients presenting with flow-limiting coronary stenosis in order to reduce myocardial ischemia and its negative clinical symptoms (14). PCI intervention is performed in several patients with various manifestations of coronary artery disease. The PCI treatment is an established treatment in patients with ST-segment elevation myocardial infarction in order to improve survival and survival free of recurrent myocardial infarction. Early invasive therapy in non-ST-segment elevation acute coronary syndrome patients improves their long-term survival and reduces late MI. In patients presenting with stable coronary artery disease the PCI procedure reduces the symptoms and may improve long term survival compared with medical treatment only (26).

Drug eluting stents are basically used for the treatment of coronary artery disease. The first generation of drug eluting stents consists of a metallic stent platform and sets free antiproliferative drugs including sirolimus or paclitaxel. The new generation drug eluting stents have thin-strut, metallic platforms which release limus-based antiproliferative drugs from permanent polymers with improved biocompatibility and lower polymer mass, biodegradable polymers or polymer free surfaces. In terms of efficacy and safety new generation drug eluting stents exceed the first-generation DES in recent studies.

One study shows superiority of everolimus eluting stent compared to paclitaxel eluting stent regarding all-cause mortality, myocardial infarction, stent thrombosis, target lesion failure, target vessel failure and major adverse cardiac events (27).
A loading dose of acetylsalicylic acid per os (150-325mg) or i.v. (80-150 mg) and of clopidogrel (300-600 mg) is recommended before the procedure. After the PCI procedure a daily dose of ASA (75-100 mg) and clopidogrel (75 mg) is continued in order to prevent stent thrombosis and myocardial infarction (14).

2 Material and methods

2.1 Study design and data acquisition

This data analysis is a retrospective study. The patient data was collected from electronic patient records, ambulatory patient charts and cath lab findings. The period under review was from 01.01.2015 to 31.12.2015. In 2015, 1478 elective coronary angiographies were performed at the cath lab at the University Hospital in Graz. The positive ethics committee vote (number 1521/2015) has been received in January 2016. The electronic patient records and the cath lab findings were compiled out of the OpenMEDOCS Clinical Documentation System (KAGES Steiermärkische Krankenanstaltengesellschaft, student access).

2.2 Inclusion criteria

All patients, who underwent both an elective coronary angiography in 2015 (01.01.2015 - 31.12.2015) at the cath lab at the University Hospital in Graz and have got at least one non-invasive cardiac investigation before the CA, were included in this trial. A list of all 3023 patients who underwent coronary angiography in 2015 in the cath lab at the University Hospital in Graz was compiled. 587 of these patients were suitable for this study.

2.3 Compiled variables

2.3.1 Risk factors

Cardiovascular risk factors including gender, age, hypertension, hyperlipidemia, diabetes mellitus, atrial fibrillation, increased BMI and peripheral artery disease were listed in a MS Excel file. Furthermore, a history of previous CA, PCI, MI and CABG was added to the Excel file. In addition, the symptoms using the CCS and NYHA classification system were collected. Furthermore the results of echocardiography in the course of inpatient stay were added to the Excel data file (28, 29).

2.3.2 Current therapy

The current medical therapy including antiplatelet therapy, anticoagulation, beta blocker, calcium channel blocker, angiotensin converting enzyme inhibitor, angiotensin receptor blocker, statin and other antianginal therapy were gathered for every patient.

2.3.3 Non-invasive workup

4 non-invasive procedures were included in the non-invasive workup for ischemia evidence in stable coronary patients: ergometry, myocardial perfusion scintigraphy, cardiac magnet resonance imaging and coronary computed tomography angiography. The results of the non-invasive procedures were collected in a MS Excel data file, separated in patients with positive previous non-invasive testing and the ones, who presented with negative tests in the non-invasive workup. Furthermore, the date of the previous non-invasive testing was added to the Excel file. Depending on where the patients underwent their non-invasive procedures, either in the University Hospital in Graz or in a peripheral hospital, their procedure results were found in medical reports or in progress notes of the Department of Cardiology at the University Hospital in Graz. The findings of the non-invasive cardiac tests, which were performed at the Department of Radiology at the University Hospital in Graz, were found in the OpenMEDOCS.

2.3.4 Coronary angiography and treatment

A coronary angiography was performed on all patients included in this trial in 2015 at the University Heart Center in Graz after at least one previous non-invasive test for coronary ischemia. The coronary angiography results for the main LCA, LAD, LCx and RCA were collected. Furthermore, the stage of stenosis in the coronary arteries starting with ≥25 -49% stenosis (stage 1), 50-74% stenosis (stage 2), 75-99% stenosis (stage 3) and total occlusion (stage 4) was gathered.
Finally, the treatment for every single participant was acquired in the Excel data file, depending on the stage of the coronary artery disease. The treatment included optimal medical therapy, percutaneous coronary intervention and coronary artery bypass grafting.

2.4 Documentation and clinical evaluation

The patient data was numbered (pseudonymized) within a consecutively patient code in a Microsoft Excel file to ensure that the data could not be associated with the participants. Only authorized staff looked through the patient data. The statistical analysis was conducted using IBM SPSS 23 statistics program provided by the Citrix server of the Medical University of Graz (student access). Every non-invasive cardiac investigation was analyzed separately within a cross tabulation. The sensitivity and specificity for the four non-invasive techniques were calculated and presented in table 7. The distribution of treatment during or after coronary angiography depending on coronary angiography results was illustrated in table 9. Finally, only the patients with a history of previous PCI were analyzed, in order to compare their results to the whole study population.

3 Results

3.1 Study population

In total 587 patients were included in the study. 386 participants (66%) were men. The distribution of cardiovascular risk factors in the study population is shown in table 2.

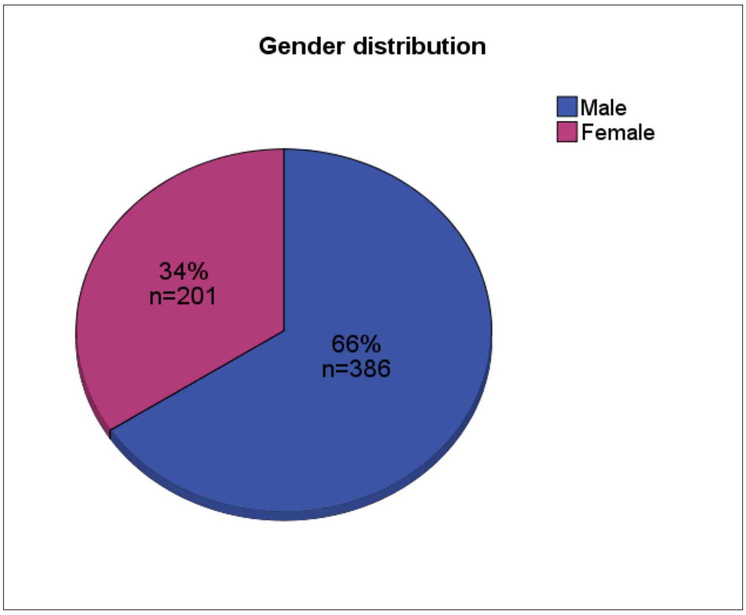

Figure 6: Gender distribution

3.1.1 Risk factors

Risk factor	Number (percentage)
Gender	386 (66%)
Age	571 (97%)
Hypertension	512 (87%)
Hyperlipidemia	344 (57%)
Diabetes mellitus	162 (28%)
Atrial fibrillation	103 (18%)
Peripheral artery disease	42 (7%)
BMI≥32	97 (17%)
Previous MI	85 (15%)
Previous CABG	32 (6%)
Previous PCI	128 (22%)

Table 2: Distribution of cardiovascular risk factors in the study population

The distribution of cardiovascular risk factors in the study population is listed in table 2. 386 patients (66%) were male participants and 571 patients (97%) had a risk factor depending on their age. 512 patients (87%) of the study population were diagnosed with hypertension and 344 participants (57%) suffered from hyperlipidemia.

162 participants (28%) presented with diabetes mellitus and 103 patients (18%) were diagnosed with atrial fibrillation. 42 participants (7%) had a history of peripheral artery disease and 97 patients (17%) presented with a body mass index over 32. 85 patients (15%) have already had a myocardial infarction before their non-invasive ischemia test for this study. 32 patients (6%) have underwent a coronary artery bypass grafting and on 128 patients (22%) a percutaneous coronary intervention was performed before their non- invasive test for this trial.

3.1.2 Age distribution

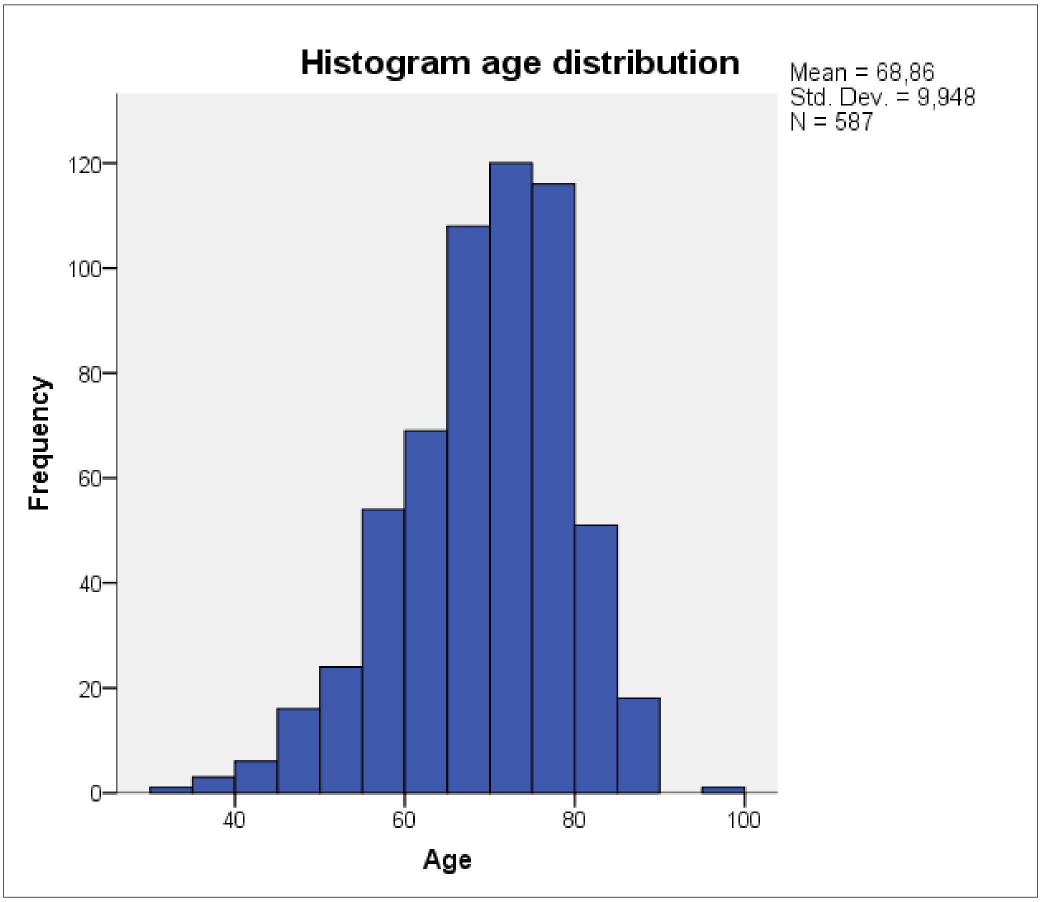

Figure 7: Age distribution in the study population

In terms of age distribution the study population is described as follows:
The mean for the participants was 69 years and the median age was 70 years in the population. The youngest patient was 33 years old and the oldest participant was 95 years old. The standard deviation in the study population amounted 9,95.

3.2 Ergometry patients

Ergometry results		Coronary angiography		Total
		Stenosis	No stenosis	
Ischemia evidence	Number	96 (53%)	86 (47%)	182 (100%)
No ischemia evidence	Number	6 (46%)	7 (54%)	13 (100%)
Total	Number	102 (52%)	93 (48%)	195 (100%)

Table 3: Cross tabulation ergometry and coronary angiography

In total 587 patients were included in the study. On 195 of them ergometry was performed as non-invasive diagnostic tool before coronary angiography. 96 of them had at least one stenosis in one of the coronary arteries, which was treated with PCI, CABG or medical therapy if an intervention was not possible, 86 did not. 182 patients had a positive sign of ischemia in ergometry, for example ST-cuts and 13 patients had an ergometry with no suspicious signs of ischemia, but nevertheless got a coronary angiography.

In 96 patients (53%) the invasive coronary angiography confirmed the result of the non-invasive diagnostic ergometry and at least one significant lesion in at least one coronary artery was diagnosed. 86 patients (47%) with an indication of coronary ischemia showed no stenosis in the coronary angiography.

The second group includes 13 patients in total that did not show any sign of cardiac ischemia in ergometry. 6 participants (46%) presented with a stenosis in at least one coronary artery in the invasive coronary catheterization and 7 patients (54%) did not. The result has a sensitivity of 94% (95% confidence interval [CI]: 0,89-0,99) and a specificity of 8% (95% confidence interval [CI] :0,02-0,13).

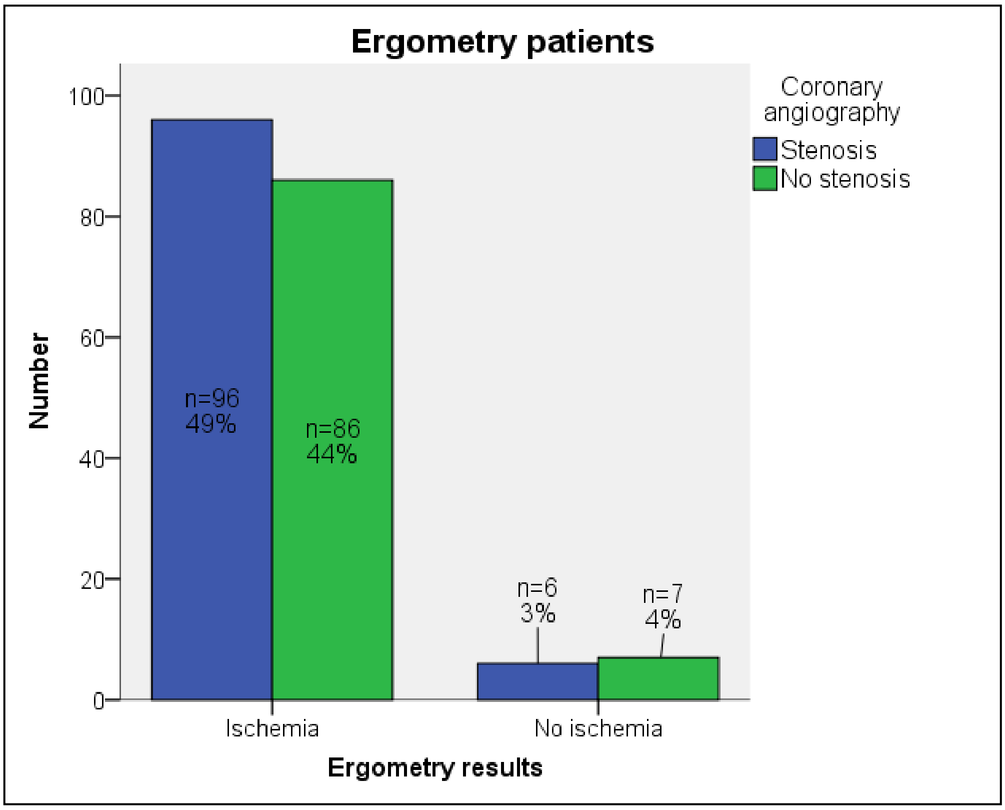

Figure 8: Ergometry versus coronary angiography findings

All participants who underwent ergometry are shown in figure 8. The blue bars show the patients (n=102) with proven stenosis in coronary angiography (52%). The green bars show the ones (n=93) with no stenosis (48%). 13 patients underwent ergometry and did not show any sign of ischemia, but nevertheless 6 patients showed stenosis in the following coronary catheterization. In 182 patients ergometry was suspicious of cardiac ischemia. In 96 of them the coronary catheterization confirmed the previous finding in ergometry and in 86 cases the coronary angiography showed a contrarious finding.

3.3 Myocardial perfusion scintigraphy patients

MPI results		**Coronary angiography**		**Total**
		Stenosis	No stenosis	
Ischemia evidence	Number	105 (45%)	129 (55%)	234 (100%)
No ischemia evidence	Number	10 (44%)	13 (56%)	23 (100%)
Total	Number	115 (45%)	142 (55%)	257 (100%)

Table 4: Cross tabulation myocardial perfusion imaging and coronary angiography

257 persons underwent myocardial perfusion scintigraphy. 234 of them had a positive sign of ischemia in the procedure, 23 got a negative result, but nevertheless underwent coronary angiography afterwards.

In 105 patients (45%) out of the 234 patients with positive ischemia sign in the previous MPI, the invasive coronary angiography proved the result and showed at least one stenosis in the CA. 129 patients (55%) out of the 234 patients got a negative result in the coronary angiography after having a previous MPS with ischemia sign.

In the patient pool with no proven ischemia in the previous MPI 10 patients (44%) out of 23 had positive result in the CA and 13 (56% %) had not.

A total of 257 patients underwent MPI before coronary angiography, 115 (45%) of these had a stenosis in coronary angiography and 142 (55%) did not. The result has a sensitivity of 91 % (95% confidence interval [CI]: 0,86-0,96) and a specificity of 9% (95% confidence interval [CI]: 0,04-0,14).

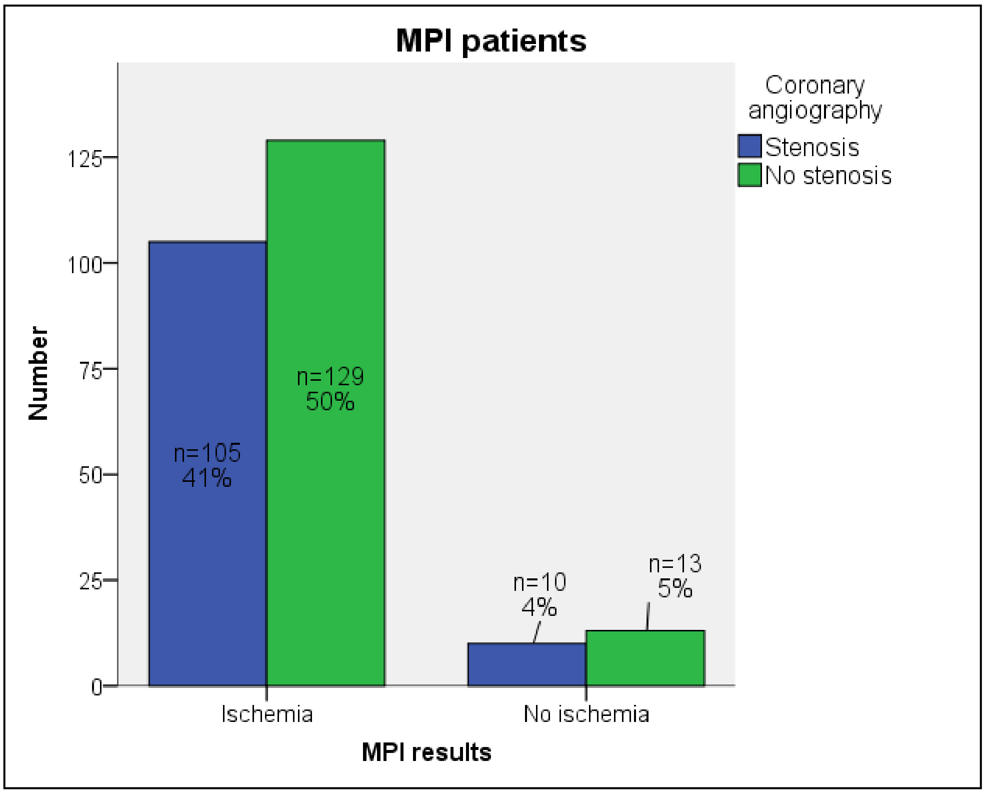

Figure 9: MPI versus coronary angiography findings

In figure 9 the patient pool, which had at least a myocardial perfusion scintigraphy before coronary catheterization, as non-invasive testing for coronary ischemia, is included. Among the participants the previous MPI showed a positive result in 234 patients (91%). The remaining 23 patients (9%) are the ones with no indication of coronary ischemia in the previous myocardial scintigraphy. In the catheter lab 115 patients (45%) had a stenosis and 142 (55%) did not. 105 out of the 115 also had a positive finding of coronary ischemia in the previous MPI, while 10 out of the 115 had a negative finding before, but nevertheless had a stenosis.

As a result, 105 patients (41 %), who received myocardial perfusion imaging analyses and invasive coronary angiography, got a congruent finding in both of them.

3.4 CCTA patients

CCTA results		Coronary angiography		Total
		Stenosis	No stenosis	
Positive CCTA	Number	114 (47%)	130 (53%)	244 (100%)
Total	Number	114 (47%)	130 (53%)	244 (100%)

Table 5: Cross tabulation coronary computed tomography angiography and coronary angiography

Initially, 244 patients underwent coronary computed tomography angiography as non-invasive diagnostic tool, before invasive coronary catheterization. The whole CCTA patient population had a positive CCTA, which was suspicious of obstructive CAD. In the following coronary angiography 114 patients (47 %) of these had stenosis. 130 patients (53% %) showed no stenosis in coronary angiography.

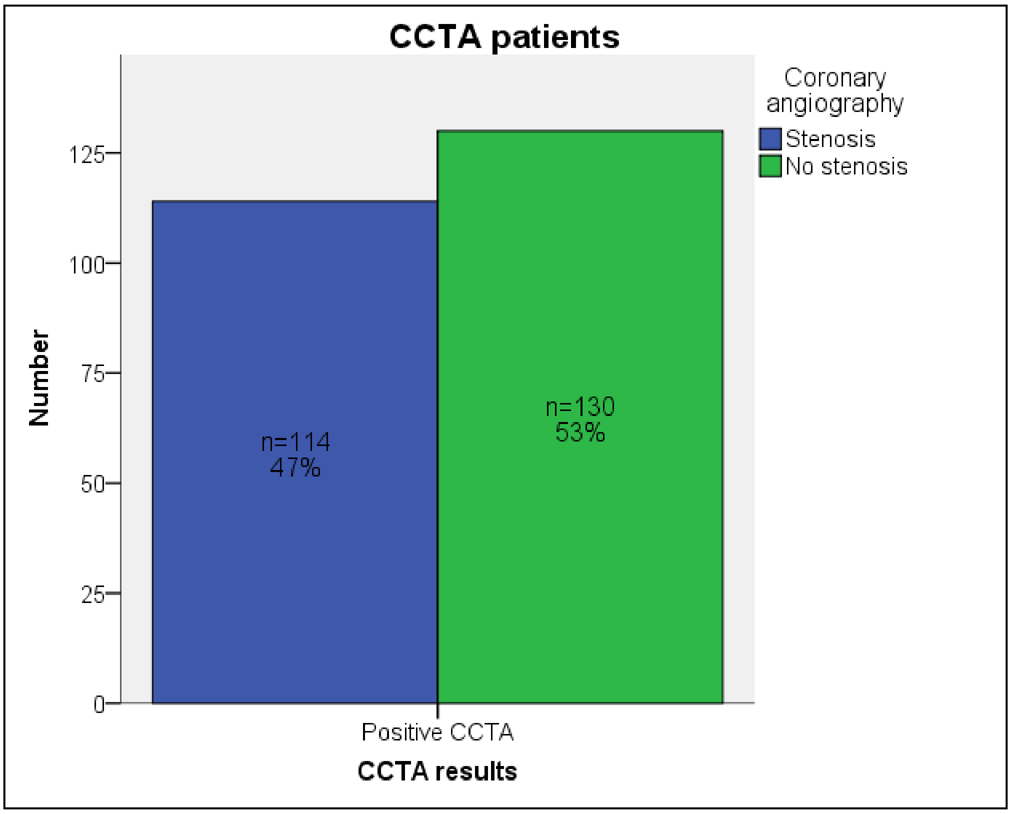

Figure 10: CCTA versus coronary angiography findings

In Figure 10 all patients, who underwent CCTA, are included. In 114 cases (47%) both CCTA and coronary angiography showed a stenosis, which was worth for treatment within PCI, CABG or optimal medical therapy. In 114 out of 244 cases the findings were congruent with previous CCTA and coronary angiography.

3.5 MRI patients

MRI results		Coronary angiography		Total
		Stenosis	No stenosis	
Positive MRI	Number	10 (63%)	6 (37%)	16 (100%)
Total	Number	10 (63%)	6 (37%)	16 (100%)

Table 6: Cross tabulation magnet resonance imaging and coronary angiography

The patient population, who underwent magnet resonance imaging, referred to non-invasive diagnostic testing, is the smallest group (n=16). In all of them screening was considered positive for ischemia. All of them underwent coronary angiography, of these 10 (63 %) had a stenosis in coronary angiography and 6 (37%) did not. Both previous magnet resonance imaging and following coronary catheterization showed an evidence of ischemia in 10 patients (63%). In 6 patients (37%) no stenosis was found in the catheter lab, although they had positive non-invasive diagnostic testing.

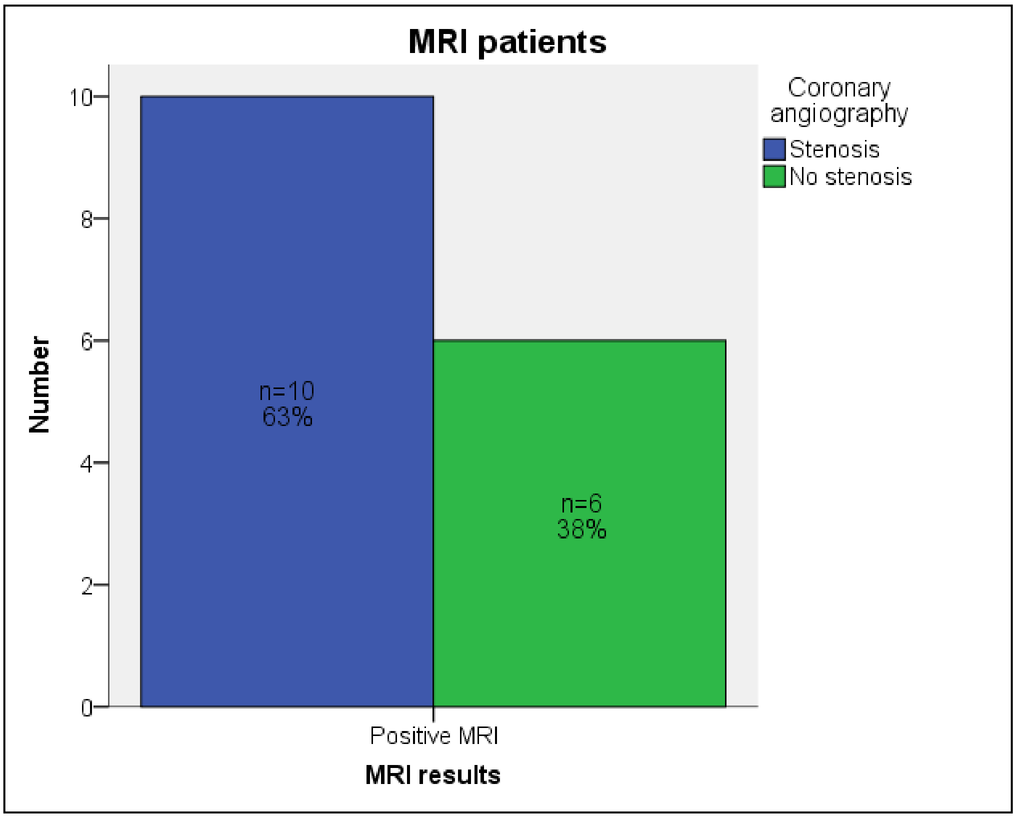

Figure 11: MRI versus coronary angiography findings

In figure 11 all patients with a magnet resonance imaging test are figured. The non-invasive testing for all of them was considered positive and 10 patients (63%) also had a stenosis in at least one coronary artery or its main branches.

3.6 Cross tabulation non-invasive testing versus coronary angiography result

Previous non-invasive test		**Coronary angiography**		**Total**
		Stenosis	No stenosis	
Positive test	Number	**265 (47%)**	304 (53%)	569 (100%)
Negative test	Number	9 (50%)	9 (50%)	18 (100%)
Total	Number	274 (47%)	313 (53%)	587 (100%)

Table 7: Cross tabulation previous non–invasive test versus coronary angiography result

In table seven the result of previous non -invasive testing versus following coronary angiography for all included patients (n=587) is presented. 569 patients showed ischemia evidence or a stenosis in a coronary artery in at least one previous non-invasive test. 265 participants (47%) of these were diagnosed with a stenosis in coronary angiography and 304 patients (53%) were not.

18 patients got a negative result for ischemia evidence or a lesion in previous non-invasive testing, but nevertheless 9 patients (50%) of these were diagnosed with stenosis in coronary angiography and 9 participants (50%) did not show stenosis in coronary angiography.
The result has a sensitivity of 97% (95% confidence interval [CI]: 0,95-0,99) and a specificity of 3 % (95% confidence interval [CI]: 0,01-0,05).

3.7 Proportion of patients related to non-invasive testing

Ergometry		MPI		CCTA		MRI	
Ischemia	No ischemia	Ischemia	No ischemia	Stenosis	No stenosis	Ischemia/ stenosis	No ischemia /stenosis
n=182	n=13	**n=234**	n=23	**n=244**	n=0	**n=16**	n=0

Table 8: Proportion of patients in 4 non-invasive tests before CA

The whole patient population (n=587) underwent at least one of the four non-invasive tests shown in Table 8. On 257 of them a SPECT was performed, followed by CCTA (n=244), ergometry (n=195) and MRI (n=16). The CCTA and MRI patients all got positive results in their previous tests. In the ergometry patient population 13 patients showed no sign of coronary ischemia and in the SPECT patient population 23 patients got a negative result in the SPECT finding, but nevertheless all included patients underwent coronary angiography.

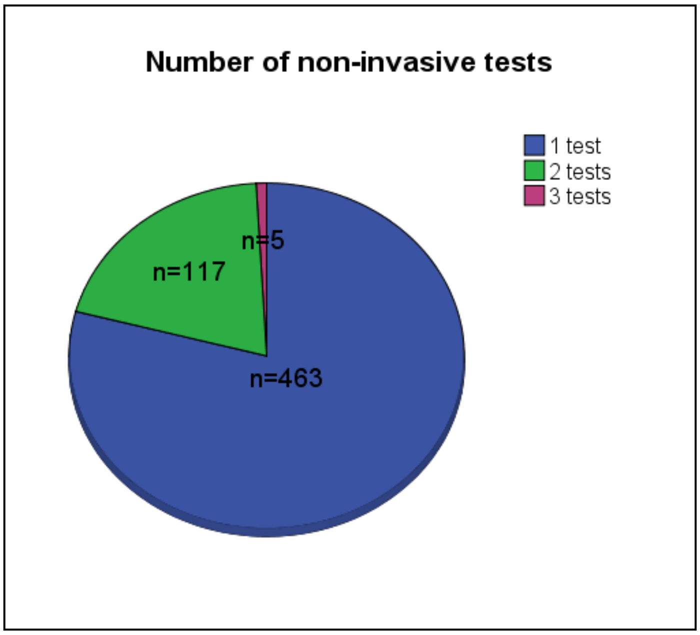

Figure 12: Proportion of patients with one or more non-invasive tests

Proportion of patients with one, two or three non-invasive tests is presented in figure 12. 463 patients underwent one test, 117 patients got two procedures and on 5 patients three non-invasive tests were performed, before invasive coronary catheterization.

3.7.1 Ergometry

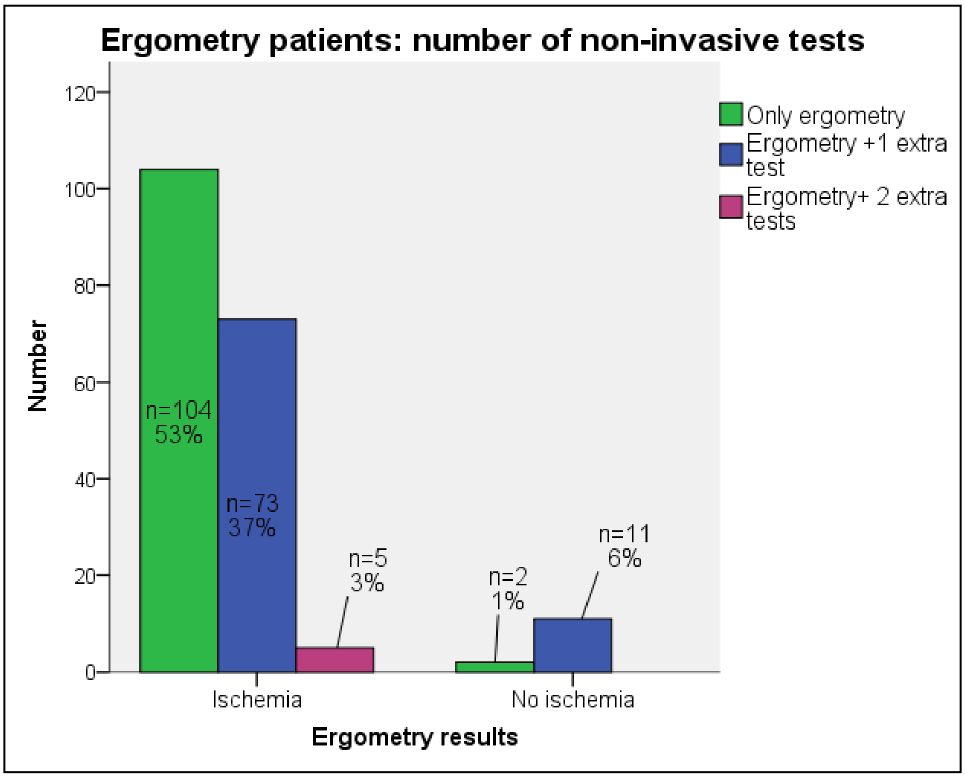

Figure 13: Number of non-invasive tests for ergometry patients

Figure 13 shows all ergometry patients and their number of non-invasive tests before CA. On 195 patients 289 non-invasive tests were performed. 106 of 195 patients got only an ergometry, 84 participants underwent ergometry and one extra non-invasive test and five patients got three non-invasive procedures. The distribution of the patients with two non-invasive tests is described as follows: 50 patients out of these got a coronary computed tomography angiography, 32 underwent myocardial perfusion scintigraphy with SPECT and two out of these underwent magnet resonance imaging. The five participants with three procedures got an ergometry, myocardial perfusion scintigraphy and CCTA.

3.7.2 Myocardial perfusion scintigraphy

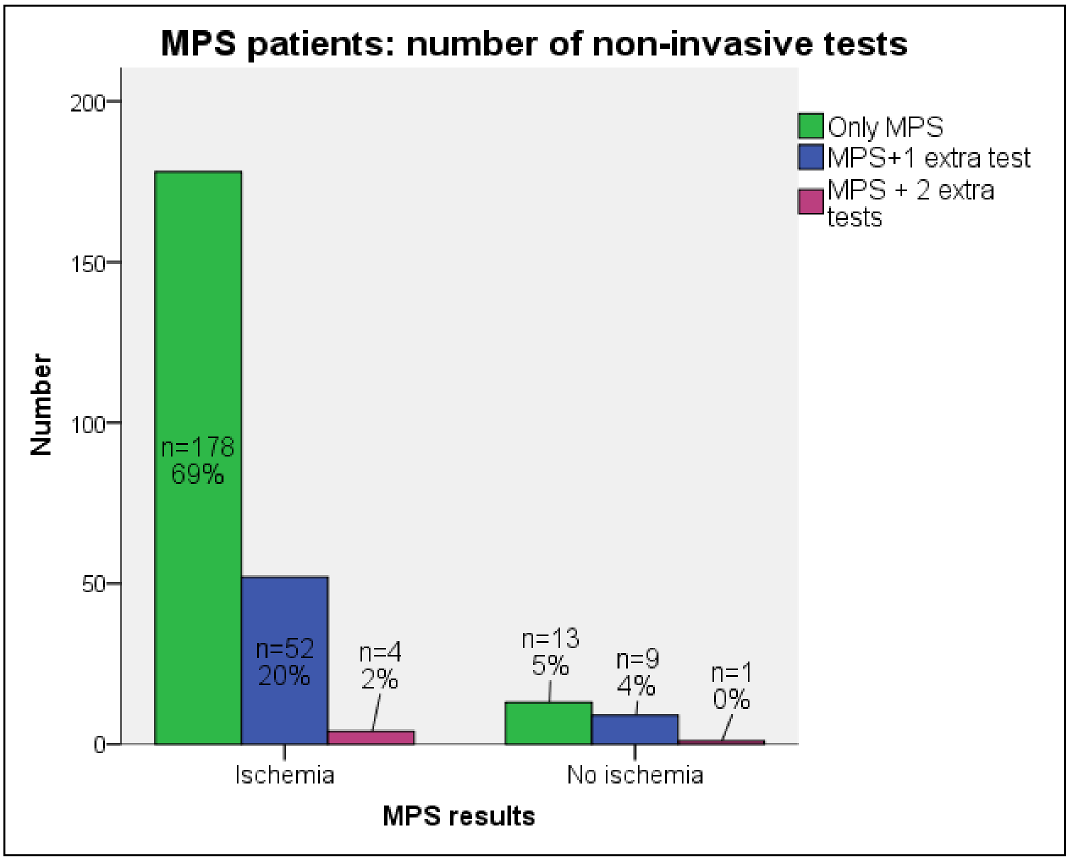

Figure 14: Number of non-invasive tests for MPS patients

All 257 patients with previous myocardial perfusion imaging are resumed in figure 14. On 257 MPI patients 328 non-invasive tests were performed, before coronary angiography. MPI patient population is divided as follows: 191 patients got myocardial perfusion scintigraphy with SPECT, 61 patients underwent MPS and one extra test and five patients had three non-invasive tests before CA. The biggest part of the patients with two tests had an ergometry as second procedure (n=32), tightly followed by the ones who underwent CCTA (n=27) and the ones with second MRI (n=2). The patients with three procedures are the ones who underwent myocardial perfusion scintigraphy, ergometry and CCTA as non-invasive procedures.

3.7.3 CCTA

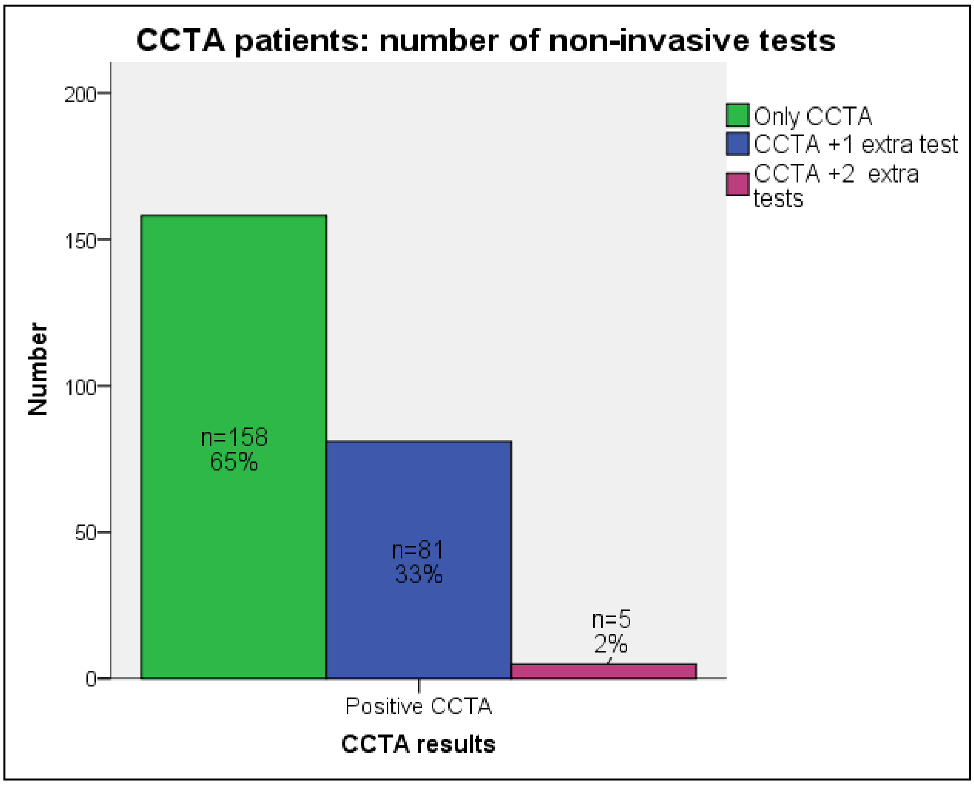

Figure 15: Number of non-invasive tests for CCTA Patients

Figure 15 presents 244 patients with at least coronary computed tomography angiography as non-invasive diagnostic tool. 244 patients underwent 335 non-invasive tests before coronary catheterization. On 158 of them only CCTA was performed, 81 patients underwent CCTA and one extra procedure and five got three tests.

The distribution referred to non-invasive testing for the participants with two procedures is as follows: most of them got an ergometry (n=50), 27 of them underwent MPS and four patients underwent MRI in addition to CCTA. Five patients underwent three procedures: these are CCTA, MPS and ergometry.

3.7.4 MRI

MRI study population represents the smallest group in the study (n=16). Half of them (n=8) underwent only magnet resonance imaging and the other ones got two tests. Taken as a whole, 16 patients underwent 24 non-invasive tests. Nobody of the MRI patients underwent three tests. The distribution for the ones with two previous procedures is as follows: two got an ergometry, on two a myocardial perfusion scintigraphy with SPECT was performed and four underwent CCTA in addition to magnet resonance imaging.

MRI patient population reached the highest percentage of patients with two procedures (50%), followed by ergometry patients (43%), CCTA patient population (33%) and MPI participants (24%).

3.8 Statistic analyses cath lab University Hospital Graz 2015

3.8.1 Coronary angiographies and percutaneous coronary interventions altogether

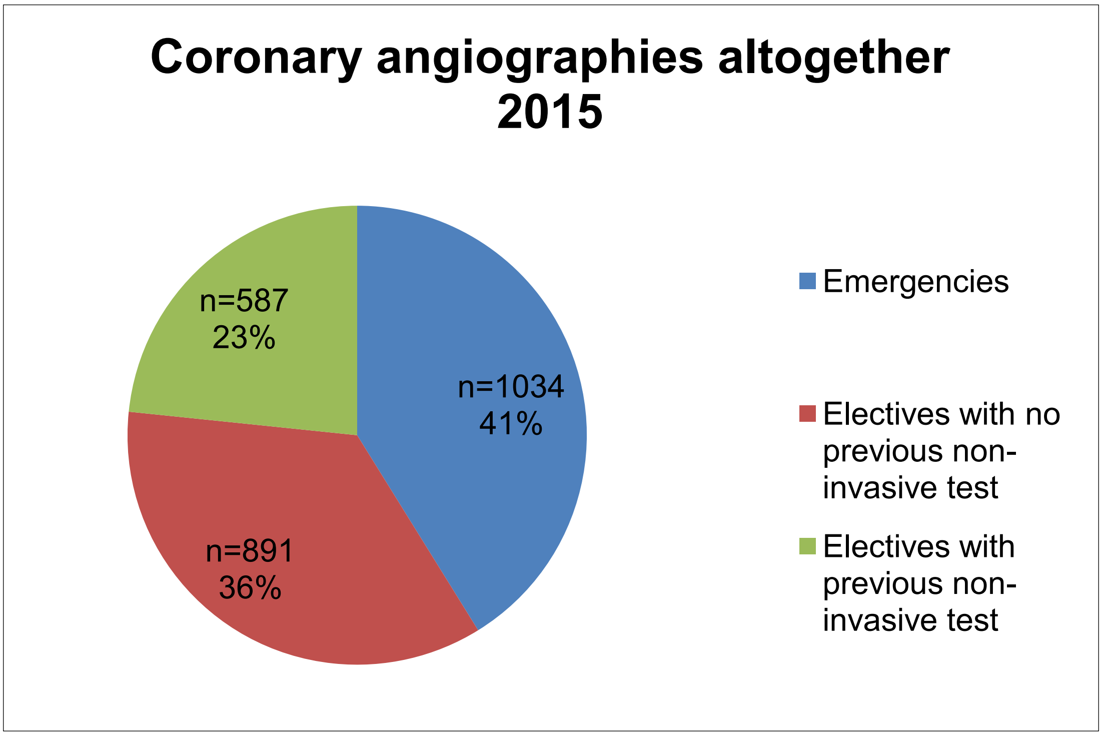

Figure 16: Coronary angiographies University Heart Center Graz 2015

In 2015 2512 patients underwent coronary angiography at the University Heart Center in Graz. 1034 patients (41%) of them were emergencies, separated in: STEMI, NSTEMI, unstable angina pectoris and shock patients. 891 patients (36%) were elective patients that did not receive any previous non-invasive test for cardiac ischemia. 587 patients (23%) were elective patients with at least one non-invasive test for cardiac ischemia before CA.

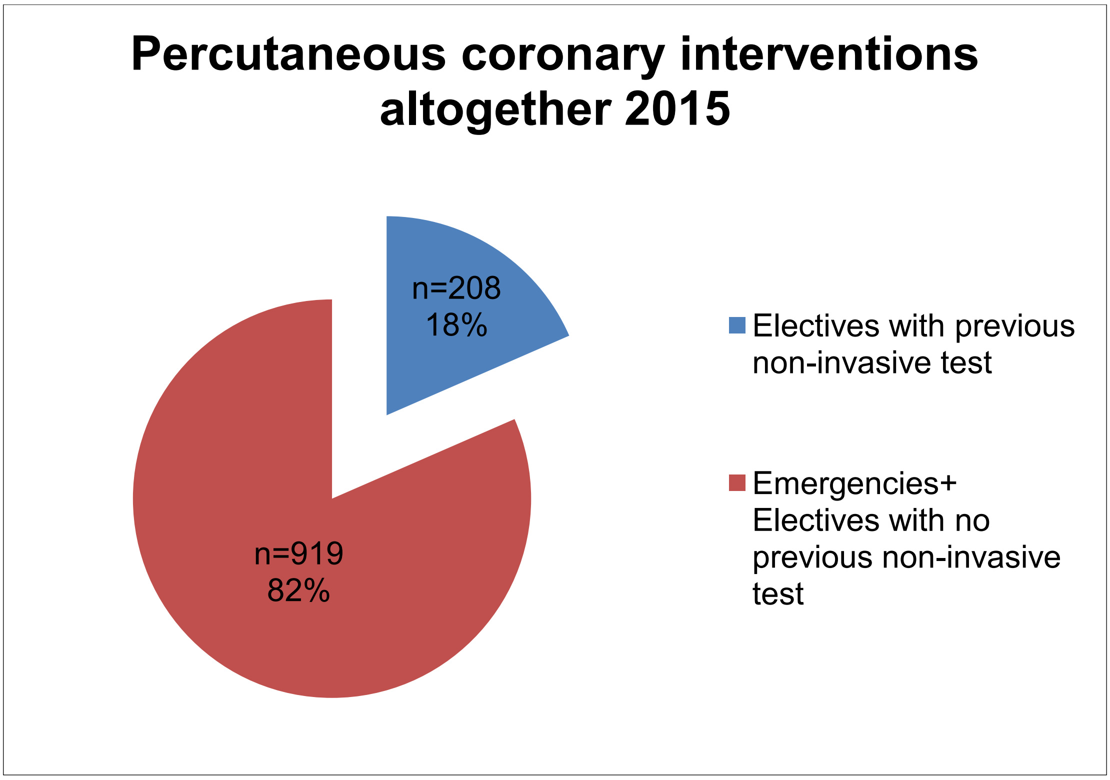

Figure 17: Percutaneous coronary interventions University Heart Center Graz 2015

Figure 17 shows all percutaneous coronary interventions performed at the University Heart Center in Graz in 2015. Taken as a whole, 1127 PCIs were performed in 2015. 919 PCIs were emergency PCIs or elective patients with no previous non-invasive procedure in the past history, that's a percentage of 82%. Patients with non-invasive test before CA underwent 208 percutaneous coronary interventions in 2015 (18%).

3.8.2 Distribution of treatment during or after coronary angiography

	Intervention required	No intervention required
No positive test (n=18)	n=9 (50%)	n=9 (50%)
1 positive test (n=466)	n=211 (45%)	n=255 (55%)
2 positive tests (n=99)	n=54 (55 %)	n=45 (45%)
3 positive tests (n=4)	n=3 (75%)	n=1 (25%)

Table 9: Number of positive non-invasive tests related to the treatment during or after coronary angiography

The distribution of positive non-invasive tests related to the decision of treatment during or after invasive coronary angiography is presented in table 9. In this table, the included patients are separated in two different groups presented in the two columns. The first column represents the participants who were diagnosed with at least one lesion in CA, which requires intervention such as percutaneous coronary intervention, coronary artery bypass grafting or optimal medical therapy for the ones, where intervention was not possible because of their age and co-morbidities. The second group includes the patients, who were diagnosed with no obstructive coronary artery disease in CA both the ones with lesions, which needed no intervention and the ones, who got a negative result in CA.

Altogether on 18 patients a non-invasive test was performed and revealed a negative result, but although all of them underwent CA afterwards. As a result, nine of these showed a lesion in CA, which was worth of intervention and the other nine patients revealed non-obstructive coronary artery disease. In total 466 participants got one positive non-invasive test for coronary ischemia. In this patient group 211 patients underwent PCI, CABG or optimal medical therapy, if an intervention was not possible, after their diagnostic coronary angiography. Of these, 255 patients needed no intervention after diagnostic heart catheterization.

99 patients got two positive non-invasive tests before invasive CA and in 54 patients of these the CA confirmed the previous result from the non-invasive test and revealed obstructive coronary artery disease, which needed intervention. Of these 45 patients showed no obstructive CAD and were treated conservatively.
The smallest group includes the persons with three positive non-invasive tests (n=4). Of these three patients underwent intervention in the form of PCI, CABG or OMT and one patient revealed no need for intervention in diagnostic CA.

3.9 Special analyses for patients with risk factors

3.9.1 Patients with previous percutaneous coronary intervention

128 patients have already had a percutaneous coronary intervention at the time they underwent their non-invasive test for this study. On 42 participants of these an ergometry was performed, 83 underwent myocardial perfusion scintigraphy with SPECT, 13 got a CCTA and 5 underwent MRI.
The MRI reached the highest percentage (80%) based on the patients, who were diagnosed with ischemia evidence or at least one stenosis in one coronary artery in the previous non-invasive test and an obstructive coronary artery disease in coronary angiography. 64% of the patients with positive results in ergometry also had a lesion in coronary angiography, which was required for treatment including PCI, CABG or optimal medical therapy in cases, where an intervention was not possible. Myocardial perfusion scintigraphy with SPECT reached 55% followed by coronary computed tomography angiography with 31%.
In conclusion three out of four positive preprocedural tests performed on patients presenting with previous PCI (n=128) resulted in a higher percentage of necessities for intervention including PCI and CABG than for the all-comer population (n=587). As an exception, the positive CCTA indicated interventions including PCI and CABG in a lower percentage (31%) in participants with previous PCI than for all included patients (47%).

Ergometry results		Coronary angiography		Total
		Stenosis	No stenosis	
Ischemia evidence	Number	25 (64%)	14 (36%)	39 (100%)
No ischemia evidence	Number	1 (33%)	2 (67%)	3 (100%)
Total	Number	26 (62%)	16 (38%)	42 (100%)

Table 10: Ergometry versus CA findings for patients with previous PCI

MPI results		Coronary angiography		Total
		Stenosis	No stenosis	
Ischemia evidence	Number	43 (55%)	35 (45%)	78 (100%)
No ischemia evidence	Number	3 (60%)	2 (40%)	5 (100%)
Total	Number	46 (55%)	37 (45%)	83 (100%)

Table 11: MPS versus CA findings for patients with previous PCI

CCTA results		Coronary angiography		Total
		Stenosis	No stenosis	
Positive CCTA	Number	4 (31%)	9 (69%)	13 (100%)
Total	Number	4 (31%)	9 (69%)	13 (100%)

Table 12: CCTA versus CA findings for Patients with previous PCI

MRI results		Coronary angiography		Total
		Stenosis	No stenosis	
Positive MRI	Number	4 (80%)	1 (20%)	5 (100%)
Total	Number	4 (80%)	1 (20%)	5 (100%)

Table 13: MRI versus CA findings for patients with previous PCI

4 Discussion

According to the gender distribution this study population (34% women, 66% men) represents the lifetime prevalence for CAD in German-speaking countries (8).
In this all-comer population 569 participants were tested positive for ischemia in their previous non-invasive procedure. 265 out of these 569 patients (47%) were diagnosed with obstructive CAD in CA.
MRI demonstrated the highest accuracy (63%) in the study population with 10 patients out of 16 who presented with obstructive CAD in CA and a previous positive MRI, but these data are limited by a small number of patients. 96 patients out of 182 patients with a positive ergometry result presented with a lesion needed to treat in CA hence ergometry reached the second highest accuracy (53%). 114 patients had a positive CCTA and showed an obstructive CAD in coronary angiography thus CCTA reached an accuracy of 47%. CCTA is tightly followed by MPI, which reaches an accuracy of 45% and presents the lowest percentage for non-invasive procedures in the whole study population. In this all comer population MRI and ergometry represent the most reliable procedures to detect obstructive CAD within non-invasive testing.
Diagnostic coronary angiography required an intervention in 277 patients of the study population (n=587) and of these 208 patients underwent percutaneous coronary intervention. In one out of three patients, the non-invasive procedure resulted in percutaneous coronary intervention. Patients who were diagnosed with more than one positive test had a higher feasibility to undergo an intervention after diagnostic coronary angiography (table 9).
Finally, patients with a history of previous PCI (n=128) were compared to the whole study population (n=587) with the result that MRI also demonstrated the highest accuracy in these patients (80%). The ergometry procedure shows the second highest percentage (64%).

MPI reached an accuracy of 55% in the patients with previous PCI which means that MPI is a better predictor for obstructive CAD in the patients, who have already had a PCI, compared to the whole study population. CCTA shows the lowest accuracy in the participants with a history of PCI (31%). In conclusion, the four non-invasive procedures demonstrated more reliable results in patients with a history of previous PCI compared to the all-comer population.

4.1 Comparison to other studies

The following studies also evaluate the non-invasive testing strategies for patients with suspected coronary artery disease. The non-invasive procedures in these studies include both anatomical and functional testing.

In the retrospective study of Demir et al. 778 patients in two hospitals in the UK with suspected stable coronary artery disease were included. In hospital A the patients underwent exercise tolerance test and in hospital B either CCTA, stress echocardiography or myocardial perfusion scintigraphy were performed on the included patients. According to the procedure results 127 patients in hospital A underwent CA and 52 patients of these (41%) presented with obstructive CAD. In hospital B 63 coronary angiographies were performed and 32 patients (50,8%) were diagnosed with obstructive CAD. This study suggests that cardiac imaging in comparison to ETT testing causes fewer coronary angiographies and a higher percentage of patients diagnosed with obstructive CAD in CA (30).

In comparison to our study 195 patients with previous ergometry underwent CA and 102 of these were diagnosed with obstructive CAD (52%). With regard to our study 501 patients had CA after previous CCTA or MPI non-invasive testing and of these 229 patients presented with obstructive CAD (46%). In our study, the exercise testing showed a higher accuracy compared to cardiac imaging strategy.

Compared to the patients in Demir et al. our study had a higher number of cases who underwent CA (587 vs. 190). The patient population in Demir et al. included more female patients (48% vs. 34%) and the patients were younger (60±12,3 years, 57,5±11 years vs. 69± 9,95 years).

The second study is a prospective multicenter imaging trial called the PROMISE study with 10,003 included patients in 193 sites in North America analyzed by Douglas et al. The included patients presented with symptoms suspicious for stable CAD and received either functional or anatomical testing. The patients in the anatomical testing group underwent CCTA (n= 4996) and the ones in the functional testing group had either exercise ECG, nuclear stress testing or stress echocardiography (n=5007).

On 609 patients in the PROMISE trial both CCTA and coronary angiography were performed and 310 patients underwent revascularization (PCI or CABG) after diagnostic CA. 406 patients underwent functional testing and of these 160 participants had revascularization. The PROMISE trial shows that CCTA strategy was associated with a higher incidence of showing obstructive CAD in invasive CA compared with functional testing (exercise ECG, stress echocardiography, nuclear stress testing) (31, 32).

	Previous CCTA	**Previous functional-testing**
PROMISE trial	51%	39%
University Heart Center Graz	46%	45%

Table 14: Comparison of percentages of revascularizations in patients who underwent CCTA or functional testing and invasive CA

In our study 244 patients underwent CCTA and on 113 revascularization was performed. In terms of functional testing our patients did not undergo stress echocardiography but also exercise ECG and MPI compared to the PROMISE trial. 452 participants had functional testing and 205 of these got a revascularization. In comparison to the PROMISE trial our study also shows a higher accuracy in CCTA than in functional testing (table 14), but the difference is small (46% vs. 45%). The PROMISE trial shows a bigger difference between CCTA and functional testing (51% vs. 31%) according to revascularizations after different non-invasive testing procedures.

MR-INFORM study accomplished by Nagel et al. is a prospective multi-centre study with 918 included patients presenting with stable angina. The patients were randomized in one FFR-informed group and one MR-informed group.
The FFR-informed group received CA supplemented by FFR-measurements and the MRI-informed group underwent stress perfusion MRI to guide the following treatment. In the FFR-informed group 44,2% of the included patients underwent revascularization and on 36% of the MR-informed group revascularization was performed. The study suggests that MR-perfusion imaging is non-inferior to a strategy with CA supported by FFR during a follow up of one year in patients presenting with stable angina and an intermediate to high risk for CAD (33, 34).

In our study only 16 patients underwent MRI and on 10 out of those revascularization was performed (63%). In terms of case numbers our study is not comparable to the study of Nagel et al., but both the patients in the MR-INFORM study and in our study presented with symptoms suspicious for CAD. Furthermore, the MR-INFORM study shows CMR perfusion imaging could be an attractive non-invasive alternative to current diagnostic procedures. Based on our study MRI showed the highest accuracy in non-invasive testing and represented a reliable method to detect obstructive CAD.

4.2 Limitations

The patient data in this retrospective study was collected out of the MEDOCS system, which basically includes procedure results which were performed at the University Clinic in Graz. More than a half of our patients underwent their previous non-invasive procedures in hospitals and/or diagnostic centers outside the University Clinic. The results of these procedures were received out of first case histories, medical reports and progress notes. Thus, it can be assumed that several previous non-invasive procedures of elective patients have not been gathered in the OpenMEDOCS.

Another limitation is the relatively small number of MRI patients compared with the patients who underwent ergometry, CCTA or MPI. In order to verify the result of this study it would be necessary to have comparable patient populations.

Not unexpected for all-comers, the patient population was inhomogeneous according to their age and cardiovascular risk factors. The range reached from patients who were diagnosed with CAD for the first time and the ones who already have had CABG.

In terms of calculation of sensitivity and specificity of every single non-invasive method it would have been necessary to have more patients with previous negative non-invasive test and CA. These patients do not really exist in a high number, because usually a negative non-invasive test does not lead to invasive testing.

4.3 Conclusion

In conclusion, this study suggests that MRI could be an attractive alternative in non-invasive testing and that MRI is an effective gatekeeper for invasive coronary angiography. This study evaluates that ergometry both in the all-comer population and in patients with previous PCI has a higher accuracy in terms of prediction of significant coronary artery disease compared to CCTA and MPI.

Furthermore, this study shows that the accuracy of non-invasive tests may vary in patients with a history of previous investigations e.g. previous PCI.

5 References

1. AUSTRIA S. Gestorbene 2015 nach Hauptgruppen der Todesursachen und Geschlecht (in Prozent). In: Todesursachenstatistik, editor. Wien: STATISTIK AUSTRIA; 2016.

2. Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, Budaj A, et al. ESC guidelines on the management of stable coronary artery disease. European Heart Journal(2013) 34. 2013:2949-3003.

3. Sun Z, Choo GH, Ng KH. Coronary CT angiography: current status and continuing challenges. The British journal of radiology. 2012;85(1013):495-510.

4. Harrison T, Longo D, Fauci A, Kasper D, Hauser S, Jameson J, et al. Harrison`s Principles of Internal Medicine. 18th ed: The McGraw Hill companies; 2012.

5. Nabel EG, Braunwald E. A tale of coronary artery disease and myocardial infarction. The New England journal of medicine. 2012;366(1):54-63.

6. Pichlhofer O, Maier M, Badr-Eslam R, Ristl R, Zebrowska M, Lang IM. Clinical presentation and management of stable coronary artery disease in Austria. PloS one. 2017;12(4):e0176257.

7. Loscalzo J, Fauci A, Kasper D, Longo D, Braunwald E, Hauser S, et al. HARRISON´S
Cardiovascular Medicine. Loscalzo J, editor: The McGraw-Hill Companies; 2010. 639 p.

8. Herold G. Innere Medizin. Köln: Herold,G; 2015.

9. Ambrosio G, Komajda M, Mugelli A, Lopez-Sendon J, Tamargo J, Camm J. Management of stable angina: A commentary on the European Society of Cardiology guidelines. European journal of preventive cardiology. 2016;23(13):1401-12.

10. Pischon T, Boeing H, Hoffmann K, Bergmann M, Schulze MB, Overvad K, et al. General and abdominal adiposity and risk of death in Europe. The New England journal of medicine. 2008;359(20):2105-20.

11. Prescott E, Hippe M, Schnohr P, Hein HO, Vestbo J. Smoking and risk of myocardial infarction in women and men: longitudinal population study. BMJ (Clinical research ed). 1998;316(7137):1043-7.

12. Perk J, De Backer G, Gohlke H, Graham I, Reiner Z, al. e. European Guidelines on cardiovascular disease
prevention in clinical practice. European Heart Journal (2012) 33. 2012:1635-701.
13. Khera AV, Emdin CA, Drake I, Natarajan P, Bick AG, Cook NR, et al. Genetic Risk, Adherence to a Healthy Lifestyle, and Coronary Disease. The New England journal of medicine. 2016;375(24):2349-58.
14. Windecker S, Kolh P, Alonso F, Collet J, Cremer J, Falk V, et al. ESC/EACTS Guidelines on myocardial revascularization. European Heart Journal (2014) 352014. p. 2541-619.
15. Erdmann E. Klinische Kardiologie. 8th ed. Erdmann E, editor. Heidelberg: Springer Medizin Verlag Heidelberg; 2011. 13-44 p.
16. Balfour PC, Jr., Gonzalez JA, Kramer CM. Non-invasive assessment of low- and intermediate-risk patients with chest pain. Trends in cardiovascular medicine. 2017;27(3):182-9.
17. Alexanderson-Rosas E, Guinto-Nishimura GY, Cruz-Mendoza JR, Oropeza-Aguilar M, De La Fuente-Mancera JC, Barrero-Mier AF, et al. Current and future trends in multimodality imaging of coronary artery disease. Expert review of cardiovascular therapy. 2015;13(6):715-31.
18. Alkadhi H, Leschka S, Stolzmann P, Flohr T. Praxisbuch Herz-CT. Heidelberg: Springer Verlag Berlin Heidelberg; 2013. p. 47-52.
19. Sun Z, Aziz YF, Ng KH. Coronary CT angiography: how should physicians use it wisely and when do physicians request it appropriately? European journal of radiology. 2012;81(4):e684-7.
20. Pundziute G, Schuijf JD, van Werkhoven JM, Nucifora G, van der Wall EE, Wouter Jukema J, et al. Head-to-head comparison between bicycle exercise testing and coronary calcium score and coronary stenoses on multislice computed tomography. Coronary artery disease. 2009;20(4):281-7.
21. Kato S, Kitagawa K, Ishida N, Ishida M, Nagata M, Ichikawa Y, et al. Assessment of coronary artery disease using magnetic resonance coronary angiography: a national multicenter trial. Journal of the American College of Cardiology. 2010;56(12):983-91.
22. Sakuma H. Coronary CT versus MR angiography: the role of MR angiography. Radiology. 2011;258(2):340-9.

23. Sicari R, Nihoyannopoulos P, Evangelista A, Kasprzak J, Lancellotti P, Poldermans D, et al. Stress Echocardiography Expert Consensus Statement--Executive Summary: European Association of Echocardiography (EAE) (a registered branch of the ESC). European heart journal. 2009;30(3):278-89.
24. Bruschke AV, Sheldon WC, Shirey EK, Proudfit WL. A half century of selective coronary arteriography. Journal of the American College of Cardiology. 2009;54(23):2139-44.
25. Fihn SD, Gardin JM, Abrams J, Berra K, Blankenship JC, Dallas AP, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. Journal of the American College of Cardiology. 2012;60(24):e44-e164.
26. Schomig A, Mehilli J, de Waha A, Seyfarth M, Pache J, Kastrati A. A meta-analysis of 17 randomized trials of a percutaneous coronary intervention-based strategy in patients with stable coronary artery disease. Journal of the American College of Cardiology. 2008;52(11):894-904.
27. Dangas GD, Serruys PW, Kereiakes DJ, Hermiller J, Rizvi A, Newman W, et al. Meta-analysis of everolimus-eluting versus paclitaxel-eluting stents in coronary artery disease: final 3-year results of the SPIRIT clinical trials program (Clinical Evaluation of the Xience V Everolimus Eluting Coronary Stent System in the Treatment of Patients With De Novo Native Coronary Artery Lesions). JACC Cardiovascular interventions. 2013;6(9):914-22.
28. Campeau L. Letter: Grading of angina pectoris. Circulation. 1976;54(3):522-3.
29. Criteria Committee NYHA. Inc. Diseases of the Heart and Blood Vessels. Nomenclature and Criteria for diagnosis. 6th edition Boston,Little,Brown and Co. 1964.
30. Demir OM, Bashir A, Marshall K, Douglas M, Wasan B, Plein S, et al. Comparison of clinical efficacy and cost of a cardiac imaging strategy versus a traditional exercise test strategy for the investigation of patients with suspected

stable coronary artery disease. The American journal of cardiology. 2015;115(12):1631-5.
31. Douglas PS, Hoffmann U, Lee KL, Mark DB, Al-Khalidi HR, Anstrom K, et al. PROspective Multicenter Imaging Study for Evaluation of chest pain: rationale and design of the PROMISE trial. American heart journal. 2014;167(6):796-803.e1.
32. Douglas PS, Hoffmann U, Patel MR, Mark DB, Al-Khalidi HR, Cavanaugh B, et al. Outcomes of anatomical versus functional testing for coronary artery disease. The New England journal of medicine. 2015;372(14):1291-300.
33. Hussain ST, Paul M, Plein S, McCann GP, Shah AM, Marber MS, et al. Design and rationale of the MR-INFORM study: stress perfusion cardiovascular magnetic resonance imaging to guide the management of patients with stable coronary artery disease. Journal of cardiovascular magnetic resonance : official journal of the Society for Cardiovascular Magnetic Resonance. 2012;14:65.
34. Nagel E, al. e. MR-INFORM trial results released: MR perfusion imaging could replace invasive procedures in patients with stable angina Insitute for Experimental and Translational Cardio Vascular Imaging University Hospital Frankfurt; 2017 [cited 2017 05.06.2017]. Available from: www.cardiac-imaging.org/news.