# Diploma Thesis

## Early Identification of Acute Coronary Occlusion in Patients with Non-ST-Elevation Myocardial Infarction (NSTEMI) by Wall Motion Analysis.

Submitted by

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Graz, 21st August 2017

# Statement of Authorship

I hereby confirm that the work presented has been performed and interpreted solely by myself except for where I explicitly identified the contrary. I assure that this work has not been presented in any other form for the fulfilment of any other degree or qualification. Ideas taken from other works in letter and in spirit are identified in every single case.

Graz, 21st August 2017 Markus Haar, eh

# Acknowledgement

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Furthermore, I would like to thank Univ.-Prof. Dipl.-Ing. Dr.techn. Andrea Berghold for assisting me with the statistical considerations for the study protocol.

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# List of Abbreviations

| | |
|---|---|
| **2D-STE** | Two-dimensional speckle tracking echocardiography |
| **3D-STE** | Three-dimensional speckle tracking echocardiography |
| **A2C** | Apical 2 chamber view |
| **A4C** | Apical 4 chamber view |
| **A5C** | Apical 5 chamber view |
| **ACS** | acute coronary syndrome |
| **AMG** | Adjusted mini-GRACE |
| **ApoB100** | Apolipoprotein B 100 |
| **ASA** | Acetylsalicylic acid |
| **ASE** | American Society of Echocardiography |
| **AUC** | Area under the curve |
| **CA** | Coronary angiography |
| **CABG** | Coronary artery bypass graft |
| **CAD** | Coronary artery disease |
| **CAD** | Coronary artery disease |
| **CI** | Confidence interval |
| **CK** | Creatine kinase |
| **CK-MB** | Creatine kinase myocardial bland |
| **CKD** | Chronic kidney disease |
| **CMR** | Cardiac magnetic resonance |
| **CPR** | Cardiopulmonary resuscitation |
| **cTn** | Cardiac Troponin |
| **CV** | cardiovascular |
| **CVD** | Cardiovascular disease |
| **DAPT** | Dual antiplatelet therapy |
| **DCM** | Dilated cardiomyopathy |
| **DESL** | Duration of end-systolic lengthening |
| **EACVI** | European Association of Cardiovascular Imaging |
| **EC** | Endothelial cell |
| **ECG** | Electrocardiogram |
| **Echo** | Echocardiography |
| **ECM** | Extracellular matrix |
| **ESC** | European Society of Cardiology |
| **FRA** | Functional risk area |
| **GCS** | Global circumferential strain |
| **GDF** | Growth differentiation factor |
| **GLPSS** | Global longitudinal peak systolic strain |
| **GLS** | Global longitudinal strain |
| **GRACE** | Global registry of acute coronary events |
| **GRS** | Global radial strain |
| **HDL** | High-density lipoprotein |
| **HR** | Hazard ratio |
| **hs** | High-sensitive |
| **IHD** | Ischemic heart disease |
| **IL** | Interleukin |
| **IMI** | Inducible myocardial ischemia |
| **LA** | Left atrium |
| **LAD** | Left anterior descending |
| **LBBB** | Left bundle branch block |
| **LCX** | Left circumflex artery |
| **LDL** | Low-density lipoprotein |
| **LMCA** | Left main coronary artery |
| **LV** | Left ventricular |
| **LV** | Left ventricle |
| **LVEF** | Left ventricular ejection fraction |
| **MACE** | Major adverse cardiac event |
| **MCP** | |
| **MI** | Myocardial infarction |
| **MMP** | Matrix metalloproteinase |
| **NPV** | Negative predictive value |

| | |
|---|---|
| **NSTE-ACS** | Non-ST-elevation acute coronary syndrome |
| **NSTEMI** | Non-ST-Elevation myocardial infarction |
| **NT-proBNP** | n-terminal pro-brain-natriuretic-peptide |
| **OCT** | Optical coherence tomography |
| **P** | P-value |
| **PCI** | Percutaneous coronary intervention |
| **PLAX** | Parasternal long axis |
| **PM** | Pacemaker |
| **PPV** | Positive predictive value |
| **RCA** | Right coronary artery |
| **ROC** | Receiver operator characteristics |
| **ROI** | Region of interest |
| **RWMA** | Regional wall motion analysis |
| **S4C** | Subcostal 4 chamber view |
| **SMC** | Smooth muscle cell |
| **SR** | Strain rate |
| **STEMI** | ST-Elevation myocardial infarction |
| **TCFA** | Thin-cap fibroatheroma |
| **TIMI** | Thrombolysis in myocardial infarction |
| **TLPSS** | Territorial longitudinal peak systolic strain |
| **Tn** | Troponin |
| **TNF** | Tumour necrosis factor |
| **UFH** | Unfractionated heparin |
| **ULN** | Upper limit of normal |
| **URL** | Upper reference limit |
| **VCAM** | Vascular cell adhesion molecule |
| **WBC** | White blood cell |
| **WMS** | Wall motion score |
| **WMSI** | Wall motion score index |

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# Abstract

**Background.** Patients with non-ST elevation acute coronary syndromes (NSTE-ACS) frequently lack typical electrocardiographic signs when the coronary artery is occluded. Since acute coronary occlusions (ACO) are associated with worse outcome, further measures are needed to increase diagnostic sensitivity in this subgroup. The aim of this thesis is to evaluate the feasibility of regional wall motion analysis (RWMA) by two-dimensional echocardiography to detect ACO in patients with non-ST elevation myocardial infarction (NSTEMI).

**Methods.** For this interim analysis twenty patients with NSTEMI and onset of chest pain within 24 hours at presentation to the emergency department were prospectively enrolled to undergo echocardiography before coronary angiography. Patients were recruited from July 2016 to July 2017 in four centres and underwent echocardiographic RWMA by either strain echocardiography (speckle tracking) or wall motion score index (WMSI) based the availability of strain echocardiography.

**Results.** Out of twenty patients five (25 %) had an ACO on coronary angiography. RWMA by strain echocardiography and WMSI both showed a trend towards impaired regional left ventricular function in patients with ACO, although none of the obtained parameters were significant. Functional risk areas (FRA) by strain (8 vs. 3 segments) and WMSI (4 vs. 2 segments) were higher in patients with ACO when compared to those without. Furthermore, absolute territorial longitudinal peak systolic strains were lower in patients with ACO regardless of the culprit artery (LAD: 11.7 ± 2.3 % vs. 15.0 ± 4.4 %; LCX: 13.1 ± 1.4 % vs. 14.4 ± 4.9 %; RCA: 14.3 ± 3.1 % vs. 15.8 ± 3.8 %).

**Conclusion.** Although this thesis cannot contribute to the hypothesis of detecting ACO by two-dimensional echocardiography (mostly due to the low sample size), the currently available literature strongly suggests an increase in sensitivity for detecting ACO by using echocardiography in addition to the already employed diagnostic approach.

# Abstract (German)

**Hintergrund.** Bei Patienten mit non-ST elevation acute coronary syndrome (NSTE-ACS) liegen im Elektrokardiogramm häufig keine typischen Zeichen vor, die auf das Vorliegen eines akuten Koronarverschlusses (ACO) hindeuten. Da das Vorhandensein eines ACO mit einer schlechteren Prognose einhergeht, sind weitere ergänzende Verfahren notwendig, um die diagnostische Sensitivität in dieser Subgruppe zu steigern. Das Ziel dieser Arbeit ist es, den Nutzen regionaler Wandbewegungsanalysen mittels zweidimensionaler Echokardiographie zur Detektion von ACO in Patienten mit non-ST elevation myocardial infarction (NSTEMI) zu ermitteln.

**Methoden.** Für diese Zwischenauswertung wurden zwanzig Patienten mit NSTEMI und Symptombeginn innerhalb von 24 Stunden zum Zeitpunkt der Präsentation in der Notaufnahme prospektiv eingeschlossen. Die echokardiographische Untersuchung erfolgte vor der Koronarangiographie. Die Studienteilnehmer wurden von Juli 2016 bis Juli 2017 in vier teilnehmenden Zentren rekrutiert. Je nach Möglichkeit der Durchführung wurden die regionale Wandbewegungsanalyse entweder mittels Strain-Echokardiographie (Speckle tracking) oder per Wall Motion Score Index (WMSI) vorgenommen.

**Ergebnisse.** Von den zwanzig untersuchten Patienten wurde bei fünf (25 %) ein akuter Koronarverschluss festgestellt. Beide Untersuchungsmodalitäten deuteten auf eine beeinträchtige regionale linksventrikuläre Funktion bei Patienten mit akutem Koronarverschluss hin. Allerdings zeigte sich bei keine der erhobenen Parameter ein signifikanter Unterschied zwischen beiden Gruppen. Die sog. „Functional Risk Area“ (FRA) war sowohl bei Beurteilung durch Strain (8 vs. 3 Segmente), als auch mittels WMSI (4 vs. 2 Segmente) in Patienten mit akutem Koronarverschluss größer als in der Vergleichsgruppe. Des Weiteren zeigte sich, dass der absolute territoriale longitudinale peak systolic Strain, unabhängig vom betroffenen Koronargefäß, bei Koronarverschluss niedriger war (LAD: 11,7 ± 2,3 % vs. 15,0 ± 4,4 %; LCX: 13,1 ± 1,4 % vs. 14,4 ± 4,9 %; RCA: 14,3 ± 3,1 % vs. 15,8 ± 3,8 %).

**Zusammenfassung.** Obwohl diese Arbeit nicht zur Stützung der Hypothese, dass akute Koronarverschlüsse mittels zweidimensionaler Echokardiographie detektiert werden können, beitragen kann, gibt es in der zur Verfügung stehenden Literatur starke Hinweise darauf, dass die diagnostische Sensitivität durch die zusätzliche Verwendung von Echokardiographie gesteigert werden kann.

# Introduction

## 1 Acute Coronary Syndrome (ACS)

### 1.1 Definitions

As stated by the *European Society of Cardiology (ESC),* myocardial infarction is defined as myocardial necrosis owing to prolonged ischemia. Beside the detection of a rise and/or fall of cardiac biomarkers, at least one of the below criteria must apply[1]:

- Symptoms of ischemia
- New or presumed new ST-segment or T wave changes or new left bundle branch block (LBBB)
- Development of pathologic Q waves
- Imaging evidence of new loss of viable myocardial tissue or new regional wall motion abnormality
- Identification of intracoronary thrombus

Furthermore, the following types of MI can be distinguished[1]:

- **Type 1:** Spontaneous MI
- **Type 2:** MI Secondary to ischemic imbalance
- **Type 3:** MI resulting in death when biomarker values were unavailable
- **Type 4a:** MI related to percutaneous coronary intervention (PCI)
- **Type 4b:** MI related to stent thrombosis
- **Type 5:** MI related to coronary artery bypass grafting (CABG)

Apart from this classification, ACS can be divided into three clinically relevant subgroups *(see **Figure 1**)*[1, 2]:

- Unstable Angina (UA)
- Non-ST Elevation MI (NSTEMI)
- ST Elevation MI (STEMI)

Since UA and NSTEMI lack to show persistent ST elevation in the 12-lead ECG they are referred to as Non-ST Elevation Acute Coronary Syndrome (NSTE-ACS) and generally lead to a more restrictive treatment in the acute setting. UA represents a reversible damage to the myocardial tissue and is thereby not accompanied by a rise in cTn levels.

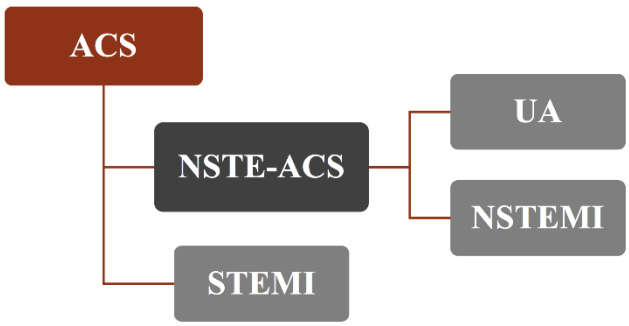



**Figure 1:** Acute Coronary Syndrome (ACS) subgroups. *Modified from Braunwald et al. 2012*

## 1.2 Cardiac Biomarkers for the Diagnosis of Acute Myocardial Infarction

### 1.2.1 Cardiac Troponins

Cardiac troponins (cTn) represent the gold standard for the laboratory diagnosis of MI, as they show high myocardial tissue specificity along with considerable clinical sensitivity. Elevated cTn levels are specified as a value surpassing the 99$^{th}$ percentile (upper reference limit, URL) and vary between various assays.[1] In general, imprecisions smaller than 10 % at the 99$^{th}$ percentile are considered acceptable.

The cTn complex – consisting of three isoforms (cTnI, cTnT, and cTnC) – plays an important role in the regulation of excitation-contraction coupling and can exclusively be found in cardiomyocytes, whereas other Tn isoforms are expressed in skeletal muscles. Therefore, detection of cTns in the blood is highly specific for myocardial damage. However, it is less specific for the detection of an ischemic cause of cTn release. About 4 to 8 % of cTns are physiologically present within the cytosol of cardiomyocytes[3, 4] and seem to be exposed to lower binding forces to intracellular components. Hence, this small proportion of cTn is more easily released and represents an “early appearing pool” as opposed to cTn complexes that are firmly bound within the contractile apparatus (“structural pool”). This early appearing

pool, however, can also be released in the absence of myocardial necrosis and – due to the relatively short half-life within the blood of approximately two hours – can appear as rapid rise and fall of cTn within 24 hours, thereby reflecting reversible myocardial injury. The prolonged appearance of cTn in myocardial necrosis over the period of approximately four to ten days is thought to be due to ongoing breakdown of the contractile proteins both intracellularly and within the blood. This leads to the appearance of various forms of the originally identical cTn molecules that need to be captured by cTn assays so as to maintain high sensitivity.[4-6]

*White* suggested six potential mechanisms of Tn release[4]:

- **Type I:** Myocyte necrosis
- **Type II:** Apoptosis
- **Type III:** Normal myocyte turnover
- **Type IV:** Cellular release of proteolytic troponin degradation products
- **Type V:** Increased cellular wall permeability
- **Type VI:** Formation and release of membranous blebs

Notably, there are various causes of myocardial damage other than ischemia or ACS that can lead to elevation of cTns (e.g. tachy- or bradyarrhythmias, myocarditis, etc.; *see **Figure 38** for further differential diagnoses, Appendix A)*.[5]

To increase diagnostic specificity in patients with comorbidities (e.g. renal failure) – that would also evoke elevated cTn levels – it is important, however, to consider a rise and/or fall of cTn for the diagnosis of MI. Therefore, serially drawn blood samples are necessary.[5, 7] If cTn is unavailable, creatine kinase myocardial band (CK-MB) is the best option available and is interpreted equally, although a lower specificity must be considered.[1]

Even though the detection of cTns for establishing the diagnosis of MI has been applied for decades, their sensitivity was poor in the early hours after symptom onset, hence,

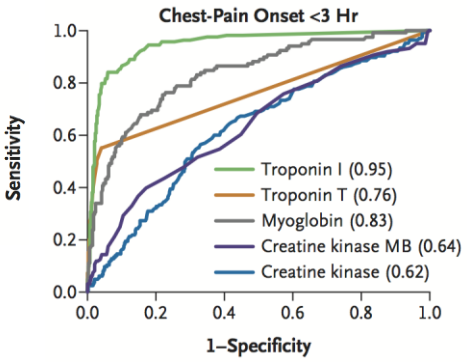



**Figure 2:** ROC curves and corresponding AUCs. *From Keller et al. 2009*

leading to a delay in diagnosis, especially in inconclusive cases. Over the last decade a novel generation of cTn assays with high sensitivity (hs-cTn) was introduced in order to shorten this period of time.[8] In a study by *Keller et al.*[9] a hs-cTn-I assay *(6 ng/l limit of detection)* with a cut-off level of 40 ng/l *(representing the 99th percentile based on 5000 normal subjects)* was compared to a standard cTn-T assay, myoglobin, as well as CK and CK-MB *(see **Figure 2**)*. 1818 patients presenting with new-onset chest pain were included, 413 *(22.7 %)* of which were discharged with the diagnosis of MI. Sensitivity, specificity, PPV, NPV, and AUC (ROC curve) of the hs-cTn-I assay within three hours after chest pain onset were 84.0 %, 93.2 %, 82.0 %, 94.0 %, and 0.95 as compared to 55.2 %, 95.7 %, 82.7 %, 85.2 %, and 0.76 of the standard cTn-T assay, respectively. The good diagnostic performance of hs-cTn assays was also shown by another multicentre study by *Reichlin et al.*[10] Thereby, a marked improvement of diagnostic accuracy and a reliable rule-out even within the early hours after pain onset was achieved.

### 1.2.2 CK and CK-MB

With its description in the 1960's and further improvements the years after, creatine kinase activity in serum represented a cornerstone in the laboratory diagnosis of acute MI, as it not only allowed for the confirmation of myocardial damage within 24 hours but also for the estimation of MI size and prognosis.[11, 12]

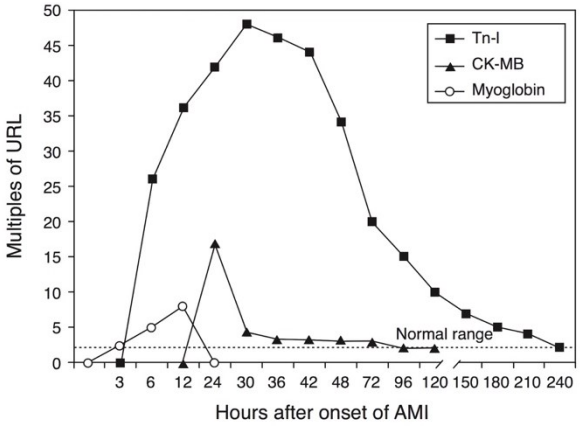



**Figure 3:** Kinetics of CK-MB, myoglobin, and cTn-I release in acute MI. *From Montorsi et al. 2009*

The detection of the isoenzyme CK-MB (for myocardial band) brought about a large improvement since it accounts for 22 to 30 % of the total CK in the myocardium as compared to only 1 to 3 % in the skeletal muscle.[13, 14] Thus, a relative increase of CK-MB over 3 to 5 % of total CK activity most likely represents a damage of myocardial rather than skeletal muscle tissue. However, false-positive

results were frequently encountered leading to a determination of mass rather than enzymatic activity of CK-MB with a subsequent improvement of specificity.[12]

In a study by *Young et al.* 1042 patients who presented to the emergency department with chest pain and a non-diagnostic ECG for MI *(defined as at least two contiguous ST-elevations of ≥ 1 mm)* were assessed for the diagnostic performance of CK-MB mass. In 8.6 % of the study population MI was diagnosed. CK-MB mass measurements at 0 and 3 hours showed a sensitivity, specificity, PPV, and NPP of 57 %, 97 %, 52 %, 96 % and 88 %, 96 %, 55 %, 99 % for MI, respectively.[15]

CK-MB exceeds the URL after 3 to 12 hours of symptom onset in MI. A peak is reached at 24 hours before it markedly decreases within the next several hours and returns to normal within 72 hours *(see **Figure 3**)*.[16, 17]

## 1.3 ST-Elevation Myocardial Infarction (STEMI)

When MI occurs, ST elevations can develop in the 12-lead ECG. In order to meet STEMI criteria, significant ST elevation must be present at the J point (with the TP- or PR-segment as reference) in at least two contiguous leads. The cut-points for significant ST elevation in patients without left ventricular hypertrophy and LBBB are[1, 18]:

- ≥ 0.1 mV in all leads other than $V_2$ and $V_3$
- for $V_2$ and $V_3$:
  - ≥ 0.2 mV in men ≥ 40 years
  - ≥ 0.25 mV in men < 40 years
  - ≥ 0.15 mV in women

In order to increase sensitivity of the ECG in the diagnosis of STEMI it is recommended to record the extended leads $V_{3R}$ and $V_{4R}$ as well as $V_7$ to $V_9$ in patients with suspected right ventricular infarction and suspected acute circumflex occlusion, respectively. For the extended leads the following cut-points apply[1, 18]:

- in $V_{3R}$ and $V_{4R}$ ≥ 0.05 mV

- in $V_{3R}$ and $V_{4R}$ ≥ 0.1 mV in men < 30 years
- in $V_7$ to $V_9$ ≥ 0.05 mV
- in $V_7$ to $V_9$ ≥ 0.1 mV in men < 40 years

Against general perception STEMI criteria proof to possess a relatively low sensitivity in detection of coronary occlusion and are often not transmural.

## 1.4 Non-ST Elevation Myocardial Infarction (NSTEMI)

Whereas STEMI and NSTEMI both are clinically accompanied by chest pain and elevation of cTn (or rise and/or fall, when elevated), the electrocardiographic features differ. Whenever the ECG criteria for STEMI are not met under these conditions (elevated cTn level or rise and/or fall, when elevated), the MI is termed NSTEMI. The patient may present with an either normal or abnormal 12-lead ECG. In the latter case, ST depression *(≥ 0.05 mV)* or T wave inversion *(≥ 0.1 mV)* may evolve and are expected to occur in at least two contiguous leads (together with a prominent R wave) in order to be considered significant.[1, 19]

Furthermore, *(significant [≥ 0.1 mV])* ST elevation may occur but they need to be temporary so as to meet NSTEMI criteria. Moreover, subtle ST elevation *(0.01 to 0.09 mV)* can be observed. Nevertheless, they are considered as features of NSTEMI since STEMI criteria are not met.[20]

## 1.5 Stable and Unstable Angina Pectoris

Unstable angina is defined as myocardial ischemia that does not lead to myocardial necrosis – hence cTn levels are not elevated (or no rise and/or fall, when elevated).

Angina pectoris can be subdivided into typical and atypical angina, depending on the chest pain characteristics. Therefore, the following features are taken into account:

- Substernal chest pain or discomfort
- Provoked by exertion or emotional stress
- Relieve of symptoms by rest and/or nitroglycerin

If all three features are present, angina is considered as typical, otherwise it is considered as atypical (2 features) or non-cardiac chest pain (≤ 1 feature).[21-23] Based on the extent of constraint the *Canadian Cardiovascular Society (CCS)* derived another frequently used grading score.[24]

## 1.6 STEMI Equivalents

### 1.6.1 New or presumed new Left bundle branch block (LBBB)

According to the *ESC,*[1] new or presumed new left bundle branch block (LBBB) is considered as STEMI equivalent. Therefore, immediate coronary reperfusion in patients with clinical suspicion of MI is recommended. This appears to stand in contrast with the recommendation of the *AHA* who now (in comparison to their 2004 guidelines[25]) ascribes less benefit in the diagnosis of MI to this electrocardiographic abnormality.[26] Indeed, a retrospective study by *Jain et al.* revealed that only 33 % *(12 of 36)* of patients with new or presumed new LBBB and suspected MI truly had MI and only 5 of these showed to have coronary occlusion.[27] The presence of LBBB in the majority of patients presenting with chest pain is therefore considered to be more the consequence of a fibrotic or aging conduction system rather than an acute event indicating MI.[28]

Against general presumption it is possible to diagnose MI in the presence of LBBB using Sgarbossa's criteria[29-34]:

A) ST-segment elevation ≥ 1 mm and concordant with QRS complex in ≥ 1 lead (5 points), or
B) ST-segment depression ≥ 1 mm in lead $V_1$, $V_2$, or $V_3$ in ≥ 1 lead (3 points), or
C) Excessively discordant ST-elevation (≥ 5 mm) in leads with a negative QRS complex (2 points)

For the diagnosis of MI in the presence of LBBB at least 3 points are required in the weighted approach, as initially described by *Sgarbossa et al*. This approach achieved a sensitivity and specificity of 78 and 90 %, respectively.[29] However, in a review of 10 studies with 1,614 patients included sensitivity was shown to be low

(20 %) while remaining high specificity *(98 %)*. Furthermore, ≥ 2 points (representing Sgarbossa criteria C) for the electrocardiographic diagnosis of MI showed sensitivities of 20 to 79 %, specificities of 60 to 100 % and ineffective positive likelihood ratios *(0.7 to 6.6)*.[35] In a study by *Smith et al.* different modifications of the original criteria by Sgarbossa were compared in terms of their diagnostic sensitivity and specificity.[36] It was shown that sensitivity was markedly improved when a modified Sgarbossa rule *(no weighting and proportional discordance of at least 25 %)* was applied *(91 %)* when compared to the sensitivity of the original Sgarbossa criteria *with (52 %)* and *without (67 %)* weighting and the requirement of absolute discordance of at least 5 mm. Specificity remained high in this revised Sgarbossa rule *(90 %)*, although it was lower than that of the original Sgarbossa criteria *(98 %)*. It is noted, that all mentioned studies, except that one by *Smith and colleagues*, used laboratory (CK or CK-MB) rather than angiographically endpoints.

### 1.6.2 DeWinter ST/T-wave complexes

This ECG pattern was first described in 2008 by *DeWinter and colleagues* and is associated with significant LAD occlusion. It is characterised by an upsloping ST-segment depression of at least 1 mm followed by a prominent, positive, symmetrical T wave and absence of ST-elevation in the precordial leads ($V_1$ to $V_6$). This ECG pattern is seen in approximately 2 % of patients with anterior MI.[37-39] *(see **Figure 39** and **Figure 40**, Appendix B)*

### 1.6.3 Wellen's Syndrome

This ECG pattern is associated with critical LAD stenosis most commonly seen in the leads $V_2$ and $V_3$. Importantly, the patient can be pain free by the time the ECG is obtained, however, he or she is at high risk of developing anterior wall MI. Wellen's syndrome can be discriminated in a type A and type B pattern, showing biphasic (initially positive and terminally negative) T-waves or deeply and symmetrically inverted T-waves, respectively. The *type A* pattern *(see **Figure 41**, Appendix C)* can be found in 25 % of cases whereas the *type B* pattern *(see **Figure 42**, Appendix C)* is present in 75 % of Wellen's syndrome.[40, 41]

### 1.6.4 Isolated posterior MI

A standard 12-lead-ECG is not capable of capturing isolated posterior MI due to LCX occlusion which occurs with a rate of about 4 to 7 %. It may present with isolated ST-depressions in the anterior leads and can easily be missed. However, characteristic ST-elevations could be observed when applying leads $V_7$ to $V_9$ additionally.[42-44]

Furthermore, *Schmitt et al.* investigated 120 patients with MI with angiographically proven occlusion of the left circumflex artery (LCX). At a mean time of 5.5 hours after pain onset only 46 % showed significant ST-segment elevation *(>1 mm in peripheral leads, > 2 mm in V1 to V6 in two contiguous leads)* in the standard 12-lead ECG. In a subgroup of patients with extended leads *(> 1 mm in right precordial and posterior in 2 contiguous leads)* sensitivity improved to 61 %.[45]

### 1.6.5 Acute Left Main Coronary Artery (LMCA) occlusion

Although complete LMCA occlusion is a relatively rare event, it is live threatening as it supplies about 75 % of the myocardium in the majority of individuals.[46] Common electrocardiographic features of LMCA occlusion are widespread ST depressions (especially in leads I, II, and $V_4$ to $V_6$), ST elevation in $aV_R \geq 1$ mm, and ST elevation in $aV_R \geq V1$.[47]

# 2 Epidemiology

Cardiovascular disease (CVD) constitutes the main cause of death globally.[48] The major portion of these deaths is – with large distance – ascribed to ischemic heart disease (IHD) – accountable for approximately eight million deaths (worldwide) in 2013 – followed by cerebrovascular disease and hypertensive heart disease.[49] In contrast to the pathogenesis of atherosclerosis which evolves over decades[50] the possibly resulting myocardial infarction (MI), however, emerges rapidly and represents a life-threatening event due to myocardial necrosis, possibly leading to arrhythmias and heart failure.

Although the absolute number of CVD deaths increases steadily since 1990 owing to ageing and expansion of the global population, the age-adjusted death rate shows a contrary trend and reached a low of 293 per 100,000 in 2013.[51] This progress has been brought about by changes in initial treatment strategies of myocardial infarction in conjunction with consecutive management of acute complications as well as rehabilitation and reduction of risk factors.[52]

## 2.1 Incidence rates of STEMI and NSTEMI

Observing trends of MI in a community-based population from 1999 to 2008, incidence rates of MI, overall, decreased steadily from 287 per 100,000 in 2000 to 208 per 100,000 in 2008 (relative decrease of 24 %). Furthermore, a decline in the incidence rates of STEMI was observed, whereas those of NSTEMI slightly increased (*see* ***Figure 4***). Overall, a proportion of about one third (33.1 %) of patients with MI presented with STEMI, leaving about two thirds (66.9 %) of patients that presented with NSTEMI.[53] This trend was also monitored in other trials with similar results.[54, 55]

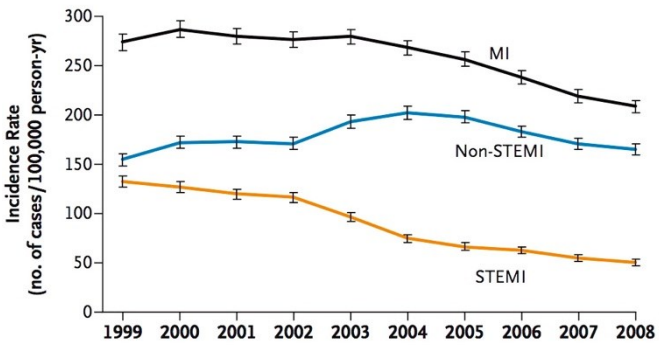



**Figure 4:** Incidence rates of MI, STEMI and NSTEMI from 1999 to 2008. *From Yeh et al. NEJM 2010; 362:2155-2165*

## 2.2 Distribution of Culprit Artery Lesions and Coronary Artery Occlusions in NSTEMI

*Bahrmann and colleagues* investigated 448 patients with NSTEMI within 72 hours of pain onset and found the culprit artery to be LAD, LCX, and RCA 28 %, 31 %, and 41 % in patients with occluded coronary artery and 52 %, 25 %, and 23 % in patients without coronary artery occlusion, respectively.[56]

Against general perception, coronary occlusion is not exclusively observed in patients with STEMI. This is shown in several angiographic studies investigating patients with NSTE-ACS: *Wang et al.* performed a retrospective analysis of the *PARAGON-B trial* in order to determine the rate of coronary artery occlusion in 1,957 patients with NSTE-ACS. Among these patients, an occlusion of the culprit artery was detected in 528 patients, accounting for 27 %. In 63 % of these 528 patients the inferolateral region was concerned, as compared to 45 % in the remaining patients with a non-occluded culprit coronary artery.[57] Another retrospective study that was performed with data derived from the *TRITION-TIMI 38 trial* identified 1,198 patients with isolated ST depression in leads $V_1$ to $V_4$ (NSTE-ACS). Among the study population 26.2 % had NSTEMI with coronary artery occlusion, 53.5 % had NSTEMI without coronary artery occlusion, and 20.3 % had unstable angina. Hence, of patients with NSTEMI rather than NSTE-ACS coronary artery occlusion was detected in 32.8 %.[58] Similar rates were found by Grenne and colleagues with coronary artery occlusion of 31.3 % and 18.9 % in patients classified as having NSTEMI and NSTE-ACS, respectively.[59]

To recapitulate, in patients classified as having NSTE-ACS coronary occlusion is detected in 18.9 to 27 % (about one forth). When considering patients classified as having NSTEMI coronary occlusion is detected in 31.3 to 32.8 % (about one third).

## 2.3 Distribution of transmurality in STEMI and NSTEMI

The use of cardiac magnetic resonance imaging (CMR) allows for the detection and differentiation of transmurality as well as the assessment of the affected myocardium in MI. Against general perception that STEMI leads to transmural and

NSTEMI to non-transmural myocardial infarction *Sarafoff et al.* managed to show that patients with STEMI were transmural in only 63 %. More interestingly, in 27 % of patients with NSTEMI transmural MI was observed (n = 220). Furthermore, the number of transmural segments (17-segment model) was significantly higher in patients with STEMI as opposed to those with NSTEMI *(2.4 ± 2.6 vs. 0.8 ± 1.5, p = 0.001)*, as was the total infarct size. Within the group of patients with NSTEMI the median infarct size was significantly larger in patients with transmural MI compared to those with non-transmural MI *(23.7 vs. 13.0 %LV, p = 0.001)*. The authors came to the deduction that the presence of ST-segment elevation is more useful for estimating the total infarct size rather than drawing conclusions about transmurality.[60]

## 2.4 Outcome

### 2.4.1 STEMI vs. NSTEMI

Looking at in-hospital mortality, *Rogers and colleagues* recognised a significant decline in both STEMI *(from 11.5 to 8.0 %)* and NSTEMI *(from 7.1 to 5.2 %)* patients – defining MI referring to *The Joint European Society of Cardiology/American College of Cardiology Committee for the Redefinition of Myocardial Infarction* in the year 2000[61] (with only minor differences to the current definition of MI[1]) – over the period of thirteen years (from 1994 to 2006).[54] Furthermore, *Yeh and associates*[53] found a significant reduction of age- and sex-adjusted 30-day mortality after MI from 10.5 % in 1999 to 7.8 % in 2008.

Although the short-term prognosis of patients presenting with STEMI is worse than that of patients with NSTEMI, multiple studies showed that the opposite seems to be true when comparing long-term outcomes of both groups:

A study conducted by *Setoguchi et al.* observed a long-time mortality rate of 20 %, 41 % and 57 % at one, three and five years after MI (STEMI and NSTEMI), respectively.[62] This trend was also recognised by a study of *Darling et al.* in a more

recent study period.[55] Breaking down the prognosis of MI by means of the presence of ST-segment elevation, a study[63] found the 28-day mortality in STEMI and NSTEMI to be 5.26 and 2.99 % *(p = 0.02)*, respectively. Those who survived these first 28 days were followed for seven years where the mortality rate was found to be higher in NSTEMI patients *(HR 1.31, 95 % CI [1.02 - 1.68], p = 0.035)* regardless of the acute revascularisation strategy (*see* ***Figure 5***). The worst short- and long-term mortality rate was observed in a third group, described as *"Undefined MI"* by the underlying ECG pattern (LBBB or PM). While a review[64] of 23 retrospective studies found that 30-day mortality was higher in patients with STEMI (*OR = 1.55, 95 % CI [1.16 - 2.06], p < 0.001)* and not different (p for difference ns) at one year *(OR = 1.02, 95 % CI [0.8 - 1.3], p = 0.85)*, several other studies found a higher[65-69] or similar[70] long-term mortality rate of NSTEMI.

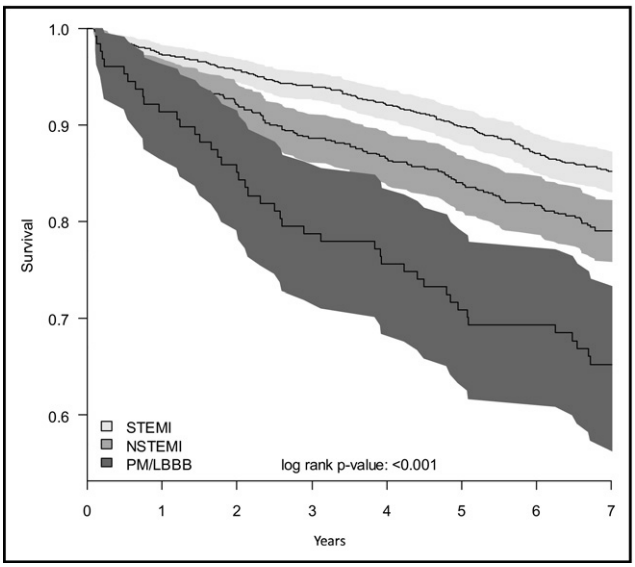



**Figure 5:** Kaplan-Meier plot of seven-year mortality by means of the underlying ECG pattern on admission among 28-day survivors (with the corresponding 95 % CIs)

A review[71] of several relatively old studies – recruitment years ranging from 1920 to 1977 – showed death rates in untreated patients before and during hospital admission to be 36 % in patients presenting with their first MI and 53 % in patients with subsequent MIs. All-cause mortality after the first MI was 10.3 % at one year and the annual death rate per year thereafter was found to be 5.3 %. These obtained data may function as a reference to different treatment strategies.

### 2.4.2 Coronary occlusion vs. non-occlusion in NSTEMI

Other than the discrimination by the presence or absence of ST elevation, MI can also be classified by either occlusion or non-occlusion of the culprit coronary artery.

A study by *Bahrmann et al.*[56] showed that patients with NSTEMI *(n = 448)* and coronary occlusion had significantly higher levels of CK and CK-MB on hospital

admission *(CK-MB: 1.4 ± 1.3 µmol/L s vs. 0.9 ± 0.8 µmol/L s, p = 0.001)* and during hospitalisation *(CK-MB: 2.1 ± 2.3 µmol/L s vs. 1.2 ± 1.1 µmol/L s, p = 0.001)* as well as lower left ventricular ejection fractions *(48 ± 20 % vs. 42 ± 21 %, p = 0.01)*. Although there were no differences in the clinical outcomes at 30 days after MI, there were significantly higher proportions of non-fatal reinfarctions *(33 % vs. 15 %, HR = 3.19, 95 % CI [1.41-7.21], p = 0.01)*, major adverse cardiovascular events *(MACE; 42 % vs. 25 %, HR = 2.16, 95 % CI [1.04-4.50], p = 0.04)*, and a non-significantly higher proportion of death *(10 % vs. 5 %, p = 0.24)* in patients with acute coronary occlusion within 6 months and after multivariate adjustment. This trend of worse long-term outcome in patients with coronary occlusion *(TIMI-flow grad 0 or 1)* compared to patients with non-occluded *(TIMI-flow grade 2 or 3)* coronary arteries was also observed in several other studies.[57, 58, 72, 73] *Pride and colleagues* found a significantly higher rate of a 30-day composite of death and MI in patients with NSTEMI and culprit artery occlusion (8.6 %) when compared to patients with NSTEMI but without occlusion (6.3 %) and those with unstable angina *(2.9 %) (3-way p = 0.006)*.[58] Furthermore, one study by *Kim et al.* showed a significant difference in mortality rates when comparing patients with TIMI-flow grade 0 to those with a TIMI-flow grade of ≥ 1 in-hospital, at one month, and at six months.[74] *See* ***Table* 1** *for further details.*

| Study | n | Time | NOC [%] | OC [%] | p |
|---|---|---|---|---|---|
| **Shin et al.[72] 2013** | 2878 | | | | |
| Cardiac mortality | | 12 months | 4.4 | 6.6 | 0.006 |
| | | 48 months | 5.4 | 8.6 | < 0.001 |
| Recurrent non-fatal MI | | 12 months | 5.9 | 9.3 | < 0.001 |
| | | 48 months | 9.4 | 16.2 | < 0.001 |
| **Wang et al. [57] 2009** | 1957 | | | | |
| Mortality | | 1 month | 2.3 | 3.6 | 0.11 |
| | | 6 months | 3.5 | 5.5 | 0.03 |
| Recurrent non-fatal MI | | 1 month | 11.1 | 14.4 | 0.66 |
| | | 6 months | 11.1 | 14.4 | 0.62 |
| **Kim et al.[74] 2012 *** | 2094 | | | | |
| Mortality | | 0 months | 1.5 | 3.6 | 0.004 |
| | | 1 month | 2.1 | 5.1 | 0.001 |
| | | 12 months | 4.1 | 8.1 | 0.001 |
| **Bahrmann et al.[56] 2011** | 448 | | | | |
| Mortality | | 1 month | 2.0 | 5.0 | 0.45 |
| | | 6 months | 5.0 | 10.0 | 0.24 |
| Recurrent non-fatal MI | | 1 month | 15.0 | 7.0 | 0.79 |
| | | 6 months | 15.0 | 33.0 | 0.01 |
| MACE | | 1 month | 16.0 | 10.0 | 0.95 |
| | | 6 months | 25.0 | 42.0 | 0.04 |

**Table 1:** Cumulative outcome of patients with NSTEMI with occluded coronary artery (OC; TIMI-flow grade 0-1) and non-occluded coronary artery (NOC).

## 2.5 Risk Stratification

### 2.5.1 Risk Stratification for Primary Prevention

#### *2.5.1.1 Biochemical Markers*

Since highly sensitive cTn assays have been introduced, several studies found an association of elevated baseline cTn levels – in both patients with stable CAD[75] and normal population cohorts[76, 77] (as well as elderly patient cohorts[78, 79]) – and cardiovascular risk. More specifically, the detection of elevated cTn at baseline was shown to be associated with increased rates of CV risk[77] or death[75, 78, 80, 81], HF[75, 78, 80], structural heart disease[76], CKD[76], non-fatal MI[81], and mortality in general. *Zeller and colleagues*[77] suggested a threshold of cTnI of 4.7 pg/ml in women *(52.4 %*

*sensitivity, 68.6 % specificity)* and 7.0 pg/ml in men *(39.1 % sensitivity, 81.8 % specificity)* to detect individuals with high risk of future CV events, derived by ROC curve analysis. *Omland et al.*[80] compared the predictive performances of elevated cTnI and cTnT which were significant for CV death or HF *(HR: 1.88; 95 % CI: 1.33 to 2.66; p < 0.001)*, whereas only cTnI predicted the risk of future MI *(HR: 1.44; 95 % CI: 1.03 to 2.01; p < 0.031)*. When cTnI decreases by more than 25 % – as compared to baseline values, this trend seems to be associated with a marked decrease in coronary events, independently of statin (pravastatin) or placebo therapy (in a middle-aged cohort of men).[81] However, in this trial pravastatin was capable of reducing cTnI levels by 13 % as compared to placebo which correlated with a reduction in LDL cholesterol concentrations *(r = 0.20; p < 0.001)*.

## 2.5.2 Risk Stratification in NSTE-ACS

### *2.5.2.1 ECG*

In a study conducted by *Kaul and colleagues*[82] the prognostic impact of the extent of ST-segment abnormalities in a subgroup of patients with NSTE-ACS in the *PARAGON-A trial*[83] was investigated. Patients were divided into three groups by their baseline ECG characteristics *(no ST-segment abnormalities, ≥ 1 mm ST depression, and ≥ 2 mm ST-segment depression in at least two contiguous leads in each case)*. Those who presented with ST-segment depressions of at least 2 mm were significantly more likely to meet the primary endpoint of death at one year *(OR 5.73; 95 % CI 2.8 to 11.6)* when compared to patients with no ST-segment abnormalities. Death at 30 days, 6 months, and 1 year after the index event occurred at a rate of 6.3 %, 12.0 %, and 13.4 % in patients with ≥ 2 mm, 2.8 %, 6.2 %, and 7.8 % in patients with ≥ 1 mm, and 0.7 %, 1.1 %, and 2.0 % in patients with no ST-segment abnormalities, respectively *(see **Figure 6**)*. Comparable results were achieved in a subgroup analysis of patients with NSTE-

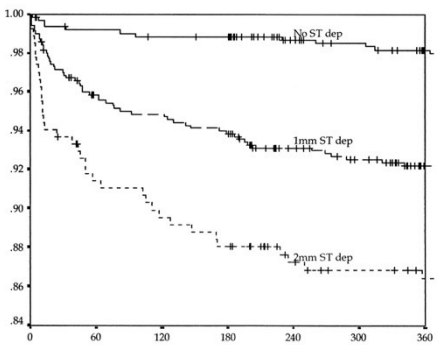



**Figure 6:** Survival rates corresponding to categories of ST-segment abnormalities in the PARAGON-Trial. From *Kaul et al. 2001*

ACS in the *GUSTO-IIb trial*.[84] However, T-wave inversions *(defined as ≥ 1 mm of baseline deviation)* do not further add to the prediction of outcome.[85]

### *2.5.2.2 Biochemical Markers*

In a subgroup analysis of the *Prospective Randomized Platelet Inhibition and Patient Outcomes (PLATO) trial*[86] *Wallentin and colleagues*[87] identified increased levels of hs-TnT, GDF-15 (growth differentiation factor-15), and NT-proBNP *(a median time of 15 hours after the index event)* as predictors for increased risk of cardiovascular death, myocardial infarction and stroke in non-invasively managed patients with NSTE-ACS. The same association was described with elevated levels of NT-proBNP and GDF-15 in patients treated invasively.

Cardiac Troponins have been used for risk stratification in patients with NSTE-ACS since 1992, when their potential as prognostic parameter was first demonstrated by *Hamm et al.*[88] Thereafter, several other studies confirmed these findings (*see* ***Figure 7***).[89-91]

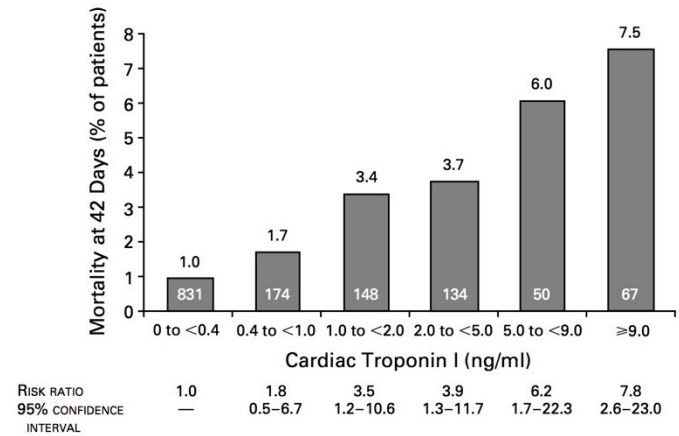



**Figure 7:** Mortality rates of patients with unstable angina or non-Q-wave MI at 42 days with respect to initially assessed cTnI values. From: Antman et al. 1996

In another study cTnI and NT-proBNP levels were correlated to death at 30 days after admission in patients with both NSTE-ACS and STE-ACS. Interestingly, in patients with NSTE-ACS who died, NT-proBNP levels were significantly higher than in those who survived at 30 days (2,725 vs. 882 pg/ml), whereas no significant cTnI difference was found in the same subgroup. Patients with Killip class greater than II were excluded.[92] This association between increased incidence of cardiovascular events and elevated BNP/NT-proBNP levels has been observed in several other studies.[93-104]

### *2.5.2.3 Quantitative Risk Assessment*

Several evaluation tools have been developed to quantitatively estimate the risk of adverse outcomes in NSTE-ACS.

#### *2.5.2.3.1 TIMI Risk Score for Unstable Angina and Non-ST Elevation MI*

Considering two randomised, double-blinded trials (*TIMI-11B* and *ESSENCE*) seven variables proved to be useful to assess the risk of death and the occurrence of ischemic events in patients with NSTE-ACS.[105] Each variable is assigned a value of 1 or 0, depending on its presence or absence, respectively, in an individual patient. These variables are:

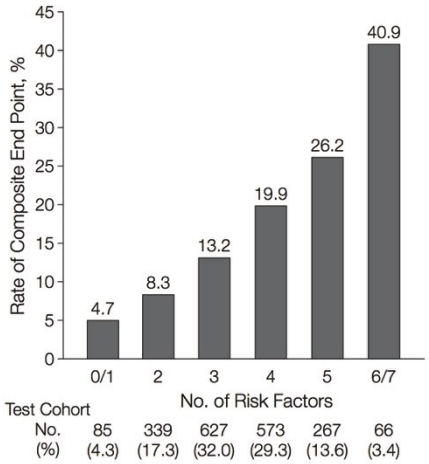



**Figure 8:** Rates of adverse events (incl. all-cause mortality, MI, and severe recurrent ischemia with the need for urgent revascularisation) at 14 days after randomisation in patients with NSTE-ACS. *From Antman et al. 2000*

- » Age ≥ 65 years
- » Presence of ≥ 3 risk factors for CAD *(family history of CAD, hypertension, hypercholesterolemia, diabetes, currently smoking)*
- » Significant coronary stenosis (≥ 50 %)
- » ST-segment deviation on initial ECG
- » Severe anginal symptoms
- » Use of ASA within the last 7 days
- » Elevated serum cardiac biomarkers (CK-MB and/or cTn)

The rate of adverse events – defined as all-cause mortality, MI, and severe recurrent ischemia with the need for urgent revascularisation – within 14 days, correlates almost linearly with increasing TIMI risk scores *(see **Figure 8**)*. Furthermore, the score was validated in the *TACTICS-TIMI-18 trial* by *Cannon et al.* for a composite primary endpoint of death, non-fatal MI, or rehospitalisation within the follow-up period of 6 months.[106]

The application of this risk score represents a simple and fast approach on risk stratifications in daily clinical practice. However, the predictive performance may

differ significantly, even when the same risk scores are achieved, since serum cardiac biomarkers are merely taken into account dichotomously, rather than quantitatively. Hence, due to the interlinked relationship between elevated cTn and reduction in preferable outcome (*see* ***Figure* 7**), estimation of adverse events may be underestimated considerably depending on the extent of cardiac biomarker elevation.

The *TIMI risk score for NSTE-ACS* has been validated in several other studies.[107-110]

*2.5.2.3.2 GRACE Risk Score*

Whereas the TIMI Risk Score for Unstable Angina and Non-ST Elevation MI predicts a composite endpoint of all-cause mortality, MI, and severe recurrent ischemia with the need for urgent revascularisation, the *GRACE Risk Score*[111] predicts the risk of death in-hospital in all patients with ACS. It was derived from the *GRACE registry* based on data from 11,389 patients. Eight variables were found to provide adequate prediction of outcome:

- Age
- Heart rate
- Systolic blood pressure
- Creatinine
- Cardiac arrest at admission
- ST-segment deviation on the ECG
- Elevated cardiac biomarkers
- Killip class

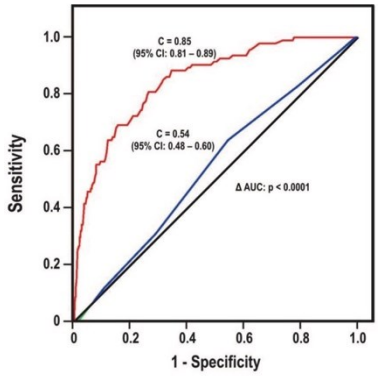



**Figure 9:** ROC curves of the TIMI risk score for UA/NSTEMI (blue) and GRACE score (red) for in-hospital mortality. *From Aragam et al. 2009*

Each factor is assigned a certain point score. After calculating the sum of all assessed point scores, the probability of mortality in-hospital can be predicted.

Even though it was initially derived to estimate the in-hospital mortality risk the *GRACE score* can as well be used to calculate the mortality rate at 6 and 12 months:

In a study by *Aragam and colleagues*[112], patients with ACS were categorized in groups of STEMI *(n = 698)* and NSTE-ACS *(n = 2753)*. Among all patients 4 % died in hospital and 7.4 % from hospital discharge until 6 months. When comparing the performance of the *TIMI (UA/NSTEMI) score* and *GRACE score* in the subgroup of patients with NSTE-ACS, the *GRACE score* performed better in predicting both in-hospital *(C = 0.85, 95 % CI: 0.81 to 0.89 vs. 0.54, 95 % CI: 0.48 to 0.60; p < 0.01)* and 6-month *(C = 0.79, 95 % CI: 0.76 to 0.83 vs. 0.56, 95 % CI: 0.52 to 0.60; p < 0.01)* mortality. The performance in the STEMI subgroup did not differ significantly at both points in time.

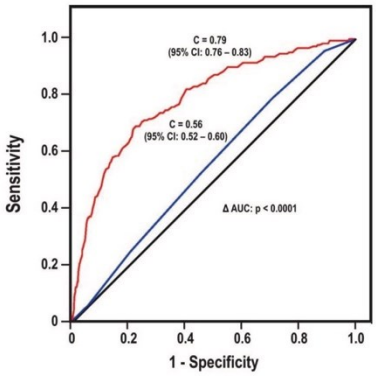



**Figure 10:** ROC curves of the TIMI risk score for UA/NSTEMI (blue) and GRACE score (red) for mortality at 6 months. *From Aragam et al. 2009*

Using data from 17,142 patients with ACS from the *GRACE registry* between 1999 and 2002, that were discharged alive, all-cause mortality was assessed for the development of a 6-mortality estimation model.[113] Among the development and validation subgroup mortality rates at 6 month were found to be 4.8 and 4.7 %, respectively. The developed model consists of 9 predictive risk factors:

- Age
- Heart rate
- Systolic blood pressure
- Creatinine
- Congestive heart failure
- PCI not performed in hospital
- Past history of MI
- ST-segment depression on presenting ECG
- Elevated cardiac biomarkers

The derived model achieved c-statistics of 0.81 and 0.75 for the development and validation cohort, respectively.

The *GRACE 2.0 risk score* was developed in 32,037 patients (from 94 hospitals in 14 countries) to account for non-linear relationships of risk factors and to further improve usability, especially in emergency clinical settings when certain variables are not yet available. Non-linear relationships were found for age, systolic blood pressure, pulse, and creatinine. With this adapted risk score c-indices were found to be 0.83 and 0.78 for death at 1 year and 3 years, respectively, adding a valuable prediction tool for long-term prognostication. *GRACE 2.0* was validated in the *FAST-MI 2005 registry* in 2,959 patients with ACS showing c-indices of 0.83 and 0.82 for 1- and 3-year death, respectively.[114, 115]

In addition, the *adjusted mini-GRACE (AMG) score* was introduced by *Simms and colleagues* using data from 137,084 patients with ACS *(38.8 % STEMI, 61.2 % NSTEMI)* within the *Myocardial Ischemia National Audit Project (MINAP)*, substituting a lack of Killip classification and creatinine levels with renal failure and the use of diuretics with .[116] The *AMG* for 6-month mortality prediction presented c-statistics of 0.84, 0.86, and 0.82 for AMI (all patients), STEMI, and NSTEMI, respectively, with demonstrating good accuracy. The model performance was constricted in patients with NSTEMI, chronic heart failure, chronic renal failure, and elderly patients (≥ 85 years), as well as in higher risk subgroups.

In another study the prognostic performance of *TIMI (UA/NSTEMI)*, *PERSUIT*, and the *GRACE risk score* were compared at 30 days and 1 year regarding a composite endpoint of MI or death in patients with NSTE-ACS.[117] When compared at 1 year the *GRACE risk score* performed significantly better *(C = 0.715, 95 % CI: 0.672 to 0.756)*.

A GRACE 2.0 score calculator can be accessed online.[118]

*2.5.2.3.3 ACTION Score*

This risk score was derived from the *Acute Coronary Treatment and Intervention Outcomes Network (ACTION)* containing data of 243,440 patients from 655 hospitals for the estimation of in-hospital mortality in ACS.[119] The in-hospital mortality rate was 4.6 % and the derived score showed excellent accuracy (c-statistic: 0.88) under inclusion of the following risk factors:

- Age
- Heart rate
- Systolic blood pressure
- Presentation after cardiac arrest
- Presentation in cardiogenic shock
- Presentation in heart failure
- Presentation with ST-segment elevation MI
- Creatinine clearance
- Troponin ratio

# 3 Evolution of Coronary Artery Disease (CAD)

## 3.1 Structure of the Normal Artery

The arterial wall consists of three layers – tunica intima, tunica media and adventitia.[120, 121]

The tunica intima comprises endothelial cells (EC) building the inner surface (endothelium) of the arteries. Active measures of the endothelium are needed so as to prevent platelets from aggregating and the coagulation cascade from being activated when blood gets in contact with this inner surface of the arteries. On the downside, the mentioned measures are indispensable when coping with blood loss as a consequence of injuries.[122]

Although disorders of this balancing act may be considered as one of the major mechanisms in the pathophysiology of ACS, metabolically active secretion of vasoactive substances and providing a barrier to the passage of blood and its constituents are important features of the endothelium, as well.[123]

The endothelium lies on a basement membrane containing molecules of the extracellular matrix (ECM). About half of the ECM – that is produced by smooth muscle cells (SMC) of the tunica media[122] – consists of the structural proteins elastin and collagen and thereby plays a significant role in meeting the biomechanical demands of normal physiological requirements to the arterial wall.[124, 125] Besides these two constituents, laminin, fibronectin and many other molecules can be found in the ECM.[122, 126] In the ageing, individual SMCs migrate into the intima and collagen type I and III can more frequently be found compared to the previous more often occurring collagen type IV. A process leading to a thickened intima and other subsequent biomechanical consequences.[122] The tunica media consists of SMCs which enable the arteries to relax or to contract, thereby playing a significant role in – not only but also – coronary autoregulation. The adventitia constitutes the most external layer of the arterial wall and consists mainly of fibroblasts and mast cells. It contains nerve endings and vasa vasorum.[122, 126]

## 3.2 Atherosclerosis

The understanding of the underlying pathophysiologic processes and aetiology of atherosclerosis has steadily evolved over the last decades[127], yet leading the way to inflammatory sequences as key elements of its pathogenesis. Thus, atherosclerosis is defined as multifocal, chronic, inflammatory and progressive disease leading to the accumulation of lipids and fibrous elements in the wall of medium- and large-sized arteries.[128, 129]

Typically, ECs efficiently prevent white blood cells (WBC) from connecting with them. However, when certain irritative stimuli are present the ECs change their behaviour in terms of their surface composition and permeability. The increase in permeability contributes to the entry and retention of low-density lipoproteins (LDL) and their retention in the arterial wall. Furthermore, ECs now express specific receptors on their surface that are capable of binding leukocytes. One type of these receptors (*others are likely to be intercellular adhesion molecule-1, E selection, and P-selection*[129]) – that is considered essential in the pathogenesis of atherosclerosis – is the vascular cell adhesion molecule-1 (VCAM-1). The expression of VCAM-1 – which is possibly the consequence of a diet high in cholesterol[130] and is markedly increased at sites of "low average shear but high oscillatory shear stress"[131] – results in adhesion of monocytes and T lymphocytes. When attached to VCAM-1 the monocyte diapedeses between the sound ECs so as to reach the intima of the arterial wall, by means of the monocyte chemoattractant protein-1 (MCP-1). The monocyte then transforms to a macrophage and enhances the expression of scavenger receptors on its surface. This leads to an uptake of oxidised or glycated lipoproteins and their characteristic appearance they are named after – foam cells.

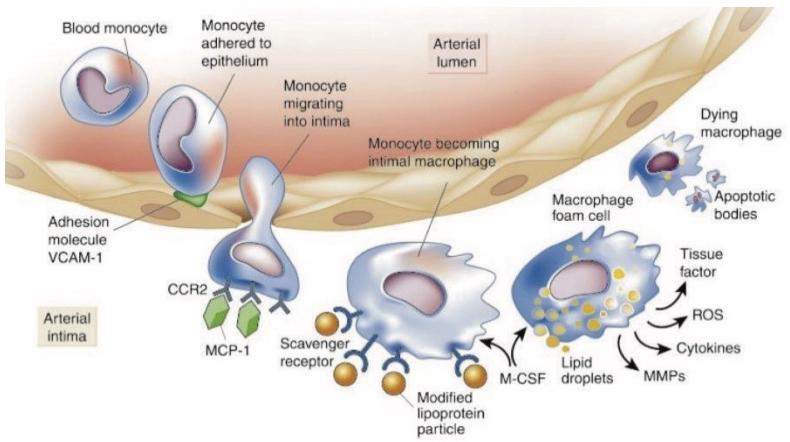



**Figure 11:** Pathogenesis of atherosclerosis. *From Libby 2002*

The pro-inflammatory cytokines further enhance the local inflammatory response of the growing atheroma. This inflammatory response plays a key role in both the pathogenesis and the complication of arterial plaques.[128, 132, 133]

The occurrence of atherosclerosis in the coronary arteries is called coronary artery disease (CAD).

### 3.2.1 Characteristics of Atheroma

As described above, SMCs – normally present in the tunica media – play a key role in the development of the ECM. During the progressing atherogenesis these SMCs migrate into the intima of the arterial wall and proliferate as response to certain mediators. Consequently, the production of ECM molecules enhances leading to the formation of a plaque-covering fibrous cap, separating its procoagulant content from the blood. The complex interaction of inflammatory processes underneath this cap lead to the formation of foam cells, some of which happen to die, consequently releasing lipids and other intracellular material into the extracellular space *(see **Figure 13:** )*.[132]

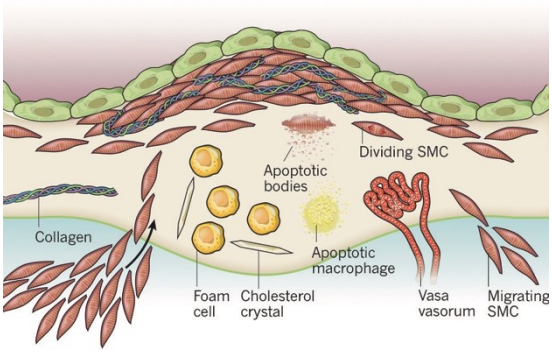



**Figure 13:** Migration of SMCs into the tunica intima with consecutive intimal storage of ECM. *From Libby et al. 2011*

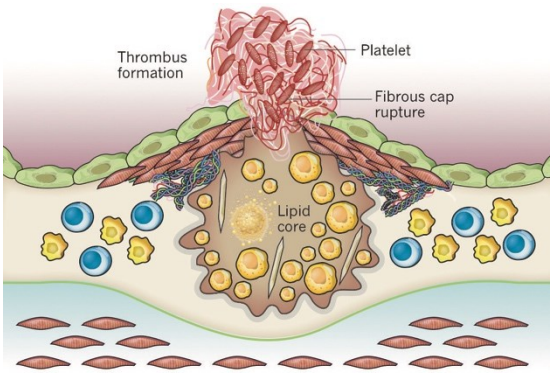



**Figure 12:** Illustration of the lipid core and rupture of the fibrous cap. *From Libby et al.*

Due to the lack of efficient efferocytosis (clearance of cellular debris) a lipid-rich necrotic core is formed *(see **Figure 13**)*. A process, especially occurring in presence of late rather than early lesional macrophage death.[134]

### 3.2.2 Initiation and Perpetuation of Inflammatory Processes in the Arterial Wall

Even though the underlying processes for the initiation of inflammation in the arterial wall are still not fully understood in humans, experiments in mice show that hyperlipidaemia leads to the differentiation of pro-inflammatory monocytes.[28, 35, 132] Lipoprotein A, homocysteine, Chlamydia pneumonia, herpes viruses, angiotensin II and retention of apoB100-containing lipoproteins[135] may also represent risk factors for inflammation.[128] Macrophages seem to perpetuate the inflammatory response by releasing interleukin-1β (IL-1β) and tumour-necrosis factor (TNF).[37, 39-41, 132, 136, 137] The inhibition of these two and other pro-inflammatory cytokines could lead to novel treatment strategies.[42]

## 3.3 Coronary Arteries

The coronary blood supply consists of three arteries which arise from the ascending aorta just above the aortic valve. These are the right coronary artery (RCA), as well as the left anterior descending (LAD) and the left circumflex artery (LCX/CX) with the two latter ones originating from the left main coronary artery (LMCA/LM/LCA).

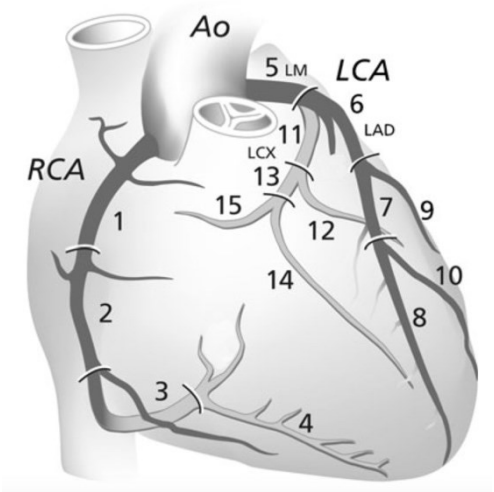



**Figure 14:** Coronary artery segments in regards to the American Heart Association classification. The associated nomenclature is addressed in ***Table 2***. *Adapted from Habets et al. 2012*

The LMCA arises from the upper part of left sinus of Valsalva and exhibits a length of 1 to 3 cm. After its origin, it runs down between the pulmonary artery and the left atrial appendage where it splits into the LAD and LCX. The LAD then runs down in the left interventricular sulcus to or around the apex of the heart. However, in some cases the LAD may not reach the apex wherefore it is supplied by the posterior interventricular artery of the RCA. On its course to the apex, several branches originate from the LAD. These are the both diagonal arteries – with the first one usually originating within the first third and the

second one within the second third of the LAD – and several smaller septal branches. The LCX follows the left part of the coronary sulcus and usually releases one to three left marginal branches that supply the LV free wall.[138]

In 15 to 31 % of the population, a third artery originates from LMCA in between the LAD and LCX. This artery is termed ramus intermedius.[139, 140]

The RCA travels down the right coronary sulcus and splits at the crux cordis into the right posterolateral ramus (right marginal artery) and the posterior interventricular artery. Furthermore, the RCA releases the conus arteriosus branch and the sinoatrial nodal artery. In 63 % of cases the sinoatrial nodal artery arises from the RCA and in 37 % from the LCX. The right marginal artery supplies the inferior wall of the LV and releases the atrioventricular nodal artery in 90 % of the cases, as opposed to the remaining 10 % of the population in which it arises as a branch of the LCA.[138, 141]

| Segment no. | Coronary artery |
|---|---|
| **1** | RCA proximal |
| **2** | RCA mid |
| **3** | RCA distal |
| **4** | Posterior descending artery |
| **5** | Left main |
| **6** | LAD proximal |
| **7** | LAD mid |
| **8** | LAD apical |
| **9** | First diagonal |
| **10** | Second diagonal |
| **11** | Proximal circumflex artery |
| **12** | Intermediate/anterolateral artery |
| **13** | Distal circumflex artery |
| **14** | Left posterolateral |
| **15** | Posterior descending |

**Table 2:** Segmentation of the coronary arteries. *From Sianos et al. 2005*

***Figure 14*** shows the coronary artery segments as suggested by the *American Heart Association (AHA)*. The nomenclature of these segments is addressed in ***Table 2***.[142-144]

## 3.4 Pathogenesis of Non-ST Elevation Acute Coronary Syndrome (NSTE-ACS)

In the pathogenesis of NSTE-ACS there are four major mechanisms, all of which can occur simultaneously. These mechanisms are[145]:

» Rupture of plaque

» Coronary artery vasoconstriction
» Imbalance between oxygen supply and demand
» Gradual intraluminal narrowing due to progressive atherosclerosis

Since the first mechanism represents the classical trigger of ACS in general, it is highlighted in the following paragraph.

### 3.4.1 Rupture of Plaques

Plaque rupture, which is defined as structural defect (interruption) of the fibrous cap[146], has been identified as main cause for the formation of coronary thrombi (73 %).[147] Interestingly, the majority of ruptures was identified to occur at the shoulder (63 %) and not in the centre of the plaque (37 %).[148] Vulnerable plaques mainly show to have a thin-layered fibrous cap *(usually 50 to 65 µm; TCFA, thin-cap fibroatheroma[147])* that covers a large necrotic core.[149, 150]

Since smooth muscle cells (SMCs) are capable of synthesising collagen – that is thought to be the most important determinant for biomechanical resilience to plaque rupture – in the fibrous cap, any reduction in synthesis or excessive depletion of collagen contributes to an increase in vulnerability. As well as inflammation represents an essential mechanism in the evolution of atheroma through contribution of SMC migration, it can also lead to destabilisation of the fibrous cap by inducing apoptosis of SMCs and breakdown of collagen by overexpression of matrix-metalloproteinases (MMPs). These inflammatory processes in the intima – that mainly originate from macrophages and T lymphocytes (*see **Figure 15***) – are therefore linked to plaque stability and coronary thrombosis.[2, 147, 150-155]

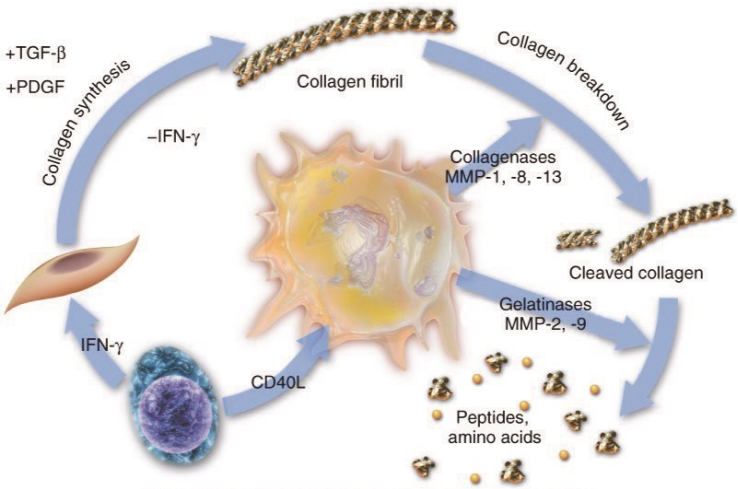



**Figure 15:** Effects of inflammatory pathways in the regulation of collagen metabolism *(Bottom left: T lymphocyte, centre: macrophage)*. *From Libby et al. 2008*

Another cause of the formation of coronary thrombi is the superficial erosion of plaques. Rather than a tear in the fibrous cap, these erosions show a loss or dysfunction of the luminal endothelium.[146, 147, 151] This condition of the plaque tends to provoke more fatal acute MIs in female patients, as well as in patients with diabetes mellitus and hypertriglyceridemia. Although most plaque disruptions do not lead to a clinically noticeable thrombosis, they are thought to undergo repetitive episodes of plaque disruption with consecutive thrombosis and healing, therefore, adding to lesion development and plaque growth.[151] In a study using optical coherence tomography (OCT) the proportion of plaque erosion in patients with acute MI was found to be 23 % in a cohort of 30 patients.[156]

# 4 Myocardial Contractile Performance

The foundation of normal myocardial function is the result of sufficient myocardial blood (and oxygen) supply and electro-mechanical coupling. In order to, eventually, fulfil its purpose of an effective pump there are several more requirements to be met to deliver adequate mechanical performance (cardiac output)[157]:

- loading condition (preload and afterload)
- contractile state (inotropy and lusitropy)
- heart rate (chronotropy)

## 4.1 Left Ventricular Myocardial Contraction

### 4.1.1 Left Ventricular Architecture

Over the last decades there have been developed various models of how the LV is composed.[158] Nowadays, it is believed that the LV consists of two helical fibre geometries in a manner that the right-handed subendocardial helix progressively devolves into a left-handed subepicardial one (*see **Figure 16***).[158-163]

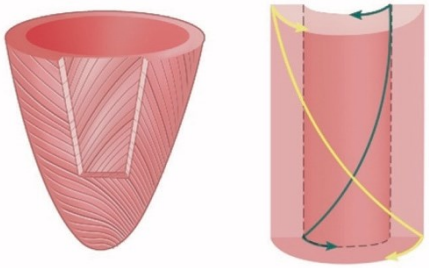


**Figure 16:** Cylindrical myofibre model proposed by Ingels et al. The subendocardial fibres are wrapped into a right-handed helix, whereas the supepicardial fibres are wrapped in a left-handed helix. *From Sengupta et al. 2008 (Illustration by Rob Flewell)*

### 4.1.2 Myocardial Mechanics

The principle mechanics of myocardial contraction consist of myocardial wall shortening, thickening and twisting (counterclockwise from apex to base) along the long axis.[158]

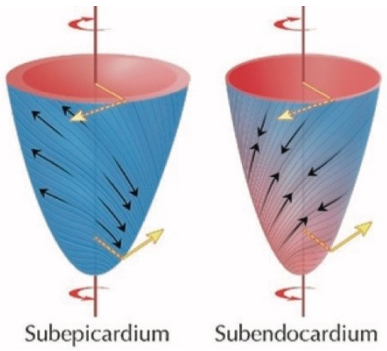



**Figure 17:** Initial clockwise rotation of the apex during isovolumetric contraction. *From Sengupta et al. 2008 (Illustraion by Rob Flewell)*

Due to its special architecture, the LV will rotate counterclockwise when the subepicardial layer contracts, whereas the LV will rotate clockwise when the subendocardial fibres contract. However, when both layers are activated simultaneously, the LV rotates counterclockwise

near the apex, whereas the base will rotate clockwise. The dominance of the subepicardial layer is a consequence of the higher torque that is achieved due to a greater radius when compared to its counterpart. Nevertheless, the developed subendocardial exceeds the subepicardial force.

On the basis of the cardiac conduction system, apical regions are the first to be activated by the electrical excitation wave front which, thereafter, subsequently progresses to more basal segments (apex-to-base sequence).[162] However, it was shown that LV regions that are activated early – which is true for the subendocardium – shorten (along the right-handed helical direction), whereas late activated regions (subepicardium) are stretched simultaneously (lengthening along the left-handed helical direction) during the preejection period (isovolumetric contraction, phase 1). Thereby, a brief clockwise rotation precedes the thereafter dominating counterclockwise rotation (*see **Figure 17***). This short inverse motion is seen during isovolumetric relaxation as well.[164, 165]

The already mentioned subepicardial torque translates transmurally to the mid wall and to the subendocardium, thereby leading to a twisting motion of the LV. As a consequence, fibres are rearranged, hence, leading to shearing of subendocardial fibres with consecutive LV thickening. As a result of this shearing deformation, 15 % shortening of the myocytes are augmented into 40 % radial thickening, resulting in 60 % change in ejection fraction. In addition, the produced potential energy is partially stored and utilised for diastolic torsional recoil. When isovolumetric relaxation commences, subendocardial basal segments are still shortening while apical subendocardial segments already lengthen. This allows diastolic retrieval to be commenced without LV volume change.[162, 164]

# 5 Echocardiography

Two-dimensional echocardiography is a valuable diagnostic tool for the examination of various cardiac conditions and is frequently used in patients with MI for both acute and prognostic evaluation.

## 5.1 Sections

There are several default sections that are obtained so as to evaluate the heart in regards to myocardial wall motion analysis and other purposes. Potential sections are the parasternal short and long axis view and the apical two (A2C), three (A3C), four (A4C) and five (A5C) chamber view. Additionally, the heart can also be visualised in the subcostal view (S4C).

The preferred probe used is the sectorial probe as it allows for a wide – up to 90° – sector even though there might only be a small acoustic window between the rips.

## 5.2 Parameters of Myocardial Function

For the sake of uniformity, several terms should be used for myocardial function assessment[164]:

- **Displacement** (d, [cm]) defines the distance that a certain structure has moved between two consecutive frames.
- **Velocity** (v, [cm/sec]) represents the displacement per time.
- **Strain** (e, S [%]) describes the fractional change of myocardial deformation. Depending on shortening or lengthening, strain can take negative and positive values, respectively. Strain can reflect segments (segmental strain), averages of segments (global strain), or segments of vascular distribution (territorial strain).
- **Strain rate** (SR, [1/sec]) describes the fractional change of length per time.
- **Rotation** [°] describes the rotation around the LV long axis.
- **Twist** [°] represents the absolute difference between apical and basal rotation.

» **Torsion** [°/cm] is used to describe the base-to-apex gradient in the rotation angle along the LV long axis.

There are three principal directions of movement with respect to the LV.[166] These are:

» Longitudinal strain
» Circumferential strain
» Radial strain

***Figure 18*** shows the three different directions of strain with respect to the LV.

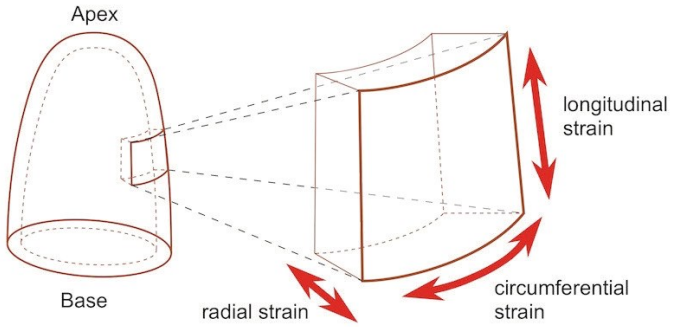



**Figure 18:** Directions of strain with respect to the left ventricle. *Adapted from Flachskampf et al. 2010*

Territorial strain reflects the averaged strain of segments assigned to theoretical coronary distribution areas.[167, 168]

## 5.3 Technical Approaches for the Assessment of Myocardial Function

### 5.3.1 Doppler Tissue Imaging (DTI)

In general, Doppler is used to assess frequency shifts of the echoes returning to the ultrasound probe. Thereby, velocities of flowing liquids can be calculated. The same principle is true for DTI. Since blood and the myocardial wall exhibit different velocity ranges it feasible to isolate them by the application of high- and low-pass filters, respectively. In order to acquire reliable measurements of myocardial function with spectral Doppler it is of great importance that the ultrasound beam is aligned with the direction of movement. The angle between the ultrasound beam and the ROI should not exceed 15° so as to keep the measurement error (underestimation) beneath 4 %. Hence, from the apical view the longitudinal strain or strain rate can be assessed exclusively. In addition, radial and circumferential strain and strain rate can merely be assessed from the short axis view. This angle dependency is yet the biggest disadvantage of DTI. However, the great temporal resolution of this already

available tool as well as the great reproducibility of peak tissue velocities is a tremendous advantage.[164]

### 5.3.2 Two-Dimensional Speckle Tracking Echocardiography (2D-STE)

2D-STE enables wall motion analysis by the tracing of during the cardiac cycle temporally stable speckles. These speckles can then be followed in each obtained frame to get an overall picture of each individual region of interest. This analysis can further be extended to retrieve deformational data of separate layers of the myocardial wall (subendocardial wall, mid wall, subepicardial wall).[164]

When it comes to image acquisition, it is important to obtain loops with a high frame rate (40 to 80 frames/sec for non-tachycardic heart rates). Although foreshortening of the LV is not advisable for any analysis of myocardial function it is particularly unfavourable in 2D-STE since it results in genuine measurement errors leading to a distortion of the truly present myocardial performance. Furthermore, the pericardium must not be included in the semiautomatic analysis since this would lead to serious measurement errors as well.[164]

The application of 2D-STE has several advantages. First and foremost, all strain and strain rate vectors can be assessed independent of the alignment between the myocardium and the ultrasound beams. Therefore, the only limitation for image assessment is the lateral image resolution. Furthermore, speckle tracking is an offline tool and therefore allows for independent retrospective wall motion analysis. One limitation of this feature is its susceptibility to reverberation artefacts and acoustic shadowing.[164]

### 5.3.3 Three-Dimensional Speckle Tracking Echocardiography (3D-STE)

Although 2D-STE is indeed a useful feature, it may not always be able to assess myocardial function with the highest accuracy. This is mostly due to the complex three-dimensional architecture and mechanics of the LV that are assessed in only two dimensions and my not always be picked up adequately, especially when out-of-plane motion of the speckles occurs. This disadvantage does not apply to 3D-STE where vectors can be tracked irrespective of their direction.[164]

In a study by *Nesser and colleagues* 2D- and 3D-STE were compared to cardiac magnetic resonance (CMR) as gold standard for the estimation of LV end-diastolic and end-systolic volume. 3D-STE performed significantly better than 2D-STE for LV volume estimations regarding both correlation *(r = 0.87 to 0.92 vs. r = 0.72 to 0.88)* and extent of volume deviation *(1 to 16 ml vs. 10 to 30 ml)* from CMR. Furthermore, lower inter- and intra-observer variabilities were reported.[169]

### 5.3.4 Technical Aspects to be considered for Strain Measurement

Although 2D-STE is a reliable feature for the quantitative assessment of LV function, measurement results can deviate significantly based on the speckle-tracking software. In a study[170] with the aim to determine reference values for 2D-STE in 228 healthy adults, 52 were examined with both a GE Vivid 7 and a Philips iE33 xMATRIX ultrasound system. The global longitudinal (difference: 2.4 ± 2.9) and circumferential (difference basal: 3.0 ± 7.2, difference mid: 3.0 ± 8.9) strains were significantly higher when the measurement was obtained Philips system. Conversely, radial strain (difference basal: 5.8 ± 28.0, difference mid: 2.4 ± 20.8) was lower when measured with the Philips system. In another study, the software of two ultrasound systems with regards to their results in 2D-STE analysis were compared. The GE Vivid 7 and the Toshiba Artida 4D, however, achieved comparable results in 28 healthy adults.[171]

To recapitulate, care should be taken when interpreting 2D-STE results if specific reference values for an individual ultrasound system are not available.

## 5.4 Segmentation of the Left Ventricle

As stated by the consensus document of the European Association of Cardiovascular Imaging (EACVI) and the American Society of Echocardiography (ASE) on "Definitions for a common standard for 2D speckle tracking echocardiography" the complete myocardial region of interest (ROI) is defined at end-diastole by the endocardial border, the epicardial border, and the myocardial midline (between the endo- and epicardial border). Irrespective of the obtained apical section the LV is divided into the left and right ROI by the LV long axis (mid-base to apex). As far as the 16- or 18-segment model are concerned, each ROI (left and right) is divided into three segments equal in length (left or right ROI length/3).

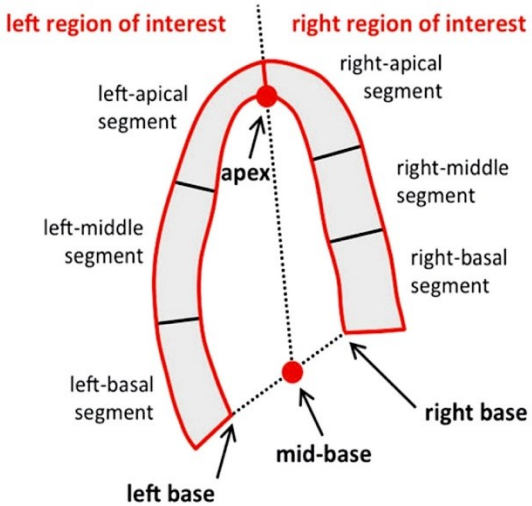



**Figure 20:** Segmentation of the LV/ROI in apical views. This scheme applies to the 16- and 18-segment model. *From Voigt et al. 2015*

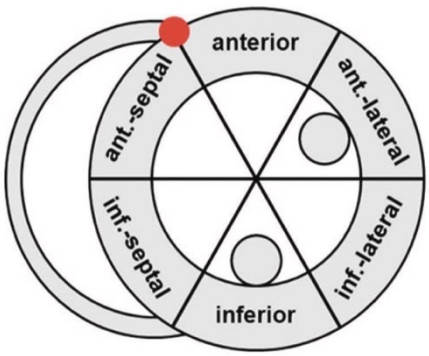



**Figure 19:** Segmentation of the LV/ROI in the short axis view. The red point denotes the starting point of the LV/ROI segmentation. *From Voigt et al. 2015*

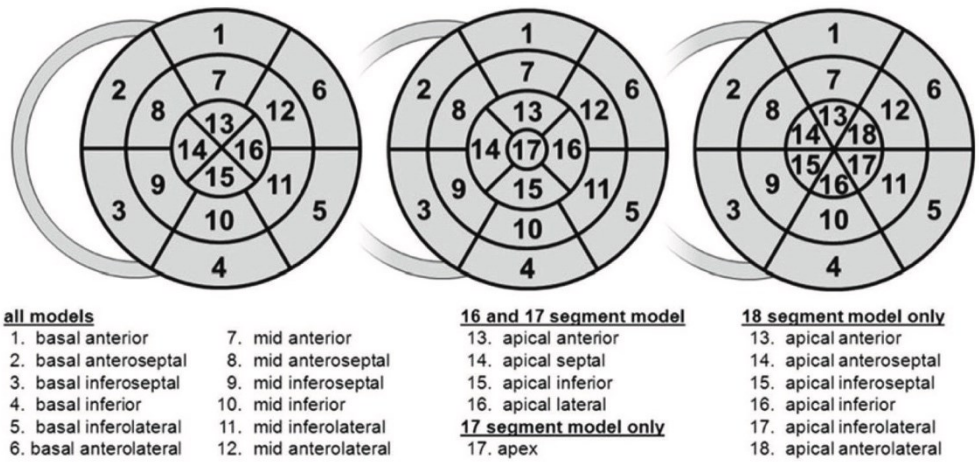



**Figure 21:** Bull's-eye view of the 16-, 17-, and 18-segment model of the LV/ROI. *From Voigt et al. 2015*

These six segments are termed as “left-basal”, “right-basal”, “left-middle”, “right-middle”, “left-apical”, and “right-apical”-segment. In the case of the 17-segment model the basal, mid, and apical segments have a length of 2/7$^{th}$ of the left and right ROI length. The cap is composed of 1/7$^{th}$ of the left and the right ROI. Notably, the lengths of the segments in the 17-segment model are different when compared to the 16- or 18-segment model. ***Figure 21*** shows the 16-, 17-, and 18-segment model and the individual nomenclatures.[172]

***Figure 22*** shows the coronary artery supply of the individual segments in a 17-segment model.

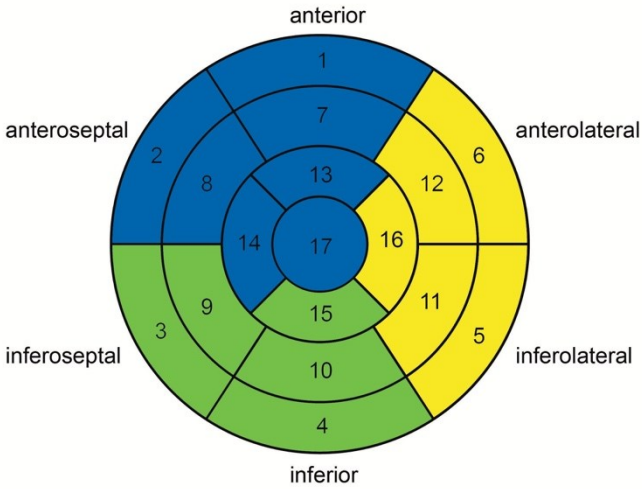



**Figure 22:** Coronary artery supply of the left ventricle in a 17-segment model.

## 5.5 Calculation and Measurement of Myocardial Deformation

### 5.5.1 Calculation of Strain and Strain Rate

As described above, strain represents the fractional change of myocardial deformation. Considering one dimension, an object can either lengthen or shorten. However, strain can be expressed differently depending on the reference value or reference length ($L_0$). When $L_0$ is considered as fixed reference, strain is referred to as “Lagrangian strain” and is calculated as follows[172]:

$$S_L(t) = \frac{L(t) - L_0}{L_0}$$

The “Lagrangian strain rate” can be calculated by the derivative of $S_L$[172]:

$$SR_L(t) = \frac{dS_L(t)}{dt} = \frac{1}{L_0}\frac{dL(t)}{dt}$$

In contrast, the “natural strain rate” (or “Eulerian strain rate”) refers to a reference length that changes continuously with the deformation of the myocardium. For instance, when looking at three consecutive points in time ($t_0$, $t_1$, $t_2$) the reference length at the time $t_1$ refers to the length of the object at the time $t_0$ and so on: $L_0(t_1) = L(t_0)$, $L_0(t_2) = L(t_1)$, etc. This can mathematically also be described as[172, 173]:

$$SR_N(t) = \frac{dS_N(t)}{dt} = \frac{1}{L(t)} \frac{dL(t)}{dt}$$

By integrating the “natural strain rate” the “natural strain” can be calculated[172, 173]:

$$S_N(t) = \int_{t_0}^{t} SR_N(t)dt = \int_{t_0}^{t} \frac{1}{L(t)} \frac{dL(t)}{dt}\, dt = ln\left(\frac{L(t)}{L_0}\right)$$

In comparison, “Lagrangian strain” is preferred over “natural strain” for speckle tracking echocardiography (STE), whereas natural strain is mostly used with Doppler imaging. However, “Lagrangian” and “natural” variables can be transformed into one another.[172]

### 5.5.2 Timing of Deformation Measurements

Since myocardial contraction and relaxation are periodic events and therefore obtained parameters depend on when they are measured, certain points in time need to be defined as reference points. Conventionally, end-diastole constitutes the main reference point. Therefore, events that can easily be determined and are correlated to end-diastole are used as surrogates for end-diastole. Most commonly, the ECG (R-peak, beginning of QRS, etc.) is used for the determination of end-diastole, since it can be measured without difficulty and automatically. However, when conduction delays are present using ECG events as surrogates may lead to incorrect timing. In this case, mechanical events like mitral valve closure can be utilised to define end-diastole. Conversely, aortic valve closure represents end-systole.[172]

***Figure 23*** depicts a strain curve with delineated clinically important measurement points. These measurement points are (in the order of occurrence):

- » Peak positive strain (P)
- » Peak systolic strain (S)
- » End-systolic strain (ES/ESS)
- » Post-systolic strain (PSS)

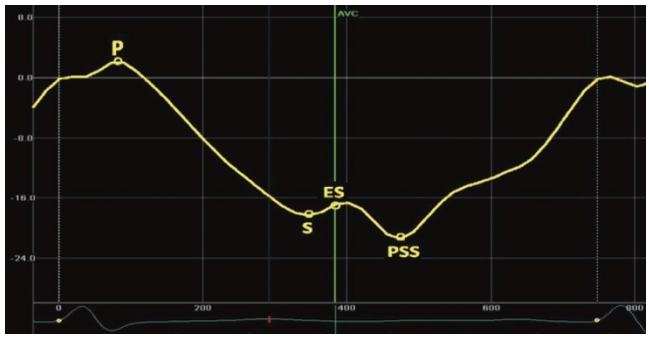



**Figure 23:** Strain curve with measurement points (explained within the text). The green line represents the aortic valve closure. *From Voigt et al. 2015*

As defined by the consensus document of the EACVI and ASE, end-systolic strain (ESS) should be used as the default parameter for myocardial wall motion analysis by speckle tracking.[172]

### 5.5.3 Reference Values for Left Ventricular 2D Speckle Tracking Echocardiography

Since myocardial contractility is equivalent to shortening of the LV in the longitudinal and circumferential dimension, the measured values of these parameters are negative, whereby more negative values represent higher contractility and vice versa. As a decline in myocardial contraction is associated with higher values of longitudinal and circumferential strain – which is counterintuitive – it is recommended to report the absolute values of strain. Hence, higher values represent increased myocardial contractility and lower values represent decreased myocardial contractility.[172]

Even though normal ranges of strain have been described in several trials[164, 174-179], deviating measurements carried out by 2D-STE cannot be excluded since different methods were used.

#### *5.5.3.1 Global Strain*

In a review containing 24 studies and 2,597 patients, normal global values of strain were gathered. The mean absolute values of global longitudinal strain (GLS), global circumferential strain (GCS), and global radial strain (GRS) were 19.7 % (95 % CI:

18.9 to 20.4 %), 23.3 % (95 % CI: 22.1 to 24.6 %), and 47.3 % (95 % CI: 43.6 to 51.0 %), respectively.[180]

#### *5.5.3.2 Segmental Strain*

Although, there exist considerable variations between normal segments, age groups and states of haemodynamic conditions, longitudinal systolic strains ≤ 12 % are generally considered as abnormal.[164] Sun et al.[170] studied a healthy adult population (n = 228, 44 ± 12 years) to determine reference values for 2D-STE with an 18-segment model. The results for absolute longitudinal, circumferential and radial strain are presented in ***Table 3*** to ***Table 5***, respectively.

#### *5.5.3.3 Territorial Strain*

The territorial strain represents the average strain within the theoretical perfusion areas of the three major coronary vessels (RCA, LAD, LCX) in a model of balanced coronary perfusion (*see* ***Figure 22***).

| Wall / Segments | Longitudinal Strain % | | | |
|---|---|---|---|---|
| | **All segments** | **Basal** | **Mid** | **Apical** |
| **All walls** | 20.4 ± 3.4 | 18.3 ± 3.2 | 20.0 ± 3.2 | 23.0 ± 4.2 |
| **Anterior** | 20.4 ± 5.1 | 19.3 ± 4.6 | 19.9 ± 4.6 | 21.9 ± 5.6 |
| **Anteroseptal** | 20.7 ± 4.8 | 18.8 ± 4.1 | 20.8 ± 4.0 | 22.7 ± 5.1 |
| **Inferoseptal** | 20.0 ± 5.0 | 16.6 ± 3.8 | 19.8 ± 3.2 | 23.6 ± 4.9 |
| **Inferior** | 21.2 ± 4.7 | 19.1 ± 4.4 | 20.7 ± 3.4 | 23.7 ± 4.9 |
| **Inferolateral** | 20.1 ± 4.8 | 18.5 ± 4.6 | 19.9 ± 4.0 | 22.2 ± 4.8 |
| **Anterolateral** | 20.9 ± 5.1 | 19.2 ± 3.9 | 19.9 ± 3.2 | 23.5 ± 6.1 |

**Table 3:** Reference values for the segmental longitudinal peak systolic strain. All values are reported as absolute numbers. *From Sun et al. 2013*

| Wall / Segments | Circumferential Strain % | | | |
|---|---|---|---|---|
| | **All segments** | **Basal** | **Mid** | **Apical** |
| **All walls** | 22.9 ± 3.1 | 21.1 ± 3.0 | 22.3 ± 3.2 | 26.0 ± 5.2 |
| **Anterior** | 23.7 ± 6.2 | 21.7 ± 5.3 | 23.2 ± 5.8 | 26.3 ± 6.7 |
| **Anteroseptal** | 25.5 ± 6.0 | 24.7 ± 5.9 | 25.5 ± 5.8 | 26.3 ± 6.4 |
| **Inferoseptal** | 24.8 ± 6.1 | 23.5 ± 6.2 | 24.2 ± 5.5 | 26.6 ± 6.2 |
| **Inferior** | 22.1 ± 6.0 | 19.5 ± 5.2 | 21.1 ± 4.7 | 25.9 ± 6.1 |
| **Inferolateral** | 21.2 ± 6.6 | 19.0 ± 5.5 | 19.2 ± 6.0 | 25.4 ± 6.4 |
| **Anterolateral** | 21.0 ± 6.7 | 17.2 ± 5.1 | 20.3 ± 5.8 | 25.7 ± 6.2 |

**Table 4:** Reference values for the segmental circumferential peak systolic strain. All values are reported as absolute numbers. *From Sun et al. 2013*

| Wall / Segments | Radial Strain % | | | |
|---|---|---|---|---|
| | **All segments** | **Basal** | **Mid** | **Apical** |
| **All walls** | 42.6 ± 12.9 | 44.6 ± 12.3 | 47.1 ± 12.0 | 35.7 ± 11.4 |
| **Anterior** | 42.2 ± 9.4 | 43.5 ± 14.0 | 47.5 ± 13.5 | 35.5 ± 13.1 |
| **Anteroseptal** | 40.1 ± 9.3 | 41.8 ± 13.8 | 43.8 ± 13.7 | 34.2 ± 12.8 |
| **Inferoseptal** | 38.8 ± 8.8 | 43.8 ± 13.3 | 44.4 ± 13.6 | 35.8 ± 12.3 |
| **Inferior** | 43.3 ± 15.0 | 45.6 ± 15.0 | 47.8 ± 14.4 | 36.2 ± 13.0 |
| **Inferolateral** | 44.3 ± 9.3 | 46.2 ± 15.1 | 50.0 ± 14.1 | 36.4 ± 13.0 |
| **Anterolateral** | 44.2 ± 15.4 | 46.0 ± 15.6 | 50.0 ± 14.1 | 36.3 ± 13.2 |

**Table 5:** Reference values for the segmental radial peak systolic strain. All values are reported as absolute numbers. From *Sun et al. 2013*

## 5.6 Myocardial Infarction and Echocardiographic Deformation Imaging

Since myocardial tissue is highly oxygen dependent, myocardial infarction resulting as a consequence of restricted coronary blood supply leads to impaired myocardial contractile function. Hence, ischemic myocardium can be identified by reduced or absent systolic radial thickening, longitudinal shortening, and circumferential shortening. Furthermore, delayed systolic shortening (after aortic valve closure) can frequently be found in acute ischemia. Due to the coronary anatomy and thereby specific blood supply of individual territories (consisting of multiple segments) deviations of normal myocardial function may allow conclusions on the culprit coronary artery.[164]

### 5.6.1 Detection of Myocardial Infarction

In several studies a significant reduction of longitudinal strains was observed in patients with MI[181]:

In a study by *Jurcut et al.* 32 patients *(29 men, mean age 61.2 ± 8.1 years)* with myocardial infarction. Based on MRI and CA studies, LV segments were categorised as infarcted, adjacent, and remote. When infracted were compared to remote segments infarcted areas showed a reduced longitudinal systolic strain *(9.6 % vs. 14.6 %, $p < 0.0001$)*, as well as a reduced systolic strain rate *(0.75 $s^{-1}$ vs. 1.08 $s^{-1}$, $p < 0.0001$)* and a higher post-systolic shortening index *(21.0 % vs. 8.3 %, $p < 0.001$)*.[182]

In another study 157 patients *(78.3 % men, mean age 60.0 ± 11.0)* with STEMI showed to have a significantly reduced peak systolic strain in the infarcted area when compared to the global peak systolic strain *(11.3 ± 4.5 vs. 14.4 ± 3.2, $p < 0.001$)*. Furthermore, the study population was divided into three groups based on the symptom-to-balloon time *(mean symptom-to-balloon time 212 ± 92 min)*. In patients with longer symptoms-to-balloon times, global and infarcted area longitudinal peak systolic strain were significantly more reduced than in patients with shorter symptoms-to-balloon times.[183]

*Gjesdal and colleagues* sought to identify myocardial infarction areas in 38 patients *(73.7 % male, mean age 55 ± 10 years)* with chronic ischemic heart disease by 2D-STE in comparison to cMRI. There was a significant difference between patients non-infarcted, subendocardial infarcted, and transmurally infarcted segments *(18.1 ± 3.9 %, 13.1 ± 6.1 %, 9.0 ± 5.8 %, respectively)* assessed by 2D-STE. Global peak longitudinal strain values ≤ 15 % identified MI with a sensitivity and specificity of 83 % and 93 % (AUC 0.95), respectively, whereas a sensitivity of 76 % and a specificity of 95 % were found when applied to territorial areas.[167]

In another study, LV untwisting rate and LV twist were investigated as parameters for the diagnosis of MI in 50 patients *(76 % male, 60 ± 11 years)* with STEMI. When compared to 29 subjects without evidence of structural heart disease peak LV twist (net difference between basal and apical rotation) was significantly decreased in patients with MI *(11.6° ± 3.8 vs. 15.7° ± 3.1, p < 0.001)*. In addition, peak LV untwisting rate was significantly reduced as well *(78°/s ± 35 vs. 107°/s ± 29, p = 0.002)*. Furthermore, a strong correlation between peak LV twist and LV ejection fraction was observed *(r = 0.87, p < 0.001)*.[184]

By using a cut-off of 15 % for longitudinal strain, a sensitivity of 76 % and a specificity of 95 % for the detection of infarcted segments were achieved with 2D-STE.[185]

Furthermore, an increase in duration of early systolic lengthening (DESL) is another parameter for the detection of MI.[186] See chapter 5.6.3.2 for further details.

### 5.6.2 Distinguishing Transmural from Non-Transmural Myocardial Infarction

*Gjesdal et al.* sought to determine parameters of global systolic LV function that allow to estimated myocardial infarct size. Therefore, 40 patients *(77.5 % men, 58 ± 10 years)* that underwent PCI after STEMI were examined with cMRI (gold standard), 2D-STE, and TDI 8.5 ± 5.4 months after the acute event. Based on cMRI patients were categorised as having small *(n = 19)*, medium *(n = 13)*, or large *(n = 8)* MI. Global longitudinal and circumferential strain by 2D-STE were both able to

correctly discriminate between these categories when compared to cMRI. A significant correlation between infarct mass and all global strain and strain rate values was observed *(global longitudinal strain by 2D-STE: $r = 0.91$, $p < 0.01$)*. Furthermore, it was shown that subendocardial *(< 50 % segmental myocardial area)* and transmural *(≥ 50 % segmental myocardial area)* MI can be distinguished by global longitudinal (*normal: 18.4 ± 4.1, subendocardial: 14.1 ± 5.6, transmural: 9.8 ± 6.5, $p < 0.05$)*, circumferential *(normal: 22.1 ± 6.4, subendocardial: 17.0 ± 7.9, transmural: 10.5 ± 7.9, $p < 0.05$)*, and radial *(normal: 31.8 ± 19.4, subendocardial: 24.7 ± 19.7, transmural: 12.7 ± 16.0, $p < 0.05$)* strain values.[185]

Another study reported differing absolute values of global circumferential and radial strain (longitudinal strain was not assessed). However, transmural and non-transmural MI could be differentiated as well. For the differentiation of transmurality, global circumferential strain with a cut-off of 11.10 % showed a sensitivity and specificity of 70.4 % and 71.2 %, respectively. Sensitivity and specificity for radial strain with a cut-off of 16.50 % were 70.0 % and 17.2 %, respectively.[187]

### 5.6.3 Detection of Coronary Occlusion

#### *5.6.3.1 Balloon-Induced Coronary Occlusion*

When coronary occlusion is established by balloon inflation *(mean balloon inflation period: 61 ± 4 sec)* during PCI of patients with > 90 % coronary artery stenosis, marked transient declines in LV peak systolic radial strain – in both proximal and distal segments at risk – can be observed. However, when reperfusion is achieved strain parameters return to near normal pre-occlusion values at 24 hours after the procedure.[188]

In a comparable study, circumferential and radial strain during balloon-induced myocardial ischemia were examined in 8 patients undergoing PCI. Balloon-induced ischemia lead to a marked reduction circumferential and radial strain. Furthermore, a prolongation of circumferential and radial time to peak strain were observed.[189] This course was also described in a study by *Kukulski et al.* regarding longitudinal and radial strain. In addition, an increase in post-systolic strain during coronary occlusion was noted.[190]

### *5.6.3.2 Coronary Occlusion in NSTEMI*

As already mentioned above, around one fourth of patients with NSTE-ACS and about one third of patients with the final diagnosis of NSTEMI show to have a coronary occlusion of the culprit artery *(see **chapter 2.2**)*.[57-59] Since these patients do not meet the criteria for immediate coronary reperfusion in the majority of cases which may lead to an increase in infarct size. As a consequence of acute coronary occlusion LV dysfunction develops which can be captured with echocardiography (2D-STE, 3D-STE).

In a study[191] including 150 patients presenting with NSTE-ACS the feasibility of 2D-STE to detect acute coronary occlusion was investigated. All patients were haemodynamically stable during the index event and patients with the need for urgent PCI were not included. For the detection of abnormal segments using a 16-segment model, a cut-off of 14 % *(≤ 14 % for identification of impaired myocardial function)* for longitudinal peak systolic strain was defined. Coronary angiography was obtained within a maximum of three days *(mean of 2.2 ± 0.7 days)* after hospitalisation. Echocardiography was obtained shortly before coronary angiography. WMSI and longitudinal strain could be gathered in 99.8 % and 98.4 %, respectively. In the study cohort, coronary occlusion was determined in 22 % of patients and was independent of the prevalence single- or multi-vessel disease *(26 vs. 30 %, p = 0.61)*. When comparing coronary non-occlusion to coronary occlusion LVEF *(59.1 ± 7.6 % vs. 54.9 ± 9.6 %, p = 0.02)*, WMSI *(1.00 [1.00 to 1.13] vs. 1.16 [1.03 to 1.36], p < 0.001)*, global strain *(17.4 ± 2.5 % vs. 15.0 ± 2.4 %, p < 0.001)*, functional risk area by WMSI *(0 [0 to 2] segments vs. 3 [0.5 to 4] segments, p < 0.001)*, functional risk area by strain *(2 [0 to 5] segments vs. 7 [4.5 to 9] segments, p < 0.001)*, and end-diastolic LV volume/body surface area *(53.2 ± 9.3 ml/m² vs. 58.8 ± 11.15 ml/m², p = 0.01)* were all significantly different. However, after applying multivariate logistic regression only functional risk area by strain

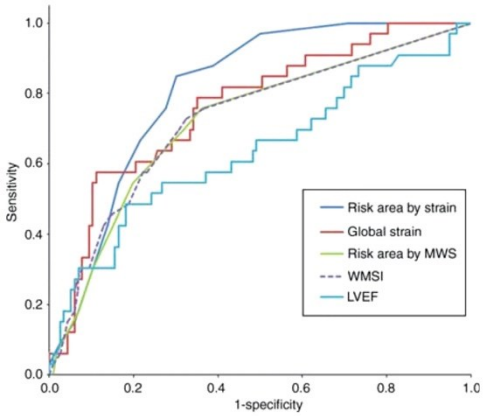



**Figure 24:** ROC analysis for various parameters for LV function for the detection of coronary occlusion. *From Eek et al. 2010*

remained statistically significant for the detection of coronary occlusion. This is also reflected by the ROC analyses for each individual parameter showing the highest AUC of 0.81 (0.74 to 0.88) with a sensitivity and specificity of 85 % and 70 % for a cut-off of ≥ 4 segments for the detection of coronary occlusion, respectively. See ***Table 6*** for further details.

| | Cut-off | Sensitivity | Specificity | AUC | NPV | PPV |
|---|---|---|---|---|---|---|
| **LVEF** | 57 % | 58 % | 60 % | 0.64 (0.52 to 0.75) | 81 % | 34 % |
| **WMSI** | 1.08 | 70 % | 70 % | 0.73 (0.63 to 0.83) | 89 % | 39 % |
| **Global strain** | 16.3 % | 67 % | 71 % | 0.76 (0.67 to 0.85) | 87 % | 38 % |
| **FRA by WMSI** | ≥ 2 segments | 70 % | 68 % | 0.73 (0.62 to 0.82) | 88 % | 38 % |
| **FRA by strain** | ≥ 4 segments | 85 % | 70 % | 0.81 (0.74 to 0.88) | 94 % | 44 % |

**Table 6:** Various parameters of left ventricular function for the detection of coronary occlusion in NSTE-ACS. FRA, Functional risk area; All AUCs reach p-values < 0.05 when compared to LVEF as reference. *From Eek et al. 2010*[191]

On the same study population, a retrospective analysis[186] was performed so as to examine the interrelation between the duration of early systolic lengthening (DESL) and acute coronary occlusion as well as the final infarct size. DESL was defined as the period in which the strain curve is positive, starting at the beginning of the QRS (RS) complex. Among the initially included 150 patients, 95 % underwent an echocardiographic follow-up examination at 9 ± 3 months. From 121 patients with the confirmed diagnosis of NSTEMI, 61 underwent ceMRI in addition to echocardiography, 29 of which had acute coronary occlusion. Among these 61 patients, the median infarct size was 5.4 % of total LV volume at follow-up *(9 ± 3 months)*. By ceMRI examination, 26 % of the analysed segments showed evidence of myocardial infarction, 80 % and 20 % of which showed subendocardial and transmural infarction, respectively. Infarcted segments demonstrated a significantly longer DESL when compared to non-infarcted segments *(110 ± 77 ms vs. 61 ± 57 ms, p < 0.001)*. A prolonged DESL *(> 50 ms)* demonstrated the highest AUC *(0.92, 95 % CI: 0.82 to 0.97)* for the detection of minimal myocardial infarction (defined as inability to visualise myocardial scar on ceMRI) and a sensitivity and specificity of 77 % and 92 %, respectively.

However, the ability to distinguish between coronary occlusion and non-occlusion with a cut-off of 100 ms was only moderate with an AUC in the ROC analysis of 0.65 *(95 % CI: 0.57 to 0.73, p = 0.009)* and a sensitivity and specificity of 33 % and 91 %, respectively. When DESL at the index event was compared to that at follow-up a significant reduction was found *(61 ± 34 ms vs. 68 ± 36 ms, p = 0.04)*. This reduction was even more pronounced in the group of patients with minimal myocardial infarction *(44 ± 20 ms vs. 71 ± 41 ms, p = 0.002)*.

Another study carried out on 60 patients (within 48 h after pain onset) with the diagnosis of NSTEMI reported similar, although somewhat reduced, predictive power. For global longitudinal peak systolic strain *(cut-off < 15.5 %)* and FRA by strain *(cut-off ≥ 5 segments)* AUC, sensitivity, specificity, PPV, and NPV were reported to be 0.702, 68.9 %, 77.7 %, 70 %, 57.7 %, and 0.689, 63.6 %, 77.7 %, 71 %, 60 %, respectively.[192]

*Grenne and colleagues*[59] conducted a prospective trial to assess the feasibility of 2D-STE to identify coronary occlusion in NSTE-ACS. In 111 patients, echocardiography was performed within a median of 1 hour *(IQR: 0.5 to 4 h)* after presentation and coronary angiography at a median time of 36 ± 21 hours of symptom onset. Territorial strain values were calculated by averaging segmental peak systolic strains within the individual perfusion areas. Territorial longitudinal and circumferential post-systolic shortening (PSS) was calculated by subtracting end-systolic from peak post-systolic strain. Of the included patients, 61 % were diagnosed as NSTEMI, 23 % as non-coronary chest-pain, and 16 % as unstable angina. In 31 % of the 67 patients with NSTEMI acute coronary occlusion was detected by coronary angiography. Multiple echocardiographic features were able to discriminate coronary occlusion from non-occlusion. However, territorial circumferential strain with a cut-off of 10 % showed the highest AUC of 0.93 in the ROC curve analysis with a sensitivity and specificity of 90 % and 88 %, respectively (see **Table 7**), regardless of the culprit artery (RCA, LAD, LXC). On the contrary, ECG interpretation *(ST deviation ≥ 0.05 mV, symmetrical T-wave inversion, sum of ST-deviation, number of leads with suspected ischemia, ECG changes while awaiting coronary angiography)*

failed to demonstrate significant differences between patients with and without coronary occlusion.

| | Cut-off | Sensitivity | Specificity | AUC |
|---|---|---|---|---|
| **Territorial circumferential strain** | 10 % | 90 % | 88 % | 0.93 |
| **Territorial longitudinal strain** | 14 % | 76 % | 66 % | 0.78 |
| **WMSI** | 1.23 | 71 % | 73 % | 0.81 |
| **Territorial circumferential PSS** | 3.4 % | 81 % | 70 % | 0.79 |
| **Territorial circumferential PSS** | 1.9 % | 71 % | 76 % | 0.74 |
| **CK-MB (admittance)** | 5.0 µg/l | 53 % | 53 % | 0.60 |
| **LVEF** | 55 % | 57 % | 56 % | 0.61 |

**Table 7:** Identification of coronary occlusion in patients with NSTE-ACS. PSS, peak systolic strain, *From Grenne et al. 2010*

Patients with coronary occlusion had significantly reduced LVEF *(48 ± 6 % vs. 57 ± 6 %, p < 0.001)*, increased myocardial necrosis by cTnT level *(4,900 ± 4,700 ng/l vs. 900 ± 1,100 ng/l, p < 0.001)*, and increased infarct size by ceMRI *(13.8 ± 8 % vs. 3.0 ± 3 %, p < 0.001)* when compared to those with non-occluded coronary arteries. Moreover, patients with NSTEMI and coronary artery occlusion who underwent PCI within 12 hours of symptom onset *(n = 6)* had a major improvement in longitudinal and circumferential strain at 3 months when compared to those who underwent PCI after 12 hours *(n = 15) (p < 0.01)*.

*Dahlslett and colleagues* demonstrated that patients presenting with NSTE-ACS showing an inconclusive ECG, normal cardiac biomarkers at arrival, and do not have a history of CAD can be excluded for having significant (> 50 %) coronary artery stenosis by 2D-STE. Therefore, global peak longitudinal strain was superior to other measures in the ROC curve analysis with an AUC of 0.87 and a sensitivity and specificity of 93 % and 78 %, respectively. PPV and NPV in this trial with 64 patients included were 74 % and 92 %, respectively.[193]

### 5.6.4 Estimation of Myocardial Infarct Size

Since mortality and MACE are increased by myocardial infarct size it is of great importance to suspend necrosis of ischemic but viable myocardial tissue as rapid as possible in the acute phase of myocardial infarction. However, estimating the myocardium at risk at an early stage is challenging and often not possible in clinical practice, particularly in patients with NSTEMI. As a consequence, several studies

were performed to investigate the potential of 2D-STE for the estimation of myocardial infarct size.

In study already described above[59], among the 61 patients that underwent both ceMRI and echocardiography at follow-up *(9 ± 3 months)* the median infarct size was 5.4 % (IQR: 1.7 % to 11.4 %) of total LV volume at follow-up. A prolonged DESL *(> 50 ms)* demonstrated the highest AUC *(0.92, 95 % CI: 0.82 to 0.97)* for the detection of minimal myocardial infarction (defined as inability to visualise myocardial scar on ceMRI) and a sensitivity and specificity of 77 % and 92 %, respectively. *Eek and colleagues[194]* classified these patients on whether or not they had a myocardial infarct size ≥ 12 % which was true for 21 % of the patients. LVEF *(48.5 ± 9.3 % vs. 57.7 ± 7.7 %, p = 0.001)*, WMSI *(1.44 [1.28 to 1.50] vs. 1.08 [1.00 to 1.21], p < 0.001)*, GLS *(12.6 ± 1.7 % vs. 16.9 ± 2.2 %, p < 0.001)*, GCS *(18.2 ± 5.5 % vs. 22.1 ± 3.8 %, p = 0.030)*, and GRS *(27.6 ± 8.3 % vs. 35.0 ± 13.2 %, p = 0.018)* were all able to discriminate between the two groups by indicating significantly reduced systolic function. After applying a logistic regression model for MI size ≥ 12 % WMSI *(OR 3.55, 95 % CI: 1.20 to 10.47)* and GLS *(OR 3.51, 95 % CI: 1.33 to 9.25)* remained significant surrogates for infarct size. In the receiver operator curve analysis WMSI and GLS showed the highest AUC for the determination of MI size ≥ 12 % (*see **Table 8***).

| | Cut-off | Sensitivity | Specificity | AUC | NPV | PPV | Accuracy |
|---|---|---|---|---|---|---|---|
| **LVEF** | 51 % | 69 % | 79 % | 0.80 (0.68 to 0.89) | 91 % | 47 % | 77 % |
| **WMSI** | 1.30 | 77 % | 92 % | 0.93 (0.83 to 0.98) | 94 % | 71 % | 89 % |
| **GLS** | 13.8 % | 85 % | 96 % | 0.95 (0.86 to 0.99) | 96 % | 85 % | 93 % |
| **GCS** | 19.2 % | 62 % | 81 % | 0.71 (0.58 to 0.82) | 89 % | 47 % | 77 % |
| **GRS** | 27.4 % | 69 % | 69 % | 0.68 (0.53 to 0.83) | 89 % | 38 % | 69 % |

**Table 8:** Receiver operator curve analysis for the detection of myocardial infarct size ≥ 12 %. Values of strain parameters are reported in absolute numbers. *From Eek et al. 2010.*

In several other studies examining myocardial infarction size after STEMI, GLS[185, 195, 196] and GCS[185] assessed by 2D-STE proved to have good correlations as well.

# 6 Diagnosis and Treatment of NSTEMI

Currently, diagnosing MI in clinical practice mainly depends on the clinical presentation, ECG abnormalities, and cardiac biomarkers (e.g. cTn). As a result, decisions on treatment strategies are mostly based on these criteria as well. Since signs and symptoms are not always typical in patients with chest pain and ECG diagnosis of MI can be challenging in the absence of diagnostic ST-segment elevations, detecting patients with NSTEMI can be difficult and may lead to substantial delays in diagnosing MI.

## 6.1 Clinical Presentation

Chest pain remains the leading symptom in patients with myocardial ischemia. However, if chest pain is absent or not addressed as the chief complaint by the patient, MI can be missed in the emergency department. *Brieger and colleagues*[197] conducted a sub-analysis of patients in the GRACE registry for which they divided 20,881 patients into two groups on whether their chief complaint was chest pain or not. 8.4 % of the included patients did not present with chest pain. These patients were more likely to be female and to have a history of hypertension, diabetes, or heart failure. Moreover, they were less likely to have a history of smoking, hyperlipidaemia, or PCI. The dominant presenting symptoms in patients without chest pain were dyspnoea, diaphoresis, nausea and vomiting, and syncope accounting for 49.3, 26.2, 24.3, and 19.1 %, respectively. Note that more than one chief complaint may have been present in individual patients. In-hospital mortality was found to be significantly higher (18.7 % vs. 6.3 %) in patients that presented with STEMI but without chest pain as compared to patients with STEMI and chest pain ($p < 0.001$). The same was true for patients with NSTEMI *(11.9 % vs. 4.2 %; $p < 0.001$)* and unstable angina *(8.0 % vs. 2.5 %; $p < 0.001$)*. When corrected for baseline characteristics (e.g. factors associated with higher mortality rates) the risk for death was reduced but remained significant in patients with STEMI *(adjusted OR: 1.7; 95 % CI: 1.2 to 2.2)* and UA *(adjusted OR: 2.2; 95 % CI: 1.4 to 3.5)*. Similar results were obtained in another study.[198]

*Swap et al.*[199] conducted a literature review (1979 to 2005) and identified 8 components of the patient's history that correlated with the presence of MI. Radiation to the right arm or shoulder *(LR 4.7; 95 % CI: 1.9 to 12)* and to both arms or shoulders *(LR 4.1; 95 % CI: 2.5 to 6.5)* showed the strongest correlation with the presence of MI. Association with exertion, radiation to the left arm, association with diaphoresis, association with nausea and vomiting, and chest pain worse than previous angina or similar to previous MI showed similar positive likelihood ratios (1.8 to 2.4). Interestingly, the description of chest pain as pressure showed the lowest positive LR of 1.3 *(95 % CI: 1.2 to 1.5)*. Conversely, the lowest LRs were achieved in patients with pleuritic, positional, sharp, and reproducible chest pain with palpation *(0.2 to 0.3)*.

| | Females | | Males | |
|---|---|---|---|---|
| Symptom* | Sensitivity (%) | Specificity (%) | Sensitivity (%) | Specificity (%) |
| Chest pressure | **66** | 36 | **63** | 41 |
| Shoulder pain | 45 | **67** | 29 | **72** |
| Sweating | 37 | **70** | 33 | **70** |
| Palpitations | 27 | **66** | 17 | **77** |
| Chest discomfort | **66** | 33 | **69** | 34 |
| Upper back pain | 34 | **64** | 14 | **78** |
| Shortness of breath | 58 | 39 | 41 | 40 |
| Arm pain | 49 | **69** | 32 | **72** |
| Unusual fatigue | 40 | 54 | 32 | 52 |
| Nausea | 38 | 58 | 30 | **70** |
| Lightheaded | 40 | 55 | 34 | 58 |
| Chest pain | **67** | 37 | **72** | 36 |
| Indigestion | 30 | **78** | 18 | **76** |

**Table 9:** Various symptoms with their sensitivity and specificity for the diagnosis of MI based on sex. *Bolded values are considered sensitive or specific.* *From DeVon et al. 2014*

In another study, sensitivity and specificity were calculated for various symptoms based on the sex category and are depicted in **Table 1**.[200] *Body et al.*[201] conducted a similar study to assess the value symptoms and signs for the diagnosis of ACS. Of 796 patients with suspected cardiac chest pain 18.6 % were diagnosed for having acute MI. After adjustment for age, sex, and ECG changes pain radiating to the right arm *(2.23; 95 % CI: 1.24 to 4.00)*, both arms *(2.69; 95 % CI: 1.36 to 5.36)*, vomiting *(3.50; 95 % CI: 1.81 to 6.77)*, central chest pain *(3.29; 95 % CI: 1.94 to 5.61)*, and diaphoresis *(5.18; 95 % CI: 3.02 to 8.86)* increased the likelihood of MI. In contrast, in patients with pain in the left anterior chest MI was significantly less likely *(0.25; 95 % CI: 0.14 to 0.46)* and chest pain at rest *(0.67; 95 % CI: 0.41 to 1.10)* and pain radiating to the left arm *(1.36; 95 % CI: 0.89 to 2.09)* did not make the diagnosis of MI significantly more or less likely. For detailed table containing data on sensitivity, specificity, PPV, NPV, LR+, and LR- of each assessed symptom or sign *see **Figure 38**, Appendix A*.

For decades, patients with chest pain were categorised into groups of "typical angina", "atypical angina", and "non-anginal chest pain" as these categories

correlated with the prevalence of CAD (88.9, 49.9, and 16.0 %, respectively).[202] *Hermann and colleagues*[21] sought to evaluate the accuracy of this categorisation in predicting the presence of inducible myocardial ischemia (IMI) using retrospective data from cardiac stress testing in patients with suspected ACS. All patients that presented with substernal chest pain or discomfort that was provoked by physical or emotional stress and was relieved by rest and/or nitroglycerin were categorised as having "typical angina". If any of these three criteria was not met they were categorised as having "atypical" or "non-anginal" chest pain. Of 2,525 patients that were included 11.7 % *(95 % CI: 11.0 to 13.0 %)* showed to have IMI. 9 % of the total study population were classified as having "typical", 85 % as having "atypical", and 6 % as having "non-anginal" chest pain. 14 % *(95 % CI: 10.0 to 19.0 %)* of patients with "typical" chest pain developed IMI and 11.0 % *(95 % CI: 10.0 to 13.0 %)* of those with atypical/non-anginal chest pain, representing no significant difference in the likelihood of IMI *(LR+ 1.25; 95 % CI 0.89 to 1.78 %)*. Thus, the application of this traditional classification of patients with typical or atypical chest pain may not be beneficial or misleading. The ESC defines typical chest pain as "retrosternal sensation of pressure or heaviness (angina) radiating to the left arm (less frequently to both arms or to the right arm), neck or jaw, which may be intermittent (usually lasting several minutes) or persistent".[19] Furthermore, the ESC states that patients with NSTE-ACS may present with the following symptoms:

- Prolonged (> 20 min) anginal pain at rest
- New onset (de novo) angina (class II or III of the CCS classification)
- Recent destabilisation of previously stable angina with at least CCS class III angina characteristics (crescendo angina)
- Post-MI angina

Especially women[19, 203, 204], the elderly[19, 198, 204], patients with diabetes[19], renal disease[19] or dementia[19, 198] are prone to present with atypical symptoms. However, there is evidence available that women do not present with significantly different symptoms than men.[205-207]

Symptoms that are not characteristic for myocardial ischemia are described more detailed by the *AHA*[208], rather than in that by the *ESC*:

- Pleuritic pain (sharp or knifelike pain provoked by respiration or cough)
- Primary or sole location of discomfort in the middle or lower abdomen
- Pain localised by the tip of 1 finger, particularly at the LV apex or costochondral junction
- Pain reproduced with movement or palpation of the chest wall or arms
- Brief episodes of pain lasting a few seconds or less
- Pain that is of maximal intensity at onset
- Pain that radiates into the lower extremities

However, although uncommon in general perception, 5 % of patients with the final diagnosis of MI and 17 % of patients with the final diagnosis of unstable angina described the chest pain as sharp or stabbing, and only 24 % described it as pressure.[209]

## 6.2 Approach for Establishing the Diagnosis of NSTEMI (ESC)

Due to the high rate of patients that present to the emergency department with chest pain, it is crucial to filter out those who are truly experiencing symptoms caused by myocardial ischemia and are at high risk. Therefore, criteria to quickly rule-in or rule-out patients is of great importance.

### 6.2.1 0h/3h Algorithm in NSTE-ACS

As the *Third Universal Definition of MI*[1] desires a rise and/or fall of cTn (in combination with at least one other feature) blood samples have to be drawn at least twice to confirm the diagnosis of NSTEMI. The assessment of cTn levels require a certain amount of time – for themselves – and the need for a second laboratory analysis further delays the diagnosis of MI. However, this period of time can substantially be shortened with the application of hs-cTn assays.[5, 19, 210] The 0h/3h rule-out algorithm for NSTEMI is suggested to be used by the ESC guidelines on NSTEMI.[19] The initial step to evaluate patients with acute chest pain and non-

diagnostic ECG is to discriminate whether or not hs-cTn lies over or under the upper limit of normal (ULN). Patients with hs-cTn < ULN and pain for a period of longer than 6 hours can safely be discharged if they are pain free, have a GRACE score < 140 and other diagnosis have been excluded. A stress test in this group of patients is recommended. The same is true for patients with a history of pain for more than 6 hours that show no change in hs-cTn levels in the re-test at 3 hours. Patients that present with an initial positive hs-cTn (hs-cTn > ULN) should be managed immediately if the clinical presentation is suggestive of MI and hs-cTn levels are highly abnormal (beyond 5-fold the ULN). For all others with a hs-cTn > ULN a re-test at 3 hours is required. If a significant rise or fall is detected by the re-test, these patients should be managed invasively as well.

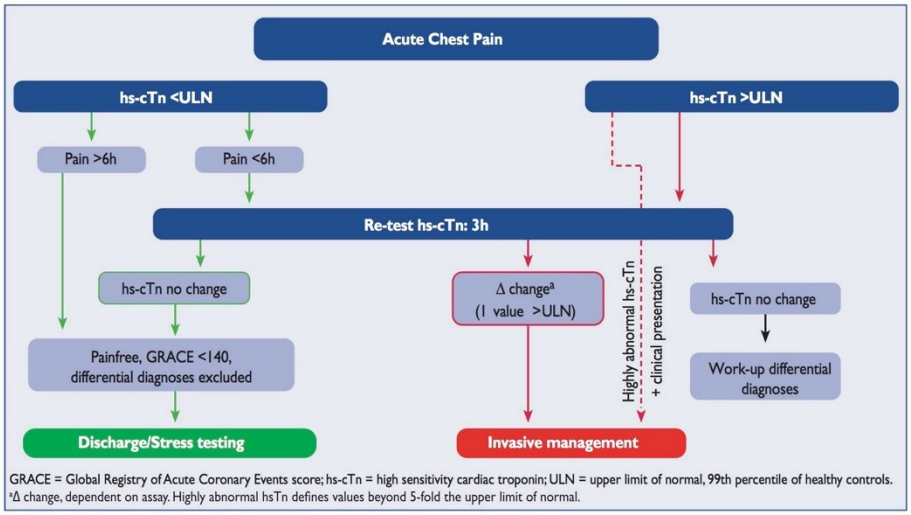
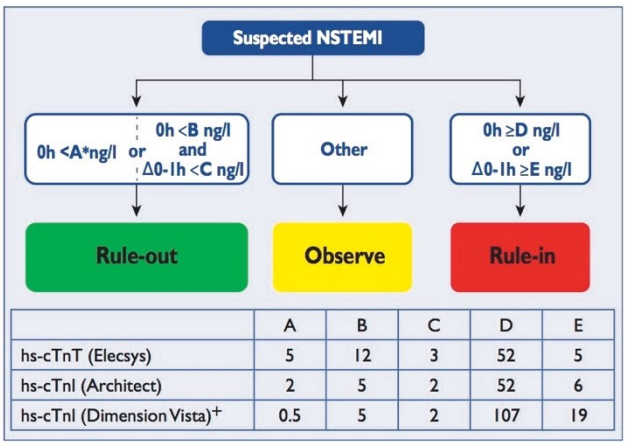



**Figure 25:** 0h/3h algorithm for rule-out/rule-in of NSTEMI with hs-cTn assays. *From Roffi et al. 2015*

## 6.2.2 0h/1h Algorithm in NSTE-ACS

In their recent guidelines, the *ESC* also proposed a 0h/1h algorithm. With the application of hs-cTn assays most of the patients with suspected MI can be ruled-in or ruled-out within a reduced amount of time. This approach, however, is assay-dependent.




| | A | B | C | D | E |
|---|---|---|---|---|---|
| hs-cTnT (Elecsys) | 5 | 12 | 3 | 52 | 5 |
| hs-cTnI (Architect) | 2 | 5 | 2 | 52 | 6 |
| hs-cTnI (Dimension Vista)+ | 0.5 | 5 | 2 | 107 | 19 |

**Figure 26:** 0h/3h algorithm for rule-out/rule-in of NSTEMI with hs-cTn assays. *From Roffi et al. 2015*

In a prospective multicentre study by *Reichlin and colleagues*[211] 827 unselected patients that presented to emergency department with chest pain were randomly assigned to either the derivation or to the validation cohort in equal parts. Blood was drawn at baseline and after 1 hour for the assessment of cTnT levels. Overall, 17 % of patients were diagnosed as having MI. When the algorithm obtained from the derivation cohort was applied to the validation cohort 60 % were classified as "rule-out", 17 % as "rule-in" and in 23 % further observation was required. Considering all included patients sensitivity, specificity, PPV, and NPV were found to be 100, 94, 76, and 100 %, respectively. Furthermore, short- and long-term survival were observed. In patients classified as "rule-out", "observe", and "rule-in" by the developed algorithm, 30-day survival rates were 99.8, 98.6, and 95.3 % and 24-month survival rates were 98.1, 89.1, and 85.4, respectively. All differences between the groups were statistically significant *(p < 0.001 by log rank test)*.

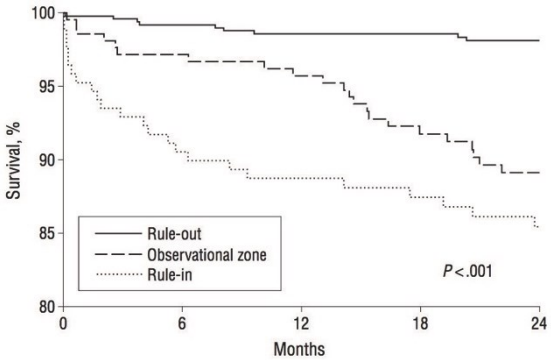



**Figure 27:** Kaplan-Meier plot for the cumulative survival of patients within two years that were assigned to either the "rule-out", "observe" or "rule-in" cohort. *From Reichlin et al. 2012*

The proposed 0h/1h algorithm by the *ESC*[19] relies on two presumptions:

- The likelihood of MI increases with increased levels of hs-cTn
- Absolute changes of hs-cTn levels within one hour can be utilised as surrogates for changes at 3 and 6 hours

## 6.3 Treatment Strategies in Patients with NSTEMI

In patients with NSTEMI there are three options for re-establishing coronary blood supply and to reduce myocardial ischemia: Coronary angiography (CA) with percutaneous coronary intervention (PCI), thrombolysis, and coronary artery bypass grafting (CABG). Whatever strategy is chosen, a pharmacologic treatment regimen goes along with it. However, CA and PCI for diagnosis and (initial) treatment is preferred over thrombolysis and CABG in the majority of cases.

If the patient's symptoms do not resolve rapidly after treatment, immediate CA is indicated.

### 6.3.1 Pharmacological treatment

As stated by the ESC, oxygen should be administered if the patient is breathless or blood oxygen saturation lies below 90 %.[19] Although there are no studies available comparing air vs. oxygen in patients with NSTE-ACS, the *AVOID* study (investigating patients with STEMI) showed no benefit and possibly harm in patients that were normoxaemic (≥ 94 % $SpO_2$).[212] In this multicentre trial *(n = 441)*, there was no significant difference between to oxygen and the no-oxygen group with regards to peak troponin concentration. However, there was a significant increase in mean peak CK-MB *(1,948 U/l vs. 1,543 U/l; 95 % CI: 1.04 to 1.52; p = 0.01)*, in the rate of recurrent myocardial infarction *(5.5 % vs. 0.9 %; p = 0.006)*, and the frequency of myocardial arrhythmia *(40.4 % vs. 31.4 %, p = 0.05)* in the group of patients receiving oxygen. At 6 months, the myocardial infarct size on ceMRI was significantly increased in the group that received oxygen *(n = 139; 20.3 g vs. 13 g; p = 0.04)*.

Patients lacking symptom relief after treatment with nitrates and beta-blockers should receive opiates while awaiting CA.[19] However, opiates may reduce the absorption of orally administered platelet inhibitors.[213-215]

#### *6.3.1.1 Platelet Inhibition*

The positive effect of Aspirin on mortality in MI was highlighted in several trials. Therefore, an intravenous loading dose of 150 mg (or 150 to 300 mg orally) is recommended.[19] In 2001, two studies reported decreased rates of recurrent ischemic events in patients with NSTE-ACS when aspirin was combined with clopidogrel ($P2Y_{12}$-inhibitor).[216, 217] However, a few years later prasugrel[218] *(60 mg loading dose)* and ticagrelor[86] *(180 mg loading dose)* were shown to be superior when compared to clopidogrel *(300 to 600 mg loading dose)* in both patients with STEMI and NSTEMI. More recently, a meta-analysis[219] on three trials was conducted to investigate the effect of the newer $P2Y_{12}$-inhibitor cangrelor in comparison to

clopidogrel and placebo. Cangrelor showed reduced PCI periprocedural thrombotic complications. However, increased bleeding rates were reported.

As a consequence, a combination of aspirin with a $P2Y_{12}$-inhibitor (dual antiplatelet therapy, DAPT) is recommended. Prasugrel should be preferred in patients undergoing PCI and ticagrelor in patients with increased risk of ischemic events. Clopidogrel should only be used if prasugrel or ticagrelor are contraindicated or cannot be given, or if the patient requires oral anticoagulation.[19]

#### *6.3.1.2 Anticoagulation*

In patients in the acute phase of NSTE-ACS, parenteral anticoagulation is recommended at the time of diagnosis. The preferred agent is fondaparinux as it shows the most favourable efficacy-safety profile. As an alternative, bivalirudin, unfractionated heparin (UFH), and enoxaparin can be used as well.[19]

### 6.3.2 Routine Invasive vs. Selective Invasive Approach

Invasive coronary angiography is of great importance for the management of NSTE-ACS, as it allows for the confirmation of the diagnosis, identification of the culprit artery, and revascularisation.

A meta-analysis of 7 trials by *Bavry and associates* sought to determine whether an early invasive therapy improves the outcome in patients with NSTE-ACS.[220] Overall, 8,375 patients were included. At 2 years mean follow-up, the rate of all-cause mortality was significantly lower in patients with an early invasive strategy *(4.9 % vs. 6.5 %; RR = 0.75, 95 % CI: 0.63 to 0.90, p = 0.001)*. The same was true for non-fatal MI at 2 years *(7.6 % vs. 9.1 %; RR = 0.83, 95 % CI: 0.72 to 0.96, p = 0.012)*. However, very early performed invasive coronary angiographies *(median time of 9.3 h)* did not show additional positive effects on outcome when compared to those treated at a mean time of 39.4 hours.

Conversely, the investigators of a recently conducted analysis of the ICTUS trial found no benefit of an early invasive strategy in reducing the composite outcome of death or spontaneous MI at 10-years follow-up. Moreover, the early invasive group

showed a significantly increased rate of procedure-related MI when compared to the selective invasive group (6.5 % vs. 2.4 %, HR: 2.82, 95 % CI: 1.53 to 5.20, p = 0.001).[221]

### 6.3.3 Timing of Invasive Diagnosis and Treatment

Unlike the goal for immediate revascularisation in patients with STEMI, the timing of invasive diagnosis and treatment in patients with NSTE-ACS depends on the risk stratification. Patients with very-high-risk NSTE-ACS should undergo immediate (< 2 h) invasive strategy. An early invasive strategy (< 24 h) is indicated in patients within the high-risk group. Patients in the intermediate risk group should undergo CA within 72 hours.

| Very-high-risk criteria (< 2 h) | High-risk criteria (< 24 h) | Intermediate-risk criteria (<72 h) |
|---|---|---|
| Haemodynamic instability or shock | Rise or fall in cardiac troponin compatible with MI | Diabetes mellitus |
| Recurrent or ongoing chest pain refractory to medical treatment | Dynamic ST- or T-wave changes | Renal insufficiency (GFR < 60 ml/min/1.73 $m^2$ |
| Life-threatening arrhythmias or cardiac arrest | GRACE score > 140 | LVEF < 40 % or congestive heart failure |
| Mechanical complications of MI | | Early post-infarction angina |
| Acute heart failure | | Prior PCI or CABG |
| Recurrent dynamic ST-T wave changes, particularly with intermittent ST-elevation | | GRACE score > 109 and <140 |

**Table 10:** Risk criteria mandating invasive strategy in patients with NSTE-ACS. *Adapted from the ESC Guidelines on NSTE-ACS 2015.*

# Methods

## 1 Study Design

ICON is a prospective multicentre non-interventional study to analyse the detectability of coronary occlusion in patients with NSTE-ACS by 2D-STE. As this study is still in its recruiting phase this diploma thesis covers the results of an interim analysis of all participating centres. Therefore, patients that were enrolled until June 22, 2017 are taken into account.

The first version of the study protocol was completed in January 2016 and is now present in its fifth revision *(V1.3 [1.0, 1.1, 1.2, 1.2.1, 1.2.2])*. The major adjustments on the original study protocol resulted from changes on the participating centres, exclusion criteria, primary and secondary objectives, and statistical considerations. However, all major changes were carried out before the commencement of the study in the first centre. *The study protocol can be found in the appendix.*

### 1.1 Participating Centres

The participating study centres were:

- **LKH Graz Süd-West – Standort West** *(coordinating centre)*, Department für Kardiologie und Intensivmedizin; Göstinger Straße 22, A-8020 Graz; *Local study coordinator: DeptL Dr. Wolfgang Weihs*
- **LKH Univ. Klinikum Graz,** klinische Abteilung für Kardiologie; Auenbruggerplatz 15, A-8036 Graz; *Local study coordinator: Assoz.Prof. Priv.-Doz. Dr. Dirk von Lewinski*
- **Hanusch-Krankenhaus,** 2. Medizinische Abteilung; Heinrich-Collin-Straße 30, A-1140 Wien; Local study coordinator: Dr. Martin Gessner, MSc
- **Wilhelminenspital,** 3. Medizinische Abteilung mit Kardiologie mit Ambulanz; Montleartstraße 37, A-1160 Wien, *Local study coordinator: Dr. Bernhard Jäger*

» **Klinikum Klagenfurt am Wörthersee,** Abteilung für Innere Medizin und Kardiologie; Feschnigstraße 11, A-9020 Klagenfurt am Wörthersee: *Local study coordinator: Dr. Michael Hackl*

## 1.2 Ethics Commission Approval

For each centre, an individual application for approval by the responsible ethics commissions was required. In general, ethic commissions required the study protocol, an informed consent file, all CRFs, and the CE certificates of all ultrasound machines used in connection with the study. In addition, for the approval of applications with the ethics commission in Vienna (EK d. Stadt Wien) two notes to file were required: The use of pregnancy tests prior to the echocardiographic examinations in women of childbearing age and a declaration of not including patients that are unresponsive at the time of screening were dictated.

***Table 11*** shows relevant data in regards to the individual applications.

| Study site | Desig nation | Date of application | Date of approval | Validity date | Ethics commiss ion ID | Ethics commission |
|---|---|---|---|---|---|---|
| **LKH Graz Süd-West – Standort West** | A | 06/06/2016 | 13/07/2016 | 13/07/2017 | 28-464 ex 15/16 | EK d. Med Uni Graz |
| **LKH Univ. Klinikum Graz** | B | 07/10/2016 | 17/10/2017 | 17/10/2017 | 29-035 ex 16/17 | EK d. Med Uni Graz |
| **Hanusch-Krankenhaus** | C | 18/10/2016 | 25/11/2016 | 25/11/2017 | EK-16-182-0916 | EK d. Stadt Wien |
| **Wilhelminenspital** | D | 19/08/2016 | 14/10/2016 | 14/10/2017 | EK-16-182-0916 | EK d. Stadt Wien |
| **Klinikum Klagenfurt am Wörthersee** | E | 24/11/2016 | 20/12/2016 | 20/12/2017 | A 43/16 | EK Kärnten |

**Table 11**: Study site specific data with regards to the ethic commission approvals.

# 2 Primary and Secondary Objectives

## 2.1 Primary Objective

The primary objective of this prospective multicentre study is to assess the feasibility to detect coronary occlusion in patients presenting with NSTEMI by two-dimensional

or speckle-tracking echocardiography. We hypothesise that at least three segments with wall motion abnormality allow for determining coronary occlusion.

## 2.2 Secondary Objectives

Secondary objectives are to assess the number of patients presenting with regional wall motion abnormalities and to compare speckle-tracking to eye-balling in terms of detecting wall motion abnormalities.

# 3 Data Acquisition

For the acquisition of study data, five case report forms (CRF) were developed. All study files included a unique study identification number (ID) which was assigned to each recruited patient. For the electronic data entry, this study ID was used exclusively to anonymise the subjects. Each CRF-file was assigned a letter from B to F to allow for simple allocation to the individual study periods. Furthermore, a study schedule was developed to provide a quick overview on the whole study process.

To provide and maintain confidentiality of participant records all forms are collected by the on-site study coordinator.

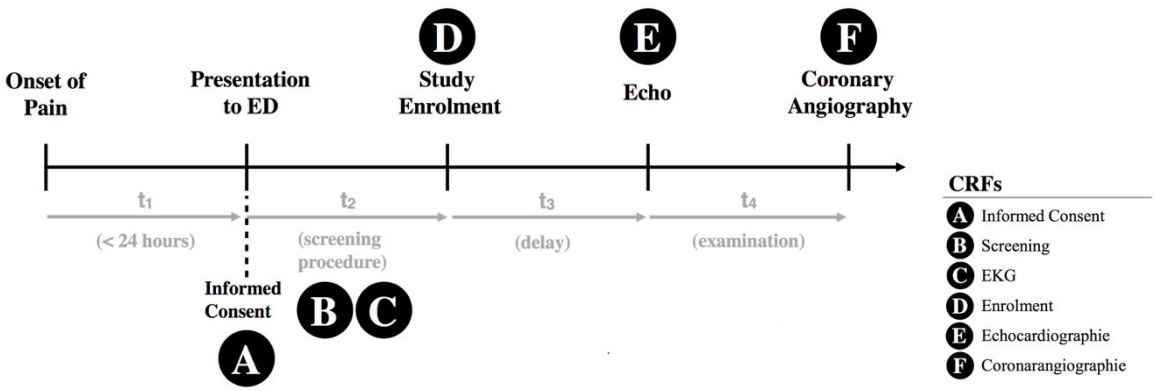



**Figure 28:** Overview on the study procedure. The original overview includes a listing of all inclusion and exclusion criteria.

## 3.1 Screening Case Report Form (CRF B)

CRF B included gender, age, body weight and height as well as the commencement and completion of the screening process. In regards to the chest pain, the time of commencement and the character (cardiac vs. non-cardiac) were documented. The type of cTn that was measured by the laboratory, the time of blood sampling and the time of when the test results were present were documented as well. Moreover, the existence of any exclusion criteria was queried.

## 3.2 Electrocardiogram Case Report Form (CRF C)

In CRF C a detailed ECG report was required with a focus on J-point deviations. J-point deviations were required to be documented if they were equal or great than 0.5 mm (0.05 mV). J-point elevations were assigned a positive sign, whereas j-point depressions were assigned a negative sign.

## 3.3 Enrolment Case Report Form (CRF D)

In CRF D vital signs (heart rate, first blood pressure) and the application of any circulation altering medication (e.g. catecholamines or antihypertensives) prior to the vital sign assessment were reported. In addition, further laboratory values such as CK, CK-MB, Creatinine, and blood glucose levels were collected. CRF D included a questionnaire about risk factors following constituents of the GRACE and TIMI (NSTEMI) score as well.

## 3.4 Echocardiography Case Report Form (CRF E)

In this CRF both global *(LV end-diastolic volume [LVEDV], LV end-systolic volume [LVESV], LV ejection fraction [LVEF], E/e')* and regional left ventricular function (wall motion score index [WMSI], segmental peak systolic strain by speckle tracking) were obtained. Therefore, a 17-segment model of the LV was provided. Moreover, the mitral and aortic valve were assessed for scleroses, stenosis, and insufficiencies.

## 3.5 Coronary Angiography Case Report Form (CRF F)

By this CRF stenosis, TIMI flow grade, and the culprit artery were documented based on a 15-segment model of the coronary arteries as suggested by the AHA.[143, 144]

# 4 Patients

27 patients were prospectively enrolled from July 2016 to July 2017. The following inclusion and exclusion criteria were applied.

## 4.1 Inclusion Criteria

The following criteria had to be met for inclusion:

- ≥ 18 years of age
- acute anginal pain within the last 24 hours at presentation
- elevation of troponin levels
- declaration of informed consent

## 4.2 Exclusion Criteria

The following properties led to exclusion from the study:

- ST-elevation (according to the latest definition by the ESC[1]) for ≥ 30 minutes
- New left bundle branch block (LBBB)
- Previous cardiopulmonary resuscitation (CPR)
- Recent administration of fibrinolytic agent
- Known dilated cardiomyopathy (DCM)
- Known hypertrophic cardiomyopathy (HCM)
- Pericarditis
- Myocarditis
- Echocardiography not available

Eight of the 28 included patients had to be excluded due to missing study data *(n = 7)* and persistent ST elevations *(n = 1)*. In the remaining 20 patients, coronary angiography revealed coronary occlusion in 5 patients *(25 %)*. See ***Figure 29*** for further details.

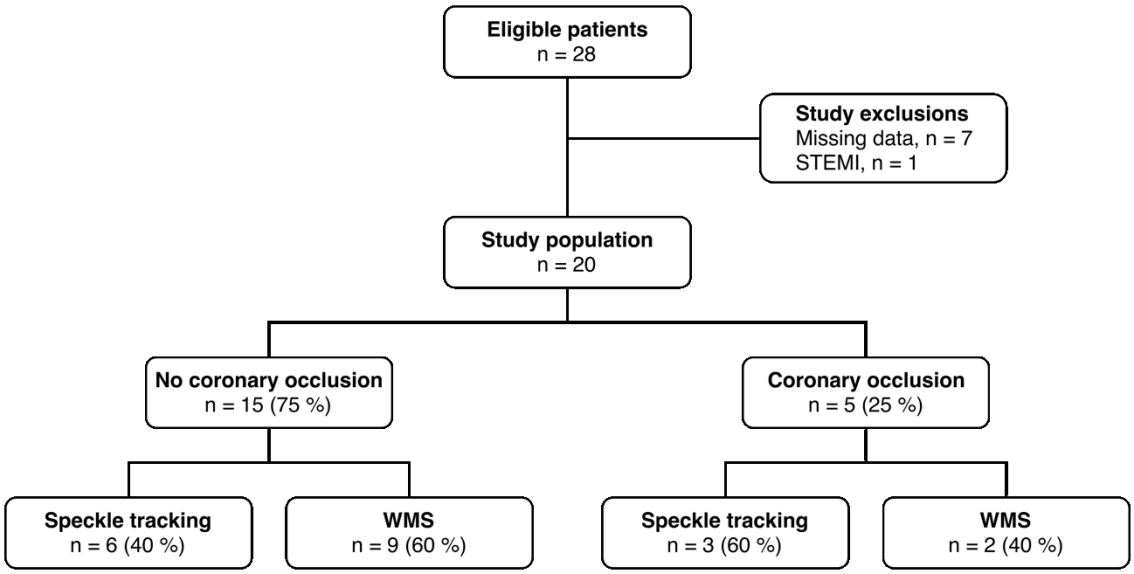



**Figure 29:** Flowchart of patient inclusion and distribution of the applied regional wall motion analysis method.

# 5 Patient Characteristics

***Table 12*** shows the patient characteristics that were found in the study population. In both groups hypertension and hypercholesterolaemia were the most commonly observed risk factors.

| **Characteristics** | **Non-occlusion** (n = 15) | **Occlusion** (n = 5) |
|---|---|---|
| **Age** (years) | 69.3 ± 9.8 | 68.2 ± 10.1 |
| **BMI** (kg/m$^2$) | 22.1 ± 2.0 | 24.5 ± 3.6 |
| **Risk factors** | | |
| **Male gender** | 12 (80 %) | 2 (40 %) |
| **Family history of CAD** | 4 (27 %) | 2 (40 %) |
| **Hypertension** | 11 (73 %) | 4 (80 %) |
| **Hypercholesterolaemia** | 12 (80 %) | 4 (80 %) |

| | | |
|---|---|---|
| **Diabetes mellitus type II** | 3 (20 %) | 1 (20 %) |
| **Current smoker** | 4 (27 %) | 0 (0 %) |

**Table 12:** Data are presented as mean ± SD or n (%). BMI, body mass index; CAD, coronary artery disease

# 6 Electrocardiography (ECG)

At one 12-lead ECG was obtained at presentation to the emergency department. The number of performed ECGs as well as the use of accessory leads were not limited by the study design and were determined by the treating physician. The diagnostic ECG leading to the decision of performing coronary angiography (in conjunction with other clinical parameters) was evaluated. Patients that fulfilled STEMI criteria as stated by the "Third universal definition of myocardial infarction" of the ESC and AHA *(ST elevation in two contiguous leads defined as > 0.1 mV in all leads, except V2 and V3 where ST elevation is defined as > 0.15 mV in women of any age and > 0.2 in men ≥ 40 years and > 0.25 in men < 40 years of age)* for more than 30 minutes were excluded. If deemed necessary, treating physicians were allowed to apply additional leads ($V_{3R}$, $V_{4R}$, $V_7$ to $V_9$). Study site D (Wilhelminenspital) used posterior leads ($V_7$ to $V_9$) by default.

# 7 Biochemical Analysis

Different markers were used by individual centres for the diagnosis of myocardial ischemia. Troponin results were judged as positive when the measured cTn concentration exceeded the upper reference limit independent of the used assay. Initial samples were drawn at the presentation to the emergency department. Further evaluations of cTn permitted. However, they were not included in the study. ***Table 13*** provides an overview on the used cTn assays of the participating centres.

| Study site | Assay | Type | Limit of detection | Upper reference limit | Unit |
|---|---|---|---|---|---|
| **A** | | Troponin I hs | | 25.9 | ng/l |
| **B** | Elecsys | Troponin T hs | 3 | 14 | ng/l |
| **C** | Access AccuTnI+3 | Troponin I | 10 | 40 | ng/l |
| **D** | Siemens Dimension Vista | Troponin I | 15 | 45 | ng/l |

**Table 13:** Used troponin assays and their reference values per study site. A LKH Graz Süd-West Standort West, B LKH Univ. Klinikum Graz, C Hanusch-Krankenhaus, D Wilhelminenspital

# 8 Echocardiography

Two-dimensional echocardiographic images were assessed before coronary angiography by one experienced echocardiographer from apical two-, three- and four-chamber views. LVEF calculation was performed from an apical two- and four-chamber view by applying the modified Simpson's rule.[222]

## 8.1 Strain Analysis

Strain analysis by 2D-STE was performed offline after the completion of echocardiographic examination. The segmental longitudinal peak systolic strain was reported in the provided 17-segment model on CRF E. Where strain analysis could not be carried out segmental WMSI was reported as an alternative measure.

Global longitudinal peak systolic strain (GLPSS) was calculated as an average of all available segments. Territorial longitudinal peak systolic strain (TLPSS) was calculated by averaging the longitudinal peak systolic strain values in segments within the theoretical perfusion area of the three major coronary vessels (RCA, LAD, LCX) in a model of balanced coronary perfusion.[168] The functional risk area (FRA) was defined as the number of adjacent segments with systolic dysfunction based on the GLPSS.

For the discrimination between normal and abnormal systolic function a cut-off of 14.0 % on the segmental level was used since this cut-off was reported to have the

largest AUC in the ROC analysis for the identification of abnormal segments in a previous study.[191]

## 8.2 Visual Evaluation

For the visual assessment ("eye-balling") of the regional wall motion each segment was ascribed a wall motion score (WMS) based on the following itemisation:

- X … not assessable
- 1 … normokinetic or hyperkinetic
- 2 … hypokinetic
- 3 … akinetic
- 4 … dyskinetic

This method was used when speckle tracking analysis was unavailable.

## 8.3 Functional Risk Area

As described by Eek et al., the so called *functional risk area (FRA)* represents the number of adjacent segments with systolic wall motion dysfunction.[191] The FRA was determined either by speckle tracking or visual evaluation based on the availability of data. A cut-off of 14.0 % was defined for speckle tracking analysis and a WMS ≥ 2 for visual assessment. As represented by the primary objective, we hypothesise that a FRA of ≥ 3 segments is predictive of acute coronary occlusion.

## 8.4 Technical Equipment

All study centres used their pre-existing ultrasound machines which were all from General Electric (GE). ***Table 14*** gives an overview on the individual models that were used at each study site.

| Ultrasound machine | A | B | C | D | E |
|---|---|---|---|---|---|
| **GE Vivid 7 Dimension** | | | | ✓ | |
| **GE Vivid E9** | ✓ | ✓ | ✓ | | ✓ |

| | | |
|---|---|---|
| **GE Vivid E95** | | ✓ |
| **GE LOGIQ E9** | ✓ | |

**Table 14:** Ultrasound machines used for the examination of the study subjects. A LKH Graz Süd-West Standort West, B LKH Univ. Klinikum Graz, C Hanusch-Krankenhaus, D Wilhelminenspital, E Klinikum Klagenfurt am Wörthersee

# 9 Coronary Angiography

Coronary angiography (CA) was performed by experienced interventionists and was not restricted to any criteria for study inclusion. The 15-segment model of the coronary arteries provided on *CRF F* was used for reporting individual TIMI flow grades and the culprit lesion. A TIMI flow grade of 0 or 1 was defined as coronary occlusion. The appearance of the coronary occlusion was taken into account for the discrimination between acute and chronic coronary occlusion and was based on the opinion of the treating interventionist. For the purpose of this study, treatment strategy based on coronary angiography and patient outcome were not investigated.

# 10 Statistical Analysis

For the detection of coronary occlusion in patients presenting with NSTE-ACS wall motion analysis (WMSI or 2D-STE) we hypothesise that ≥ 3 segments with wall motion abnormality (defined as segmental WMSI > 1 or LPSS < 14 %) in a 17-segment model of the LV allow for an 80 % diagnostic sensitivity. With 315 subjects, the lower limit of the observed one-sided 95 % CI will be expected to exceed -0.050 with 80 % power when no difference is expected and the proportion of discordant pairs is 0.12. Results are based on 5,000 simulations using the Newcombe-Wilson score method to construct the CI.[223] Including a dropout rate of 15 %, 370 patients are required to be included in the study.

## 10.1 Statistical Analysis of the Entire Study Population

The data will first be described by descriptive statistics using mean, standard deviation (SD), median, minimum and maximum for continuous variables as appropriate and absolute and relative frequency for categorical variables. Sensitivity, specificity and area under the curve (AUC) will be determined for

different cut-off values to identify acute coronary occlusion by receiver operator characteristic (ROC) curve analysis.

## 10.2 Statistical Considerations on the Interim Analysis

As for the entire study population after the completion of the recruiting phase, data gathered for the interim analysis will be described by descriptive statistics using mean, SD, median, minimum and maximum for continuous variables as appropriate. Absolute and relative frequencies are being used for the description of categorical variables. Due to the relatively small number of included patients, when compared to the calculated number of cases, further statistical tests for the calculation of p-values as well as ROC curve analyses are not expected to be significant and, therefore, not carried out for this interim analysis

# Results

*Due to the low number of patients included in this interim analysis (n = 20), a comparison for differences between the two groups is not expected to reach significance. Therefore, a descriptive analysis of the obtained data is provided in this section.*

## 1 Feasibility

In the entire study population, no patient was excluded due to impaired image acquisition. Of 153 total segments 150 *(98 %)* could be assessed using speckle tracking echocardiography. In patients undergoing visual wall motion analysis, all 187 segments could be analysed and ascribed a WMSI.

## 2 Clinical Findings

When undergoing the examinations required for the study, all patients were stable. Interestingly, only one of five patients with coronary occlusion was complaining of severe chest pain. In all patients cTn was elevated as required by the study design. Since all study centres used different cTn assays, ***Table 15*** shows the median cTn values of the coordinating centre (A), as it constitutes the largest individual study subgroup *(n = 12)*. The median hs-cTn I was higher in patients without coronary occlusion than in those with coronary occlusion. The mean creatinine levels did not indicate a difference in renal function. The blood glucose levels were higher in the group of patients with coronary occlusion.

| **Characteristics** | **Non-occlusion** (n = 15) | **Occlusion** (n = 5) |
|---|---|---|
| **Systolic blood pressure** (mmHg) | 144 ± 23.0 | 142 ± 10.6 |
| **Diastolic blood pressure** (mmHg) | 85 ± 15.9 | 86 ± 5.5 |
| **Heart rate** (bpm) | 76 ± 14.6 | 65 ± 7.4 |
| **Currently severe angina** | 7 (50 %) | 1 (20 %) |
| **Laboratory values** | | |

| | | |
|---|---|---|
| **Troponin positive** | 15 (100 %) | 5 (100 %) |
| **Troponin I hs*** (ng/l) | 770.2 (70.5 - 4978.1) | 438.0 (308.1 - 953.1) |
| **CK** (U/l) | 278.9 ± 185.0 | 247 ± 251.0 |
| **CK-MB** (U/l) | 41 ± 27.3 | 54.2 ± 39.1 |
| **Creatinine** (mg/dl) | 1.11 ± 0.34 | 0.85 ± 0.13 |
| **Blood glucose level** (mg/dl) | 118 ± 32.7 | 130 ± 8.9 |

**Table 15:** Clinical findings of patients included. The values are presented as mean ± SD or n (%). *based on values obtained at the coordinating centre (A, *n = 12*)

## 2.1 Electrocardiogram (ECG)

All investigated patients were in sinus rhythm at the time of ECG acquisition. Interestingly, in a majority of patients no ischemic ECG abnormalities were found irrespective of the presence or absence of coronary occlusion. Moreover, all five patients with an acute coronary occlusion had no ECG abnormality at all. Five patients presented with a pre-existing bundle branch block which, however, did not interfere with the defined exclusion criteria.

| **ECG characteristics** | **Non-occlusion** (n = 15) | **Occlusion** (n = 5) |
|---|---|---|
| **Sinus rhythm** | 15 (100 %) | 5 (100 %) |
| **Sum of ST-deviation*** (mm) | 1.07 ± 1.4 | 0 ± 0 |
| **Inverted T-waves** | 3 (20 %) | 2 (40 %) |
| **Presence of bundle branch block** | 4 (27 %) | 1 (5 %) |
| **LBBB** | 2 (13 %) | 1 (5 %) |
| **RBBB** | 2 (13 %) | 0 (0 %) |

**Table 16:** ECG characteristics of patients with and without coronary occlusion. *ST-deviation represents the absolute sum of all ST-elevation and ST-depressions. RBBB, right bundle branch block; LBBB, left bundle branch block

# 3 Coronary Angiography

Coronary angiography was performed in all patients after echocardiography, as required by the study protocol. In 75 % the culprit artery could be identified. An acute coronary occlusion *(TIMI flow grade 0-1)* was identified in five of the 20 patients,

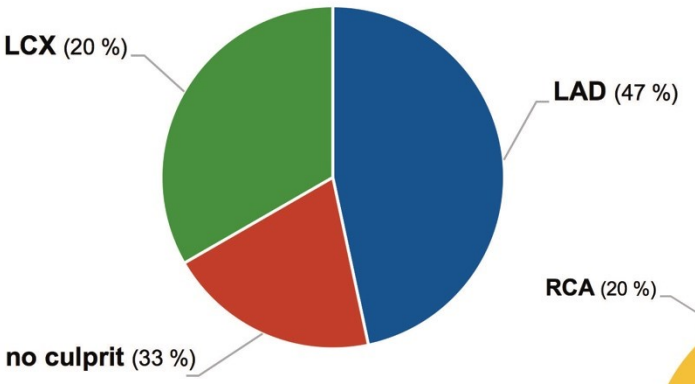



**Figure 31:** Distribution of the culprit artery in patients without acute coronary occlusion (TIMI-flow grade 2-3). *n = 15*

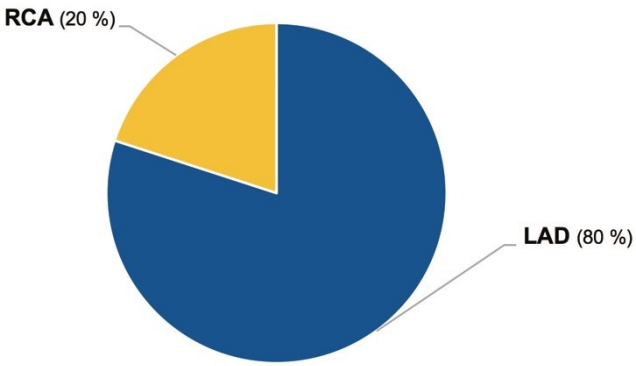



**Figure 31:** Distribution of the culprit artery in patients with acute coronary occlusion (TIMI-flow grade 0-1). *n = 5*

accounting for 25 %. The LAD was the most commonly affected in both patients with and without acute coronary occlusion (*see **Figure 31***).

# 4 Echocardiography

## 4.1 Territorial Wall Motion Analysis

Echocardiography was successfully performed in all included subjects. Overall, the mean TLPSS of patients with non-occluded coronary arteries exceeded that of occluded coronary arteries, representing impaired regional LV contraction when a coronary occlusion was identified. This was true regardless of the culprit artery perfusion area *(see **Figure** **32**)*. Similar results were obtained by comparing the mean territorial WMSI of both groups, although, this was only true for the LAD territorial and the global WMSI *(see **Figure** **33**)*. Furthermore, a reduced contractile performance of the LAD territorial could also be identified when patients where the culprit artery was the LAD were analysed exclusively *(TLPSS: 10.93 ± 2.73 % vs. 13.00 ± 3.80 %; WMSI: 1.93 ± 0.10 vs. 1.33 ± 0.30)*.

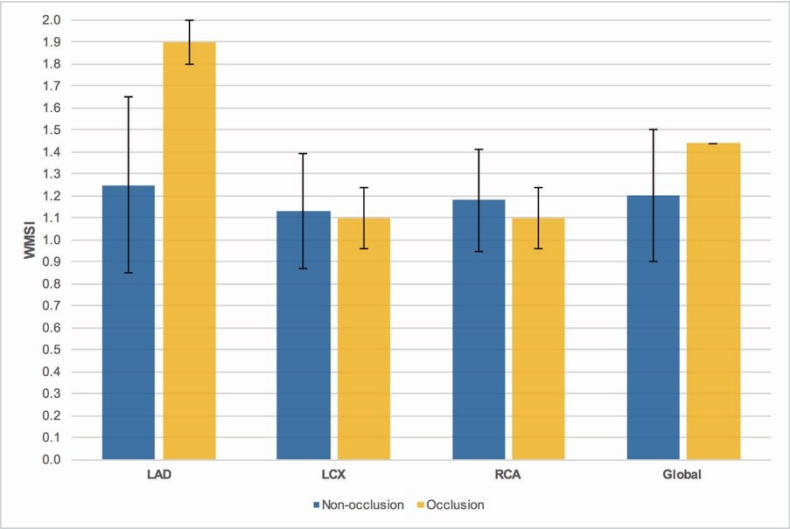



**Figure 33:** Comparison of the WMSI between patients with and without coronary occlusion irrespective of the culprit artery. Data shown: mean ± SD

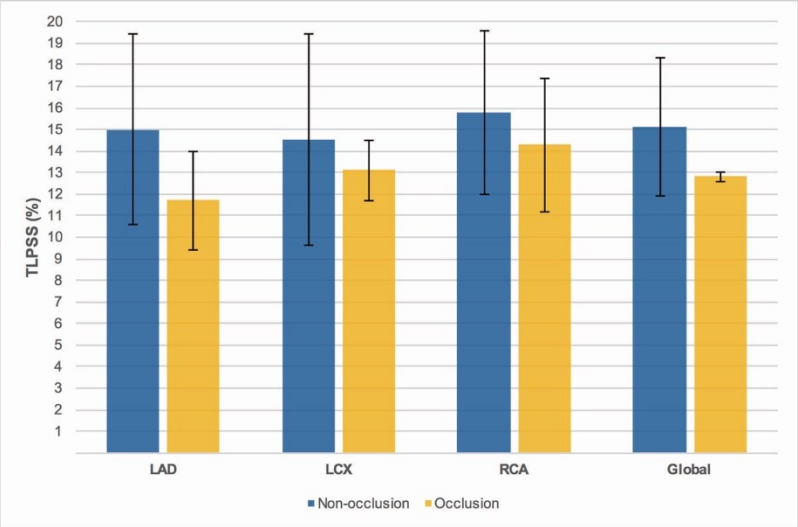



**Figure 32:** Comparison of the TLPSS between patients with and without coronary occlusion irrespective of the culprit artery. Data shown: mean ± SD

| Characteristics | Non-occlusion (n = 15) | Occlusion (n = 5) |
|---|---|---|
| **LVEF** (%) | 45.4 ± 26.8 | 50.6 ± 17.3 |
| **GLPSS** (%) | 15.1 ± 3.2 | 12.8 ± 0.2 |
| **TLPSS – LAD** (%) | 15.0 ± 4.4 | 11.7 ± 2.3 |
| **TLPSS – LCX** (%) | 14.5 ± 4.9 | 13.1 ± 1.4 |
| **TRLPS – RCA** (%) | 15.8 ± 3.8 | 14.3 ± 3.1 |
| **GWMSI** | 1.12 (1.00 - 1.18) | 1.44 (1.43 - 1.46) |
| **TWMSI – LAD** | 1.25 ± 0.40 | 1.9 ± 0.10 |
| **TWMSI – LCX** | 1.13 ± 0.26 | 1.10 ± 0.14 |
| **TWMSI – RCA** | 1.18 ± 0.23 | 1.10. 0.14 |
| **FRA by strain** (segments) | 3 (0 - 7.0) | 8 (6 - 8.5) |
| **FRA by WMS** (segments) | 2 (0.0 - 2.0) | 4 (-) |
| **EDV/BSA** | 46.5 ± 29.3 | 53.2 ± 15.9 |

**Table 17:** Echocardiographic characteristics of patients with and without coronary occlusion. Data shown: mean ± SD, median (Q1-Q3)

## 4.2 Functional Risk Area (FRA)

The median FRA was larger in patients with coronary occlusion when compared to patients without coronary occlusion *(FRA by strain: 8 [0 - 2] segments vs. 3 [0 - 7]; FRA by WMSI: 4 segments vs. 2 [0 - 2] segments)*. Furthermore, the FRA assessed by strain echocardiography was larger as compared to the FRA assessed by WMSI within both groups *(see **Figure 34**)*.

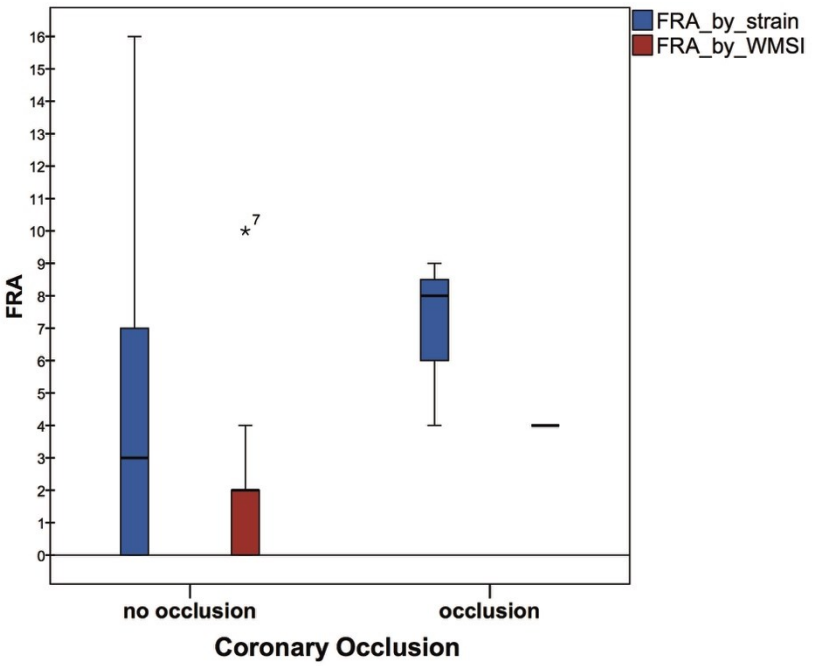



**Figure 34:** Comparison of the assessed functional risk areas (FRA) in dependence on the assessment method and the presence or absence of coronary occlusion.

# 5 Risk Scores

The GRACE-, TIMI (UA/NSTEMI)-, and ACTION-Score were calculated for both patient groups. All risk scores were higher in the group without coronary occlusion *(see **Table 18**)*.

| Score | Non-occlusion (n = 15) | Occlusion (n = 5) |
|---|---|---|
| **GRACE** | 135 ± 32 | 105 ± 1.5 |
| **TIMI (UA/NSTEMI)** | 3.27 ± 1.22 | 2.60 ± 0.55 |
| **ACTION** | 31.4 ± 8.8 | 26.0 ± 1.0 |

**Table 18:** GRACE-, TIMI (UA/NSTEMI)-, and ACTION-Score of both patient groups. Data shown: mean ± SD

# Discussion

This thesis represents a basic overview on the knowledge of coronary occlusion in patients with NSTEMI/NSTE-ACS and their association with regional wall motion abnormalities. Although patient history, ECG, and cTn do not show optimal sensitivity to detect acute coronary occlusion, the current approach for establishing the diagnosis of NSTEMI (and STEMI) and guiding the treatment strategy still relies mainly on these three measures. Since patients with NSTEMI and acute coronary occlusion have a worse outcome than those without coronary occlusion, the early identification and treatment of this subgroup may lead to an improvement in outcome. As shown several times by other studies, echocardiography with regional wall motion analysis is capable of accounting for a large part of this lack of sensitivity for the detection of coronary occlusion.

Due to the low number of patients included in this interim analysis, it cannot be expected to reach significant differences between both groups. However, one can recognise in the data presented a trend towards impaired regional LV function in patients with coronary occlusion that was shown for both strain echocardiography and “eye-balling” (WMSI). It is noted, however, that, as a consequence of the mentioned reasons, this observed trends could just be the results of chance.

## 1 ECG for the Detection of Coronary Occlusion

It was shown that an acute coronary occlusion can be found in up to one third of patients with NSTEMI.[58, 59] In this interim analysis of 20 patients, 25 % had a coronary occlusion. In four of the five concerned cases, there were no ST depressions or elevations at all. In the remaining case, inverted T waves in the leads V7 to V9 were picked up. However, inverted T waves are unspecific and these would not have been captured by recording a standard 12-lead ECG. This poor sensitivity of the ECG or the STEMI criteria for the detection of acute coronary occlusion is especially important, as the timing of the acute treatment strategies differs considerably based on the ECG diagnosis (rapid vs. delayed coronary

angiography). As a consequence of a delayed treatment strategy in patients with acute coronary occlusion, viable myocardial tissue is lost, leading to a worse outcome. This loss, however, is preventable if more sensitive measures (echocardiography with wall motion analysis) are applied. The sensitivity of the STEMI criteria for the detection of coronary occlusion lies around 50 %,[224] whereas that of echocardiographic wall motion analysis can reach a sensitivity of about 85 %.[191] Similarly, the STEMI criteria are quite insensitive for the detection of transmurality as well. Hence, about one fourth of patients with NSTEMI have a transmural myocardial infarction.[60]

## 2 Regional Wall Motion Dysfunction in NSTEMI

As already discussed, wall motion analysis by either 2D-STE or “eye-balling” (WMSI) is capable of both increasing the sensitivity of detecting acute coronary occlusion and decreasing the time until diagnosis and treatment. Based on the current evidence echocardiography and regional wall motion analysis should be performed as a mandatory measure along with the already used triad of ECG, cTn, and medical history.

## 3 Example

The following example shows a frequent clinical course of a patient with myocardial infarction:

A 69-year-old female patient was admitted to the emergency department after experiencing chest pain for about eight hours. A standard 12-lead ECG was obtained and showed no ischemic changes *(see **Figure 35**)*.

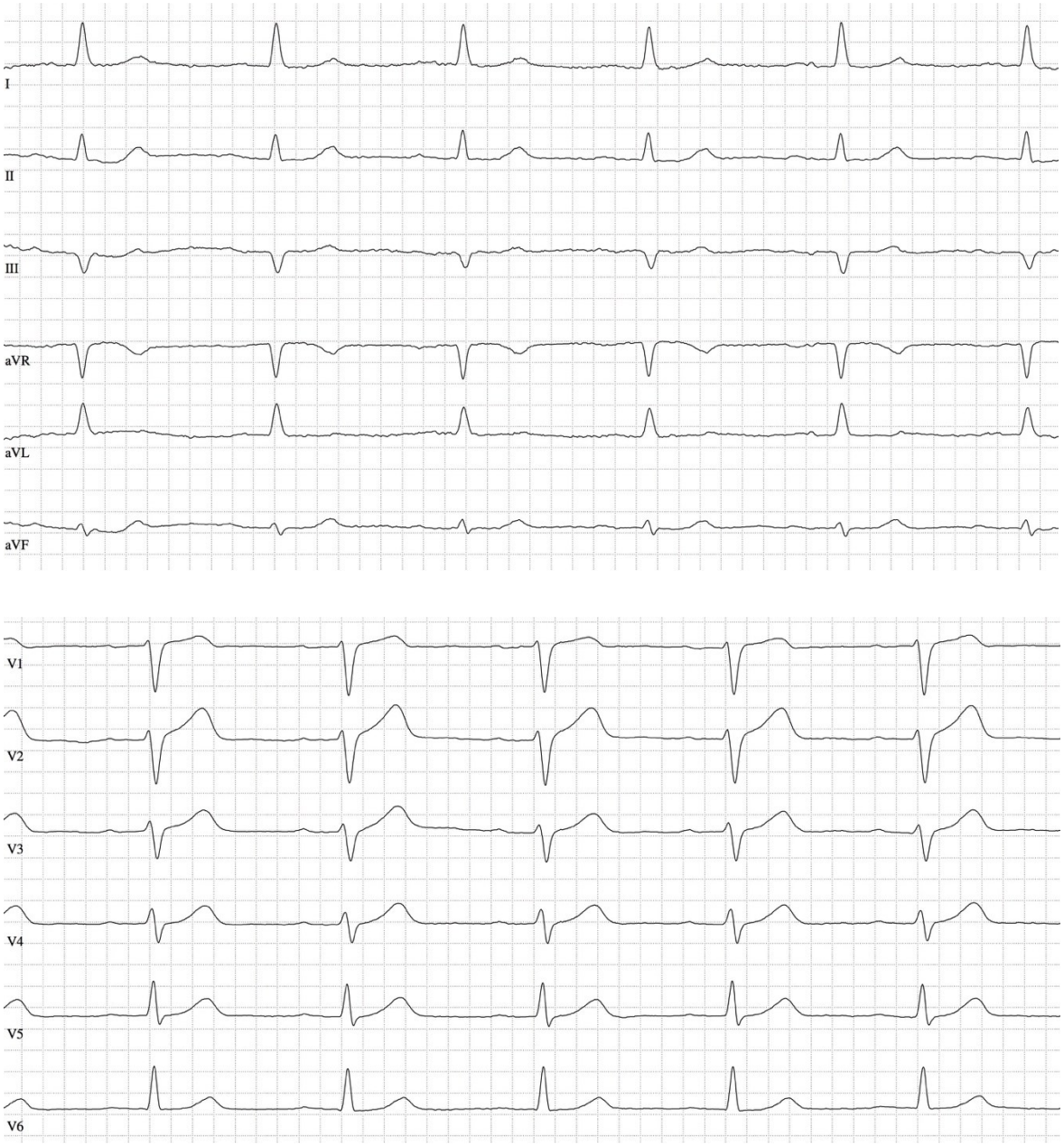



**Figure 35:** 12-lead ECG of a 69-years-old patient with chest pain for eight hours. No abnormalities were detected. (50 mm/s)

Repetitive ECGs were obtained in order to screen for dynamic ST changes. However, no changes occurred. About thirty minutes after hospital admission the troponin results came back positive (166.5 ng/l, hs-cTn I), thereby confirming myocardial ischemia. The CK-MB levels were reported to be 113 U/l. An echocardiographic examination with wall motion analysis by speckle tracking was carried out and showed reduced left ventricular contractility in the apical and septal regions *(see **Figure 37**)*.

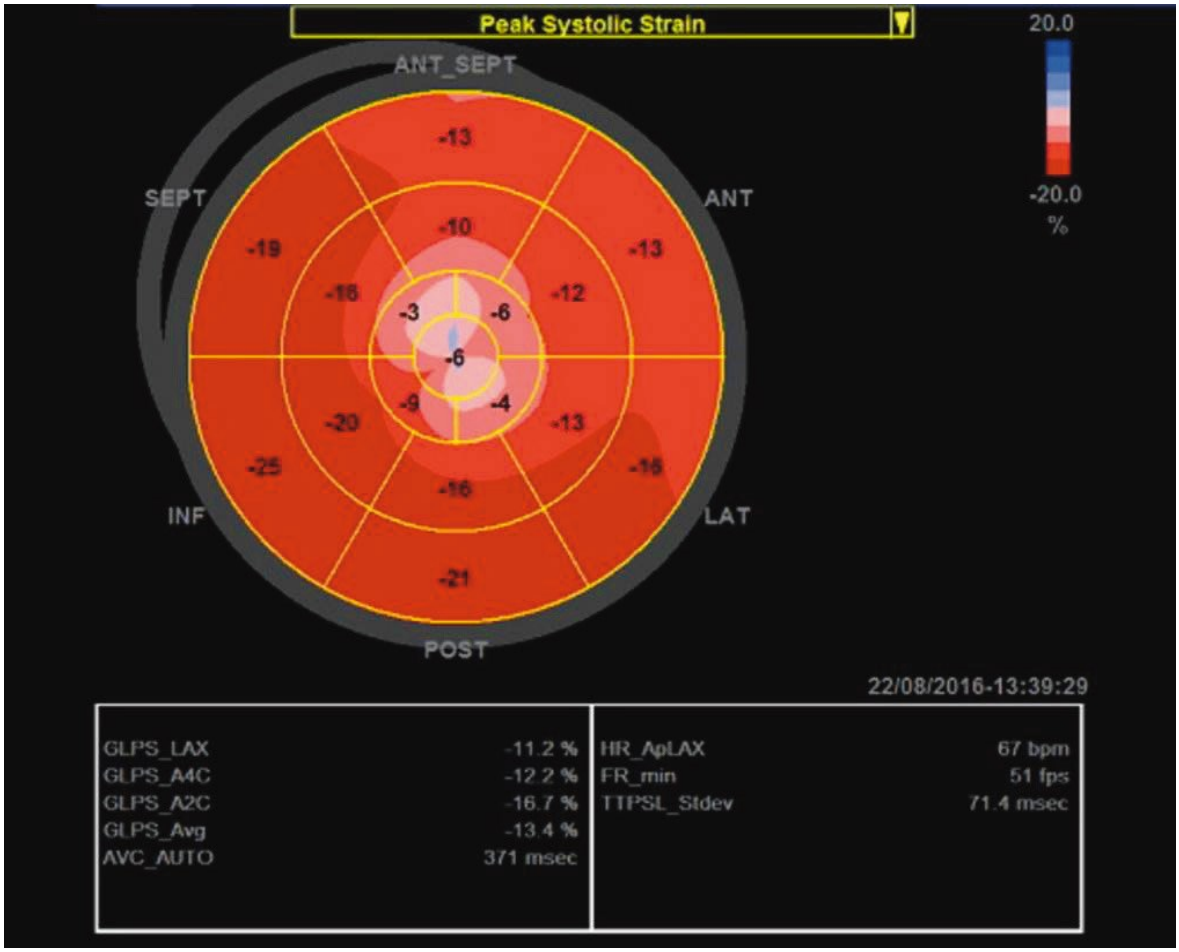



**Figure 37:** Speckle tracking analysis (longitudinal peak systolic strain) of the left ventricle with apical and septal wall motion abnormalities.

On the next day, about 24 hours after symptom onset, coronary angiography was performed and revealed an acute total coronary occlusion of the mid LAD *(see **Figure 36**)*.

The patient had a GRACE- and TIMI(UA/NSTEMI)-Score of 103 and 3, respectively.

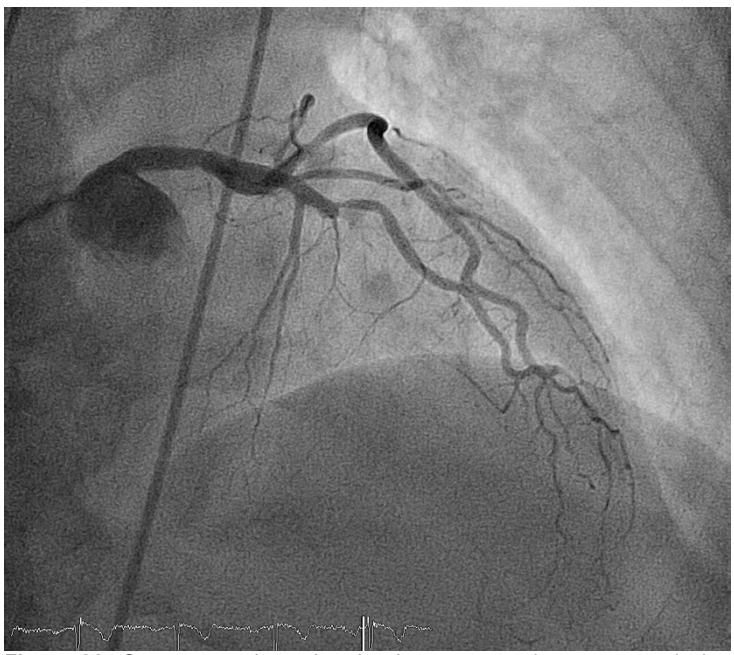


**Figure 36:** Coronary angiography showing acute total coronary occlusion (TIMI-flow grad 0) of the mid LAD.

# 4 Limitations

The greatest limitation of this interim analysis is its low number of included patients. As a consequence, significant differences between the two groups (coronary occlusion vs. no coronary occlusion) are not reached.

Furthermore, it is not possible to make any statements on the timing of the echocardiographic examination and coronary angiography in relation to the commencement of symptoms, since these points in time were not collected. In contrast, the times of completion of the individual forms were captured. However, the captured times cannot be used since the majority of the files were not completed at the time of the individual examination.

# Conclusion

Although this interim analysis is, due to its limitations, not capable of supporting the hypothesis of identifying acute coronary occlusion in patients with NSTEMI by echocardiography with regional wall motion analysis, the currently available literature does. Based on the available literature, the routine application of echocardiography in addition to the already available measures would be capable of increasing the sensitivity for the detection of acute coronary occlusion. Further studies are needed to investigate the differences of outcomes in patients undergoing rapid coronary angiography based on regional wall motion analysis rather than electrocardiographic findings.

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# Appendix

## 1 Differential Diagnoses of cTn Elevation

**Table I Elevations of cardiac troponin in the absence of overt ischaemic heart disease**

| |
|---|
| Damage related to secondary myocardial ischaemia (MI type 2) |
| Tachy- or bradyarrhythmias |
| Aortic dissection and severe aortic valve disease |
| Hypo- or hypertension, e.g. haemorrhagic shock, hypertensive emergency |
| Acute and chronic heart failure without significant concomitant coronary artery disease (CAD) |
| Hypertrophic cardiomyopathy |
| Coronary vasculitis, e.g. systemic lupus erythematosus, Kawasaki syndrome |
| Coronary endothelial dysfunction without significant CAD, e.g. cocaine abuse |
| Damage not related to myocardial ischaemia |
| Cardiac contusion |
| Cardiac incisions with surgery |
| Radiofrequency or cryoablation therapy |
| Rhabdomyolysis with cardiac involvement |
| Myocarditis |
| Cardiotoxic agents, e.g. anthracyclines, herceptin, carbon monoxide poisoning |
| Severe burns affecting >30% of body surface |
| Indeterminant or multifactorial group |
| Apical ballooning syndrome |
| Severe pulmonary embolism or pulmonary hypertension |
| Peripartum cardiomyopathy |
| Renal failure |
| Severe acute neurological diseases, e.g. stroke, trauma |
| Infiltrative diseases, e.g. amyloidosis, sarcoidosis |
| Extreme exertion |
| Sepsis |
| Acute respiratory failure |
| Frequent defibrillator shocks |

**Figure 38:** Differential diagnoses of elevated cTn. *From Thygesen et al. 2010*[5]

# 2 DeWinter ST/T Complex

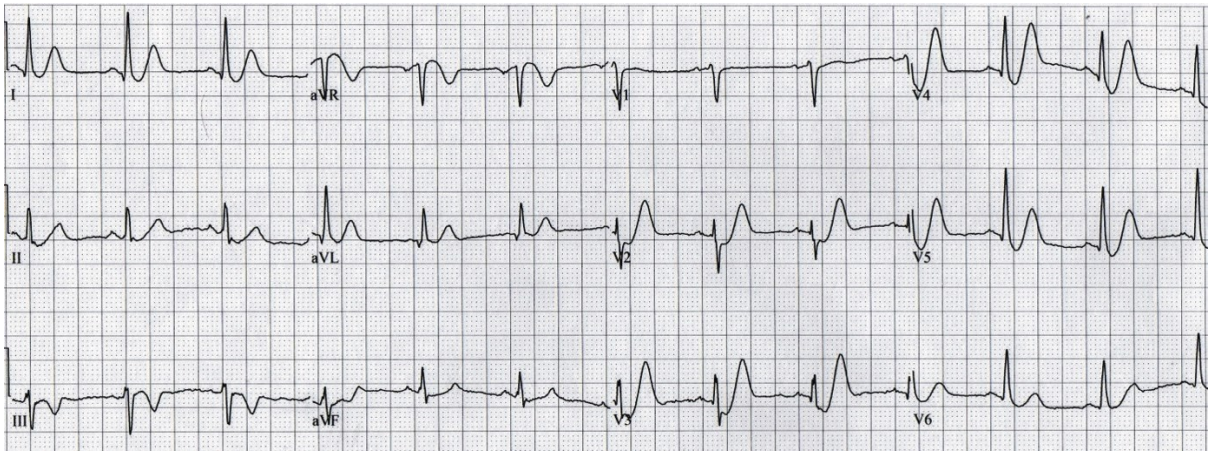


**Figure 39:** DeWinter T waves, example 1. From LITFL[225]

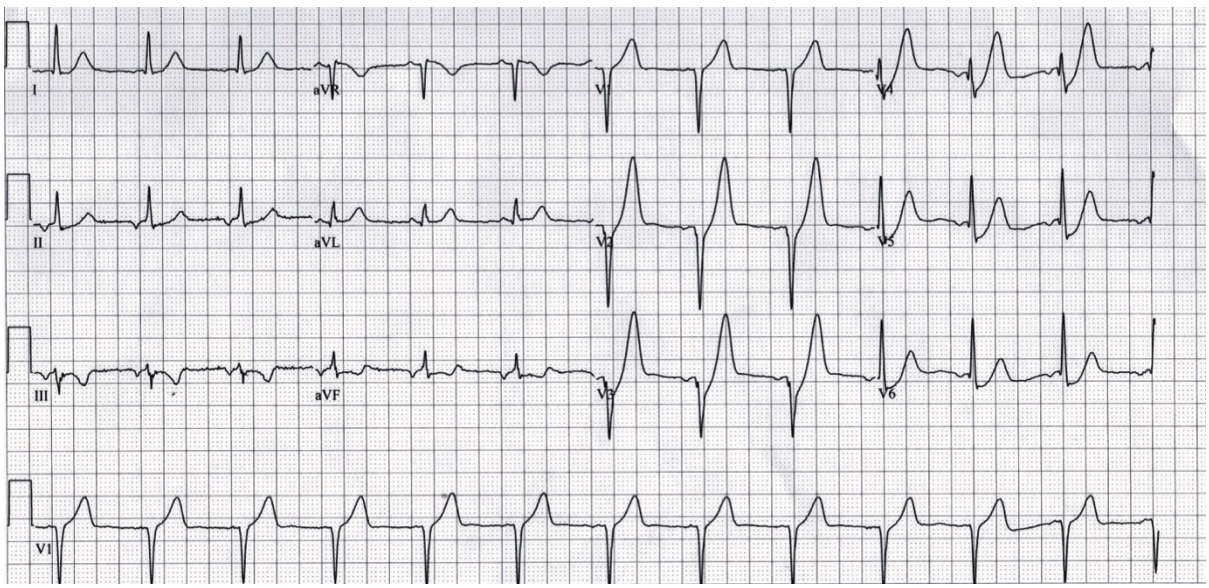


**Figure 40:** DeWinter T waves, example 2. *From LITFL*[226]

# 3 Wellen's Syndrome

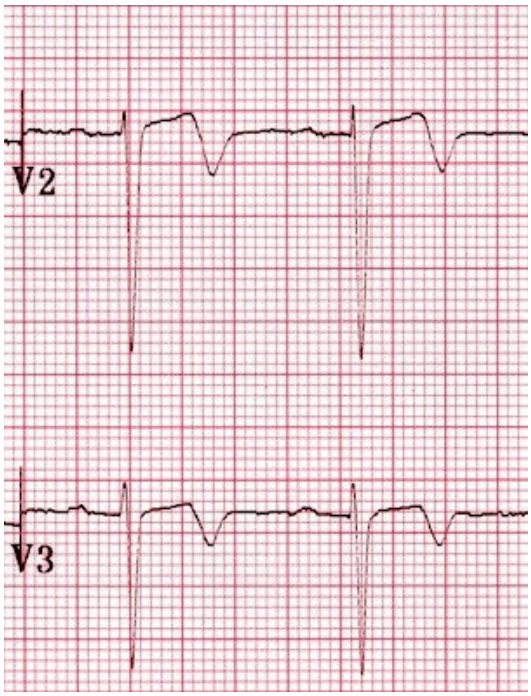


**Figure 41:** Wellen's Syndrome Type A, *From LITFL*[41]

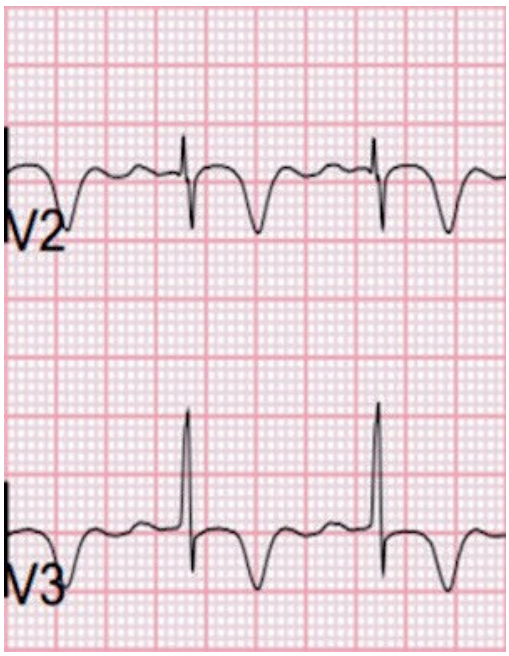


**Figure 42:** Wellen's Syndrome Type B, *From LITFL*[41]

# 4 Signs and Symptoms of Myocardial Infarction

| Predictor | Sensitivity, % (95% CI) | Specificity, % (95% CI) | PPV, % (95% CI) | NPV, % (95% CI) | LR+ (95% CI) | LR− (95% CI) |
|---|---|---|---|---|---|---|
| Same as previous ischaemia | 22.3 (15.9–29.9) | 69.4 (65.7–73.0) | 14.3 (10.0–19.5) | 79.7 (76.1–82.3) | 0.73 (0.53–1.01) | 1.12 (1.01–1.24) |
| Duration >1 h | 77.0 (69.4–83.5) | 44.9 (41.0–48.8) | 24.2 (20.4–28.3) | 89.5 (85.7–92.6) | 1.40 (1.25–1.56) | 0.51 (0.38–0.70) |
| Pain radiates to right shoulder/arm | 18.9 (13.0–26.2) | 91.8 (89.4–93.8) | 34.6 (24.4–46.0) | 83.2 (80.3–85.9) | 2.31 (1.52–3.53) | 0.88 (0.81–0.96) |
| Pain radiates to both shoulders/arms | 13.5 (8.5–20.1) | 94.8 (92.7–96.3) | 37.0 (24.3–51.3) | 82.8 (79.8–85.4) | 2.58 (1.53–4.34) | 0.91 (0.85–0.98) |
| Pain central | 85.1 (78.4–90.4) | 34.1 (30.5–37.9) | 22.8 (19.4–26.5) | 91.0 (86.6–94.2) | 1.29 (1.18–1.41) | 0.44 (0.29–0.65) |
| Pain left anterior | 11.5 (6.8–17.8) | 68.2 (64.5–71.8) | 7.6 (4.5–11.9) | 77.1 (73.5–80.5) | 0.36 (0.23–0.57) | 1.30 (1.20–1.40) |
| Reported sweating | 59.5 (51.1–67.4) | 54.3 (50.4–58.2) | 22.9 (18.8–47.5) | 85.4 (81.7–88.7) | 1.30 (1.11–1.52) | 0.75 (0.61–0.92) |
| Reported vomiting | 16.2 (10.7–23.2) | 94.8 (92.7–96.3) | 41.4 (28.6–55.1) | 83.2 (80.3–85.8) | 3.09 (1.89–5.05) | 0.88 (0.82–0.95) |
| Hypotension | 6.8 (3.3–12.1) | 97.7 (96.2–98.7) | 40.0 (21.2–61.3) | 82.1 (79.2–84.7) | 2.92 (1.34–6.37) | 0.95 (0.91–1.00) |
| Basal crackles | 16.2 (10.7–23.2) | 90.6 (88.1–92.7) | 28.2 (19.0–39.0) | 82.6 (79.6–85.3) | 1.72 (1.11–2.67) | 0.92 (0.86–1.00) |
| Sweating observed | 36.5 (28.7–44.8) | 94.3 (92.2–96.0) | 59.3 (48.5–69.5) | 86.7 (83.9–89.1) | 6.39 (4.38–9.33) | 0.67 (0.60–0.76) |
| Acute ischaemic ECG changes | 71.0 (62.9–78.1) | 81.3 (78.1–84.3) | 46.5 (39.8–53.2) | 92.5 (90.0–94.5) | 3.80 (3.14–4.60) | 0.36 (0.28–0.46) |

**Figure 43:** Signs and symptoms of myocardial infarction and their test perfomance. *From Body et al. 2010.*[201]

# 5 Clinical Study Protocol

# Clinical Study Protocol

**I**dentification of **C**oronary **O**cclusion in **N**on-ST-Elevation Myocardial Infarction **(ICON)**

**Version 1.2.2 – September 23, 2016**

## Preface

The present Clinical Study Protocol contains essential information about the study design in order to provide you sufficient knowledge about requirements, research questions, execution and arrangement, as well as information about how to handle necessary tasks in your daily clinical practice.

Please do not hesitate to contact us if you have any questions.

## Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, host organisation, and members of the Research Ethics Committee, unless authorised to do so.

# Early Identification of Acute Coronary Occlusion in Patients with Non-ST-Elevation Myocardial Infarction (NSTEMI) by Wall Motion Analysis: A Non-Interventional Echocardiographic Trial.

**Study Chairman**

**DeptL Dr. Wolfgang Weihs,**
*LKH Graz Süd-West – Standort West*
Department of Cardiology

## Revision History

**Version Number: 1.0**

*Version Date: January 26, 2016*

**Version Number: 1.1**

*Version Date: April 16, 2016*

Summary of Revisions made:

- Adjustment of the study title
- Inclusion of participating centres
- Definition of study design as non-interventional
- Modification of primary and secondary objectives
- Adjustment of exclusion criteria
- Inclusion of statistical considerations (e.g. definition of necessary sample-size)
- Other minor changes in various text passages
- (Modification of CRFs)

**Version Number: 1.2**

*Version Date: June 23, 2016*

Summary of Revisions made:

- Further specification of statistical considerations
- Inclusion of evaluation of previous cardiac illnesses
- Inclusion of required medical devices
- (Modification of Informed Consent Form)
- (Modification of CRF B – comments field added)

**Version Number: 1.2.1**

*Version Date: July 26, 2016*

Summary of Revisions made:

- Update of study sites

**Version Number: 1.2.2**

*Version Date: August 23, 2016*

Summary of Revisions made:

- Update of study sites
    - Exclusion of the study site *„Klinikum Wels-Grieskirchen“* (participation not possible due to staff reasons)
    - Addition of local study coordinators
- Declaration of the study as “verification of a medical device with CE certificate”
- Declaration of study site specific examinations and used medical devices

## Table of Contents

## 1. Study Team Roster

- **Weihs** Wolfgang**,** DeptL Dr.
  *Study Chairman*

- **Berghold** Andrea**,** Univ.-Prof. Dipl.-Ing. Dr. techn.
  *Statistics*

- **Haar** Markus**,** cand. med.

## 2. Participating Study Sites

- **LKH Graz Süd-West – Standort West**
  **Department für Kardiologie und Intensivmedizin**
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  *A-8020 Graz*
  **Local Study Coordinator:** *DeptL Dr. Wolfgang Weihs*

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  **Klinische Abteilung für Kardiologie**
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  *A-8036 Graz*
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  *A-1140 Wien*
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- **Wilhelminenspital**
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  *A-3500 Krems*
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  **Abteilung für Innere Medizin und Kardiologie**
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  *A-9020 Klagenfurt am Wörthersee*
  **Local Study Coordinator:**

# 3. Background and Rationale

## 3.1. Background

Currently, risk stratification in patients presenting with NSTEMI takes account of physical examination, electrocardiogram (ECG) and laboratory values, such as Troponin and Creatinine. By means of these parameters the temporal priority of cardiac catheter examination is planned.

Current guidelines [1] state that – due to a lack of studies – in patients classed as "very-high-risk" immediate invasive strategy (within a maximum of two hours) is indicated regardless of ECG or biomarker findings suggesting poor sensitivity of the mentioned features. Also, detection of acute coronary occlusion is frequently missed by the present approach leading to a preventable loss of viable myocardium as a result of inadequate delay to acute coronary intervention.

Therefore a more sensitive approach is needed. As a non-invasive diagnostic imaging tool echocardiography may play a significant role in detecting patients at great risk of losing large amounts of viable myocardial tissue. Also, ultrasound devices are immediately available at the bedside so that echocardiography can generously be applied. Present guidelines [1] of the *European Society of Cardiology (ESC)* recommend echocardiographic examination as immediate measure in the emergency department in order to exclude possible differential diagnosis, as well as to detect regional wall motion abnormalities as an expression of acute ischemic conditions. In the case of regional wall motion abnormalities the *ESC* recommends to strive for immediate clarification or intervention. In these cases acute coronary occlusion (TIMI-flow-grade 0 or 1) is very likely. Objective quantification of wall motion abnormality can easily be obtained with speckle-tracking and may be superior to the common subjective assessment of the myocardial function that also requires high experience.

However, the necessary extent of wall motion abnormality to justify an invasive strategy has not been investigated in larger trials and is therefore not defined. [2] A previously conducted retrospective study at the *LKH Graz-West Standort West* revealed a correlation between the number of affected segments with wall motion abnormality and coronary occlusion in NSTEMI *(information from the author)*. Moreover,

echocardiographic examinations, to our knowledge, are not frequently performed in non-ST-elevation acute coronary syndrome in many centres.

This prospective multicentre trial aims to fill this lack of knowledge in order to provide a more adequate classification and therefore better timed treatment to NSTEMI patients.

### 3.2. Study Rationale

Ischemic heart disease represents the leading cause of death worldwide. [3] Therefore, appropriate management of acute coronary syndrome plays an important role as it enables prevention of death, recurrent myocardial infarction, and loss of quality of life.

Currently, risk stratification in patients presenting with NSTEMI takes account of physical examination, ECG and laboratory values. Although these parameters have been used for diagnosis and risk stratification for decades they prove incapable of detecting a significant amount of myocardial infarction or acute coronary occlusion.

Schmitt et al. [4] investigated 120 patients with an acute myocardial infarction with angiographically proven occlusion of the left circumflex artery. At a mean time of 5.5 hours after pain onset only 46 % showed ST-segment elevation (>1 mm in I-aVF, > 2 mm in $V_1$-$V_6$ in 2 contiguous leads) in the standard 12-lead ECG. In a subgroup of patients with extended leads (> 1 mm in right precordial and posterior in 2 contiguous leads) sensitivity improved to only 61 %. Another study [5] showed a sensitivity and specificity of 46.8 and 98.5 % (> 1 mm in all leads, except V1-V3 where > 2 mm were required in 2 contiguous leads), respectively. Marti et al. conducted a study [6] in which they looked at subtle ST-elevation (0.1-1.0 mm) in a total of 504 patients with suspected STEMI that underwent coronary angiography. 18.3 % of these patients showed subtle ST-elevation, 86 % of which presented with TIMI flow grad 0 or 1.

Against general perception that STEMI leads to transmural and NSTEMI to non-transmural myocardial infarction Sarafoff et al. [7] managed to show that patients with STEMI were transmural in only 63 %. More interestingly, 27 % of patients with NSTEMI presented with transmural myocardial infarction.

Hence, a more sensitive approach is needed to avoid preventable loss of viable myocardial tissue. As the 2015 Guidelines on NSTEMI (ESC) state echocardiography

is recommended to evaluate regional and global left ventricular function for distinction between myocardial ischemia and other pathologies. However, this recommendation relies on consensus of expert opinion and has not been investigated. Echocardiography, particularly speckle-tracking, may play a vital role in the early identification of wall motion abnormities due to acute myocardial infarction and is to be inspected for its capability to do so.

## 4. Study Design and Objectives

### 4.1. Study Design

In this prospective multicentre study patients presenting with NSTEMI are enrolled. The study is defined as *"verification of a medical device with CE certificate"*. Both male and female patients that are older than 18 years of age are included. For risk stratification the following parameters or examinations are required: Demographic patient data (age, gender), medical history (clinical presentation, physical examination, past medical history), 12-lead-ECG, laboratory values (Troponin, total Creatine Kinase, Creatine Kinase MB, Creatinine, blood count), vital parameters (heart rate, blood pressure), as well as the GRACE- und TIMI risk-score for further risk stratification.

Within 24 hours prior to the cardiac catheter examination an echo is obtained. The following parameters are raised: global left ventricular ejection fraction (LVEF), wall motion score index (WMSI) by means of visual assessment or (optional) speckle tracking analysis, and existence of other conspicuous issues (e.g. left ventricular hypertrophy, valvular abnormalities).

### 4.2. Primary Objective

The primary objective of this prospective multicentre study is to assess the feasibility to detect coronary occlusion in patients presenting with NSTEMI by two-dimensional or speckle-tracking echocardiography. We hypothesise that more than two segments with wall motion abnormality allow for determining coronary occlusion.

If two-dimensional or speckle-tracking echocardiography proofs to be a success in detecting NSTEMI patients at risk of (preventable) high loss of viable myocardial tissue, this should lead to an obligatory use of two-dimensional or speckle-tracking

echocardiography in patients presenting with non-ST-elevation acute coronary syndrome. As a consequence, percutaneous coronary intervention (PCI) in patients with echocardiographic features of high-risk NSTEMI should be performed early.

### 4.3. Secondary Objectives

Secondary objectives are to assess the amount of patients presenting with regional wall motion abnormalities and to compare speckle-tracking to eye-balling in terms of detecting wall motion abnormalities.

## 5. Selection and Enrollment of Participants

### 5.1. Inclusion Criteria

The participants of this study must meet all of the following inclusion criteria:

- over 18 years of age
- male or female
- acute anginal pain within the last 24 hours at presentation
- elevation of troponin levels
- declaration of consent

### 5.2. Exclusion criteria

All candidates that meet any of the following criteria will be excluded:

- ST-elevation (according to the "Third universal definition of myocardial infarction" [8]) over 30 min
- new left bundle branch block (LBBB)
- previous cardiopulmonary resuscitation (CPR)
- recent administration of fibrinolytic agent
- known dilated cardiomyopathy (DCM)
- known hypertrophic cardiomyopathy (HCM)
- pericarditis

- myocarditis
- echocardiography not available

### 5.3. Study Enrolment Procedures and Informed Consent

#### 5.3.1. Study Enrolment Procedures

Possible candidates are identified and recruited in the emergency department. If a candidate (over the age of 18) presents with acute anginal pain (onset within 24 hours at presentation) and a positive Troponin level, study staff is to be informed by the physician in charge. The study staff member will initialise the informed consent and screening procedure. All data must be recorded on the forms provided (CRF A to F).

If the screening procedure shows the candidate to be eligible for study inclusion, he or she will be enrolled. If the candidate fails to show eligible for study inclusion, the reasons for ineligibility must be recorded (CRF B) and the patient will not be enrolled.

#### 5.3.2. Informed Consent

Informed consent must be obtained before any data collection on behalf of this study. If the candidate is not capable of signing the informed consent form or the candidate does not gain full accountability during hospital stay in order to sign the informed consent form, a legal representative can sign it instead. If there is no legal representative that can sign the informed consent form, the case will be discussed by the study committee in order to decide whether to enrol or not enrol the patient in the best sense of him or her. The informed consent form must be forwarded to the local study coordinator by the entrusted study staff member, a copy remains with the patient.

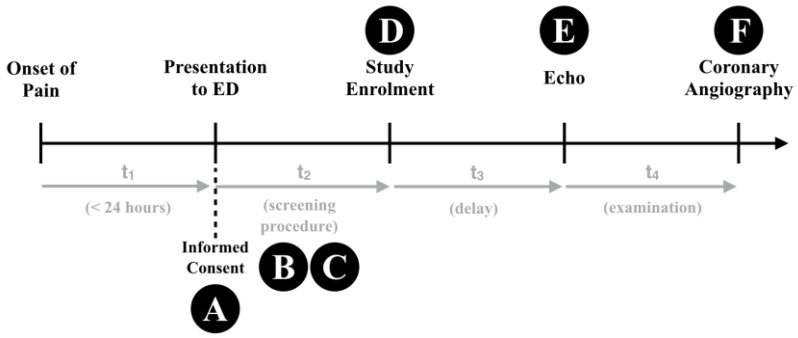
## 6. Study Interventions and Adverse Events

Within the scope of this study there are no additional interventions compared to routine care. This trial is limited to access the acquired data or results of routine care interventions (e.g. coronary angiography). Consequently there will not be any adverse events in the course of this study.

## 7. Study Procedures

| Assessment | Screening | Enrolment | Examination 1 | Examination 2 |
|---|---|---|---|---|
| *Informed Consent Form* | + | | | |
| *Demographics* | + | | | |
| *Medical History* | + | | | |
| *ECG-CRF* | + | (+) | | |
| *Blood chemistries* | + | (+) | | |
| *Inclusion/Exclusion Criteria* | + | | | |
| *Vital Signs* | | + | | |
| *Risk-Assessment* | | + | | |
| *Echo-CRF* | | | + | |
| *Coronary-Angiography-CRF* | | | | + |
| *Adverse Events* | | | | + |

### 7.1. Schedule of Evaluation



### 7.2. Description of Evaluation

#### 7.2.1. Screening Evaluation

These evaluations occur to determine if the candidate is eligible for the study.

*Screening Procedure*

If a candidate (over the age of 18) presents with acute anginal pain (onset within 24 hours at presentation) and a positive Troponin level, study staff is to be informed by the physician in charge.

The on-site study staff, consisting of a team around the local study coordinator, will, among other things, conduct the screening procedure. Study staff must be familiar with all associated protocols and processes and must have been instructed by the local study coordinator. The local study coordinator has final responsibility for all on-site processes concerning the study.

The screening procedure must be completed in order to determine if the candidate is eligible for study inclusion. If so, enrolment to the study and further examination (echocardiographic examination and coronary angiography) can be performed.

In order to complete the screening procedure the following parameters/examinations need to be recorded:

- **Demographics** (age, sex)
- **Medical history**
  As part of the medical history, patients undergoing the screening procedure need to be asked about any previous cardiovascular events so as to get a complete picture of the patient's cardiovascular health. If previous cardiovascular events have occurred they should be listed in the comments field at the bottom of CRF B. Previous cardiovascular events can only be assessed by medical history.
  It is noted that cardiovascular events other than those described as exclusion criteria, however, do not influence study inclusion. As a consequence, no specific tests are required to confirm previous cardiovascular events.
- **ECG**
  The ECG must not meet STEMI criteria according to current guidelines [8]. If STEMI criteria are met no longer than 30 minutes, this is referred to as transient

ST-elevation and the patient can and should be enrolled. If ST-elevation(s) is/are present, but STEMI criteria are not met, the patient can be enrolled.

- **Troponin**
  The number and intervals of Troponin determinations is the responsibility of the physician in charge.
- **Pregnancy test**
  The *"Ethics Committee of the City of Vienna" (Ethikkommission der Stadt Wien)* prescribes the conduct of pregnancy tests in women of childbearing age in their area of responsibility. These tests are to be conducted before the study inclusion can take place. An appropriate note to file must be set up among the study sponsor and the local study coordinator at the concerned study sites.
- **Absence of any exclusion criteria**

### 7.2.2. Enrolment and Further Assessment

*Enrolment*

If the screening procedure shows the candidate to be eligible for study inclusion, he or she will be enrolled. The time of determination of study eligibility complies with the time of study enrolment and must be recorded.

*Further Assessment*

After enrolment the following parameters and forms must be recorded or filled out:

- **Enrolment-CRF (D)**
  - Blood pressure, heart rate
  - Laboratory values
    - CK
    - CK-MB
    - Creatinine
    - Blood count
    - Blood glucose
  - Risk stratification

### 7.2.3. Examinations

*Examination 1 – Echocardiographic Examination*

When the patient finally is enrolled to the study, echocardiographic examination can be performed at any time. The examination should be performed by an experienced physician that has been instructed by the on-site study coordinator and therefore is familiar with the study documentary. If an individual centre is capable of performing speckle-tracking analysis this approach should always be preferred over eye-balling. If an individual centre is not capable of performing speckle-tracking analysis, eye-balling and classification by means of the Wall Motion Score Index (WMSI) of each wall segment should be performed.

All obtained data must either be recorded on the Echo-CRF (E) form or printed and to be attached to the Echo-CRF form.

*Examination 2 – Coronary Angiography*

If the patient underwent echocardiographic examination, coronary angiography must be obtained as early as possible and within 24 hours afterwards. All required data must be filled out on the coronary angiography form.

Since there are no further examinations planned, this is the last procedure required for the study.

### 7.2.4. Medical devices

Since this clinical study is an observational study, no further interventions than those carried out in routine care will be performed. It is underlined that all utilised medical devices are required to have a valid CE label and must be used exclusively within their intended purpose. The required CE certificates are present to the ethics commissions.

**Used ultrasound devices in different centres:**

- **Wilhelminenspital**
  - Vivid 7 Dimension/Vivid 7 Pro
  - Logiq E9 Ultrasound System

- **Hanusch-Krankenhaus**
  - Vivid E9

## 8. Study Discontinuation and Study Exclusion

### 8.1. Study Discontinuation

If the study is discontinued because auf any reason, all data acquisitions in behalf of the study must be stopped and all files must be forwarded to the study coordinator.

### 8.2. Study Exclusion

If any exclusion criteria occur after study enrolment, the individual participant will be excluded retrospectively and he or she must be informed. The so far collected data still need to be provided.

## 9. Statistical Considerations

To detect coronary occlusion in patients presenting with NSTEMI by two-dimensional or speckle-tracking echocardiography we hypothesise that more than two segments with wall motion abnormality allow for determining coronary occlusion with 80% sensitivity. With 315 subjects, the lower limit of the observed one-sided 95.0% confidence interval will be expected to exceed -0.050 with 80% power when no difference is expected and the proportion of discordant pairs is 0.12. Results are based on 5,000 simulations using the Newcombe-Wilson score method to construct the confidence interval. [9] Including a dropout rate of about 15% 370 patients will be included in the study.

### 9.1. Statistical analysis

The data will first be described by descriptive statistics using mean, standard deviation, median, minimum and maximum for continuous variables as appropriate and absolute and relative frequency for categorical variables. Sensitivity, specificity and area under the curve (AUC) will be determined for different cut-off values to identify acute coronary occlusion by receiver operator characteristic (ROC) analysis.

## 10.Data Collection and Quality Assurance

### 10.1. Data Collection Forms

All acquired data is to be collected for each participant in the Case Report Forms (CRF) provided. Each form is characterised by a letter from A to F in order to easily define the sequence of the examinations that need to be performed. Study staff members will coordinate the examinations that are normally performed by the respective physician in charge. To provide and maintain confidentiality of participant records all forms are collected by the on-site study coordinator.

### 10.2. Data Management

The local study coordinator has final responsibility for all on-site processes concerning the study. All forms concerning the study are, finally, collected by the local study coordinator after termination of the study procedure. All corresponding documents will then be forwarded to the coordinating centre (LKH Graz Süd-West – Standort West), that is responsible for data management and interpretation of study outcomes.

## 11. Participant Rights

### 11.1. Informed Consent

The study candidate must agree to data acquisition in behalf of the study. Patient data will not be recorded until informed consent is provided. *For further details see section 5.3.2*

### 11.2. Revoke of Study Participation

If informed consent was provided by any individual participant, he or she can revoke study participation at any time and without giving reasons.

## 12. References

### References

1. Authors/Task Force M, Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, et al. 2015 Esc Guidelines for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent St-Segment Elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent St-Segment Elevation of the European Society of Cardiology (Esc). Eur Heart J. 2015.

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3. The Top 10 Causes of Death: World Health Organisation (WHO); 2012 [13/01/2016]. Available from: http://www.who.int/mediacentre/factsheets/fs310/en/.

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5. Macfarlane PW, Browne D, Devine B, Clark E, Miller E, Seyal J, et al. Modification of Acc/Esc Criteria for Acute Myocardial Infarction. J Electrocardiol. 2004;37:98-103.

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7. Sarafoff N, Schuster T, Vochem R, Fichtner S, Martinoff S, Schwaiger M, et al. Association of St-Elevation and Non-St-Elevation Presentation on Ecg with Transmurality and Size of Myocardial Infarction as Assessed by Contrast-Enhanced Magnetic Resonance Imaging. J Electrocardiol. 2013;46(2):100-6.

8. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al. Third Universal Definition of Myocardial Infarction. Eur Heart J. 2012;33(20):2551-67.

9. Newcombe RG. Improved Confidence Intervals for the Difference between Binomial Proportions Based on Paired Data. Stat Med. 1998;17(22):2635-50.

# 6 Informed Consent Form *(ICF)*

**Informed Consent_V1.2**
**I**dentification of **C**oronary **O**cclusion in **N**on-ST-Elevation Myocardial Infarction **(ICON)**

**A**

**PatientInneninformation[1] und Einwilligungserklärung zur Teilnahme an der klinischen Studie**

## Frühzeitige Identifizierung von akutem Verschluss der Herzkranzgefäße bei Patienten mit nicht-ST-Hebungsinfarkt[2] mittels Wandbewegungsstörungsanalyse[3]: Eine nicht-interventionelle echokardiografische Studie.

*Early Identification of Acute Coronary Occlusion in Patients with Non-ST-Elevation Myocardial Infarction (NSTEMI) by Wall Motion Analysis: A Non-Interventional Echocardiographic Trial.*

**Sehr geehrte Teilnehmerin, sehr geehrter Teilnehmer!**

Wir laden Sie ein an der oben genannten klinischen Studie teilzunehmen. Die Aufklärung darüber erfolgt in einem ausführlichen ärztlichen Gespräch.

**Ihre Teilnahme an dieser klinischen Studie erfolgt freiwillig. Sie können jederzeit ohne Angabe von Gründen aus der Studie ausscheiden. Die Ablehnung der Teilnahme oder ein vorzeitiges Ausscheiden aus dieser Studie hat keine nachteiligen Folgen für Ihre medizinische Betreuung.**

Klinische Studien sind notwendig, um verlässliche neue medizinische Forschungsergebnisse zu gewinnen. Unverzichtbare Voraussetzung für die Durchführung einer klinischen Studie ist jedoch, dass Sie Ihr Einverständnis zur Teilnahme an dieser klinischen Studie schriftlich erklären. Bitte

[1] Wegen der besseren Lesbarkeit wird im weiteren Text zum Teil auf die gleichzeitige Verwendung weiblicher und männlicher Personenbegriffe verzichtet. Gemeint und angesprochen sind – sofern zutreffend – immer beide Geschlechter.

[2] Bei einem nicht-ST-Hebungsinfarkt handelt es sich um einen Herzinfarkt, der sich im Elektrokardiogramm (EGK) ohne typische Hebungen der sog. ST-Strecke präsentiert. Dadurch ergeben sich Änderungen in der Akuttherapie, da von einer geringeren Größe des Herzinfarktes ausgegangen wird.

[3] Bei der Wandbewegungsstörungsanalyse handelt es sich um eine Beurteilung der Kontraktion verschiedener Herzmuskelabschnitte mittels einer Herzultraschalluntersuchung (Echokardiographie).

lesen Sie den folgenden Text als Ergänzung zum Informationsgespräch mit Ihrem Arzt sorgfältig durch und zögern Sie nicht Fragen zu stellen.

Bitte unterschreiben Sie die Einwilligungserklärung nur,

- wenn Sie Art und Ablauf der klinischen Studie vollständig verstanden haben,
- wenn Sie bereit sind, der Teilnahme zuzustimmen und
- wenn Sie sich über Ihre Rechte als Teilnehmer an dieser klinischen Studie im Klaren sind.

Zu dieser klinischen Studie, sowie zur Patienteninformation und Einwilligungserklärung wurde von der zuständigen Ethikkommission eine befürwortende Stellungnahme abgegeben.

**1. Was ist der Zweck der klinischen Studie?**

Der Zweck dieser klinischen Studie besteht in der Ermittlung, ob mittels Echocardiographie (Herzultraschall) ein akuter Verschluss eines Herzkranzgefäßes (Herzinfarkt) nachgewiesen werden kann. Hierbei kann eine relativ neue Interpretationsmethode (Speckle Tracking[4]) zum Einsatz kommen. Bisher erfolgt die Therapieplanung im Wesentlichen aufgrund der vom Patienten angegebenen Beschwerden, bestimmten Blutwerten und des EKG. Das Vorliegen eines Herzkranzgefäßverschlusses ist durch die angeführten Untersuchungen nicht immer eindeutig zu bestimmen, was zu einer Verzögerung der notwendigen Therapie führen kann. Es ist deshalb von großer Bedeutung, dass neue Untersuchungsmethoden zur Risikoeinschätzung herangezogen werden.

**2. Wie läuft die klinische Studie ab?**

Diese klinische Studie wird an mehreren Orten in Österreich durchgeführt, und es werden insgesamt ungefähr 400 Personen daran teilnehmen.

Ihre Teilnahme an dieser klinischen Studie erfolgt während Ihres stationären Aufenthaltes, der durch die Studienuntersuchungen nicht verlängert wird. Es werden Blutabnahmen, eine Ultraschalluntersuchung und eine Herzkatheteruntersuchung durchgeführt, die alle

[4] Beim „Spackle Tracking“ handelt es sich um eine spezielle Auswertung von Videosequenzen der durchgeführten Herzultraschalluntersuchung, womit eine genauere Beurteilung der Herzmuskelkontraktion möglich ist.

Bestandteil der Routineversorgung sind und sich deshalb nicht von den durchgeführten Untersuchungen bei Patienten, die nicht an der Studie teilnehmen, unterscheiden.

**3. Worin liegt der Nutzen einer Teilnahme an der Klinischen Studie?**

Es ist möglich, dass Sie durch Ihre Teilnahme an dieser klinischen Studie keinen direkten Nutzen für Ihre Gesundheit ziehen. Die durchgeführte Herzultraschalluntersuchung kann dazu beitragen, dass Sie früher einer Herzkatheteruntersuchung zugeführt werden und ein etwaig bestehendes Problem der Herzkranzgefäßversorgung früher behoben wird. Die Ihnen zukommende Therapie unterscheidet sich nicht von der Therapie eines Patienten, der nicht an der Studie teilnimmt.

Durch die Teilnahme an dieser klinischen Studie leisten Sie einen wichtigen und wertvollen Beitrag für die medizinische Wissenschaft und spätere Patienten, die dasselbe Krankheitsbild wie Sie aufweisen.

**4. Gibt es Risiken, Beschwerden und Begleiterscheinungen?**

An Ihnen werden im Rahmen dieser Studie keine zusätzlichen invasiven Eingriffe durchgeführt. Das Risiko der Teilnahme an der Studie unterscheidet sich deshalb nicht von Patienten, die nicht an der Studie teilnehmen.

**5. Zusätzliche Einnahme von Arzneimitteln?**

Im Rahmen dieser klinischen Studie erhalten Sie keine zusätzlichen Arzneimittel.

**6. Hat die Teilnahme an der klinischen Studie sonstige Auswirkungen auf die Lebensführung und welche Verpflichtungen ergeben sich daraus?**

Aus der Teilnahme an der Studie ergeben sich keine Auswirkungen auf ihre weitere Lebensführung. Ebenso entstehen dadurch keine zusätzlichen Verpflichtungen.

**7. Wann wird die klinische Studie vorzeitig beendet?**

Sie können jederzeit auch ohne Angabe von Gründen, Ihre Teilnahmebereitschaft widerrufen und aus der klinischen Studie ausscheiden ohne dass Ihnen dadurch Nachteile für Ihre weitere medizinische Betreuung entstehen.

Ihr Studienarzt wird Sie über alle neuen Erkenntnisse, die in Bezug auf diese klinische Studie bekannt werden, und für Sie wesentlich werden könnten, umgehend informieren. Auf dieser Basis können Sie dann Ihre Entscheidung zur weiteren Teilnahme an dieser klinischen Studie neu überdenken.

Es ist aber auch möglich, dass Ihr Studienarzt entscheidet, Ihre Teilnahme an der klinischen Studie vorzeitig zu beenden, ohne vorher Ihr Einverständnis einzuholen. Die Gründe hierfür können sein:

a) Sie können den Erfordernissen der Klinischen Studie nicht entsprechen;

b) Ihr Studienarzt hat den Eindruck, dass eine weitere Teilnahme an der klinischen Studie nicht in Ihrem Interesse ist;

**8. In welcher Weise werden die im Rahmen dieser klinischen Studie gesammelten Daten verwendet?**

Sofern gesetzlich nicht etwas anderes vorgesehen ist, haben nur die Studienärzte und deren Mitarbeiter Zugang zu den vertraulichen Daten, in denen Sie namentlich genannt werden. Diese Personen unterliegen der Schweigepflicht.

Die Weitergabe der Daten erfolgt ausschließlich zu statistischen Zwecken und Sie werden ausnahmslos nicht namentlich genannt. Auch in etwaigen Veröffentlichungen der Daten dieser klinischen Studie werden Sie nicht namentlich genannt.

**9. Entstehen für die Teilnehmer Kosten? Gibt es einen Kostenersatz oder eine Vergütung?**

Durch Ihre Teilnahme an dieser klinischen Studie entstehen für Sie keine zusätzlichen Kosten. Für Ihre Teilnahme an dieser klinischen Studie erhalten Sie keine Vergütung.

**10. Möglichkeit zur Diskussion weiterer Fragen**

Für weitere Fragen im Zusammenhang mit dieser klinischen Studie stehen Ihnen Ihr Studienarzt und seine Mitarbeiter gern zur Verfügung. Auch Fragen, die Ihre Rechte als Patient und Teilnehmer an dieser klinischen Studie betreffen, werden Ihnen gerne beantwortet.

**Name der Kontaktperson:** DeptL Dr. Wolfgang Weihs

**Ständig erreichbar unter:** +43 (316) 5466 - 6410

**11. Sollten andere behandelnde Ärzte von der Teilnahme an der klinischen Studie informiert werden?**

Ihr Hausarzt oder andere Ärzte müssen bzgl. der Teilnahme an dieser klinischen Studie nicht informiert werden, da sich daraus keine therapeutische Konsequenz ergibt.

**12. Einwilligungserklärung**

Name des Patienten in Druckbuchstaben: _____

Geb.Datum: _____ Studien-ID: 01001

Ich erkläre mich bereit, an der klinischen Studie *„Identification of Coronary Occlusion in Non-ST-Elevation Myocardial Infarction (ICON)"* teilzunehmen.

Ich bin von Herrn/Frau _____ ausführlich und verständlich über mögliche Belastungen und Risiken, sowie über Wesen, Bedeutung und Tragweite der klinischen Studie, sich für mich daraus ergebenden Anforderungen aufgeklärt worden. Ich habe darüber hinaus den Text dieser Patientenaufklärung und Einwilligungserklärung, die insgesamt 6 Seiten umfasst, gelesen. Aufgetretene Fragen wurden mir vom Studienarzt verständlich und genügend beantwortet. Ich hatte ausreichend Zeit, mich zu entscheiden. Ich habe zurzeit keine weiteren Fragen mehr.

Ich werde den ärztlichen Anordnungen, die für die Durchführung der klinischen Studie erforderlich sind, Folge leisten, behalte mir jedoch das Recht vor, meine freiwillige Mitwirkung jederzeit zu beenden, ohne dass mir daraus Nachteile für meine weitere medizinische Betreuung entstehen.

Ich bin zugleich damit einverstanden, dass meine im Rahmen dieser klinischen Studie ermittelten Daten aufgezeichnet werden. Um die Richtigkeit der Datenaufzeichnung zu überprüfen, dürfen Beauftragte der zuständigen Behörden beim Studienarzt Einblick in meine personenbezogenen Krankheitsdaten nehmen.

Die Bestimmungen des Datenschutzgesetzes in der geltenden Fassung werden eingehalten.

Eine Kopie dieser Patienteninformation und Einwilligungserklärung habe ich erhalten. Das Original verbleibt beim Studienarzt.

_____

(Datum und Unterschrift des Patienten)

_____

(Datum, Name und Unterschrift des verantwortlichen Arztes)

***(Der Patient erhält eine unterschriebene Kopie der Patienteninformation und Einwilligungserklärung, das Original verbleibt im Studienordner des Studienarztes.)***

# 7 Screening-CRF *(CRF B)*

**Screening – Case Report Form** (Screening-CRF)_V1.3

B

## Patientendaten und Zeiten

**Studien-ID:** 01001

**Geschlecht:** ☐ männlich ☐ weiblich

**Nachname, Vorname:** _____

**Alter:** _____ Jahre

**Gewicht:** _____ kg

**Größe:** _____ cm

**Datum:** _____

**Screening-Start um:** _____ Uhr

**Screening-Ende um:** _____ Uhr

## Anamnese und Labor

**Schmerz**

Cardialer Thoraxschmerz: ☐ ja ☐ nein

Beginn am: _____ (Datum)

Beginn um: _____ Uhr

**Labor**

Troponin-Typ: ☐ I ☐ T ☐ hs-Trop.

Troponinwert + Einheit: _____

Trop. über oberem Referenzwert: ☐ ja ☐ nein

Zeitpunkt Blutabnahme: _____ Uhr

Zeitpunkt Troponinwert vorliegend: _____ Uhr

Identification of Coronary Occlusion in NSTEMI (ICON)

ICON Trial ID: 01001 Seite 1 von 2

**Screening – Case Report Form** (Screening-CRF)_V1.3

B

## Studieneinschluss

☐ **Einschlusskriterien erfüllt**

Alle Einschlusskriterien sind erfüllt, wenn:

- der Patient älter als 18 Jahre ist.
- der Schmerzbeginn (cardialer Thoraxschmerz) innerhalb von 24 Stunden vor dem Erstkontakt in der Notaufnahme war.
- der bestimmte Troponinwert über dem oberen Referenzbereich liegt.

☐ **Ausschlusskriterien vorliegend**

Etwaig vorliegende Ausschlusskriterien sind anzukreuzen:

☐ ST-Hebung (nach aktuellen ESC-Leitlinien[1]) über einen Zeitraum von mind. 30 min
☐ Neu aufgetretener Linksschenkelblock (LSB)
☐ Z.n. cardiopulmonaler Reanimation (CPR)
☐ kürzliche Verabreichung eines Fibrinolytikums (< 7 Tage)
☐ bekannte dilatative Kardiomyopathie (DCM)
☐ bekannte hypertrophe Kardiomyopathie (HCM)
☐ Perikarditis *(Ausschluss muss in dieser Phase noch nicht erfolgen!)*
☐ Myokarditis *(Ausschluss muss in dieser Phase noch nicht erfolgen!)*

☐ **Der Patient wird in die Studie eingeschlossen.**

☐ Der Patient wird **nicht** in die Studie **eingeschlossen.**

*Anmerkungen:*

[1] Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al. Third universal definition of myocardial infarction. European heart journal. 2012;33(20):2551-67.

# 8 ECG-CRF *(ECG C)*

**Elektrokardiogramm – Case Report Form** (EKG-CRF)_V1.2

C

In diesem CRF ist das EKG zu protokollieren, das entscheidend zur Diagnosefindung beiträgt. Über die Anzahl der durchgeführten EKG-Untersuchungen entscheidet der behandelnde Arzt. **Das EKG muss diesem Formular beigelegt werden!**

## Patientendaten und Zeiten

**Studien-ID:** 01001

**Geschlecht:** ☐ männlich ☐ weiblich

**Initialen:** _____

**Alter:** _____ Jahre

**Erfassungsdatum:** _____

**Erfassungszeit:** _____ Uhr

**Zeit seit Schmerzbeginn:** _____ min

**Anzahl zuvor erfasster EKG:** _____

## Allgemeine EKG-Diagnostik

**Rhythmus:**
☐ Sinusrhythmus (SR)
☐ Vorhofflimmerarrhythmie (VHFA)
☐ anderer: _____

**Frequenz:** _____ /min

**Lagetyp:**
☐ Linkstyp ☐ Rechtstyp
☐ Indifferenztyp ☐ Überdrehter Linkstyp
☐ Steiltyp ☐ Überdrehter Rechtstyp

**Intervalle:**
P _____ ms
PQ _____ ms (AV-Block ☐ 1., ☐ 2., ☐ 3. °)
QRS _____ ms (☐ LSB, ☐ RSB)
QT _____ ms
QTc _____ ms

Identification of Coronary Occlusion in NSTEMI (ICON)

ICON Trial ID: 01001 Seite 1 von 2

**Elektrokardiogramm – Case Report Form** (EKG-CRF)_V1.2

C

## ST-Strecken-Beurteilung

Dieser Abschnitt dient zur Beurteilung der ST-Streckenabweichungen am J-Punkt in Bezug auf die TP-Linie (= Baseline). Jede Abweichung des J-Punktes, die mehr als 0,5 mm (entspr. 0,05 mV) von der Baseline beträgt, muss hier quantitativ angeführt werden. Ableitungen, in denen sich geringere oder keine Abweichungen am J-Punkt zeigen, müssen nicht angeführt werden. **Die Richtung der Abweichung wird durch das entsprechende Vorzeichen festgelegt (z.B. – 1,2 mm = Senkung des J-Punktes; + 0,5 mm = Hebung des J-Punktes)!**

☒ **Standardableitungen**

| | | | | | |
|---|---|---|---|---|---|
| I | _____ | mm | $V_1$ | _____ | mm |
| II | _____ | mm | $V_2$ | _____ | mm |
| III | _____ | mm | $V_3$ | _____ | mm |
| aVL | _____ | mm | $V_4$ | _____ | mm |
| aVF | _____ | mm | $V_5$ | _____ | mm |
| aVR | _____ | mm | $V_6$ | _____ | mm |

☐ **Erweiterte Ableitungen (optional)**

☐ posteriore Ableitungen ☐ rechtsgerichtete Ableitungen

| | | | | | |
|---|---|---|---|---|---|
| $V_7$ | _____ | mm | $V_{3R}$ | _____ | mm |
| $V_8$ | _____ | mm | $V_{4R}$ | _____ | mm |
| $V_9$ | _____ | mm | | | |

☐ **Erweiterte EKG-Zeichen (optional)**

☐ invertierte T-Wellen in Abl. _____

☐ verzögerte R-Progression

☐ pathologische Q-Zacken in Abl. _____

*Anmerkungen*

ICON Trial ID: 01001 Seite 2 von 2

Identification of Coronary Occlusion in NSTEMI (ICON)

# 9 Enrolment-CRF *(CRF D)*

**Enrolment – Case Report Form** (Enrolment-CRF)_V1.2

D

## Patientendaten und Zeiten

**Studien-ID:** 01001

**Geschlecht:** ☐ männlich ☐ weiblich

**Initialen:** _____

**Alter:** _____ Jahre

**Erfassungsdatum:** _____

**Erfassungszeit:** _____ Uhr

## Vitalparameter

Erster Blutdruck _____/_____ mmHg

Erster Puls _____ /min

Kreislaufwirksame Medikamente wurden verabreicht (z.B. Ebrantil, Nitro lingual, etc.):

☐ ja ☐ nein

## EKG-Diagnostik

☐ **EKG-CRF (Formular C) ausgefüllt**

## Laborwerte

**Zu jedem Laborwert ist die entsprechende Einheit anzugeben!**

**Bitte das Blutbild beilegen.**

CK _____

CK-MB _____

Kreatinin _____

Blutzucker _____

Identification of Coronary Occlusion in NSTEMI (ICON)

ICON Trial ID: 01001 Seite 1 von 2

**Enrolment – Case Report Form** (Enrolment-CRF)_V1.2

D

## Risikostratifikation

In diesem Abschnitt werden Parameter zur Risikostratifikation mittels TIMI-(UA/NSTEMI)- und GRACE-Score ermittelt.

- ☐ KHK in der Familie
- ☐ Arterielle Hypertonie
- ☐ Hypercholesterinämie
- ☐ Diabetes mellitus
- ☐ Patient raucht zurzeit

  pack years: _____
- ☐ ASS-Einnahme innerhalb der letzten 7 Tage
- ☐ aktuell starke Angina pectoris
- ☐ Chronische Herzinsuffizienz
- ☐ Erhöhter Jugularvenendruck
- ☐ Auskultatorische Rasselgeräusche
- ☐ Lungenödem
- ☐ Kardiogener Schock

*Anmerkungen*

# 10 Echo-CRF *(CRF E)*

**Echocardiographie – Case Report Form** (Echo-CRF)_V1.2

E

## Patientendaten und Zeiten

**Studien-ID:** 01001

**Geschlecht:** ☐ männlich ☐ weiblich

**Initialen:** _____

**Alter:** _____ Jahre

**Untersuchungsdatum:** _____

**Untersuchungszeit:** _____ Uhr

## Globale Linksventrikelfunktion

**Quantitativ:**

LVEDV _____ ml

LVESV _____ ml

LVEF _____ %

E / e' _____

**Visuell:**

☐ normal (> 52 %)

☐ gering reduziert (> 41 – 51 %)

☐ mittelgradig reduziert (> 30 – 40 %)

☐ hochgradig reduziert (< 30 %)

## Herzklappenbeurteilung

**Aortensklappe**

☐ Aortensklerose

☐ Aortenstenose

Schweregrad: _____

**Mitralklappe**

☐ Mitralsklerose

☐ Mitralinsuffizienz

Schweregrad: _____

Identification of Coronary Occlusion in NSTEMI (ICON)

ICON Trial ID: 01001 Seite 1 von 2

**Echocardiographie – Case Report Form** (Echo-CRF)_V1.2

E

## Regionale Linksventrikelfunktion

Die Beurteilung der regionalen Linksventrikelfunktion soll vorzugsweise mittels „speckle tracking“ erfolgen. Die ermittelten **Werte können entweder in das Kreisdiagramm eingetragen werden, oder es wird ein Ausdruck der „Speckle tracking“-Analyse beigelegt.**

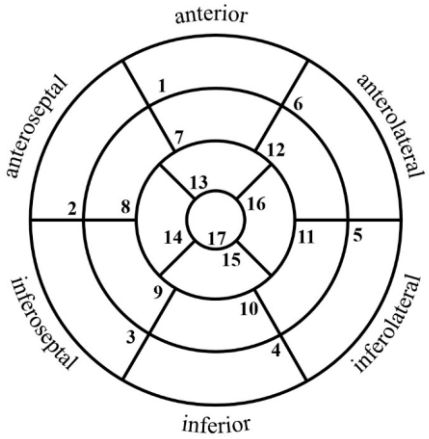
**Ist dies nicht möglich, soll die Beurteilung mittels „wall motion score index“ (WMSI) erfolgen.** In diesem Fall genügt es, nur die pathologischen Segmente anhand untentstehender Tabelle zu beurteilen und in das Kreisdiagramm einzutragen.

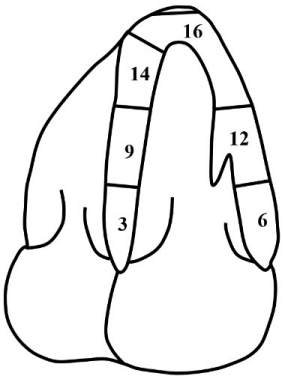
**Beurteilung anhand:**

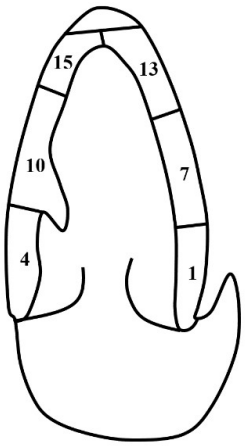
☐ WMSI

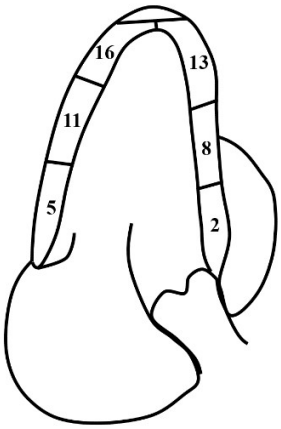
☐ Speckle Tracking

| Wall Motion Score Index (WMSI) | |
|---|---|
| nicht beurteilbar | X |
| hypokinetisch | 2 |
| akinetisch | 3 |
| dyskinetisch | 4 |




*Anmerkungen*

Identification of Coronary Occlusion in NSTEMI (ICON)

# 11 CA-CRF *(CRF F)*

**Coronarangiographie – Case Report Form** (CA-CRF)_V1.2

**F**

## Patientendaten und Zeiten

**Studien-ID:** **01001**

**Geschlecht:** ☐ männlich ☐ weiblich

**Initialen:** _____

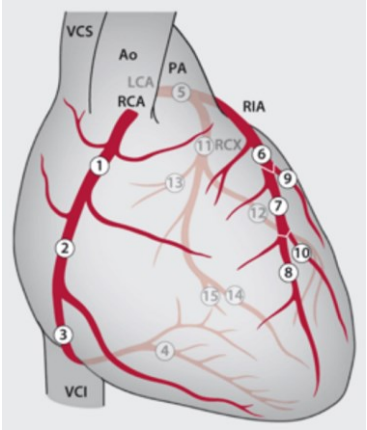
**Alter:** _____ Jahre

**Untersuchungsdatum:** _____

**Untersuchungszeit:** _____ Uhr

## Gefäßbeurteilung

| Nr. | Segment | Stenose (%) | TIMI (0-3) | Culprit |
|---|---|---|---|---|
| **1** | prox. RCA | | | ☐ |
| **2** | mittl. RCA | | | ☐ |
| **3** | dist. RCA | | | ☐ |
| **4** | R. interventr. post. | | | ☐ |
| **5** | LMA | | | ☐ |
| **6** | prox. LAD | | | ☐ |
| **7** | mittl. LAD | | | ☐ |
| **8** | dist. LAD | | | ☐ |
| **9** | 1. ALA | | | ☐ |
| **10** | 2. ALA | | | ☐ |
| **11** | prox. LCX | | | ☐ |
| **12** | dist. LCX | | | ☐ |
| **13** | OM | | | ☐ |
| **14** | 1. PLA | | | ☐ |
| **15** | R. posterolat. sin. | | | ☐ |




*Anmerkungen*

Identification of Coronary Occlusion in NSTEMI (ICON)

# 12 Overview


Identification of Coronary Occlusion in NSTEMI (ICON)
Onset of Pain
Presentation to ED
Informed Consent
Study Enrolment
Echo
Coronary Angiography
t1
t2
t3
t4
(< 24 hours)
(screening procedure)
(delay)
(examination)
A
B C
D
E
F
CRFs
A Informed Consent
B Screening
C EKG
D Enrolment
E Echocardiographie
F Coronarangiographie
Einschlusskriterien
✓ Alter über 18 Jahre
✓ Akute Angina pectoris innerhalb der letzten 24 Stunden (zum Zeiptunkt der Präsentation)
✓ Troponinerhöhung
✓ Informed Consent unterzeichnet
Ausschlusskriterien
✓ ST-Hebungen (nach ESC 2012*) über einen Zeitraum von mind. 30 min
✓ Neu aufgetretener Linksschenkelblock
✓ Z.n. CPR im Rahmen des aktuellen Akutereignisses
✓ Verabreichung eines Fibrinolytikums innerhalb der letzten 7 Tage
✓ Bekannte dilatative Cardiomyopathie
✓ Bekannte hyptertrophe Cardiomyopathie
✓ Pericarditis
✓ Myocarditis
* ST-Hebung nach ESC 2012: > 0,1 mV in I, II, III, aVF, aVL, aVR, V1, V4-V6; > 0,15 mV in V2 u. V3 bei Frauen;
> 0,25 mV in V2 u. V3 bei Männern unter 40 Jahren; > 0,2 mV in V2 u. V3 bei Männern über 40 Jahren