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Microcirculation Measurements in Critical and Non-critical Myocardial Ischemia

DOCTORAL DISSERTATION

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LIST OF PUBLICATIONS

This doctoral thesis is based on the following publications, which are referred to in the Roman numerals in this text.

I. **Šerpytis R,** Lizaitis M, Majauskienė E, Navickas P, Glaveckaitė S, Petrulionienė Ž, Valevičienė N, Laucevičius A, Chen QM, Alpert JS, Šerpytis P. Type 2 myocardial infarction and long-term mortality risk factors: a retrospective cohort study. Adv Ther. 2023 Apr 5. doi: 10.1007/s12325-023-02485-2. PMID: 37017913.

II. Šulskutė K, Pilkienė A, Meškėnė E, Kersnauskaitė D, **Šerpytis R**, Petrulionienė Ž, Šerpytis P. High-Sensitivity Cardiac Troponin Impact on the Differential Diagnosis of Non-ST Segment Elevation Coronary Syndromes—Is It Helping? ***Medicina*** **58**, 1084 (2022).

III. **Serpytis R**, Majauskiene E, Navickas P, Lizaitis M, Glaveckaite S, Rucinskas K, Petrulioniene Z, Valeviciene N, Samalavicius RS, Berukstis A, Baranauskas A, Gargalskaite U, Laucevicius A, Chen QM, Alpert JS, Serpytis P. Randomized Pilot Trial on Optimal Treatment Strategy, Myocardial Changes, and Prognosis of Patients with Myocardial Infarction with Nonobstructive Coronary Arteries (MINOCA). ***Am J Medicine*** **135**, 103–109 (2021).

IV. Wijntjens, G., Fengler, **Šerpytis, R.,** K., Fuernau, G., Jung, C., Uil, C., Akin, S., Hoef, T., Diletti, R., Henriques, J., Šerpytis, P., Thiele, H., Piek, J. (2019). Prognostic implications of microcirculatory perfusion versus macrocirculatory perfusion in cardiogenic shock: a CULPRIT-SHOCK substudy. **European Heart Journal. Acute Cardiovascular Care** https://dx.doi.org/10.1177/2048872619870035

V. Alpert, J. S., **Serpytis, R**., Serpytis, P., & Chen, Q. M. (2019). Myocardial Infarction with Nonobstructive Coronary Arteries (MINOCA). ***The American Journal of Medicine***, *132*(3), 267–268. http://doi.org/10.1016/j.amjmed.2018.12.005

VI. *Alonderytė A, Šerpytis P,* ***Šerpytis R****, Alpert JS, Chen QM.* Miokardo infarkto, nesant vainikinių arterijų obstrukcijos (MINOVA), diagnostikos ir gydymo ypatumai; **SVEIKATOS MOKSLAI**; 2020, 30 tomas, Nr.2, p. 100-105.

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LIST OF ABBREVIATIONS

ACEi - angiotensin converting enzyme inhibitors.
ACO - adverse clinical outcome
ACS - acute coronary syndrome
AHA - American Heart Association
ARB - angiotensin receptor blocker
BAB - Beta Adrenergic Blocker
BNP - brain natriuretic peptide
CAD - coronary artery disease
CAG - coronary angiography
CCB - calcium channel blocker
CFR - coronary flow reserve
CMR - cardiac magnetic resonance
CO - cardiac output
CS - cardiogenic shock
CRP - C reactive peptide
DAPT - dual antiplatelet therapy
ECG - Electrocardiogram
EF - ejection fraction
ESC - European Society of Cardiology
FFR - fractional flow reserve
hs-cTnI - high sensitivity cardiac troponin I
hsTroponin - high sensitivity troponin
IMR - index of microvascular resistance
INOCA - ischemia with nonobstructive coronary arteries
IVUS - Intravascular ultrasound
LGE - late gadolinium enhancement
LV - left ventricle
MAP - mean arterial pressure
MI - myocardial infarction
MI-CAD - myocardial infarction with coronary artery disease
MINOCA - myocardial infarction with non-obstructive coronary arteries
MFI - microvascular flow index
OCT - optical coherence tomography
PCD - perfused capillary density
PCI - percutaneous intervention
PPC - proportion perfused capillaries
SBP - systolic arterial pressure

SCS - spinal cord stimulation
SDF - side stream dark field
SCAD - Spontaneous coronary artery dissection
SVR - systemic vascular resistance
T2MI - type 2 myocardial infarction
TCD - Total capillary density
UA - Unstable angina
VUH SK - Vilnius University Hospital Santaros Klinikos

1. INTRODUCTION

1.1 Research Problem and Relevance of the Study

Cardiovascular science has made tremendous progress within the last 50 years. There has been observed a sharp decline of mortality from acute myocardial infarction. Since the introduction of coronary care units, the advent of different antithrombotic drugs, thrombolysis, percutaneous interventions, and long term secondary prevention medications the myocardial infarction survival improved by 40-50% [1]. However, in the past 15 years the decline of mortality has apparently reached a "plateau" [2]. According to the 4th universal definition of myocardial infarction (MI) it is diagnosed when there are symptoms of myocardial ischemia that are followed by detection of a rise or fall of cardiac troponin, accompanied by new ischemic electrocardiographic changes and/or identification of a coronary thrombus by angiography. When no obstructive coronary angiography changes are found – then the diagnosis of myocardial infarction with non-obstructive coronary changes is made [3]. As mentioned before, the survival of patients with acute coronary events has increased significantly within the last decades. Unfortunately, if the patient develops cardiogenic shock, then the in-hospital mortality risk increases significantly, accounting for 40-50% within recent decades without improvement [4].

Cardiogenic shock remains one of the most common complications of MI. An important factor in the pathophysiology of normal tissue functioning is microcirculation. Microcirculation is crucial to life because it is a medium for gases, nutrients, hormones, and drugs to enter the tissue cells and to excrete gases and metabolites from cells away. The microcirculation is unique in its ability to adapt oxygen and nutrient supply to the metabolic demands of all cells throughout the body through the adjustment of vascular tone and release of different vasoactive elements [5]. In critical settings (e.g., cardiogenic, or septic shock), the circulation may be insufficient, so the blood is redistributed from less vital to crucially important organs (heart, brain and kidney). Unfortunately, even when adequate mean arterial pressure and normal cardiac output is maintained, a general condition may worsen and lead to multiple organ failure [6]. Often the insufficiency of microcirculation is one of the causes of the organ dysfunction. Perfusion parameters of the microvascular capillaries have independent prognostic value for early mortality [7, 8]. Microcirculation has an important role independently of global hemodynamics either in septic of cardiogenic shock [9, 10]. Evaluation and monitoring of microcirculation by trying to modify the course of cardiogenic

shock might have important benefits for the patients. Microvascular parameters could help identify extremely high-risk patients that need intensive care. These measures could help improve the care for cardiogenic shock and improve the hospital survival.

Moreover, in clinical practice it is often noticed that there are some patients with acute myocardial infarction that do not have any significant changes in coronary arteries. This diagnosis is defined as myocardial infarction with non-obstructive coronary arteries (MINOCA), according to the 4th universal definition of myocardial infarction. These patients account for 5-10% of all myocardial infarction cases when coronary angiography is performed. It should be noted that it can meet the criteria for type 1 myocardial infarction due to coronary artery damage and/or type 2 myocardial infarction in the presence of endothelial dysfunction, myocardial oxygen supply and demand mismatch, or myocardial injury. MINOCA first is considered a working diagnosis, so a specific examination and assessment of the patient is required to determine the cause of myocardial ischemia and to select an appropriate and effective treatment that improves the prognosis [3]. Troponins play an important role in the diagnosis of MINOCA. Cardiac troponins are "organ-specific" but not "disease-specific" marker. Their increase does not necessarily reflect MI but can also represent myocardial damage or necrosis (myocarditis, Takotsubo cardiomyopathy or other disease). Presence of coronary atherosclerotic lesions does not exclude noncardiac causes of troponin elevation. An alternative concomitant disease (e.g., pulmonary embolism, renal injury, etc.) also may be found. In patients with symptoms of ischemia, ST segment elevation, non-obstructive atherosclerotic disease does not rule out the etiology of atherothrombosis. MINOCA has become a novel research topic in recent years. That is because it is not a benign disease: 4.5 years mortality for patients with MINOCA can reach up to 14% [11].

One of the pathophysiological mechanisms that cause MINOCA is the impairment of coronary microcirculation. Coronary micro-vessels are known to contribute to >50% of total coronary vascular resistance and regulate coronary flow [12]. Frequently, when patients are not diagnosed with obstructive coronary artery disease, they are also not prescribed secondary prevention medication that significantly raises the risk of adverse events and subsequent visits to hospital.

This study is the first in Lithuania to investigate the value of testing microcirculation in the setting of critical myocardial ischemia during cardiogenic shock, and myocardial infarction. There is still a significant gap in the knowledge how microcirculation status could guide decision-making.

1.2 The hypothesis of the study

Impaired microcirculation perfusion parameters are significant predictors of cardiovascular mortality risk and has (have) higher risk accuracy that (than) macrohemodynamic parameters in patients with cardiogenic shock.

1.3 The objectives of the study

Establish the method of monitoring microcirculation in the cardiogenic shock patient.

Asses the effect of microcirculation on the prognosis of cardiogenic shock.

Evaluate the prevalence of MINOCA and type 2 MI in clinical practice.

1.4 The scientific novelty of the study

This research marks an attempt to find a link between microcirculation in the clinical settings of acute coronary syndromes and cardiovascular outcomes. Mortality from heart disease has decreased over the last 50 years, but in recent years cardiovascular deaths do not decrease further. With the introduction of high sensitivity troponin, it has been a blessing and a curse for cardiologists. Currently even slightest cardiac injury can be detected that shows the elevated risk from any cause. Prospective clinical trials are needed to define the diagnostic work-up and efficacy and safety of secondary prevention therapies in patients with type 2 myocardial infarction or myocardial injury, which have the potential to modify future outcomes [13]. Microcirculation is the final destination of cardiovascular system that is one of the most important area of oxygen transfer from the red blood cells in the capillaries to the tissues where oxygen is delivered in order to meet the metabolic demands of the tissue cells in support of their function. Microcirculation measurements have been increasingly studied as a predictor of cardiovascular outcomes due to its ability to provide novel insights into cardiovascular health on a microscopic level. Microcirculation monitoring is well established in the treatment of septic shock but the monitoring of microcirculation in cardiogenic shock and the correlation with hospital mortality is not yet well known. Studies have suggested that microcirculation measurements may be useful in assessing the early reperfusion of MI, and the microcirculation assessment in patients with MINOCA may be an especially promising field for future research. It is estimated that 50% of patients who suffer an acute MI also present with microvascular dysfunction following a successful percutaneous coronary intervention (PCI), which results in poorer

clinical outcomes [14]. MINOCA and type 2 myocardial infarction are conditions where it probably plays a significant role in the pathophysiology. These conditions have been and remain a puzzling heterogeneous entity. Investigation of the possible causes remains a cornerstone component of the diagnosis and treatment work-up. Microcirculation has evolved in recent years as a very potent pathophysiological cause. This research work fills the gap of clinical trials in this field.

1.5 Defense statements of the doctoral thesis

1. Status of systemic microcirculation is associated with clinical outcomes in MI and shock (**paper I**).
2. Microcirculation better predicts outcomes than macrohemodynamic parameters in cardiogenic shock. (**Paper I**).
3. Type 2 MI diagnosis is significantly underutilized and has significant high mortality burden. (**Paper II**)
4. Specific treatment of type 2 MI improves the decreases the mortality and reduces the occurrence of complications. **(Paper II)**
5. There is a significant amount of unstable angina cases that should be reclassified to myocardial infarction. (**Paper II and III**)

2. LITERATURE REVIEW

2.1 Microcirculation and MINOCA

The Universal Definition of Myocardial Infarction categorized myocardial infarction into 5 subtypes. Myocardial infarction caused by atherothrombotic coronary artery disease and usually precipitated by atherosclerotic plaque disruption (rupture or erosion) is designated as a type 1 myocardial infarction. Type 2 myocardial infarction is defined as a myocardial infarction caused by imbalance between myocardial oxygen supply and demand unrelated to acute coronary atherothrombosis [3]. The Fourth Universal definition of myocardial infarction defined another type of myocardial infarction—myocardial infarction with nonobstructive coronary arteries (MINOCA). A diagnosis of MINOCA can be made in patients presenting with features consistent with acute myocardial infarction and a coronary angiogram demonstrating nonobstructive coronary artery disease. Nonobstructive coronary artery disease on angiography is defined as the absence of coronary artery stenosis ≥50% in any potential infarct-related artery. This includes patients with normal coronary arteries (no evident stenosis) or with minimal stenosis (stenosis 30% or less), or mild-moderate coronary atherosclerosis (stenosis >30% but <50%) [15]. According to pathophysiological mechanisms, MINOCA patients are located between type 1 and type 2 myocardial infarction, although this entity may encompass underlying causes that fall under both type 1 and type 2 definitions. Type 1 myocardial infarction is caused by atherosclerotic plaque disruption, and type 2 myocardial infarction is due to various causes (epicardial coronary vasospasm, coronary microvascular dysfunction, coronary thromboembolism, spontaneous coronary artery dissection, supply−demand mismatch). MINOCA patients can have coronary artery disease, but it is usually not severe enough to cause a significant blockage of the coronary artery. Therefore, the underlying cause may be temporary thrombus formation that resolves until the coronary angiography is performed. Thus, in some cases it may be difficult to distinguish whether it is type 1 or type 2 MI. Multimodal techniques are often required to diagnose, confirm, and evaluate MINOCA. Beyond coronary angiography, the use of echocardiography, cardiac magnetic resonance imaging, computed tomography, and intravascular ultrasound frequently assist the clinician in detecting the etiology of MINOCA. The prevalence of up to 10% of myocardial infarction patients having MINOCA indicates that this condition is not uncommon. The analysis of CRUSADE study showed that among non-ST elevation MI patients 15.1% of women and

6.8% of men had nonobstructive coronary artery disease [15, 16]. Because there are no completed randomized clinical trials involving MINOCA patients, and because treatment guidelines for these patients are lacking, a better understanding of the mechanisms and management of these patients is necessary. The current protocol describes a proof-of-concept study with statistical tests that are exploratory.

MINOCA is like a dustbin of several different diseases. Substantial amount of these patients are the ones with disturbances in microcirculation.

A common cause of MINOCA is coronary artery spasm. As many as 46% of patients who underwent invasive provocation tests were found to have vasospasm [17]. In this condition a severe coronary vasoconstriction (>90%) may arise resulting in impaired myocardial blood flow. [18]. Spasm can involve a localized segment of an artery, but sometimes it involves two or more segments of the same (multifocal) or different (multivascular) artery [19]. These processes can be triggered by a response to drugs or toxins (e.g. cocaine, fluorouracil) that manifests as vascular smooth muscle hyperactivity or can occur spontaneously as a result of changes in coronary artery tone [18].

2.2 Distinction between type 1, type 2 MI and MINOCA

According to 4th definition of MI there are 5 types of myocardial infarction.

Type 1 MI: acute MI caused by atherothrombotic coronary artery disease and usually precipitated by atherosclerotic plaque rupture and/or erosion.

Type 2 MI: Acute MI due to secondary myocardial ischemia in the context of oxygen supply and demand mismatch: spasm, embolus, anemia, hypertension or hypotension, tachyarrhythmia and bradyarrhythmia.

MINOCA is diagnosed when:

Acute MI diagnosis based on the fourth universal definition of myocardial infarction:

a) Elevation of at least one value above the 99th percentile upper reference limit. N

b) clinical signs of MI together with an increase in troponin:

○ symptoms of myocardial ischemia;

○ newly identified ECG changes reflecting ischemia;

○ formation of pathological Q waves;

○ newly confirmed loss of viable myocardium by imaging studies or newly identified regional myocardial wall motion abnormality corresponding to an ischemic cause;

○ a thrombus in the coronary artery detected during coronary angiography or autopsy.

There are no obstructions in the coronary arteries during angiography: no stenosis ≥50%.

There is no other alternative diagnosis:

Alternative diagnoses include, but are not limited to, non-ischemic causes such as sepsis, pulmonary embolism, or myocarditis [15].

2.3 Type 2 MI.

Type 2 MI etiology is often secondary to ischemia due to either tachyarrhythmias that are followed by significant hypoxia and hypotension. Less common coronary causes may be:

Coronary spasm;

Microvascular dysfunction;

Embolus;

Spontaneous coronary artery dissection.

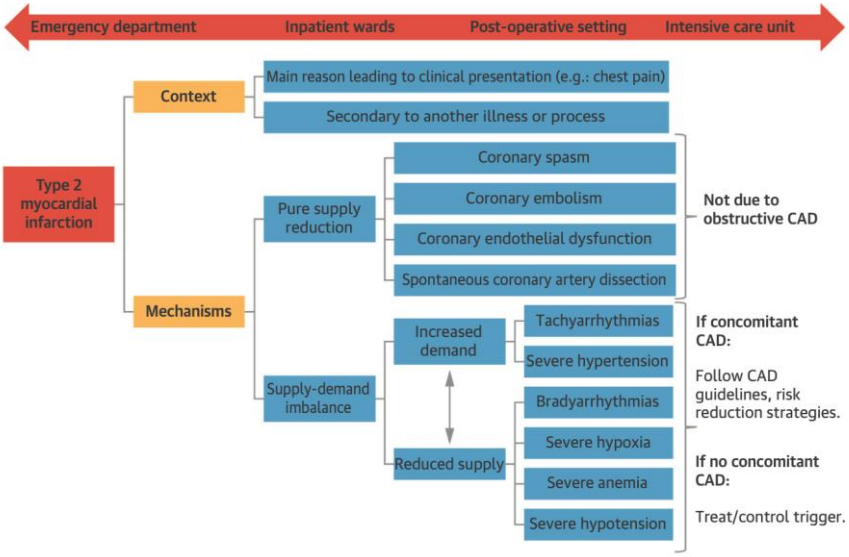


Figure 1. Type 2 myocardial infarction clinical framework

(Adapted from Sandoval Y, Jaffe AS. Type 2 Myocardial Infarction: JACC Review Topic of the Week. J Am Coll Cardiol. 2019 Apr 16;73(14):1846-1860. doi: 10.1016/j.jacc.2019.02.018. PMID: 30975302) [20].

Type 2 myocardial infarction can occur both in individuals with intact coronary arteries and in obstructive/non-obstructive coronary artery disease.

It is often difficult to distinguish the mechanism that caused the myocardial infarction. During sepsis, despite sufficient blood flow in the coronary vessels of the heart, the need for oxygen can increase significantly, which leads to the development of myocardial ischemia, especially if there are changes in the coronary arteries. An increase in troponin can also be caused by the toxic effect of tumor necrosis factor, catecholamines. On the other hand, a diagnosis of type 2 myocardial infarction cannot be made based on troponin elevation alone - myocardial ischemia must be confirmed to establish this diagnosis [20].

Possible causes of increased troponin:

Coronary causes:

- plaque rupture or erosion;
- coronary artery spasm;
- spontaneous coronary artery dissection;
- aortic dissection with coronary artery damage;
- microvascular dysfunction of coronary vessels;
- spontaneous coronary artery thrombosis - thrombophilia disorders;
- embolism of the juvenile arteries;
- drugs affecting the sympathomimetic system: cocaine, methamphetamine.

Non-coronary causes:

related to myocardial injury:

- myocarditis;
- Takotsubo syndrome;
- cardiomyopathies;
- cardiac traumas;
- particularly heavy physical exertion;
- tachyarrhythmias;
- cardiotoxins - drugs used in chemotherapy.

Not related to myocardial injury:

- stroke;
- pulmonary embolism;
- sepsis;
- severe acute respiratory syndrome;
- end-stage renal failure [15, 21].

2.3.1 Type 2 MI subtypes

Takotsubo syndrome, also known as stress cardiomyopathy, is a heart condition caused by a sudden surge of stress hormones, which leads to a temporary weakening of the left ventricle of the heart. It is similar to a heart attack and is classified as a form of Non-ST-elevation Myocardial Infarction (NSTEMI).

2.4 Main Causes of MINOCA

Possible pathophysiological mechanisms include coronary vasospasm, microvascular coronary dysfunction, atherosclerotic plaque rupture and erosion, spontaneous coronary thrombosis or embolism, and coronary dissection. Currently, one of the main diagnostic tests is cardiac magnetic resonance imaging. With the help of this test, the main cause of MINOCA is determined in 74% of patients. Also, other additional tests such as provocation tests, intravascular ultrasound (IVUS), diagnostic tests for thrombophilia may be useful in identifying the mechanisms causing MINOCA. It should be noted that compared to common type MI, these patients tend to be younger. MINOCA is more common in women, but hyperlipidemia is less often detected in these patients, although other cardiovascular disease risk factors remain similar.

Also, one of the frequently encountered causes of MINOCA is the rupture or erosion of the atheromatous plaque of the coronary arteries without vessel obstruction [19]. Plaque rupture can lead to thrombus formation leading to acute coronary syndrome (ACS) due to distal embolization or, in some cases, transient thrombosis with spontaneous thrombolysis. Plaque erosion is characterized by a different pathophysiological mechanism - it occurs due to apoptosis of endothelial cells, and as a result the endothelium loses its integrity. In pathological studies, plaque erosion is more often associated with later-stage thrombus (compared to rupture) and with more frequent distal embolization [18].

MINOCA can also be caused by microvascular coronary artery dysfunction (sometimes called cardiac syndrome X), which is characterized by transient ST-segment elevation myocardial ischemia and angina in the absence of coronary artery obstruction and epicardial coronary artery spasm [19, 22]. Microvascular dysfunction can be a cause of ischemia or a consequence of myocardial injury from ischemic or non-ischemic causes, so elucidating the role of microvascular dysfunction in MINOCA patients

requires differentiation of these mechanisms through detailed patient workup [18].

If a partial dissolution of a thrombus in a coronary artery occurs, which manifests as non-obstructive coronary artery disease angiographically and microcirculation is involved - a coronary embolism (thrombosis) occurs, which will also be considered one of the causes of MINOCA [18]. Coronary thrombosis can occur due to congenital or acquired disorders of the coagulation system, and embolism can occur due to coronary or systemic arterial thrombus. Hereditary thrombophilia results from factor V Leiden, protein S and C deficiency. As many as 14% of MINOCA patients can have these congenital disorders. An acquired coagulation disorder (antiphospholipid syndrome, myeloproliferative diseases) can also cause MINOCA. In patients with atrial fibrillation, valvular heart disease, valvular vegetations, cardiac tumors (e.g.: myxoma), the possibility of embolism as a cause of MINOCA should be considered [22]. Myocardial thrombus is demonstrated to be the cause of most MIs, as shown in the first paper in this field (in 1980) when thrombus was observed in coronary angiographies performed within 2 hours following myocardial infarctions (87.3% of patients). In the discussion of this paper that coronary spasm was suggested to play a role in the formation of thrombus possibly by disrupting the intimal surface or rupturing an atherosclerotic plaque is selected patients [23]. There is possibility that spontaneous thrombolysis can occur, and no thrombus or significant atherosclerotic plaque can be observed. Even without significant changes in coronary arteries following acute myocardial infarction, late gadolinium enhancement in CMR can BE assessed if myocardial scar is available. T2-weighted technique can be used to delineate the ischemic risk region, which typically extends beyond the scar and was to differentiate acute from chronic infarctions. Moreover, invasive coronary imaging techniques like optical coherence tomography or intravascular ultrasound might help identify high risk coronary artery plaques and possible erosions [24].

Spontaneous coronary artery dissection (SCAD) is a relatively rare non-atherosclerotic cause of acute myocardial infarction, occurring more often in young women (<50 years of age). Although SCAD often causes partial diminishing of perfusion, sometimes the arteries may appear normal due to gradual narrowing, so this could be seen as another possible cause of MINOCA [18]. In a study of 38 patients with MINOCA, atherosclerotic plaque rupture occurred in 40% of patients, coronary thrombus was detected in 7 patients [25]. In patients with spontaneous coronary artery dissection (SCAD), OCT was used to determine the presence and absence of fenestrations between true and false lumens [26].

2.5 Diagnostics of MINOCA

Evidence-based guidelines are used for the diagnosis and treatment of ACS, with special emphasis on ST- and non-ST-segment elevation myocardial infarction. It should be noted that MINOCA diagnostics are not sufficiently studied, due to the lack of evidence-based research data and clinical trials. Currently, MINOCA is used as a "working" diagnosis, so the algorithms suggest ruling out other possible causes to diagnose MINOCA.

The initial evaluation of patients with suspected AMI and nonobstructive coronary disease requires a careful clinical examination. It is also important to evaluate the causes of myocardial damage that develops without signs of ischemia. However, if the clinical diagnosis of acute myocardial infarction remains, the coronary angiogram should be re-reviewed and other tests should be considered to help determine the cause of the disease [18]. Patients that are diagnosed with type 2 myocardial infarction less frequently undergo coronary angiography or revascularization and are less often treated with dual antiplatelet therapy, statins, and ACEi/ARBs or beta blocker than patients with type 1 myocardial infarction. However, mortality in these patients can reach up to 50% in two years [27].

Cardiac magnetic resonance imaging is considered the main test for MINOCA, as in 87% of cases it can confirm the cause of ACS, exclude myocarditis, Takotsubo syndrome and other cardiomyopathies. Myocarditis is detected in up to third of patients with the initial diagnosis of MINOCA.

Practitioner must perform a detailed examination of the patient according to the possible pathophysiological mechanisms. A thrombus resulting from plaque rupture or erosion may not be visible angiographically in the major epicardial vessels, but myocardial necrosis results from distal thrombi embolization. Optical coherence tomography (OCT) may also show a calcified nodule with ill-defined contours encroaching on the arterial lumen [28]. The intravascular ultrasound reflects plaque rupture better than erosion. According to Reynolds et al., plaque rupture was found in 38% of women with MINOCA [29], while Ouldzein et al. showed that in a cohort of 68 patients with MINOCA 38% had plaque rupture [30]. The diagnostic findings could be more accurate if a higher resolution imaging study were used, e.g.: OCT. OCT can detect not only tears, but also erosions, which can also cause MINOCA [31]. Plaque rupture was found at a site where the vessel appeared normal on angiography in almost half of the patients, and plaque rupture was found in all patients with even mild atherosclerosis seen on angiography [32]. Based on patient history, it should be noted that plaque erosion is more

common in women, smokers, patients with single coronary artery disease, and younger patients with multiple coronary artery disease risk factors [33]

Spontaneous coronary artery dissection could be suspected in younger women (<50 years) with acute coronary syndrome or sudden cardiac death. The angiographic appearance of coronary arteries can vary from nearly normal coronary arteries to diffuse stenoses, including <50% stenoses. Spontaneous aortic dissection is also characterized by tortuosity of one coronary vessel (including the "corkscrew" image) and symmetrical tortuosity of several vessels. On the other hand, to clarify the diagnosis, intravascular imaging studies are required: intravascular ultrasound, optical coherence tomography, highlighting the atherosclerotic plaque, dissection or intramural hematoma. These studies are very important and informative due to their sufficiently high resolution [18].

Coronary microvascular dysfunction can be detected in 30% to 50% of patients with chest pain, even though on angiography no obstructive changes could be seen [34]. There is limited overlap between MINOCA and INOCA. It is important to emphasize that in MINOCA patients, a myocardial infarction is diagnosed and a scar can be documented, but only 8% of women with INOCA were found to have a scar in the myocardium with CMR (WISE study) [35]. Microvascular dysfunction during MINOCA can be a cause of ischemic changes but there are also possibilities of sequela of other ischemic or nonischemic reasons [18].

Pulmonary thromboembolism should also be considered as a possible cause of myocardial injury, and D-dimer, B-natriuretic peptide, and/or computed tomography angiography of the chest should be performed. Other causes that could have caused an increase in troponin due to a decrease in oxygen delivery or an increase in its utilization should also be considered, for example: hypertensive crisis, tachyarrhythmias, sepsis, severe anemia or cardiac trauma.

Initial assessment of left ventricular (LV) wall motion by LV angiography, considering renal function, or echocardiography is particularly important to confirm the diagnosis in the acute period of the disease. Regional LV wall motion abnormalities may confirm an epicardial cause of MINOCA, or may just help identify other causes that rule this diagnosis out.

An intracoronary acetylcholine or ergonovine provocation test may be performed when coronary or microvascular spasm is suspected.

If it is suspected that the cause of MINOCA may be thrombosis or embolization of the coronary vessels, tests for blood coagulation indicators should be performed. Diagnostic tests for hereditary coagulopathies should be performed in consultation with a hematologist, and the patient should be tested

for Leiden factor V, prothrombin 20210A, factor VIII, protein C and S, antithrombin, lupus anticoagulant, and antiphospholipid antibodies.

2.5.1 Risk of Myocardium Injury measured by Troponin.

Troponin change is paramount for the diagnosis of MI. It has been noted that an increase in troponin can indicate both acute and chronic injury to the cardiac muscle. In some cases, chronic myocardial damage has persistently elevated troponin. Such a condition can be detected when a person has chronic kidney failure, cardiomyopathies, hypertension, or advanced chronic heart failure [3]. Individuals with elevated high-sensitivity troponins are at increased risk of adverse events regardless of whether they have coronary heart disease or not. Elevated troponin concentrations are likely due to more comorbidities. The test is very sensitive, so even in the absence of established cardiovascular disease, the concentration of troponin may be elevated. In high-risk patients without a diagnosis of coronary heart disease, elevated troponin above the normal value has been shown to be an independent prognostic marker [36]. In a study conducted in Scotland, it was found that among healthy people, those with the highest troponin compared to those with low troponin had the probability of dying from coronary heart disease or having a first myocardial infarction by 2.3 times over what period? (CI, 95% 1.4-3, 7) [37]. Myocardial damage is often detected when the body experiences extreme stress. This is especially true for patients who have a high cardiovascular risk and are undergoing non-cardiac surgery. An increase in troponin has been associated with a worse prognosis in these patients. It was found that perioperative myocardial damage can be detected in 16% of all patients. If troponin level is elevated after surgery, the 30-day mortality is 8.9%, and for those without myocardial damage - 1.5% [38].

A total of 21,842 patients were included in another international study of patients undergoing non-cardiac surgery. A direct correlation was found between peak high-sensitivity troponin T concentration and 30-day postoperative mortality. If the maximum concentration of troponin T was 20-65ng/l, the 30-day mortality was 3%, if 65 – 1000 ng/l, then 9.1% and if the maximum troponin T was more than 1000ng/L – then the 30-day mortality was even 29.6 % [39].

2.5.2 Cardiac magnetic resonance imaging

There is also substantial amount of noninvasive testing. Since in recent years imaging has progressed in huge lapses, microcirculation can be measured by the means of heart MRI and single photon emission tomography.

Cardiac magnetic resonance imaging (CMR) has high sensitivity and specificity in differentiating between "work diagnosis" MINOCA (or true diagnosis of MI) and MINOCA-like conditions (Takotsubo syndrome, myocarditis, cardiac amyloidosis, sarcoidosis, and other myocardial diseases). Anatomical and functional structural changes of the heart are evaluated with the help of CMR. This diagnostic method is useful in that it does not involve any intervention and does not use ionizing radiation [40].

A recent large observational study showed that in MINOCA patients when CMR is performed at a median of 37 days after first symptoms it identified the cause of dynamic troponin elevation in 74% of patients. [41]. The most common diagnoses were MI (25%), myocarditis (25%), and cardiomyopathies, including Takotsubo syndrome (25%), and the remaining 25% had no significant changes and „normal“ result. When CMR is performed within two weeks of the onset of symptoms, a specific diagnosis is established in 84% of cases due to transient and reversible myocardial changes (myocardial hyperemia/inflammation/edema) that usually disappear after several weeks and are not detected on MRI after several weeks or months [42]. By combining MRI with optical coherence tomography and performing the examination early (median 6 days), even 85% patients (116 women suspected of MINOCA) were given a specific diagnosis [43].

Both the European Society of Cardiology (ESC) and the American Heart Association (AHA) recognize the important role of CMR in the examination of MINOCA patients. In 2020 ESC guidelines for non-ST-segment elevation acute coronary syndromes state that CMR is recommended (class IB) in all MINOCA cases when the cause of myocardial injury is unclear [44]. AHA indicates that CMR is the only non-invasive examination method recommended after invasive coronary angiography [18]. The most recent guidelines for the diagnosis and treatment of chest pain from the American College of Cardiology, the AHA and other societies state that in high-risk patients with acute chest pain, CMR or echocardiography has a class IIa indication for an alternative diagnosis when obstructive coronary artery disease is ruled out by coronary computed tomography angiography or by invasive coronary angiography. Stress CMR can be performed to confirm myocardial ischemia in symptomatic stable patients with microvascular angina or no obstructive coronary disease (IIa) [45].

In MINOCA patients, the characteristic typical features of conventional MI are determined with the help of CMR. Contrast-enhanced CMR can be used to visualize the transmural extent of myocardial infarction with high spatial resolution. CMR gives an opportunity to evaluate very accurately the contractile function of left and right ventricles, biventricular volumes and

localize the area of injury with late gadolinium enhancement (LGE) [46]. Myocardial edema is evaluated on short-inversion-time recovery sequence images which is called T2w-STIR and gives insight into mechanisms. An area of LGE in the subendocardium (or a transmural extension) indicates an ischemic cause of injury, but it does not specify the particular mechanism of ischemia, while a non-ischemic appearance of LGE (mesocardial or subepicardial localization) speaks in favor of other myocardial disorders such as myocarditis and other cardiomyopathies [47]. "True" MINOCA should be differentiated from other diseases with clinical pictures resembling MINOCA. In these cases, CMR is very important in differential diagnosis.

Newer MRI techniques, such as parametric T1 and T2 imaging, allow more detailed characterization of myocardial tissue and improve diagnostic accuracy. Using T1 and T2 mapping sequences, it is possible to quantify features of myocardial tissue associated with increased myocardial water content (e.g., inflammation and edema, T2 mapping) and diffuse myocardial fibrosis, which cannot be visualized by MRI (T1 mapping and extracellular volume) [48].

With the help of CMR, after establishing the diagnosis, the most appropriate medical treatment is selected, avoiding the unnecessary administration of antiplatelet agents and the associated increased risk of bleeding [47].

2.5.3 Invasive MINOCA testing

Coronary angiography is a very informative and useful study to determine the anatomy of coronary vessels when a patient has a type 1 myocardial infarction. It helps to rule out myocardial infarction due to significant atherosclerosis, however sometimes borderline changes can lead to different results in the assessment of stenosis between different investigators. There may also be changes invisible to the naked eye, which simply cannot be detected during a conventional angiography. In such cases, invasive coronary imaging modalities can be very helpful. They enable detecting atherosclerotic plaques that narrow the lumen significantly, thrombosis or vasospasm in MINOCA patients.

Intravascular ultrasound is an invasive method of examining coronary vessels, during which a special catheter is used, which has an ultrasound mini transducer at the end. With the help of this technique, it is possible to evaluate blood vessel structures and atherosclerotic plaques morphology. IVUS has a resolution of 100μm and can deeply penetrate vascular structures, including the outer elastic membrane. With the help of IVUS, it is possible to accurately

assess the structures of the blood vessel, to see the transverse "histological" section of the blood vessel in real time [49].

OCT is a laser-based invasive vascular imaging technique that can examine the internal structures of the coronary blood vessel. It uses light rays with a length of 1300 nm, and their reflection in the tissues is recorded. It is possible to accurately assess the blood vessel layers and their thicknesses. This is especially important when angiography cannot determine the clear cause of myocardial infarction. Compared to IVUS, OCT has 10 times better tissue resolution, as a result the possible pathophysiological cause of vascular dysfunction can be identified more precisely. Compared to IVUS, with OCT the depth of tissue visualization is less: 1-2 mm vs 5-6mm. Also, if a fresh red thrombus is present, the quality of the OCT image deteriorates significantly. Red blood cells cause "structural noise" and can distort the image [50].

During coronary angiography, IVUS or OCT can detect atherosclerotic plaque rupture, coronary artery dissection or thrombosis [15]. Atherosclerotic plaque rupture is a common cause of MINOCA and accounts for 5-20% of all type 1 AMI cases. In two studies using IVUS, atherosclerotic plaque rupture was detected in approximately 40% of MINOCA patients [29, 30].

Invasive coronary imaging has many advantages adding to coronary angiography. During optical coherence tomography, it is possible to significantly better: 1. differentiate vascular tissue changes, including the compositional properties of atherosclerotic plaque (consisting of connective tissue, calcified or containing a large amount of fatty tissue) [51]; 2. identify unstable plaques [52]; 3. differentiate between plaque rupture and erosion [28] [53]; 4. differentiate between fresh and old thrombi [31]; Given the wide potential application of intracoronary imaging, it is also useful in patients with MINOCA, as it can identify the pathophysiological process and etiology.

Spasm is also a common cause of MINOCA. Patients with VAS usually experience ST-segment elevation angina attacks at rest, at night, or in the early morning. Since ECG changes are not documented, the diagnosis is based on the provocation test of acetylcholine or ergonovine, where spasm is defined as at least 75% narrowing of the vascular lumen in the presence of symptoms of myocardial infarction [54]. In one of the conducted studies, spasm was diagnosed in as many as 46% of MINOCA patients when provocative samples were applied [55]. Currently, many provocation tests are used for the diagnosis of MINOCA, but the gold standard is a high-dose intracoronary acetylcholine test (20-100 μg intracoronary dose of 5 ml over 20 seconds), followed by coronary response during contrast angiography [56].

2.5.4 Assessing the Microcirculation in the Catheterization Laboratory

Since coronary microcirculation cannot be directly visualized, the assessment of microcirculatory parameters is based largely on microcirculatory flow. Normal coronary arteries can augment blood flow greater than 4-fold. Coronary low reserve which is considered a reliable measure of coronary epicardial flow and microvascular function. It is mainly defined as the ratio of hyperemic CBF to CBF of rest. CFR less than 2 to less than 2.5 in the absence of epicardial coronary diseases is considered abnormal and reflects microvascular dysfunction [57]. In a prospective trial patients with spasm and microvascular coronary artery dysfunction were investigated. They were tested with an acetylcholine challenge followed by measurement of cardiac fractional flow reserve (FFR), coronary flow reserve (CFR), and index of microvascular resistance (IMR). The obtained results show that coronary spasm, decreased microvascular vasodilatation and increased IMR coexisting in various combinations is common. It turns out that an increase in IMR (cut-off value 18.0) correlates with the occurrence of major adverse cardiovascular events. Also, coronary spasm, if diagnosed, is an independent indicator of increased IMR (>18.0). Therefore, the prognosis of patients with inducible spasm and increased IMR is worse, compared to other patients [58].

Moreover, IMR is an important marker of infarcted artery damage and its extent as well. McAllindon at al. showed that when assessed IMR and microvascular obstruction (MVO) by performing CMR on day 2 following STEMI and successful primary PCI. MVO was assessed on first pass rest perfusion (assessing early MVO) and in the late gadolinium enhancement (LGE) images (late MVO) along with infarct size. Late MVO was significantly predicted by IMR ($p<0.01$) and as IMR increased, the MVO index increased as well [59]. Significant number of clinicians are afraid of prescribing and performing provocation tests due to increased risk of adverse events. Montone et al. performed a safety evaluation of a provocation with acetylcholine tests in 80 MINOCA patients. In these patients, the provocative test was performed within 48 hours of admission to the hospital The provocative test was performed to assess coronary vasoreactivity. During a period of 3 minutes, acetylcholine (ACh) was injected into the left coronary artery (20–200 mg) or the right coronary artery (20–50 mg) with a 2–3 min interval between injections. Procedure-related arrhythmias occurred in 5% of patients, and no major adverse events (such as death or recurrent MI) were identified [55].

In the presence of a marked increase or decrease in troponin and monitoring of a possible mismatch between myocardial oxygen supply and its

demand, it should first be ruled out whether it is a type 1 myocardial infarction. If the probability of type 1 MI is high (typical symptoms, ECG dynamic changes, or very high troponin levels), coronary angiography should be performed. A diagnosis of type 1 MI is made if coronary artery damage or thrombus is detected during angiography or other intravascular examination. If the coronary arteries do not have significant atherosclerotic changes or thrombosis is not detected a diagnosis of type 2 MI is made. It should be noted that in the absence of a clear cause in the coronary vessels and the observation of a clear discrepancy in myocardial oxygen supply and demand, a diagnosis of type 2 MI could be formulated. Finally, in the absence of any cause, acute non-ischemic myocardial injury should be considered.

2.6 Possible treatment of type 2 myocardial infarction and MINOCA

Treatment recommendations for type 1 myocardial infarction are very clear due to the large amount of research and data published, but treatment of type 2 MI is not very clear and usually is based on treating the underlying cause.

When confirming diagnosis of type 2 MI, the mismatch between myocardial oxygen supply and demand should be treated first. To reduce myocardial oxygen demand, administration of beta-blockers (BABs) should be considered in the absence of contraindications (e.g., bradycardia, hypotension, acute heart failure) until the cause is determined. At the same time, it is important to determine whether the patient simultaneously has atherosclerotic or structural heart disease - type 2 MI may reflect an already existing atherosclerosis (with a high oxygen demand, oxygen supply to the myocardium is significantly reduced due to atherosclerotic narrowing in the coronaries). In about 50% of type 2 MI patients, there is no significant coronary artery disease, and they could be classified as MINOCAs [60].

Patients diagnosed with a specific etiology for MINOCA, should be treated and monitored according to diagnosis-specific guidelines. In the absence of a clear cause, treatment should be focused on the most common causes - vasospastic angina, rupture of an atheromatous plaque or prevention of a possible thromboembolism [61, 62].

If vasospastic angina is suspected, then gradual treatment algorithm of microvascular angina is recommended. The treatment scheme is showed in picture 2.

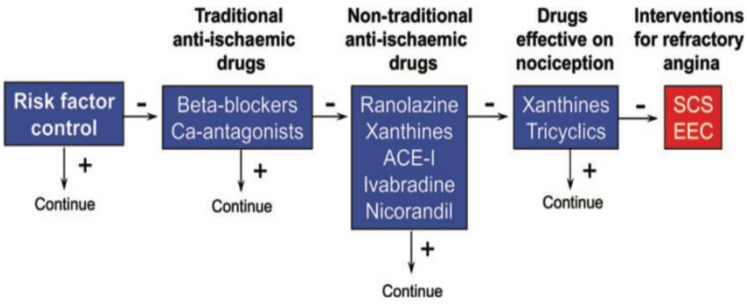


Figure 2. Treatment algorithm of microvascular angina.

SCS, spinal cord stimulation; EEC, enhanced external counterpulsation.
(Crea, F et al. 2014. "Coronary Microvascular Dysfunction: an Update." [63].

Despite a detailed examination, the cause of MINOCA is not determined in 8-25% of cases, which might give clinicians therapeutic dilemma of treatment strategy. Patients diagnosed with MINOCA of unknown mechanism should be followed up and managed in the same way as patients with coronary artery obstruction after AMI. Because a significant number of patients experience anginal pain after a MINOCA episode, symptomatic antianginal therapy with beta-blockers, calcium channel blockers, or long-acting nitrates is often required. If the underlying mechanism is vasospasm, calcium channel blockers are the most effective symptomatic therapy; nitrates are another option. When LV function declines, patients with MINOCA should be initiated on therapy such as Angiotensin Converting Enzyme Inhibitors (ACEi) or ARBs, beta-blockers, and other evidence-based treatments for heart failure [64].

Choo et al. did an observational study of patients with MINOCA. They found that the use of renin-angiotensin system blockers and statins was associated with lower mortality [65]. Similar data were obtained in an analysis of 9138 MINOCA patients in the SWEDEHEART registry, with significantly lower all-cause mortality, fewer hospitalizations for MI, stroke, and heart failure after an average follow-up of 4.1 years, and this beneficial effect was attributed to the use of statins and ACEi [66, 67].

An association of statin use, and outcomes was observed not only in this but also in other trials [68]. The main mechanism that may explain the effectiveness of statins is that they stabilize atherosclerotic plaques, making them less vulnerable. This means that the rupture of even minor atherosclerotic plaques can cause myocardial infarction in MINOCA patients

and special attention should be paid to this [69]. In addition, a protective function of the vascular endothelium may be one of the mechanisms responsible for the better outcomes of MINOCA patients [70]. There are a number of studies demonstrating the benefits of renin-angiotensin system blockers in patients not only with myocardial infarction with heart failure and left ventricular dysfunction, but also in atherosclerotic patients without heart failure and LV dysfunction in whom ACEi treatment reduced mortality [71, 72]. In this group of patients, the positive effect of ACEi is possibly due to the blood pressure-lowering effect, the effect of suppressing the sympathetic system, as well as the positive effect on the endothelium and the anti-fibrotic effect on the myocardium, which should theoretically be beneficial for MINOCA patients [73, 74]. There is experimental evidence that activation of the sympathetic autonomic nervous system may be associated with cardiovascular events, and the use of beta-blockers after MI may be appropriate [73], however, in the SWEDEHEART trial, beta-blockers did not show a clear beneficial effect in reducing major adverse cardiovascular events in MINOCA patients [75]. According to current guidelines, dual antiplatelet therapy is recommended for one year after acute MI [76], because it reduces the risk of cardiovascular events [77]. Dual antiplatelet therapy (aspirin + P2Y12 receptor inhibitors) is not yet widely used in type 2 MI? due to the lack of evidence, although keeping in mind the pathophysiological mechanisms could be considered. Data on the efficacy of percutaneous coronary intervention (PCI) are limited, and the use of PCI in MINOCA patients is not recommended. In a pilot study, Prati et al. evaluated dual antiplatelet therapy (DAPT) and angioplasty with stenting in 31 patients with plaque erosion detected by optical coherence tomography. During the 753 days of patient follow-up, all subjects were asymptomatic. This study was the first to propose an alternative treatment strategy for patients with acute coronary syndromes in the absence of obstructive changes. The EROSION study confirmed this finding. Treatment with DAPT and no PCI resulted in an acceptable one-year revascularization rate of 5.7%. The endpoint in these studies were the rate of major adverse cardiovascular outcomes. In an OCT study, Imola et al. evaluated the role of stent position in the management of equivocal/intermediate lesions in 40 patients. Drug-eluting stent implantation was performed according to protocol in the presence of local thrombosis due to ulceration or erosion. No deaths, acute myocardial infarctions, or stent thrombosis were reported for an average of 4.6±3.2 months. Variant angina is a diffuse coronary disease that usually occurs in different areas of the coronary arteries. PCI with stenting cannot be performed in vasospastic angina without

severe atherosclerotic stenosis. However, for patients with vasospastic angina refractory to medical therapy stenting may be discussed [64].

In general, for patients with this diagnosis medical treatment with aspirin, statins, ACEi/ARBs and calcium channel blockers (CCBs) (when vasospasm is suspected) should be given. These medications have long-term positive effects on total mortality and major adverse cardiovascular events.

2.7 Microcirculation physiology

The microcirculation is the passage of blood in the smallest vessels of the body that are smaller than 100μm: arterioles, capillaries, and venules. The term microcirculation is often used to describe blood flow through capillary beds, which lie between the arterioles and the venules. It has been described that there are two types of vessels in capillary beds, which exist in most areas of the body: true capillaries that are actual exchange vessels, and vascular shunts, also called metarterioles, which are short vessels directly connecting arterioles and venules at the different ends of capillary beds. In each capillary bed, there may be between 10 and 100 capillaries, and the amount may vary per organ or type of body tissue. Picture of sublingual microcirculation capillary bed is showed in Figure 3. Each feeding artery in the organ branches 6-8 times before becoming less than 100 μm in diameter. Such an artery is called an arteriole. Arterioles branch 2-5 times before becoming capillaries. The wall of larger arterioles is three-layered. The inner layer consists of the endothelium on the inner elastic membrane, the middle layer consists of smooth muscles arranged in a circular direction and the elastic membrane, and the outer layer consists of elastic and collagen fibers. Metarterioles (terminal arterioles) no longer have a continuous layer of smooth muscle, and smooth muscle fibers only surround the vessel at intervals. At the point where the metarteriole passes into the capillary, smooth muscle fibers form a precapillary sphincter, which can open or close the entrance to the capillary. The diameter of capillaries is less than 20 μm. Their wall is composed of a single layer of endothelial cells, which are located on the basement membrane. The capillary wall does not have a smooth muscle layer, so it cannot contract. The main function of capillaries is to ensure the exchange of molecules between blood and tissues [78]. Depending on the condition the capillary bed may be full of blood or bypassed almost entirely. The precapillary sphincters constrict or relax based on the specific demand of the body or the tissue to meet the tissue cellular requirements. In the capillaries oxygen and other gases, nutrients and metabolic by-products are exchanged.

In the heart from the main coronary vessels to the heart muscle the coronary circulation can be divided into 3 different sections: the major vessels are from 500 μm to 5 mm in size that course along the epicardium and can be easily seen on coronary angiography [79]. These vessels have been focus of coronary interventions, or "stenosis driven" treatment, for the last 50 years. The smallest of these vessels, the pre-arterioles, have a diameter of less than 500 μm, while the coronary arterioles have a diameter of less than 200 μm. The capillaries, which are the smallest blood vessels in the body, have a diameter of less than 10 μm. These tiny vessels play a crucial role in exchanging oxygen, nutrients, and waste products between the blood and the heart muscle cells. The coronary venules, which have a diameter of 10-50 μm, collect the blood from the capillaries and transport it back to the heart. Finally, the small coronary veins, with a diameter of 50-300 μm, drain the blood from the heart muscle and return it to the systemic circulation [80].

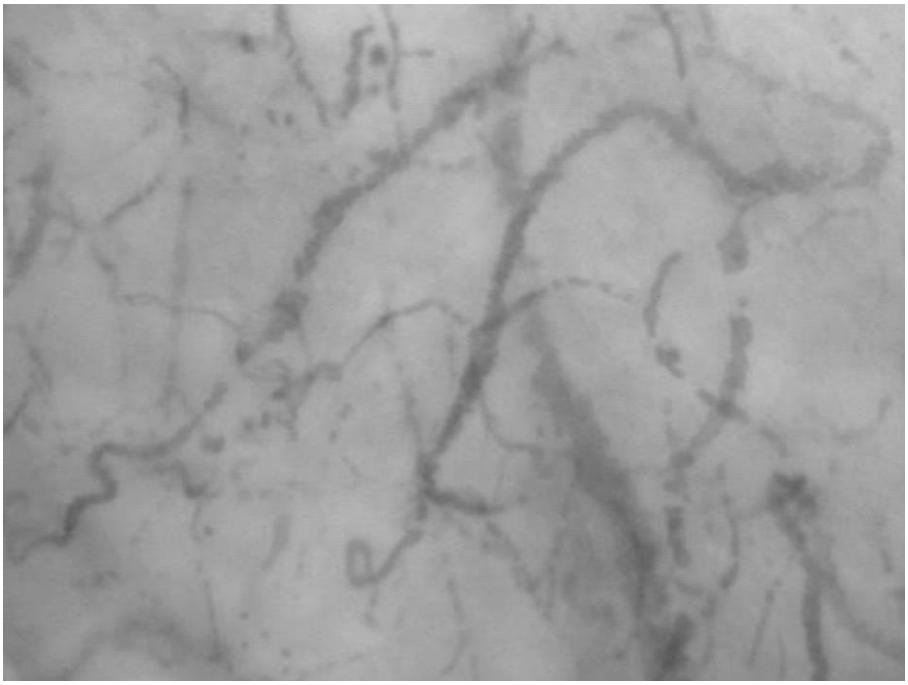


Figure 3. Image of sublingual microcirculation.

2.8 Pathophysiology of Cardiogenic Shock

Cardiogenic shock (CS) is a clinical condition which is characterized by decreased cardiac output, hypoperfusion, multiple organ failure and high mortality. Acute myocardial infarction is the main cause of CS, which accounts for about 80% of all CS cases. After MI less frequent causes are due

to mechanical complications: ventricular acute severe mitral regurgitation (7%), septal defect (4%) or free wall rupture (2%) [81]. Vasopressors and inotropes are prescribed to restore hemodynamics and improve organ perfusion [82].

Nevertheless, CS is very common cause of mortality for patients in acute coronary care units. It remains challenging to treat CS despite the advances in therapeutic options. The mortality still remains high [83].

Clinical diagnosis of CS is usually based on hemodynamic criteria and signs of hypoperfusion. Established criteria for the diagnosis of CS are:

systolic blood pressure less than 90 mmHg for >30 min or vasopressors required to achieve a blood pressure ≥90 mmHg;

pulmonary congestion or elevated left-ventricular filling pressures.

Signs of impaired organ perfusion with at least one of the following criteria: (a) altered mental status; (b) cold, clammy skin; (c) oliguria; (d) increased serum lactate [84].

CS can be diagnosed solely by clinical criteria without advanced hemodynamic monitoring although it has previously been recommended to assess cardiac index and pulmonary capillary wedge pressure [84].

The primary reason for the progression of CS is profound reduction in myocardial contractility which leads to a vicious spiral of reduced cardiac output, hypotension, systemic hypotension, systemic vasoconstriction and cardiac ischemia, further coronary insufficiency, and further reduction in contractility and CO. The classic paradigm implies that compensatory systemic vasoconstriction with high systemic vascular resistance (SVR) should occur in response to the depression of CO. The systemic inflammation that is also observed is responsible for pathologic vasodilation, which additionally can aggravate organ dysfunctions [85, 86].

2.9 Evaluation of Microcirculation in Shock

Since all the tissues are provided with blood, capillaries can be found in all parts of the body. Most indicative area is the skin. There is a method of visual evaluation of skin tone and blushing. It is possible to evaluate indirectly the microcirculation in clinical practice by measuring the lactate serum levels and it is possible to monitor the dynamics of shock [8]. It is possible to observe the mottling of the knee skin, that indirectly allows quickly evaluate tissue perfusion. The mottling score was developed with ancient definitions of sepsis severity when there was no possibility to measure lactate or blood markers levels [87]. There are methods that may directly visualize the microcirculation and may contribute to further knowledge and understanding of the

microcirculation. Older technologies such as nail-fold video capillaroscopy are highly dependent on body temperature and catecholamine use [88].

In recent decades side stream dark field microscopy has become as one of the leading noninvasive measures to evaluate the function of microcirculation. The benefit of this method is that it is possible to perform it by the bed side, it is not expensive, and can be repeated several times in order to monitor the progress of the diseases and microcirculatory parameters. Side stream dark field (SDF) imaging was discovered more than 20 years ago. It was implemented much later as a compact hand-held device in clinical practice. This device consists of a hand-held microscope with a light source and a disposable lens that is attached to the top of the microscope. A light source with a disposable lens at the tip is held close to the tissue to be examined (e.g. sublingual or intestinal mucosa). A 530 nm polarized light wave is emitted from the light source, which is absorbed by hemoglobin in erythrocytes. The method of cross-polarized detection helps to penetrate deeper into tissues where the micro vessels are located. This method is based on the principle that light waves polarized in one direction are blocked by tissue structures, while light waves polarized in another direction are not. This allows only the light that has penetrated deeper into the tissue to be detected, allowing the micro vessels to be visualized. Since the wavelength of the emitted light is selectively absorbed by hemoglobin in erythrocytes, regardless of oxygenation, moving erythrocytes are seen as dark gray bodies. This way by patient bed side functioning number of capillaries and the flow in the capillaries can be measured: capillaries filled with continuously flowing erythrocytes and capillary density [89].

Figure 4. Photograph of side stream dark field camera and characteristics
Adapted from Coppel et al. [90]

Decreased function of microcirculation has been well established in sepsis. This is due to the inflammatory process caused by the release of pro-inflammatory cytokines, which cause vasoconstriction, reduce capillary permeability, and inhibit angiogenesis. Furthermore, microcirculation thrombosis can occur, due to the increased levels of pro-coagulant cytokines and hyperfibrinolysis, leading to reduced blood flow and tissue ischemia[91, 92].

Moreover, it has been showed that short-term survival after out-of-hospital cardiac arrest is predicted by changes in sublingual microcirculation. Survivors showed a higher proportion of small, perfused vessels six hours after admission than non-survivors (85 ± 7.9 vs. $75 \pm 6.8\%$, $p = 0.01$). Global hemodynamics did not differ significantly among survivors and non-survivors [93]. After cardiac surgery severe impairment of microcirculatory parameters is associated with postoperative levels of lactate and acute organ injury [94].

2.10 Possible treatment options

In general, patients with CS should best be treated at based on the etiology of CS, left and right ventricles as well as mechanical complications as cause, treatment in the catheterization laboratory or operating theatre, subsequent treatment at intensive care unit and possible selection of microcirculatory support system. The main treatment aim in cardiogenic shock is the urgent coronary angiography and urgent reperfusion if the CS is due to acute ischemic event [95]. For patients with cardiogenic shock after cardiac surgery, low-dose topical nitroglycerin solution proved to be feasible to identify nitroglycerin responsiveness in patients with circulatory shock [96].

2.11 Ischemia with nonobstructive coronary arteries in clinical practice

Stable ischemic heart disease is associated with angina, decreased physical exertion and in clinical practice often leads to invasive imaging like coronary angiography. Usually that is because it is often attributed to atherosclerosis. Even though almost 10% of acute coronary syndromes patients and almost half of patients who undergo invasive coronary angiography for the evaluation of cardiac vessels do not have obstructive coronary heart disease [97]. This clinical scenario when situation is stable is referred as ischemia with nonobstructive coronary arteries (INOCA) [98]. When the same situation arises during an acute coronary event it is called myocardial infarction with nonobstructive coronary arteries [44].

2.12 Small vessels and neurodegenerative disorders

Microcirculation is a crucial element in cerebral activity as well. There is increasing data over the recent years investigating the possible link between microcirculatory impairments (endothelial dysfunction, morphological irregularities in capillaries and disturbances in of blood cell influx) can compromise the tissue oxygen availability. There is a possible link of microcirculation and Alzheimer disease pathophysiology as well. Alois Alzheimer a doctor that first described it at the end of 19th century considered it to be a vascular disorder, naming it arteriosclerotic atrophy of the brain [99]. Early during Alzheimer disease, a reduction in cerebral blood flow is observed. It has been suspected as a possible predictor of progression of the disease from mild cognitive decline to Alzheimer disease [100]. Mouse models confirmed that impaired cerebral perfusion may stimulate amyloid-beta deposition [101]. Moreover, hypertension and dyslipidemia are independent risk factors for Alzheimer disease and can impair pericyte structure and function which can potentially initiate neurodegenerative changes [102, 103]. There is a prospective heart-brain axis. It has been shown for patients with subclinical carotid plaques cerebral blood flow impairment is observed when analyzing with magnetic resonance imaging technique for measuring tissue perfusion. High carotid plaque volume is associated with brain hypoperfusion [104].

2.13 Summary of literature review

It has been observed in clinical practice that there are some patients with acute myocardial infarction that do not have any significant changes in coronary arteries when no significant atherosclerotic changes (≥50% stenoses can be identified). Troponins play an important role in the diagnosis of MINOCA. Cardiac troponins are "organ-specific" but not "disease-specific". One of the pathophysiological mechanisms that cause MINOCA is the impairment of coronary microcirculation. Coronary micro vessels are known to contribute to >50% of total coronary vascular resistance and regulate coronary flow. One of critical manifestations of acute coronary syndromes is cardiogenic shock. Traditionally macrohemodynamic variables like arterial blood pressure, heart rate, cardiac output, and oxygen saturation) have been used to determine the severity of shock and aid in determining possible treatment strategies. The macrohemodynamic parameters should be normalized as soon as possible. Despite this optimization, patients are sometimes not protected from the development of organ failure. There is a

suggestion that in these cases capillary perfusion and tissue oxygenation might be a better prognostic measure.

The diagnosis of MINOCA can be challenging, and there is a lack of consensus on the best diagnostic approach and treatment strategy. Further research is needed to develop standardized diagnostic criteria and effective treatments for these patients. Finally, there is a need for biomarkers that can help identify patients with type 2 MI who are at high risk of adverse outcomes and guide treatment decisions. While there has been some research on the relationship between microcirculation and cardiogenic shock, there is still a need for more studies to better understand the mechanisms involved and to develop new treatment targets. Our aim is to develop new therapies that target microcirculatory dysfunction in cardiogenic shock. This could involve testing the efficacy of drugs that improve microcirculatory perfusion, such as vasodilators or anti-inflammatory agents, or evaluate the effect of novel techniques such as extracorporeal membrane oxygenation to support microcirculatory function.

3. METHODS

3.1 Ethical Approval

Research methodology differed between the four papers that formed the basis of this thesis. Therefore, multiple ethical approvals were sought. All research was conducted in accordance with the Declaration of Helsinki. The main protocol of the study was approved by the Lithuanian Bioethics Committee (protocol code number Nr. 158200-19/4-1015-52) for **papers I, II and III**. For **paper IV** study protocol was approved by the Lithuanian Bioethics Committee (protocol code number L-14-01/1).

3.2 Study design and data source

In **paper I** a retrospective data analysis was conducted. Data was collected from February 1st in 2015 to January 1st in 2019. Totally 6495 patients who were diagnosed with MI (all types) were identified. Hospital electronic record files were reviewed. After all, 129 patients met inclusion and did not meet exclusion criteria and were included in the study. Demographic and clinical characteristics data were collected.

The primary study endpoint was all-cause mortality during the hospital stay and 2 years follow-up. The laboratory tests values gathered during hospital stay including blood hemoglobin, D-dimer, creatinine, BNP, CRP and troponin level for the estimation of their predictive values. These characteristics were compared between groups of patients who survived and died during 2 years of follow-up. Abbot high sensitivity troponin I assay was used for the troponin evaluation (Abbott Architect, Abbott Laboratories, Abbott Park, IL, USA). Upper reference limits were 16 ng/L for women and 34 ng/L for men with limit of detection 1.1–1.9 ng/L.

Unstable angina, type 2 myocardial infarction and MINOCA sub study.

Since MINOCA is usually considered a working diagnosis in clinical guidelines of STEMI and NSTEMI.

In **paper II** as another prevalent working diagnosis, UA was investigated. A retrospective analysis of 840 patients with UA diagnosis who were hospitalized in Vilnius University Hospital Santaros Klinikos during the period of 2017-2018. Year 2017 was chosen because at this timepoint Santaros Klinikos started to use high sensitivity troponin in clinical practice. The aim of the study was to investigate the patients with the diagnosis of unstable angina, because often this diagnosis includes all the patients that do not fall

into usual clinical practice. Since MINOCA is a novel diagnosis for clinicians we suspected that significant number of patients could have fallen into this category. The main inclusion criterion was the diagnosis of unstable angina. Patients who have not been tested for a high-sensitivity cardiac troponin I (hs-cTnI) and have not undergone coronary angiography (CAG) were excluded. The final research sample included 715 patients. The normal range of hs-cTnI was referred to as ≤15.6 ng/l in women and ≤35.2 ng/l in men. We used the data of hs-cTnI which was taken on admission (in the emergency room) with smallest and largest values during time of hospitalization. Inverted T, ST-segment depression, and newly found left bundle branch block were considered as ischemic ECG changes.

It was considered that patients were correctly diagnosed with UA if they had normal or <3 times increased hs-cTnI and met one or more of the following criteria:

Prolonged chest pain (usually > 20 minutes);

New-onset angina of at least class 3 severity in the Canadian Cardiovascular Society classification.

Destabilization of previously stable angina.

In usual clinical practice there is no clear cut-off value for the cardiac troponin elevation. In 4th universal definition of MI. The cut-off for periprocedural MI is arbitrarily defined by elevation of troponin values >5 times the 99th percentile upper reference limit. That is why we chose this cut-off value for UA reclassification. UA was reclassified to myocardial infarction in when hs-cTnI was increased ≥5 times:

To type 1 NSTEMI if followed by obstructive CAD (≥50% diameter stenosis in a major epicardial vessel); To myocardial infarction with non-obstructive coronary artery (MINOCA) in cases with no angiographic obstructive coronary artery disease.

Patients were considered as “probable” MI or “probable” MINOCA if they met the criteria of increased hs-cTnI ≥3 but <5 times.

In **paper IV** data from the CULPRIT-SHOCK microcirculation substudy is presented. The design and outcome of the CULPRIT-SHOCK trials have been published previously [7, 105]. In brief, the CULPRIT-SHOCK study encompasses an investigator-initiated, open-label, European multicenter trial, that randomized 706 patients.

The inclusion criteria were patients with acute ST-segment elevation or non–ST-segment elevation myocardial infarction complicated by cardiogenic shock and multivessel disease. The patients were randomized to either culprit lesion-only revascularization with potential planned-staged revascularization

of non-culprit lesions or immediate multivessel revascularization in a 1:1 fashion.

Cardiogenic shock was defined as systemic hypotension <90mmHg for at least 30 minutes or dependence on inotropes to maintain a systolic blood pressure (SBP) of 90mmHg, signs of pulmonary congestion, and signs of impaired organ perfusion with at least one of the following altered mental statuses, cold, clammy skin, urine output<30ml/hour, or lactate levels >2.0mmol/liter. Exclusion criteria were cardiogenic shock for >12hours, cardiopulmonary resuscitation >30 min, severe cerebral deficit, mechanical causes of cardiogenic shock or shock by other cause, creatinine clearance less than 30 ml/h, and severe concomitant disease with life expectancy less than 6 months.

Patients for the microcirculation sub-study were screened for participation in 6 centers with ample experience in sublingual microcirculatory imaging (University of Vilnius, Vilnius University Hospital, Lithuania (VUHSK); Amsterdam UMC - Academisch Medisch Centrum, The Netherlands (AMC); University of Leipzig - Heart Centre, Germany (ULEIHC); University of Lübeck - Heart Centre, Germany (ULHC), University of Düsseldorf – Institute for Cardiology, Pulmonology and Angiology, Germany (UD); Erasmus Medical Centre, Rotterdam, The Netherlands (EMC) . The relevant local institutional ethics committees approved the study protocol and for all eligible patients informed consent was obtained according a prespecified process that varied among participating centers according to local law.

Systemic microvascular function was assessed by evaluating the sublingual microvascular network using videomicroscopy directly post primary PCI. A total of three stable high-quality video-microscopy loops of at least 50 frames were collected for analysis of microvascular perfusion. In AMC, ULEIHC, UL, UD and VUHSK sublingual microcirculatory network was evaluated by videomicroscopy applying the side stream dark field (SDF) imaging-technique (Microscan, Microvision Medical, Amsterdam, The Netherlands), whereas in EMC the sublingual microcirculatory network evaluated by videomicroscopy applying the incident dark field (IDF) imaging-technique (CytoCam, Braedius, Huizen, The Netherlands). The validated SDF and IDF techniques comprehend handheld videomicroscopies equipped with green light-emitting diodes that illuminate the red blood cells of the sublingual microcirculatory network, thereby providing two-dimensional video images of sublingual microcirculatory blood flow as described previously [8, 106].

Thirty-day follow up was performed to document the occurrence of all-cause death or severe renal failure leading to renal-replacement therapy.

Renal-replacement therapy (dialysis, hemofiltration, or hemodiafiltration) was considered for otherwise untreatable volume overload, hyperkalemia (potassium level >6.0 mmol per liter), severe uremia (blood urea level >50 mg per deciliter), or persistent severe metabolic acidosis (pH <7.2).

Sublingual sequences were analyzed offline in a core lab at AMC by a trained investigator blinded to the treatment allocation and clinical outcome. Dedicated software (Automated Vascular Analysis (AVA) version 3.2, Microvision Medical, Amsterdam, The Netherlands) was used to quantify the sequences obtained by SDF and IDF. Imaging acquisition and offline analysis was performed according to the consensus on imaging acquisition and analysis [8, 107]. Capillaries were defined as vessels with diameter <20μm. Vessel flow was categorized as absent, intermittent, sluggish, or normal, of which vessels with sluggish or normal flow were defined as perfused and vessels with absent or intermittent flow were defined as non-perfused. The values of perfusion parameter were averaged over representative sequences per time-point and defined as:

De Backer's score = grid crossings / total vessel length

Total capillary density (TCD) = total length of capillaries / image area

Perfused capillary density (PCD) = length of perfused capillaries / image area

Proportion perfused capillaries (PPC) = perfused capillaries / number of capillaries) X 100

Microvascular flow index (MFI) = average of predominant type of flow in the four quadrants of the image

In addition, macrohemodynamic parameters were collected at the time of sublingual measurements. A MAP<60 or SBP<90 mmHg was considered abnormal.

3.3 Study population

For **paper I,** the study population included all patients with type 2 myocardial infarction, include g MINOCA patients. Patients who had the diagnosis of Takotsubo cardiomyopathy were excluded from the analysis. For **papers II** we collected data on troponin and other biomarkers measurements for patients whom unstable angina was diagnosed at VUH SK. Data on false negatives, i.e., NSTEMI cases that were not identified by the referring physicians, were also collected. **Paper III** included all patients whom the diagnosis of MINOCA was made. **Paper IV** included all patients with

myocardial infarction and cardiogenic shock who had sublingual microcirculation measurements taken.

3.4 Statistical analysis

In **paper I** continuous variables are presented as mean with standard deviation, categorical variables are presented as counts (percentage). The normality of the distribution was assessed using Kolmogorov-Smirnov test. Student-t and Mann-Whitney-Wilcoxon tests were used to evaluate the differences between the two independent normally and non-normally distributed data sets, respectively. The differences between independent two qualitative data groups were evaluated by Fisher exact test. Risk factors for overall survival were assessed by univariate Cox regression analysis. Multivariable Cox regression model with stepwise selection algorithm was performed to identify independent risk factors for overall survival. Survival trends were evaluated by Kaplan-Meier method. Statistical analysis was performed using the Statistical Analysis System (SAS Institute, Cary, NC, USA) package version 9.2. All tests were 2-sided and a p value of <0.05 was considered significant. No imputation was used for missing data.

In **paper II** MS Excel, R-Commander, and SPSS21 for statistical analysis was used. P-value <0.05 indicated significant findings. To determine if a data set is in a normal distribution we used Kolmogorov–Smirnov test. Mean and standard deviation present normally distributed data. Median and interquartile range present not normally distributed data. For numerical data comparisons we used Mann-Whitney-Wilcoxon test. To compare proportions between UN and type 1 NSTEMI we applied Chi-squared and Fisher's exact tests.

In **paper III** we The normality of the distribution of values was assessed using the Shapiro–Wilk statistic and Levene's test to assess homogeneity of variances. Continuous variables are presented as mean ± standard deviation or median (1st, 3rd quartile (Q1, Q3)), according to the distribution. Between-group differences were compared with Student's t-test or Mann–Whitney U-test according to the distribution. Categorical variables are presented as frequency (percent- age), and between-group differences and were compared with the chi-square test. Prognostic receiver operating characteristic (ROC) curves were generated, and the area under the curve (AUC) was used to compare the discriminative value of videomicroscopy-derived microcirculatory perfusion parameters for the combined endpoint of all-cause death and renal replacement therapy at 30 days' follow-up. The optimal clinical cut points were defined as the cut point with the highest sum of

specificity and sensitivity. The prognostic value of perfusion parameters for the composite endpoint of death and renal replacement therapy was assessed by Cox regression analysis. The best fit model for adjustment was identified by univariate Cox regression, in which candidate covariates were: clinical and procedural variables (Table 1). Variables with a significant association with the combined clinical endpoint ($P<0.05$) were used for adjustment. Cox proportional hazards models were pre- ceded by verification of the proportional hazard assumption using Schoenfeld's residuals. Next, primary endpoint rates specified by normal or abnormal microcirculatory perfusion parameters were estimated using the Kaplan–Meier method and compared using the Gehan–Breslow– Wilcoxon (Breslow) method. A P value below the two- sided α-level of 0.05 was considered statistically significant. The STATA 13.1 statistical software package (StataCorp, College Station, TX, USA) was used for all calculations.

4. RESULTS

4.1 Results of type 2 MI sub study

Of 6495 patients with MI there were 129 type 2 MI patients (73 women [55%]; mean (SD) age, 74.45 (10.68) years). Hospital mortality for type 2 MI was 8.5% (n=11). Patients that did not survive were older: mean (SD) age for dead and alive patients were 81 (6.99) and 71.1 (12.08) (p = 0,008), respectively (Table 1). At 6 months all-cause mortality was 19.4%, at one year 27.1% and at 2 years 36.4% (Table 2). Older age was a significant risk factor for overall survival. People who died during the 2 years follow up were mostly older than 65 years (43% vs. 19.4%).

Utilization of coronary angiography was quite common and was performed for 73.9% of patients with type 2 myocardial infarction. During angiography 57 patients (44.2%) had stenoses <50%, 10 patients (7.8%) had stenoses 50-75% and 37 patients (28.7%) had stenoses >75%. Out of all patients in whom coronary angiography was performed 18.6% had undergone PCI. The utilization of PCI did not show an inverse relationship to patient's mortality risk.

Most common reason for cause of type 2 MI was anemia with 38 cases. Other reasons include sepsis (8), acute respiratory failure (8), or combination of these conditions (8). 13 cases later were reclassified as Takotsubo cardiomyopathy and 67 cases were left as myocardial infarction with non-obstructive coronary arteries (MINOCA) where no exact cause could be identified (Table 3).

The average values of laboratory biomarkers between patients who survived and died is showed in Table 4. People who died had significantly higher creatinine, CRP, BNP, D-dimer and lower hemoglobin levels. The influence of laboratory biomarkers on long-term survival are summarized in Table 5. A multivariable model with stepwise selection method after adjusting for age, renal function and C reactive protein showed that older age and higher Hs Troponin I maximal value remained independent statistically significant mortality predictors (Table 6).

Kaplan-Meier survival analysis shows significant differences between age groups (

Figure 5) and prescribed medication. Overall people who were treated with statins or ACEi had an increased two-year survival rate. These differences were prominent for ACEi (HR 0.485 [0.286-0.820]) and statins (0.549 [0.335-0.900]). While there appeared to be a trend for better outcomes for beta-blockers (HR 0.662 [0.371-1.181]; p=0.163) and prescription of

aspirin (HR 0.901 [0.527-1.539], p=0.702), these differences did not attain statistical significance (Table 7). Moreover, the use of beta blockers or aspirin did significantly influence long term survival (**Error! Reference source not found.**).

Table 1**.** Patient characteristics during hospitalization

	During hospitalization		
	Survived (n=118)	Died (n=11)	P value
Age, mean (SD)	71.1 (12.08)	81 (6.99)	0,008
Female sex, n (%)	68 (57.6)	5 (45.5)	0.724
Arterial hypertension, n (%)	92 (77.9)	7 (63.6)	0.8
Dyslipidemia, n (%)	44 (37.3)	2 (18.2)	0.33
Diabetes mellitus (type II), n (%)	37 (31.3)	1 (9)	0.254
Chronic heart failure, n (%)	71 (60.2)	5 (45.5)	0.688
CKD (eGFR < 60 ml/min/1.73m2) , n (%)	21 (17.8)	3 (27.3)	0.342
Previous PCI, n (%)	13 (11.0)	1 (9)	0.913
Previous CABG, n (%)	9 (7.6)	3 (27.3)	0.018
Oncological disease, n (%)	10 (8.5)	1 (9)	0.812
Average LV EF (%)	45.44	36.07	0,034

CKD – chronic kidney disease, CABG – coronary artery bypass graft, LV EF – left ventricle ejection fraction, PCI – percutaneous intervention, SD – standard deviation.

Table 2**.** Follow up for survival according to age.

Survival	Category	All (N = 129) N (%)	</=65 (N = 36) N (%)	>65 (N = 93) N (%)	P value
6 months	Alive	104 (80.6)	35 (97.2)	69 (74.2)	0.002
	Dead	25 (19.4)	1 (2.8)	24 (25.8)	
12 months	Alive	94 (72.9)	32 (88.9)	62 (66.7)	0.014
	Dead	35 (27.1)	4 (11.1)	31 (33.3)	
	Additional deaths	10 (7.7)	3 (8.3)	7 (7.5)	
24 months	Alive	82 (63.6)	29 (80.6)	53 (57.0)	0.014
	Dead	47 (36.4)	7 (19.4)	40 (43.0)	
	Additional deaths	12 (9.3)	3 (8.3)	9 (9.7)	

Table 3**.** The main causes of type 2 MI.

Main cause of MI	Number of cases (%)
Anemia	38 (29.46)
Sepsis	8 (6.20)
Acute respiratory failure	8 (6.20)
Combination of conditions	8 (6.20)
No clear cause can be specified	67 (51.94)

Table 4**.** Laboratory variables in alive and not survived patients.

Laboratory	All (N= 129) Mean (SD)	Alive (N=82) Mean (SD)	Dead (N=47) Mean (SD)	P value
Hemoglobin	107.1 (29.42)	116.6 (28.69)	98.9 (27.73)	<0.001
Creatinine	127.7 (118.62)	90.0 (40.82)	161.9 (151.73)	<0.001
GFR MDRD	59.5 (26.92)	70.0 (21.38)	48.9 (28.00)	<0.001
CRP	49 (61.3)	31.4 (56.29)	63.3 (61.90)	0.004
Procalcitonin	9.8 (27.28)	1.5 (2.56)	11.4 (29.72)	0.159
Hs Troponin I max	12439.5 (23669.2)	8114.0 (11200.9)	16476.0 (30670.7)	0.052
D-dimer	865 (926.94)	595.3 (676.38)	1104.8 (1055.43)	0.020

BNP – brain natriuretic peptide; CRP – C reactive protein; GFR – glomerular filtration rate.

Table 5**.** Markers for total survival

Laboratory value	HR (95%CI)	P

Hemoglobin	0.985 (0.977-0.993)	<0.001
Creatinine	1.003 (1.001-1.004)	<0.001
Glomerular filtration rate (MDRD)	0.977 (0.965-0.990)	<0.001
C reactive protein	1.005 (1.002-1.008)	0.002
Procalcitonin	1.013 (0.998-1.028)	0.087
Hs Troponin I maximal value*	1.010 (1.002-1.018)	0.015
BNP*	1.059 (1.027-1.092)	<0.001
D dimers*	1.347 (1.017-1.785)	0.038
Left ventricle ejection fraction	0.960 (0.939-0.982)	<0.001

*increase step was set to 1000 units due to low level of hazard risk when respective markers increase by 1 unit.
BNP – brain natriuretic peptide; HR – hazard ratio.

Table 6. Significant mortality predictors after accounting for age, renal function and C reactive protein

Laboratory value	**HR (95%CI)**	**P**
Older than 65 years	9.484 (1.615-55.706)	0.013
Creatinine		n.s.
Glomerular filtration rate (MDRD)		n.s.
C reactive protein		n.s.
Hs Troponin I maximal value*	1.021 (1.009-1.032)	<0.001
BNP*		n.s.
D dimers*		n.s.

*increase step was set to 1000 units due to low level of hazard risk when respective markers increase by 1 unit.
BNP – brain natriuretic peptide; HR – hazard ratio, n.s. – nonsignificant.

Table 7**.** Two-year mortality risk by individual medications (univariate Cox regression)

Drug	Reference category	HR (95%CI)	P
ACEi	Untreated	0.485 (0.286-0.820)	0.007
ARB	Untreated	0.418 (0.168-1.042)	0.061
B-blockers	Untreated	0.662 (0.371-1.181)	0.163
Vasopressors	Untreated	2.829 (1.574-5.085)	<0.001
Digoxin	Untreated	1.230 (0.300-5.037)	0.774
Aspirin	Untreated	0.901 (0.527-1.539)	0.702
Other antiagregants	Untreated	1.210 (0.741-1.978)	0.446
Warfarin	Untreated	0.562 (0.278-1.137)	0.109
NOAC	Untreated	0.708 (0.222-2.257)	0.559
Heparin	Untreated	1.133 (0.683-1.881)	0.629
LMWH	Untreated	1.403 (0.858-2.295)	0.177
Statins	Untreated	0.549 (0.335-0.900)	0.017
Diuretics	Untreated	1.734 (1.025-2.934)	0.040
Antibiotics	Untreated	2.476 (1.521-4.031)	<0.001

ACEi - angiotensin converting enzyme inhibitor; ARB - angiotensin receptor blocker; NOAC – novel oral anticoagulants; LMWH - low molecular weight heparin.

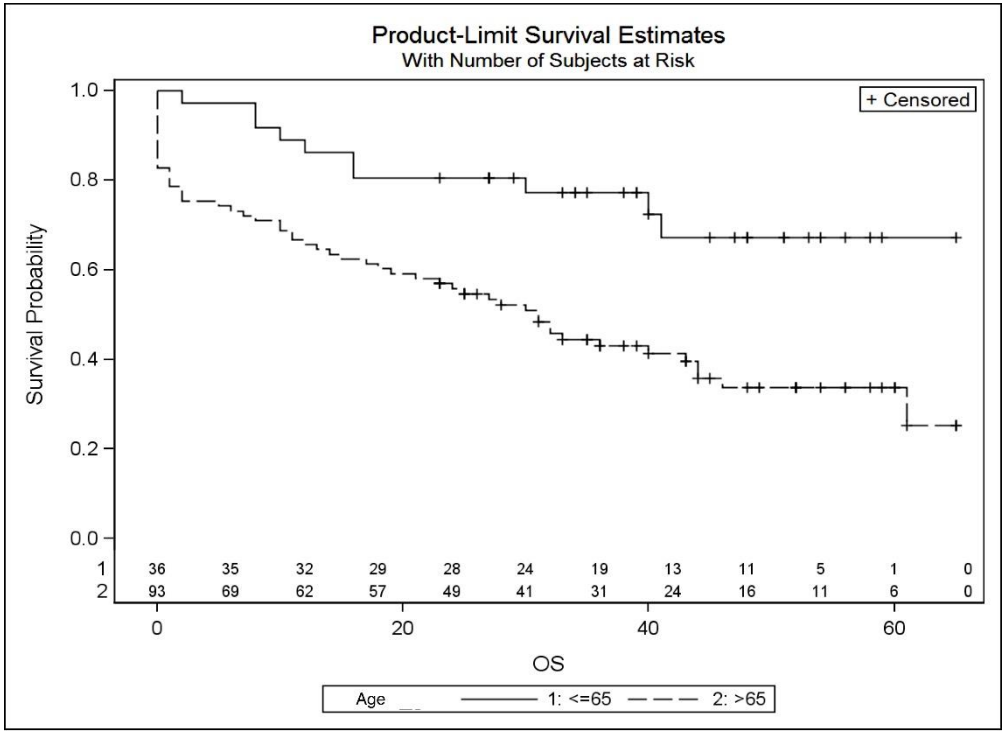
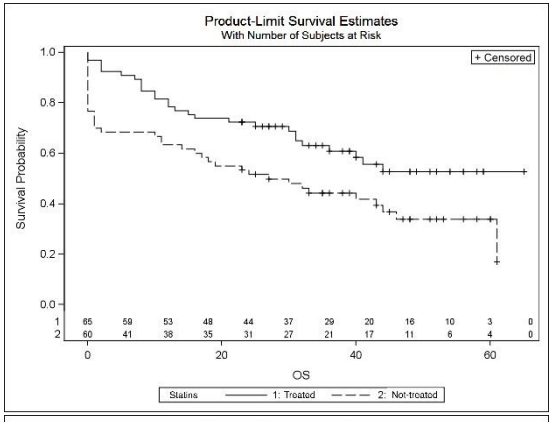
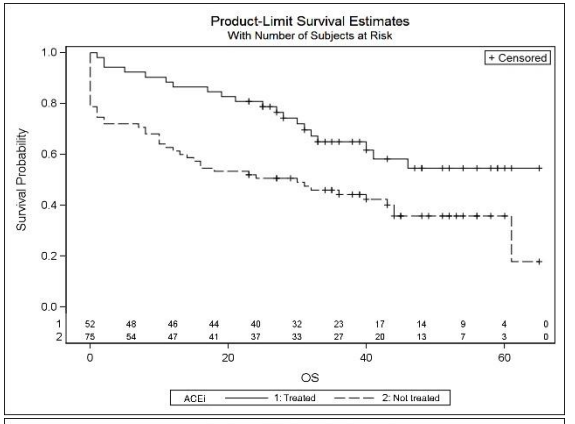


Figure 5**.** Kaplan-Meier survival curves according to age**.**

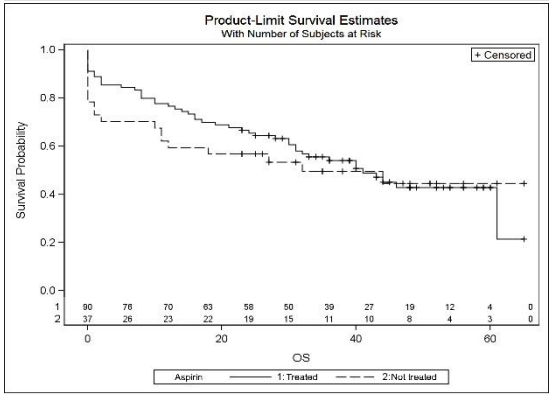
a.



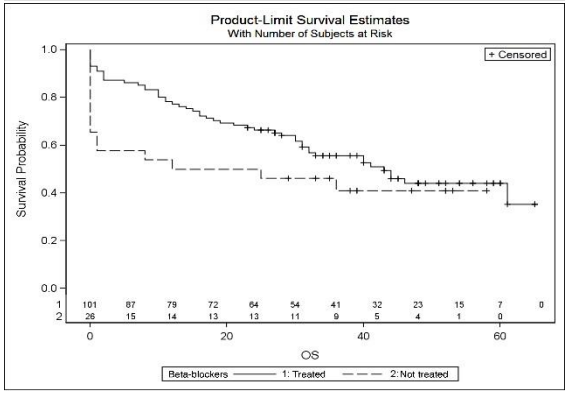
b.



c.



d.



Adjustment for Multiple Comparisons for the Logrank Test: a. statins (p=0.017); b. ACEi (p=0.007); c. aspirin (p=0.702); d. beta-blockers (p=0.163). ACEi - angiotensin-converting enzyme inhibitors

Figure 6**.** Kaplan-Meier survival analysis for different drug groups. There was a significant survival benefit for patients who were prescribed with statins or ACEi, but no significant benefit was found among patients who received aspirin or betablockers.

4.2 Unstable angina reclassification results

In **paper II** an analysis of patients with unstable angina was performed. Since we found that the prevalence of type 2 MI is very low, we considered that substantial amount of these patients could have been diagnosed as unstable angina. This was especially important after the introduction of high sensitivity troponin assays in clinical practice. It has improved the ability to accurately diagnose and classify patients with acute coronary syndromes (ACS), including unstable angina and myocardial infarction. These assays can detect much lower levels of troponin in the blood than previous generations of troponin tests, allowing for earlier and more accurate diagnosis.

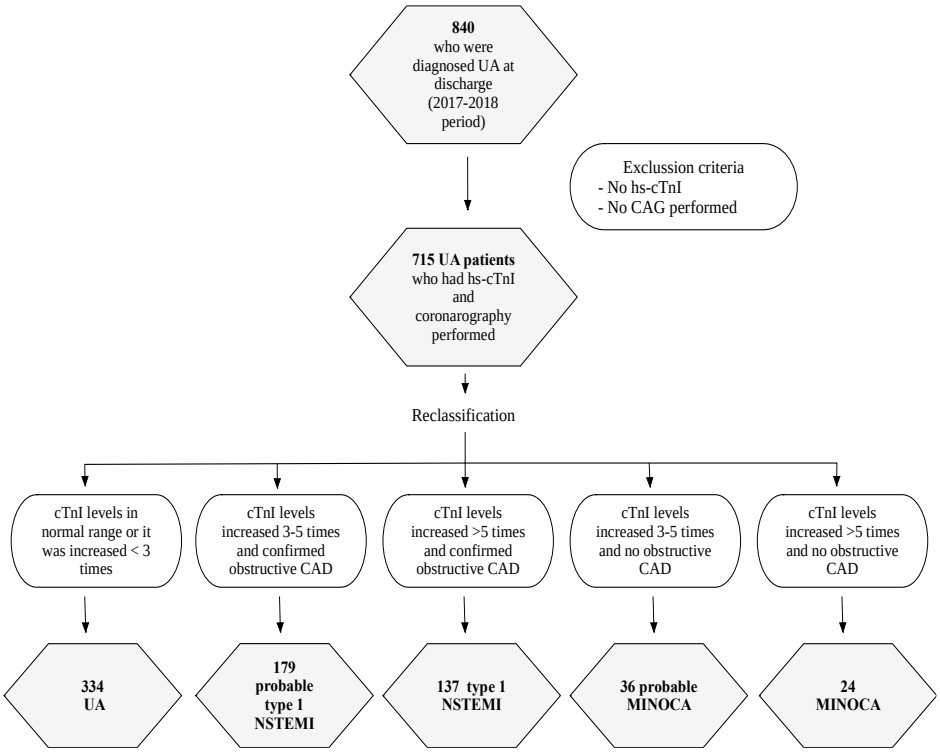


Figure 7. Flowchart of the patient selection process and reclassification results.

hs-cTnI level was increased 5 or more times in 161 (22,5%) cases (measured on admission in emergency department) (Figure 7).

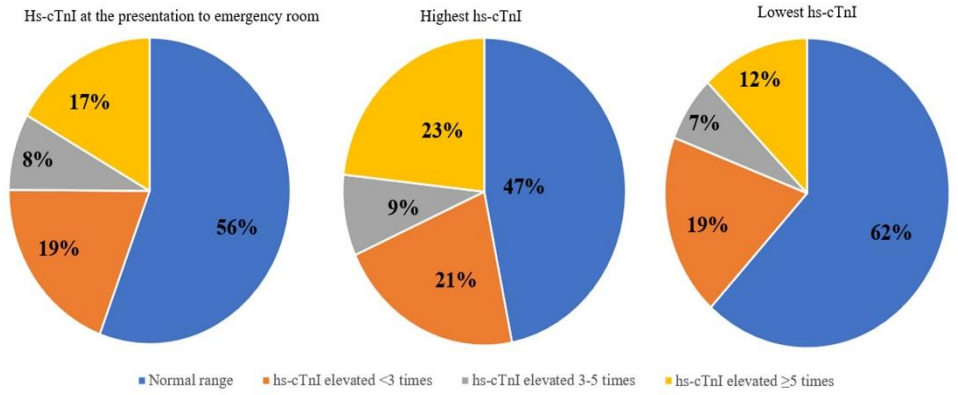


Figure 8. The proportion of normal range and elevated high sensitivity cardiac troponin-I values at the presentation to the emergency room, the highest and the lowest hs-cTnI values during hospitalization. hs-cTnI - high sensitivity cardiac troponin-I

Recommendations of Fourth Universal Definition of Myocardial Infarction were followed and according to elevated hs-cTnI levels and changes of CAG, 137 (19.16%) patients could have been diagnosed with type 1 NSTEMI. Median level of hs-cTnI on admission for these patients was 184.32 ng/l. When the patients were admitted the median of the lowest hs-cTnI during time of hospitalization was 114.0ng/l and the median of the highest - 304.0 ng/l (Table 8). In most cases the troponin measurement was repeated several times. The time difference between the measurements was not consistent and varied considerably.

The median level of hs-cTnI for patients in the “probable” type 1 NSTEMI was 47.15 ng/l on admission. The median of the lowest hs-cTnI level during hospitalization was 37.0 ng/l and the median of the highest hs-cTnI - 61.2 ng/l (Table 2).

There were 24 (3.36%) patients who could have been diagnosed with MINOCA. They median hs-cTnI on admission was 184.7. We also found “probable” MINOCA for 36 (5.03%) patients and their median hs-cTnI on admission was 47.0.

Table 4. Median values of high sensitivity cardiac troponin-I after reclassification.

	All patients	**UA**	**Type 1 NSTEMI**	**MINOCA**	**Probable type 1 NSTEMI**	**Probable MINOCA**	**Elevated after coronary angiography**
	Median	**Median**	**Median**	**Median**	**Median**	**Median**	**Median**
Hs-cTnI at the presentation, ng/l	17.6	6.4	184.4	184.7	47.2	47.0	6.9
Lowest hs-cTnI, ng/l	51.7	5.7	114.0	125.6	37.0	38.7	6.9
Highest hs-cTnI, ng/l	115.2	7.1	304.0	200.3	61.2	49.5	1522.0

hs-cTnI - high sensitivity cardiac troponin-I; MINOCA - myocardial infarction with non-obstructive coronary arteries; NSTEMI - non-ST segment elevation myocardial infarction, UA - unstable angina.

Table 8. Unstable Angina compared to reclassified Myocardial Infarction

According to requalification criteria, patients were divided into two groups: the genuine UA group (a total of 334 patients) and type 1 NSTEMI (a total of 137 patients). We excluded patients with "probable" type 1 NSTEMI and MINOCA. In this study we distinguished two significant groups of diagnoses, and the patients of grey zone were excluded.

There were significantly more men in the UA group than women (227 (68%) vs. 107 (32%), p=0.005). In the type 1 NSTEMI group there was no significant difference between sexes (Table 1). Patients with type 1 NSTEMI were older than UA patients (71.41 vs. 65.59 years old, p<0.001).

Patients in the type 1 NSTEMI group experienced pain longer than 20 minutes more often compared to those in the UA group (31 patients (64.6%) vs. 54 (40.0%), p=0.003). We found that UA group patients had previous episodes of pain (especially in the chest) more than type 1 NSTEMI group (276 (85.7%) vs. 79 (57.7%), p<0.001). The type of pain, irradiation site, history of MI, and frequency of coronary interventions did not differ between type 1 NSTEMI and UA groups. However, we found that type 1 NSTEMI group had ischemic ECG changes more often compared to the UA group (75 (54.7%) vs. 148 (44.3%), p=0.039).

4.3 Microcirculation study results

In **paper IV,** results are presented of patients with cardiogenic shock and measurements of microcirculation. Between March 2013 and April 2017, 66 patients with CS, which complicated acute MI, and multivessel disease were enrolled in all participating centers where microcirculation measurements were performed. Of these, 27 had double-vessel disease and 39 had triple-vessel disease. Fifty-eight percent of patients (38 out of 66) presented with ST-segment elevation acute MI, and 43% of patients (28 out of 66) with non-ST-segment elevation AMI. The median age of the study population was 69 (Q1, Q3: 60, 75) years, and 67% of patients were men (44 out of 66). Complete multivessel revascularization was per- formed as randomly assigned in 50% of patients (33 out of 66), of which successful complete revascularization was achieved in 67% of patients (22 out of 33). Culprit lesion- only revascularization was performed in 50% of patients (33 out of 66). In VUHSK a total number of 7 patients were included among all other centers. All patients finalized complete follow-up.

Prognostic implications of sublingual videomicroscopy

Sublingual microvascular perfusion measurements were successful in 66 out of 66 patients. The relevant variables identified by univariate analysis for adjustment included age, oliguria at admission, smoking, mechanical circulatory support, and duration of intensive care treatment. Cox proportion hazard models adjusted for these variables demonstrated that PCD, PPC and capillary MFI measured post-PCI were significantly and independently associated with the combined clinical endpoint at 30 days (PCD hazard ratio (HR) 0.947, 95% confidence interval (CI) 0.900–0.996, P=0.035; PPC HR 0.986, 95% CI 0.976–0.998, P=0.020); capillary MFI HR 0.614, 95% CI 0.424–0.890, P=0.010). Adjusted Cox regression analysis demonstrated a modest but insignificant association between TCD or de Backer score and the combined clinical endpoint (TCD HR 0.932, 95% CI 0.860–1.009, P=0.082; de Backer score HR 0.893, 95% CI 0.784–1.010, P=0.070; Table 2). In comparison, adjusted Cox regression analysis demonstrated no significant relation between macrocirculatory perfusion parameters, either at admission or post-PCI, and the combined clinical endpoint (Table 2). The discriminative value for the combined endpoint of death and renal replacement therapy did not significantly differ between the systemic microcirculatory perfusion parameters (AUC PPC 0.640; AUC PCD 0.632), overall P value 0.801. Optimal discriminative cut points for the combined endpoint were identified at 86.4% or less for PPC and 10.1 mm^2 or less for PCD. Figure 3 shows the Kaplan– Meier curves for the combined endpoint according to nor- mal versus abnormal PPC, PCD and SBP. The Kaplan–Meier estimate of the combined endpoint was significantly higher for patients with abnormal PPC (PPC ≤86.4 63.6% vs. PPC >86.4 33.3%; Breslow P=0.005; Figure 1(a)), and abnormal PCD (PCD ≤10.1 mm mm−2 73.6% vs. PCD >10.1 mm mm−2 38.3%; Breslow P=0.007; Figure 1(b)). Also, the Kaplan–Meier estimate of the combined clinical endpoint was significantly higher for patients with abnormal SBP than for patients with normal SBP (SBP <90 mmHg 62.5% vs. SBP ≥90 mmHg 44.0%; Breslow P=0.037; Figure 3(c)). The difference was mainly driven by a significantly lower mortality for patients with normal PPC or PCD (Table 3). However, the combined clinical endpoint was not significantly different for patients with abnormal versus normal MAP (MAP <65 mmHg 53.3% vs. MAP ≥65 mmHg 47.1%; Breslow P=0.274.

Loss of hemodynamic coherence between macrohaemodynamic and microhaemodynamic parameters

Post-PCI SBP was 90 mmHg or greater in 75.8% of patients (50 out of 66). In patients with SBP of 90 mmHg or greater, PPC was abnormal in 42% of patients (21 out of 50) and normal in 58% of patients (29 out of 50), and

PCD was abnormal in 20% of patients (10 out of 50) and normal in 80% of patients (40 out of 50). Figure 9 shows the Kaplan– Meier curves for the combined clinical endpoint for patients with SBP of 90 mmHg or greater and normal or abnormal PPC/PCD. A normal PPC or PCD was generally associated with a favorable outcome, whereas an abnormal PPC or PCD was generally associated with an adverse clinical outcome (ACO). Table 11 shows clinical parameters according to macrocirculatory and microcirculatory parameters. Post-PCI MAP was 65 mmHg or greater in 77.3% of patients (51 out of 66). In patients with MAP 65 mmHg or greater, PPC was abnormal in 41.2% of patients (21 out of 51) and normal in 58.8% of patients (30 out of 51), and PCD was abnormal in 17.6% of patients (nine out of 51) and normal in 82.4% of patients (42 out of 51). Figure 9 the Kaplan–Meier curves for the combined clinical endpoint for patients with MAP of 65 mmHg or greater and normal or abnormal PPC/PCD. A normal PPC or PCD was generally associated with a favorable outcome, whereas an abnormal PPC or PCD was generally associated with an adverse clinical outcome, despite normal MAP (MAP ≥65 mmHg and PPC >86.4). In normotensive patients the difference in clinical outcome was driven by a significantly lower mortality for patients with normal PPC and a lower rate of renal replacement therapy for PCD.

Table 9. Baseline, procedural a d hemodynamic characteristic of microcirculation study patients

	Overall	Survivor and no renal replacement therapy	Non-survivor or renal replacement therapy	*P* value
Baseline characteristics	*N*=66	*N*=34	*N*=32	
Age (years)	67 ± 10	64 ± 10	70 ± 9	0.022
Male	44 (66.7)	23 (67.6)	21 (65.6)	0.862
Cardiovascular risk factors				
BMI	27.5 ± 3.5	27.2 ± 3.5	28.8 ± 3.5	0.459
Current smoking	14 (21.2)	11 (32.4)	3 (9.4)	0.022
Hypertension	31 (47.0)	18 (52.9)	13 (40.6)	0.316
Hypercholesterolemia	18 (27.3)	13 (38.2)	5 (15.6)	0.039
Diabetes mellitus	20 (30.3)	11 (32.4)	9 (28.1)	0.709
Previous MI	10 (15.2)	6 (17.6)	4 (12.5)	0.560
Previous PCI	11 (16.7)	6 (17.6)	5 (15.6)	0.826
Previous CABG	5 (7.6)	3 (8.8)	2 (6.3)	0.693
Previous stroke	3 (4.5)	1 (2.9)	2 (6.3)	0.519
Positive family history	8 (12.1)	6 (17.6)	2 (6.3)	0.170
Peripheral artery disease	10 (15.2)	5 (14.7)	5 (15.6)	0.917
Signs of impaired organ perfusion on admission				
Altered mental status	40 (60.6)	21 (61.8)	19 (59.4)	0.834
Cold, clammy skin and limbs	37 (56.1)	21 (61.8)	16 (50.0)	0.129
Oliguria	16 (24.2)	5 (14.7)	11 (34.4)	0.052
pH <7.36	49 (74.2)	23 (67.6)	26 (81.3)	0.207
Arterial lactate >2.0 mm/litre	59 (74.2)	22 (64.7)	27 (84.4)	0.068
ST-segment elevated myocardial infarction	38 (57.6)	21 (61.8)	17 (53.1)	0.679
Infarct-related artery				
Left anterior descending artery	29 (43.9)	12 (35.3)	17 (53.1)	0.145
Left circumflex artery	20 (30.3)	10 (29.4)	10 (31.3)	0.874
Right coronary artery	15 (22.7)	10 (29.4)	5 (15.6)	0.182
Left main artery	2 (3.0)	2 (5.9)	0 (0.0)	0.164
Left ventricular ejection fraction, %	35.1 ± 13.0	39.4 ± 13.2	30.1 ± 11.3	0.057
Two-vessel disease	28 (42.4)	17 (50.0)	11 (34.4)	0.199
Three-vessel disease	38 (57.6)	17 (50.0)	21 (65.6)	0.295
Procedural characteristics				
Fibrinolysis <24 hours before randomisation	1 (2.0)	1 (2.9)	0 (0.0)	0.632
Resuscitation <24 hours before randomisation	35 (53.0)	19 (55.9)	16 (50.0)	0.632
Immediate PCI of non-culprit lesion	33 (50.0)	16 (47.1)	17 (53.1)	0.622
Successful immediate complete revacularisation	22 (33.3)	12 (35.3)	10 (31.3)	0.728
Mechanical circulatory support	10 (15.2)	2 (5.9)	8 (25.0)	0.030
Catecholamine therapy	59 (89.4)	29 (85.3)	30 (93.8)	0.265
Levosimendan therapy	0 (0.0)	0 (0.0)	0 (0.0)	–
Phosphodiesterase inhibitor therapy	0 (0.0)	0 (0.0)	0 (0.0)	–
Total dose of contrast material (ml)	200 (150–300)	200 (120–230)	220 (180–300)	0.086
Total duration of fluoroscopy (min)	13.8 (7.5–20.0)	12.0 (7.1–17.5)	15.4 (8.0–25.1)	0.128
ICU treatment (days)	4 (2–13)	10 (3–17)	3 (2–8)	0.013
Haemodynamic characteristics				
Macrocirculatory perfusion parameters (at admission)				
Systolic blood pressure (mmHg)	100 (87–120)	110 (90–132)	90 (82–107)	0.016
Diastolic blood pressure (mmHg)	64 (50–78)	70 (60–80)	60 (50–77)	0.278
Mean arterial blood pressure (mmHg)	77 (62–93)	81 (73–95)	69 (59–87)	0.066
Heart rate (*N*/min)	85 (70–102)	85 (70–98)	85 (70–110)	0.515
Macrocirculatory perfusion parameters (post-PCI)				
Time since revascularisation (hours)	6.5 (3.0–18.5)	7.0 (3.0–18.5)	6.0 (2.5–18.8)	0.946

Table 9. (Continued)

	Overall	Survivor and no renal replacement therapy	Non-survivor or renal replacement therapy	*P* value
Systolic blood pressure (mmHg)	102 (90–114)	106 (95–116)	95 (86–110)	0.048
Diastolic blood pressure (mmHg)	63 (54–70)	64 (54–70)	63 (54–69)	0.822
Mean arterial blood pressure (mmHg)	76 (68–84)	78 (70–86)	72 (66–81)	0.259
Heart rate (*N*/min)	86 (73–100)	86 (67–93)	86 (77–102)	0.199
Microcirculatory perfusion parameters (post-PCI)				
Time since revascularisation (hours)	6.5 (3.0–18.5)	7.0 (3.0–18.5)	6.0 (2.5–18.8)	0.946
de Backer score (*n*/mm)	11.9 (9.7–13.1)	12.4 (10.3–13.5)	10.3 (9.1–12.9)	0.078
TCD (mm mm^{-2})	18.0 (14.3–20.3)	19.0 (16.2–21.3)	16.7 (13.1–19.4)	0.057
PCD (mm mm^{-2})	14.1 (8.7–18.6)	16.6 (11.9–19.7)	12.3 (3.9–17.7)	0.065
PPC (%)	86.6 (51.5–94.5)	89.4 (75.4–97.2)	79.4 (27.6–93.8)	0.050
Capillary MFI	2.3 (1.5–3.0)	2.6 (2.0–3.0)	2.1 (0.8–2.8)	0.058

Numbers are given as *N* (%), mean ± standard deviation or median (Q1, Q3), or as specified otherwise.
BMI: body mass-index; MI: myocardial infarction; PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft; LAD: left anterior descending; LCx: left circumflex; RCA: right coronary artery; ICU: intensive care unit; TCD: total capillary density; PCD: perfused capillary density; PPC: proportion perfused capillaries; MFI: microvascular flow index.

Table 10. Univariate and adjusted Cox regression for the combined clinical endpoint (all-cause death or renal replacement therapy)

Study population (*N*=66)					
Univariate analysis			Adjusted analysis*		
Variable	HR (95% CI)	*P* value	Variable	HR (95% CI)	*P* value
Macrocirculatory perfusion parameters (at admission)			Macrocirculatory perfusion parameters (at admission)		
Systolic blood pressure (mmHg)	0.984 (0.971–0.998)	0.025	Systolic blood pressure (mmHg)	0.998 (0.984–1.013)	0.820
Diastolic blood pressure (mmHg)	0.988 (0.967–1.009)	0.264	Diastolic blood pressure (mmHg)	–	–
Mean arterial pressure (mmHg)	0.983 (0.965–1.002)	0.078	Mean arterial pressure (mmHg)	–	–
Heart rate (beats/min)	1.007 (0.996–1.018)	0.237	Heart rate (beats/min)	–	–
Macrocirculatory perfusion parameters (post-PCI)			Macrocirculatory perfusion parameters (post-PCI)		
Systolic blood pressure (mmHg)	0.976 (0.957–0.995)	0.015	Systolic blood pressure (mmHg)	0.987 (0.966–1.007)	0.203
Diastolic blood pressure (mmHg)	0.996 (0.968–1.023)	0.752	Diastolic blood pressure (mmHg)	–	–
Mean arterial pressure (mmHg)	0.982 (0.957–1.009)	0.192	Mean arterial pressure (mmHg)	–	–
Heart rate (beats/min)	1.011 (0.992–1.030)	0.254	Heart rate (beats/min)	–	–
Microcirculatory perfusion parameters (post-PCI)			Microcirculatory perfusion parameters (post-PCI)		
de Backer's score (1/mm)	0.892 (0.798–0.997)	0.043	de Backer's score (1/mm)	0.889 (0.784–1.010)	0.070
Total capillary density (mm mm^{-2})	0.928 (0.862–0.999)	0.046	Total capillary density (mm mm^{-2})	0.932 (0.860–1.009)	0.082
Perfused capillary density (mm mm^{-2})	0.949 (0.906–0.994)	0.028	Perfused capillary density (mm mm^{-2})	0.946 (0.900–0.996)	0.035
Proportion perfused capillaries (%)	0.989 (0.980–0.999)	0.026	Proportion perfused capillaries (%)	0.986 (0.976–0.998)	0.020
Microvascular flow index	0.701 (0.510–0.963)	0.028	Microvascular flow index	0.614 (0.424–0.890)	0.010

[a]Adjusted for age, oliguria at admission, current smoking, mechanical circulatory support and duration of intensive care unit treatment.
PCI: percutaneous coronary intervention.

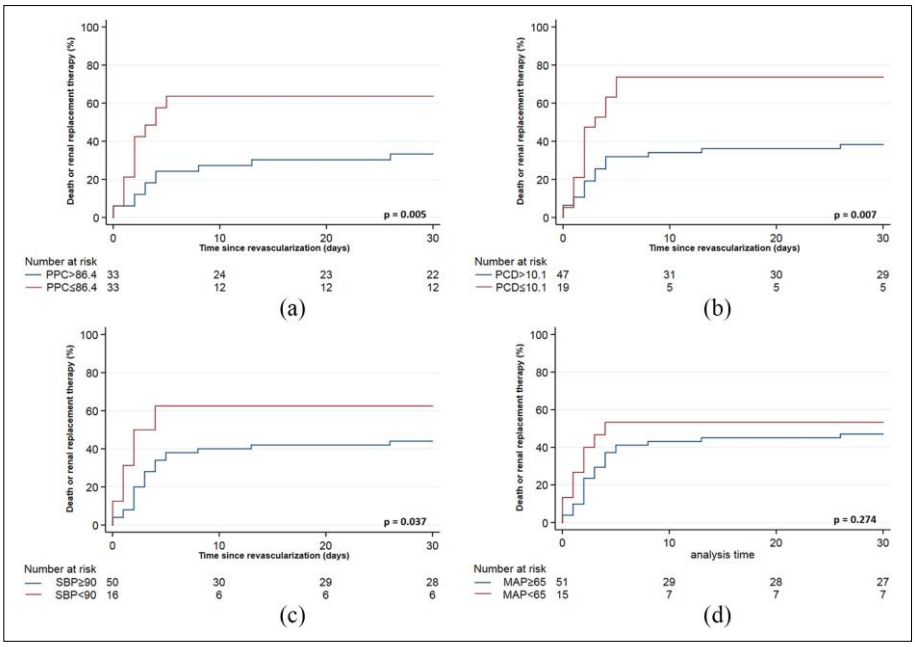


Figure 9. Kaplan–Meier estimates for patients with (a) normal or abnormal proportion perfused capillaries (PPC); (b) normal or abnormal perfused capillary density (PCD); (c) normal or abnormal systolic blood pressure (SBP); (d) normal or abnormal mean arterial blood pressure (MAP).

Table 11. Clinical parameters according to macrocirculatory and microcirculatory parameters

Overall cohort												
	PPC ≤86.4	PPC >86.4	Breslow *P*	PCD ≤10.1	PCD >10.1	Breslow *P*	SBP <90	SBP ≥90	Brewlow *P*	MAP <65	MAP ≥65	Breslow *P*
Combined clinical endpoint	63.6%	33.3%	0.005	73.7%	38.3%	0.007	62.5%	44.0%	0.037	53.3%	47.1%	0.274
All-cause death	60.6%	33.3%	0.012	68.4%	38.3%	0.011	62.5%	42.0%	0.064	53.3%	45.1%	0.134
Renal replacement therapy	18.8%	6.3%	0.120	22.2%	8.7%	0.166	20.0%	10.2%	0.266	0.0%	16.0%	0.120
	SBP ≥90 mmHg subgroup						MAP ≥65 mmHg subgroup					
	PPC ≤86.4	PPC >86.4	Breslow *P*	PCD ≤10.1	PCD >10.1	Breslow *P*	PPC ≤86.4	PPC >86.4	Breslow *P*	PCD ≤10.1	PCD >10.1	Breslow *P*
Combined clinical endpoint	61.9%	31.0%	0.014	70.0%	37.5%	0.076	66.7%	33.3%	0.005	77.8%	40.5%	0.054
All-cause death	57.1%	31.0%	0.049	60.0%	37.5%	0.325	61.9%	33.3%	0.012	66.7%	40.5%	0.178
Renal replacement therapy	20.0%	3.5%	0.061	33.3%	5.0%	0.014	28.6%	6.9%	0.033	44.4%	9.8%	0.033

Numbers are given in %, and represent the cumulative event percentage.
PCD: perfused capillary density; PPC: proportion perfused capillaries; SBP: systolic blood pressure; MAP: mean arterial pressure.

DISCUSSION

Paper I presented that out of 6495 patients with all types of MIs there were only 1,98 % (n=129) that were specified as type 2 MI. In literature there are some centers where the proportion of type 2 MI was like ours: 2 and 5% [108, 109]. It contrasts with the data from other studies where type 2 MI proportion of all MIs varies from 16 to 58% [110-116]. However, in many of these studies the investigators retrospectively analyzed elevated troponin values, compared them with clinical context and specified the diagnoses as type 1 or type 2 MI. We know that type 2 MI diagnosis should be common, but real-life data from our center and probably from other hospitals as well this diagnosis is not so prominent and often is not noticed. Patients who are not diagnosed type 2 MI may less often receive guideline-directed medical therapy and thus loose the possible benefit for overall survival. In many cases these patients most likely are diagnosed with unstable angina or the diagnosis might be omitted completely. The implementation of preventive guideline directed therapy for appropriate patient groups is challenging but may lead to improved long-term prognosis.

Moreover, in literature there is still irregular understanding of the classification of Takotsubo, whether it is a different entity or a form of type 2 MI. For example, Montone et al. evaluated the prognostic relevance of invasive provocative tests for MINOCA patients, and they classified Takotsubo as a separate cause of this disease [55].

Even though there is huge underdiagnosis of type 2 MI, in our study we found that people who died had significantly higher troponin levels (15929ng/l vs. 7393.0 ng/l). We found that after accounting for age, renal function and CRP, older age and hs Troponin levels remained a strong predictor of mortality. The underlying mechanism for the troponin elevation in type 2 MI is usually multifactorial and often indicates myocardial necrosis rather than myocardial ischemia [117].

In our study we found out that the use of antibiotics or diuretics is associated with a higher two-year mortality. Several studies have implicated macrolides prescribed for patients with stable coronary heart disease are contributing to cardiovascular mortality (i.e., prolonged QT) that can lead to torsades de pointes. In addition, macrolides may result in an inflammatory cascade that increases plaque vulnerability over time, which leads to a higher risk of plaque rupture[118, 119]. Furthermore, it is likely that patients who needed antibiotics and/or diuretics were in significantly worse shape. One study investigating the influence of diuretics found that the use of loop

diuretics increased mortality among patients with suspected coronary artery disease, and a potential dose-response relationship was observed [120].

We found out that one of the most important possible causes of type 2 MI is anemia which can increase the injury for myocardium and in itself cause tachyarrhythmia as well that can also be part of pathophysiological pathway to type 2 MI. Systemic illnesses are also a very common reasons and have higher all-cause death. Type 2 MI is a heterogenous condition that may be caused by several factors that may be associated with reduced myocardial oxygen supply (due to hypotension, hypoxemia, anemia, coronary embolism or vasospasm) or to increased myocardial oxygen demand (due to hypertension and tachyarrhythmia) [20, 121]. So, in every distinct type 2 MI case the etiological factor may predispose different risk and specific treatment strategy [122]. Our findings show that renal dysfunction is a potential confounder for higher mortality in patients with type 2 myocardial infarction. There are several potential links between renal insufficiency and decreased long term survival. Renal functional impairment may cause increase in cardiac filling pressures and progressive ventricular dilation by sodium and water retention [123]. As such, careful monitoring of renal function is essential to prevent any negative outcomes in these patients.

Uncertainties regarding the most appropriate definition and treatment of type 2 MI due to supply-demand mismatch have contributed to inconsistent adoption in clinical practice. We found out that elevation of troponin shows significantly higher mortality risk. In literature, the prognostic value of elevated troponins has been demonstrated in both patients with STEMI and NSTEMI as well as non-cardiac pathology. Any detectable elevation at the time of presentation is of significance [124-127]. More favorable prognosis is associated with lower troponin values [128] and evidence suggest that even values below the 99th percentile upper reference limit, especially if in the higher ranges, may be of prognostic importance [129].

In our study we provide additional insights into the prognosis and in-hospital laboratory markers for long-term mortality in patients with type 2 MI. We found that after hospitalization for type 2 MI all-cause mortality after 2 years is 35,2%. This shows that type 2 MI is not a benign disease and has a high overall risk. Raphael et al. shows that after type 2 MI there is a high likelihood of a repeat of type 2 rather than type 1 MI (estimated rates 9.7% and 1.7% at 5 years) [122]. This is probably due to the same pathophysiological causes that are not treated or treated not completely on the first index event of MI. Lambrecht et al. showed that patients with type 2 MI or cardiac injury had significantly higher 3 year mortality than patients with type 1MI (62.2% and 58.7% vs. 31.7%) [130]. Chapan et al showed similar

results. After 5 years the patients all-cause mortality for type 2 MI was 62.5% vs. 36.7 for type 1 MI. Moreover, the majority of excess deaths in those with type 2 MI were due to non-cardiovascular causes [13].

The observed higher risk for elder people shows higher frailty and smaller physiological reserve in response to the main systemic illness. Moreover, in these patients who have some severe systemic illness, the occurrence of type 2 MI may show the higher degree of illness severity. That may be one of the reasons why not all the patients (73.9%) in our study underwent invasive angiography and only those who were the healthiest were referred for this investigation [131].

Paper II found out that every fifth patient that was treated at the hospital with the diagnosis of unstable angina has been underdiagnosed thus not receiving adequate treatment. There are studies stating that hs-cTn increases by more than 3 but less than 5 times may be explained by other conditions and those patients should not be diagnosed with NSTEMI [76]. Research has revealed that every fourth patient had an increase in cardiac troponin level from 3 to 5 times. Further analysis showed that all of them could be reclassified to the NSTEMI group due to having ischemic ECG changes, symptoms, and obstructive CAD confirmed by CAG. We suggest that the group of patients with hs-cTn increase by 3 to 5 times should be taken into care and investigated more closely to prevent underdiagnosing and undertreatment. This is particularly important because a nation-wide SWEDEHEART study showed that hs-cTnI level >30 ng/l is the cut point when invasive strategy improves outcomes [132].

The timely stratification of patients with symptoms suggestive of acute MI is crucial for providing fast, evidence-based treatment. In clinical practice it is very important to follow the 0/3h or 0/1-hour troponin algorithm. A recent meta-analysis of 32 studies and 30,066 patients presenting to the ED with chest pain compared the accuracy of the 0/1-, 0/2-, and 0/3-hour high-sensitivity cardiac troponin algorithms in ruling out AMI. It has found that ESC's 0/1- and 0/2-hour algorithms have higher sensitivity and negative predictive values when compared to ESC's 0/3-hour algorithm [133].

In paper III we presented the protocol of our randomized trial of patients with MINOCA The study focuses on determining possible etiology factors, the use of novel biomarkers, and the effects of different treatment strategies on MINOCA patients. MINOCA is not a benign disease, but rather a condition requiring clinical attention and intensive medical treatment. Although, previous meta-analyses have demonstrated that patients with MINOCA have a lower likelihood of death or cardiovascular events than those with MI with obstructive CAD (MI-CAD) [134, 135], MINOCA remains an unresolved

clinical issue, because completed prospective randomized clinical trials do not exist and evidence-based clinical guidelines for MINOCA are lacking.

In comparison with those with MI-CAD, the patients with MINOCA are more likely to be younger and female but less likely to have hyperlipidemia, although other cardiovascular risk factors are similar [134, 136] . The clinical factors predicting new MACE and death are also similar [137]. Data from a large registry showed comparable clinical outcomes for patients with MINOCA and those with MI-CAD [65], also for those at a young age [138]. Moreover, the onset of MINOCA shows a circadian and circaseptan variation with increased risk at early mornings and Mondays, similar to previous studies on MI-CAD [139].

High-sensitivity cardiac troponins are at least as prognostic in patients with MINOCA compared to MI-CAD [140]. Lower levels of total cholesterol and higher levels of creatinine are independent predictors for MACE in MINOCA [137]. Greater inflammatory activity indicated by biomarker concentrations are more common in MINOCA patients than in both MI-CAD patients and healthy controls [141]. However, new laboratory tests have not been analyzed in detail in MINOCA patients. In the current study, comprehensive laboratory evaluation will be performed including traditional and novel biomarkers, such as galectin-3 and MR-proADM. These latter tests have demonstrated prognostic potential in cardiovascular diseases (CVD). Elevated levels of galectin-3 are associated with an elevated risk of CVD and all-cause mortality in the general population [142]. Galectin-3 plasma levels may predict vascular dysfunction which leads to high systemic vascular resistances in post-myocardial infarction patients [143]. MR-proADM is associated with long-term mortality and heart failure and may be a marker for prognosis after ST-segment–elevation MI [144].

The most controversial issue is the treatment of MINOCA. Most drugs used for secondary prevention in patients with MI-CAD are aimed at atherosclerotic disease prevention which may be a minor problem in MINOCA. Therefore, the use of standard MI treatment protocols has been questioned. However, recent research demonstrated that patients with MINOCA are at risk for repeat infarction associated with progression of the underlying coronary arterial stenosis [145]. Some authors state that aspirin, statins and, in cases of vasospasm, calcium antagonists, should be administered routinely for MINOCA patients, since these would be of benefit for the underlying coronary plaque disease, coronary spasm and thromboembolism [22]. In our study patients will be randomized into two different treatment groups. Whereas there still are no completed randomized trials, conventional MI treatment is common in MINOCA patients.

Accordingly, in our study, the first group will receive conventional MI treatment with optimal doses of statin, ACEI/ARB, BB and DAPT. Based on recent evidence, a second group will receive only statins and ACEI/ARB, and in cases with vasospasm, CCB will be prescribed.

Paper IV presented a potent association between systemic microvascular perfusion at the level of the capillaries determined by sublingual videomicroscopy and the composite clinical endpoint of 30-day all-cause death and renal-replacement therapy in patients with CS complicating acute MI. Moreover, this study showed that microvascular perfusion parameters have stronger prognostic value than macrohemodynamic parameters for the combined clinical endpoint.

Prognostic implications of systemic microvascular perfusion parameters.

Restoration of hemodynamic parameters is the primary endeavor in the management of CS complicating acute MI. In addition to emergency revascularization of the culprit-vessel, pharmacologic treatment with vasopressor agents and/or inotropes or mechanical hemodynamic support are routinely required post-PCI to improve cardiac output and systolic blood pressure to ensure vital organ perfusion. A target mean arterial blood in the range of 60–65 mmHg or normal systolic blood pressure (>90 mmHg) is generally recommended, but this target blood pressure has not been validated in randomized clinical trials [146]. Notwithstanding the technical and clinical improvements in macrohemodynamic support modalities to maintain normal blood pressure, the mortality for CS complicated acute MI has not improved. This may be explained by perfusion abnormalities that extend beyond the macrocirculation. Accumulating evidence suggests that CS complicated acute MI not only involves perfusion abnormalities of the systemic macrocirculation, but also involves perfusion abnormalities of the systemic microcirculation [9, 10, 147, 148]. The present study compared the prognostic implications of macrohemodynamic parameters versus microvascular perfusion parameters. In the present cohort, we documented a potent association between systemic microvascular perfusion parameters and the combined clinical end-point, while the association between macrohemodynamic parameters and the combined clinical end-point was weaker. Our data shows that patients with impaired systemic microvascular perfusion parameters associate with an adverse clinical outcome, whereas patients with normal microvascular perfusion parameters show a favorable clinical outcome. More interesting, we demonstrate that normotensive cardiogenic shock patients with impaired microvascular perfusion have a significant higher risk for mortality or renal replacement therapy than

normotensive patients with normal microvascular perfusion. These observations indicate dissociation between macrohemodynamic and microvascular perfusion parameters and show that microcirculatory perfusion at the level of the capillaries is the profound determinant for clinical outcome after CS complicated acute MI, regardless of macrohemodynamic conditions.

Comparison with previous studies.

The observations in the this study confirm previous studies that microvascular perfusion parameters have distinct prognostic value in the setting of CS complicated acute MI. Den Uil and colleagues, as well as Jung and colleagues documented that abnormal PCD measured post-PCI is associated with adverse clinical outcome [7, 8]. The distribution of PCD in the present study is comparable with the distribution reported by den Uil and colleagues, which suggest inter-observer reproducibility of sublingual assessment in patients with CS complicated AMI. In addition, we demonstrate profound dissociation between macrohemodynamic parameters and microvascular perfusion parameters in the present cohort: a substantial proportion of normotensive patients show abnormal PCD or PPC. Previous studies documented dissociation between macrohemodynamic parameters and microvascular perfusion parameters [107, 147, 149]. This indicates that normal macrohemodynamic parameters not necessarily ensure perfusion, and thus oxygen exchange, at the microvascular level. The present study is the first to demonstrate that dissociation between macrohemodynamic parameters and microvascular perfusion parameters translates into meaningful prognostic value.

Clinical considerations

Although emergency revascularization is undisputedly associated with improved clinical outcome, the clinical benefit of potent vasopressors or mechanical hemodynamic support remains debated. A recent meta-analysis demonstrated that hemodynamic management of CS patients with epinephrine is even associated with a threefold increase in mortality[150]. This may be explained by observational studies involving patients with septic shock showing no improvement or even worsening in impaired microvascular perfusion after vasopressor therapy [151-153], and are supported by studies showing that increasing MAP>65 mmHg in septic shock patients does not improve oxygen consumption nor lactate levels nor renal function [154]. Moreover, the efficacy of hemodynamic support with intra-aortic balloon on microvascular perfusion remains to be established [10, 155]. The present study shows that microvascular perfusion parameters may be abnormal during

normotensive macrohemodynamic conditions and *vice versa*, and that microvascular perfusion parameters confer dominant prognostic value. Yet, contemporary clinical practice thrives solely on macrohemodynamic parameters for guidance of hemodynamic support therapy. Microvascular perfusion monitoring, in addition to macrohemodynamic monitoring, may enhance risk stratification of patients with CS complicating AMI and, more importantly, may direct appropriate treatment to those likely to benefit. In short, hypotensive patients with normal microvascular perfusion may benefit from mechanical or pharmacologic hemodynamic support, while studies suggest that this treatment strategy may negatively affect or does not affect patients with abnormal microvascular perfusion [152-154]. *Vice versa*, small reports suggest that normotensive patients with impaired microvascular perfusion may benefit from low–dose intravenous nitroglycerin infusion or levosimendan [156]. The time has come for large randomized trials involving microcirculation measurement to investigate the clinical benefit of a tailored approach in the management of CS complicated acute MI. Currently, there is one observational study in France that investigates skin capillary refill time, mottling and central-to-toe temperature difference in a cardiogenic shock population and asses their prognostic value [157].

STRENGTHS AND WEAKNESSES OF THE SCIENTIFIC WORK

The scientific work is based on a well-defined research question and a thorough literature review. The data is collected and analyzed in a systematic manner from the prevalence of the current situation and insights in the reasons for significant underdiagnosis. However, since there is big underdiagnosis of type 2 MI, the patient cohort was not very big. Moreover, the findings in retrospective analysis of type 2 MI were not compared to type 1 MI, which could give some more insights into the differences of these two diseases. In the microcirculation study only one method of SDF imaging was used. Due to technological issues, there was no possibility to investigate the microcirculation in the coronary vessels. The results of the MINOCA randomized study measuring coronary vessel microcirculation by CMR will be published soon.

CONCLUSIONS

1. There is a significant underdiagnosis of type 2 myocardial infarction in clinical practice.
2. Preventive medication like ACEi or statins decreases the mortality risk for type 2 MI patients. Increased awareness of elevation of creatinine and troponin could help to identify most vulnerable patients that need highest attention.
3. Significant number of patients with diagnosis of unstable angina could be reclassified to non-ST elevation myocardial infarction or myocardial infarction with non-obstructive coronary arteries.
4. There is a direct independent association of systemic sublingual microcirculation with clinical treatment outcomes in patients with acute myocardial infarction. There is a significant and independent link between the microvascular perfusion parameters PCD and PPC and the combined clinical endpoint of all-cause death and renal replacement therapy at 30-days follow up.
5. When disagreement occurs with macrohemodynamic parameters, microvascular perfusion parameters confer dominant prognostic value.

PRACTICAL RECOMMENDATIONS

1. During the treatment of cardiogenic shock microcirculation monitoring can help to identity high risk patients.
2. Troponin elevation distinguishes patients with elevated risk who should be extensively evaluated and given progressive preventive medication in order to limit the risk of adverse cardiovascular outcomes.
3. During the treatment of patients with unstable angina, significant amount of these patients could be reclassified to myocardial infarction which is either NSTEMI or MINOCA.
4. Patients with MINOCA should undergo extensive differential diagnostic algorithm and heart MRI can help identify the main cause of the disease.

FUTURE OBJECTIVES

There is a plan to establish a research lab to investigate these issues in our institution. There is a focus of investigation of microcirculation in type 2 MI and MINOCA patients. The data of patients with the diagnosis of MINOCA is planned to be published that will show the insights of pathophysiological mechanisms and medication therapy strategies effectiveness on long term survival. Moreover, a new project of investigating of cardiac injury and possible type 2 MI during non-cardiac surgeries for patients without diagnosed atherosclerotic disease by measuring the high sensitivity troponins before and after the surgery is established. It will allow to gain more knowledge into how implementation of simple diagnostic measures could identify high risk patients in clinical practice that could benefit of further cardiac diagnostic work-up and preventive medication.

Copies of publications included in the thesis.

FULL COPIES OF 4 PUBLICATIONS WILL BE ADDED

List of publications not included in the thesis.

1. *Giménez, M., Miller, P., Alviar, C., Diepen, S., Granger, C., Montalescot, G., Windecker, S., Maier, L., Serpytis, P.,* ***Serpytis, R****., Oldroyd, K., Noc, M., Fuernau, G., Huber, K., Sandri, M., Waha-Thiele, S., Schneider, S., Ouarrak, T., Zeymer, U., Desch, S., Thiele, H.* (2020). Outcomes Associated with Respiratory Failure for Patients with Cardiogenic Shock and Acute Myocardial Infarction: A Substudy of the CULPRIT-SHOCK Trial; **Journal of Clinical Medicine** 9(3), 860. https://dx.doi.org/10.3390/jcm9030860
2. Serpytis R, Puodžiukaitė L, Petrauskas S, Misonis N, Kurminas M, Laucevičius A, Serpytis P. Outcomes of a percutaneous coronary intervention versus coronary artery bypass grafting in octogenarians. ACTA MEDICA LITUANICA. 2018. Vol. 25. No. 3. P. 132–139. (1 autorius).
3. Serpytis, P., Navickas, P., Lukaviciute, L., Navickas, A., Aranauskas, R**., Serpytis, R**., et al. (2018). Gender-Based Differences in Anxiety and Depression Following Acute Myocardial Infarction. ***Arquivos Brasileiros De Cardiologia***, *111*(5), 676–683. http://doi.org/10.5935/abc.20180161
4. **Serpytis R**, Navickaite A, Serpytiene E, Barysiene J, Marinskis G, Jatuzis D, Petrulioniene Z, Laucevicius A, Serpytis P. "Impact of atrial fibrillation on cognitive function, psychological distress, quality of life and impulsiveness". **Am J Med**, 2017
5. Lurz P**, Serpytis R**, Blazek S, Seeburger J, Mangner N, Noack T, Ender J, Mohr FW, Linke A, Schuler G, Gutberlet M, Thiele H. Assessment of acute changes in ventricular volumes, function, and strain after interventional edge-to-edge repair of mitral regurgitation using cardiac magnetic resonance imaging. **Eur Heart J Cardiovasc Imaging** 2015.
6. Thiele, Holger, Ibrahim Akin, Marcus Sandri, Georg Fuernau, Suzanne de Waha, Roza Meyer-Saraei, Peter Nordbeck, et al. 2017. "PCI Strategies in Patients with Acute Myocardial Infarction and Cardiogenic Shock." ***New England Journal of Medicine*** 377 (25): 2419–32. doi:10.1056/NEJMoa1710261. (Kaip studijos tyrėjas).
7. Daškevičiūtė, Aurelija, Aurelija Navickaitė, **Rokas Serpytis**, and Pranas Serpytis. 2017. "Ūminė Plaučių Arterijos Trombinė Embolija:

Wells Ir Modifikuotos Geneva Skalių Bei D-Dimerų Koncentracijos Prognostinės Vertės Senyvo Amžiaus Pacientams" ***Sveikatos Mokslai*** 27 (2): 53–59. doi:10.5200/sm-hs.2017.025.

List of presentations

1. **Serpytis R**. *Cardiogenic shock: treatment options and outcomes.* International conference "Progress of ECMO in Lithuania". September 9, 2017.
2. **Serpytis R**. *Coronary Spasm*. Oral presentation. 6th International Meeting on Acute Cardiac care and Emergency Medicine. September 14-15, 2018, Vilnius.
3. Poster abstract „Myocardial infarction with non-obstructive coronary arterines treatment optimization trial: design and rationale" at 6th International Meeting on Acute Cardiac care and Emergency Medicine, 14-15d. September, 2018, Vilnius.
4. **Serpytis R.** Oral presentation „MINOVA – šiuolaikinė diagnostika ir galimas gydymas" at 1-sis jungtinis Lietuvos ir išeivijos gydytojų seminaras, 2021-02-26 (online).
5. **Serpytis R.** Oral presentation "Troponin T and I in Clinical practice". September 10-11, 2021, Vilnius, Lithuania.
6. Oral presentation „MINOCA study results overview„ at 7th Meeting on Intensive Cardiology and Emergency Medicine" on 2022-09-09.
7. Oral presentation "Mikrocirkuliacijos sutrikimai ir šiuolaikinė diagnostika kardiogeninio šoko atveju" at local meeting **"**Ūminių koronarinių sindromų ir skubios medicinos naujienos", 2017-05-26, Alytus, Lithuania
8. Oral presentation „Ką žinome apie MINOVA?" at local meeting „Išeminės širdies ligos gydymas – nuo prevencijos iki intervencijos" at Panevezio ligonine on 2022-11-25, Panevezys, Lithuania.
9. Poster presentation "Management of acute myocardial infarction in patients over 80 years old" at **"**Acute Cardiovascular Care 2019", on 2019-03-02 - 2019-03-04, Malaga, Spain.
10. **Serpytis R**, Puodziukaite L, Petrauskas S, Serpytis P.
11. Outcomes after percutaneous coronary intervention versus coronary art ery bypass surgery in octogenarians. Poster presentation. Acute Cardiovascular Care 2016. Lisbon, Portugal.

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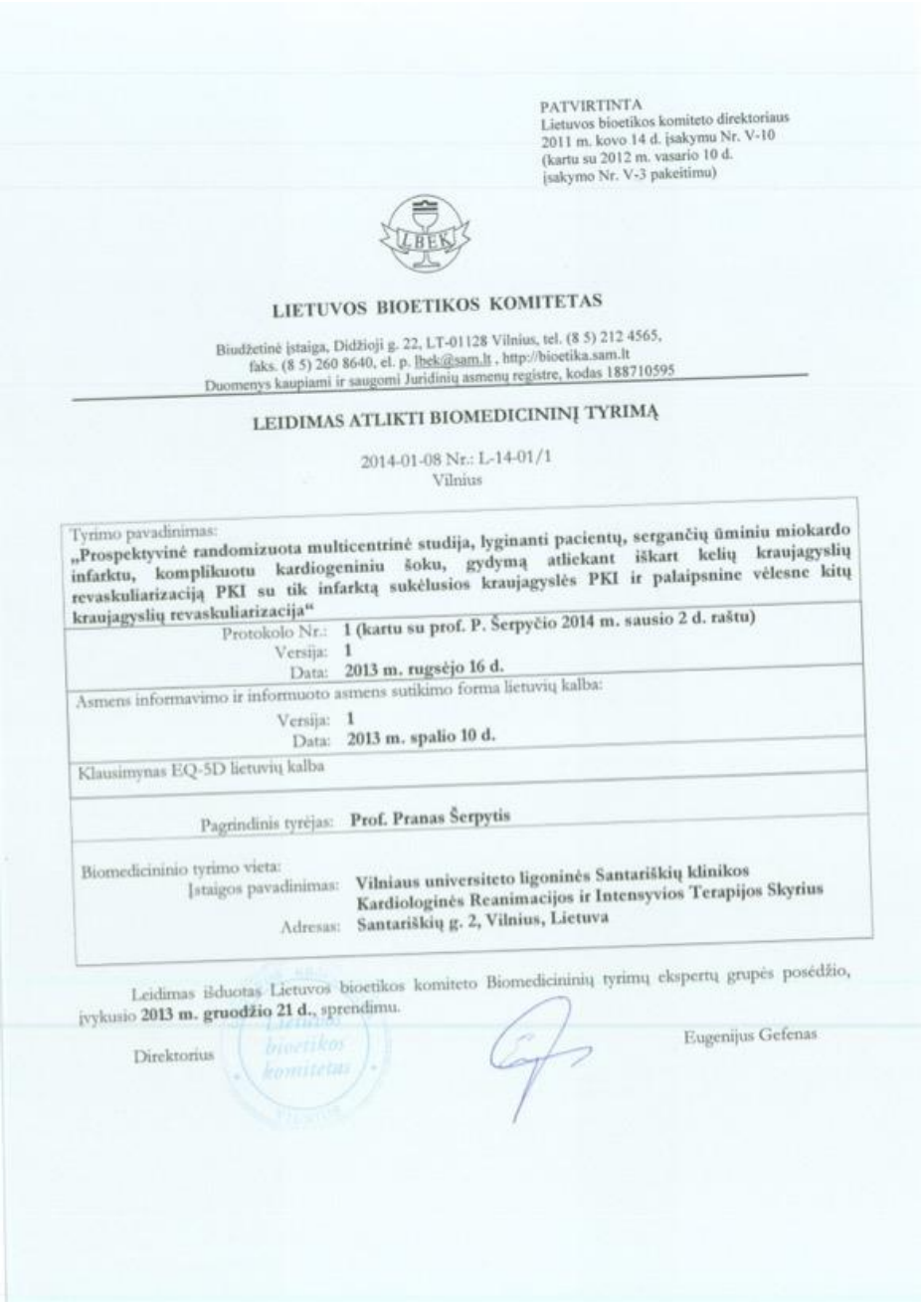
ANNEXES

Authorisations provided by the National Bioethics Committee and Vilnius regional Bioethics committee



PATVIRTINTA
Lietuvos bioetikos komiteto direktoriaus
2011 m. kovo 14 d. įsakymu Nr. V-10
(kartu su 2012 m. vasario 10 d.
įsakymo Nr. V-3 pakeitimu)

LBEK

LIETUVOS BIOETIKOS KOMITETAS

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LEIDIMAS ATLIKTI BIOMEDICININĮ TYRIMĄ

2014-01-08 Nr.: L-14-01/1
Vilnius

Tyrimo pavadinimas:
„Prospektyvinė randomizuota multicentrinė studija, lyginanti pacientų, sergančių ūminiu miokardo infarktu, komplikuotu kardiogeniniu šoku, gydymą atliekant iškart kelių kraujagyslių revaskuliarizaciją PKI su tik infarktą sukėlusios kraujagyslės PKI ir palaipsnine vėlesne kitų kraujagyslių revaskuliarizacija“

Protokolo Nr.: **1 (kartu su prof. P. Šerpyčio 2014 m. sausio 2 d. raštu)**
Versija: **1**
Data: **2013 m. rugsėjo 16 d.**

Asmens informavimo ir informuoto asmens sutikimo forma lietuvių kalba:
Versija: **1**
Data: **2013 m. spalio 10 d.**

Klausimynas EQ-5D lietuvių kalba

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Leidimas išduotas Lietuvos bioetikos komiteto Biomedicininių tyrimų ekspertų grupės posėdžio, įvykusio **2013 m. gruodžio 21 d.**, sprendimu.

Direktorius Eugenijus Gefenas

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LEIDIMAS
ATLIKTI BIOMEDICININĮ TYRIMĄ

2018-04-03 Nr.158200-18/4-1015-522

Tyrimo pavadinimas:

2 tipo miokardo infarkto diagnostikos optimizavimas ir gydymo strategijos sukūrimas

Protokolo Nr.:	2MI-I
Versija:	2.0
Data:	2018 03 20
Informuoto asmens sutikimo forma:	2.0 2018 03 19
Pagrindinis tyrėjas:	**Joseph Stephen Alpert**
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Leidimas galioja iki:	**2021 09 30**

Leidimas išduotas Vilniaus regioninio biomedicininių tyrimų etikos komiteto posėdžio (protokolas Nr. 158200-2018/4), vykusio 2018 m. balandžio 3 d. sprendimu.

Pirmininkas 

prof. Saulius Vosylius

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