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An Overview on Predictor of Heart Failure

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Abstract:

Background: Heart failure (HF) is a complex clinical syndrome resulting from structural or functional cardiac disorders that impair the ability of the heart to pump blood effectively. It is a leading cause of hospitalization and mortality worldwide. Identifying reliable predictors of heart failure is essential for early intervention, risk stratification, and optimizing patient outcomes. Several clinical, biochemical, and imaging markers have been investigated to predict the development or progression of heart failure in both at-risk individuals and patients with established cardiovascular disease.

Keywords: Heart Failure, Predictors, Left Ventricular Ejection Fraction, Natriuretic Peptides, Cardiovascular Risk Factors, Risk Stratification, Biomarkers, Prognosis.

Introduction:

Heart failure (HF) remains a major global health issue, affecting over 64 million people worldwide, with increasing prevalence driven by aging populations and improved survival from acute cardiovascular events **(1).** It is a complex clinical syndrome characterized by structural or functional cardiac abnormalities that impair the ability of the heart to fill or eject blood adequately **(2).** Despite advancements in pharmacological and interventional therapies, heart failure continues to be associated with high rates of hospitalization, reduced quality of life, and premature mortality **(3).**

Identifying early predictors of HF is crucial for guiding clinical decision-making, risk stratification, and the implementation of preventive strategies. Recent studies have emphasized the role of biomarkers such as NT-proBNP, troponins, and galectin-3, as well as imaging parameters like left ventricular ejection fraction (LVEF) and global longitudinal strain (GLS) in predicting incident HF **(4).** Comorbidities including diabetes mellitus, chronic kidney disease, atrial fibrillation, and obesity have also been strongly associated with increased risk of heart failure development **(5).**

Cardiac biomarkers such as troponin and BNP have established core use for the diagnosis of MI and HF, and also demonstrate prognostic value for long-term outcome. A recent study shows that combining serial measurement of traditional biomarkers (*e.g.*, NT-proBNP, hs-cTnT, aspartate transferase, alanine transaminase, lactate dehydrogenase and high-sensitivity C-reactive protein) gives an area under the curve of 0.85 for prediction of LV remodelling**(6)**.

1) Biochemical markers

A) Biomarkers of infarct size (Cardiac Troponin)

- **Physiology of the Troponin**

The troponin complex plays a critical role in regulating myocyte contraction. This complex consists of three subunits that regulate actin–myosin interaction: C, T and I. Troponin T binds the complex to tropomyosin,

which is wrapped around actin. Troponin I inhibits the actin–myosin interaction. Troponin C binds calcium thereby regulating actin–myosin inhibition. In the presence of an action potential, intracellular calcium concentration increases and calcium binds troponin C leading to a conformational change in troponin I and tropomyosin, thus removing the inhibition of the actin–myosin interaction. This process occurs in skeletal and cardiac muscle, but not in smooth muscle **(7)**.

Troponin C is expressed as one isoform that is the same in skeletal and cardiac muscle. The isoforms for troponin T and I are different between skeletal and cardiac muscle; this difference is exploited in clinical assays. One notable aspect of cTn physiology is that not all cardiac troponin T or I (cTnT or cTnI) is bound to the contractile apparatus. Less than 10 % is free in the cytosol, with cTnI consisting of a larger proportion than cTnT. This cytosolic pool may play an important role in cTn release in heart failure **(8)**.

As the isoforms of troponin T and I are specific to cardiac muscle, this has allowed the development of clinical assays for the quantitative assessment of cTnT and cTnI. While several companies make cTnI assays, the cTnT assay is strictly owned by Roche Diagnostics (Indianapolis, IN, USA). Most studies evaluating troponin in heart failure involved the use of early conventional assays **(9)**.

These assays are able to detect troponin at microgram levels. However, assays for both these subunits have gone through multiple generations, with each generation increasing the sensitivity to detect cTn at lower levels. This has led to the latest generation of hsTn assays, with the ability to detect troponin at nanogram and picogram levels. These assays by definition should be able to detect cTn in >50 % of healthy subjects and ideally >95 %. Both conventional and hsTn assays have demonstrated important prognostic value in AHF **(10)**.

- **Pathophysiology of Troponin in Heart Failure**

The exact mechanism for increased cTn levels in acute and chronic heart failure is unknown, but many mechanisms are believed to play a role. ACS is always a consideration and a Type I MI should be evaluated for in a patient presenting with AHF.Another possibility is a Type II MI from supply–demand mismatch. This can occur in patients both with and without ischaemic cardiomyopathy **(11)**.

While the primary mechanism is believed to be subendocardial ischaemia, other potential drivers could contribute, including elevated filling pressures, increased wall stress, endothelial dysfunction, tachycardia, arrhythmias, anaemia, and hypotension. Increased cardiomyocyte stretch and plasma membrane permeability can lead to release of cTn from the cytosolic pool. In addition, increased wall stress can lead to cardiomyocyte apoptosis, autophagy, and breakdown of the contractile apparatus releasing cTn. Inflammatory cytokines and neurohormones may be directly toxic to cardiomyocytes as proposed in stress-induced cardiomyopathy. Toxic substances such as alcohol, cocaine, methamphetamine or chemotherapy may lead to cTn release by various mechanisms. The exact mechanisms leading to cTn elevation in AHF are unknown, but multiple process including both ischaemic and non-ischaemic mechanisms may contribute **((12)**.

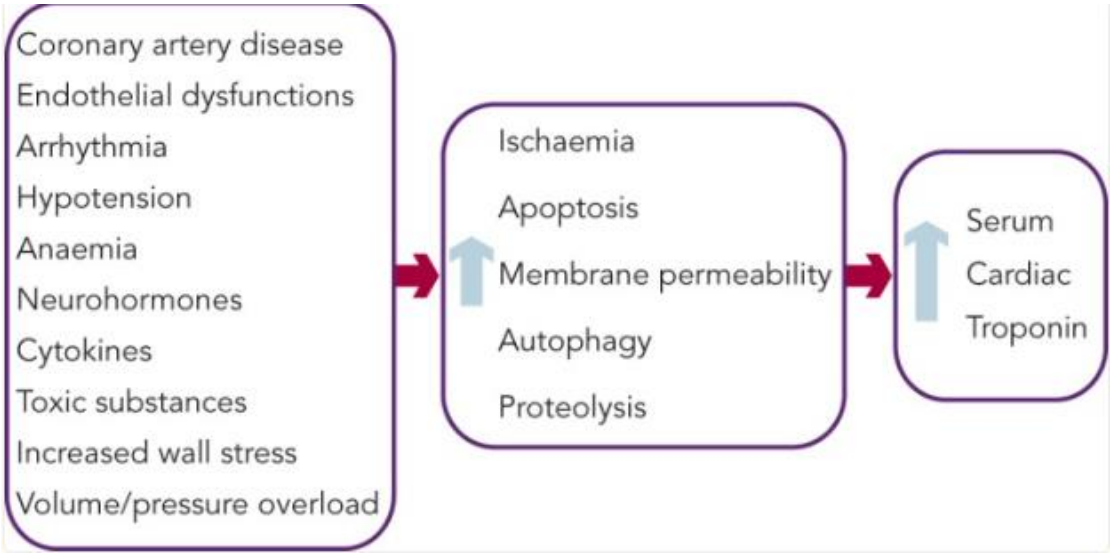

Figure 1: Different Pathophysiologic Processes that Can Lead to Elevated Troponin Levels (7)

While troponin level elevation is clearly not diagnostic of acute heart failure, there is overwhelming evidence demonstrating increased morbidity and mortality rates in patients presenting with AHF and an elevated cTn level. Studies have varied in the type of troponin assay used (I or T) as well as the cut-off values used to define a positive test. In addition, as discussed above, as cTn assays have been further refined, they are able to detect cTn at smaller quantities in the blood. Through all of these iterations of troponin assays, cTn has retained its prognostic ability **(13)**.

Cardiac troponin, a biomarker of choice in MI diagnostics, measured at plateau phase (48–72 h after MI symptom onset) is associated with MRI determined infarct size. Similarly, peak levels of creatine kinase (CK) and CK-MB are associated with infarct size on single-photon emission computed tomography. Several studies have shown the association of troponin or CK-MB level with MACE, including HF. Yet the association of peak troponin or CK-MB with HF has not been seen in all investigations**(6)**.

B) Natriuretic peptides

- **Basic Natriuretic peptide**

Natriuretic peptide (NP) levels are now widely measured in clinical practice and have been extensively assessed in cardiovascular research throughout the world. B-type natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP) are the most commonly used to diagnose heart failure (HF) **(14)**.

Atrial (A-type) natriuretic peptide (ANP) and BNP are cardiac hormones that bind to GC-A. ANP is synthesized mainly in the atria and BNP mainly in the ventricles **(15)**.

Both ANP and BNP are synthesized as pre-prohormones. ANP is primarily expressed and stored in the atrium. The primary stimulus for ANP release is atrial wall stretch resulting from increased intravascular volume. ANP is translated into prepro-ANP that is cleaved into pro-ANP, which is stored in intracellular granules. The plasma level of ANP in healthy individuals is approximately 20 pg/mL and is evaluated to be 10–100-fold higher in patients with HF. The half-life of ANP is approximately 2 min **(15)**.

The clearance of ANP mainly occurs in the lung, liver, and kidney, with extraction ratios reported to be 24%, 30%, and 35%, respectively. In the kidney, a good correlation was shown between creatine clearance and ANP clearance. BNP is minimally stored in granules in the ventricles and secreted directly in large bursts following stimulation **(14)**.

The plasma level of BNP in healthy individuals is approximately 3.5 pg/mL and is evaluated to be 100-fold higher in patients with HF. The half-life of BNP is approximately 20 min. Subsequently, the peptide is cleaved first into pro-BNP, then to biologically active BNP and the inactive NT-proBNP. BNP and NT-proBNP are secreted in equal concentrations, and the half-life of NT-proBNP is approximately 120 min. BNP clearance is dependent on neutral endopeptidase, and NT-proBNP clearance is dependent on direct renal filtration **(14)**.

In normal subjects, although the BNP concentration is much lower than the ANP concentration, the BNP concentration is markedly increased in patients with HF in proportion to its severity. Thus, the BNP concentration is increased to a much greater degree than is the ANP concentration **(16)**.

- **Natriuretic peptide role in HF**

1) Acute HF

Natriuretic peptides have a short half-life, so they are easily measured and provide quantitative markers of HF severity and prognosis, and they might be a useful guide to judging the success of therapy in acute HF. The goal of using natriuretic peptides in acute-care settings was to determine whether patients received adequate decongestive therapy and whether their risk of rehospitalization was reduced as much as was feasible during acute treatment **(17)**.

Natriuretic peptides at discharge are reflective of the achievement of a more stable hemodynamic state following treatment for acute HF, and levels measured at hospital discharge when compared to admission values, were likely more appropriately related to both HF rehospitalization and mortality **(18)**.

Measuring natriuretic peptide levels before discharge when optivolemic status has been achieved sets a baseline for continued longitudinal monitoring and further allows for individualized decision making about the timing, frequency and intensity of follow-up. Patients with lower natriuretic peptide values at the time of discharge and those who achieved greater relative reduction after acute HF treatment had substantially better prognoses than those who were released from acute care with higher concentrations **(19)**.

Patients with acute HF and with higher or nonfalling concentrations may merit close follow-up, including monitoring at home. Thus, evaluating relative modifications (%) based on each patient's plasma levels when stable (dry levels) may be more informative about the severity of intracardiac pressure/volume overload than using a single measurement. In this context, a practical approach would be to consider changes > 30% as being clinically relevant **(19)**.

2) Chronic HF

Diagnostic performance characteristics of natriuretic peptides in the ambulatory setting differ from those of the acute setting, because natriuretic peptide concentrations are generally lower in ambulatory patients

with HF and, thus, there is greater overlap with the normal range of values, especially in older patients. Additionally, comorbidities, such as atrial fibrillation, renal dysfunction, aging, and obesity, can all modify natriuretic peptide levels **(20)**

Despite these potential limitations, major clinical guideline authors recommended the use of natriuretic peptide assessment in the ambulatory setting with the highest recommendation and level of evidence, although guideline authors differ somewhat on the proposed diagnostic cut-points **(15)**.

Just as for diagnosis, establishing prognosis is a critical part of optimal HF management. Prognosis in HF varies substantially, and some more invasive or expensive therapies (such as mechanical cardiac-support devices or cardiac transplantation) are reserved for patients with the highest probability of poor outcomes. Although there are abundant prognostic markers that have been validated in HF, generally, natriuretic peptides have proved to be among the strongest single predictors of prognosis in patients with chronic HF **(15)**.

Natriuretic peptides have been validated as prognostic markers in both chronic HF with reduced EF (HFrEF) and HFpEF. Natriuretic peptides also predict the risk of incident HF in at-risk populations. Although BNP and NT-proBNP provide generally similar information, they may diverge after initiating treatment with sacubitril/valsartan, although during longitudinal treatment, both provide prognostic value **(21)**.

As in the case with diagnosis, natriuretic peptides are recommended for use in establishing prognosis in chronic HF by major society guidelines with the highest level of evidence. 2021 ESC Guidelines proposed that a plasma concentration of BNP < 35 pg/mL, NT-proBNP < 125 pg/mL, or MR-proANP < 40 pmol/L make a diagnosis of HF unlikely **(22)**.

C) Inflammation markers

There is growing evidence that prolongation or expansion of the post-infarction inflammatory response significantly contributes to LV remodelling and HF development. Numerous methods of inflammatory response quantification have shown promise in HF prediction. C-reactive protein level predicted the risk of adverse events after MI, including HF, in several studies. The neutrophil-to-lymphocyte ratio, an indicator of systemic inflammation, predicted MACE and HF in a meta-analysis of 14 studies **(23).**

Cytokines are strategic regulators of inflammation. In a study of 4939 patients with ACS, pro-inflammatory cytokine interleukin 6 (IL-6) was an independent predictor of MACE and HF. IL-32 is a relatively novel pro-inflammatory cytokine that induces the release of other inflammatory cytokines such as tumour necrosis factor-α, IL-1β, IL-6, IL-8, and IL-18. Xuan et al. showed that IL-32 is an independent predictor of cardiac death and HF among patients after MI **(24).**

D) Renal biomarkers

The estimated glomerular filtration rate (eGFR) is independently associated with HF risk after MI. Fox *et al*. used a creatinine-based MDRD equation for eGFR calculation to show that, after multivariate adjustments, the excess risk of HF attributable to renal dysfunction ranged from 30% to 90% depending

on CKD stage. Similar results were reported from the VALIANT study where the risk of HF rose by 10% for each 10 mL/min/1.73 m^2 decrease in eGFR**(25)**.

Cystatin C is a sensitive marker of renal impairment that, unlike creatinine, is not affected by age, sex, and muscle mass. In the SOLID-TIMI 52 study among patients with ACS, cystatin C provided incremental information for risk stratification, including HF hospitalization, independent of other biomarkers including eGFR (**26)**.

E) Biomarkers of fibrosis

Suppressor of tumourigenesis (ST2) is a member of the IL-1 receptor family that is involved in the process of myocardial remodelling and fibrosis. It has two isoforms: transmembrane ligand and soluble form. Binding of the soluble form (sST2) to IL-33 prevents the beneficial effect of this IL on the reduction of cell death and fibrosis. While several studies demonstrated the prognostic utility of sST2 testing in HF, there is less evidence for the predictive value of sST2 after MI. Among consecutive MI patients from the Mayo Clinic, sST2 elevation was independently associated with excess risk of death and HF. Patients in the upper tertial of sST2 had three-fold the risk of HF as compared with the lowest tertial **(27)**.

Galectin-3, a β-galactoside-binding lectin mainly secreted by activated macrophages, is also reflective of fibrosis and cardiac remodelling in response to myocardial injury. The American College of Cardiology/American Heart Association guidelines recommend measurement of both sST2 and galectin-3 for risk prediction in patients with HF. It has been suggested that an independent predictive value of galectin-3 also among unselected MI patients. In a prospectively enrolled incident MI cohort, galectin-3 was associated with increased risk of death and HF even after adjustment for MI severity, co-morbidities, and sST2 **(28)**.

F) Creatine Kinase

- **Physiology of creatine and phosphocreatine in cardiomyocytes**

Chemical energy in the form of ATP is produced from multiple substrates (principally long-chain fatty acids, lactate, and glucose), predominantly in the mitochondria via oxidative phosphorylation. To ensure that energy is readily available at sites of utilization, a phosphagen system is required, consisting in the reversible interaction of Cr and ATP under the control of CK enzymes **(29)**.

Tissue- and cell-specific CK isoforms are well known. At cardiac level, muscle-type CK and mitochondrial CK are the most represented. Mitochondrial CK catalyses direct transfer of a high-energy phosphoryl group from ATP to Cr to form PCr, acting as a highly mobile, short-term energy store, as it is smaller and less polar than ATP. The reverse reaction is catalysed by the cytosolic CK dimers and generates ATP; then, the free Cr diffuses back to signal the need for further ATP production **(30)**.

In addition to its role in ATP regeneration, PCr acts as membrane stabilizer. PCr may therefore promote the transition of the mobile domain of membranes into a structured phase, leading to a decreased rate of phospholipids degradation into lysophospholipids and lipid peroxidation. This second mechanism is

particularly relevant for cardiac function, since the PCr/Cr plays a protective role against ischaemic insults **(29)**.

- **Creatine deficiency in heart failure**

Decreased cardiac Cr content and total CK activity are observed in HF regardless of underlying aetiology, prominently in advanced stages. Additionally, low PCr is an early indicator of an energetic deficit and PCr/ATP ratio is associated with more severe HF symptoms, low contractile function, and myocardial structural remodelling, proving to be an excellent predictor of cardiovascular mortality in patients with dilated cardiomyopathy. Cr loss is likely to occur secondary to a reduced expression of the CrT. However, it is not completely clear to what extent the reduced PCr buffer activity contributes to the pathophysiology of HF and if a correction of this energetic deficit would prove beneficial **(31)**.

The functional role of high-energy phosphate metabolism in HF should be investigated focusing on the depletion of myocardial PCr and Cr levels. A way to achieve that condition could be by means of a pharmacological compound known to specifically reduce PCr and Cr in the heart, the β-guanidinopropionate. Specifically, β-guanidinopropionate is a Cr analogue that is taken up by the cardiomyocyte via the CrT and is then phosphorylated, causing the inhibition of CK reaction **(32)**

In normal heart, the depletion of PCr and Cr due to β-guanidinopropionate treatment impaired the capability of CK system to ensure high levels of sustained contractile function. In ischaemic condition, the β-guanidinopropionate-induced depletion of PCr (65%) and reduction of CK flux (75%) make the heart unable to overcome the stress of an acute myocardial infarction; specifically, this finding might be due either to the remaining intact myocardium not being able to face the acute haemodynamic stress or to the induction of fatal ventricular arrhythmias — or both **(32)**

However, chronic PCr and Cr depletion, obtained by β-guanidinopropionate treatment started after the recovery from coronary ligation, did not further impair myocardial performance, suggesting an adaptation of the chronically failing heart and highlighting the functional relevance of the PCr-CK system only in acutely induced HF. However, β-guanidinopropionate has many limitations such as off-target effects, slow and incomplete creatine depletion, and the ability to partially compete in the creatine kinase reaction **(33)**.

G) D-dimer

D-dimer, a specific degradation product of XIIIa-crosslinked fibrin, is an early marker of *in vivo* coagulation activation and thrombogenesis. Measurement of D-dimer plasma concentration is commonly used in the diagnosis of pulmonary embolism, deep vein thromboembolism, acute coronary syndrome, and acute aortic dissection. With respect to HF, increased D-dimer concentrations have been found in acute HF, and in outpatients; however, the prognostic significance of this finding has been scarcely investigated. In particular, unexplored is the possible prognostic role of D-dimer measurements in HF patients with different phenotypes **(34)**.

Other biomarkers

Matrix metalloproteinases (MMPs) are proteolytic enzymes that degrade collagen and other proteins of the extracellular matrix. After MI, MMPs regulate the remodelling process by facilitating extracellular matrix turnover and inflammatory signalling. MMP-8 and MMP-9 were shown to predict LV remodelling and adverse outcomes, including HF development**(25)**.

Clusterin is a protein that regulates complement activity, apoptosis, and lipid transport. Proteomic analysis of plasma from patients after the first anterior MI identified increased plasma levels of clusterin to be associated with LV remodelling. Whether clusterin is also associated with the risk HF after MI needs to be determined**(25)**.

The prognostic utility of serial biomarker measurement and multi-marker approach after MI was evaluated by Reinstadler *et al*., who measured several biomarkers as aspartate and alanine aminotransferases, high-sensitivity troponin T, N-terminal prohormone brain natriuretic peptide, lactate dehydrogenase, and high-sensitivity C-reactive protein daily for 4 days after admission for an MI **(35)**.

2) Genetic aspects

There is a paucity of data on genetic predictors of HF development after MI. A recent study using weighted gene co-expression network analysis identified genes BCL3, HCK, PPIF, S100A9, SERPINA1, and TBC1D9B to be involved in the inflammatory response, apoptosis, and HF development after MI **(36)**.

MicroRNAs are products of non-coding DNA transcription consisting of approximately 22 nucleotides that act as significant regulators of mRNA translation. In the heart, they control various processes including cardiac cell death, cardiomyocyte regeneration, and cardiac fibroblast transformation into cardiomyocytes. A study by Niu *et al*. recognized miR-142-3p as a contributor to HF after MI **(36)**.. Shah *et al*. identified lower concentrations of miR-17-5p, miR-20a-5p, and miR-106b-5p to be associated with a higher incidence of HF after MI **(37)**. Lakhani *et al*., found that miRNA-24 and 29a levels were reduced in patients with acute MI and low ejection fraction, whereas miRNA-34a, miRNA-208b, and miRNA-126 were increased in these patients **(38)**.

3) Imaging

A) Echocardiography

Echocardiography is a commonly used imaging method after MI. In regard to HF prediction, optimal timing of echocardiography is not well defined, as the early post-MI examination may underestimate systolic function due to myocardial stunning. Therefore, repeated echocardiographic examinations after MI are recommended **(39)**.

- **Systolic function**

Reduced LV ejection fraction (LVEF) is associated with the risk of HF development. A 5% decrease in LVEF determined by ventriculography performed during the MI hospitalization increases the risk of HF development after the hospital discharge by 12–18%. Similarly, a 5% decrease in LVEF evaluated by echocardiography 5–20 months after MI increases the risk of HF by 20% **(40)**.

The wall motion score index (WMSI) reflects wall motion abnormalities better than LVEF because compensatory hyperkinesia of non-affected regions may compensate for the impaired systolic function **(39)**.

Right ventricular (RV) dysfunction significantly contributes to HF development after MI**(25)**. The tricuspid annular plane systolic excursion (TAPSE) is the most commonly used parameter to evaluate RV systolic function. In patients after MI, RV dysfunction defined by TAPSE ≤ 14 mm was able to predict early cardiac events, including cardiogenic shock **(41)**.

However, TAPSE assesses only longitudinal contraction of RV and as such provides only partial information on RV function. Fractional area change reflects RV function better than TAPSE. In several studies among patients after MI, decreased fractional area change was associated with an increased risk of adverse events, including HF **(42)**.

- **Diastolic function**

Standard Doppler examination of transmitral flow provides valuable information in patients after MI **(43)**.

- **Left ventricular remodelling**

Left ventricular remodelling is commonly defined as a 20% increase in LV end-diastolic volume. Post-MI remodelling is exacerbated by a larger infarct size, transmural MI, microvascular obstruction, myocardial haemorrhage, and advanced age. In the contemporary era, almost half of patients after MI demonstrate LV remodelling on echocardiography within 1 year from MI. Among patients with LV remodelling, the risk of hospitalization for HF is 2.7 times higher than in those without LV remodelling **(44)**.

- **Speckle tracking echocardiography**

Speckle tracking echocardiography (STE) measures regional and global myocardial deformation. Global longitudinal (apico-basal) strain is the most used and is superior to LVEF measurement, especially in the early phases of systolic dysfunction. Ersbøll *et al*. found among MI patients with LVEF > 40%, global longitudinal (apico-basal) strain higher than −14 was associated with a five times higher risk of HF and 12 times higher risk of cardiac death **(45)**.

3D STE is a novel method offering more realistic and accurate models of LV than 2D STE **(46)**. Global area strain, one of the 3D STE parameters, combines both longitudinal and circumferential strains. Among patients after MI, global area strain is an independent predictor of MACE and HF hospitalization, superior to conventional 2D echocardiography parameters **(47)**.

- **Myocardial contrast echocardiography**

Myocardial contrast echocardiography (MCE) visualizes myocardial perfusion by intravenous or intracoronary infusion of microbubbles. MCE can distinguish reversible and irreversible ischaemia, thus detecting myocardial viability. Lack of perfusion signals caused by microvascular obstruction on MCE is consistent with the results of cardiac magnetic resonance **(39)**. To detect no-reflow, MCE should be ideally performed 24–48 h after coronary intervention for MI. In several studies, no-reflow after MI was an independent predictor of LV recovery and adverse outcomes including HF **(48)**.

- **Stress echocardiography**

Dobutamine stress echo-derived parameters such as infarction zone non-viability and ischaemia/infarction at a distance were identified as independent predictors of adverse outcomes, including HF, in patients 2 to 7 days after MI**(25)**.

B) Cardiac magnetic resonance

- **Infarct size**

Magnetic resonance imaging is currently the gold standard imaging modality for quantifying infarct size using late gadolinium enhancement. According to a meta-analysis of studies measuring infarct size by MRI or single-photon emission computed tomography in patients after STEMI, for every 5% increase in MI size, the risk of hospitalization for HF increases by 20%**(25)**.

On the other hand, a recent prospective study showed no additional long-term prognostic value of infarct size measured by MRI over LVEF in patients after non-STEMI. The difference in prognostic value in STEMI and non-STEMI may be explained by a different magnitude of myocardial damage **(49)**.

- **Microvascular obstruction**

Microvascular obstruction refers to the lack of perfusion in the coronary microcirculation, despite revascularization of the epicardial vessels. Microvascular obstruction can be identified as a hypointense core within the area of hyperenhancement on either early (referred to as early microvascular obstruction) or late gadolinium enhancement (late microvascular obstruction). Microvascular obstruction is associated with larger MI size and adverse remodelling. In a recent individual patient data meta-analysis, microvascular obstruction increase by 10% elevated the risk of hospitalization for HF by 80% and all-cause mortality by 114% **(50)**.

- **Intramyocardial haemorrhage**

If the microvascular injury after MI is severe and the integrity of microcirculation is compromised, extravasation of red blood cells into the myocardium can occur. Red blood cell extravasation is referred to as intramyocardial haemorrhage and can be detected by MRI as a hypointense zone within the MI core on T2* imaging or mapping. Several studies suggest that iron deposits from red blood cells trigger pro-inflammatory response and lead to adverse LV remodelling. Smaller studies in patients after STEMI suggested that myocardial haemorrhage was more closely associated with adverse outcomes, including HF, than microvascular obstruction **(51).**

- **Multiple scars**

A MRI substudy of the third Danish Study of Optimal Acute Treatment of Patients with ST-segment Elevation Myocardial Infarction (DANAMI 3) proved that multiple scars (characterized by late gadolinium enhancement in more than one myocardial areas remote from acute infarction area) were associated with almost three-fold risk of all-cause mortality and HF hospitalization after adjustment for clinical risk factors and MI size **(52)**.

C) Molecular imaging

Molecular imaging is an emerging method studying different phases of the post-MI period at a molecular level. The principle is based on the existence of specific tracers that bind to molecules of interest. Various methods of nuclear medicine have shown potential to predict adverse LV remodelling [e.g. tracers binding to MMP-2 or MMP-9 within the infarct zone, angiotensin-converting enzyme inhibitor (ACEi) and angiotensin receptor antagonist-based tracers, growth factor receptors, and $\alpha_v\beta_3$ integrin tracers]. Currently, data showing predictive value of these methods for HF prediction after MI are lacking **(53)**.

4) Parameters of coronary angiography

A) Thrombolysis in Myocardial Infarction Risk Index

Thrombolysis in Myocardial Infarction Risk Index (TIMI-RI) is an easily obtainable index that is calculated using 3 variables, age, heart rate (HR), and systolic blood pressure (SBP), which are universally available for all patients. This index was initially developed to predict mortality and HF following acute myocardial infarction but was later found to be a useful index for predicting short-term mortality in patients with acute HF **(54)**.

The Thrombolysis in Myocardial Infarction (TIMI) risk index (TRI) for ST-Elevation Myocardial Infarction (STEMI) is a simple risk score designed to be used at initial presentation to predict 30-day mortality in STEMI patients treated with fibrinolytics. The TRI is a continuous index derived from three readily available clinical variables and is calculated using the equation: (heart rate × $[age/10]^2$/systolic blood pressure). The TRI was originally developed in the Intravenous NPA for the Treatment of Infarction Myocardium Early (InTIME-II) study and validated in the TIMI 9 trial with high prognostic discriminatory capacity (c statistic 0.79) as a tool to triage STEMI patients **(55)**.

Furthermore, the TRI was found to have even better discriminatory capacity for predicting in-hospital mortality when validated in the general population of STEMI patients treated with reperfusion therapy, including fibrinolytic or primary percutaneous coronary intervention (PCI) **(55)**.

B) Myocardial Blush Grading

Myocardial perfusion can be assessed in many ways but the most studied of these is myocardial blush grade (MBG). MBG is determined on the angiograms made immediately after primary coronary angioplasty using the best projection angles to assess the myocardial region of the infarct-related coronary artery. Unlike TIMI flow grade, which evaluates blood flow along the main epicardial artery, MBG evaluates the microvascular patency of the distal capillaries perfusing the myocardium **(56)**

MBG is defined as follows: 0 – either no myocardial blush or persistent myocardial blush 'staining'; 1 – minimal myocardial blush or contrast density; 2 – moderate myocardial blush or contrast density, but less than that obtained during angiography of a contralateral or ipsilateral non-infarct-related coronary artery; and 3 – normal myocardial blush or contrast density that is comparable with that obtained during angiography of a contralateral or ipsilateral non-infarct-related coronary artery**(56)**.

It has been shown that a post-angioplasty MBG of 0/1 is a strong negative prognostic marker for mortality and MACE and, on the other side of the spectrum, an MBG of 2 or 3 is strong positive prognostic marker for survival among STEMI patients **(56, 57).**

C) Coronary Sinus Filling Time

Coronary sinus filling time can be used as a marker of microvascular dysfunction in patients with angina and normal coronaries. Patients with recurrent chest pain symptoms after one year follow up were found to have significantly high CSFT value compared with asymptomatic patients **(58)**.

CSFT (in frame count) started from the frame, in which left anterior descending artery (LAD) has completely opacified, and ended when the contrast reached to the coronary sinus origin. In fact, CSFT is a time mandatory for the contrast in order to transfer throughout myocardial capillaries and reach to the coronary sinus starting site. By dividing the CSFT in frame count into 15, second CSFT can be counted **(59)**.

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