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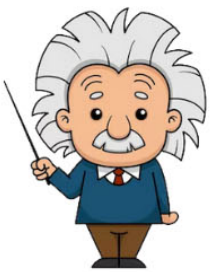




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ODDÍL 13. LÉKAŘSKÉ VĚDY

§13.1 CURRENT APPROACHES TO THE ASSESSMENT OF CARDIOMETABOLIC BIOMARKERS, TREATMENT OF MYOCARDIAL INFARCTION, AND PREDICTION OF POST-INFARCTION HEART FAILURE

(Koteliukh M.Yu., Kharkiv National Medical University)

Introduction

Acute myocardial infarction (AMI) is still one of the leading causes of cardiovascular morbidity and death. In patients with obesity or type 2 diabetes mellitus (T2DM), the disease often runs a more complicated course: metabolic disturbances, chronic low-grade inflammation, endothelial dysfunction and a shift in myocardial substrate use all play a part. These changes influence how much myocardium is lost to ischemia, how well it recovers, and whether heart failure develops later.

In this chapter we first discuss what is known about adropin, irisin, FABP4 and CTRP3 in cardiometabolic disease and whether they carry prognostic information. We then turn to pharmacoinvasive reperfusion in ST-segment elevation myocardial infarction and, finally, to our own model for predicting post-infarction heart failure. Where possible, we indicate whether a finding comes from experimental work, from clinical association studies, or from evidence that is already used in practice.

Main Discussion

1.1. Pathogenetic Role of Adropin and Irisin in Patients with Acute Myocardial Infarction, Obesity, and Type 2 Diabetes Mellitus

Adropin and irisin take part in the regulation of energy metabolism in obesity and T2DM [36]. Adropin is encoded by the energy homeostasis-associated gene



(ENHO) and is found in the liver, brain, coronary arteries, heart, endothelial cells and several other tissues [10; 14; 19; 99]. In experimental models its expression appears to be controlled, at least in part, by signal transducer and activator of transcription 3 (STAT3), a transcription factor that relays signals from interleukin and growth-factor receptors. In diabetes, STAT3 can increase hepatic ENHO expression and, as a result, circulating adropin [168].

Adropin affects carbohydrate, lipid and protein metabolism and modulates glucose-stimulated insulin secretion [150]. It improves glucose uptake and insulin signaling via Akt phosphorylation and glucose transporter 4 (GLUT4), and has been associated with lower tissue levels of tumor necrosis factor α (TNF-α) and interleukin 6 (IL-6) [20]. In adipose tissue and liver it regulates lipogenic genes and peroxisome proliferator-activated receptor γ (PPAR-γ). In experiments, adropin stimulated preadipocyte proliferation through extracellular signal-regulated kinase 1/2 (ERK1/2) and Akt, but inhibited their differentiation into mature adipocytes, lipid accumulation and the expression of adipogenic genes [37; 77]. An important partner in these processes is AMP-activated protein kinase (AMPK), a serine/threonine kinase that senses the energy state of the cell and is activated, among other things, by hypoxia. When ATP stores fall, AMPK switches off energy-consuming processes and turns on ATP-producing pathways. Low AMPK activity in the myocardium is accompanied by mitochondrial dysfunction [80].

Adropin also has immunological effects. Chen S. et al. (2017) [12] found that adropin deficiency was accompanied by a reduced number of regulatory T lymphocytes, which may matter in autoimmune disease. K. Sato et al. (2018) [11] showed that adropin can shift macrophages between pro- and anti-inflammatory phenotypes by increasing PPAR-γ expression, so this pathway probably underlies part of its anti-inflammatory action. W. Hu and L. Chen (2016) [103] reported that

patients with T2DM and lower adropin levels had worse renal function. Reduced adropin expression therefore seems to be a feature of several inflammatory conditions.

In the heart, adropin enhanced insulin signaling and reduced the inhibitory phosphorylation of pyruvate dehydrogenase [15]. By facilitating glucose oxidation, it may change myocardial fuel selection in insulin resistance. Whether this can be used therapeutically in humans is not yet known.

Zhang H. et al. (2017) [18] found a positive correlation between circulating adropin and high-density lipoprotein cholesterol (HDL-C), as well as an association with the reactive hyperemia index, a measure of endothelial function. Adropin may therefore have a role in the vasculature, although these data do not prove causality.

In multivariable analysis, low serum adropin was an independent predictor of coronary artery disease (CAD), and the more severe the clinical picture (stable angina, AMI), the lower the adropin level [28]. Low adropin has also been suggested as a marker of coronary involvement [22]. Lower concentrations accompanied more extensive angiographic atherosclerosis, with an inverse correlation to the SYNTAX score [13], and Akkaya H. et al. (2022) [26] found inverse associations with age and the Gensini score. Because all of these studies were observational, adropin should be regarded as a candidate marker of CAD burden rather than a proven causal factor.

The link between adropin and coronary disease may partly reflect its role in glucose and lipid metabolism. Adropin has been implicated in insulin resistance, impaired glucose tolerance and dyslipidemia in diabetes and obesity [20; 177]. In humans, serum adropin rose with dietary fat intake and fell with carbohydrate intake [111]. This does not mean, however, that changing the diet would modify cardiovascular risk via adropin.



Jurrissen T.J. et al. (2022) [176] showed that adropin reduced the number of filamentous actin (F-actin) stress fibers in endothelial cells and made the cells less stiff. When nitric oxide synthase was blocked, these effects disappeared, while a nitric oxide mimetic reduced the stiffness of smooth muscle cells. Nitric oxide signaling thus seems to mediate the vascular effects of adropin.

Circulating adropin is lower in patients with T2DM [187] and in those with AMI [27], which has led to its study as a marker of endothelial dysfunction in diabetes [166]. Zang H. et al. (2018) [188] also described an inverse relationship between adropin and body mass index (BMI) in T2DM. From such data, however, one cannot tell whether low adropin precedes metabolic and vascular damage or is a consequence of it.

Mushala B.A.S. and Scott I. (2021) [153] suggested that liver dysfunction lowers adropin expression and may thereby contribute to endothelial abnormalities and cardiovascular complications. According to Gao S. et al. (2019) [204], adropin suppresses cAMP-dependent protein kinase A, which reduces phosphorylation of the inositol trisphosphate receptor (responsible for calcium release from the endoplasmic reticulum) and of the cAMP-responsive element-binding protein. In primary hepatocytes, adropin may therefore reduce glucose production by inhibiting protein kinase A.

Adropin and irisin have been tested as markers for the early detection of T2DM and for distinguishing metabolically healthy obesity from obesity with diabetes [206]. Adropin expression declines with age [217]. Zhao Z.W. et al. (2018) [222] found lower adropin in patients with coronary slow flow, and the levels fell further as the angiographic picture worsened. None of these markers has yet been validated in independent populations.

Serum adropin was significantly lower in AMI than in stable angina (Zheng J. et al., 2019 [29]), and Ertem A.G. et al. (2017) [27] reported low levels in non-ST-

segment elevation myocardial infarction, suggesting that adropin might help to assess CAD severity. Adropin and endothelial nitric oxide synthase (eNOS) are both involved in the pathophysiology of AMI, and positive correlations between adropin, cardiac troponin I and eNOS have been described [105]. In a Cox regression analysis of recurrent myocardial infarction, the independent predictors were age, the number of affected vessels and HDL-C; adropin was not, although patients with lower levels had a higher risk of reinfarction [51].

Obesity is a well-known risk factor for cardiovascular disease (CVD) and heart failure (HF) [46; 95]. Data from CARDIA, MESA, EMPHASIS-HF, INSPIRE ME IAA and INTERHEART Latin America [8; 33; 134] show that it can contribute to both systolic and diastolic left ventricular (LV) dysfunction. Plasma adropin has been reported to rise significantly with HF severity, and BMI independently affects its circulating level. Obesity has also been associated with atrial fibrillation (AF) [156; 186].

In an experimental study, four weeks of adropin administration reduced the stiffness of mesenteric arteries [176]. This fits the idea that adropin regulates arterial stiffness through endothelial nitric oxide, and makes adropin signaling a possible target for treating arterial stiffening in obesity and T2DM. Berezin A.A. et al. (2023) [202] found that adropin levels predicted improvement in hemodynamic parameters during treatment with sodium–glucose cotransporter 2 (SGLT2) inhibitors.

In cultured cardiac cells, adropin lowered the expression of pyruvate dehydrogenase kinase 4 (PDK4), which normally inhibits pyruvate dehydrogenase (PDH), and so reduced inhibitory PDH phosphorylation [16]. This effect was lost after knockdown of GPR19, a putative adropin receptor, in H9c2 cells. GPR19 loss on its own raised PDK4 expression and lowered mitochondrial respiration. The authors further showed that the GPR19 pathway depends on p44/42 mitogen-



activated protein kinase (MAPK): when MAPK was blocked pharmacologically, adropin no longer affected PDK4. Adropin thus appears to regulate cardiac substrate use through a G protein-coupled receptor pathway that controls mitochondrial metabolism.

Adropin activates pyruvate dehydrogenase, the rate-limiting enzyme of glucose oxidation, and down-regulates PDK4, which inhibits it. In experiments, adropin treatment improved glucose tolerance, reduced insulin resistance and shifted energy production from fatty acids towards carbohydrates [207].

Gao S. et al. (2019) [204] studied adropin in hepatic glucose metabolism and found that it strengthened the intracellular pathways through which insulin controls hepatic glucose output. Adropin also reduced endoplasmic reticulum stress and hepatic c-Jun N-terminal kinase (JNK) activity, which may explain the improved hepatic insulin signaling. In obesity, then, the better glycemic control seen with adropin seems to depend partly on its effects in the liver.

Altamimi T.R. et al. (2019) [15] also found that, after adropin administration, insulin was still able to suppress fatty acid oxidation. Adropin improved cardiac performance and insulin signaling, inhibited fatty acid oxidation and markedly stimulated glucose oxidation, shifting the heart towards glucose as its main fuel.

Thapa D. et al. (2019) [17] gave adropin for three days to animals on a high-fat diet. Adropin altered the expression of a mitochondrial acetyltransferase, which changed the acetylation and activity of metabolic enzymes in favor of glucose use. Cardiac glucose oxidation increased despite the high-fat diet, and the authors saw this as a possible approach to treating diabetic cardiomyopathy.

In middle-aged and older adults, aerobic training increased circulating adropin, and higher levels went together with lower arterial stiffness and greater nitric oxide availability [19]. The study did not show, however, that adropin itself is responsible for the vascular benefits of exercise.

In summary, adropin is involved in metabolic regulation, endothelial function and myocardial substrate use. Most mechanistic data come from experimental models, and clinical studies so far report associations only. Prospective studies are needed to find out whether adropin adds independent prognostic information after AMI, especially in patients with obesity or T2DM.

Irisin: Roles in Metabolic Regulation and Cardiovascular Function

Irisin is a peptide hormone cleaved from fibronectin type III domain-containing protein 5 (FNDC5), a membrane protein whose expression rises with physical exercise; it is involved in thermoregulation and thermogenesis [90]. Geng Z. et al. (2019) [89] showed that a high-fat diet markedly increased body weight and the expression of hypertrophy-related genes in the heart. Irisin deficiency made the hypertrophy worse and enlarged cardiomyocytes, with more inflammatory cytokines, more oxidative stress and activation of the Janus kinase 2 (JAK2)/STAT3 pathway. Depleting irisin in cardiomyocytes amplified inflammation, whereas exogenous irisin reduced hypertrophy, cytokine expression and oxidative stress.

Irisin has attracted attention as a possible antidiabetic mediator because of its effects on adipose tissue and glucose homeostasis. One of these is the 'browning' of white adipose tissue, which increases energy expenditure. Circulating irisin has been associated with obesity, T2DM, CVD and other chronic conditions [65; 155; 175; 191].

The effects of irisin on the heart are not uniformly favorable. Ho M.-Y. et al. (2018) [83] found that irisin overexpression increased mitochondrial respiration and oxygen consumption, but also the production of reactive oxygen species (ROS) in the heart and in irisin-treated cardiomyocytes. Under hypoxia, irisin increased cardiomyocyte apoptosis and the expression of cleaved caspase-9. Pathway analysis showed changes in angiopoietin–Tie2, interleukin-8 (IL-8),



interleukin-13 (IL-13), transforming growth factor beta (TGF-β) and thrombopoietin signaling. Too much irisin may therefore increase mitochondrial stress and ROS formation and promote apoptosis in hypoxic cardiomyocytes. In another study [97], exercise enhanced mitochondrial fission and mitophagy via peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), and this was accompanied by an improvement in myopathic changes.

In patients with arterial hypertension, low irisin was associated with obesity-related cardiac changes such as reduced LV contractility and enlarged LV chambers [82]. Through the AMPK pathway, irisin may enhance fatty acid oxidation and glucose use in T2DM [117]; it also acts via AMPK to modify cardiomyocyte morphology in pressure-overload hypertrophy [112] and to improve endothelial function [116]. In experimental diabetes AMPK activity is reduced, and blocking AMPK abolishes the protective effects of irisin on mitochondria and apoptosis [114]. These metabolic pathways may be worth targeting in AMI and HF, but this has yet to be studied.

Akyuz A. et al. (2021) [32] found that in people with obesity, higher irisin levels went together with a greater fall in blood glucose and insulin after weight loss. Low irisin was also associated with macrovascular complications of diabetes.

El-Lebedy D.H. et al. (2018) [79] reported significantly lower irisin in patients with T2DM and CVD. In T2DM, irisin was related to the homeostatic model assessment (HOMA) index and BMI, and in CVD to triglyceride levels. The authors regarded irisin as an independent predictor of cardiovascular risk.

In T2DM, irisin correlated positively with BMI, waist-to-hip ratio, fasting insulin and HOMA index. It was elevated in obese people without diabetes and reduced in those with diabetes, so its level reflects both the anthropometric and the metabolic features of obesity and T2DM [65]. By contrast, Tang L. et al. (2019) [200] found lower irisin in overweight individuals and inverse associations with

waist-to-hip ratio, HOMA index and fasting insulin, pointing to a link with obesity-related insulin resistance. Khajebishak Y. et al. (2023) [128] also observed reduced irisin in obesity and T2DM and an inverse relationship between irisin and IL-6.

Irisin in Coronary Disease and Acute Myocardial Injury

Lower serum irisin was found in patients with coronary stenosis of more than 50%, and the lower the irisin, the more severe the narrowing [198]. Another study [62] looked at the relationship between irisin and major adverse cardiovascular events (MACE) after percutaneous coronary intervention (PCI).

Pan J.-A. et al. (2021) [30] found reduced serum irisin in CAD, with the lowest values in AMI, and irisin levels were related to outcomes after PCI. Ozturk D. et al. (2023) [158] proposed low irisin as a prognostic sign in ST-segment elevation myocardial infarction (STEMI); in their patients, irisin correlated with cardiac troponin I and the QT interval. These results justify further study of irisin as a biomarker in AMI.

Irisin is also low in HF, and low levels are associated with higher mortality, so it may have prognostic value; this, however, still needs clinical confirmation [192]. Patients whose AMI was complicated by HF had lower irisin, which correlated inversely with BMI, waist-to-hip ratio, cardiac troponin I, triglycerides and low-density lipoprotein cholesterol (LDL-C), and positively with LV ejection fraction (LVEF) and HDL-C. The authors therefore suggested irisin as a biomarker in AMI with HF [7]. Low irisin has also been reported in chronic HF, both with preserved systolic function and with LV systolic dysfunction [63].

Irisin behaves differently in obesity and in T2DM. After six months of metformin, the levels of regulatory peptides in patients with T2DM rose significantly from baseline, and irisin was proposed as a marker of the metabolic response to metformin [206]. In another study, metformin markedly reduced



adropin while increasing eNOS activity; on histology there was less inflammatory infiltration, myocardial fibrosis and necrosis [105].

Mechanisms Underlying the Cardioprotective Effects of Irisin

Part of the cardioprotective effect of irisin may be explained by its interaction with superoxide dismutase 2 (SOD2). In experiments, irisin increased SOD activity and restored the normal localization of SOD2 in cardiomyocytes, which suggests that it protects the myocardium from ischemic injury by supporting mitochondrial antioxidant defense [48; 119].

Irisin has also been shown to increase SOD1 phosphorylation and to reduce the expression of activated caspase-3 and annexin V. In cardiomyoblasts exposed to hypoxia it limited cell injury: lactate dehydrogenase release fell and there were fewer apoptotic cells. Irisin also reduced mitochondrial swelling and preserved mitochondrial integrity, so its protective effect probably depends, at least in part, on better mitochondrial function [113; 118].

Xin C. et al. (2020) [114] found that irisin reduced myocardial injury, improved cardiac function, increased ATP production and preserved mitochondrial membrane potential. In diabetes, AMPK signaling was impaired, and when it was blocked experimentally irisin no longer reduced infarct size or improved cardiac function, ATP production, membrane potential or apoptosis. AMPK activation therefore seems to be necessary for irisin to protect mitochondria in diabetes.

Irisin also significantly stimulated angiogenesis in infarcted myocardium and reduced cardiomyocyte apoptosis. In endothelial cells it increased phosphorylation in the extracellular signal-regulated kinase (ERK) pathway, and ERK inhibition abolished these effects. Irisin improved cardiac function and reduced infarct size, probably in part through this ERK-dependent proangiogenic action [115].

In macrophages, irisin reduced lipid accumulation in a concentration-dependent manner and markedly reduced apoptosis. These effects were associated

with inhibition of protein kinase R-like endoplasmic reticulum kinase (PERK) signaling and lower endoplasmic reticulum stress [6; 120]. Irisin has also been reported to decrease cardiac troponin C expression, and exogenous irisin increased heart rate and LV cardiac output in experimental settings [121; 122].

Overall, adropin and irisin are involved in metabolic regulation, endothelial function, inflammatory signaling and the response of the myocardium to ischemia. They may affect the development and course of AMI, especially in patients with obesity and T2DM, but their prognostic value in AMI with metabolic comorbidity has not yet been established.

1.2. The Role of Adipose Tissue Biomarkers (FABP4 and CTRP3) in the Development and Clinical Course of Acute Myocardial Infarction in Patients with Obesity and Type 2 Diabetes Mellitus

Adipose tissue releases many signaling molecules, among them fatty acid-binding protein 4 (FABP4) and C1q/tumor necrosis factor-related protein 3 (CTRP3), which act both locally and systemically. Changes in circulating adipokines accompany insulin resistance (IR), endothelial dysfunction and the progression of obesity. Adipokines form a heterogeneous group: some are secreted by abdominal fat itself, others come from different tissues and affect the growth and function of adipose tissue indirectly. Studying them helps to explain how obesity develops and why it is so closely tied to cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM), and may improve early diagnosis, prevention and treatment. Obesity, T2DM and atherosclerosis all involve chronic inflammation, and obese adipose tissue produces many inflammatory mediators that drive disease progression and metabolic disturbances. Adipokines can therefore serve as biomarkers of these processes and possibly as targets for prevention and therapy [5].



Fatty Acid-Binding Protein 4 (FABP4) in Metabolic and Cardiovascular Disease

Fatty acid-binding protein 4 (FABP4), also called adipocyte protein 2 (aP2), is produced mainly in adipose tissue. It helps to maintain glucose homeostasis and to coordinate metabolism between energy-storing tissues and internal organs, particularly under physiological stress. Under immunometabolic stress, however, FABP4 can promote metabolic and immune disorders, including diabetes and atherosclerosis [58].

Preclinical studies have linked circulating FABP4 with metabolic disorders [34]. Within adipocytes, FABP4 regulates lipolysis and adipogenesis by interacting with hormone-sensitive lipase and peroxisome proliferator-activated receptor gamma (PPAR-γ). During lipolysis, for example in fasting, it binds free fatty acids in the cytoplasm, limits their inhibitory effect on lipolytic enzymes and helps to move fatty acids out of the cell [87].

A genome-wide study of more than 500,000 people found an association between FABP4 and the risk of both T2DM and coronary artery disease (CAD) [107]. FABP4 is expressed mostly in adipocytes and macrophages, where it handles the uptake, intracellular transport and storage of fatty acids. Because it also influences the expression of lipid-metabolism genes, it affects metabolic regulation and energy balance more broadly, and is considered a mediator of insulin sensitivity, inflammation, lipid metabolism and coronary atherosclerosis [132].

Patients with obesity and T2DM have higher FABP4 levels than people without metabolic abnormalities [34; 35]. FABP4 correlated significantly with body mass index (BMI), triglycerides, insulin resistance indices, waist and hip circumference, interleukin-6 (IL-6) and high-density lipoprotein cholesterol (HDL-C), so it probably contributes to insulin resistance and inflammation in T2DM with obesity. Doi M. et al. (2011) [31] found raised FABP4 in CAD, and the association

was stronger in men under 65 than in older men. FABP4 may thus link obesity to coronary atherosclerosis, and measuring it could help in cardiovascular risk assessment.

Takagi W. et al. (2017) [56] studied FABP4 and prognosis in patients with stable angina after percutaneous coronary intervention (PCI), and their results suggest that measuring FABP4 may be clinically useful. Tsai H.-Y. et al. (2021) [61] likewise found FABP4 to be an independent predictor of adverse cardiovascular events after intervention in stable CAD.

Women usually have higher circulating FABP4 than men, which may reflect differences in the amount and distribution of body fat; FABP4 is also strongly and independently associated with obesity [66]. Elevated FABP4 has been linked to obesity, insulin resistance, T2DM, arterial hypertension, cardiac dysfunction and atherosclerosis [76; 81]. In obese patients its levels were significantly higher than in non-obese ones and correlated positively with waist circumference, blood pressure and insulin resistance.

After an oral glucose tolerance test or a high-fat meal, plasma FABP4 fell significantly while insulin rose [84; 93]. Rodriguez-Calvo R. et al. (2018) [85] studied FABP4 as a possible marker of myocardial steatosis in T2DM and examined how it promotes lipid accumulation and insulin resistance in cardiac cells.

At the cellular level, FABP4 is abundant in mature adipocytes and activated macrophages, where it binds fatty acids, carries them inside the cell and takes part in the regulation of lipid metabolism. Several studies have found close associations between FABP4 and obesity, diabetes and metabolic syndrome [94; 106; 110; 126].

Trojnar M. et al. (2019) [34] found elevated FABP4 in T2DM together with an association between FABP4 and endothelial function, suggesting that FABP4

directly affects the endothelium in diabetes. In the study by Wang H. et al. (2021) [190], higher serum FABP4 in T2DM went together with lower insulin sensitivity, higher insulin secretion and higher fasting glucagon. Laryushina Y. et al. (2020) [205] also reported raised FABP4 in diabetic patients at high cardiovascular risk. Among men with T2DM, high plasma FABP4 was associated with higher cardiovascular mortality [167]. FABP4 has also been related to subclinical coronary atherosclerosis in T2DM [61] and studied as a prognostic marker in acute coronary syndrome [60].

Obesity contributes substantially to the development and progression of heart failure (HF) [95]. Circulating FABP4 has been associated with left ventricular (LV) hypertrophy and with systolic and diastolic dysfunction [160; 178]. Fuseya T. et al. (2014) [81] found an inverse association between FABP4 and indices of LV diastolic function, and in multivariable linear analysis FABP4 independently predicted LV mass. In overweight and obese women, FABP4 was independently associated with LV remodeling parameters [86].

Jeinsen von B. et al. (2020) [199] found that higher FABP4 went together with a lower LV mass index and higher N-terminal pro-B-type natriuretic peptide (NT-proBNP). The inverse relation with LV mass index was stronger at low FABP4 concentrations, and the positive relation with NT-proBNP was stronger at higher NT-proBNP levels.

In CAD, FABP4 has been associated with LV dysfunction and impaired myocardial perfusion [199]. Engeli S. et al. (2013) [86] found a significant independent relationship between serum FABP4 and LV mass in overweight and obese women, and patients with high FABP4 had worse LV systolic and diastolic function. Liu M. et al. (2013) [57] showed that rising FABP4 accompanied worsening LV function in non-obese patients admitted with acute decompensated HF. FABP4 was significantly higher in HF, the association became stronger as HF

became more severe, and a direct correlation with LV ejection fraction was also described.

More recent work shows that FABP4 is also expressed in cardiomyocytes, and that its overexpression may promote cardiac hypertrophy by activating extracellular signaling pathways [47]. Conversely, FABP4 deficiency in experiments was associated with better LV function [73].

Since FABP4 is related to atherosclerosis and cardiac dysfunction, it may be useful as a cardiovascular biomarker. Furuhashi M. et al. (2016) [173] studied how omega-3 polyunsaturated fatty acids affect FABP4. In vitro, omega-3 fatty acids suppressed adipocyte differentiation and lipid accumulation and lowered FABP4 expression. In patients with dyslipidemia, ethyl esters of eicosapentaenoic and docosahexaenoic acids reduced circulating FABP4, probably by suppressing its expression and secretion by adipocytes, and this may be one of the ways omega-3 fatty acids benefit the cardiovascular system. In another study, Furuhashi M. et al. (2015) [23] found that FABP4 decreased during treatment with angiotensin II receptor blockers.

Because of its role in metabolism, FABP4 is also a possible therapeutic target in CVD and HF, and several synthetic FABP4 inhibitors have been developed [52]. BMS309403, a small molecule that prevents fatty acids from binding to FABP4 [55; 164], protected against insulin resistance, diabetes, fatty liver disease and atherosclerosis in preclinical studies. Another inhibitor, HTS01037, dampened proinflammatory macrophage responses [210], which suggests a use in inflammation-related disorders. Neutralizing antibodies against circulating FABP4 are also being developed to improve insulin sensitivity and glucose homeostasis [203].

Furuhashi M. et al. (2015) [174] studied 12 weeks of sitagliptin in patients with T2DM. Sitagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, increases the



availability of glucagon-like peptide-1 (GLP-1), and during treatment circulating FABP4 decreased. Experiments with recombinant DPP-4 and DPP-4 inhibition showed that sitagliptin probably lowers FABP4, at least in part, by directly suppressing its expression and secretion in adipocytes.

Experimental data [196] support FABP4 inhibition as a possible treatment for metabolic and cardiovascular disorders, but the efficacy and safety of FABP4 inhibitors in patients still have to be shown. If they are, these drugs could widen the options for treating insulin resistance, diabetes and atherosclerosis.

Apart from its role in metabolic syndrome, FABP4 deserves study as a biomarker of cardiovascular disease, including AMI in patients with metabolic disorders.

C1q/TNF-Related Protein 3 (CTRP3): Inflammatory Regulation and Cardioprotection

CTRP3 belongs to the C1q/tumor necrosis factor-related protein family [137] and takes part in regulating inflammation, including monocyte responses. It inhibits Toll-like receptor (TLR) and nuclear factor kappa B (NF-κB) signaling and reduces the production of interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α), and in this way may damp down the inflammation that accompanies obesity and T2DM. Inflammation is one of the main mechanisms behind both T2DM and atherosclerosis [59; 194; 201]. Petersen P.S. et al. (2016) [108] examined the immunomodulatory role of CTRP3 in the systemic, chronic inflammation associated with insulin resistance and obesity.

When CTRP3 expression was increased, the levels of C-reactive protein, TNF-α, IL-6, CD40 and CD40 ligand (CD40L) fell significantly (Chen L. et al., 2019 [53]). CTRP3 overexpression improved cell viability, reduced lactate dehydrogenase release and markedly reduced apoptosis caused by oxidized low-density lipoprotein (ox-LDL). It also increased the phosphorylated forms of

phosphoinositide 3-kinase (p-PI3K), Akt (p-Akt) and endothelial nitric oxide synthase (p-eNOS), that is, it activated the PI3K/Akt/eNOS pathway. Blocking this pathway with LY294002 or L-NAME weakened the protective effect, so CTRP3 probably counteracts ox-LDL-induced inflammation and endothelial dysfunction through PI3K/Akt/eNOS.

Mononuclear immune cells are involved in atherosclerosis, which underlies most coronary artery disease. Gene expression in circulating mononuclear cells may be related to serum CTRP3, so these cells may help to regulate its level. Both Wolf R.M. et al. (2015) [139] and Deng W. et al. (2015) [189] found lower serum CTRP3 in obese than in non-obese individuals.

Alyahya A.M. et al. (2018) [21] found markedly lower CTRP3 in CAD, and the level fell further as the disease became more severe. This may reflect the participation of CTRP3 in the inflammatory and metabolic mechanisms of atherosclerosis.

Choi K.M. et al. (2014) [109] found reduced CTRP3 in stable CAD and in AMI. CTRP3 correlated inversely with blood glucose and high-sensitivity C-reactive protein and positively with HDL-C and adiponectin.

The relationship between CTRP3 and diabetes or obesity seems to differ between men and women, possibly for hormonal reasons, although the mechanism is not clear. Wagner R.M. et al. (2016) [214] found that obesity was associated with higher CTRP3 in men but significantly lower CTRP3 in women. For this reason, sex should be analyzed as a separate variable in studies of CTRP3 and cardiometabolic disorders.

Moradi N. et al. (2020) [64] and Wolf R.M. et al. (2015) [139] found that low CTRP3 was associated with a higher risk of CAD and T2DM, which suggests a role in the metabolic disturbances underlying both. Kratochvilova H. et al. (2020) [70] reported reduced serum CTRP3 in CVD and reduced CTRP3 messenger RNA



(mRNA) expression in epicardial adipose tissue of patients with CAD and T2DM, so altered CTRP3 expression may contribute to cardiovascular complications of diabetes.

Matloch Z. et al. (2022) [72] also found significantly lower CTRP3 mRNA in epicardial fat of patients with CAD and T2DM, while TNF-α and IL-6 gene expression did not differ. Reduced CTRP3 in epicardial fat may therefore add to the risk of atherosclerosis in these patients. Mohamadinar M. et al. (2020) [193] found inverse correlations between CTRP3 and BMI, insulin, the homeostatic model assessment (HOMA) index, IL-6, TNF-α and transforming growth factor beta (TGF-β), and a positive correlation with adiponectin.

In experimental diabetes, CTRP3 expression is reduced. CTRP3 overexpression lessened oxidative stress and inflammation, reduced cardiomyocyte death and improved cardiac function through activation of AMP-activated protein kinase (AMPK) and protein kinase B (Akt) [67]. In HF, circulating CTRP3 is reduced, and the more severe the HF, the lower the level [43].

The Role of CTRP3 in Post-Infarction Remodeling

Yi W. et al. (2012) [45] showed experimentally that CTRP3 expression in adipocytes dropped sharply one day after AMI and then gradually recovered. Plasma CTRP3 also fell significantly, reaching its lowest level about three days after infarction. CTRP3 expression and secretion therefore change over the course of post-infarction remodeling. The authors suggested that endogenous CTRP3 helps to regulate myocardial repair and that recombinant CTRP3 might be used therapeutically after AMI.

In the same work [45], CTRP3 administration improved survival, increased LV ejection fraction and lowered LV end-diastolic pressure. Restoring CTRP3 to physiological levels improved both systolic and diastolic LV function. The authors

proposed that preventing the post-infarction fall in CTRP3, or giving it exogenously, might help to form stable, functional blood vessels.

AMI triggers a time-dependent immune response in which monocytes drive inflammation and influence myocardial repair, which is why the anti-inflammatory properties of CTRP3 are of interest. After AMI, monocyte numbers rose for a short time, and their phagocytic and migratory activity increased at about day three. CTRP3 modulated these monocyte responses and prevented the rise in inflammatory cytokines, particularly IL-6. CTRP3 thus takes part in the regulation of post-infarction inflammation and may support myocardial repair [69].

CTRP3 is regarded as a potentially cardioprotective adipokine because it is proangiogenic, antiapoptotic and antifibrotic. In experimental models, it gradually reduced phosphorylation of cardiac troponin I and increased cardiomyocyte contractility and myofilament sensitivity to calcium (Ca^{2+}), so it may act as an endogenous calcium sensitizer [44].

After AMI, CTRP3 administration was also associated with better cardiac function, less interstitial fibrosis and fewer myofibroblasts. CTRP3 modulated the expression of alpha-smooth muscle actin (α-SMA) and of profibrotic molecules induced by TGF-β1, increased AMPK and Akt phosphorylation, and limited cardiac fibrosis by inhibiting myofibroblast differentiation and extracellular matrix production [68].

In short, FABP4 and CTRP3 both take part in the pathogenesis of cardiometabolic disorders and may affect the development and course of AMI in obesity and T2DM. FABP4 is associated with metabolic dysregulation, inflammation, atherosclerosis and myocardial dysfunction, whereas CTRP3 shows anti-inflammatory, antiapoptotic, proangiogenic and antifibrotic effects in experimental studies.



1.3. Pharmacoinvasive Strategy for the Treatment of ST-Segment Elevation Myocardial Infarction

Not every patient can undergo percutaneous coronary intervention (PCI) in time, and for some the interval from first medical contact to balloon inflation is long. Delayed PCI in acute coronary syndrome (ACS) increases the rate of complications, including fatal ones, both early and late in the hospital course of acute myocardial infarction (AMI) [129; 208].

Studies comparing mortality after AMI in women and men have given conflicting results [98; 123]. One study [4], however, found marked sex differences in in-hospital complications, especially when primary PCI was performed more than six hours after symptom onset. Women had a more severe course: acute left ventricular failure was diagnosed 37.2% more often, rhythm and conduction disturbances 66.2% more often, and recurrent myocardial infarction 60.2% more often than in men ($p < 0.05$). Mortality after infarction was 2.7 times higher in women when primary PCI was performed more than six hours after symptom onset ($p < 0.001$), although the groups were comparable in comorbidities, treatment and the timing of PCI.

Hrebenyk M.V. and Levchyk O.I. [1] showed that in patients with arterial hypertension and diabetes mellitus the post-infarction period is marked by potentially life-threatening complications: cardiogenic shock, cardiac asthma, acute left ventricular failure and pulmonary edema. These are often accompanied by myocardial proarrhythmic activity and conduction block. PCI significantly reduced adverse events in the acute phase, including rhythm and conduction disturbances, severe acute heart failure (Killip class III–IV) and mechanical complications, and lowered the incidence of early post-infarction angina. One-year survival was considerably higher in patients who underwent invasive revascularization than in those who did not.

A multicenter study [92] of 7,244 patients with ST-segment elevation myocardial infarction (STEMI) from 29 reperfusion centers in Sweden, Iceland and Denmark compared aspiration thrombectomy followed by primary PCI with primary PCI alone. One-year mortality was 5.3% and 5.6%, respectively, and rehospitalization for reinfarction occurred in 2.7% of patients in each group. Routine aspiration thrombectomy before primary PCI therefore did not reduce all-cause mortality or the composite of death, rehospitalization for myocardial infarction and stent thrombosis at one year [133].

In another study of 10,732 patients with STEMI undergoing primary PCI, thrombectomy did not lower the 180-day risk of cardiovascular death, reinfarction, cardiogenic shock or New York Heart Association (NYHA) class IV heart failure compared with PCI alone, but it was associated with more strokes within 30 days [124].

According to the Seattle Angina Questionnaire, patients with coronary artery disease (CAD) were clinically better 12 months after coronary stenting: angina functional class improved, attacks became less frequent, they needed less nitroglycerin, left ventricular systolic function improved and quality of life was higher. A lower risk of cardiac complications after stenting was associated with lower total cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL-C) and atherogenic index, and with higher high-density lipoprotein cholesterol (HDL-C) on adequate statin therapy [3].

Clopidogrel and ticagrelor differed in their effect on platelet aggregation. Clopidogrel did not achieve the desired inhibition of spontaneous aggregation, whereas with ticagrelor platelet activity came close to reference values. Both regimens suppressed aggregation after PCI, but ticagrelor inhibited arachidonic acid- and adenosine diphosphate-induced aggregation 4.2 and 3.0 times more strongly than clopidogrel. Tests with adrenaline and collagen showed the same



tendency, and ristocetin-induced aggregation decreased only with ticagrelor. Platelet hemostatic activity was most strongly suppressed on days 2–3 after PCI in AMI patients on dual antiplatelet therapy with acetylsalicylic acid and ticagrelor [2].

Clinical Trial Evidence for Pharmacoinvasive Reperfusion

The Strategic Reperfusion Early After Myocardial Infarction (STREAM-1) trial asked whether early fibrinolysis followed by coronary intervention could keep its benefit in patients for whom timely primary PCI was not possible. In the pharmacoinvasive arm, patients received a fibrinolytic with enoxaparin, clopidogrel and aspirin and then underwent catheterization within 6–24 hours; if reperfusion had not occurred within 90 minutes of fibrinolysis, rescue PCI was performed. In everyday practice, many patients cannot be reperfused within the recommended 90–120 minutes of first medical contact [25].

STREAM-2 compared a modified pharmacoinvasive strategy with routine primary PCI in patients over 60 years of age who presented with STEMI within three hours of symptom onset. In the pharmacoinvasive group, half-dose tenecteplase was given as early as possible before transfer to a PCI-capable center; the primary PCI group received standard care. The primary efficacy endpoint was the 30-day composite of death, congestive heart failure, shock or reinfarction, and the main safety endpoints were intracranial hemorrhage, stroke and major extracranial bleeding [24].

The Clopidogrel as Adjunctive Reperfusion Therapy–Thrombolysis in Myocardial Infarction trial tested whether clopidogrel added to standard fibrinolytic therapy was effective and safe. The primary endpoint was an occluded infarct-related artery on predischarge angiography, or death or reinfarction before angiography; in patients who did not undergo angiography, it was death or reinfarction by day 8 or discharge, whichever came first. Major bleeding was the main safety endpoint. The results supported clopidogrel as part of pharmacological reperfusion in STEMI [180].

In the trial of fondaparinux in STEMI [220], the drug reduced the 30-day composite of death or reinfarction and compared favorably with unfractionated heparin. In patients who did not undergo primary PCI, fondaparinux lowered mortality and reinfarction without increasing bleeding or stroke.

Both mechanical revascularization and fibrinolysis therefore have a place in restoring coronary flow in myocardial infarction. Which strategy is better depends on the clinical situation and on how long treatment is delayed; fibrinolysis remains an important option where PCI-capable centers cannot be reached in time.

Glycemic Management During Myocardial Infarction in Patients with Diabetes

DIGAMI-1 enrolled 620 patients with diabetes mellitus and AMI: 306 received an insulin–glucose infusion followed by multidose subcutaneous insulin for at least three months, and 314 received conventional treatment. One-year all-cause mortality was significantly lower with intensive insulin therapy (18.6% vs. 26.1%; relative reduction 29%; $p = 0.027$) [141].

DIGAMI-2, with 1,253 patients with AMI and T2DM, did not confirm that starting long-term insulin immediately improves survival compared with conventional treatment when glycemic control is similar. Insulin-based therapy also did not reduce nonfatal myocardial infarction or stroke. Blood glucose, however, was a strong independent predictor of long-term mortality [142].

In the trial of reviparin and metabolic modulation in Acute Myocardial Infarction Treatment Evaluation, which included about 20,000 patients with STEMI, reviparin reduced death, reinfarction and stroke during the first seven days [221].

Thiazolidinediones (glitazones) should be used with caution in patients with AMI and heart failure, since they cause fluid retention, which can worsen heart failure and lead to rehospitalization [100].



In the UK Prospective Diabetes Study (UKPDS), metformin was associated with lower all-cause mortality, diabetes-related mortality and risk of myocardial infarction, although glycemic control was similar to that achieved with other glucose-lowering drugs [209]. The benefit persisted during ten years of post-trial follow-up [101].

In the Study on the Prognosis and Effect of Antidiabetic Drugs on Type 2 Diabetes Mellitus with Coronary Artery Disease (SPREAD-DIMCAD), patients with T2DM and cardiovascular disease had fewer cardiovascular complications on metformin than on glipizide [78; 96].

The cardioprotective action of metformin may be partly explained by suppression of protein synthesis in cardiomyocytes, a decrease in cardiac mass and lower expression of prohypertrophic cytokines [49]. Metformin also reduces oxidative stress and inflammation, directly and indirectly: it lessens cellular metabolic overload, suppresses tissue inflammation related to insulin resistance and modulates monocyte activity [42]. It inhibits proinflammatory macrophage responses and promotes their shift to an anti-inflammatory phenotype [211]. Its anti-inflammatory effect is associated with reduced oxidative metabolism [182], and the fall in reactive oxygen species may involve inhibition of protein kinase C and of mitochondrial respiratory chain complex I [127].

In patients with diabetes and AMI, peak levels of cardiomyocyte injury markers were lower in those taking metformin than in those not taking it. Another analysis found smaller infarct areas in metformin-treated patients with T2DM than in patients without diabetes who did not receive the drug [149].

Pharmacoinvasive Treatment Versus Primary PCI

EARLY-MYO, a randomized controlled trial of 344 patients in China, compared a pharmacoinvasive strategy with half-dose alteplase against primary PCI in patients presenting within six hours of STEMI onset when PCI was

expected to be delayed. The pharmacoinvasive strategy was noninferior to primary PCI in achieving complete myocardial reperfusion [169]. Fibrinolysis can therefore be considered in selected patients when PCI cannot be performed in time [104].

PCI reduced cardiovascular mortality and myocardial infarction in unstable coronary artery disease, but had no significant effect on these outcomes in stable disease [50].

PARADISE-MI (5,661 patients) tested whether sacubitril/valsartan, an angiotensin receptor–neprilysin inhibitor (ARNI), started soon after AMI in patients with reduced left ventricular ejection fraction and/or pulmonary congestion, would prevent cardiovascular death and heart failure events better than the angiotensin-converting enzyme inhibitor ramipril [162].

The primary composite endpoint was not significantly reduced with sacubitril/valsartan compared with ramipril [91]. A later analysis, however, found fewer total heart failure events, first and recurrent, with sacubitril/valsartan [163], and a possible benefit in patients undergoing PCI after AMI has also been discussed [162].

Evidence-based drug therapy after AMI lowers cardiovascular mortality and hospitalization in patients with reduced left ventricular ejection fraction and/or heart failure. In eligible patients, mineralocorticoid receptor antagonists may be useful early after infarction [165].

Early Discharge and Adjunctive Lipid-Lowering and Antithrombotic Therapy

Rathod K.S. et al. (2021) [172] studied early discharge after primary PCI in 600 patients. Discharge within 24 hours was considered safe if primary PCI had been successful and uncomplicated, there were no significant arrhythmias, the patient was hemodynamically stable, left ventricular ejection fraction (LVEF) exceeded 40% and no further in-hospital revascularization was needed. These



patients had been reperfused very quickly, with a median symptom-to-reperfusion time of only 80 minutes, so they were a highly selected, low-risk group. The Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications and Global Registry of Acute Coronary Events risk scores can help to identify patients at higher risk of in-hospital events who need a longer stay [183].

In the trial of alirocumab in AMI, 300 patients were randomized within 24 hours of urgent PCI of the infarct-related artery to subcutaneous alirocumab 150 mg (n = 148) or placebo (n = 152) for 52 weeks, on top of high-intensity statin therapy with rosuvastatin 20 mg. At 52 weeks, plaque regression in non-infarct-related arteries was significantly greater with alirocumab [171].

A pooled analysis of 12 randomized trials with 52,816 patients with acute coronary syndrome (ACS) showed that prasugrel and ticagrelor reduced ischemic events but caused more bleeding than clopidogrel. Only ticagrelor significantly reduced mortality, and prasugrel and ticagrelor did not differ significantly from each other in efficacy or safety [154].

ISAR-REACT 5 compared prasugrel and ticagrelor head-to-head in 4,018 patients with ST-segment elevation or non-ST-segment elevation myocardial infarction. Death, myocardial infarction or stroke occurred significantly less often with prasugrel, and major bleeding did not differ significantly [185].

Over the past twenty years, wider use of invasive management and more intensive antithrombotic therapy have led to more bleeding, but also to a substantial fall in ischemic events and better survival [143; 195].

In a randomized trial of anti-IL-6 therapy, 199 patients with ST-segment elevation myocardial infarction (STEMI) received tocilizumab (n = 101) or placebo (n = 98); there was a trend towards less myocardial necrosis with tocilizumab [41].

Regenerative approaches tested in STEMI include granulocyte colony-stimulating factor, bone marrow mononuclear cells and cardiosphere-derived cells [9; 140; 147]. A clear clinical benefit of cell therapy in AMI has not been shown [40], although new technologies may make regenerative treatment more effective.

Beta-Blockers in Post-Infarction Management

In COMMIT, patients with suspected AMI received intravenous metoprolol within the first 24 hours and then oral metoprolol for 28 days. This reduced reinfarction and ventricular fibrillation, but early beta-blocker administration increased the risk of cardiogenic shock. Beta-blockers should therefore be started after the patient is hemodynamically stable [54].

In CAPRICORN, long-term carvedilol reduced all-cause and cardiovascular mortality and nonfatal myocardial infarction in patients after AMI with left ventricular systolic dysfunction (LVEF ≤40%) [71], and beta-blockers are recommended for patients with LVEF ≤40% [88].

Bangalore S. et al. (2014) [38] compared beta-blockers before and during the reperfusion era: they reduced cardiovascular events in the prereperfusion era, but no comparable benefit was found once reperfusion became routine.

A beta-blocker prescribed at discharge has been associated with better survival in STEMI treated with primary PCI, and earlier guidelines recommended long-term beta-blockade for all STEMI patients regardless of reperfusion strategy or baseline risk [218].

Some registries, however, have not found lower mortality among AMI survivors without heart failure (HF) or left ventricular systolic dysfunction. In the French Registry of Acute ST-Elevation and Non-ST-Elevation Myocardial Infarction, the survival benefit of beta-blockers in such patients waned over time: early treatment was associated with significantly lower 30-day mortality, but continuing beyond one year was unlikely to add anything [170].



In the Myocardial Ischaemia National Audit Project, beta-blockers did not reduce all-cause mortality during the first year after discharge in survivors of STEMI or non-STEMI without HF or left ventricular systolic dysfunction, which has called routine use in patients with preserved LVEF into question [75].

In patients with reduced LVEF, on the other hand, beta-blockers improved survival both when LVEF was mildly reduced (40–49%) and when it was below 40%. Invasive treatment was independently associated with survival at any LVEF, which confirms the prognostic importance of revascularization [152].

Whether beta-blockers need to be continued for more than a year after infarction in patients with LVEF >50% has recently been reconsidered [216]. European recommendations supported long-term treatment after myocardial infarction even without HF or left ventricular systolic dysfunction, whereas the American Heart Association has questioned the benefit [131].

In a Korean registry, patients who took beta-blockers for more than two years after AMI had a lower risk of death, reinfarction and hospitalization for new HF than those treated for less than two years [130]. The Danish National Registry, by contrast, found no long-term association between beta-blockers and mortality or reinfarction between three months and three years after discharge in patients without HF [102].

In the KAMIR-NIH registry, oral beta-blockers did not reduce mortality in survivors without HF or left ventricular systolic dysfunction. Beta-blockers at discharge were beneficial in reduced or mildly reduced LVEF, but not in preserved LVEF [125].

In the Swedish SWEDEHEART registry, cardiovascular outcomes did not differ between patients receiving less than 50% and those receiving at least 50% of the target beta-blocker dose in the first year after AMI. The same was true over five years of follow-up and in clinically relevant subgroups, including patients who developed HF in hospital [144].

Cardiovascular Outcomes with Sodium–Glucose Cotransporter 2 Inhibition

Empagliflozin was beneficial in patients hospitalized for acute or decompensated chronic HF, irrespective of LVEF or diabetes; started in hospital, it was well tolerated and gave significant clinical benefit within 90 days [213].

After a recent myocardial infarction, empagliflozin reduced N-terminal pro-B-type natriuretic peptide (NT-proBNP) significantly more over 26 weeks [212] and improved functional and structural echocardiographic parameters [157].

In patients with AMI and T2DM, starting dapagliflozin in hospital and continuing it after discharge was associated with a significantly lower risk of rehospitalization for HF [138]. Patients taking sodium–glucose cotransporter 2 (SGLT2) inhibitors also had significantly lower serum creatinine 72 hours after PCI, with or without chronic kidney disease (CKD), and a lower risk of contrast-associated acute kidney injury, particularly in the absence of CKD [159].

Antiplatelet Treatment in Patients with Diabetes

In older patients with STEMI and diabetes, triple antiplatelet therapy with aspirin, ticagrelor and tirofiban led to significantly fewer complications after PCI than dual therapy with aspirin and ticagrelor [219].

Patients with T2DM, low HDL-C and a recent AMI who were on insulin remained at high risk of recurrent major adverse cardiovascular events (cardiovascular death, nonfatal myocardial infarction and nonfatal stroke) despite modern evidence-based treatment. The association between insulin use and risk persisted after adjustment for demographic, clinical and treatment variables. Apabetalone had a consistent favorable effect on cardiovascular risk whether or not patients were on insulin [184].

Patients with STEMI and T2DM undergoing PCI had a high intracoronary thrombus burden. An intracoronary bolus of tirofiban was more effective than an



intravenous one: it improved cardiac and renal function, reduced myocardial cell injury and limited myocardial inflammation [197].

In the ASPECT study, patients with CAD and T2DM taking aspirin 81 mg were more often aspirin-resistant and had significantly higher adenosine diphosphate- and collagen-induced platelet aggregation and higher 11-dehydrothromboxane B2 than patients without diabetes. Diabetes is thus associated with generally increased platelet reactivity, which higher aspirin doses can partly overcome [74].

CURRENT-OASIS 7 examined antiplatelet dosing in ACS patients referred for invasive management. The primary composite of cardiovascular death, myocardial infarction or stroke did not differ significantly between the seven-day double-dose and standard-dose clopidogrel regimens, nor between higher-dose (300–325 mg/day) and lower-dose (75–100 mg/day) aspirin [148].

Cardiovascular Effects of Glucose-Lowering Treatments

In 677 patients with STEMI and T2DM, metformin was associated with smaller infarcts [136], whereas in another 493 such patients it had no effect on infarct size or left ventricular function [39]. The effect of metformin on infarct size therefore remains controversial.

In the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients–Removing Excess Glucose (EMPA-REG OUTCOME), empagliflozin significantly reduced cardiovascular mortality and hospitalization for HF [223]. Because glycated hemoglobin fell only modestly, the benefit probably goes beyond glucose lowering [179].

In LEADER, liraglutide reduced the composite of cardiovascular death, nonfatal myocardial infarction or nonfatal stroke in T2DM; gastrointestinal side effects were the most common reason for stopping treatment [146]. Semaglutide showed similar cardiovascular benefits in T2DM [145].

EXAMINE studied alogliptin in patients with T2DM who had had an AMI 15–90 days before enrollment. Cardiovascular and all-cause mortality outcomes were favorable with alogliptin, and triple therapy with metformin, a sulfonylurea and alogliptin lowered glycated hemoglobin more than metformin plus a sulfonylurea [215].

In ELIXA, adding lixisenatide to standard therapy in patients with T2DM and recent AMI did not change the incidence of major adverse cardiovascular events [161].

According to the Acute Coronary Syndrome Israeli Survey, patients on sitagliptin had significantly fewer in-hospital complications, including post-infarction angina, reinfarction, pulmonary edema, infections and acute renal failure, than those on metformin or other oral glucose-lowering drugs [135].

In another analysis, metformin reduced all-cause mortality, HF and cardiovascular events in patients with HF and T2DM, but had no significant effect on myocardial infarction or in patients without T2DM. In the Metformin to Reduce Metabolic and Cardiac Risk in Patients with Coronary Artery Disease (MET-REMODEL) trial, 12 months of metformin in patients with CAD and insulin resistance and/or prediabetes reduced left ventricular mass index, left ventricular mass, systolic blood pressure, body weight and oxidative stress [151].

Stress Hyperglycemia in Relation to Intracoronary Thrombus Burden

Sardu C. et al. (2018) [181] studied thrombus aspiration in patients with hyperglycemia at the time of STEMI. Their data suggested that aspiration may benefit these patients and that stress hyperglycemia may promote intracoronary thrombus formation in AMI. Thrombus aspiration did not, however, reduce mortality in patients undergoing PCI for STEMI.

Treatment of AMI therefore still needs to be optimized, above all with regard to reperfusion timing, antithrombotic therapy, cardiovascular drug therapy and the management of concomitant metabolic disorders.



1.4. Prediction of Chronic Heart Failure Development Following Myocardial Infarction

We used generalized linear mixed models (GLMMs) to model the risk of chronic heart failure (CHF) after day 1 in patients with myocardial infarction (MI). These models are flexible: hypotheses can be built and tested in terms of the means, variances and covariances of variables. The linear predictor of a GLMM combines fixed effects (β) and random effects (υ).

In this notation, η is the GLMM linear predictor, β and υ are the fixed and random effects, and X and Z are the design matrices for fixed and random effects, respectively.

The observed outcomes are described by a model that includes the response variable and a residual term, where y is the vector of observed values to be predicted and ε is the vector of residuals. The expected values are then derived, and the GLMM links the observed values to the linear predictor.

This means that the distribution of y is determined by the predictor η, with a given mean and variance R. All GLMM analyses were performed in IBM SPSS Statistics.

Selection of Variables for Prediction

The dependent variable y was CHF severity, coded as category 1 (CHF stage I), category 2 (CHF stage II) and category 3 (CHF stage III).

In total, 138 parameters were measured on days 1 and 14 after MI. The sample, however, included only patients with CHF stages I and II, so reliable correlations between the outcome and the full set of parameters could not be established.

We therefore first used principal component analysis (PCA) to select the variables with the highest extraction values, which considerably reduced the number of candidate predictors for the GLMM. The selected parameters are listed in Table 1.

Table 1. Parameters Selected for GLMM Analysis, Measured on Days 1 and 14 in Patients with Myocardial Infarction

Indicator	Statistical significance	Variable Extraction Value (out of 1.0)
Adropin on Day 1	$p < 0,05$	0,743
Adropin on Day 14	$p < 0,05$	0,816
CTRP3 on Day 1	$p < 0,05$	0,780
CTRP3 on Day 14	$p < 0,05$	0,782
Systolic Blood Pressure on Day 1	$p < 0,05$	0,906
Systolic Blood Pressure on Day 14	$p < 0,05$	0,872
Diastolic Blood Pressure on Day 1	$p < 0,05$	0,880
Diastolic Blood Pressure on Day 14	$p < 0,05$	0,783
Left Ventricular End-Diastolic Dimension (cm)	$p < 0,05$	0,844
Platelet Count	$p < 0,05$	0,775
Total Cholesterol (mmol/L)	$p < 0,05$	0,746
Atherogenic Coefficient	$p < 0,05$	0,791
Acute Left Ventricular Failure Within the First 14 Days	$p < 0,05$	0,896

The variables in Table 1 were then entered into the model in different combinations, as fixed or random effects, or left out.

Models were compared by the Akaike information criterion (AIC), the Bayesian information criterion (BIC), the overall significance of the model and the significance of each variable ($p < 0.05$).

We looked for the statistically significant combination that predicted y most accurately. The independent variables of the final model are shown as fixed effects in Table 2 and as random effects in Table 3.



Table 2. Parameters Measured on Days 1 and 14 in Patients with Myocardial Infarction Representing Fixed Effects in the GLMM

Indicator	Statistical significance, p	Coefficient in the GLMM, X
Single-Factor Predictors		
Adropin on Day 1	p = 0,017	0,061
Adropin on Day 14	p = 0,019	-0.099
Three-Factor Predictors (Combined Effects of Two Variables)		
Acute Left Ventricular Failure Within the First 14 Days, CTRP3 on Day 1, and CTRP3 on Day 14	p = 0,041	$-1{,}3\ 10^{-5}$
Multifactor Predictors (Combined Effects of More Than Three Variables)		
Acute Left Ventricular Failure Within the First 14 Days, Systolic and Diastolic Blood Pressure on Day 1, and Systolic and Diastolic Blood Pressure on Day 14	p < 0,01	$-7{,}5\ 10^{-9}$
Acute Left Ventricular Failure Within the First 14 Days, CTRP3 on Day 1, CTRP3 on Day 14, Left Ventricular End-Diastolic Dimension, Platelet Count, and Total Cholesterol	p < 0,01	$1{,}6\ 10^{-9}$

Table 3. Parameters Measured on Days 1 and 14 in Patients with Myocardial Infarction Representing Random Effects in the GLMM (Only Statistically Significant Effects, p < 0.05)

Indicator	Covariance
Single-Factor Predictors	
Acute Left Ventricular Failure Within the First 14 Days	2,281
CTRP3 on Day 14	0,013
Atherogenic Coefficient	0,001

The final model contains two single-factor, one three-factor and two multifactor fixed effects (Table 2) and three single-factor random effects (Table 3). Its overall characteristics are shown in Figure 1.

Model Summary

Target: AJ

Target		AJ
Probability Distribution		Binomial
Link Function		Probit
Information Criterion	**Akaike Corrected**	859.270
	Bayesian	868.695

Information criteria are based on the -2 log pseudo likelihood (853.132) and are used to compare models. Models with smaller information criterion values fit better. When comparing models using pseudo likelihood values, caution should be used because different data transformations may be used across the models.

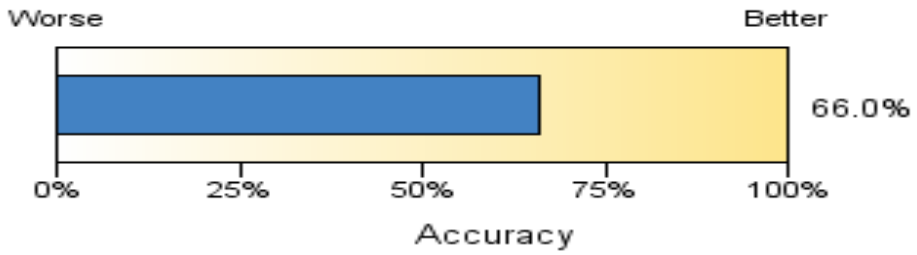


Figure 1. The overall characteristics of the model

Assessment of Model Predictive Performance

The predictive performance of the model is shown in Figure 2.



Classification

Target:AJ

Overall Percent Correct =66.0%

Observed	Predicted	
	1.00	2.00
1.00	44.9%	55.1%
2.00	19.1%	80.9%

Row Percent
100.00
80.00
60.00
40.00
20.00
0.00

Figure 2. Predictive performance characteristics

For CHF stage I, the one-year prediction after MI was correct in 44.9% of cases; the remaining 55.1% of patients were wrongly assigned to stage II. In this group, then, the model tended to overestimate the risk of progression to a more severe stage.

For CHF stage II, accuracy was 80.9%, so the model identified patients who would develop this degree of post-infarction HF fairly reliably. The overall accuracy of the model was 66.0%.

Using clinical and laboratory data from days 1 and 14, the model predicted the development of CHF stage II within one year after MI with an accuracy of 80.9%.

Prognostic Contributions of Adropin, CTRP3, and Clinical Measures

Among the fixed effects, adropin on day 1 had a strong positive coefficient, and adropin on day 14 a strong negative one.

The interaction of acute left ventricular failure severity (Killip class I–IV during the first 14 days) with CTRP3 levels on days 1 and 14 had a negative effect, as did the combined effect of systolic and diastolic blood pressure on days 1 and 14.

A positive effect was found for the combination of acute left ventricular failure severity (Killip class I–IV during the first 14 days), CTRP3 on days 1 and 14, left ventricular end-diastolic dimension, platelet count and total cholesterol. Overall, the model predicted the outcome correctly in 66% of patients.

Conclusions

Adropin and irisin take part in the regulation of energy metabolism, inflammation and cardiovascular function. Data on their circulating levels and prognostic value in obesity, type 2 diabetes mellitus and acute myocardial infarction are, however, inconsistent, and both peptides need further validation before they can be used as routine clinical biomarkers.

FABP4 and CTRP3 are involved in the metabolic and inflammatory pathways that drive atherosclerosis and myocardial remodeling. Studying them may help to explain cardiometabolic comorbidity, but experimental results cannot be transferred to clinical practice without clinical confirmation.

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