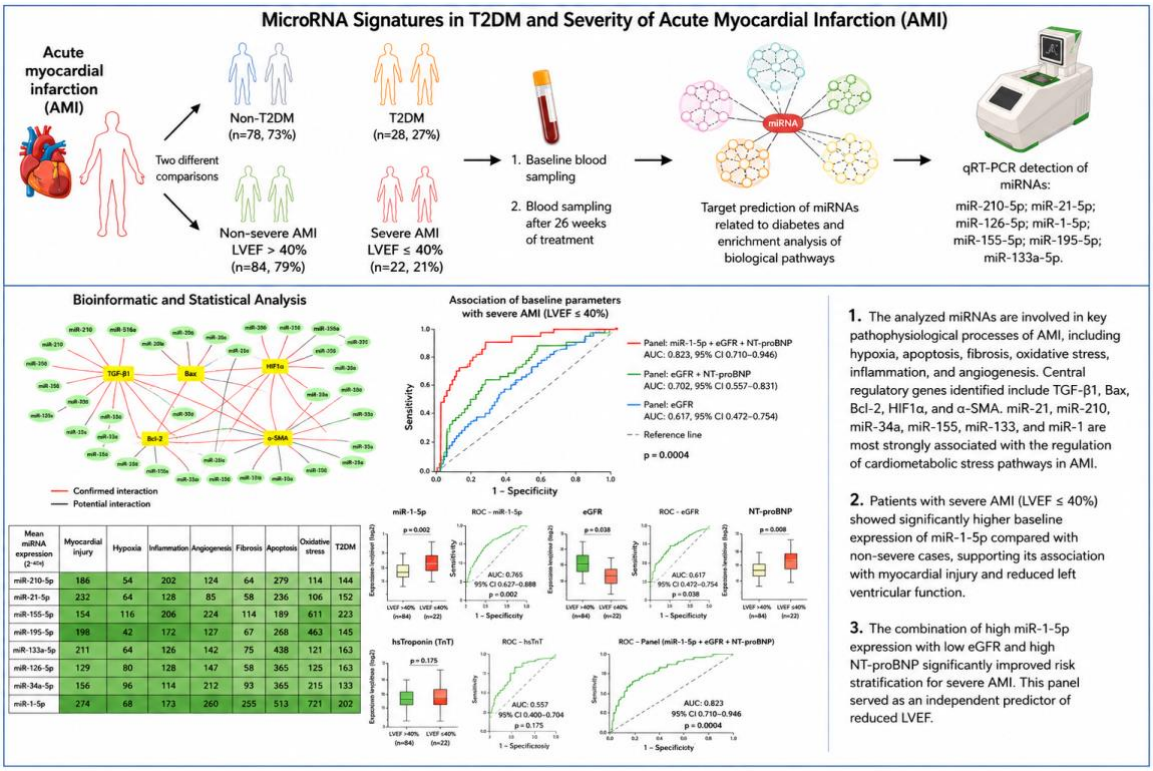
Streszczenie w języku angielskim



Mean miRNA expression (2^-ΔCt)	Myocardial injury	Hypoxia	Inflammation	Angiogenesis	Fibrosis	Apoptosis	Oxidative stress	T2DM
miR-210-5p	186	54	202	124	64	279	114	144
miR-21-5p	232	64	128	85	58	236	106	152
miR-155-5p	154	116	206	224	114	189	611	223
miR-195-5p	198	42	172	127	67	268	463	145
miR-133a-5p	211	64	126	142	75	438	121	163
miR-126-5p	129	80	128	147	58	365	125	163
miR-34a-5p	156	96	114	212	93	365	215	133
miR-1-5p	274	68	173	260	255	513	721	202

Figure 1. Study workflow and microRNA signatures associated with type 2 diabetes and acute myocardial infarction severity.
Abbreviations: **α-SMA,** ang. *alpha-smooth muscle actin*; **AMI**, ang. *acute myocardial infarction*; **AUC**, ang. *area under the curve*; **Bax**, ang. *BCL2-associated X protein*; **Bcl-2**, ang. *B-cell lymphoma 2*; **CI**, ang. *confidence interval*; **eGFR**, ang. *estimated glomerular filtration rate*; **HIF1α**, ang. *hypoxia-inducible factor 1 alpha*; **LV**, ang. *left ventricle*; **LVEF**, ang. *left ventricular ejection fraction*; **miR**,**miRNA** ang. *microRNA*; **NF-κB**, ang. *nuclear factor kappa B*; **Non-T2DM,** ang. *non-type 2 diabetes mellitus*; **NT-proBNP**, ang. *N-terminal pro-B-type natriuretic peptide*; **qRT-PCR**, ang. *quantitative reverse transcription polymerase chain reaction*; **ROC**, ang. *receiver operating characteristic*; **T2DM**, ang. *type 2 diabetes mellitus*; **TGF-β1**, ang. *transforming growth factor beta 1*; **TnT,** ang. *troponin T*.

Cardiometabolic diseases, including acute coronary syndrome (ACS) and type 2 diabetes mellitus (T2DM), remain major clinical challenges because of their association with heart failure, adverse left ventricular remodeling, and long-term cardiovascular complications. Sodium-glucose cotransporter type 2 (SGLT2) inhibitors, including empagliflozin, exert cardioprotective effects that extend beyond glucose lowering; however, the molecular mechanisms underlying these effects are not fully understood. Non-coding RNAs, particularly microRNAs (miRNAs), may represent a mechanistic link between SGLT2-related signaling, metabolic dysregulation, and post-infarction remodeling, as they regulate gene expression pathways involved in hypoxia, apoptosis, fibrosis, oxidative stress, inflammation, and angiogenesis.

The aim of this doctoral thesis was to evaluate selected circulating miRNAs as biomarkers of metabolic status and ACS severity and to integrate clinical findings with bioinformatic analysis of the SGLT2 and noncoding RNA axis (**Figure 1**). The study was performed as a secondary biomarker substudy of the EMMY trial (NCT03087773). The final analysis included 106 patients after ACS treated with empagliflozin 10 mg once daily, for whom paired plasma samples were available at baseline and after 26 weeks of treatment. In total, 212 plasma samples were analyzed. T2DM was present in 28 patients (26%), whereas 78 patients (74%) did not have T2DM. Severe ACS was defined as left ventricular ejection fraction (LVEF) ≤40% and was observed in 22 patients (21%). The expression of selected circulating miRNAs was assessed using qRT-PCR, while predicted target genes and enriched biological pathways were evaluated using bioinformatic and statistical analyses.

Bioinformatic analyses demonstrated that the investigated miRNAs were linked to processes central to myocardial remodeling and cardiometabolic disease. The main shared genes and regulatory nodes included *TGF-β1*, *Bax*, *Bcl-2*, *HIF1α*, and *α-SMA*, whereas miR-21, miR-210, miR-34a, miR-155, miR-133, and miR-1 showed high network connectivity. These findings support the interpretation of selected miRNAs not only as markers of injury, but also as potential regulators of biological pathways related to hypoxia, inflammation, fibrosis, angiogenesis, and left ventricular remodeling.

In the clinical part of the study, T2DM was associated with a distinct miRNA expression profile in patients after ACS. At baseline, patients with T2DM had significantly lower miR-210-5p expression and significantly higher miR-195-5p expression. MiR-210-5p showed good discriminatory ability for identifying T2DM (AUC 0.811), whereas miR-195-5p achieved an AUC of 0.723. Longitudinal analysis showed that miR-210-5p increased over 26 weeks, although its levels remained consistently lower in patients with T2DM, while miR-21-5p significantly decreased in both groups. These findings suggest that miR-210-5p may reflect an impaired hypoxia-adaptive response in T2DM, miR-195-5p a chronic metabolic-vascular component, and miR-21-5p the dynamics of inflammatory and fibrotic post-infarction remodeling.

MiR-1-5p showed the strongest association with ACS severity. Patients with LVEF ≤40% had significantly higher baseline miR-1-5p levels than patients with LVEF >40%. In ROC analysis, miR-1-5p reached an AUC of 0.765, exceeding selected conventional parameters such as eGFR and NT-proBNP, whereas hsTroponin was not significantly associated with ACS severity. A multimarker panel combining high miR-1-5p, low eGFR, and high NT-proBNP improved discrimination, reaching an AUC of 0.823, and remained an

independent predictor of LVEF ≤40% in logistic regression analysis (OR 8.037; 95% CI 2.207-29.265; p = 0.002).

In conclusion, this doctoral thesis identifies the SGLT2-ncRNA axis and selected circulating miRNAs as important elements of the molecular characterization of patients after ACS. MiR-210-5p and miR-195-5p are primarily associated with the metabolic phenotype of T2DM, miR-21-5p may reflect the temporal dynamics of post-infarction remodeling, and miR-1-5p provides additional value in assessing ACS severity and left ventricular dysfunction. These findings support the potential role of miRNAs as precision-medicine biomarkers, particularly when integrated with clinical and laboratory parameters. Given the secondary and exploratory nature of the analysis, the limited sample size, and the absence of direct placebo comparison in the biomarker analysis, further validation in larger cohorts and mechanistic studies is required.

Keywords: type 2 diabetes mellitus; acute myocardial infarction; empagliflozin; SGLT2 inhibitors; microRNA; miRNA; non-coding RNA; LVEF; biomarkers; precision medicine.