# REVIEW

Regarding the PhD work titled: "Blood Levels of Circulating Long Noncoding Ribonucleic Acids – LncRNAs in Cardiovascular Diseases", submitted for public defense by a scientific jury for the awarding of the educational and scientific degree "PhD" in the professional field 7.1 Medicine, specialty "Internal Medicine".

**Author of the PhD work: Dr. Yordanka Doneva-Kashlova,** full-time PhD student in the doctoral program "Internal Medicine", professional field 7.1 Medicine, enrolled by Order No. P-109-74/31.01.2020 at the Medical University – Varna.

**Reviewer: Prof. Dr. Zhaneta Georgieva Tyaneva, DM, Medical University of Varna**, member of the Scientific Jury, appointed by Order No. P-109-161/14.03.2025 of the Rector of the Medical University of Varna.

**Biographical data:**

Dr. Doneva graduated from First Language High School in Varna in 2004. In 2013, she completed her higher education in medicine at the Medical University of Varna. Since the same year, she has been specializing in Internal Medicine at the Department of Propedeutics of Internal Diseases, Medical University of Varna, within the Clinic of Internal Diseases at the University Hospital "St. Marina". She completed a four-month specialization at the University Hospital in Rostock, Germany. In 2018, she obtained a specialty in Internal Medicine. Since 2021, she has been undergoing specialization in "Endocrinology and Metabolic Diseases". Since 2021, she has been a full-time doctoral student at the Department of Propedeutics of Internal Diseases, Medical University of Varna. She speaks English and German.

**Scientific research activity:**

The PhD work "Blood Levels of Circulating Long Noncoding Ribonucleic Acids – LncRNAs in Cardiovascular Diseases" is a current and highly specialized work that explores novel

mechanisms of dynamic regulation of lncRNAs and considers potential new therapeutic strategies. The necessity of high-specificity studies is emphasized to establish the role of lncRNAs as diagnostic biomarkers and therapeutic targets in cardiovascular diseases. The conducted research highlights the role of LncRNAs in the physiology and pathophysiology of myocardial cellular processes. Dr. Doneva's study investigates the plasma expression level of two newly identified and not enough studied long noncoding RNA molecules – lncRNA Wisper and lncRNA NRF – in the context of acute myocardial infarction (AMI) and heart failure (HF). The plasma expression of the analysed. LncRNAs is altered in cardiovascular diseases and displays distinct characteristics. LncRNA Wisper, associated with fibroblast activation, appears to be a potential early predictor of fibrosis and is significantly elevated in patients with AMI and those with HF. LncRNA NRF, involved in the regulation of necrosis, is expressed at significantly higher levels in patients with STEMI and acute myocardial injury compared to those with HF.

**Structure of the PhD work:**

The PhD work comprises 120 pages and includes 28 figures and 21 tables. The bibliography consists of 299 literature sources. The PhD candidate has two full-text publications related to the dissertation topic, published in specialized scientific journals.

The literature review demonstrates a thorough understanding of the existing research and the ability to extract in-depth information. The research aim is clearly defined and specific: to investigate and analyze the plasma expression of long noncoding ribonucleic acids in patients with heart failure and those with acute myocardial infarction. The research objectives are precisely formulated and aligned with the main goal. The study examines and compares the plasma expression levels of lncRNA Wisper in patients with heart failure and patients with ST-elevation myocardial infarction, as well as the expression of another RNA molecule, lncRNA NRF, in the same patient groups. The influence of additional factors, such as comorbidities, on the plasma expression of lncRNA Wisper and lncRNA NRF in patients with heart failure and acute myocardial infarction is also analyzed.

The statistical analysis was conducted using the SPSS Statistics software, version 23. Modern statistical methods were applied, enabling the consideration of interactions between the observed parameters.

The results and the conclusions derived from them are convincing, scientifically valuable, and contribute to the field. The PhD work establishes a connection between the author's own findings and those presented in the literature review.

The conclusions are logically drawn from the study results. Plasma expression of lncRNA Wisper is significantly elevated in patients with heart failure classified as NYHA functional class III-IV, and it also significantly increases in patients with STEMI within the first 12 hours from the onset of myocardial infarction.

**Scientific Contributions of the PhD work:**

For the first time in Bulgaria, it is examined the expression of lncRNA Wisper and lncRNA NRF is in human plasma of patients with acute myocardial infarction and heart failure. It is established that plasma expression level of lncRNA Wisper increases both in heart failure and acute myocardial infarction. Furthermore, it is noted that age influences plasma expression of lncRNA Wisper.

This is the first report in Bulgaria for the potential predictive value of lncRNA Wisper for the development of fibrosis in patients with heart failure. Also for the first time in the country, a significant correlation is reported between plasma expression of lncRNA Wisper and HMGB1. The study analyzes the elevated expression of lncRNA NRF in patients with STEMI compared to a control group.

The dissertation identifies the value of lncRNA Wisper as a biomarker for myocardial fibrosis, which is not affected by additional factors such as sex or the most common comorbidities accompanying cardiovascular diseases. The potential of lncRNA NRF is underlined as a biomarker for acute myocardial necrosis.

The aberrant expression of lncRNA Wisper and lncRNA NRF in the blood plasma of patients with cardiovascular diseases reveals the potential importance of these long noncoding RNA molecules as markers of acute or chronic myocardial injury. These findings offer opportunities for conducting more in-depth and targeted studies to support their application as biomarkers in clinical practice.

I accept the conclusions and scientific contributions presented in the dissertation.


**Conclusion:**

**The presented PhD work by Dr. Doneva is highly relevant to contemporary medicine. It combines an in-depth analysis of the scientific literature with original research and conclusions. The dissertation and related scientific publications meet the scientific criteria required for awarding the educational and scientific degree "PhD," according to the Academic Staff Development Act and the Rules of the Medical University of Varna. The dissertation includes original and confirmatory contributions. I give a positive vote for awarding the scientific degree "PhD" to Dr. Yordanka Doneva-Kashlova.**


**04.03.2025**

**Varna**

Revie

Prof. Dr. Mr. Georgieva, DM