

N P-109-131 / 05.04.2021.

STATEMENT

From Prof. Branimir Nikolov Kanazirev, MD,
Chairman of the Scientific Committee for awarding the scientific and educational degree "Ph
Doctor" in the field of higher education 7. "Health and Sports", professional field 7.1. "Medicine"
and scientific specialty "Internal Medicine", by order of the Rector of the Medical University,
Varna

Regarding the PhD thesis of Dr. Anton Levanevski Dinkov, PhD student on independent
training on *"Monitoring of natriuretic peptide levels in patients with type 2 diabetes mellitus
and heart failure with preserved ejection fraction of therapy with the SGLT2 receptor antagonist
empagliflozin inhibitor"* PhD supervisor - Assoc. Prof. Dr. Yavor Kostadinov Kashlov, MD

Dr. Anton Levanevski Dinkov presented all necessary documents - dissertation, abstract in
Bulgarian and English and documents in accordance with the requirements of the Law on the
Development of Academic Staff in the Republic of Bulgaria and the Regulations of the Ministry
of Education and the Medical University - Varna. that I have no conflict of interest with the
candidate.

Significance of the problem

The topic of the dissertation is extremely relevant. Type 2 diabetes mellitus (DMT2), heart failure
with preserved ejection fraction(HFpEF), and treatment with SGLT2 antagonists are in the focus
of treatment of heart failure in diabetics. Diabetes is one of the main risk factors for the
development of cardiovascular disease and especially heart failure both after myocardial
infarction and reduced pumping function and the premature development of heart failure with an
ejection fraction over 50% with poor outcome and increased mortality.

For several years, a new class of antidiabetic drugs, so-called SGLT2-inhibitors, has been
introduced in clinical practice, which have also proven to be potential drugs for the prevention
and treatment of heart failure. At the beginning was the EMPA-REG study trial with a surprising
and unexpected positive effect of reducing hospitalizations for heart failure by 35%,
cardiovascular mortality by 38% and overall mortality by 32%. The effect of slowing the
progression of renal failure and even improving renal function, which has no analogue in modern
pharmacotherapy of heart failure, was also unexpected. In previous studies or at the time of the
first publication of Dr. Anton Dinkov, the effect of Empagliflozin was not clinically monitored
in patients with DM2 and HF with preserved ejection fraction. The dissertation of Dr. Dinkov is
presented on 139 pages and meets the requirements with an introduction, literature review, goals
and objectives, materials and methods, results, discussion, conclusions, contributions and
bibliography. The dissertation is illustrated with 52 figures and 24 tables. The presented literature
review without being exhaustive reveals the dynamics of new publications from the last two years
in the field such as treatment of T2DM and the manifestation of heart failure, pathophysiological
mechanisms, benefits of therapy with SGLT2 inhibitors, the relationship between T2DM and
heart failure, differentiation of heart failure. With HFpEF and HFReEF and conflicting data from
some studies on biomarkers. The analysis of the moment of initiating the medication is
insufficient - in a hospital setting or immediately after discharge or when heart failure stabilizes.
Additional emphasis is placed on renal changes in the administration of the drug

Dr. Anton Dinkov aims to monitor the levels of biomarkers in short-term treatment with standard
doses of the drug without changing the existing prior therapy in a noticeable correctly and

currently selected group of patients with heart failure with preserved ejection fraction and type 2 diabetes mellitus.

To achieve this goal, the dissertation has set itself the following tasks:

- o Evaluation of the effect of empagliflozin on NT pro-BNP levels in patients with T2HD indicated for Empagliflozin therapy and with established echocardiographic presence of CH3IF at baseline, day 30 and 90 from the start of continuous antidiabetic therapy of the drug and without changing the rest of the therapy
- o Monitoring the functional capacity of patients through a 6-minute exercise test.
- o Assessment of renal function before and after initiation of therapy by examining creatinine clearance and urinary albumin / creatinine ratio.
- o Monitoring the effect of the drug on systolic and diastolic function of the heart by echocardiographic assessment

The statistics were processed on the SPSS program 26.

The obtained results are presented and illustrated consistently and logically.

The discussion compares the results of the study with large randomized trials from recent years. The explanation of the differences in the results with some studies should refer primarily to the groups with heart failure - chronic and stabilized patients, etc. dry patients in the large studies and the group of modern drug administration in the earliest stages after discharge, as is the case in this study.

The contributions are significant:

- o For the first time worldwide, albeit in a small group, albeit short-term, patients with T2HD and CH3FI are being studied for NT-proBNP levels, functional capacity, and renal function with SGLT2 receptor inhibitor empagliflozin.
- o For the first time, cardiac function is assessed using some echocardiographic criteria - EF%, TDO, TCO, indexed left atrial volume, mitral blood flow and tissue Doppler in patients on empagliflozin therapy in an attempt to explain the positive effects of the drug.

In connection with the dissertation the author presents 2 abstracts from the participation in scientific forums and 4 publications.

However, as it became known on the day of publication of the reviews and opinions on the website of MU-Varna in the department "Doctoral School" of the Medical University - Varna received information in connection with the dissertation of Dr. Anton Dinkov from the Department of Propaedeutics. internal diseases ", as follows:

1. Irregularities and inconsistencies in the research part of the work have been identified. In this regard, we got acquainted with the reports from the Head of the Department of Propaedeutics of the UK and from the Head of the Hospital Laboratory, where the research for the dissertation was done. The reports of these supervisors present data on the misuse of research on biomarkers used in the dissertation, contrary to the academic ethics of research.

2. It is additionally established that no procedure for evaluation of the scientific research has been conducted by the Commission for Ethics of Scientific Research of the Medical University - Varna. The Attestation Card of the doctoral student states that a permit has been issued by the commission and a protocol from a certain date is cited. However, it is established that such an opinion was not issued by the commission due to the absence of the doctoral student at the meeting at which the discrepancies in the research part of the dissertation should have been commented after the submitted information. In this sense, there is a discrepancy with the Declaration of authenticity of the submitted data and documents filed by the doctoral student, according to Art. 313 of the Criminal Code.

3. In fact, the internal defense of the dissertation of Dr. Anton Dinkov was not conducted in the Department of Propaedeutics of Internal Medicine - no copies of dissertation and abstracts were presented and the members of the department could not get acquainted with the dissertation, the

presence of the members of the Department did not provide a quorum at the meeting, in the speeches the opinions about the dissertation were negative on the basis of the presented data for discrepancy in the research part with the biomarkers, no proposal for review committee was presented, the result of the voting is not clear whether to launch a public defense. Instead of repeating the internal defense, there was an extension of 6 months for processing and corrections, which is obvious that it cannot be implemented, given the data on misuse of scientific data and the lack of opportunities for such corrections.

Conclusion: Based on all these data, the dissertation "Levels of NT pro-BNP in patients with heart failure with preserved ejection fraction and type 2 diabetes mellitus on empagliflozin therapy" although relevant and important both scientifically and for clinical practice does not meet the requirements for awarding the educational and scientific degree "Doctor" of the Law for development of the academic staff in the Republic of Bulgaria and of the Regulations for development of the academic staff of the Medical University - Varna.

Based on the above, I recommend the members of the esteemed Scientific Jury to vote negatively and not to award Dr. Anton Dinkov the educational and scientific degree "Doctor" in the specialty "Internal Medicine", professional field 7.1 Medicine, higher education 7. Healthcare and sports.

05/21/2021

Prof. Branimir Kanazirev, PhD