

To the Chairman of a Scientific Jury appointed
by order of the Rector of the Medical
University, Varna
N P-109-131/05.04.2021

Review

From Prof . Borislav Georgiev Georgiev, MD,
Head of Cardiology Clinic at National Cardiology Hospital
Member of the scientific jury awarding the educational and scientific degree "Philosophy doctor" in
the higher education sphere 7 Health and Sport", professional field 7.1." Medicine" and "Internal
Medicine" scientific specialty,
on the basis of order of the Rector of the Medical University, Varna
N P-109-131/05.04.2021

Subject: Dissertation of Dr. Anton Levanevsky Dinkov, PhD student in independent training in the
Doctoral Program on the topic
*"Monitoring of levels of natriuretic peptides in patients with type 2 diabetes mellitus and heart failure
with a preserved ejection fraction with the inhibitor of SGLT2 receptor antagonist empagliflozin"*
Scientific adviser – Assoc. Prof. Dr Yavor Kostadinov Kashlov MD, PhD

For the competition Dr. Anton Levanevsky Dinkov has submitted all necessary documents -
dissertation, author's abstract (Bulgarian and English) and additional documents, in accordance of
the Academic Staff Development Act in the Republic of Bulgaria and the Regulations of the Ministry
of education and the Medical University of Varna.

I can't find any gaps in the documentation submitted.

I declare that I have no conflict of interest with the candidate.

All presented materials are well arranged and described.

There is no evidence of plagiary.

Biographical data

Anton Levanevski Dinkov graduated in medicine at the Medical University of Varna in 1997.
Dr. Dinkov acquired a degree in Internal Medicine, and in the period 1997-2018 he was an assistant
professor at the Department of "Propedeutics of Internal Diseases" at the Medical University of
Varna.

Title of the dissertation work

The title of the dissertation work "*Monitoring the levels of natriuretic peptides in patients with
type 2 diabetes mellitus and heart failure with a preserved ejection fraction of the inhibitor of SGLT2
receptor antagonist empagliflozin*" contains the wrong names of the class of medications to which
empagliflozin belongs.

Importance of the topic

The topic of the dissertation work is contemporary and relevant. Diabetes is one of the main risk factors for the development of cardiovascular disease and its presence is associated with a more severe course and increased mortality. In patients with diabetes, the likelihood of developing heart failure is increased. It is known that patients with T2DM develop heart failure earlier than those without diabetes. A new class of antidiabetic drugs was introduced – sodium glucose co-transporter 2 blockers called SGLT2 inhibitors. They block the reabsorption of glucose filtered through glomeruli into proximal renal tubules. The EMPA-REG study clearly took into account the positive macrovascular effects of empagliflozin – a decrease in cardiovascular mortality by 38%, death from any cause by 32%, hospitalizations due to heart failure by 35%. Positive effects on renal function are also reported – progression to macroalbuminuria is delayed, the risk of occurrence of clinically relevant kidney events such as doubling the level of serum creatinine and the inclusion of hemodialysis is reduced. Heart failure with a preserved ejection fraction has been a new subgroup in recent years. At this stage of the development of medical science, it does not have specific therapy. Patients with T2DM who develop this type of heart failure are high in terms of cardiovascular morbidity and mortality.

The author presents an in-depth knowledge of the global topic of diabetes and heart failure.

Structure of the dissertation work:

Dr. Dinkov's scientific work is shaped on 139 p. according to the requirements and contains an introduction, literary overview, objectives and tasks, materials and methods, results, discussion, and results, conclusion, contributions and bibliography.

The literary review presented on 31 pages shows very good awareness of the author regarding T2DM and its treatment, The benefits of SGLT2 inhibitors therapy, the relationship between T2DM and heart failure and pathophysiological mechanisms and the criteria for their evaluation. Special attention is paid to the mechanisms and benefits of using empagliflozin in the treatment of T2DM.

Dr. Anton Dinkov aims **for his** research work to track cardiac status in patients with heart failure with a preserved ejection fraction and type 2 diabetes mellitus of empagliflozin therapy.

In order to achieve this goal, the author shall set himself the following **tasks**:

1. Assessment of the effect of empagliflozin on blood levels of the sodium peptide in patients with T2DM, who are indicated for therapy with this drug and HFrEF, followed on the 30th day after the start of antidiabetic therapy and after three months with constant intake of the drug.
2. Monitoring the functional capacity of patients by means of a 6-minute load test.
3. Evaluation of renal function before and after initiation of empagliflozin therapy with a view to its monitoring and to refine the preparation or to stop it from its deterioration by examining the creatinine clearance according to the Cockcroft formula and assessing renal impairment with a study of the albumin/creatinine ratio in the urine.
4. Monitoring of the effect of empagliflozin on the heart by means of an echocardiographic study with a 2.5-5 MHz sectoral transducer, including measurement of the telediastolic and telesystolic volumes of the left ventricle, the left ventricle ejection fraction from the apical position in four

chambers on Simpson, the left atrium volume at the same position, assessment of diastolic function by tissue Doppler.

If we read the goals and tasks in depth, it can be seen that the keyword in the title – natriuretic peptides is only a small part of them. The objectives and tasks are much more general than the short wording in the title of the dissertation work.

Methodological approach: The scientific study included 50 patients with a proven diagnosis of T2DM; heart failure with a preserved ejection fraction, preserved renal function, conducting standard therapy with respect to their heart disease; and receiving empagliflozin for therapy of T2DM.

The statistical analysis shall include various analyses which are consistent with the hypothesis and the objectives set. The collected data was processed on the SPSS 26 program.

Results: The results obtained by Anton Dinkov are set out in 30 pages of the dissertation work.

The chapter begins with Descriptive statistics in tables and graphs, where many results are presented without comments and analyses to them. The following are the data from the tracked parameters - NT-proBNP and EchoCG. A six-minute load test was incorrectly labelled, it would have to be called a six-minute walking test. Since the topic is related to natriuretic peptides, the relationship with the natriuretic peptides should be sought when presenting the other results (EchoCG and functional analyses).

There are many things to be desired in presenting the results. Interesting analyses may be included.

Discussion The dissertant compared its results with that obtained from large randomised studies such as EMPA-REG OUTCOME, EMPIRE-HF and EMPEROR. Some data are interesting and divergent compared to randomized studies, but the author acknowledges that the disadvantage of this study is the relatively small number of patients tracked, the lack of a control group, the small number with accompanying diseases such as atrial fibrillation, which affect the level of NT-proBNP and the short follow-up period.

Conclusions: Dr. Anton Dinkov offers 6 conclusions. The purpose and tasks are not reflected in the conclusions that sound more like contributions. The author even divides them into conclusions of an original nature and conclusions of a confirmatory nature. The content of the conclusion is closer to conclusions from the scientific study.

Contributions: Contributions are 3:

1. For the first time in Bulgaria, NT-proBNP levels in diabetics with heart failure with a preserved ejection fraction of empagliflozin therapy are examined.
2. For the first time, cardiac function shall be evaluated using certain echocardiographic criteria - EF%, TDV, TSV, 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 reported by EMPA-REG OUTCOME.
3. For the first time, the functional capacity was tracked by a six-minute walking test in diabetics at empagliflozin therapy.

There is no mention of whether the results are of an original or confirmatory nature.

The bibliography contains 157 quoted titles, of which 5 in Cyrillic and 152 in Latin. Citation N 34 contains 3 publications, citation N 60 contains 2 publications.

The author abstract is presented in Bulgarian and English. The Bulgarian version contains 52 pages and reflects what was written in the dissertation.

Publications: In connection with the dissertation work, the author presents 4 full-text publications and 2 summaries of participation in scientific forums.

General remarks:

The title of the dissertation work is wrong and the name of the drugs class should be written correctly. When presenting the results, there should be a comment, not just a list and figures. Analyses must be subject to the based theme of natriuretic peptides. The discussion should be requisitioned with comparisons with other publications related to the theme of the dissertation. It is necessary to recast the conclusions and restructure the contributions. There are incorrect sources in the Bibliography.

Recommendations to the PhD student:

- To revise the dissertation work taking into account the critical remarks made.

Conclusion: I appreciate the work of Dr. Anton Dinkov on the topic "*Monitoring of levels of natriuretic peptides in patients with type 2 diabetes mellitus and heart failure with a preserved ejection fraction with the inhibitor of SGLT2 receptor antagonist empagliflozin*" as interesting in scientific terms and important for clinical practice. I believe that at this stage the dissertation work is subject to revision and in its presented form does not meet the requirements for the award of educational and scientific degree "Philosophy doctor", in accordance of the Academic Staff Development Act in the Republic of Bulgaria and the Regulations of the Ministry of education and the Medical University of Varna.

Based on the above facts and problems with the dissertation work of Dr. Anton Dinkov, I could not vote positively for the award of educational and scientific degree "Philosophy doctor", in the scientific specialty "Internal Medicine", professional direction 7.1 Medicine, field of higher education 7 Health and Sport.

I propose that the dissertation work be returned for processing and, if possible, new public protection.

May 17th 2021

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(Prof. Borislav Georgiev, MD PhD)

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