

OPINION

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Member of the Scientific Jury of 5 habilitated persons, determined by order №P-109-131 /
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on dissertation work

Monitoring the levels natriuretic peptide in patients with diabetes mellitus type 2 and cardiac failure with preserved ejection fraction on therapy with inhibitor of SGLT 2 receptor antagonist EMPAGLIFLOZIN

developed by Dr. Anton Levanevski Dinkov , PhD student in full-time education in the doctoral program "Internal Medicine", professional field 7.1. Medicine, enrolled by order № P-109-463 / 16.07.2018. of the Rector of MU-Varna

The opinion has been prepared in accordance with the Law for the Development of the Academic Staff in the Republic of Bulgaria (RAASRB), the Regulations on the Terms and Conditions for Acquiring Scientific Degrees and Occupying Academic Positions at the Medical University - Varna

In the recent years, data from clinical trials that have led to a change in the treatment model of patients with type 2 diabetes mellitus (DMT2) and established cardiovascular disease (CVD) have been presented. Data from Europe and the United States concerning the diagnosis and treatment of acute heart failure (AHF) for the past 10 years show that diabetes is one of the most common comorbidities, as its current incidence has become even more pronounced. Despite the availability of many different therapies for treatment of HF, mortality in patients with this diagnosis still remains high. This also explains the need to study the different methods for treatment of DMT2 in HF, in addition to standard therapy. For a long time, approaches to the treatment of DMT2 were focused on lowering blood sugar levels and the available therapies have not provided any additional cardio-vascular (CV) protection.

EMPA-REG OUTCOME is the first clinical trial for CV results with an antidiabetic drug - the SGLT-2 inhibitor empagliflozin. It convincingly demonstrates not only the CV safety profile but also the cardioprotective benefits of therapy for DMT2 and high CV risk: reduced risk of death by 38%, of hospitalization due to HF by 35% and a reduction in overall mortality by 32%. (... reduced risk of death and hospitalization due to HF by 38% and 35%, respectively, as well as a reduction in overall mortality by 32%).

Subsequently, results have been presented from other SS safety studies, some of which have shown benefits beyond glycemic control of relevant antidiabetic therapies. It should be borne in mind (It must be considered) that in the presence of HF there is a 4 times higher risk of developing diabetes than in patients without HF. Also, patients with DMT2 have a 2.5 times higher risk of developing HF than those without diabetes. DMT2 disease has been strongly associated with a worse prognosis in HF than the two categories of HF – with preserved ejection fraction and with reduced ejection fraction .

The current recommendations of the European Society of Cardiology from 2019 recommend empagliflozin as a means of preventing or delaying HF in patients with DMT2.

Empagliflozin is an oral, once-a-day, highly selective and reversible sodium-glucose cotransporter inhibitor 2 (SGLT-2) and the first approved drug for the treatment of DMT2, whose product information includes data on reducing the risk of cardiac death. Inhibition of SGLT2 with empagliflozin in patients with DMT2 and high blood sugar levels results in the removal of excess glucose in the urine. In addition, treatment with empagliflozin increases the excretion of sodium from the body, along with water, and thus reduces the volume load in the circulatory system (i.e. reduces the intravascular volume). Glucosuria, natriuresis, and osmotic diuresis observed with empagliflozin therapy may contribute to improved cardiovascular outcomes.

In light of the foregoing, I believe the thesis of Dr. Anton Dinkov is extremely actual and present new clinical evidence of cardiovascular effects of empagliflozin administered for treatment of patients with DM type 2 and HF with preserved ejection fraction (HFpEF).

The dissertation is presented on 139 pages, of which the review occupies 63 pages, purpose, tasks, methods and results - 43 pages, discussion of the results, conclusions and contributions - 6 pages. The used literature includes 157 sources, of which 5 in Bulgarian. The work includes 24 tables and 52 figures.

The goal is clearly formulated and substantiated by the literature review, namely - monitoring of cardiovascular parameters, renal function and metabolic status in diabetics with type 2 diabetes mellitus and heart failure with preserved ejection fraction of standard prior therapy for diabetes mellitus and heart failure. With the addition of empagliflozin 10 mg for 90 days. Achieving this goal is a prerequisite for obtaining new information to help the clinician. The tasks are placed clearly and specifically, to resolve the purpose intended. They are achievable.

The design of the study is not taken into account correctly - it is not clear whether the study is prospective or retrospective. The group of 50 patients with type 2 diabetes and HFpEF is from the contingent of UMHAT "St. Marina ", but it is not specified whether they have been hospitalized or outpatient. However, the study was based on using modern diagnostic methods developed on the rich clinical material. The information is arranged systematically, the methods used for processing and presenting the results give a clear idea of what has been achieved.

To accomplish the tasks the author uses a wide range of methods: clinical methods, echocardiography with all the detailed parameters, ultrasound of the kidneys, 6-minute walking test, laboratory tests - NT-proBNP levels, changes in blood pressure and heart rate, changes in body weight, monitoring of renal function. The author has used a sufficient number of methods for a modern statistical analysis, which are correctly applied depending on the type of variables and their type of distribution.

There are some extensive explanatory notes in the Results section, which should rather be in the Methods section. The results obtained are plausible in their essence. Not all are statistically significant or reliable, which is probably due to the small number of patients studied. But all are enough for the conclusions drawn.

The discussion of the results was done in the generally accepted format, with a discussion in the context of international studies on the topic. Here the disadvantage of the dissertation is the relatively small volume of the section, 6 pages, some of the results could be discussed in more depth.

Based on the results obtained, the author draws his conclusions with an original and confirmatory nature. The conclusions are logical, 5 in number, but

do not completely coincide with the set tasks. The author notes 3 significant contributions to the dissertation:

1. For the first time in Bulgaria the levels of NT - proBNP in diabetics with heart failure with preserved ejection fraction of therapy with an inhibitor of SGLT 2 receptors-empagliflozin are studied.

2. For the first time, cardiac function is assessed using some echocardiographic criteria - EF%, TDV, TSV, indexed left atrial volume, mitral blood flow and tissue Doppler in patients treated with empagliflozin in an attempt to explain the positive effects of the drug reported by EMPA -REG OUTCOME.

3. For the first time, functional capacity was monitored by a six-minute exercise test in diabetics on empagliflozin therapy.

Attached are 6 scientific activities of the author - publications and participation in scientific forums related to the topic of the dissertation , of which 4 in Bulgarian and 2 in English.

Remarks on the dissertation:

1. The survey is too large for the volume of work presented and occupies about 87%
2. The discussion of the results occupies about 8%, which is insufficient.
3. Some methods (e.g the 6-minute walking test) are extremely poorly explained and poorly researched and interpreted.
4. The review uses mainly figures copied from English sources, which could be adapted and translated into Bulgarian. The titles of the figures do not indicate their original author and there is no copyright clarification!
5. The tables and figures explaining the results are not well presented, they transmit the statistical tables directly and do not comply with the necessary presentation in scientific work.
6. The conclusions do not fully correspond to the set tasks.
7. There is a discrepancy in the texts presenting the goals and objectives in the abstract and the dissertation. The first representative pages of the dissertation, which begins directly with "Content", are missing.
8. There are a number of grammatical and stylistic errors in the dissertation. It is not well formatted according to the requirements for presenting a scientific paper.

In conclusion, I believe that the topic is particularly relevant, provides new information on the problem, but the dissertation requires additional work - supplementing the description of the methods used, improved graphical presentation of the results, more in-depth and extensive interpretation and discussion of the results, correction of grammatical and stylistic errors.

I propose to the Scientific Jury to vote negatively for awarding Dr. Anton Levanevski Dinkov the educational and scientific degree "Doctor" in the scientific specialty " Internal Medicine ".

15.05.2021

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