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Complications Research

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Herrn Jens Spahn
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IQWiG report on proteomics

Dear Minister Spahn,

We, the investigators of the PRIORITY study, many of us leading experts in the field of diabetes and/or nephrology, have seen the press release (https://www.iqwig.de/en/press/press-releases/diabetic-nephropathy-study-results-on-proteomic-analysis-do-not-show-benefit.13130.html) and the report of the IQWiG on the results of the PRIORITY study. We are concerned about the many inaccuracies in these documents, leading to a misinterpretation of the PRIORITY study results. As such, we wish to clarify certain facts, as misunderstandings may lead you to erroneous conclusions:

The primary endpoint of the PRIORITY study was development of confirmed microalbuminuria in all individuals with available data (observational cohort). Secondary endpoints included reduction in incidence of microalbuminuria with spironolactone (trial cohort, intention-to-treat population) and association between CKD273 risk score and measures of impaired renal function based on estimated glomerular filtration rate (eGFR; observational cohort).

IQWiG was commissioned by the Federal Joint Committee to investigate to the best of its knowledge and belief the potential benefit of urine proteome analysis based on the following 3 scenarios:

1) Significant early detection and significant benefit of early spironolactone therapy (optimum)

2) Significant early detection but no benefit of the spironolactone therapy

3) No significant early detection

The main conclusion of the PRIORITY study was "In people with type 2 diabetes and normoalbuminuria, a high-risk score from the urinary proteomic classifier CKD273 was associated with an increased risk of progression to microalbuminuria over a median of 2·5 years, independent of clinical characteristics." The study could not demonstrate a significant benefit of the intervention with spironolactone.

Thus, the study clearly and significantly demonstrated the ability to predict microalbuminuria and renal disease based on several parameters, including loss of renal function. Based on the questions raised by the G-BA, the study shows that scenario 2, "significant early detection" but no benefit of spironolactone therapy, is correct.

Contrary to the opinion expressed in the report, both microalbuminuria and loss of glomerular filtration rate are highly patient-relevant endpoints as acknowledged by regulatory agencies, as they are associated with increased morbidity and mortality. This has been known for decades and was further substantiated at a recent conference

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held in collaboration with National Kidney Foundation, FDA and EMA with data from epidemiology and clinical studies which were metaanalysed and published. The current knowledge and state-of-the-art is clearly mentioned in several directives and guidelines and accepted by the European Medical Agency.

In terms of medical expertise, the report is as far as we can see, based solely on the assessment of the independent expert, Dr Egidi. Dr. Egidi is a general practitioner with focus on chirotherapy. It is incomprehensible why no experts on diabetes or kidney disease was consulted.

The primary objective of the PRIORITY study was to evaluate the prognostic value of proteome analysis. This objective and the results related to the primary objective were not mentioned in the report. The endpoints defined as the primary study objective (occurrence of micro- or macroalbuminuria) and secondary objectives to determine 30 and 40% reduction of eGFR, achievement of CKD stage 3 or 4) were excluded from the consideration. This makes it difficult, if not impossible, to conclude correctly on the task commissioned by the Federal Joint Committee as mentioned above.

The Rapid Report contains other erroneous and/or misleading statements, e.g:

a.

- In the report, IQWiG claims that questions put to the study director, Prof. Rossing, remained unanswered.

- This is incorrect: Prof. Rossing replied to the mail and informed IQWiG that the current corona situation required delays.

b.

- IQWiG further states: "The manufacturer mosaiques diagnostics and therapeutics AG has not signed the agreement on the complete transfer of information.

- This is misleading. It is correct that mosaiques diagnostics and therapeutics AG stated that it does not have the requested data, which are under the sole control of the head of the study, Prof. Rossing, and therefore cannot sign an agreement on the transfer of data. It was recommended to contact Prof. Rossing.

Overall, we resent IQWiG's statement as neither objective nor scientifically correct, and apparently biased. We are concerned by the level at which our scientific results from the PRIORITY study are being applied by IQWiG and the apparent lack of medical expertise in the relevant areas of nephrology and diabetology.

Diabetes with chronic kidney disease is a major and increasing health problem. We are in urgent need for innovative tools for early diagnosis, and new medications to tackle this challenge as doctors and as society. Despite our positive results from the PRIORITY study showing the benefit or such a new diagnostic tool, affected patients who are in urgent need of necessary improvements would hope in vain.

To avoid misunderstanding: In the context of the current knowledge on therapeutic options for diabetic kidney disease, the PRIORITY study demonstrates that the current optimal management of type 2 diabetic patients consists of early detection of the risk of diabetic kidney disease based on the CKD273 scoring, and, in case of a positive result, other large studies suggest intervention with SGLT2 inhibitors can prevent or delay progression of kidney disease in diabetes.

Sincerely

Professor Peter Rossing MD on
behalf of

Professor Christian Delles MD

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Dr Goce Spasovski MD

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/cc.: The Gemeinsame Bundesausschuss

German Diabetes foundation, and European

Kidney Health Alliance.