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Proteomic analysis for detection of diabetic nephropathy in patients with diabetes mellitus and arterial hypertension[1]

Extract

[1] Translation of Chapters 1 to 6 of the rapid report D19-02 *Proteomanalyse zur Erkennung einer diabetischen Nephropathie bei Diabetes mellitus und arteriellem Hypertonus* (Version 1.1; Status: 2 July 2020 [German original], 5 August 2020 [English translation]). Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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This report was prepared in collaboration with external experts.

The responsibility for the contents of the report lies solely with IQWiG.

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Key statement

Research question

The objective of this investigation is to

- assess the benefit of a diagnostic-therapeutic strategy using proteomic analysis in comparison with a diagnostic-therapeutic strategy using no proteomic analysis and/or no diagnostics (= "conventional diagnostic-therapeutic strategy")

with regard to patient-relevant outcomes in patients with diabetes mellitus and arterial hypertension.

This is an update of one of the research questions of a prior report (D13-01), taking into account recently published literature.

Conclusion

The basis of the assessment was a randomized controlled trial that examined the effect of spironolactone 25 mg in persons deemed at high risk of developing diabetic nephropathy as predicted by proteomic analysis and CKD273 score.

With regard to the outcomes of all-cause mortality, chronic kidney disease, cardiovascular morbidity, retinopathy requiring treatment, serious adverse events, and discontinuation due to gynaecomastia, there was no hint of benefit or harm of proteomic analysis-based spironolactone administration in patients with type 2 diabetes mellitus, arterial hypertension, and normoalbuminuria. Data on health-related quality of life were not available.

All things considered, there is therefore no benefit or harm of a diagnostic-therapeutic strategy using proteomic analysis.

No ongoing or planned studies were found.

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List of abbreviations

Abbreviation	Meaning
ACE	angiotensin-converting enzyme
AE	adverse event
CI	confidence interval
DNP	diabetic nephropathy
eGFR	estimated glomerular filtration rate
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HbA1c	glycated haemoglobin
HR	hazard ratio
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
OR	odds ratio
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)

1 Background

Proteomic analysis is a diagnostic method intended to detect or predict diabetic nephropathy (DNP) at a very early stage – before conventional diagnostics.

In report D13-01 [1], a diagnostic-therapeutic strategy using proteomic analysis was investigated in comparison with a diagnostic-therapeutic strategy using no proteomic analysis and/or no diagnostics. The target population was patients with diabetes mellitus and arterial hypertension. In addition to assessing the benefit with regard to patient-relevant outcomes, the diagnostic and prognostic quality of proteomic analysis for the detection of DNP was to be investigated in the same patient group.

Due to a lack of suitable studies, the benefit or harm of a diagnostic-therapeutic strategy using proteomic analysis for the detection of DNP remained unclear. However, 1 ongoing study (Proteomic prediction and Renin angiotensin aldosterone system Inhibition prevention Of early diabetic nephRopathy In TYpe 2 diabetic patients with normoalbuminuria; PRIORITY) [2] was found which might contribute to answering the research question.

Subsequently, the Federal Joint Committee (G-BA) decided in September 2016 to suspend its decision making on proteomic analysis in patients with diabetes mellitus and arterial hypertension. The suspension was conditioned on questions still open in the G-BA's assessment being answered by informative scientific documents [3].

In December 2019, the assessment process was resumed. On 19 December 2019, the Institute for Quality and Efficiency in Health Care (IQWiG) was commissioned with assessing the benefit of proteomic analysis in patients with diabetes mellitus and arterial hypertension, particularly in consideration of the results of the meanwhile completed PRIORITY study.

The pathophysiology, epidemiology, and treatment of the affected patient group have already been described in report D13-01 [1].

2 Research question

The objective of this investigation is to

- assess the benefit of a diagnostic-therapeutic strategy using proteomic analysis in comparison with a diagnostic-therapeutic strategy using no proteomic analysis and/or no diagnostics (= “conventional diagnostic-therapeutic strategy”)

with regard to patient-relevant outcomes in patients with diabetes mellitus and arterial hypertension.

This is an update of one of the research questions of a prior report (D13-01), taking into account recently published literature.

3 Methods

This assessment represents an update of the assessment of proteomic analysis published in 2015 [1]. Unlike report D13-01, the present assessment is limited to the research question of the benefit assessment.

The target population of the benefit assessment are patients with diabetes mellitus and arterial hypertension. The experimental intervention is a diagnostic-therapeutic strategy using urine proteomic analysis. The comparator intervention is any diagnostic-therapeutic strategy using no proteomic analysis and/or no diagnostics.

The investigation examined the following patient-relevant outcomes:

- Mortality
- Morbidity (e.g. end-stage kidney disease as well as coronary, cerebrovascular, and peripheral artery disease)
- Health-related quality of life (including activities of daily living)
- Adverse events

Only randomized controlled trials (RCTs) were included in the benefit assessment. There were no restrictions regarding the study duration.

A systematic search for studies was conducted in the databases MEDLINE, Embase, and Cochrane Central Register of Controlled Trials.

The following sources of information and search techniques were additionally used: Study registries, manufacturer queries, and author queries.

Relevant studies were selected by 2 persons independently from one another. Any discrepancies were resolved by discussion between them. Data were extracted into standardized tables. To assess the qualitative certainty of results, the risk of bias at study and outcome levels, if applicable, was assessed and rated as high or low. The results of the individual studies were described grouped by outcome.

For each outcome, a conclusion was drawn on the evidence for (greater) benefit and (greater) harm, with 4 levels of certainty of conclusions: Proof (highest certainty of conclusions), indication (moderate certainty of conclusions), hint (lowest certainty of conclusions), or neither of the above 3. The latter was the case if no data were available or the available data did not permit classification into one of the 3 other categories. In that case, the conclusion “There is no hint of (greater) benefit or (greater) harm” was drawn.

4 Results

4.1 Results of the comprehensive information retrieval

The information retrieval found 1 randomized controlled trial to be relevant for the research question of this benefit assessment. No planned or ongoing studies were found.

The search strategies for bibliographic databases and trial registries are found in the appendix. The most recent search was conducted on 24 January 2020.

To supplement other information sources, an author query asked the sponsor of the PRIORITY study to transfer the complete study data. In response, the sponsor transferred various study documents containing information on methods and results (see Table 1) but no document corresponding to a study report in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E3. In drug approval studies, a study report in accordance with ICH E3 can be assumed to be available, but the PRIORITY study is not an approval study. An inquiry to the sponsor requested, among other items, confirmation of complete data transfer and of non-availability of a study report in accordance with ICH E3, but the inquiry was left unanswered. Hence, it remained unclear whether the data transfer was complete.

Table 1: Study pool of the benefit assessment

Study	**Available documents**					
	Full publication (in professional journals)		**Registry entry / results report from the study registries**	**Study report / publicly accessible**	**Study protocol / publicly accessible**	**Further documents**
	Public-ation of study design	**Public-ation of study results**				
PRIORITY	Yes [4]	Yes [5-7]	Yes [2,8,9] / no	Yes (Statistical Report [10], ICH-E3 synopsis [11]) / No	Yes (study protocol [12], SAP [13]) / Yes	Yes (manuscript submitted for publication [14])
ICH: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; SAP: Statistical Analysis Plan						

4.2 Characteristics of the study included in the assessment

The PRIORITY study [6] is described as a multicentre, prospective cohort study with embedded double-blind RCT. A total of 2277 persons were examined with regard to their eligibility for the study, and ultimately, 1775 patients with type 2 diabetes mellitus, normoalbuminuria, and preserved renal function were included and treated in accordance with local guidelines. Urine proteomic analysis was conducted in all participants, and the CKD273 score was determined on this basis. Using a predefined threshold, participants at high DNP risk based on their CKD273 score (> 0.154; n = 216) were compared with participants at low DNP risk (≤ 0.154; n = 1559). Among the persons deemed at high risk, 95% had arterial hypertension [7] and nearly

90% took either an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin II receptor blocker (ARB). Participants were to continue taking their existing medication, including the renin-angiotensin-aldosterone system inhibitors, unless otherwise recommended by the treating doctors.

The PRIORITY study has a hybrid design. In this type of design, only a defined subpopulation is randomized (like in an enrichment design) – but all participants are followed up [15]. Using the high-risk group formed on the basis of the CKD273 score, 209 persons were randomly allocated to spironolactone 25 mg once daily or placebo, and the persons in the low-risk group were followed up as well. Hence, the study consists of 2 different parts. The randomized part of the study, hereinafter referred to as PRIORITY RCT, aimed to answer the question whether patients deemed at high DNP risk will benefit from an early proteomic analysis-based intervention. Hence, the RCT investigated an aspect of the research question of the report. The study also included a prognostic research question, for which it compared the high-risk versus low-risk groups formed on the basis of the CKD273 score. Below, this part is referred to as the PRIORITY prognosis study. In terms of contributing to the benefit assessment, the PRIORITY prognosis study is suitable only under certain conditions, particularly proof of treatment effect in the PRIORITY RCT.

Measures were taken to blind both patients and treatment providers. The primary outcome of the study – both in the PRIORITY RCT and PRIORITY prognosis study – was confirmed microalbuminuria. RCT participants were examined after 2 weeks, 13 weeks and every 13 weeks thereafter. The study started in March 2014 (start of recruitment). At study start, the original plan was to follow up all participants for 3 years. Briefly after study start, a protocol amendment scheduled the last data collection, i.e. the end of the study, for September 2018, for a potential maximum follow-up of 4.5 years. The median actual follow-up was 2.51 years for the PRIORITY prognosis study (n = 1775) and 2.5 years for the PRIORITY RCT (n = 209).

4.3 Overview of patient-relevant outcomes

Table 2 presents an overview of the available data on patient-relevant outcomes from the included PRIORITY RCT. The following patient-relevant outcomes were collected and usable for the benefit assessment: all-cause mortality; chronic kidney disease (end-stage kidney disease); a composite outcome consisting of serious fatal and non-fatal cardiovascular events and all-cause mortality with reported events on ischaemic heart disease, stroke, heart failure, and all-cause mortality; laser treatment due to retinopathy; serious adverse events; discontinuation due to gynaecomastia.

Data on health-related quality of life were not available.

Table 2: Matrix of patient-relevant outcomes

Study	Outcomes						
	Mortality	Morbidity					QoL
					Adverse events		
	All-cause mortality	Chronic kidney disease	Cardiovascular morbidity	Retinopathy requiring treatment	SAE	Discontinuation due to AEs	Health-related quality of life
PRIORITY RCT	●	●[a]	●[b]	●	●	●[c]	–

●: Data were reported and were usable.
–: Outcome not surveyed.

a: Usable were data on end-stage renal disease. Further operationalizations available for stage 3 and 4 chronic kidney disease are unsuitable for distinguishing permanent loss of kidney function from eGFR fluctuations; therefore, they cannot be used as patient-relevant outcomes.

b: Results were available on a composite outcome consisting of serious fatal and non-fatal cardiovascular events and all-cause mortality as well as on the individual components which occurred, namely ischaemic heart disease, stroke, heart failure, and all-cause mortality.

c: Usable data were available only on the outcome of discontinuation due to gynaecomastia. At least some of the events on further specific reasons for discontinuation (hypertension, hyperkalaemia) represent treatment discontinuations due to defined laboratory parameters; therefore, it cannot be assumed that all events were of patient-relevant severity. These events (and potential further non-patient-relevant events) are also included in the analysis on the outcome of discontinuation due to AEs (total); hence, due to unclear patient relevance, they were likewise deemed unusable for the benefit assessment.

AE: adverse event; eGFR: estimated glomerular filtration rate; QoL: health-related quality of life; SAE: serious adverse event

Given that the available operationalizations were unsuitable for distinguishing permanent loss of kidney function from, e.g., fluctuations in estimated glomerular filtration rate (eGFR), it was not possible to include the results on stage 3 and 4 chronic kidney disease as well as on 30% or 40% reduction in eGFR from baseline in the consideration of patient-relevant outcomes.

Further, the following PRIORITY RCT outcomes were disregarded in the benefit assessment since they were either not viewed as sufficiently valid surrogate outcomes or their patient relevance was unclear: microalbuminuria, macroalbuminuria, change in albuminuria, eGFR changes, hyperkalaemia, discontinuation due to hypertension, total rate of adverse events (AEs), a composite outcome of laser treatment and/or retinopathy, glycated haemoglobin (HbA1c), and blood pressure values. This is discussed in more detail in Section A4.2.2 of the full report.

The report presented selected non-patient-relevant outcomes as supplementary information.

4.4 Assessment of the risk of bias of results

The risk of bias of the PRIORITY RCT was rated as high across outcomes. This was due to the unclear patient flow as a result of various data sources providing discrepant data with regard to study and treatment discontinuation as well as potentially large between-group differences in the percentage of study drop-outs.

While a total of 58 people prematurely discontinued treatment ("stopped IMP [investigational medicinal product] prematurely" [10]) according to the statistical report, the same total is reported as "withdrew from the study early" in the results publication ([6], p.7). In addition, while the statistical report identifies 38 out of 216 patients as "early termination", these patients are not reflected in the published data.

According to the publication, the premature discontinuation rates were 36 out of 102 (35.3%) in the spironolactone group versus 22 out of 107 (20.6%) in the placebo group. This means a potential between-group difference in premature discontinuations of 14.7 percentage points. In addition, it was unclear when the discontinuations occurred and whether patients were followed up after premature treatment discontinuation. No information was available on data replacement strategies.

All things considered, this resulted in a high risk of bias across outcomes. An author query including questions intended to clarify these aspects remained unanswered.

Therefore, a high risk of bias on the study level meant that, on this basis alone, the outcome-specific risk of bias of results on all outcomes was already deemed high.

4.5 Results on patient-relevant outcomes

4.5.1 Results on all-cause mortality

With regard to all-cause mortality, there was no statistically significant difference between treatment with spironolactone 25 mg and placebo: hazard ratio (HR) 1.13, 95% confidence interval (CI) [0.07; 18.1]; p = 0.93.

For the outcome of all-cause mortality, there is consequently no hint of benefit or harm of early proteomic analysis-based spironolactone administration.

4.5.2 Results on chronic kidney disease

The results on chronic kidney disease stage 3 and 4 or measured as relative (30% or 40%) eGFR deterioration were excluded from the benefit assessment because patient relevance was not ensured by the operationalizations.

Although end-stage kidney disease was not prespecified as an outcome, the report stated that no events arose.

For chronic kidney disease, there is consequently no hint of benefit or harm of early proteomic analysis-based spironolactone administration.

4.5.3 Results on cardiovascular morbidity

With regard to cardiovascular morbidity, results were available on a composite outcome consisting of serious fatal and non-fatal cardiovascular events and all-cause mortality as well as on the individual components which occurred, namely ischaemic heart disease, stroke, heart failure, and all-cause mortality. No significant difference between treatment with spironolactone 25 mg and placebo was found for either the composite outcome (HR 0.57, 95% CI [0.17; 1.88], p = 0.35) or any individual component.

For the outcome of cardiovascular morbidity, there is consequently no hint of benefit or harm of early proteomic analysis-based spironolactone administration.

4.5.4 Results on retinopathy requiring treatment

For the outcome of retinopathy requiring treatment, data were available on laser treatment due to retinopathy. No statistically significant difference was found between treatment with spironolactone 25 mg and placebo: HR = 4.22, 95% CI [0.88; 20.3]; p = 0.073.

Despite the notably large numerical difference to the disadvantage of spironolactone in the point estimate, there is no hint of benefit or harm of early proteomic-based spironolactone administration for retinopathy requiring treatment because the p-value is above the significance level of 0.05 and the lower limit of the associated 95% CI is far below the zero effect.

4.5.5 Results on (serious) adverse events

Results were used on serious adverse events and discontinuation due to gynaecomastia. Gynaecomastia is a known AE of spironolactone and was therefore an area of focus of the PRIORITY RCT.

With regard to serious AEs, there was no statistically significant difference between treatment with spironolactone 25 mg and placebo: odds ratio (OR) 0.82, 95% CI [0.40; 1.66]; p = 0.608.

For discontinuation due to gynaecomastia, there was likewise no statistically significant difference between treatment with spironolactone 25 mg and placebo: p = 0.065. Treatment was prematurely discontinued due to gynaecomastia by 3 men (4.3%) in the intervention group and 0 in the control group (effect estimator and CI not presented since they are of no informative value).

With regard to (serious) adverse events, there is consequently no hint of benefit or harm of early proteomic analysis-based spironolactone administration. The same is true for the outcome of premature discontinuation due to gynaecomastia, despite the fact that gynaecomastia is a well-known AE of spironolactone [16-18].

4.5.6 Results on health-related quality of life

No results on health-related quality of life were available.

For this outcome, there is consequently no hint of benefit or harm of early proteomic analysis-based spironolactone administration.

4.6 Evidence map

Table 3 below shows the evidence map regarding patient-relevant outcomes.

Table 3: Evidence map regarding patient-relevant outcomes

Mortality	Morbidity					QoL
				Adverse events		
All-cause mortality	Chronic kidney disease	Cardiovascular morbidity	Retinopathy requiring treatment	SAE	Discontinuation due to AEs	Health-related quality of life
	(⇔)	(⇔)[a]	⇔[b]	⇔	⇔	(⇔)[c]

⇔: no hint, indication, or proof

(⇔): no hint, indication, or proof; the 95% confidence interval for relative effect is so imprecise that neither halving nor doubling of effect can be ruled out

-: No (usable) data reported

a: Based on data on end-stage kidney disease. Further operationalizations available for chronic kidney disease are unsuitable for distinguishing permanent loss of kidney function from, e.g., eGFR fluctuations; therefore, they cannot be used as patient-relevant outcomes.

b: Based on data on the composite outcome consisting of serious fatal and non-fatal cardiovascular events and all-cause mortality (individual components which occurred: ischaemic heart disease, stroke, heart failure, and all-cause mortality).

c: Based on data on discontinuation due to gynaecomastia.

AE: adverse event; QoL: health-related quality of life; SAE: serious adverse event

5 Classification of the assessment result

The PRIORITY study was the first to examine early therapy (spironolactone 25 mg) based on the results of proteomic analysis in patients with type 2 diabetes mellitus and arterial hypertension; according to the authors, the study provides the first prospectively planned analysis of prognostic quality of proteomic analysis [6].

The available information does not suggest publication bias.

Since no study report according to ICH E3 was supplied, it remained unclear whether the data transfer by the sponsor was complete. But since the analyses planned as per the protocol were in fact included in the sent data, there was no evidence of selective reporting.

Classification of results of the PRIORITY RCT

For individuals at high risk based on their CKD273 score, the PRIORITY RCT showed no advantages with regard to patient-relevant outcomes in comparison with a diagnostic-therapeutic strategy without proteomic analysis and/or without diagnostics.

With regard to the primary outcome of confirmed microalbuminuria, the study did not reveal any potential advantages either. In addition, the study examined a series of further surrogate outcomes. However, any identified statistically significant differences were consistently to the disadvantage of spironolactone therapy. This was true for the surrogate outcomes of hyperkalaemia, eGFR < 60 mL/min/1.73 m^2 (considered stage 3 chronic kidney disease in the study), and the combined outcome of retinopathy and/or laser therapy due to retinopathy. These results are not interpretable as harm due to their lack of (or unclear) patient relevance. However, none of the examined outcomes suggest any potential advantages of early proteomic analysis-based spironolactone administration.

In this light, it must be noted that the use of spironolactone in the PRIORITY RCT was covered neither by regulatory approval [19,20] nor by guideline recommendations [21,22]. In addition, taking spironolactone in combination with ACE inhibitors, as done by the majority of patients, is potentially harmful due to the risk of life-threatening hyperkalaemia and therefore not recommended [20]. Regardless of its results, Overall, the PRIORITY RCT is unsuitable for justifying the off-label use of spironolactone in the therapeutic indication, particularly due to this combination therapy with ACE inhibitors.

Despite the results of the PRIORITY RCT, it therefore remains unclear which therapeutic consequence of proteomic analysis results might offer any benefit to patients.

The study's hybrid design is a special variant of an enrichment design. However, this study design covers only one aspect of the report's research question. Hence, the study design permits drawing a conclusion only about the extent to which persons deemed at high risk exhibit a nephroprotective effect of spironolactone administration. Without further suitable data on the

low-risk group, it does not allow any conclusions on whether performing this test and subsequent treatment is superior to not testing at all, as conceded by the authors (see [7]).

Classification of results of the PRIORITY prognostic study

Initially, it must be noted that in 2 respects, the PRIORITY prognostic study would not have met the inclusion criteria of IQWiG report D13-01. First, none of the relevant outcomes were considered, and second, only 77% of study participants met the inclusion criterion of arterial hypertension [7], a figure slightly below the minimum of 80% defined in the methods of the report.

Comparing the persons with high versus low DNP risk on the basis of their CKD273 scores allows drawing conclusions on the prognostic quality of the test. Since proteomic analysis is intended to prevent manifest kidney disease by means of therapy tailored to the test result, the primary question of interest is how well it can predict exactly these types of events. In their consideration of the study's limitations, the authors concede that the PRIORITY prognostic study did not examine prognostic quality with regard to outcomes which reliably indicate manifest chronic kidney disease (e.g. via multiple eGFR readings below defined thresholds, taken at adequate intervals), but instead primarily considered (confirmed) microalbuminuria [4]. As a rationale for this approach, the authors state that in a normoalbuminuric population, it takes up to 20 years, i.e., too long for events to occur in "hard" renal outcomes. However, this does not change the fact that microalbuminuria has limited informative value with regard to the progression of diabetic nephropathy [23]. In other words, even very good prognostic characteristics with regard to the development of microalbuminuria are unsuitable for demonstrating the test's predictive value for manifest kidney disease.

The results show that persons in the high-risk group are at nearly 2.5-fold higher risk of (confirmed) microalbuminuria than those in the low-risk group (HR 2.48, 95% CI [1.80; 3.42], $p < 0.001$; model adjusted for age, sex, HbA1c, systolic blood pressure, retinopathy, eGFR, and log[urine albumin-to-creatinine ratio]). Therefore, proteomic analysis and the CDK273 score can be used to identify patients at a higher risk of developing microalbuminuria. Simultaneously proteomic analysis identified only slightly less than one-third of the persons who developed microalbuminuria during the investigation period (sensitivity: 30.5%, 95% CI [24.5; 37.2]). Hence, it overlooked a majority of patients who might also benefit from intensified therapy in accordance with the study authors' hypothesis. Only slightly more than a quarter of those deemed at high risk developed microalbuminuria within the investigation period (positive predictive value: 28.2%, 95% CI [22.7; 34.6]). Hence, the majority of patients will not develop microalbuminuria in the medium term, despite being deemed at higher risk of DNP.

Statement on the potential of proteomic analysis

On the basis of the documents on the method overall available to the Institute, the potential of a required treatment alternative cannot be identified.

6 Conclusion

The basis of the assessment was an RCT that examined the effect of spironolactone 25 mg in persons deemed at high risk of developing diabetic nephropathy as predicted by proteomic analysis and CKD273 score.

With regard to the outcomes of all-cause mortality, chronic kidney disease, cardiovascular morbidity, retinopathy requiring treatment, serious AEs, and discontinuation due to gynaecomastia, there was no hint of benefit or harm of proteomic analysis-based spironolactone administration in patients with type 2 diabetes mellitus, arterial hypertension, and normoalbuminuria. Data on health-related quality of life were not available.

All things considered, there is therefore no benefit or harm of a diagnostic-therapeutic strategy using proteomic analysis.

No ongoing or planned studies were found.

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Please see full rapid report for full reference list.

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Appendix A – Search strategies

A.1 – Searches in bibliographic databases

1. MEDLINE

Search interface: Ovid

- Ovid MEDLINE(R) 1946 to January Week 3 2020
- Ovid MEDLINE(R) Daily Update January 22, 2020

The following filter was adopted:

- RCT: Lefebvre [24] – Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version (2008 revision)

#	**Searches**
1	Diabetic Nephropathies/
2	*Kidney Diseases/ur [Urine]
3	((diabetic* or diabetes*) adj6 nephropath*).ti,ab.
4	chronic kidney disease*.ti,ab.
5	or/1-4
6	Proteomics/
7	Proteome/an [Analysis]
8	Biological Markers/ur [Urine]
9	proteom*.ti,ab.
10	((urine* or urinary*) adj6 biomarker*).ti,ab.
11	or/6-10
12	randomized controlled trial.pt.
13	controlled clinical trial.pt.
14	(randomized or placebo or randomly or trial or groups).ab.
15	drug therapy.fs.
16	or/12-15
17	16 not (exp animals/ not humans.sh.)
18	and/5,11,17
19	18 not (comment or editorial).pt.
20	19 and (english or german).lg.
21	20 and 20150809:3000.(dt).

Search interface: Ovid

- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations 1946 to January 22, 2020
- Ovid MEDLINE(R) Epub Ahead of Print January 22, 2020

#	**Searches**
1	((diabetic* or diabetes*) adj6 nephropath*).ti,ab.
2	chronic kidney disease*.ti,ab.
3	or/1-2
4	proteom*.ti,ab.
5	((urine* or urinary*) adj6 biomarker*).ti,ab.
6	or/4-5
7	3 and 6
8	(clinical trial* or random* or placebo).ti,ab.
9	trial.ti.
10	or/8-9
11	7 and 10
12	11 not (comment or editorial).pt.
13	12 and (english or german).lg.
14	13 and 20150809:3000.(dt).

2. Embase

Search interface: Ovid

- Embase 1974 to 2020 January 22

The following filter was adopted:

- RCT: Wong [25] – Strategy minimizing difference between sensitivity and specificity

#	**Searches**
1	Diabetic Nephropathy/
2	((diabetic* or diabetes*) adj6 nephropath*).ti,ab.
3	*Kidney Diseases/co, di [Complication, Diagnosis]
4	chronic kidney disease*.ti,ab.
5	or/1-4
6	proteom*.ti,ab.
7	Proteomics/
8	Protein Analysis/
9	Proteome/an [Analysis]
10	Biological Markers/
11	((urine* or urinary*) adj6 biomarker*).ti,ab.
12	Urinary Proteomics/
13	or/6-10
14	Urinalysis/
15	Urine Level/
16	Protein Urine Level/
17	(urine* or urinary*).ti,ab.
18	or/14-17
19	(13 and 18) or 11 or 12
20	(random* or double-blind*).tw.
21	placebo*.mp.
22	or/20-21
23	and/5,19,22
24	23 not medline.cr.
25	24 not (exp animal/ not exp human/)
26	25 not (Conference Abstract or Conference Review or Editorial).pt.
27	26 and (english or german).lg.
28	26 and 20150808:3000.(dc).

3. The Cochrane Library

Search interface: Wiley

- Cochrane Central Register of Controlled Trials: Issue 1 of 12, January 2020

#	Searches
#1	MeSH descriptor: [Diabetic Nephropathies] explode all trees
#2	(diabetic* or diabetes*) near/6 nephropath*
#3	MeSH descriptor: [Kidney Diseases] this term only and with qualifier(s): [urine - UR]
#4	chronic kidney disease*
#5	#1 or #2 or #3 or #4
#6	MeSH descriptor: [Proteomics] explode all trees
#7	MeSH descriptor: [Biomarkers] this term only and with qualifier(s): [urine - UR]
#8	proteom*
#9	(urine* or urinary*) near/6 biomarker*
#10	#6 or #7 or #8 or #9
#11	#5 and #10 with Cochrane Library publication date Between Jun 2015 and Feb 2020, in Trials

A.2 – Searches in study registries

1. ClinicalTrials.gov

Provider: U.S. National Institutes of Health

- URL: http://www.clinicaltrials.gov
- Type of search: Advanced Search

Search strategy
(proteome OR proteomics) AND (diabetic nepropathy OR kidney disease)

2. International Clinical Trials Registry Platform Search Portal

Provider: World Health Organization

- URL: http://apps.who.int/trialsearch
- Type of search: Standard Search

Search strategy
proteom* AND diabetic nephropathy OR proteom* AND kidney disease