The Effect of Fibrates on Kidney Function and Chronic Kidney Disease Progression: Protocol for a Systematic Review.

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Protocol

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Abstract

Background/Objectives: Fibrates reduce cardiovascular risk in the general population and in patients with chronic kidney disease (CKD). Although, they are commonly used as second-line agents in addition to statins for hypertriglyceridemia, their use in CKD is limited due to a decrease of glomerular filtration rate (GFR) at treatment initiation. This change in GFR is reversible with fibrate discontinuation. Importantly, randomised control trials with fibrate treatment have demonstrated reduction in proteinuria and benefit for microvascular diabetic complications. In addition, a number of experimental studies have shown nephroprotective effects with fibrates through attenuation of renal fibrosis and inflammation. Thus, the effect of fibrates on renal outcomes remains undetermined. The objective of this systematic review is to summarize the evidence from randomised controlled studies and provide pooled estimates on the effect of fibrates on short- and long-term renal outcomes.

Methods/Design: The study will be contacted according to the Cochrane Collaboration principles for Systematic reviews. We will include randomised trials comparing fibrate to placebo or studies comparing the addition of fibrate on statin versus statin alone and reporting on the short- and long-term effects on renal function, CKD progression and proteinuria. We will examine studies including patients with established CKD and those studies including patients at risk of developing CKD, separately. A comprehensive summary of the evidence will be reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses. Data from included studies suitable for metanalysis will be analyses accordingly to provide quantitative estimates using a random effects model. The Cochrane Collaboration tool for assessing the risk of bias in randomized clinical trials will be utilised. The quality of the evidence from included studies will be addressed descriptively using GRADE (Grading of Recommendations, Assessment, Development and Evaluations).

Discussion: The results of this systematic review will be informative for clinicians. A summary of high-level evidence with robust estimates of the effect of fibrates on safety and renal outcomes may be used to inform clinical practice guideline development for dyslipidaemias and primary and secondary prevention of CVD.

Systematic review registration: PROSPERO CRD42020187764

Background:

Chronic kidney disease (CKD) is highly prevalent in people with established cardiovascular disease (CVD) and in patients presenting with acute cardiovascular events.[1,2] Moreover, CKD is an independent risk factor for CVD and commonly co-exists with a combination of traditional metabolic and vascular risk factors, such as, hypertension, diabetes, obesity and dyslipidaemia.[3,4,5] In patients with renal impairment, CVD is a leading cause of mortality and the risk of death by a cardiovascular cause is higher than the risk of renal disease progression to end stage kidney disease (ESKD).[6] Thus, primary and secondary

prevention for CVD are of paramount importance in the care of patients with CKD. Lipid-lowering therapy was shown to reduce the risk of major CVD events and vascular mortality in non-dialysis CKD patients.[7,8]

Patients with CKD have a distinct lipid profile; most commonly characterised by elevated triglycerides, low HDL levels and variable LDL and total cholesterol levels.[9,10] Nonetheless, the qualitive changes in the lipid profile of patients with CKD are considered the main driver of atherosclerosis. Triglyceride-rich lipoproteins are observed in elevated levels in CKD and have been associated with subclinical atherosclerosis, as well as, coronary artery disease and mortality.[11–13] Fibrate treatment reduces cardiovascular risk in the general population and patients with CKD and can be used as a second-line agent to control hypertriglyceridemia. Although fibrates are widely used in the general population, their use in CKD is limited due to safety concerns in view of moderate decrease in glomerular filtration rate (GFR) at treatment initiation. The decrease in eGFR is reversible upon fibrate discontinuation. In addition, proteinuria reduction has been observed in CKD studies with the use of fibrates[14,15] and a number of experimental studies have shown nephroprotective benefits at the cellular level[16,17]. Thus, their effect on safety, long term renal disease and preventing CKD progression are unknown.

Objectives:

The purpose of this systematic review and metanalysis is to determine the short-term effects of fibrates on kidney function and the longer-term effects on proteinuria, renal disease progression to end stage kidney disease (ESKD) in patients with established CKD and patients at risk of developing renal disease.

Methods And Design:

The study will be contacted according to the Cochrane Collaboration principles for Systematic reviews[18] and will be reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (additional file 1).[19,20] The study is registered with the International Prospective Register of Systematic Reviews (PROSPERO, https://www.crd.york.ac.uk/PROSPERO) with the registration number CRD42020187764.

Eligibility criteria:

We have used the Population, Intervention, Comparator, Outcomes, Study design (PICOS) criteria[21] to formulate our research question and define clear study objectives.

Study population:

Adult patients (older than 18 years old) with chronic kidney disease or at risk of developing CKD will be included. The following inclusion and exclusion criteria for the examined studies were utilised (table):

Inclusion criteria:

We will use the following criteria to define patients with CKD or at risk for developing CKD:

[1] patients with eGFR < 60 ml/min/1.73m^2 with or without proteinuria estimated with any of the following formulas: Cockcroft-Gault, MDRD or CKD-EPI.

[2] patients with CKD stage I, II, III and IV according to the CKD nomenclature used by the Kidney Disease: Improving Global Outcomes (KDIGO).[22]

[3] patients with measured GFR < 60 ml/min/1.73m^2

[4] patients with proteinuria even if eGFR > 90ml/min/1.73m^2

[5] patients with major risk factors for developing CKD or proteinuria; hypertension, diabetes, dyslipidaemias, obesity, cardiovascular disease (heart failure, stroke, ischemic heart disease, coronary revascularization).

Exclusion criteria:

[1] Paediatric patients (< 18 years of age)

[2] any form of renal replacement therapy (peritoneal dialysis or haemodialysis) transplantation or eGFR < 15ml/min/1.73m^2

Types of intervention:

We will include studies which examined the use of fibrate alone or fibrate in addition to any statin. The fibrate utilised may be any of the following: fibrate, clofibrate, clofibric acid, bezafibrate, gemfibrozil, fenofibrate, procetofen.

Comparators:

The comparator group for patients receiving fibrate alone will be placebo or no intervention (fibrate vs placebo/no intervention). The comparator group for patients receiving fibrate in addition to statin will be statin and placebo or statin alone (Fibrate + Statin vs Statin alone).

Outcomes:

The primary outcomes will be change in serum creatinine, change in renal function (using any GFR estimation formula or measured GFR), CKD progression, development of ESKD, change in proteinuria, development of proteinuria, proteinuria reduction, mortality.

The secondary outcomes will include adverse events and mortality.

Study Design/Setting:

Randomized controlled trials

Languages:

We will not impose language restrictions

Search Strategy:

The electronic databases MEDLINE/SCOPUS/COCHRANE LIBRARY/ and Clinical Trial Registers (clinicaltrials.gov; clinicaltrialsregistry.eu) will be searched from inception until July 2020. We will use custom designed search algorithms consisting of Medical Subject Headings (MeSH) terms, relevant short terms and combinations of terms either in the title or abstract for the following: fibrate, clofibrate, clofibric acid, bezafibrate, gemfibrozil, fenofibrate, procetofen, renal insufficiency, kidney failure, chronic kidney disease, albuminuria, serum creatinine, eGFR, glomerular filtration, creatinine clearance, proteinuria, renal impairment, dialysis, end stage renal disease, microalbuminuria, diabetes, hypertension, mortality, cardiovascular mortality, drug-related adverse events. The references of eligible studies will be checked for missing articles. We will not impose language restrictions, however, the final analysis will include studies published in English (additional file 2).

Study screening and exclusions:

Systematic review and metanalysis will include randomized control trials of fibrate compared to placebo or fibrate+statin compared to statin alone, conducted in adults with chronic kidney disease or hypertension, diabetes or high cardiovascular risk and reporting data on proteinuria, renal disease progression, ESRD and (drug related adverse events). The summary of inclusion and exclusion criteria is provided in the eligibility criteria section of this document. Studies will be considered eligible if they describe the association with short term change of eGFR or creatinine or creatine clearance and at the end of follow-up change in eGFR, creatinine clearance or creatinine, kidney disease progression, ESKD or dialysis, proteinuria or proteinuria reduction in the form of Hazard Ratio or Relative Risk. Authors of studies that did not have data on renal function will be contacted. In the initial phase, all citations will be screened via the title and abstract. Two reviewers will screen independently all the studies identified in the initial electronic search results and thus screening will be performed in duplicate manner. A third researcher will resolve any discrepancies. Following the initial screen, all the identified studies by title and/or abstract will be retrieved for full-text review by two researchers independently. The inclusion and exclusion criteria will be applied for the final selection of studies which will be analysed. Any discrepancies by the two independent reviewers will be resolved by a third independent reviewer in order to reach consensus. In the case that further information is needed before the final decision the authors will be contacted.

Data extraction:

Data will be extracted on a pre-designed ms excel sheet and will include (a) study main characteristics, design and methodology, (b) sample characteristics, intervention and comparator group characteristics and (c) outcomes.

Primary outcomes will include the effect of fibrates on proteinuria or albuminuria (new onset, progression or regression), effects of fibrates on kidney function (serum creatinine or eGFR or mGFR or 24-h urine creatinine clearance), effects of fibrates on rate of kidney function decline (i.e. mean annualized change in eGFR), effect of fibrates on incident chronic kidney disease, effect of fibrates on ESKD (defined as starting any type of haemodialysis, peritoneal dialysis or transplantation).

The secondary outcomes will include change in serum creatinine at < 4 months or early after initiation of fibrates (timing as per individual study) and any reported side effects, biochemical abnormalities or deaths.

Analysis plan:

Characteristics of included studies will be summarized on tables and presented in the form of narrative synthesis in the text. Suitability for metanalysis of the studies will be based on clinical, methodological and statistical homogeneity. Where metanalysis is possible we will analysed data accordingly:

a. For continuous outcomes (i.e. eGFR, creatinine), we will perform a generalised inverse variance analysis of mean difference between patients in intervention and control group, pre and post administration of intervention/treatment/placebo.
b. For categorical outcomes, risk estimates from each study, reported as hazard ratio (HR) or relative risk (RR) will be synthesized.

When available, we will use adjusted estimates from multivariate model. Pooled estimates will be calculated with a random-effects model (DerSimonian-Laird method) to account for both within and between study variability. Heterogeneity between synthesized studies to be calculated using the I^2 statistic and the presence of publication bias will be investigated graphically by precision funnel plots. All statistical analyses will be performed using STATA (Version 12, StataCorp, College Station, TX, USA).

Risk of bias:

The risk of bias will be assessed using the Cochrane Collaboration tool for assessing the risk of bias in randomized clinical trials[23] and the quality of the evidence from the included studies will be addressed descriptively using GRADE (Grading of Recommendations, Assessment, Development and Evaluations)[24]. Two reviewers will perform the risk of bias and quality assessment independently. The outcome will be reported in the form of a table and critical narrative review.

Subgroup analyses:

If possible, from available data, subgroup analysis will be performed in patients with diabetes compared to non-diabetic patients.

Discussion:

With the current systematic review, we aim to provide a comprehensive summary of the existing literature on an important clinical question, pertinent to general practitioners, nephrologists, cardiologists and clinicians who provide care for the primary and secondary CVD prevention and management in the general population and for patients with CKD. If the identified studies are suitable for metanalysis, we will provide robust quantitative estimates on the short- and long-term effects of fibrates on kidney function, proteinuria and kidney disease progression. We will only be including studies with high level of evidence, in the form of RCTs, and thus our analysis will be informative for clinical decision making and guideline development. A gap in the literature on this topic is evident. We anticipate underreporting of renal function and heterogeneity of the methods used to estimate and report eGFR and proteinuria. Authors will be contacted for all studies where this information is missing and heterogeneity will be assessed and reported utilising up-to-date guidelines and tools. The results of this study will be presented in the form of abstracts in conferences and will be submitted in peer-reviewed journals.

Abbreviations:

CKD, Chronic Kidney Disease

GFR, Glomerular Filtration Rate

GRADE, Grading of Recommendations, Assessment, Development and Evaluations

CVD, Cardiovascular Disease

ESKD, End Stage Kidney Disease

HDL, High Density Lipoprotein

LDL, Low Density Lipoprotein

PICOS, Population, Intervention, Comparator, Outcomes, Study design criteria

CKD-EPI, Chronic Kidney Disease – Epidemiology Collaboration equation

MDRD, Modification of Diet in Renal Disease Study equation

Declarations:

Ethic's approval and consent to participate:

Not applicable.

Consent for publication:

Not applicable.

Availability of supporting date:

Not applicable.

Competing interests:

None declared.

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Author's contributions:

AK conceived the study. All authors contributed to the final version of the analytical plan for this study. AK constructed the initial protocol draft. All authors critically reviewed and revised the final version of the protocol. All authors have read and approved the final version of the protocol.

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