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Reduction of albumin urinary excretion is associated with reduced cardiovascular events in hypertensive and/or diabetic patients. A meta-regression analysis of 32 randomized trials

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ABSTRACT

Background: The association between renal dysfunction and risk of cardiovascular (CV) events and mortality has been reported in several studies. However, it is unclear whether reduction in urinary albumin excretion (UAE) is associated with reduced risk of clinical events. Therefore, we sought to investigate, in a meta-regression analysis of randomized studies enrolling hypertensive and/or diabetic patients, whether changes in UAE are associated with changes in CV outcomes and all-cause mortality.

Methods: MEDLINE, ISI Web of Science, Cochrane Database and Scopus were searched for randomized trials enrolling more than 200 diabetic and/or hypertensive patients, reporting UAE at baseline and at end of follow-up and CV events [CV death, myocardial infarction (MI), and stroke], as well all-cause mortality.

Results: Thirty-two trials enrolling 80,812 participants were included in analyses. Meta-regression analysis showed that each 10% reduction of UAE was significantly associated with 13% reduction of MI (Regression Coefficient [RC]:0.0055; 95% Confidence Interval [CI]:0.0014 to 0.0095; p = 0.010), with 29% reduction of stroke (RC:0.0124; CI:0.0030 to 0.0218; p = 0.013) and with 14% reduction of the composite outcome (CV death, MI, stroke)(RC:0.0059; CI:0.0027 to 0.0090; p = 0.001), whereas not significantly associated with all-cause (RC:0.0028; CI:−0.0047 to 0.0103; p = 0.486) and CV mortality (RC:0.0028; CI:−0.0047 to 0.0103; p = 0.447). Results were mostly confirmed by sensitivity analysis. No heterogeneity or publication bias was detected.

Conclusions: Reduction in UAE is associated with reduced risk of MI and stroke in diabetic and/or hypertensive patients. These findings suggest that UAE changes may represent a valuable intermediate end-point for CV risk evaluation in clinical practice.

1. Introduction

The association between renal dysfunction and cardiovascular (CV) and mortality risk has long been recognized [1]. Functional renal impairment, identified as either reduced glomerular filtration rate (GFR) or abnormal albumin excretion, is an independent predictor of CV events and all-cause mortality [2]. Additionally, the adverse independent impact of renal dysfunction on CV outcomes has been demonstrated in patients at high CV risk with concomitant kidney disease [3] and in unselected populations with renal dysfunction [4].

In a normal kidney, urinary albumin excretion (UAE) should not exceed 10 mg/day [5]. Abnormal UAE may result from either alteration of the glomerular filtration barrier integrity or from tubular damage, or from a combination of these mechanisms [6]. Abnormal UAE is, therefore, a sensitive marker of chronic kidney disease [7], being also frequent in patients with hypertension [8] or chronic heart failure [9], with a prevalence of ~7% in the general adult population [10].

UAE has been demonstrated to predict CV and all-cause mortality as well as myocardial infarction (MI) independently and incrementally to conventional CV risk factors [11] and to GFR [2,12], even at values corresponding to moderate albuminuria [2]. A recent meta-analysis also showed that UAE is associated with increased risk of stroke, mostly in patients with previous ischemic cerebral events [13]. The incremental

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prognostic value of UAE for CV risk stratification has been mainly demonstrated in diabetic and hypertensive patients [11], leading to incorporation of UAE among CV risk markers in several [14–16], but not all, guidelines on management of CV risk [17,18].

Yet, the value of UAE as surrogate end-point for predicting CV risk is not established since there is no evidence that reduction in UAE is associated with reduced risk of CV events. Therefore, we sought to investigate, in a meta-regression analysis of randomized studies in hypertensive and/or diabetic patients, whether changes in UAE are associated with changes of CV outcomes and of all-cause mortality.

2. Methods

2.1. Data sources and searches

The study was designed according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement [19]. MEDLINE, Cochrane, ISI Web of Science, and SCOPUS databases were searched for articles published until May 2013 combining the following terms "albuminuria" AND "randomized controlled trial" AND ("diabetes mellitus" OR "hypertension"). No language restrictions were applied.

2.2. Study selection

Eligible for this meta-regression were randomized trials enrolling more than 200 patients with diabetes mellitus and/or hypertension, reporting UAE at baseline and at the end of follow-up and major CV events (CV death, MI, stroke) or all-cause death. Trials satisfying these criteria might include disparate pharmacological treatments (for hypertension or diabetes mellitus), using comparison of active drug treatment versus placebo or of different doses of active drugs.

2.3. Data extraction and quality assessment

Articles were screened for fulfillment of inclusion criteria by two independent reviewers (GS, PPF). Corresponding authors were asked to provide full-text articles, when not available. Reviewers compared selected trials and discrepancies were resolved by consensus. From each study, basic information about methods, baseline characteristics, treatments, albuminuria and outcomes were collected and entered into STATA (version 12.0, StataCorps, College Station, Texas) by one author (GS) and checked by another author (PPF). Methodological quality of trials was assessed by Detsky method [20].

2.4. Data synthesis and analysis

Pre-specified outcomes of the analysis were all-cause and CV mortality, MI and stroke; additionally, a composite of CV death, MI and stroke was also analyzed. Relative risks (RRs) of the effect of randomized treatments were calculated for each trial, with grouped data, by using the intention-to-treat principle. To evaluate progression of albuminuria, the achieved differences between UAE changes in active treatment and control groups (expressed as percent of baseline values) were considered (%ΔUAE = [(UAEtf – UAEtb) − (UAEcf – UAEcb)] / (UAEb)*100 where UAEf was end-study UAE in treatments (t) and controls (c), UAEb was baseline UAE in treatments (t) and controls (c)) [21]. Weighted random-effects meta-regression analysis was performed with the metareg command to test the relationship between UAE changes and log RR of clinical events [22]. The weight used for each trial was the inverse of the sum of the within-trial variance and the residual between trial variance. For all meta-regression analyses, the residual maximum likelihood (REML) methods were employed to explain residual heterogeneity not explained by potential effect modifiers, including an additive between-study variance component Tau^2 [23]. The significance level for all analyses was set at $p \leq 0.05$ (two sided).

2.5. Sensitivity analysis

To explore the robustness of the analysis, outlier trials were identified by the Tukey formula for outliers [24] and meta-regression analysis was repeated after the exclusion of these studies.

To assess the influence of potential effect modifiers, meta-regression analyses were conducted to test the relationship between potential pre-specified confounding variables mean age, duration of follow-up, study publication year, baseline UAE, percentage of patients with baseline normal or moderate or severe albuminuria, baseline blood pressure, changes in blood pressure from baseline to the end of follow-up, history of MI, history of stroke, percentage of diabetic patients, baseline GFR, changes in GFR from baseline to the end of follow-up, baseline glycemia, changes in glycemia from baseline to the end of follow-up, baseline glycosylated hemoglobin, changes glycosylated hemoglobin from baseline to the end of follow-up, Detsky quality score, type of treatment [anti-hypertensive or anti-diabetic; inhibitors of renin–angiotensin aldosterone system] and outcomes. The variables significantly correlated to outcomes were tested in a multivariate model including UAE changes.

The assumption of homogeneity between the treatment effects in different trials was tested by Q statistic and further quantified by I^2 statistic. A significant heterogeneity was defined by a $p < 0.05$ at Q statistic and by $I^2 \geq 30\%$, whereas $I^2 \leq 40\%$ might indicate a not relevant heterogeneity.

Weighted linear regression was used to evaluate potential publication bias, with the natural log of the odds ratio as dependent variable and the inverse of the total sample size as

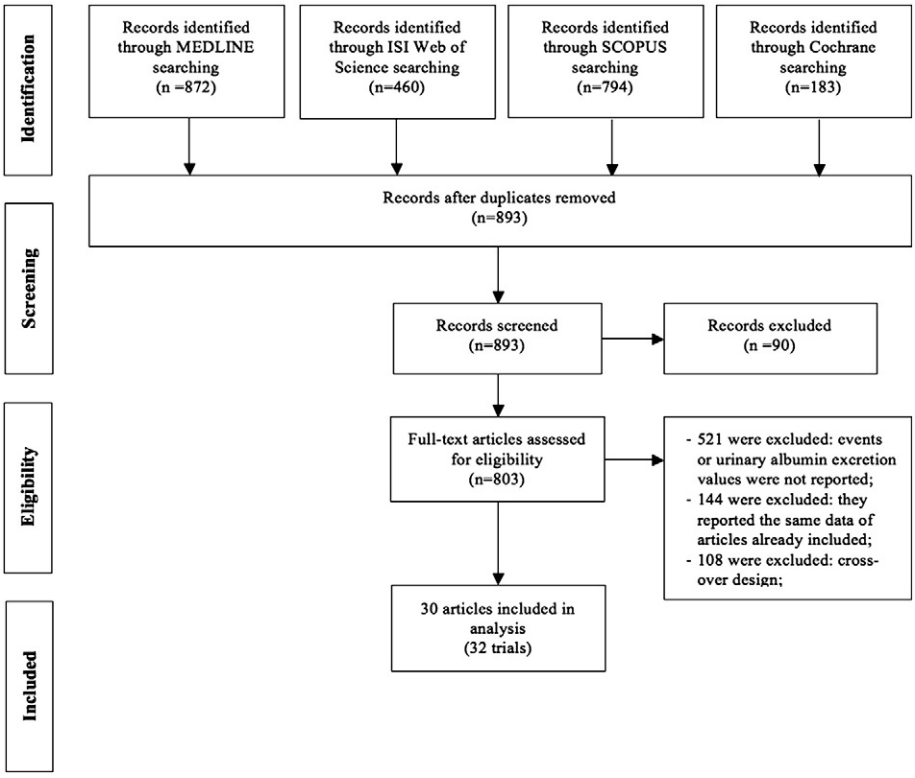

Fig. 1. Meta-analysis flow chart.