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Editorial Comments

Progression of renal disease—can we forget about inhibition of the renin–angiotensin system?

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Introduction

A recent meta-analysis by Casas *et al.* [1] concluded that ACE inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) reduce the progression of renal events by nothing more than their blood pressure (BP)-lowering effect. Surprisingly, this meta-analysis [1] contradicts most randomized controlled trials and other meta-analyses [2–5] investigating the effect of inhibition of the renin–angiotensin system (RAS) on the progression of chronic kidney disease. We have analysed the methodological quality of this meta-analysis and put it into perspective with other meta-analyses and large randomized controlled trials. We have come to the conclusion that there are serious problems, which undermine the conclusion drawn by Casas *et al.* [1].

Data analysis by Casas *et al.* [1]

How did the authors reach their surprising conclusion? Casas *et al.* [1] selected randomized controlled trials comparing inhibitors of the RAS with other regimens, defining the progression of renal disease as doubling of serum creatinine, end-stage renal disease (ESRD), change of glomerular filtration rate (GFR), change of serum creatinine or change of urine albumin. The most frequently used primary renal outcome, the combination of doubling of serum creatinine and ESRD, was not analysed. They found 127 trials, of which only 20 provided data on ESRD, and 18 on doubling of serum creatinine. They concluded from these trials

that ACEIs and ARBs are not more renoprotective than can be explained by lowering of BP in diabetic kidney disease, while in non-diabetic kidney disease a BP-independent renoprotective effect is uncertain. However, even with the inclusion of the neutral data of Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), ESRD was reduced by ACEIs/ARBs by 13% ($P = 0.04$) compared with other antihypertensive drugs, despite an insignificant difference in BP compared with the comparator group ($-1.3/-0.5$ mmHg) [1]. The ALLHAT effect was evident when, in a sensitivity analysis, the ALLHAT data were excluded when calculating a summary study effect in the meta-analysis: in this instance, there were statistically significant and clinically important renoprotective benefits of both large studies (24% reduction in risk of ESRD) and small studies (32% benefit). The latter positive findings are in stark contrast to those observed in the ALLHAT trial, i.e. a 5% increased risk of ESRD among ACEI-treated patients.

There was a similar reduction of relative risk (RR) for doubling of serum creatinine by 29% (borderline significance, $P = 0.07$) when the ALLHAT data were included in the meta-analysis, despite an insignificant difference in BP between ACEIs/ARBs and comparator groups ($-0.9/+0.2$ mmHg). Again, there was another important ALLHAT effect. Among small studies with fewer than 500 patients (i.e. those excluding ALLHAT) a statistically significant and clinically important 45% reduction in risk for doubling of serum creatinine was noted, while in the three large studies including ALLHAT, there was only a 3% reduction in risk [RR 0.97; 95% confidence interval (CI) 0.49–1.92] in the summary result. However, the crude rate of doubling serum creatinine in the intervention group was 8.7% and in the control group was 12.3% resulting in an RR of 0.7 (using a naïve calculation). Such a discrepancy between naïve calculation and pooled summary raises a suspicion about substantial heterogeneity across trials, which should probably not be pooled in the first place.

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Similar discrepancies for crude RR and the RR calculated in a random effects model apply to the six diabetic trials reporting the doubling of serum creatinine [1]. Based on the observations on doubling of serum creatinine one should conclude, in contrast to Casas et al. [1], that when compared with placebo (combined with other antihypertensives) ACEIs/ARBs reduce the RR for ESRD significantly and that the preponderance of the evidence supports an ACEIs/ARBs effect for reduction in the risk of doubling of serum creatinine.

It should be further noted that Casas et al. [1] reported a statistically significant renoprotective benefit of ACEIs/ARBs for the change in serum creatinine over study time, 7.07 μmol/l lower in ACEIs/ARBs treated subjects, and in urinary albumin excretion, 15.7 mg/day lower in ACEIs/ARBs treated subjects. In contrast, no benefit for ACEIs/ARBs was noted concerning the change of creatinine-based estimates of GFR. The latter is not entirely unexpected, given the imprecision of creatinine-based estimates of GFR. The endpoint 'change of GFR', was also strongly blurred by the overwhelming number of low-risk patients in the ALLHAT study, which did not collect data on urine albumin. It is highly likely that ALLHAT removed any effect of change in GFR in the non-ALLHAT studies. It is of further note that in diabetic patients, treatment with ACEIs/ARBs compared with other antihypertensive drugs reduced the loss of slope-based estimated GFR by 1.19 ml/min/1.73 m^2 (95% CI, −0.31, 2.69) which is clinically significant and of borderline statistical significance.

Blood pressure-independent nephroprotective effects of ACEI/ARB

Not only do we challenge the interpretation of Casas et al. [1] concerning the benefit from treatment with ACEIs/ARBs at the primary and secondary renal endpoints in their meta-analysis. We also doubt whether their assertion [1], that BP lowering per se is renoprotective, is borne out by the data they reported. They found across the three strata of mean change in systolic BP attained in the trials (−6.9, −1.6 and 1.5 mm Hg) a statistically significant and clinically important renoprotective benefit of ACEIs/ARBs: reduction of ESRD by 26 and 23%, respectively, in the first two strata and a non-significant reduction by 10% in the third. These observations are more consistent with an ACEIs/ARBs benefit that is fairly uniform over a broad range of mean BP change and are consistent with two recent large controlled trials [6,7] with different levels of target BP which do not support the assumption of Casas et al. [1], yet the AASK trial (African American study of kidney disease) supports the notion of renoprotection by ACEI [6].

The ALLHAT trap

It is important to note that Casas et al.'s [1] selection of trials may have been biased by the failure to fully consider the implications of inclusion and exclusion criteria in the selection of studies for their meta-analysis. Thus they end up with a very heterogeneous selection of trials. For example, as discussed in detail subsequently, inclusion of a single investigation, the ALLHAT study, profoundly influenced the summary measures of effect in the meta-analysis. ALLHAT [8] was the largest clinical trial of hypertension therapy ever conducted in the US. We emphasize that ALLHAT was not designed as a renal endpoint study and crucial renal data were not collected. The participants were randomly assigned to one of the three active treatment arms: chlorthalidone, amlodipine and lisinopril. ALLHAT exclusion criteria included heart failure, a serum creatinine in excess of 176.8 μmol/l and current treatment with an ACEI for underlying kidney disease (!). The net effect of these exclusion criteria may have been to create a cohort of individuals that was of considerably lower risk for renal outcomes, when compared with trials specifically designed to assess the reno-protective benefits of ACEIs and ARBs. In addition, the low renal risk of patients of the ALLHAT trial was very poorly defined. ALLHAT included about 12 000 hypertensive diabetic patients, for whom no information on urinary albumin or retinopathy was available [8], contrary to any diabetes guideline. As acknowledged by Rahman et al. [8] in the analysis of renal findings from ALLHAT but not in the meta-analysis of Casas et al. [1], presumably few patients with diabetic nephropathy were included in the ALLHAT trial. Recruitment for ALLHAT started 2 years after the publication of the landmark trial in diabetic nephropathy [9], which demonstrated the efficacy of ACEIs in diabetic nephropathy—an indication for ACE inhibition was an exclusion criteria for ALLHAT, however. The beneficial renal effect of RAS blockade is seen preferentially in patients with higher degrees of proteinuria [2]. In several trials, the effect of RAS blockade on proteinuria (and probably on progression) was enhanced by a negative sodium balance and abrogated by a high sodium intake [10]. In ALLHAT, diuretics were forbidden by protocol in the lisinopril-treated group, certainly leading to an underestimate of the renal benefits of ACE inhibition.

ACEI/ARB not indicated in diabetic nephropathy?

A further issue that must be raised is the claim by Casas et al. [1] that inhibition of the RAS is ineffective in diabetic nephropathy. Three large randomized controlled trials in patients with type 1 or type 2 diabetes and overt nephropathy [9,11,12] document

a substantial and significant reduction of progression with ACEIs or ARBs as compared with alternative antihypertensive agents achieving virtually identical BP control. These individual clinical trials have been complemented by a recent meta-analysis on primary prevention of overt diabetic nephropathy [5]. Included were 16 trials with 7603 patients that compared ACEIs with placebo, a calcium channel blocker (CCB), combined ACEIs and CCB or other antihypertensive therapy. Compared with placebo, ACEIs significantly reduced the development of microalbuminuria (RR 0.60; 95% CI 0.43–0.84) and tended to have a protective, but statistically marginal benefit for doubling of creatinine (RR 0.81; 95% CI 0.24–2.71) and all-cause mortality (RR 0.81; 95% CI 0.64–1.03). Compared with a CCB, ACEIs significantly prevented the development of microalbuminuria (RR 0.58; 95% CI 0.40–0.84).

Casas et al. [1] ignore most of these trials [5] and lump data from a smaller number of carefully defined patients (about 3500) together with data from the 12 000 people of the inadequately cared for patients in ALLHAT. We strongly suspect that in their sub-analysis on diabetes, Casas et al. [1] aggregated patients with diabetic nephropathy and diabetic patients with hypertensive nephropathy—obviously two different diseases [13]. The vast number of patients in the latter group from the ALLHAT trial [8]—in which no difference in renal outcomes was found between lisinopril and chlorthalidone, despite lower BP in the latter group—may have overridden the valid data in patients with true diabetic nephropathy which had documented a BP-independent effect of RAS blockade on progression [4,5]. Carefully designed trials [4,5,9,11,12] prompted guideline committees to declare ACEIs/ARBs as the first line treatment in patients with diabetic nephropathy. If—as we suspect—the conclusion of Casas et al. [1] is wrong (...'little justification for ACEI/ARB to be first-line choices for renoprotection in diabetes...'), numerous patients with diabetic nephropathy may be seriously at risk and harmed.

Comparison of Casas et al. with previous meta-analyses

How does the meta-analysis of Casas et al. [1]—which includes the ALLHAT trial that was not designed to be a trial on renal disease and lacks crucial information—compare with some preceding meta-analyses? Jafar et al. [2,3] published two meta-analyses of 11 trials addressing the effect of ACEIs vs active control or placebo on progression in non-diabetic renal disease. These authors used the much more valid approach in analysing individual patient data rather than restricting the analysis to the use of a published mean data, as did Casas et al. [1]. Jafar et al. [2,3] could thus appropriately adjust for confounding factors. The individual data bases the analysis

of Jafar et al. [2,3] on much firmer grounds than that of Casas et al. [1] and the results thus obtained have clinically important ramifications. ACEIs reduced the risk of progression (assessed as doubling of serum creatinine or ESRD) by 33% (95% CI 47–16) even when adjusted for BP and for several other confounders [2,3]. There was also no interaction term for current systolic BP and ACE inhibition. The latter may seem surprising. However, in placebo-controlled trials all patients received open-label anti-hypertensives (except ACEIs) to reach goal BP. In fact, the RR for progression only increased with higher on-treatment systolic BP in the presence of proteinuria; there was no relationship of progression to BP at low pressure levels.

No data—Proteinuria, the hallmark of renal risk

Jafar et al. [2,3] point out that the magnitude of the BP-independent renoprotection by ACEIs increased dramatically with increasing rates of proteinuria—an important confounder on which no information, whatsoever, is provided in the meta-analysis of Casas et al. [1]. This lack of information is the more deplorable since recent data strongly suggest that proteinuria and its reduction by therapy is pivotal when analysing the progression of renal diseases [14]. Casas et al. [1] do not even discuss the issue of proteinuria—an omission that renders this analysis virtually useless for nephrologists. What made the authors fall silent on this crucial point? Their conclusions [1] are almost totally based on the ALLHAT trial which provides roughly 90% of the data and in which quantitative data on proteinuria were not obtained—an irritating limitation even for a trial planned 10 years ago, since proteinuria is an important determinant of cardiovascular and renal risk. The publication of Rahman et al. [8] acknowledges that the subpopulation of patients in ALLHAT with renal disease presumably concerned mainly those with ischaemic renal disease—in which nephrologists would not expect an overwhelming renoprotective effect of ACEIs to begin with [2,3]. As a logical consequence, the authors of the ALLHAT trial state [8] that their findings by no means refute guidelines that recommend inhibition of the RAS in patients with diabetic or proteinuric nephropathies. This balanced statement contrasts with the blunt recommendation of Casas et al. [1] not to use ACEIs/ARBs as first line treatment in renal disease. Astonishingly the latter statement is based almost exclusively on the same ALLHAT data.

Lack of patient-level data

Unfortunately there are numerous further methodological limitations in Casas et al.'s [1] data. A meta-analysis on study level rather than on the level of

individual patient data is much more restricted in drawing valid conclusions on the effect of additional patient characteristics on study outcome. Relationships of any parameter with patient averages across trials may not be the same as relationships for patients within trials. There is a high risk for spurious relationships caused by so-called 'ecological fallacy', which can only be investigated with individual patient data [2,3]. The latter problem is specifically noteworthy for BP. Their meta-regression analysis on BP and renal outcomes relates the mean change of BP within tertiles to ESRD occurrence [1]. There is no guarantee that tertiles of mean BP within the studies reflect the relationship of individual BP with renal outcome. In addition, the authors [1] did not have information to adjust for important patient-related factors such as individual BP, age, gender, smoking, body weight and other factors that are related to renal outcomes. Finally, the meta-analysis [1] did not consider further important studies that are independent of changes in BP. RAS inhibition slowed down the progression even in advanced renal insufficiency [15] and failed to consider information that the degree of renoprotection depends on the intensity of RAS blockade [16].

Conclusions

Should we trust the meta-analysis of Casas et al. [1] or the guidelines of professional societies? Should we treat a diabetic patient with a proteinuria of 2 g/day without ACEIs or ARBs? Since the conclusion of the meta-analysis [1] is based on a very large, but for the purpose of renal outcomes, sub-optimally designed trial [8] which contradicts the bulk of much better designed trials [2–5], we are certain that the recommendation to use ACEIs/ARBs as first-line therapy in patients with proteinuric renal disease will stand the test of time. We add that the issue may be largely academic, since most patients with renal disease need several antihypertensive drugs anyway, to achieve target BP [17].

It is not a pleasant task to expose the shortcomings in other authors' works, but our conviction that the optimal treatment of our patients—specifically proteinuric patients—is at stake, overcame this inhibition and made us speak out for what we feel is the best proven treatment for our patients.

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