REVIEW ARTICLE

Should we prescribe blood pressure lowering drugs to every patient with advanced chronic kidney disease?

A comment on two recent meta-analyses

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KEY WORDS

angiotensin-converting enzyme inhibitors, antihypertensive treatment, chronic renal failure, dialysis patients

ABSTRACT

Antihypertensive treatment is an essential, life-prolonging measure in primary hypertension. It prevents apoplexy, myocardial infarction, and hypertensive kidney failure. Chronic kidney failure is associated with hypertension and an accelerated form of arteriosclerosis. Demise from cardiovascular affliction is a leading cause of death in renal patients (chronic renal failure stages II–IV, renal failure requiring dialysis, renal transplantation). What, then, is the role of antihypertensive treatment in such patients, and, specifically, what is achieved by renin-angiotensin-aldosterone (RAA) system modifying agents? Two meta-analyses have recently investigated these issues. An article in *The Lancet* evaluated eight studies on dialysis patients (n = 1679). It concluded that antihypertensives are beneficial in reducing cardiovascular morbidity and mortality. However, we criticize these conclusions and show that the data are not convincingly in favor of antihypertensive treatment. A meta-analysis in the *American Heart Journal* assessed the role of antihypertensive agents and RAA system modifying drugs in 45,758 patients (from 25 studies), who were in stages I–III of renal failure, i.e., not (yet) requiring dialysis. The authors claim that angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEI/ARB) significantly reduced cardiovascular outcomes. However, our analysis of the data is not consistent with their conclusions. It showed that the results were quite mixed, that the authors may have overemphasized the positive results, and that considering all the results, it should be concluded that antihypertensive treatments, including those with ACEI/ARB, may not be superior to placebo (sic!) in renal patients. Rather than doing meta-analyses, larger primary studies are needed to reveal the real role of antihypertensive treatments in renal patients.

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Introduction Two prestigious and widely read journals[1,2] have recently published a meta-analysis each on the potential effect of the treatment of arterial hypertension on cardiovascular endpoints in renal patients. *The Lancet* article[1] focused on patients receiving dialysis treatment (hemodialysis [HD], peritoneal dialysis [PD]), while the publication in the *American Heart Journal*[2] took interest in predialysis patients with hypertension – it specifically addressed the issue of any preferential effects of the renin-angiotensin-aldosterone (RAA) system modifier drugs. Both meta-analyses came to positive, affirmative conclusions: antihypertensive therapy, including the RAA system modifiers, significantly lowers the risk of cardiovascular events in renal patients.

It is not usual that an editor-in-chief asks scientists to comment (i.e., contribute tertiary literature) on a meta-analysis, which in itself is secondary, not primary literature. We believe that the Editor-in-Chief must have had reasons for the proposal. In the following we shall therefore scrutinize the meta-analyses in some depth.

What do the meta-analyses show when read "as usual"? *The Lancet* article[1] addresses the well-publicized notion of a markedly increased

cardiovascular mortality in dialysis patients compared to matched controls with normal renal function.[3] Although this appears to be a straightforward issue, unexpected paradoxical results have been noticed in dialysis patients before ("reverse epidemiology", e.g., reference no. 4). Hence, the meta-analysis insists on what appears to be a straightforward question: Does lowering the blood pressure with antihypertensives (in hypertensive and normotensive dialysis patients) have a significant impact on cardiovascular morbidity and mortality?

The meta-analysis was carried out on eight suitable studies including HD and PD patients (spread globally), reporting a total of 1679 patients, mean age 55–67 years. Most of these studies were prospective, randomized, placebo-controlled, and half were double-blind. The degree of blood pressure lowering is communicated by the meta-analysis.[1] The authors[1] could not always determine what was really meant by "placebo-controlled" in the eight original studies (no antihypertensive medication at all vs. no additional antihypertensives). They were also somewhat uncertain whether only hypertensive patients or also some normotensive patients were reported in the eight original publications (personal communication by Dr. Vlado Perkovic). Proper methodology for meta-analyses such as checking for publication bias, potential heterogeneity of estimates of treatment effect and study quality, and searching the ClinicalTrials.gov website was applied.

The meta-analysis found a significant overall reduction of the risk of cardiovascular events to a risk ratio of 0.71 (0.55–0.92; p = 0.009). Comparable positive results were also calculated for all-cause mortality (risk reduction to 0.80 [0.66–0.96]; p = 0.014) and cardiovascular mortality (risk reduction to 0.71 [0.50–0.99], p = 0.044); however, not all of the eight studies, but only five and four studies, respectively, had reported data on some of these issues. Taken together the authors concluded that "…agents that lower blood pressure should routinely be considered… to reduce the… cardiovascular morbidity and mortality in this (dialysis) population."

The meta-analysis in the *American Heart Journal*[2] is 15 pages long and studded with nine complicated and lengthy risk diagrams. Twenty-five trials (24 are listed), reporting a total of 45,758 patients in stages I–III of chronic renal failure with or without proteinuria were included. Most studies, but not all, were prospective, randomized, double-blind and had a control group. Duration of observation was 3.5 years on average (20 weeks – 6.4 years). Patient cohorts included patients with and without diabetes, and those with a diagnosis of hypertensive nephropathy. Protein excretion ranged from no albuminuria to microalbuminuria to overt proteinuria depending on the study. Trial selection, quality assessment, and statistical analysis are well-described and appropriate. The study found that for the total group of patients on angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEI/ARB) the risks of "cardiovascular outcomes" at 0.84 (0.78–0.91; p<0.001), heart failure (0.74 [0.58–0.95]; p = 0.02), and myocardial infarction (MI) (0.78 [0.65–0.97]; p = 0.03) were significantly reduced.

Further subgroup analyses lead the authors to conclude (discussion section): "We would recommend the use of RAA system blockade agents as first choice therapy in patients with diabetic nephropathy and (non-diabetic) proteinuria."

Surprisingly, however, a distinction between diabetes without and diabetes with proteinuria is never made in the manuscript. In addition, Figures 6 and 7 of the article[2] demonstrate that ACEI/ARB are inferior treatment in diabetic nephropathy when compared with control therapy (i.e., amlodipine, ß-blocker, other calcium channel blocker). It is only in the comparison between ACEI/ARB and placebo (supposedly indicating no antihypertensives at all) that heart failure (0.78 [0.66–0.92], p = 0.003) and MI appear improved (0.82 [0.67–1.00] [Figure 7] p = 0.005), while stroke and cardiovascular mortality show a tendency towards worsened risk under ACEI/ARB. In other words, no antihypertensive treatment at all, including no ACEI/ARB, turns out not inferior to treatment with antihypertensive agents. We therefore find it very difficult to understand the authors' recommendation (see above). Overall, this is a meta-analysis that shows mostly negative results. Yet the summary and the results section do not say so clearly. A busy reader, unable to scrutinize the microscopically small print of the 9 long tables/diagrams, will probably miss that point. By the way, there is no conflict of interest statement in this paper.

What do the meta-analyses reveal when read carefully? *The Lancet* study[1] analyzed 1679 patients that had been observed for 12–36 months to reach its conclusions about cardiovascular morbidity and mortality. However, compared with recent trials in this field[5,6] in other patient groups, this is a small patient number and a short time of follow-up for the questions asked. Yet, we would acknowledge that in dialysis patients, the length of time for a follow-up is more limited than in other patient groups. In the meta-analysis it was apparently impossible to determine the following in the eight oryginal articles:

1 What was the definition of hypertension (Systolic? Diastolic? Both? Absolute levels of blood pressure?).

2 What was considered an adequate measurement of blood pressure in an HD patient? (On the morning of the day of dialysis? On the intradialytic day? During the dialysis session? Blood pressure monitoring? Self-measurements? How often?)

Apparently, these aspects have not been taken into consideration.

The major concern, however, is plausibility of the results, i.e., the comparison of the statistically generated data with the visual logic of the diagrams, for example Figure 2. This figure shows

that out of the eight studies, five compare an antihypertensive treatment to "… placebo", i.e., supposedly to no treatment, while three studies compare it to "conventional therapy". Out of the five former studies, the two largest ones (n = 397 and n = 108) find a tendency towards an adverse effect on risk (1.12) or no effect. Of the remaining three studies, which compared with conventional therapy one finds no risk change (1.00), another one reports an increase in blood pressure by 3 mmHg (systolic), with no change of the diastolic value, yet a significant risk reduction to 0.43 (0.21–0.89) was observed. How can one be reasonably convinced of the relevance of such a multi-colored mixture of discrepant observations yielding a single overall-positive-result that we quoted? As far as our bias is concerned, we find this somewhat difficult.

With respect to the study of ACEI/ARB in predialysis patients[2] we have already mentioned some major concerns in the above section. In addition, careful reading indicates several other questions. Of the 25 studies included, 2 were *post hoc* analyses, 8 compared ACEI/ARB to placebo, presumably indicating no (additional?) antihypertensives in hypertensive patients, and 6 administered β-blockers in controls, i.e., a class of antihypertensive agents that has recently been criticized as potentially inappropriate.[7] So we are left to wonder about the fairness of some of the "controls".

The study clearly emphasizes one parameter of the evaluation called cardiovascular (CV) outcomes. This parameter demonstrated a significant improvement under ACEI/ARB in several subgroups. However, the article does not specify what we should understand by CV outcomes. Yet, because several CV endpoints, such as MI, stroke, heart failure, cardiovascular mortality, are defined individually, we have to wonder whether "CV outcomes" is a term that also covers chest pain, shortness of breath, fatigue, hospital admission for cardiac problems, dizziness, cardiac arrhythmia or other events – we just do not know.

In the overall evaluation, there was no improvement by ACEI/ARB of the most important endpoints: CV mortality and stroke. And this holds up even in the face of the fact that a sizeable proportion of patients were compared to placebo control. To make matters worse, even the "positive evaluations" (i.e., those for MI and congestive cardiac failure) reached the level of significance ($p = 0.03$ and 0.02, respectively), which is marginal when one considers that approx. 6000 patients formed the basis of this evaluation.

In the evaluation of patients with diabetic nephropathy (Figure 6) there may have been an error of reporting: in the text, the authors claim that ACEI/ARB decreased the risk for MI to 0.89 at a $p = 0.06$ (i.e., not significant), but Figure 6 shows that the risk may have a tendency to increase to 1.49 ($p = 0.09$). Which of these two "results" are we to believe?

Taken together, a close-up review of this publication – taking more time than what a busy physician may be able to invest – reveals features that put the work into a different context. Overall, the close-up review reveals that ACEI/ARB are:

1 no better than conventional antihypertensives for cardiovascular endpoints

2 not even clearly superior to placebo.

An unexpected result.

Conclusions There are frustrating messages arising from the present analysis.

Although basically against all clinical wisdom, we cannot take it for granted any longer that lowering blood pressure (mostly in hypertensives, we presume) with antihypertensive agents offers benefit in the prophylaxis of CV endpoints in renal patients. The same applies to ACEI/ARB, if we take the calculations and figures in the meta-analyses seriously.

Papers have to be read in detail in order to be fully understood. Summaries are not sufficient. Authors may not expose the negative aspects of their findings, such aspects may be buried in the text instead.

Where does this leave a busy physician? We are not sure. This is a dilemma. Perhaps one should read less but more carefully.

To come back to the Editor's introductory question: Should we prescribe blood pressure lowering drugs to every patient? We are uncertain what to say. If we follow the two meta-analyses, doing nothing to treat hypertension in renal patients is about as good as prescribing antihypertensives or ACEI/ARB. Maybe the studies and meta-analyses somehow missed the point; perhaps they need to be repeated with an intention to distinguish between renal patients that benefit and those that do not. Alternatively, we may need better "markers" of benefit than just monitoring the blood pressure level. We do not know.

Nonetheless, it is presently safe to say that a physician who is treating cannot be criticized, and a physician who is hesitant about treatment cannot be criticized either.

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Czy każdemu pacjentowi z zaawansowaną przewlekłą chorobą nerek powinniśmy przepisywać leki hipotensyjne?

Komentarz do dwóch ostatnich metaanaliz

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chorzy dializowani, inhibitory konwertazy angiotensyny, leczenie hipotensyjne, przewlekła niewydolność nerek

STRESZCZENIE

Leczenie hipotensyjne jest podstawową interwencją umożliwiającą przedłużenie życia w pierwotnym nadciśnieniu tętniczym. Zapobiega udarowi mózgu, zawałowi serca i nadciśnieniowej niewydolności nerek. Przewlekła niewydolność nerek wiąże się z nadciśnieniem tętniczym i przyspieszoną postacią stwardnienia naczyń. Choroby układu krążenia są wiodącą przyczyną zgonu chorych na nerki (z przewlekłą niewydolnością nerek w stadiach II–IV, niewydolnością nerek wymagającą dializ, po przeszczepie nerki). Jaka więc u tych chorych jest rola leczenia hipotensyjnego, a w szczególności – co można osiągnąć za pomocą leków modyfikujących układ renina–angiotensyna–aldosteron (RAA)? Zagadnienie to było ostatnio przedmiotem dwóch metaanaliz. W artykule opublikowanym w *The Lancet* oceniono 8 badań u chorych dializowanych (n = 1679). Stwierdzono, że leki hipotensyjne dają korzyści w zakresie zmniejszenia chorobowości i umieralności sercowo-naczyniowej. Krytykujemy jednak te wnioski i wykazujemy, że dane nie przemawiają przekonująco na korzyść leczenia hipotensyjnego. W metaanalizie zamieszczonej w *American Heart Journal* oceniano rolę leków hipotensyjnych i modyfikujących układ RAA u 45 758 chorych (z 25 badań) w stadiach I–III przewlekłej choroby nerek, a więc niewymagających (jeszcze) dializy. Autorzy twierdzą, że ACEI/ARB znamiennie zmniejszyły częstość sercowo-naczyniowych punktów końcowych. Jednak nasza analiza danych nie jest zgodna z ich wnioskami. Nasza analiza wykazuje, że wyniki były dość niejednorodne, autorzy być może nadmiernie podkreślili korzystne wyniki oraz, biorąc pod uwagę otrzymane wyniki, należało wyciągnąć wniosek, że leki hipotensyjne, w tym ACEI/ARB, u pacjentów z chorobą nerek mogą nie być korzystniejsze od placebo (*sic*). Zatem nie metaanalizy, ale większe badania pierwotne są konieczne do ustalenia roli leczenia hipotensyjnego u chorych na nerki.

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