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Antihypertensive Therapy: Beta-Blockers and Diuretics – What is the Evidence?

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Both diuretics and beta-blockers have been used to treat essential hypertension for more than three decades. Both of these drug classes have an impressive track record with regard to safety that is unparalleled for other drugs. Despite this, no prospective randomised study has shown that beta-blockers, either in monotherapy or when added to diuretic therapy, independently diminish cardiovascular morbidity and mortality. Quite to the contrary, our recent meta-analysis in the elderly reported little, if any, benefits of beta-blocker therapy when compared with placebo or other therapy, despite the fact that blood pressure was lowered by beta-blockers. The reason for the inefficacy of beta-blockers may come from their unfavorable effects on systemic haemodynamics and on other pathophysiologic findings in the hypertensive patient, such as arterial stiffness, hypertensive heart disease, kidney disease and cerebrovascular disease. In addition, comorbid conditions often present in the elderly, such as chronic obstructive pulmonary disease, peripheral vascular disease, diabetes, depression, and erectile dysfunction, are relative contraindications to the use of beta-blockers. *J Clin Basic Cardiol 2001; 4: 201–204.*

Key words: hypertension, diuretics, beta-blocker, haemodynamic

A variety of factors have been shown to determine prescription habits of practicing physicians, such as, authoritative guidelines, scientific reports, marketing of pharmaceutical companies, patient preferences, personal experiences, and even stock ownership in pharmaceutical companies, etc. It is, therefore, not surprising that physicians are not always willing to embrace wholeheartedly new guidelines that are thrown at them in periodic intervals for 4 to 6 years.

The most recent report of the Joint National Committee as well as the one from the World Health Organization recommend beta-blockers and diuretics as first line therapy for uncomplicated essential hypertension [1, 2]. Similar recommendations were issued over the past few years by many authoritative sources and published influential journals. Yet, these recommendations were supposedly based on multiple prospective randomized trials attesting to the fact that only beta-blockers and diuretics, both in monotherapy as well as in combination, reduced morbidity and mortality in hypertension. There is little doubt that ever since the VA study [3] in the 1970's, multiple and prospective randomized trials have documented that diuretic-based therapy reduced the risk of stroke and, to a lesser extent, of heart attacks and cardiovascular morbidity and mortality. However, the data are much less convincing for the beta-blockers [4]. In fact, no trial has shown that blood pressure lowering with a beta-blocker would reduce the risk of heart attack or cardiovascular event in patients with essential hypertension compared with placebo. In contrast, several prospective studies are now available showing that blood pressure reduction with calcium antagonists diminishes cardiovascular morbidity and mortality and, at least in meta-analysis, also all-cause mortality. Moreover, recent data showing that the long-term use of diuretics increased the risk of renal cell carcinoma (RCC) [5] also threw a shadow on the bright picture of diuretics reducing cardiovascular morbidity and mortality in hypertension. Clearly, not all patients with essential hypertension are ideal candidates for long-term exposure to diuretic therapy. In the following we present some caveats for the sweeping recommendations to use beta-blockers and diuretics as "preferred" antihypertensive therapy in the majority of the patient population.

Beta-Blockers

Morbidity and mortality studies

It is somewhat ironic that after three decades of using beta-blockers for hypertension, no study has shown that their monotherapeutic use has reduced morbidity or mortality in the elderly hypertensive patient when compared with placebo. Quite in contrast, in a recent meta-analysis we documented that although blood pressure was lowered significantly by beta-blockers, these drugs were ineffective in preventing coronary heart disease, cardiovascular and all-cause mortality (Odds Ratio 1.01, 0.98 and 1.05, respectively) (Fig. 1) [4]. In the British MRC study in the elderly [6], beta-blocker monotherapy was not only not effective but, interestingly enough, whenever a beta-blocker was added to diuretics the benefits of the antihypertensive therapy distinctly diminished [7]. Thus, patients who received the combination of beta-blockers and diuretics fared consistently worse than those on diuretics alone, but they did somewhat better than those on beta-blockers alone [7].

In contrast, in our meta-analysis diuretic therapy was superior to beta-blockers with regard to all endpoints (heart attacks, fatal and non-fatal strokes, cardiovascular events, car-

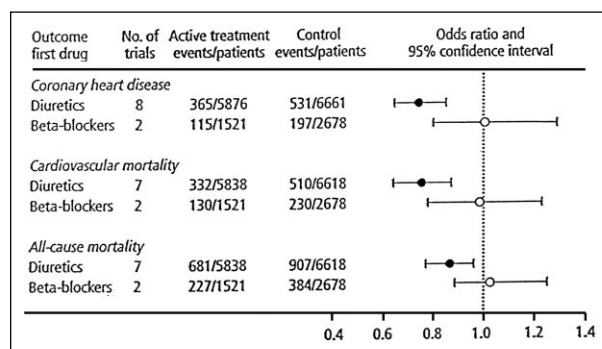


Figure 1. Meta-analysis of prospective clinical trials in elderly patients with hypertension according to first-line treatment strategy. Modified with permission from Messerli et al., *JAMA* 1998; 279: 1905 [4]. Copyright 1998, American Medical Association

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diovascular and all cause mortality) [4]. We defined elderly as a patient above the age 60, and the analysis was based on all randomised studies that lasted at least 1 year, used as first line therapy either a diuretic and/or a beta-blocker and reported morbidity and mortality. A total of ten trials involving a total of 16,164 elderly patients fit these criteria. There was also a distinct difference in the antihypertensive efficacy between the two therapeutic strategies; whereas 66 % of patients assigned to diuretics were controlled on monotherapy, less than one-third of patients were controlled on beta-blocker monotherapy. Despite this meager blood pressure control on beta-blocker monotherapy, the dropout rate was twice as high in the beta-blocker group compared with the diuretic group [6].

Dissociation of surrogate from real endpoint

Beta-blockers are a prime example documenting a dissociation of the surrogate endpoint from the real endpoint: despite their having a "beneficial" effect on blood pressure (surrogate endpoint), they fail to affect the real endpoints, ie, heart attack, stroke, cardiovascular and all-cause morbidity and mortality. This would indicate that, at the present time, millions of elderly hypertensive patients are needlessly exposed to the cost, inconvenience and adverse effects of beta-blockers while they will never harvest any benefits. Even investigators who, time and again, have recommended beta-blockers as first line therapy in hypertension have admitted the complete inefficacy of these agents to prevent a heart attack in hypertension (regardless of the age of the patient). Thus, Psaty et al. state: "Perhaps the most interesting finding from the beta-blocker component of the meta-analysis is the fact that ... beta-blockers do not appear to prevent coronary events in the primary prevention trials in patients with high blood pressure" [8]. It is ironic that these very same studies that clearly document the inefficacy of the beta-blockers in preventing cardiovascular events provided the fundament upon which the recommendations of the JNC V were built. Perhaps of even more concern is the fact that in the Medical Research Control (MRC) study in the elderly, beta-blockers had a higher risk of cardiovascular events compared with diuretics even after the difference was adjusted for the decrease in arterial blood pressure [6]. Thus, for any given fall in arterial pressure patients on diuretics fared better than those on beta-blockers [7]. Obviously, this indicates either that blood pressure lowering by beta-blockade confers an ill effect on the cardiovascular system that overrides the beneficial effects of the decrease in pressure, or that blood pressure lowering with a diuretic confers a specific benefit irrespective of the decrease in blood pressure.

Gin and tonic studies

In all prospective studies in which beta-blockers were implied to reduce morbidity and mortality, they were used in combination with a diuretic in the majority of patients. In the Swedish Trial in Old Patients (STOP) [9] more than two-thirds of patients were receiving combination therapy and no information was provided regarding the effects of beta-blockers or diuretics in monotherapy. In the Systolic Hypertension in the Elderly program (SHEP) [10] only 21 % of patients were receiving atenolol, all of these in combination with a diuretic. In the study of Coope and Warrender [11], which demonstrated a significant reduction in the rate of strokes, 70 % of patients in the treatment group were receiving atenolol and 60 % were receiving bendrofluzide, although all of them were initially started on atenolol. Coope and Warrender [11] clearly state: "Since patients were not randomised to treatment groups, it is impossible to compare response to the beta-blockers and the diuretics." It is hard to

believe that these studies actually were considered to be iron-clad scientific information documenting that beta-blockers reduced morbidity and mortality in hypertension. One could as well conclude that tonic water causes cirrhosis of the liver from a study in which in the active treatment arm the majority of patients were on gin and tonic, some on gin alone and some on tonic water alone, and no attempt was made to separately assess the effect of the individual ingredients. Neither the study of Coope and Warrender [11], nor the SHEP [10], nor the STOP [9] allows us to draw the conclusion that either the beta-blocker alone or the addition of the beta-blocker to the diuretic regimen did, indeed, significantly impact morbidity and mortality.

To the contrary, the MRC study in the elderly allows us to conclude that beta-blocker based therapy is distinctly inferior to diuretic based therapy and not different from placebo. Given this state of the art, and given the not so benign side effect profile of beta-blockers, are we really to blame practicing physicians for not following guidelines? We should, perhaps, specify that there is heterogeneity in the class of beta-blockers. Some of these drugs, such as carvedilol and labetalol, have been shown to exert an entirely different haemodynamic neuroendocrine profile than the conventional beta-blockers. Conceivably, therefore, these drugs may exert benefits that are absent with conventional beta-blockers (and, obviously, conventional beta-blockers may exert benefits in post-myocardial infarction patients that are absent with the vasodilating drugs). However, there are no good head to head comparisons of conventional vs. vasodilating beta-blockers in terms of morbidity and mortality in either hypertension or congestive heart failure that would allow us to draw firm conclusions.

Diuretics

In contrast to beta-blocker-based therapy, numerous prospective randomised trials have documented that diuretic based therapy is effective in reducing morbidity and mortality in hypertensive patients [4]. If anything, the benefits of diuretic therapy have been shown to be more marked in the elderly than in the younger patient. The effect of diuretics is particularly pronounced with regard to reduction of the risk for stroke and somewhat less impressive with regard to the risk of coronary heart disease. However, of particular concern for many years, and even decades, is the possibility that this pharmacological intervention could adversely affect that risk for extra-cardiovascular diseases. Indeed, the very recent meta-analysis [5] suggesting that long-term diuretic therapy could increase the risk for renal cell carcinoma is of distinct concern.

Case control and cohort studies

In a total of nine case control studies done over the past decade, an association between renal cell carcinoma and diuretic therapy was documented (Odds Ratio 1.55, Confidence Interval 1.42 to 1.71, $p < 0.00001$) (Fig. 2) [5]. Equally in three cohort studies, in a total study population in excess of one million, patients who were taking diuretics had about a two-fold higher risk of renal cell carcinoma than patients who were not on diuretic therapy [5]. In most studies women were found to have a higher risk of diuretic associated renal cell carcinoma than men (OR 2.01 vs. 1.69). In three studies in which this was examined, the risk of renal cell carcinoma increased with duration of diuretic therapy (cumulative dose). The association between diuretic use and renal cell carcinoma was also found in normotensive subjects who took diuretics for another reason, and it persisted even when cor-

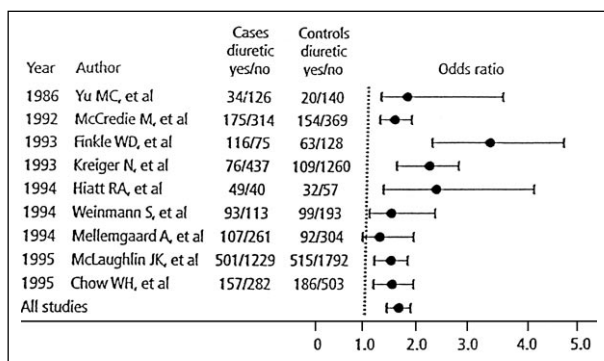


Figure 2. Case control studies assessing and relationship between renal cell carcinoma and diuretic use. Reprinted from the Am J Cardiol, Vol. 83; Grossmann E, Messerli FH, Goldbourt U: Does diuretic therapy increase the risk of renal cell carcinoma? Pages 1090–3, 1999, with permission from Excerpta Medica Inc.

rected for the presence of hypertension in the majority of the studies. This makes it unlikely that hypertension itself was the common denominator accounting for the association between renal cell carcinoma and diuretic therapy. Indeed, it seems more likely that hypertension merely is an innocent bystander. There are no plausible clinical, biochemical or pathophysiological reasons why hypertension, *per se*, should be a risk for renal cell carcinoma. However, the longstanding presence of hypertension in any patient is intrinsically linked to diuretic use. Most patients will not even remember having taken a diuretic because numerous fixed combinations containing diuretics are presently on the market. As most clinicians will easily concede, it is next to impossible to perform a “correction” for the presence of hypertension (that is to retrospectively separate hypertensive patients who used diuretics during the past 20–30 years from those who did not) as has been attempted in many studies. It seems more likely that the common denominator linking hypertension to renal cell carcinoma is, indeed, diuretic use. Regardless of these deliberations, in five out of the nine case control studies the risk of renal cell carcinoma with diuretic use persisted and remained significant even after adjustment for potentially confounding co-factors.

Hypothetical carcinogenic mechanism

Perhaps one of the most convincing arguments for the connection between renal cell carcinoma and diuretic use is the fact that the renal cell carcinoma arises from the renal tubular cell, the very cell that is the main target of the diuretic's pharmacologic effect. Conceivably, the chronic chemical bombardment of this cell over years and decades may have a low-grade carcinogenic effect.

Hydrochlorothiazide is a cyclic imide and can be converted in the stomach to a mutagenic nitroso derivative that is excreted in the kidney [12, 13]. Diuretics have been associated with both nephropathy and renal cell tumors in animals [14, 15]. The thiazide diuretics cause massive degenerative changes and cell death in the distal tubule in rats [16]. After thiazide exposure these cells looked like tumor cells and exhibited markers of tumor cells [16].

Gender difference

Renal cell carcinoma is a relatively rare malignancy that occurs two to three times more often in men than in women. The fact that most studies in our meta-analysis document women to be at a higher risk than men with regard to diuretic induced renal cell carcinoma suggests the presence of a hormonal

mechanism. Indeed, estrogens have been shown to enhance the thiazide effect in the distal tubule of ovariectomized rats [17]. This effect could possibly account for the inverse gender predominance with regard to diuretic associated renal cell carcinoma. In addition, although the use of diuretics has declined over the past decade, women still use two to three times more diuretic therapy than men do, possibly because women have a greater tendency for oedema than men [18].

Lack of evidence of renal cell carcinoma in prospective randomised trials

Carcinogenicity of diuretic therapy is low grade and certainly less than that of smoking for lung cancer. If one had to design a prospective randomised trial proving that smoking caused lung cancer, study duration of at least one, but better two decades would be required. Given the comparatively weak carcinogenicity of diuretic therapy, it probably would take longer to document a difference with regard to renal cell carcinoma. Therefore, it is hardly surprising that in none of the prospective randomised trials, duration of which is usually lower than 5 years, an excess of renal cell carcinoma was found.

Diuretics were introduced into medicine in 1958. Since it probably takes more than 20 years of diuretic exposure to significantly increase the risk of renal cell carcinoma, it is only now that we are seeing this association. Of note, the incidence of renal cell carcinoma has increased by 43 % over the past fifteen years [19].

True risk/benefit ratio

Several epidemiological studies, such as the SHEP and the MRC, allow us to estimate the true risk/benefit ratio of diuretic therapy in hypertension. Obviously, as practicing physicians we would like to know how many heart attacks and how many strokes we are preventing when a diuretic is prescribed while “causing” one renal cell carcinoma. It can be estimated that diuretic therapy for one case of renal cell carcinoma will prevent 20 to 40 strokes, 3 to 28 heart attacks, and 4 to 18 deaths in the general population [20]. In the elderly, in whom diuretics are particularly efficacious, the risk/benefit ratio may even look better. However, in middle-aged women, for one case of renal cell carcinoma only six strokes, two heart attacks, and no deaths are prevented [20]. The actual risk/benefit ratio would clearly argue against the use of diuretics in this age and gender group. We believe that younger and middle-aged women, therefore, probably should no longer be treated with diuretics for hypertension because they potentially will be exposed to these drugs for several decades, they have a well-known tendency to overuse diuretics, they are less protected by diuretics against cardiovascular morbidity and mortality than men, and the risk of diuretic associated renal cell carcinoma is higher than that in men. In contrast, in patients with congestive heart failure and other forms of oedema, the low-grade carcinogenicity of diuretic therapy can possibly be disregarded because their life expectancy is relatively short and they are unlikely to live long enough for the cumulative diuretic dose to reach the threshold of carcinogenicity.

Summary and Recommendations

Both diuretics and beta-blockers have been used to treat essential hypertension for more than three decades. Both of these drug classes have an impressive track record with regard to safety that is unparalleled for other drugs. Despite this, no prospective randomised study has shown that beta-blockers, either in monotherapy or when added to diuretic therapy, in-

dependently diminish cardiovascular morbidity and mortality. Quite to the contrary, our recent meta-analysis in the elderly reported little, if any, benefits of beta-blocker therapy when compared with placebo or other therapy, despite the fact that blood pressure was lowered by beta-blockers. The reason for the inefficacy of beta-blockers may come from their unfavourable effects on systemic haemodynamics and on other pathophysiologic findings in the hypertensive patient, such as arterial stiffness, hypertensive heart disease, kidney disease and cerebrovascular disease. In addition, comorbid conditions often present in the elderly, such as chronic obstructive pulmonary disease, peripheral vascular disease, diabetes, depression, and erectile dysfunction, are relative contraindications to the use of beta-blockers.

It is ironic that the very same studies that demonstrate the inefficacy of the beta-blockers in the elderly were used as an argument to promote them to a preferred status.

Recent data showing low rate carcinogenicity for renal cell carcinoma with diuretic therapy must be seen in proper context. In the elderly, the cardiovascular benefits of diuretics clearly outweigh the low-grade risk of renal cell carcinoma. However, in the younger patient, particularly in women, diuretics probably should no longer be used as initial antihypertensive therapy. In view of the unparalleled track record of diuretics in terms of safety and efficacy, no conclusions should be drawn with regard to safety and efficacy of other antihypertensive drugs.

We conclude that sweeping recommendations for the use of beta-blockers and diuretics as "preferred" therapeutic strategies are inappropriate and that in hypertension, as most often in medicine, a more sophisticated approach is needed.

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