Indian Heart Journal xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Indian Heart Journal

journal homepage: www.elsevier.com/locate/ihj

Editorial

Diuretics in primary hypertension – Reloaded

Keywords:
Diuretics
Hydrochlorothiazide
Chlorthalidone
Indapamide
Mortality
Cardiovascular outcome

A B S T R A C T

Diuretics have long been cherished as drugs of choice for uncomplicated primary hypertension. Robust mortality and morbidity data is available for diuretics to back this strategy. Off-late the interest for diuretics has waned off perhaps due to availability of more effective drugs but more likely due to perceived lack of tolerance and side-effect profile of high-dose of diuretics required for mortality benefit. Low-dose diuretics particularly thiazide diuretics are safer but lack the mortality benefit shown by high-dose. However, indapamide and low dose chlorthalidone have fewer side-effects but continue to provide mortality benefit.

1. Introduction

Diuretics, particularly thiazide and thiazide-like diuretics have been the gold standard of antihypertensive therapy for uncomplicated primary hypertension (formerly known as essential hypertension) till recent past. Several trials, even some relatively recent ones have demonstrated mortality benefit with diuretic therapy in uncomplicated hypertension.[1–3] Several JNC Guidelines have kept diuretics as first-line agent (even drug of choice) in management of uncomplicated hypertension.[4,5] No individual can be labeled as resistant hypertension unless a concurrent use of 3 antihypertensive agents of different classes, one of the 3 agents a diuretic, prescribed at optimal dose has been instituted.[6] However, despite robust clinical data, their use in real-world practice has continued to decline.[7] This is rather intriguing and may be related to several misconceptions prevailing about use of diuretics in primary hypertension: (1) the use of diuretics does not result in decrease in morbidity or mortality; (2) diuretics are poorly tolerated; and (3) use of diuretics is associated with significant adverse metabolic effects (increased lipid levels, adverse effects on glucose metabolism, effects on arrhythmias, etc.).[8–10] The efforts to promote newer medications may feed on these misconceptions.[11–14] However, the incidence and magnitude of these side effects are much lower with low-dose therapy (12.5–25 mg of hydrochlorothiazide or chlorthalidone) but one cannot assume that the benefits of high dose thiazides would have replicated with lower doses of hydrochlorothiazide as commonly used in the treatment of primary hypertension. Herein rests the role of indapamide or low dose chlorthalidone.

2. Mortality reduction

The early landmark trials for treatment of hypertension demonstrated significant reduction of stroke, cardiovascular morbidity and mortality associated with BP lowering, primarily with thiazide diuretics (Figs. 1–3).[15–18] Relatively recently, head-to-head comparison between various anti-hypertensive agents, in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), chlorthalidone was found superior in preventing one or more major forms of CV disease.[3] A subsequent meta-analysis also revealed a superiority of thiazide type diuretics over other anti-hypertensive agents in terms of various adverse CV outcome reductions.[19] A recent meta-analysis involving 12 RCTs (48 898 patients) revealed a reduction in relative risk for stroke (37%), heart failure (49%), CAD (18%), cardiovascular death (18%) and all-cause death (1%), all statistically significant. Nine other studies including secondary analysis (66 788 patients) in which diuretics were used in association with other drugs, risk reduction with diuretics was similar.[20] In this study, use of diuretics prevented 15 strokes, 24 major cardiovascular events and eight deaths every 1000 patients treated for 5 years (with NNT of 67, 41 and 118, respectively). Not only uncomplicated primary hypertension, there is numerous evidence to support the use of diuretics (over other anti-hypertensives) in several patient populations, so much so that the use of diuretics features in many treatment guidelines.[21–23]

3. Concerns with diuretic therapy

Lack of tolerability of diuretics has been a major concern limiting their use. Available studies reveal that diuretics either do not interfere with, or may actually improve, quality of life in hypertensive patients. Particularly, low-dose diuretic treatment is a well-tolerated and may be an excellent initial choice for hypertensive patients, even elderly. However, high-dose diuretics should be avoided, in patients with co-morbidities like diabetes, gout, or erectile dysfunction in men.[24] The potential adverse metabolic effects of thiazide and thiazide-like diuretics include

http://dx.doi.org/10.1016/j.ihj.2016.08.013

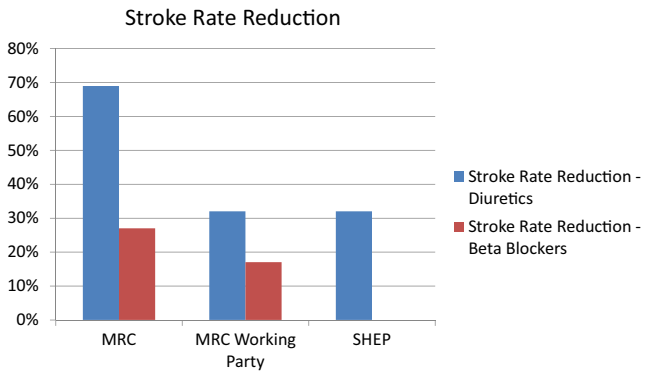

Fig. 1. Stroke rate reduction with diuretics.

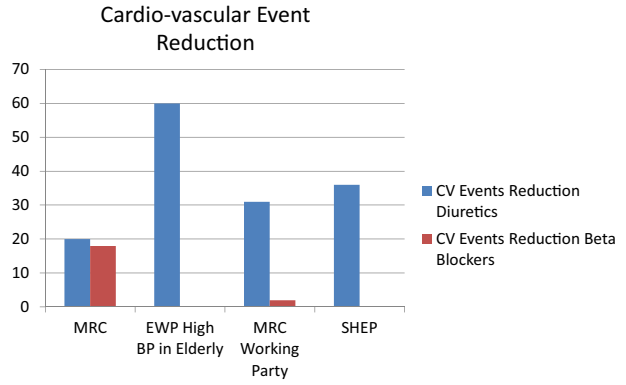

Fig. 2. Cardiovascular risk reduction with diuretics.

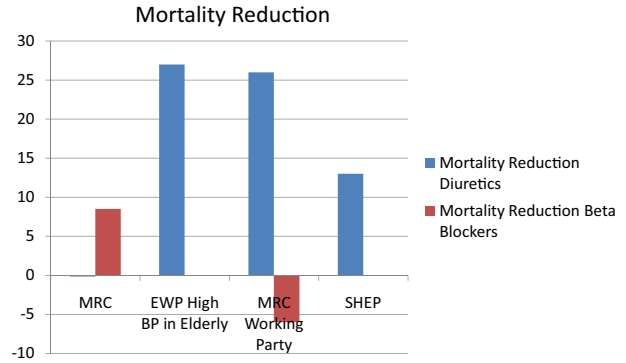

Fig. 3. Mortality reduction with diuretics.

abnormalities in carbohydrate, electrolyte, uric acid and lipid metabolism.[25,26] Again these side-effects are more common with high dose therapy. Use of high dose diuretic without a potassium-sparing agent has been even associated with sudden cardiac death.[27]

4. Low dose diuretic therapy

To reduce the side-effects of high-dose thiazide and thiazide-like diuretics, they are typically used at low doses (12.5–25 mg/day of chlorthalidone or hydrochlorothiazide, or 1.5 mg of indapamide SR) which minimizes the metabolic complications, while maintaining the antihypertensive response.[26,28,29] Among the three anti-hypertensive agents, low doses of chlorthalidone and indapamide were more effective in lowering blood pressure than hydrochlorothiazide but metabolic abnormalities (although lower than high dose) were greater with low doses chlorthalidone than with hydrochlorothiazide or indapamide.[29] Thus on balance of things it appears that indapamide is both effective and safer at low doses compared with other diuretics. Even though in ALLHAT Trial low dose chlorthalidone was associated with a plasma potassium reduction of only 0.2 meq/L, 8.5% patients required potassium supplements and a significantly higher number of non-diabetic patients at baseline developing elevation of fasting blood glucose level to values $\geq$126 mg/dL compared with amlodipine and lisinopril (11.6% vs. 9.8% {$p = 0.04$} and 8.1% {$p < 0.001$}, respectively).[1] Persistent activation of sympathetic nervous system and insulin resistance could be the reason for increased new onset of diabetes with chlorthalidone.[30]

5. Limitations of low dose diuretic therapy

An interesting point is that although low dose thiazide/thiazide like diuretic therapy minimizes the metabolic complications, it may not eliminate other side effects; 25% of men treated with 25 mg of chlorthalidone per day develop a decline in sexual function and sleep disturbances may also occur, particularly if the patient is also on a low-sodium diet.[31] Further, in a meta-analysis where 8 trials classified as low dose were compared with 4 trials of high dose diuretics, stroke rate reduction was much higher with high-dose and total cardiovascular risk was much lower in high-dose than in low-dose diuretic trials (cardiovascular death 4.8%, rather than 17.6% in 10 years).[20]

6. Are all diuretics equal?

In the International Nifedipine GITS study: Intervention as a Goal in Hypertension Treatment (INSIGHT) study, while high-dose hydrochlorothiazide was found to be equal to calcium antagonists at doses below 25 mg, there was no evidence of reduction in morbidity and mortality.[32] Chlorthalidone is 1.5–2 times as potent as hydrochlorothiazide and has shown significant CV events reduction vs. both hydrochlorothiazide and placebo.[33,18,34] However, in the largest hypertension trial ALLHAT, low dose Chlorthalidone (12.5–25 mg daily) was found superior to other anti-hypertensive agents although metabolic side effects did occur.[3] On the other hand indapamide, a thiazide like diuretic whether used alone or in combination has not only shown a consistent blood pressure lowering response but also improvement in cardio-vascular outcomes. As a matter of fact, the HYVET study had to be prematurely stopped due to a phenomenal 21% reduction in all-cause mortality in patients receiving indapamide.[35] Further, there was also a 39% reduction in fatal strokes & a 64% reduction in heart failure. Long-term (1-year extension) provided an even better reduction of 52% in all-cause mortality.[36] In the PROGRESS trial, indapamide in combination with perindopril reduced stroke by 43%.[37] In the ADVANCE trial in diabetic patients, a combination of indapamide and perindopril reduced all-cause mortality by 14%, CV mortality by 18% and renal events by 21%.[38] It further provides proof of metabolic safety of indapamide on long-term basis; hemoglobin A_1C (HbA_1C) being maintained over nearly 5 year period. In PATS, indapamide showed a significant reduction in secondary strokes by 29%.[39] However, it is important to note that these benefits of indapamide are evident even at the therapeutic dosage of either 2.5 mg immediate release or the superior 1.5 mg sustained release. One of the reasons for the salutatory effects of indapamide[4] could be its predominantly vascular effect. This minimizes the risk of diuretic related side effects like electrolytic or metabolic disturbances. In a meta-analysis by Thomopoulos et al. a separate analyses were done

Please cite this article in press as: Mishra S. Diuretics in primary hypertension – Reloaded, *Indian Heart J.* (2016), http://dx.doi.org/10.1016/j.ihj.2016.08.013