

Management Of Hypertension In Renal Disease: Results From The Imperial Study

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Abstract

THE IMPERIAL (Indian Medical Practitioners Expressions Regarding Drug Intervention In All Aspects of MetaboLic Syndrome) study, which assessed Indian physicians' prescribing habits related to metabolic syndrome, also assessed their preferred management strategies in hypertension associated with renal disease. This paper reviews the results related to renal disease, obtained from the IMPERIAL study. There is a clear consensus for the use of angiotensin converting enzyme inhibitors, followed by angiotensin receptor blockers, as first line antihypertensive therapy in patients with nephropathy. In ESRD, calcium channel blockers, and diuretics are recommended as first – line therapy by 2/3 and 1/2 of physician respectively. It is hoped that these results stimulate discussion, research, and final consensus on the management of hypertension in renal disorders, especially ESRD, while encouraging doctors to follow existing rational guidelines .

INTRODUCTION

Though hypertension is a common co-morbid condition associated with chronic kidney disease (CKD), no recommendations or consensus guidelines are available to guide antihypertensive therapy in ESRD patients, as no large randomized controlled trials are available in this subset of patients.(1)

Minimal work has been done to explore the relative efficacy of various classes of anti-hypertensive drugs in these patients.

THE IMPERIAL (Indian Medical Practitioners Expressions Regarding Drug Intervention In All Aspects of MetaboLic Syndrome) study, which assessed Indian physicians' prescribing habits related to metabolic syndrome, also assessed their preferred management strategies in hypertension associated with renal dysfunction, including ESRD.

This paper reviews the results related to renal disease, obtained from the IMPERIAL study. It is hoped that these results form the basis for an exchange of ideas, and finally lead to a consensus on the management of hypertension associated with ESRD.

MATERIAL & METHODS

The objective of this nationwide survey of physicians,

diabetologists and cardiologists across India was to assess their practicing habits and attitudes related to hypertension and other aspects of metabolic syndrome.

A structured questionnaire was distributed to 482 doctors attending continuing medical education programmes. These included 59 (12.24%) from North zone, 131 (27.18%) from East zone, 80 (16.6%) from West, 92 (19.09%) from Central zone and 120 (24.93%) from South zone.

The cohort included 472 men and 10 ladies, all with a minimum qualification of MD Medicine, with an average age of 45.55 ± 5.0 years and average experience of 20.25 ± 5.0 years.

RESULTS

First line anti hypertensive monotherapy preferred by doctors in general patients was a beta-blocker (B) by 299 (62.03%), a calcium channel blocker (C) by 255 (52.90%), and a diuretic (D) by 214 (44.40 %) physicians. Angiotensin receptor blockers (R) and angiotensin converting enzyme inhibitors (A) were used less often, by just 168 (34.85%) and 135 (28.01%) doctors respectively. (Table 1)

First line combination therapy used for hypertension without co-morbidity was BC by 305 (63.28%), BD by 178 (36.93%), RD by 161 (33.40 %), RC by 146 (30.29%) and AD by 141 (29.25 %) doctors. A lesser number of practitioners preferred AC ($114/482 = 23.65\%$) or AR

(54/482 =11.20%). (Table 2)

Figure 1

Table 1:Choice of First line Antihypertensive drugs in Hypertension with or without Diabetes(n=482)

Choice of Monotherapy	Hypertension without Diabetes	Hypertension with Diabetes
ACE-Inhibitor	135(28.01%)	379(78.63%)
ARBs	168(34.85%)	349(72.41%)
Beta-blocker	299(62.03%)	51(10.58%)
Calcium channel blocker	255(52.90%)	98(20.33%)
Diuretics	214(44.40%)	66(13.69%)

Figure 2

Table 2: Choice of Anti hypertensive combination therapy in Hypertension with/without Diabetes (n=482)

Choice of combination Therapy	Hypertension without Diabetes	Hypertension with Diabetes
ACE-I+ ARB	54(11.20%)	229(47.51%)
ACE-I+CCB	114(23.65%)	204(42.32%)
ARB+CCB	146(30.29%)	230(47.72%)
BB+ CCB	305(63.28%)	29(6.02%)
ACE-I+Diuretic	141(29.25%)	129(26.76%)
ARB+Diuretic	161(33.40%)	132(27.39%)
BB+ Diuretic	178(36.93%)	24(4.98%)

In patients with nephropathy, there was no consensus as to the preferred antihypertensive, with doctors preferring A, (61.20%), choosing R and 168 (34.85%) prescribing C. Only 48 (9.96%) doctors wrote B to such patients, while 102 physicians (21.16%) preferred D. (Table 3)

Thus, nephropathy patients were less likely to be prescribed the commonly used classes of beta-blockers, calcium-channel blockers and diuretics, and more likely to be given A and R No attempt was made to gauge the reasons for this.

An analysis of prescription habits of various zones revealed no significant differences in preference of various drugs for this indication.

In contrast large number of physicians used older drugs while treating patients with coexistent hypertension and ESRD. 323 doctors (67.01%) prescribed C, while 206 (42.74%) chose D for such patients. Only 83 (17.22%) doctors used R, 60 (12.45%) prescribed A and 59 (12.24%) used B as first –line therapy for ESRD patients with hypertension. (Table 3)

Thus, a clear consensus in favour of older drugs was noted as far as the choice of anti-hypertensives in ESRD is concerned. The structured questionnaire did not try to find the reasons for the less frequent use of A and R in ESRD.

Physicians from different states had similar prescribing habits. No differences were noted in the responses of doctors from Central, East, West and North zones.

DISCUSSION

CKD is a common co –morbidity condition in the population (2), as well as in hypertension, diabetes and metabolic clinics. Management of hypertension has added significance in these patients because both systematic and glomerular hypertension, as well as proteinuria, is important determinants of progression of renal disease. The mode of management of hypertension in CKD patients has changed in recent years. The aim of management is not only to correct blood pressure but also to inhibit the renin aldosterone angiotensin system (RAAS), and reduce proteinuria.

Renal disease is linked with hypertension, through different mechanisms. The management of hypertension involves lifestyle modifications, pharmacological treatment, or both. Weight reduction, the Dietary Approaches to Stop Hypertension (DASH) diet, limitation of alcohol consumption, and physical activity are non-pharmacological methods of controlling high blood pressure. (3)

Pharmacological therapy available includes the following drug classes: thiazide diuretics, beta blockers, calcium-channel blockers, angiotensin-converting enzyme (ACE)–inhibitors, and angiotensin receptor blockers. These medications can reduce BP as well as the complications of hypertension. (3)

Various guidelines on management have focused on the choice of drugs in various conditions including diabetes and proteinuria .None of the current guidelines, however, specifically mention optimal antihypertensive therapy for patients in different stages of neuropathy, or for ESRD patients.

There is no confusion regarding the level of serum creatinine, blood urea or creatinine clearance till which various drugs, specifically ACE (I) can be prescribed safely.

Most prescribing information leaflets recommend dosage based on creatinine clearance values, which Indian doctors are usually not comfortable with, in their day –to –day practice.

The National Kidney Foundation (NKF) Task Force on Cardiovascular Disease in Chronic Renal Disease has recommended that patients with CKD be treated

aggressively as the higher risk group for CVD events (4). Similar recommendations have been issued by the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC 7), which classify CKD patients as 'high risk' and suggest a blood pressure goal of <130/80 mm Hg in them (3).

However, in the NHANES III subgroups of patients that included individuals with CKD, only 75% received pharmacologic treatment for hypertension. Only 11% of these reached target blood pressure of <130/85 mmHg, while 27% reached a target of <140/90 mmHg (2). The mean blood pressure of treated hypertensives with elevated serum creatinine was 147/77 mmHg, and nearly half (48%) of them were on one antihypertensive drug alone (5).

This is surprising, keeping in mind the considerable research done on the renoprotective effects of various classes of antihypertensive drugs, which has translated into current guidelines.

ACE (I) have been shown to restore pressure –natriuresis relationship to normal, by inhibitors also decrease aldosterone production, reduce proteinuria, improve lipid metabolism, increase renal blood flow, decrease filtration fraction and renal vascular resistance. They help in minimizing renal scarring and fibrosis, and also counteract oxidative stress /free radicals. (5)

Similar effects are seen with angiotensin receptor blockers and both these classes have been shown to provide reno – as well as cardio –protection.

Beta –blockers, especially β_2 blockers mediate vasodilatation and increase renin secretion, but do not seem to have any beneficial effect on renal function. (5)

Calcium channel blockers have natriuretic, diuretic, vasodilatory and antiproteinuric effects. Long term effects on renal function are controversial, but they have been shown to scavenge free radicals, reduce kidney growth, decrease mesangial molecule entrapment, attenuate mitogenic platelet –derived growth factor and platelet activating factor, block mitochondrial overload of calcium, decrease lipid peroxidation, reduce glomerular basement membrane thickness, augment antioxidant effects of various enzymes, inhibit collagenolysis, suppress angiogenic growth factor, prevent renal cortical remodeling, and block vasoconstriction induced by endothelin and thromboxane.(5)

Diuretics have no specific renoprotective action beyond

blood pressure lowering, and do not improve cardiovascular or renal survival. (5)

Various guidelines on hypertension have focused on indications, targets and methods of treatment, and have dealt with certain co morbid diseases, such as diabetes mellitus, in detail.

The precise blood pressure goal for optimal Reno protection, however, is uncertain. The evidence for preferential use of drugs that block the renin – angiotensin system in patients with CKD is restricted to trials in African Americans (6).

Guidelines also do not deal with resistant hypertension, i.e. patients whose blood pressure does not reach target, which is a common occurrence in CKD and nephropathy.

Thus, there is a need to tap the collective clinical experience of senior physicians, who manage patients of resistant hypertension, CKD and nephropathy routinely. The IMPERIAL study has tried to do precisely this.

The IMPERIAL study reveals equal preference amongst Indian doctors for ACE (I) and angiotensin receptor blockers for the management of hypertension in nephropathy. The choice of the latter two drugs is perhaps due to their perceived benefit of renoprotection and cardioprotection.

At the same time, use of diuretics is lower in individuals with nephropathy than expected (21.49% in nephropathy vs. 48.85% in general patients). This difference is difficult to explain.

The IMPERIAL study also exposes a difference in prescribing behaviour of Indian doctors when faced with hypertensive patients with nephropathy, and those without any co-morbidity. The use of calcium channel blockers, beta-blockers and diuretics is more common in general patients. In really impaired patients (specified as “nephropathy”), ACE (I) and angiotensin receptor blockers are used more often. In ESRD patients, calcium channel blockers and diuretics enjoy place of pride, while ACE (I) and angiotensin receptor blockers are not utilized optimally.

ACE (I) and ARBs are popular therapies for the ESRD patient (1), and have pleiotropic effects. While there is no proof that ACE (I) are superior to other drugs such as C in ESRD, their use is suggested to decrease access failure rate. A and R reduce thirst drive and enhance erythropoiesis. R carries less risk than A and has a preferred pharmacokinetic profile, with less dialyzability and minimal systemic

accumulation (1).

LIMITATIONS

The IMPERIAL study has included responses from consulting physicians and cardiologists, from both academic and non-academic backgrounds. This should be seen as its strength, as it has relied on a cumulative experience of 6217 years of clinical practice, and should not be thought of as a limitation.

In the study, specific questions were not asked regarding combination anti-hypertensive therapy in renal disease. Only two states related to renal function were specified, viz, nephropathy in ESRD. No effort was made to assess prescribing habits in different etiology states, on in patients with co- existing nephropathy and diabetes, heart failure or cardiovascular disease.

The IMPERIAL study did not ask doctors to mention their preferred prescription in different grades of CKD based on creatinine clearance, glomerular filtration rate, or serum creatinine. The study did not ask doctors to take into account the influence of age, gender, cardiac status, other co morbid conditions, level of thyroid control, and socioeconomic status while deciding their prescription.

Other reports from the IMPERIAL study will focus on prescribing habits related to hypertension with diabetes mellitus, coronary artery disease and renal dysfunction. Further work is planned under the IMPERIAL study banner to explore prescribing habits related to metabolic syndrome in greater detail, while assessing perceived reasons and rationale for these prescriptions.

CONCLUSION

The IMPERIAL study has shed light on the way in which Indian doctors prefer to treat hypertension in patients with concomitant renal disease. It has tried to fulfill a major, unmet need of physicians, who are confronted frequently with these diseases, yet do not have access to any guidelines

to help them plan therapy.

There is a clear consensus (two thirds of doctors) for the use of calcium channel blockers as first line antihypertensive therapy in patients with ESRD, followed by diuretics (used by half of respondents).

For nephropathy patients with hypertension, ACE (I) and angiotensin receptor blockers are recommended as first – line therapy by the majority of physicians.

These results may form the basis for further debate and discussion, and ultimately a consensus, regarding the appropriate management of hypertension in thyroid disease. The results of the IMPERIAL study also form a basis for discussion and planning further continuing medical education programmes.

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