ORIGINAL ARTICLE

Hypertension in Young Adults in India: Perspectives and Therapeutic Options amongst Clinician's in a Cross Sectional Observational Study

Uday Jadhav[1*], Mangesh Tiwaskar[2], Aziz Khan[3], BC Kalmath[4], CK Ponde[5], JPS Sawhney[6], MP Tripathy[7], PK Hazra[8], PK Sahoo[9], SN Routray[10], Sharad Chandra[11], Thomas Alexander[12], VK Chopra[13]

Abstract

Background: The prevalence of hypertension in the young adult population is rising in India. Increased arterial stiffness due to RAAS activation and increased sympathetic overactivity due to stress have been implicated as primary factors for the same. This study was aimed to understand the Indian clinician's perspective on approach to management of hypertension in young adults.

Methods: A cross sectional observational survey using a structured questionnaire was conducted online with 2287clinicians (cardiologists, diabetologists, consultant physicians and family physicians).

Results: The prevalence of hypertension was 10-30% as per opinion of 64.8% clinicians. The top three risk factors for hypertension in young were perceived to be smoking, mental stress and obesity. Around 57.4% respondents opined that both increased heart rate and systolic blood pressure were markers of sympathetic overactivity. More than 60% respondents across specialities preferred ARBs to treat hypertension in young adults. Amongst the ARBs, telmisartan was the preferred ARB by >80% respondents. Metoprolol was the preferred beta blocker by almost 64% respondents. The objective of selection of beta-blocker by majority of clinicians due to sympathetic overactivity. Telmisartan and Metoprolol single pill combination achieved the BP goal in 40-60% of patients as reported by 41.3% of the physicians. The combination therapy was well tolerated in young hypertensive patients.

Conclusions: Initiation of an early and appropriate antihypertensive treatment in young population may lower the burden of cardiovascular disease in this population. ARBs and beta -blockers were the preferred class of anti-hypertensive drugs in the cohort of young hypertensive patients

Introduction

Hypertension among young people is common, affecting 1 in 8 adults aged between 20 and 40 years.[1] This number is expected to escalate with lifestyle behaviours and lowering of hypertension diagnostic thresholds to SBP/DBP of 130/80 mm Hg. Young adults with hypertension before the age of 40 are at a high risk of developing cardiovascular events.[2]Results of the analyses conducted in the prospective cohort Coronary Artery Risk Development in Young Adults (CARDIA) study indicated that stage 2 hypertension before age 40 years was associated with a significantly higher risk of all-cause mortality.[3] The prevalence of hypertension in India has been reported to be as high as 25% to 42%.[4,5] Hypertension in the south east Asian region, India accounts for more than two-third of mortality.[6]Cardiovascular disease is observed to occur at a younger age in Indians resulting in impaired health and productivity. The prevalence of hypertension was high even among young age individuals as observed in the hypertension epidemiological study conducted in India.[7] The European hypertension guidelines have identified the South Asian population across ages to be the highest risk category and is considered to be most vulnerable to the consequences of increased blood pressure (BP).[8] Hypertension escalates the risk of premature death and reduces work productivity. While hypertension is considered to be a silent disease, loss of work days can accrue with the onset of complications associated with hypertension such as ischemic heart disease.

None of the guidelines address the cohort of young hypertensives, a growing concern in India. Given the high burden of risk factors for hypertension in the cohort of young individuals, India must focus on increasing awareness of hypertension and advocating healthy BP levels for its citizens through early and effective intervention with lifestyle modification and drugs. Fortuitously, there are plenty of opportunities for intervention in the long road leading to cardiovascular disease (CVD). Indians stand to benefit immensely if early and appropriate intervention is instituted to control blood pressure in young

[1]MGM New Bombay Hospital, Vashi, Navi Mumbai, Maharashtra; [2]Shilpa Medical Research Centre, Mumbai, Maharashtra; [3]Crescent Hospital & Heart Centre, Nagpur, Maharashtra; [4]Bombay Hospital & Medical Research Centre, Mumbai, Maharashtra; [5]PD Hinduja Hospital & Medical Research Centre, Mumbai, Maharashtra; [6]Sir Ganga Ram Hospital, Delhi; [7]CARE Hospitals, Bhubaneswar, Orissa; [8]AMRI Hospital, Kolkata, West Bengal; [9]Apollo Hospital, Bhubaneswar, Orissa; [10]SCB Medical College, Orissa; [11]Indo-US Super Speciality Hospital, Hyderabad, Telangana; [12]Kovai Medical Center and Hospital, Coimbatore, Tamil Nadu; [13]Max Super Speciality Hospital, New Delhi; *Corresponding Author
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Table 1: Prevalence of hypertension in young adults

	Response rate (%)				
	< 5 %	5-10%	10 – 20 %	20 – 30 %	>30 %
Overall Prevalence (n= 2287)	2	18.4	36.2	28.6	14.6
Speciality					
Cardiologists (n= 469)	1.9	13.9	37.3	30.1	16.8
Diabetologists (n=281)	1.8	13.9	40.2*	24.9	19.2
Consultant physicians (n=1458)	1.8	20.0	35.1*	29.4	13.7
Family physicians (n=79)	7.6	30.4*	35.4 *	19.0	7.6
Zone					
North(n = 455)	3.1	31.4	30.6	21.5	13.4
South (n = 758)	2.1	16.5	38	28.0	15.4
Central(n = 177)	1.7	15.2	19.2	44.1*	19.8
East(n = 368)	1.1	10.3	43.2*	32.9	12.5
West(n = 529)	1.7	16.5	39.3*	27.6	14.9
Experience					
≤ 5 years(n = 229)	3.1	18.8	37.5*	26.6	14.0
6 -10 years(n = 473)	2.8	16.9	33.4	30.2	16.7
11-15 years(n = 424)	2.2	19.1	37	27.8	13.9
16 -20 years(n = 365)	1.4	17.3	37.8*	27.9	15.6
>20 years (n = 796)	1.8	19.0	36.3	29.0	13.9

* P = 0.001 intra group comparison.

adults. In the absence of guidelines and good-quality studies, Indian clinicians will have to lead the war against hypertension in young adults based on their clinical experience. The current study is based on the experience of Indian clinicians to lead the way for effective management of hypertension in young adults in India.

The ACD algorithm has been proposed by various guidelines for the treatment of hypertension. The first line options being Angiotensin-converting enzyme inhibitors (ACEIs) or Angiotensin II receptor blockers (ARBs) when ACEIs are not tolerated, Calcium channel blockers (CCBs) and diuretics such as thiazide diuretics.[9,10]

One of the classes of drugs not accorded due respect is the beta-blockers. In fact, beta-blockers has the potential to have a special place in the management of hypertension in young adults in India because sympathetic over-activity is one of the factors implicated in the development of hypertension. The European Society of Cardiology/European Society of Hypertension (ESC/ESH) guidelines and Indian hypertension guidelines recommend that that beta-blockers be used when there is a specific indication for their use (e.g. angina, post-myocardial infarction, heart failure with reduced ejection fraction [HFrEF], or when heart rate control is required).[9,10]

Method

A cross- sectional observational survey using a structured questionnaire for hypertension in young was conducted online. The respondents included doctors like cardiologists, diabetologists, consultant physicians, and family physicians across the five zones of India (North, South, East, West, and Central). The survey questionnaire was developed by a panel of experts treating hypertension. The 14 item questionnaire were all forced-choice, with multiple- choice response options. The survey was quite straight forward and ensured a uniform mode of reporting. Study participants were interacted after receiving data whether they faced any other difficulty or bias.

The questionnaire included important aspects related to hypertension in young adults namely: prevalence of hypertension in young observed in real world setting, rating of key risk factors contributing to hypertension in young, parameters for deciding sympathetic overactivity (increased heart rate, increased systolic blood pressure), preferred class of antihypertensive drugs including preferred drug in the class and preferred beta-blocker used to treat hypertension in the young against the backdrop of sympathetic overactivity, understand whether sympathetic overactivity was the reason to choose a beta-blocker in the regimen of antihypertensives, the reason for use of beta- blockers in spite of them not being mentioned in any current guidelines, real world insights upon telmisartan/metoprolol single pill combination therapy.

Data were collected using the pre-designed questionnaire by trained medical personnel. The questionnaire did not contain any questions that revealed the identity of the patients treated by the physicians. The subgroup analysis of the responses was conducted based on the specialty of the respondents(cardiologists, diabetologists, consultant physicians and family physicians), years of experience of the respondents (less than or equal to 5 years, 6 -10 years, 11-15 years, 16-20 years and more than 20 years) and zonal differences in prevalence and treatment approaches. Descriptive statistics were first computed. Inferential statistics, namely chi-square test was then run to test the associations among knowledge, awareness and practice among the respondents across India.

Results

Two thousand two hundred eighty seven doctors participated in the survey. Prevalence of more than 30% was reported by 14.6% clinicians, 20-30% by 28.6% clinicians, 10-20% by 36.2% clinicians, 5-10% by 18.4% clinicians and less than 5% by 2% clinicians.

Prevalence of hypertension in young adults of more than 20% was reported by 46.8%, 44.1% and 43.1% of cardiologists, diabetologists and consultant physicians respectively, while less than 10% was reported by 38% of family physicians.

The zonal analysis of the prevalence of hypertension indicated that the 10-20% prevalence of hypertension was highest in the east zone(43.2%) while prevalence of 20- 30% was reported to be 44.1% in the central zone. The prevalence of hypertension in young adults of 10-30% was reported in the range of 63-66% by clinicians irrespective of years of experience (Table 1).

The top three risk factors for hypertension in young were perceived to be smoking, mental stress and obesity. The other risk factors were high salt intake, increased alcohol intake, sedentary lifestyle, and lack of adequate sleep (less than7 hours) (Figure 1).Survey participant doctors

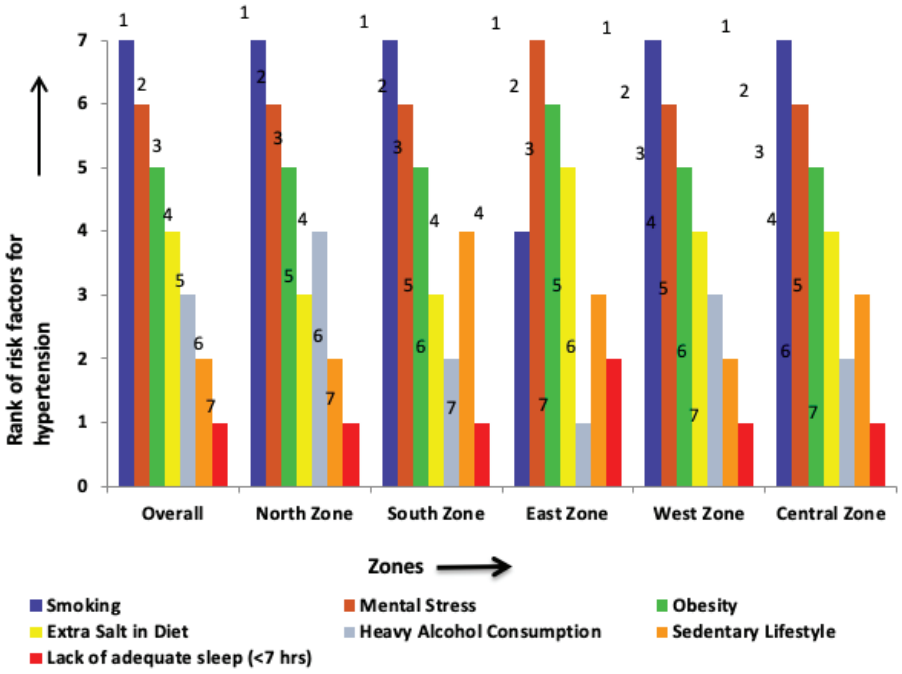

Fig. 1: Risk factors for hypertension in young in India

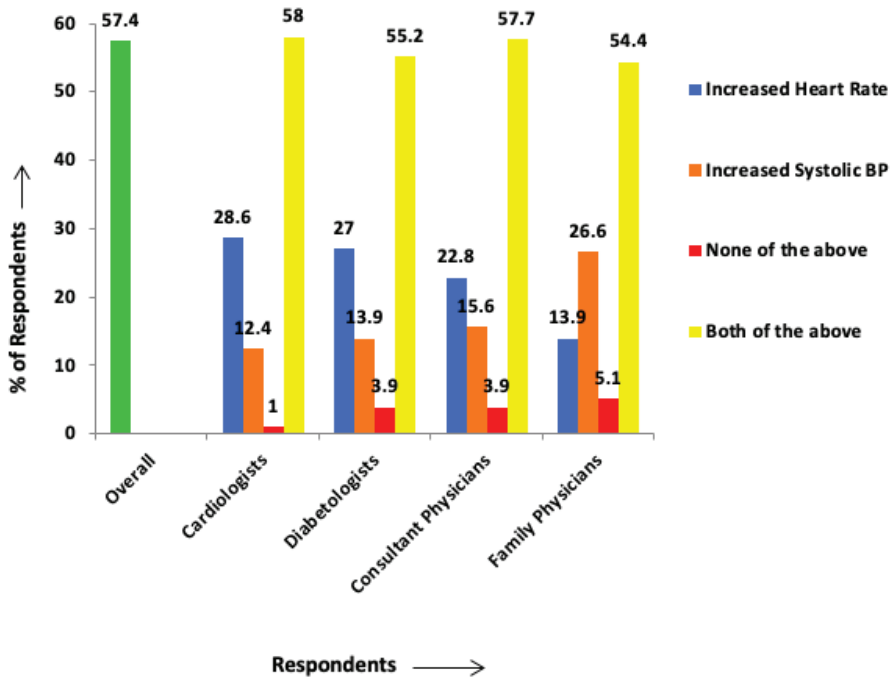

Fig. 2: Objective parameters for deciding sympathetic (SMN) over activity in young adult with hypertension

in the East Zone rated mental stress, obesity and extra salt in diet as top three risk factors followed by smoking.

Parameters of sympathetic overactivity in young hypertensive patients were considered as only increased systolic blood pressure, only increased heart rate and both increased heart rate and increased systolic blood pressure by 15.1%, 24.2% and 57.4% of respondents respectively. A similar opinion was chronicled across specialties (Figure 2).

ARBs (61.6%) were considered the most appropriate class of drugs to treat hypertension in young (Figure 3). Beta-blockers were preferred by 15.8% respondents, followed by calcium channel blockers, diuretics and ACEI by 10.4%, 7.6% and 4.6% respondents respectively. Family physicians preferred diuretics as second choice after ARBs.65.7% cardiologists preferred ARBs, while 61.2%, 61%, and 49.4% were the preference for ARBs chronicled with diabetologists, consultant physicians, and family physicians respectively. The highest preference for ARBs was reported in the east zone (72%) while the central zone, west zone, north zone and south zone registered a preference for ARBs ranging from 56.5% to 62.4% (Table 2).

Among the ARBs, telmisartan was preferred by almost 86% of respondents, while olmesartan, losartan and azilsartan were preferred by 6.5%, 2.5% and 0.7% clinicians respectively. About 4.3% of respondents showed no preference for specific ARB (Table 2). Telmisartan was the unanimous choice amongst the class of ARBs by cardiologists (89.3%), diabetologists(88.6%), consultant physicians (84.6%), and family physicians (82.3%). 93.8% clinicians in the east zone preferred telmisartan. A similar preference for telmisartan was reflected in the subgroup analysis of the choice of ARBs based on the experience of the clinicians participating in the survey.

About 62.9% of respondents were strong proponents of beta-blocker in young hypertensive patients. Of these, 68.7% cardiologists, 59% diabetologists, 61.9% consultant physicians and 62% family physicians preferred beta blockers in young hypertensive patients.

74.5% of clinicians across India selected beta-blockers as a part of the antihypertensive regimen in young hypertensive adults based on the rationale of sympathetic overactivity. In the class of beta-blockers, metoprolol (63.1%) was the preferred beta-blocker for the management of hypertension in the young (Table 3).

Combination therapy of telmisartan and metoprolol was preferred by 15.5%, 40.9%, 43.6% clinicians in young hypertension, uncontrolled hypertension, both young and uncontrolled hypertension patients respectively.

SBP reduction of 10-20 mmHg was observed in patients after the use of telmisartan/metoprolol single pill combination by 63.6% of the study investigators, while 20.1% of the

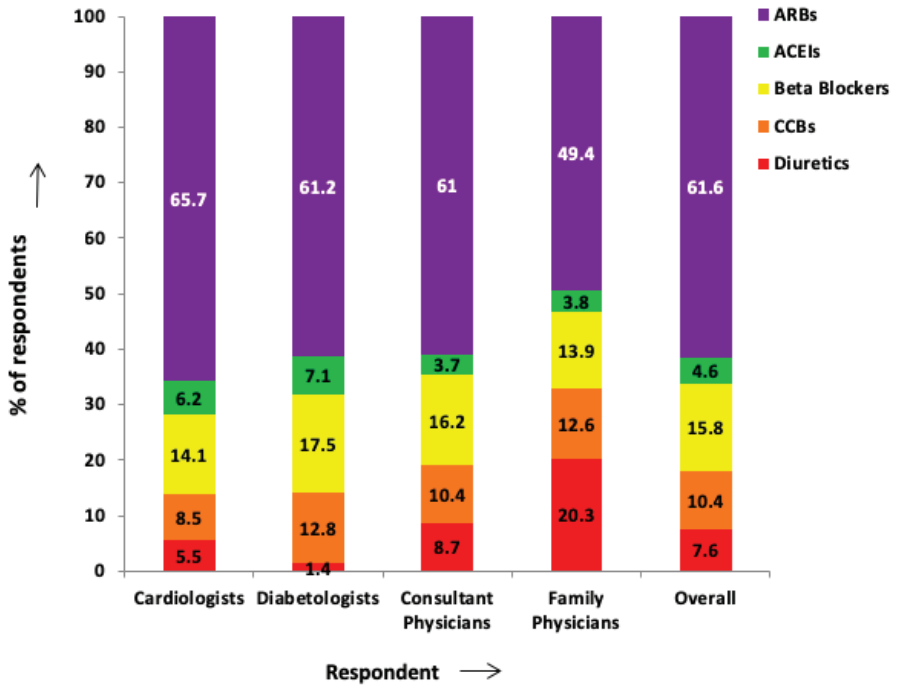

Fig. 3: Drug class preference for the management of hypertension in the young adults

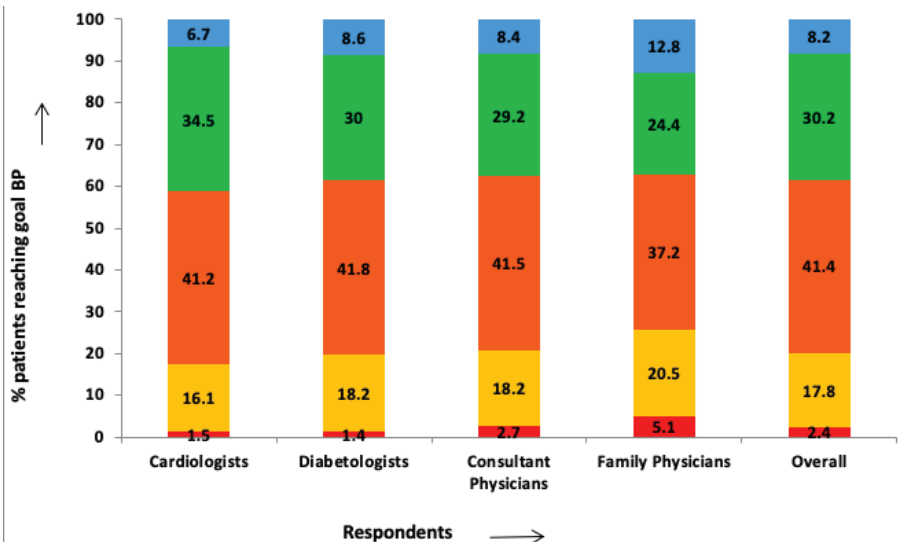

Fig. 4: Percentage of patients reaching goal BP with telmisartan/metoprolol single pill combination

investigators observed > 20 mmHg SBP reduction. 41.3% of the respondents reported that 40-60% of patients achieved the goal BP with telmisartan/metoprolol single pill combination, while about 30.2% of respondents observed that 60-80% of patients achieved the goal BP (Figure 4).

Telmisartan/metoprolol single pill combination was well tolerated in young hypertensive patients according to the 79.4% of the study physicians. 83.3% of cardiologists agreed that combination therapy was well tolerated in young hypertensive patients which were significantly more as compared to observations made by other respondents

Discussion

The high burden of risk factors for hypertension has resulted in an increasing prevalence of hypertension in the young adult population of India. The current all India survey brings forth the practice of Indian physicians treating hypertension in young Indians. Hypertension has been reported in 12.1% of young adults in the cross-sectional, nationally representative, population-based study by Geldsetzer P, et al.[11] In the current study the prevalence of hypertension

Table 2: Preference for ARB as class and Telmisartan as an ARB

	Response to preference for ARB as drug class of choice (%)	Response to Telmisartan as the ARB of choice (%)
Overall	61.6	86
Speciality		
Cardiologists (n= 469)	65.7	89.3
Diabetologists (n=281)	61.2	88.6
Consultant physicians (n=1458)	61	84.6
Family physicians (n=79)	49.4	82.3
Zone		
North (n = 455)	60.2	83.5
South (n = 758)	60.4	88.0
Central (n = 177)	56.5	81.9
East (n = 368)	72**	93.8**
West (n = 529)	59	81.1
Experience		
≤ 5 years(n = 229)	61.1	84.3
6 -10 years(n = 473)	61.1	86.5
11-15 years(n = 424)	63	82.2
16 -20 years(n = 365)	60.3	85.5
>20 years (n = 796)	61.9	88.3

* P = 0.037 ;**P = 0.001

Table 3: Preference of beta blockers in hypertension in young adults

	Response to preference for Beta blockers as drug class of choice (%)	Response to preference of Metoprolol as the Beta Blocker of choice (%)
Overall	15.8	63.1
Speciality		
Cardiologists (n= 469)	14.1	63.5
Diabetologists (n=281)	17.5	54.1
Consultant physicians (n=1458)	16.2	64.6
Family physicians (n=79)	13.9	64.6
Zone		
North (n = 455)	11.4	69.2
South (n = 758)	16.6	52.9
Central(n = 177)	30.5	58.2
East (n = 368)	10.1	76.1
West (n = 529)	17.6	65.0

in young adults was observed in up to 30%and corroborate the earlier reported prevalence statistics.

In the current survey, the top three risk factors for hypertension in young were perceived to be smoking, mental stress and obesity across India. In young adults in India, the substantial consumption of soft drinks has resulted in increased obesity and cardio-metabolic risk factors.[12] Inappropriate nutrition affects different anthropometric parameters and has a tremendous impact on the blood pressure levels even during young age either directly or indirectly. Higher intakes of fat, saturated fat, a predilection for salty, fried, oily, sweet, and fast food and higher sedentary activity levels and lower sleep duration have been implicated in the development of obesity in young Indians. Prevalence of smoking in India has been reported to be as high as 28%.[13]Even stress is a common feature amongst the young adult population.

Evaluating the underlying pathogenic features will help choose the appropriate treatment options for hypertension in young adults. In hypertension, the structure and function of the arterial wall are postulated to be altered at an early stage resulting in increased arterial stiffness. Increased arterial stiffness is an important risk marker of CVD. An abnormal collagen overproduction and diminished quantities of normal elastin contribute to vascular stiffness. Local renin-angiotensin-aldosterone system (RAAS) activation contributes to the development of arterial stiffness.[14] The reduced arterial compliance may be one mechanism whereby the increased activity of the RAAS produces adverse vascular effects. This results in increased ventricular afterload and decreased coronary perfusion pressure leading to left ventricular hypertrophy (LVH) and subendocardial ischemia. Hence the approach to the management of hypertension in the young adults must not only aim at lowering the blood pressure, but must also aim to prevent progression or reverse the process of arterial stiffness and thus reduce the risk of CVD. ARBs and ACEI have been demonstrated to decrease arterial stiffness. The appropriate treatment of hypertension in young can result in reduced morbidity and mortality. The current evidence corroborates the choice of ARBs for the management of hypertension in young adults by 61.1% clinicians involved in the survey.

In the current survey, 86% of respondents reported telmisartan to be the preferred ARB. Telmisartan displays unique pharmacologic properties, such as the highest affinity for the AT1 receptors, longer half-life than any other ARB resulting in sustained reductions of blood pressure. Telmisartan regresses left ventricular hypertrophy, reduces arterial stiffness, and confers renoprotection. Telmisartan may also reduce vascular inflammatory change. Additionally, telmisartan modulates peroxisome proliferator-activated receptor γ (PPARγ), and thus modulates insulin resistance, diabetes, and metabolic syndrome. PPARγ activation enhances the production of adiponectin resulting in anti-inflammatory, anti-oxidative,and anti-proliferative effects exerted on the vascular walls, thus lowering the risks for atherosclerosis and cardiovascular disease. This current evidence of the unique features of telmisartan corroborates the choice of telmisartan as the preferred ARB by Indian physicians.

Telmisartan is the first ARB to demonstrate cardiovascular (CV) prevention in patients at high CV risk. The ONTARGET trial demonstrated that telmisartan effectively reduced CV morbidity (including myocardial infarction and stroke) and mortality in a wide range of patients at increased CV risk.[15] In the TRANSCEND study, the reductions in risk for CV death, myocardial infarction, and stroke were 35%, 14%, and 19%, respectively.[15]

In addition to providing 24-hour blood pressure control, clinical studies in patients with diabetes show that telmisartan improves renal endothelial function, prevents progression from microalbuminuria to macroalbuminuria, slows the decline in glomerular filtration rate and reduces proteinuria in overt nephropathy. Telmisartan offers a superior reduction in proteinuria as compared to losartan.[16]

A considerable body of evidence relates sympathetic overactivity with high sodium intake, obesity, and hyperinsulinemia of obesity and mental stress.[17,18] Smoking too is associated with an increase in plasma catecholamines related to adrenergic stimulation. The sympathetic neural function plays an important role in blood pressure regulation, and overactivity of sympathetic nerves may play an important role in the development of hypertension, LVH, and related cardiovascular disorders. Sympathetic vasoconstriction decreases glucose uptake in skeletal muscle and leads to insulin resistance and compensatory hyperinsulinemia. In the early stages of hypertension, particularly in young patients, there is marked adrenergic overdrive leading to the development of essential hypertension.

The prevalence of sympathetic overactivity in newly diagnosed hypertensive patients in India has been reported to be about 62.42%. Six out of ten newly diagnosed hypertensive patients in India have sympathetic overactivity.[19] Chronically raised sympathetic nerve activity, independent of blood pressure, is a powerful predictor of myocardial infarction. The beta-1 blockade is effective in regressing and stabilizing coronary atheromatous plaque is effective in reducing the adverse effects of the raised sympathetic activity.

In our survey, the reported prevalence of sympathetic overactivity was reported to be about 74.5%. Hence, 62.9% respondents said that they were strong proponents of beta blocker in young hypertensive patients.63.1% respondents preferred metoprolol as the beta blocker for their young patients with hypertension.

Metoprolol is a cardioselective beta-1-adrenergic receptor inhibitor. Metoprolol in adult competitively blocks beta1-receptors with minimal or no effects on beta-2 receptors. Metoprolol significantly lowers the heart rate. The Metoprolol Atherosclerosis Prevention in Hypertensives (MAPHY) trial specifically showed a benefit of metoprolol over diuretics regarding sudden cardiac death as well as myocardial infarction.[38]

Combination therapy has been proven to improve blood pressure control and more patients reach target blood pressure faster. A dose-escalation approach using monotherapy reduces coronary events by 29% and cerebrovascular events by 40%, while combining two antihypertensive agents with a different mechanism of action reduces coronary events by

40% and cerebrovascular events by 54%. Hence the use of combination therapy offers greater target organ protection than increasing the dose of monotherapy. Cardiologists have been observed to prefer beta-blockers as initial antihypertensive drugs in the real-world setting in other countries and metoprolol is amongst the most commonly prescribed drug.

In the current all India survey, the preference for telmisartan and metoprolol in their respective classes paves the way for the use of combination therapy in young adults with hypertension in India. The use of combination therapy will depend on the grade of hypertension of the individual patient.

Limitation

This survey included urban, semi-urban areas and it does not reflect practice in rural India. Besides, the use of the purposive sampling technique may represent a confounding element. The survey only reflects clinician perception and does not reflect actual patient data. Real world studies and prospective trials in young patient's hypertension will throw more light on the practice trend.

The perception and choice of class of drug for treating young patients with hypertension is based on the respondent's individual opinion. Considering the uniformity of opinion amongst the specialty of varying experience in patient care, this perception can encourage further prospective studies. To overcome this limitation, it will be more prudent to collect the blood samples of young subjects with hypertension and analyze it for various biochemical parameters such as cytokines, anti-oxidants, NO, catecholamine and acetylcholine. This will lead to a better understanding of the pathobiology of hypertension in the young and correlate these findings to the response shown by the study population to various class of drugs used.

Conclusion

The data accrued from evaluation of practice pattern followed by clinicians across India for the management of hypertension in young adults will help institute an early and appropriate antihypertensive treatment in this population and may perhaps lower the burden of cardiovascular disease in this population in coming years. Amongst the current classes of drugs, ARBs and beta -blockers have been preferred by the clinicians who participated in the survey. Combination of telmisartan and metoprolol as a prototype of the respective anti-hypertensive class was preferred in the survey. ARBs are preferable and in the survey majority of Indian physicians seem to prefer telmisartan.

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References

1. Hinton TC, Adams ZH, Baker RP, Hope KA, Paton JFR, Hart EC, Nightingale AK. Investigation and Treatment of High Blood Pressure in Young People: Too Much Medicine or Appropriate Risk Reduction? *Hypertension* 2020; 75:16-22.
2. Yano Y, Muntner P. Hypertension in Young Adults and Subsequent Cardiovascular Disease. *JAMA* 2019; 321:1310-1311.
3. Yano Y, Reis JP, Colangelo LA, Shimbo D, Viera AJ, Allen NB, Gidding SS, Bress AP, Greenland P, Muntner P, Lloyd-Jones DM. Association of Blood Pressure Classification in Young Adults Using the 2017 American College of Cardiology/American Heart Association Blood Pressure Guideline With Cardiovascular Events Later in Life *JAMA* 2018; 320:1774-1782.
4. Anchala R, Kannuri NK, Pant H, Khan H, Franco OH, Di Angelantonio E, Prabhakaran D. Hypertension in India: a systematic review and meta-analysis of prevalence, awareness, and control of hypertension. *J Hypertens* 2014; 32:1170-1177.
5. Bhise MD, Patra S. Prevalence and correlates of hypertension in Maharashtra, India: A multilevel analysis. *PLoS One* 2018; 13:e0191948.
6. Jayanna K, Swaroop N, Kar A, Ramanaik S, Pati MK, Pujar A, Rai P, Chitrapu S, Patil G, Aggarwal P, Saksena S, Madegowda H, Rekha S, Mohan HL. Designing a comprehensive Non-Communicable Diseases (NCD) programme for hypertension and diabetes at primary health care level: evidence and experience from urban Karnataka, South India. *BMC Public Health* 2019; 19:409.
7. Gupta R, Ram CVS. Hypertension epidemiology in India: emerging aspects. *CurrOpinCardiol* 2019; 34:331-341.
8. Chopra HK, Ram CVS. Recent Guidelines for Hypertension. *Circ Res* 2019; 124:984-986.
9. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, Clement DL, Coca A, de Simone G, Dominiczak A, Kahan T, Mahfoud F, Redon J, Ruilope L, Zanchetti A, Kerins M, Kjeldsen SE, Kreutz R, Laurent S, Lip GYH, McManus R, Narkiewicz K, Ruschitzka F, Schmieder RE, Shlyakhto E, Tsioufis C, Aboyans V, Desormais I; ESC Scientific Document Group. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Eur Heart J* 2018; 39:3021-3104.
10. What is New in Indian Guidelines on Hypertension – Iv Supplement to Journal of The Association of Physicians of India Published on 1st of Every Month 1st October, 2019: https://japi.org/october_2019_spl/03_what_is_new.pdf . accessed on April 2nd, 2020
11. Geldsetzer P, Manne-Goehler J, Theilmann M, Davies JI, Awasthi A, Vollmer S, Jaacks LM, Bärnighausen T, Atun R. Diabetes and Hypertension in India: A Nationally Representative Study of 1.3 Million Adults. *JAMA Intern Med* 2018; 178:363-372.
12. Siddiqi Z, Karoli R, Fatima J, Khanduri S, Varshneya S, Ahmad SS. Soft Drinks Consumption and the Risk of Nonalcoholic Fatty Liver Disease. *J Assoc Physicians India* 2017; 65:28-32.
13. Krishnan MN, Zachariah G, Venugopal K, Mohanan PP, Harikrishnan S, Sanjay G, Jeyaseelan L, Thankappan KR. Prevalence of coronary artery disease and its risk factors in Kerala, South India: a community-based cross-sectional study. *BMC Cardiovasc Disord* 2016; 16:12.
14. Aroor AR, Whaley-Connell A, Sowers JR. Utility of obesity and metabolic dyslipidemia (a non-insulin based determinate of the metabolic syndrome and insulin resistance) in predicting arterial stiffness. *J Clin Hypertens (Greenwich)* 2019; 21:1071-1074.
15. Dehghan M, Mente A, Teo KK, Gao P, Sleight P, Dagenais G, Avezum A, Probstfield JL, Dans T, Yusuf S; Ongoing Telmisartan Alone and in Combination With Ramipril Global End Point Trial (ONTARGET)/Telmisartan Randomized Assessment Study in ACEI Intolerant Subjects With Cardiovascular Disease (TRANSCEND) Trial Investigators. Relationship between healthy diet and risk of cardiovascular disease among patients on drug therapies for secondary prevention: a prospective cohort study of 31 546 high-risk individuals from 40 countries. *Circulation* 2012; 126:2705-2712.
16. Ritz E, Schmieder RE, Pollock CA. Renal protection in diabetes: lessons from ONTARGET. *Cardiovasc Diabetol* 2010; 9:60.
17. Landsberg L. Diet, obesity, and hypertension: an hypothesis involving insulin, the sympathetic nervous system and adaptive thermogenesis. *QJ Med* 1986; 61:1081–1090.
18. Grassi G, Seravalle G, Calhoun DA, Bolla G, Mancia G. Cigarette smoking and the adrenergic nervous system. *Clin Exp Hypertens A* 1992; 14:251-60.
19. Cruickshank JM. Why has the primary prevention of myocardial infarction in the treatment of hypertension been so elusive? *J Hum Hypertens* 1987; 1:73-81.
20. Wikstrand J, Warnold I, Tuomilehto J, Olsson G, Barber HJ, Eliasson K, Elmfeldt D, Jastrup B, Karatzas NB, Leer J. Metoprolol versus thiazide diuretics in hypertension. Morbidity results from the MAPHY Study. *Hypertension* 1991; 17:579-588.