NEWER CLINICAL TRIALS IN HYPERTENSION:
CHANGING GUIDELINES AND CURRENT APPROACH IN MANAGEMENT

INTRODUCTION
Hypertension (HTN) is a major contributor to cardiovascular morbidity and mortality in India and worldwide. The first Indian hypertension guidelines (IGH) were revised and updated in 2007 under the aegis of Cardiological society of India, Hypertension Society of India, NSI and API. The present review discusses the newer trials in HTN in the last 4 years and the changes in guidelines for HTN that are likely to happen. While previous guidelines suggested that the minimum goal for blood pressure reduction was a systolic blood pressure <140mm Hg and a diastolic blood pressure <90mm Hg, current clinical trials show more evidence in favor of diastolic goal. Similarly, the guideline recommendation to lower blood pressure in the diabetics to <130/80mm Hg is evidence-based only for diastolic blood pressure. Recent trials have found that achieving a systolic BP goal <120mm Hg did not result in a significant reduction in overall cardiovascular events in this subset of patients. Even in patients with underlying renal disease, the current trials suggest a goal of <140/90mm Hg to protect against cardiovascular disease and progressive nephropathy. Hence, the newer trials shall alter the current approach in management of HTN, change the usual drug regimen used and newer thresholds may be defined for HTN control in different subset of patients in the forth coming guidelines.

NEWER CLINICAL TRIALS

CLINICAL TRIALS IN 2008

Hypertension in the Very Elderly Trial (HYVET)6
HYVET was randomized trial of 3845 patients who were 80 years of age or older and had a sustained systolic blood pressure of 160 mm Hg or more to receive either the diuretic indapamide (sustained release, 1.5 mg) or matching placebo. The angiotensin-converting–enzyme inhibitor perindopril (2 or 4 mg), or matching placebo, was added if necessary to achieve the target blood pressure of 150/80 mm Hg. The primary end point was fatal or nonfatal stroke. Active treatment was associated with a 30% reduction in the rate of fatal or nonfatal stroke (95% confidence interval [CI], −1 to 51; P = 0.06), a 39% reduction in the rate of death from stroke (95% CI, 1 to 62; P = 0.05), a 21% reduction in the rate of death from any cause (95% CI, 4 to 35; P = 0.02), a 23% reduction in the rate of death from cardiovascular causes (95% CI, −1 to 40; P = 0.06), and a 64% reduction in the rate of heart failure (95% CI, 42 to 78; P<0.001). Fewer serious adverse events were reported in the active-treatment group (358, vs. 448 in the placebo group; P = 0.001). The results provided evidence that antihypertensive treatment with indapamide (sustained release), with or without perindopril, in persons 80 years of age or older was beneficial (Figure 1).

The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET)7

The ONTARGET trial compared the ACE inhibitor ramipril, the ARB telmisartan, and the combination of the two drugs in patients with vascular disease or high-risk diabetes. It was a double-blind randomized trial, 8576 were to receive 10 mg of ramipril per day, 8542 were assigned to receive 80 mg of telmisartan per day, 8502 were assigned to receive both drugs (combination therapy) for a mean
of 56 months. The primary composite outcome was death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure. Mean blood pressure was lower in both the telmisartan group (a 0.9/0.6 mm Hg greater reduction) and the combination-therapy group (a 2.4/1.4 mm Hg greater reduction) than in the ramipril group. At a median follow-up of 56 months, the primary outcome had occurred in 1412 patients in the ramipril group (16.5%), as compared with 1423 patients in the telmisartan group (16.7%; relative risk, 1.01; 95% confidence interval [CI], 0.94 to 1.09). As compared with the ramipril group, the telmisartan group had lower rates of cough (1.1% vs. 4.2%, P<0.001) and angioedema (0.1% vs. 0.3%, P = 0.01) and a higher rate of hypotensive symptoms (2.6% vs. 1.7%, P<0.001); the rate of syncope was the same in the two groups (0.2%). In the combination-therapy group, the primary outcome occurred in 1386 patients (16.3%; relative risk, 0.99; 95% CI, 0.92 to 1.07); as compared with the ramipril group, there was an increased risk of hypotensive symptoms (4.8% vs. 1.7%, P<0.001), syncope (0.3% vs. 0.2%, P = 0.03), and renal dysfunction (13.5% vs. 10.2%, P<0.001). Telmisartan was found equivalent to ramipril in patients with vascular disease or high-risk diabetes and was associated with less angioedema. The combination of the two drugs was associated with more adverse events without an increase in benefit.

Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial

ACCOMPLISH trial was a randomized, double-blind trial of 11,506 patients with hypertension who were at high risk for cardiovascular events and received treatment with either benazepril plus amlodipine or benazepril plus hydrochlorothiazide. The primary endpoint was the composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, hospitalization for angina, resuscitation after sudden cardiac arrest, and coronary revascularization. The baseline characteristics of the two groups were similar. The trial was terminated early after a mean follow-up of 36 months, when the boundary of the prespecified stopping rule was exceeded. Mean blood pressures after dose adjustment were 131.6/73.3 mm Hg in the benazepril–amlodipine group and 132.5/74.4 mm Hg in the benazepril–hydrochlorothiazide group. There were 552 primary-outcome events in the benazepril–amlodipine group (9.6%) and 679 in the benazepril–hydrochlorothiazide group (11.8%), representing an absolute risk reduction with benazepril–Amlodipine therapy of 2.2% and a relative risk reduction of 19.6% (hazard ratio, 0.80, 95% confidence interval [CI], 0.72 to 0.90; P<0.001). For the secondary end point of death from cardiovascular causes, nonfatal myocardial infarction, and nonfatal stroke, the hazard ratio was 0.79 (95% CI, 0.67 to 0.92; P = 0.002). Rates of adverse events were consistent with those observed from clinical experience with the study drugs. The benazepril–amlodipine combination was superior to the benazepril–hydrochlorothiazide combination in reducing CV events in patients with hypertension who were at high risk for such events.

The Stop Atherosclerosis in Native Diabetics (SANDS) study

SANDS study compared standard versus aggressive therapy on the progression of subclinical atherosclerosis in 499 Native American adults with type 2 diabetes and no prior cardiovascular disease. Patients were randomized to one of two levels of LDL-C (<100 versus <70 mg/dL) and one of
two levels of systolic blood pressure (<130 vs <115 mm Hg). The primary endpoint was change in carotid intimal-medial thickness (c-IMT) and left ventricular mass reduction. Over the 3 years of the study, mean achieved LDL-C was 104 and 72 mg/dL and mean achieved systolic blood pressure was 129 and 117 mm Hg in the standard compared to aggressive group, respectively. The main finding was that in the more aggressively treated group, c-IMT actually regressed from baseline, while in the standard group c-IMT progressed, a difference that was statistically significant. In addition, a greater decrease in left ventricular mass occurred in those whose blood pressure was more aggressively treated. Because this study examined changes in a subclinical or surrogate atherosclerotic endpoint in a specific ethnic group and because clinical cardiovascular events did not differ significantly between groups, it remains unclear whether more aggressive treatment of LDL-C and specifically reduction of systolic blood pressure would result in an incremental benefit on cardiovascular events.

**Relation of Beta-Blocker–Induced Heart Rate Lowering and Cardioprotection in Hypertension**

This meta-analysis evaluated the role of heart rate reduction with beta-blockers on the risk of cardiovascular events in patients with hypertension. 34,096 patients taking beta-blockers against 30,139 patients taking other antihypertensive agents and 3,987 patients receiving placebo were included. Paradoxically, a lower heart rate (as attained in the beta-blocker group at study end) was associated with a greater risk for the end points of all-cause mortality (r = -0.51; p < 0.0001), cardiovascular mortality (r = -0.61; p < 0.0001), myocardial infarction (r = -0.85; p < 0.0001), stroke (r = -0.20; p < 0.001), or heart failure (r = -0.64; p < 0.0001). The same was true when the heart rate difference between the 2 treatment modalities at the end of the study was compared with the relative risk reduction for cardiovascular events. In contrast to patients with myocardial infarction and heart failure, beta-blocker–associated reduction in heart rate increased the risk of cardiovascular events and death for hypertensive patients. It should be noted that 66% of patients on BBs were on atenolol, hence meaningful extrapolation of these results to those of other BBs cannot be done.

**CLINICAL TRIALS IN 2009**

**Effect of the Direct Renin Inhibitor Aliskiren, the Angiotensin Receptor Blocker Losartan, or Both on Left Ventricular Mass in Patients With Hypertension and Left Ventricular Hypertrophy (ALLAY Trial)**

ALLAY trial was randomized trial of 465 patients with hypertension, increased ventricular wall thickness, and BMI >25 kg/m² to receive aliskiren 300 mg, losartan 100 mg, or their combination daily for 9 months. Patients were treated to standard blood pressure targets with add-on therapy, excluding other inhibitors of the renin-angiotensin-aldosterone system and beta-blockers. Patients underwent cardiovascular magnetic resonance imaging for assessment of LV mass at baseline and at study completion. The primary objective was to compare change in LV mass index from baseline to follow-up in the combination and losartan arms; the secondary objective was to determine whether aliskiren was noninferior to losartan in reducing LV mass index from baseline to follow-up. Systolic and diastolic blood pressures were reduced similarly in all treatment groups (6.5±14.9/3.8±10.1 mm Hg in the aliskiren group; 5.5±15.6/3.7±10.7 mm Hg in the losartan group; 6.6±16.6/4.6±10.5 mm Hg in the combination arm; P<0.0001 within groups, P=0.81 between groups). LV mass index was reduced significantly from baseline in all treatment groups (4.9-, 4.8-, and 5.8 g/m² reductions in the aliskiren, losartan, and combination arms, respectively; P<0.0001 for all treatment groups). The reduction in LV mass index in the combination group was not significantly different from that with losartan alone (P=0.52). Aliskiren was as effective as losartan in reducing LV mass index (P<0.0001 for noninferiority). Safety and tolerability were similar across all treatment groups. It was concluded that Aliskiren was as effective as losartan in promoting LV mass regression. Reduction in LV mass with the combination of aliskiren plus losartan was not significantly different from that with losartan monotherapy, independent of blood pressure lowering (Figure 2).

**Triple Antihypertensive Therapy With Amlodipine, Valsartan, and Hydrochlorothiazide (Aml/Val/HCTZ) A Randomized Clinical Trial**

This randomized, double-blind study evaluated the efficacy/safety of triple therapy with Aml/Val/HCTZ for moderate or severe hypertension (mean sitting systolic BP: ≥145 mm Hg; mean sitting diastolic BP: ≥100 mm Hg). The study included a single-blind, placebo run-in period, followed by double-blind treatment for 8 weeks; patients were randomly assigned to 1 of...
4 groups titrated to Aml/Val/HCTZ 10/320/25 mg, Val/HCTZ 320/25 mg, Aml/Val 10/320 mg, or Aml/HCTZ 10/25 mg once daily. Dual-therapy recipients received half of the target doses of both agents for the first 2 weeks, titrating to target doses during week 3. Those on triple therapy received Val/HCTZ 160.0/12.5 mg during week 1, Aml/Val/HCTZ 50.0/160.0/12.5 mg during week 2, and target doses of all 3 of the agents during week 3. Of the 4285 patients enrolled, 2271 were randomly assigned to treatment, and 2060 completed the study. Triple therapy was significantly superior to all of the dual therapies in reducing mean sitting systolic BP and mean sitting diastolic BP from baseline to end point (all P<0.0001). Significantly more patients on triple therapy achieved overall BP control (<140/90 mm Hg; P<0.0001) and systolic and diastolic control (P≤0.0002) compared with each dual therapy. Aml/Val/HCTZ was well tolerated. The benefits of triple therapy over dual therapy were observed regardless of age, sex, race, ethnicity, or baseline mean sitting systolic BP. In conclusion, this study demonstrates the efficacy/safety of treating moderate and severe hypertension with Aml/Val/HCTZ 10/320/25 mg.

Usual versus tight control of systolic blood pressure in non-diabetic patients with hypertension (Cardio-Sis): an open-label randomized trial.13

To investigate if a lower blood pressure goal was associated with less target organ damage, investigators from Italy randomized 1111 non-diabetic hypertensive patients to one of two systolic blood pressure goals: a goal of <130 mm Hg (tight control) or <140 mm Hg (usual control). Patients had at least one other cardiovascular risk factor and a baseline systolic blood pressure of greater than 150 mm Hg (mean 163/90 mm Hg) after being treated with antihypertensive therapy for at least 12 weeks. Treatment was open-label and individualized. The primary endpoint was prevalence of electrocardiographic left ventricular hypertrophy (LVH). At baseline, blood pressures were equal in the two groups, with roughly 20% of patients in each group having LVH. After 2 years, 27% and 72% of patients in the usual-and tight-control groups, respectively, had systolic blood pressures <130 mm Hg. More patients in the usual-control group than in the tight-control group (17.0% vs. 11 %) had LVH [odds ratio 0.63, 95% CI 0.43-0.91]. In addition, although few cardiovascular events occurred, significantly more patients in the usual-control group than in the tight-control group (9% vs. 5%) reached a secondary composite endpoint [hazard ratio 0.50, CI 0.31-0.79] that consisted of any of nine adverse clinical cardiovascular outcomes. This is the first clinical trial to target a systolic blood pressure <130 mm Hg in a non-diabetic population with normal renal function. LVH is a surrogate endpoint and studies powered to evaluate cardiovascular outcomes will be required before we can justify lowering the targeted blood pressure in this patient population to <130 mm Hg.

Treatment blood pressure targets for hypertension. Cochrane Database Syst Rev 8 CD004349

The objective was to determine if lower BP targets (≤135/85 mmHg) are associated with reduction in mortality and morbidity as compared with standard BP targets (≤140-160/90-100 mmHg). Electronic search of MEDLINE (1966-2008), EMBASE (1980-2008), and CENTRAL (up to June 2008); references from review articles, clinical guidelines, and clinical trials was done. Randomized controlled trials comparing patients randomized to lower or to standard BP targets and providing data on any of the primary outcomes were selected. No trials comparing different systolic BP targets were found. Seven trials (22,089 subjects) comparing different diastolic BP targets were included. Despite a -4/-3 mmHg greater achieved reduction in systolic/diastolic BP, p< 0.001, attempting to achieve "lower targets" instead of "standard targets" did not change total mortality (RR 0.92, 95% CI 0.86-1.15), myocardial infarction (RR 0.90, 95% CI 0.74-1.09), stroke (RR 0.99, 95% CI 0.79-1.25), congestive heart failure (RR 0.88, 95% CI 0.59-1.32), major cardiovascular events (RR 0.94, 95% CI 0.83-1.07), or end-stage renal disease (RR 1.01, 95% CI 0.81-1.27). The net health effect of lower targets could not be fully assessed due to lack of information regarding all total serious adverse events and withdrawals due to adverse effects in 6 of 7 trials. A sensitivity analysis in diabetic patients and in patients with chronic renal disease also did not show a reduction in any of the mortality and morbidity outcomes with lower targets as compared to standard targets. It was concluded that treating patients to lower than standard BP targets, ≤140-160/90-100 mmHg, does not reduce mortality or morbidity.

Renal artery stenting in patients with atherosclerotic renal artery stenosis (ARAS) and impaired renal function: A randomized trial.15

This was a randomized clinical trial to determine the efficacy and safety of stent placement in patients with ARAS and impaired renal function. 140 patients with creatinine clearance less than 80mL/min per 1.73 m² and ARAS of 50% or greater were taken. 64 patients underwent stent placement and medical treatment and 76 patients received medical treatment only. Medical treatment consisted of anti hypertensive treatment, a statin and aspirin. The Primary endpoint was a 20% or greater decrease in creatinine clearance. Secondary endpoints included safety and cardiovascular morbidity and mortality. Forty six of 64 patients assigned to stent placement had the procedure. Ten of the 64 patients (16%) in the stent placement group and 16 patients (22%) in the medication group reached the primary endpoint (hazard ratio, 0.73[95% CI, 0.33 to 1.61]). Serious complications occurred in the stent group, including 2 procedure related deaths (3%) 1 late death secondary to an infected hematoma, and 1 patient who required dialysis secondary to cholesterol embolism. The groups did not
differ for other secondary endpoints. It was concluded that stent placement with medical treatment had no clear effect on progression of impaired renal function but led to a small number of significant procedure related complications. The study findings favor a conservative approach to patients with ARAS, focused on cardiovascular risk factor management and avoiding stenting.

Revascularization vs Medical Therapy for renal artery stenosis – The ASTRAL study\(^{16}\)

One of the largest trials, the Angioplasty and Stenting for Renal Artery Lesions (ASTRAL) study, included 806 renal failure patients (mean serum creatinine approximately 2mg/dl) with atherosclerotic renal vascular disease from 54 medical centers in the UK and four medical centers in Australia and New Zealand. They were randomized to receive either revascularization and medical therapy or medical therapy alone. On average, patients had 75% RAS. At one-year follow-up there were no differences in the change in serum creatinine level (it rose by 0.2mg/dl in both groups) or in rates of renal events, including acute renal failure. There were no statistically significant differences in BP, kidney function, rates of myocardial infarction, cerebrovascular events or hospitalization due to angina, heart failure or the need for percutaneous coronary intervention or bypass surgery between the intervention and medical therapy groups.

Stent placement in patients with atherosclerotic renal artery stenosis and impaired renal function: a randomized trial\(^{17}\)

The STAR trial investigated renal artery stenting in 140 patients with impaired renal function (creatinine clearance <80 ml/1.73 m\(^2\)) and RAS of 50% or greater. In this study, patients were assigned to stenting plus medical treatment versus medical therapy alone and followed for 2 years. The primary end point was a 20% or greater decrease in creatinine clearance and this was reached in 15.6% patients who had undergone stenting and 16% of the medically treated group (hazard ratio: 0.73; 95% CI: 0.33–1.61). Three patients died from renal stenting-related complications and one patient required dialysis, likely due to atheromatous embolization. The authors concluded that renal artery stenting was equivalent to medical therapy alone and carried a significant risk of procedure-related complications. However, this study has a number of fundamental weaknesses. First, the trial included patients who had insignificant RAS, overestimated by noninvasive studies. In the intention-treat-analysis one-third of patients randomized to stenting were not treated owing to the presence of mild RAS, although the per-protocol analysis did not change the negative result. Concerns have also been expressed about the level of operator experience, given the 4% procedure failure rate and the serious complications encountered.

The ongoing CORAL (Cardiovascular Outcomes in Renal Atherosclerotic Lesions) study will compare the effect of optimal medical therapy alone to stenting with optimal medical therapy, on a composite of cardiovascular and renal end points: cardiovascular or renal death, myocardial infarction, hospitalization for congestive heart failure, stroke, doubling of serum creatinine level, and need for renal replacement therapy in patients. This National Institutes of Health (NIH)-funded multicentre trial has the potential to help us understand any incremental benefits of renal artery revascularization on clinical end points above and beyond contemporary optimal medical therapy. The CORAL trial completed enrollment in January 2010 with approximately 940 patients and the results are eagerly awaited.

CLINICAL TRIALS IN 2010

Novel Baroreflex Activation Therapy in Resistant Hypertension Results of a European Multi-Center Feasibility Study.\(^{18}\)

This study assessed the safety and efficacy of a novel implantable device therapy (Rheos system that activates the carotid baroreflex) in resistant hypertension patients. Forty-five subjects with systolic blood pressure 160 mm Hg or diastolic 90 mm Hg despite at least 3 antihypertensive drugs were enrolled in a prospective, nonrandomized feasibility study with follow-up of 2 years. Baseline mean blood pressure was 179/105 mm Hg and heart rate was 80 beats/min, with a median of 5 antihypertensive drugs. After 3 months of device therapy, mean blood pressure was reduced by 21/12 mm Hg. This result was sustained in 17 subjects who completed 2 years of follow-up, with a mean reduction of 33/22 mm Hg. It was concluded that the Rheos device sustainably reduces blood pressure in resistant hypertensive subjects with multiple comorbidities receiving numerous medications.

Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomized controlled trial\(^{19}\)

Symplicity HTN-2 was a randomized trial in which patients with systolic blood pressure above 160 mm Hg on three drugs were allocated to renal denervation with previous treatment or previous treatment alone. The primary effectiveness endpoint was change in seated office-based measurement of systolic blood pressure at 6 months. 106 (56%) of 190 patients screened for eligibility were randomly allocated to renal denervation (n=52) or control (n=54) groups between June 9, 2009, and Jan 15, 2010. 49 (94%) of 52 patients who underwent renal denervation and 51 (94%) of 54 controls were assessed for the primary endpoint at 6 months. Office-based blood pressure measurements in the renal denervation group reduced by 32/12 mm Hg (SD 23/11, baseline of 178/96 mm Hg, p<0·0001), whereas they did not differ from baseline in the control group (change of 1/0 mm Hg [21/10], baseline of 178/97 mm Hg, p=0·77 systolic and p=0·83 diastolic). Between-group differences in blood pressure at 6 months were 33/11 mm Hg (p<0·0001). At 6 months, 41 (84%) of 49 patients who
underwent renal denervation had a reduction in systolic blood pressure of 10 mm Hg or more, compared with 18 (35%) of 51 controls (p<0·0001). There was no serious procedure related or device-related complications and occurrence of adverse events did not differ between groups. One patient who had renal denervation had possible progression of an underlying atherosclerotic lesion, but required no treatment. (Figure 3). It was concluded that catheter-based renal denervation can safely be used to substantially reduce blood pressure in treatment resistant hypertensive patients.

**Action to Control Cardiovascular Risk in Diabetes (ACCORD) Study**

A total of 4733 participants with type 2 diabetes were randomly assigned to intensive therapy, targeting a systolic pressure of less than 120 mm Hg, or standard therapy, targeting a systolic pressure of less than 140 mm Hg. The primary composite outcome was nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes. The mean follow-up was 4.7 years. After 1 year, the mean systolic blood pressure was 119.3 mm Hg in the intensive therapy group and 133.5 mm Hg in the standard-therapy group. The annual rate of the primary outcome was 1.87% in the intensive-therapy group and 2.09% in the standard-therapy group (hazard ratio with intensive therapy, 0.88; 95% confidence interval [CI], 0.73 to 1.06; P = 0.20). The annual rates of death from any cause were 1.28% and 1.19% in the two groups, respectively (hazard ratio, 1.07; 95% CI, 0.85 to 1.35; P = 0.55). The annual rates of stroke, a pre-specified secondary outcome, were 0.32% and 0.53% in the two groups, respectively (hazard ratio, 0.59; 95% CI, 0.39 to 0.89; P = 0.01). Serious adverse events attributed to antihypertensive treatment occurred in 77 of the 2362 participants in the intensive-therapy group (3.3%) and 30 of the 2371 participants in the standard-therapy group (1.3%) (P=0.001). It was concluded that in patients with type 2 diabetes at high risk for cardiovascular events, targeting a systolic blood pressure of less than 120 mm Hg, as compared with less than 140 mm Hg, did not reduce the rate of a composite outcome of fatal and nonfatal major cardiovascular events (Figure 4).

**Tight blood pressure control and cardiovascular outcomes among hypertensive patients with diabetes and coronary artery disease.**

The objective was to determine the association of systolic BP control achieved and adverse cardiovascular outcomes in a cohort of patients with diabetes and CAD. Observational subgroup analysis of 6400 of the 22 576 participants in the International Verapamil SR-Trandolapril Study (INVEST) was done. For this analysis, participants were at least 50 years old and had diabetes and CAD. During 16 893 patient-years of follow-up, 286 patients (12.7%) who maintained tight control, 249 (12.6%) who had usual control, and 431 (19.8%) who had uncontrolled systolic BP experienced a primary outcome event. Patients in the usual control group had a cardiovascular event rate of 12.6% vs a 19.8% event rate for those in the uncontrolled group (adjusted hazard ratio [HR], 1.46; 95% confidence interval [CI], 1.25-1.71; P<.001). However, little difference existed between those with usual control and those with tight control. Their respective event rates were 12.6% vs 12.7% (adjusted HR, 1.11; 95% CI, 0.93-1.32; P=.24). The all-cause mortality rate was 11.0% in the tight-control group vs 10.2% in the usual-control group (adjusted HR, 1.20; 95% CI, 0.99-1.45; P=.06); however, when extended follow-up was included, risk of all-cause mortality was 22.8% in the tight control vs 21.8% in the usual control group (adjusted HR, 1.15; 95% CI, 1.01-1.32; P=.04). It was concluded that tight control of systolic BP among patients with diabetes and CAD was not associated with improved cardiovascular outcomes compared with usual control.
CLINICAL TRIALS IN 2011

Randomized Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP) trial

ROADMAP trial was randomized, double-blind, multicenter, controlled trial, of 4447 patients with type 2 diabetes to receive olmesartan (at a dose of 40 mg once daily) or placebo for a median of 3.2 years. Primary outcome was the time to the first onset of microalbuminuria. The times to the onset of renal and cardiovascular events were analyzed as secondary end points. The target blood pressure (<130/80 mm Hg) was achieved in nearly 80% of the patients taking olmesartan and 71% taking placebo; blood pressure measured in the clinic was lower by 3.1/1.9 mm Hg in the olmesartan group than in the placebo group. Microalbuminuria developed in 8.2% of the patients in the olmesartan group (178 of 2160 patients who could be evaluated) and 9.8% in the placebo group (210 of 2139); the time to the onset of microalbuminuria was increased by 23% with olmesartan (hazard ratio for onset of microalbuminuria, 0.77; 95% confidence interval, 0.63 to 0.94; P = 0.01). The serum creatinine level doubled in 1% of the patients in each group. Slightly fewer patients in the olmesartan group than in the placebo group had nonfatal cardiovascular events - 81 of 2232 patients (3.6%) as compared with 91 of 2215 patients (4.1%) (P = 0.37) - but a greater number had fatal cardiovascular events - 15 patients (0.7%) as compared with 3 patients (0.1%) (P = 0.01), a difference that was attributable in part to a higher rate of death from cardiovascular causes in the olmesartan group than in the placebo group among patients with preexisting coronary heart disease (11 of 564 patients [2.0%] vs. 1 of 540 [0.2%], P = 0.02). Olmesartan was associated with a delayed onset of microalbuminuria, even though blood-pressure control in both groups was excellent according to current standards. Olmesartan group had statistically significant number of fatal CV events, an outcome which remains unexplained. The higher rate of fatal cardiovascular events with olmesartan among patients with preexisting coronary heart disease is of concern.

Addition of Spiromolactone in Patients With Resistant Arterial Hypertension (ASPIRANT)

This study was designed to assess the effect of the addition of 25 mg of spironolactone on BP in patients with resistant arterial hypertension. Patients with office systolic BP>140 mm Hg or diastolic BP>90 mm Hg despite treatment with at least 3 antihypertensive drugs, including a diuretic, were enrolled in this double-blind, placebo-controlled, multicenter trial. One hundred seventeen patients were randomly assigned to receive spironolactone (n=59) or a placebo (n=58) as an add-on to their antihypertensive medication, by the method of simple randomization. Analyses were done with 111 patients (55 in the spironolactone and 56 in the placebo groups). At 8 weeks, the primary end points, a difference in mean fall of BP on daytime ambulatory BP monitoring (ABPM), between the groups was -5.4 mm Hg (95% CI -10.0; -0.8) for systolic BP (P=0.024) and -1.0 mm Hg (95% CI -4.0; 2.0) for diastolic BP (P=0.358). The ABPM nighttime systolic, 24-hour ABPM systolic, and office systolic BP values were significantly decreased by spironolactone (difference of -8.6, -9.8, and -6.5 mm Hg; P=0.011, 0.004, and 0.011), whereas the fall of the respective diastolic BP values was not significant (-3.0, -1.0, and -2.5 mm Hg; P=0.079, 0.405, and 0.079). The adverse events in both groups were comparable. It was concluded that spironolactone is an effective drug for lowering systolic BP in patients with resistant arterial hypertension.

Aliskiren and the calcium channel blocker Amlodipine combination as an initial treatment strategy for hypertension control (ACCELERATE) trial

The trial tested whether a combination of aliskiren and amlodipine is superior to each monotherapy in early control of blood pressure without excess of adverse events, and if initial control by monotherapy impairs subsequent control by combination therapy. It was a double-blind, randomised, parallel-group, superiority trial. Patients eligible for enrollment had essential hypertension, were aged 18 years or older, and had systolic blood pressure between 150 and 180 mm Hg. Patients were randomly assigned (1:1:2) to treatment with 150 mg aliskiren plus placebo, 5 mg amlodipine plus placebo, or 150 mg aliskiren plus 5 mg amlodipine. From 16–32 weeks, all patients received combination therapy with 300 mg aliskiren plus 10 mg amlodipine. The primary endpoints, assessed on an intention-to-treat basis (i.e. in patients who received the allocated treatment), were the adjusted mean reduction in systolic blood pressure from baseline over 8 to 24 weeks, and then the final reduction at 24 weeks. 318 patients were randomly assigned to aliskiren, 316 to amlodipine, and 620 to aliskiren plus amlodipine. 315 patients initially allocated to aliskiren, 316 to amlodipine, and 620 to aliskiren plus amlodipine were available for analysis. Patients given initial combination therapy had a 6.5 mm Hg (95% CI 5.3 to 7.7) greater reduction in mean systolic blood pressure than the monotherapy groups (p<0·0001). At 24 weeks, when all patients were on combination treatment, the difference was 1·3 mm Hg (95% CI –0·05 to 2·3; P=0·059). Adverse events caused withdrawal of 85 patients (14%) from the initial aliskiren plus amlodipine group, 45 (14%) from the amlodipine group, and 58 (18%) from the amlodipine group. Adverse events were peripheral oedema, hypotension, or orthostatic hypotension. It was concluded that routine initial reduction in blood pressure (>150 mm Hg) with a combination such as aliskiren plus amlodipine can be recommended.
CHANGING GUIDELINES

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7)

The JNC 7 was published in 2004 and JNC 8 is expected in 2012. The key messages from JNC 7 are as follows.

- Beginning at 115/75 mmHg, CVD risk doubles for each increment of 20/10 mmHg. Those who are normoten-
sive at 55 years of age will have a 90 percent lifetime risk of developing hypertension.

- For uncomplicated hypertension, thiazide diuretic should be used in drug treatment for most, either alone or combined with drugs from other classes. The report delineates specific high-risk conditions, which are compelling indications for the use of other antihypertensive drug classes (angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, beta blockers, calcium channel blockers).

- Two or more antihypertensive medications will be required to achieve goal BP (<140/90 mmHg, or <130/80 mmHg for patients with diabetes and chronic kidney disease). For patients whose BP is >20 mmHg above the SBP goal or 10 mmHg above the DBP goal, initiation of therapy using two agents, one of which usually will be a thiazide diuretic, should be considered.

Classification of blood pressures in adults according to JNC 7

<table>
<thead>
<tr>
<th>Blood Pressure Classification</th>
<th>SBP mmHg</th>
<th>DBP mmHg</th>
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<tbody>
<tr>
<td>Normal</td>
<td>&lt;120</td>
<td>&lt;80</td>
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<tr>
<td>Prehypertension</td>
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<td>80-89</td>
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<tr>
<td>Stage 1 Hypertension</td>
<td>140-159</td>
<td>90-99</td>
</tr>
<tr>
<td>Stage 2 Hypertension</td>
<td>&gt;160</td>
<td>&gt;100</td>
</tr>
</tbody>
</table>

INDIAN HYPERTENSION GUIDELINES –II (IGH-II)

The first Indian guidelines for management of HTN were published in 2001 which were revised and updated as IGH-II in 2007. The goal of treatment has gradually shifted from optimal lowering of blood pressure to patient’s overall well being, control of associated risk factors and protection from future target organ damage. IGH-II recommend achieving gradual reduction of blood pressure and use of low doses of antihypertensive drugs to initiate therapy. The five classes of drugs recommended as first line treatment for stage 1-2 hypertension include: 1) diuretics, 2) beta-blockers, 3) calcium channel blockers, 4) ACE inhibitors, 5) angiotensin II receptor blockers. With regard to lowering of blood pressure, all these five classes are considered equally effective. Low dose diuretics may be preferred as initial therapy unless there are compelling or specific indications for other classes. Choice of an antihypertensive agent is influenced by age, comorbid risk factors, presence of target organ damage, other co-existing diseases, socioeconomic considerations, availability of the drug and past experience of the physician. It was also recommended to combine low doses of two drugs having synergistic effect as it is likely to produce lesser side effects. Use of fixed dose formulations may be considered to improve compliance. If a diuretic is not chosen as the first drug, it is usually indicated as a second step agent because its addition enhances the effects of other agents except dihydropyridine calcium channel blockers. Use of long acting drugs that provide 24-hour efficacy with once daily administration was suggested to ensure smooth and sustained control of blood pressure. According to IGH-II step down therapy, an effort to decrease the dosage and number of antihypertensive drugs should be considered after effective control of hypertension. Moreover, due to a greater seasonal variation of temperatures in India, marginal alterations in dosages of drugs may be needed from time to time.

NICE GUIDELINES (UPDATE IN 2011)

The update of NICE clinical guidelines on HTN (2006) which were developed in partnership with the British Hypertension Society (BHS) was published in February 2011. In one of the biggest changes, the new 2011 guidelines recommended that a diagnosis of primary hypertension should be confirmed using 24-hour ambulatory blood pressure monitoring (ABPM) as gold standard rather than be based solely on measurements of blood pressure taken in the clinic. It also recommended changing the priority of medicines used to treat hypertension in people over the age of 55, focusing upon calcium channel blockers, based on evidence of event reduction and importantly, cost-effectiveness. Thiazide-like diuretics represent an alternative for those with heart failure or the very elderly who are intolerant of calcium channel blockers. In addition, amongst the choice of thiazide-like diuretics chlorthalidone or indapamide may be more effective than bendroflumethiazide. For the first time, the Guideline offered advice on treating hypertension in the very elderly (people aged over 80). The new cost-effectiveness analysis showed that the cost of treating hypertension is now cheaper than doing nothing.

ACCF/AHA 2011 EXPERT CONSENSUS DOCUMENT ON HYPERTENSION IN THE ELDERLY

Results of HYPET, documenting reduced adverse outcomes with antihypertensive drugs in persons ≥80 years of age, required updating previous recommendations which has been done in 2011.

In the elderly, the initial antihypertensive drug should be started at the lowest dose and gradually increased, depending on BP response, to the maximum tolerated dose. An achieved SBP <140 mm Hg, if tolerated, is recommended except for octogenarians. When BP is >20/10 mm Hg above goal, therapy
Principles of Hypertension Treatment

Target systolic blood pressure is ≤ 140 mm Hg in patients aged 55 to 79

Target systolic blood pressure is ≤ 140 mm Hg in patients ≥ 80+

Lifestyle Modifications

Not at target blood pressure

Initial drug choices

Without Compelling Indications

Stage 1 Hypertension
SBP 140 to 159 mm Hg or
DBP 90 to 99 mm Hg

Stage 2 Hypertension
SBP ≥160 mmHg or
DBP ≥100 mm Hg

Compelling Indication

Heart Failure
Post myocardial infarction
CAD or high CVD risk
Diabetes
Chronic kidney disease
Recurrent stroke prevention

Initial Therapy Options*
THIAZ, BB, ACEI, ARB, CA,
ALDO ANT
BB, ACEI, ALDO ANT, ARB
THIAZ, BB, ACEI, CA
BB, CA
BB, ARB, ACEI, THIAZ, CA

Optimize dosages or add additional drugs until goal blood pressure is achieved.

Refer to a clinical hypertension specialist if unable to achieve control.

Fig. 5: Algorithm for Treatment of Hypertension in the Elderly

should be initiated with 2 antihypertensive drugs. However, treatment must be individualized in the elderly. Before adding new antihypertensive drugs, possible reasons for inadequate BP response should be examined. On average, elderly patients are taking >6 prescription drugs, so polypharmacy, non-adherence, and potential drug interactions are important concerns. The following recommendations are offered for persons ≥80 years of age. Initiate treatment with a single drug followed by a second drug if needed. Achieved SBP 140 to 145 mm Hg, if tolerated, can be acceptable. Low-dose thiazides, CCBs, and RAAS blockers are preferred, but concomitant conditions often dictate which drugs are most appropriate. Although BP values below which vital organ perfusion is impaired in octogenarians are not known, SBP <130 and DBP <65 mm Hg should be avoided. The algorithm for Treatment of Hypertension in the Elderly is shown in Figure 5.

CURRENT APPROACH IN MANAGEMENT

Treating and controlling hypertension is associated with less cardiovascular and renal disease than if blood pressure remains uncontrolled. Despite the fact that many patients who experienced benefit in clinical trials did not achieve the recommended blood pressure goals, there is evidence to recommend a blood pressure goal of <140/90 mm Hg in patients with uncomplicated hypertension and a diastolic blood pressure goal of <80 mm Hg in individuals with diabetes (keeping the systolic blood pressure goal at <140 mm Hg). Although a goal of <130/80 mm Hg is recommended for patients with chronic renal disease and diabetes, there is no good clinical trial-based evidence to support this. Finally, the recommendation to achieve a blood pressure of <120/80 mm Hg in people with heart failure of ischemic origin is also without good clinical trial evidence of benefit. The results of the ACCORD trial suggest that setting a goal toward a systolic blood pressure to below 120 mm Hg rather than <140 mm Hg will not reduce cardiovascular events but will further reduce strokes, a secondary endpoint. The SPRINT trial will provide more clinical trial data on the benefit of treating to a more aggressive systolic blood pressure goal especially in those with chronic kidney disease.

Moreover, there are recent trials and guidelines for HTN management in the elderly offer recommendations for persons ≥80 years of age. It is recommended to initiate treatment with a single
drug followed by a second drug if needed. Achieved SBP 140 to 145 mm Hg, if tolerated, can be acceptable. Low-dose thiazides, CCBs, and RAAS blockers are preferred, but concomitant conditions often dictate which drugs are most appropriate. Although BP values below which vital organ perfusion is impaired in octogenarians are not known, SBP <130 and DBP <65 mm Hg should be avoided.

The recent trials also indicate a change from thiazide type diuretics as preferred initial agents to a more flexible goal directed approach. Each of the major classes (diuretics, ACE inhibitors, calcium-channel blockers, angiotensin-receptor blockers, and, to a lesser extent, β-blockers) appears reasonable as first-line therapy. The choice of a drug should depend on criteria such as compelling indications or contraindications, coexisting conditions, adverse effects, race, and the clinician’s experience. Beta blockers (atenolol, metoprolol) should be restricted to patients with compelling indications in patients with hypertension. Third generation beta-blockers (nebivolol, carvedilol) appear promising and devoid of side effects. Use of combination therapy as initial treatment should be considered in patients with stage II hypertension. Moreover, triple combination therapy appears promising in grade II hypertension. In patients with resistant hypertension (defined as BP that remains above goal in spite of use of three anti-hypertensive medications of different classes in effective doses, ideally including a diuretic) aldosterone antagonists can be used as add on therapy. Recent trials suggest that renal denervation and baroreceptor stimulation may be useful in refractory cases of hypertension.

CONCLUSION

The recent trials and changing guidelines for see a change in management of HTN. There is evidence to recommend a blood pressure goal of <140/90mm Hg in patients with uncomplicated hypertension and a diastolic blood pressure goal of <80mm Hg in individuals with diabetes (keeping the systolic blood pressure goal at <140mm Hg). In patients with chronic kidney disease, ischemic heart disease and diabetics the recent trials suggest that higher target thresholds as in uncomplicated HTN may be acceptable. Use of combination therapy as initial strategy in patients with grade II HTN and use of triple combination therapy and aldosterone antagonist in patients with refractory HTN is recommended. The upcoming guidelines for HTN shall include the role of newer therapies like renal denervation and baroreceptor stimulation in resistant HTN.

REFERENCES

1. Indian Hypertension Guidelines –II 2007.


