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AIMS & SCOPE

Hypertension Journal is a peer-reviewed journal which highlights epidemiology, health implications and cardiovascular risk from hypertension in India/South-Asia. Hypertension is much more common than diabetes. It is vastly under diagnosed and poorly treated in India/South-Asia. There are excellent therapeutic options to treat hypertension, but the available resources are not fully utilized by doctors therefore neglecting this disorder. The journal will hereby promote the significance of hypertension and the urgent need to bring it under control. The medical community should be educated on hypertension evaluation, diagnosis, workup and management simultaneously bringing up the literature, research, guidelines and scientific advances related to hypertension and its disorders. We are hereby starting a high-quality journal dedicated solely to hypertension and thus promoting the awareness, evaluation and effective management in India/South-Asia. Dr C Venkata S Ram is a world authority on hypertension with lifelong work (research, clinical and publications).

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Message

Since the beginning of the 21st century, non-communicable diseases including cardiovascular diseases have become the leading cause of death in India accounting for more than 50% of deaths. Hypertension has been the principal driver of cardiovascular disease in India. Epidemiological studies have reported prevalence rates of 25–30% urban and 10–20% rural subjects in India which translates to 100 million cases. Hypertension lead to 1.6 million deaths and 33.9 million disability-adjusted life years in 2015 in India. Worldwide too, an estimated 1.4 billion people have hypertension (1/3rd of world wide population) accounting to half of CV deaths (9.4 million deaths yearly). Thus, hypertension remains an important treatable disorder with a global impact. Despite the availability of effective therapy, treatment and control of ht is poor. In fact, less than half of the patients with hypertension are even aware of the disease.

In this issue of the Hypertension Journal, the academic faculty from the Sri Jayadeva Institute of Cardiovascular Sciences and Research, Bangalore India (SJICSR) have authored a series of articles on hypertension, its complications, management and recent advances. The authors have vast experience in treating cardiac disorders as well as providing preventive care. SJICSR is a 1000 bedded public, academic, tertiary care cardiac center in south India. It runs the largest cardiology fellowship program in the country (23 fellows each year). Last year, 6 lakh patients visited the outpatient department. 56531 patients were treated in hospital with over half being managed at highly subsidised financial rates given their low socio-economic status. The hospital had the distinction of performing the highest number of cath lab procedures in India (45000 cathlab procedures with 13000 angioplasties last year). In addition, it has the rare honor of performing the largest numbers of mitral valvuloplasties in the worldwide (annually more than 1300). This issue aims to bring a third world perspective to managing hypertension. Innovative solutions are needed to have a demonstrable impact on the health in developing countries. The lack of awareness, access to health care, out of pocket costs and prolonged treatment for a silent disorder create unique challenges. In line with the WHO-UN goal, we hope to achieve a 25% reduction in hypertension by 2025 and thereby reduce the associated premature mortality. Professor C. Venkat S Ram in his article has thrown more light on cardiovascular diseases in Women which is neglected in many countries.

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Message

Hypertension is an independent risk factor for cardiovascular morbidity and mortality in addition to stroke and chronic kidney disease. It is a big health challenge and major public health burden. The prevalence of hypertension is increasing all over the world and in India as well. The overall reported prevalence is around 30%, more in urban than in rural population. However the gap is narrowing down due to increase in urbanisation.

There have been guidelines from various scientific societies and organizations regarding targets in goals of hypertension which are changing frequently and also different threshold levels to initiate treatment. Hypertension is eminently treatable condition by available various potent therapeutic agents and life style modifications. Optimal treatment of hypertension is shown to have favourable outcomes on various cardiovascular disorders. To achieve optimal treatment goals is still a mirage. In India it is reported far below compared to other countries due to lack of awareness, poor adherence to treatment and to some extent physician inertia. We need much more epidemiological studies and concerted efforts by treating physicians and various organizations to achieve optimal goals.

Dr. Venkata S Ram, a world authority in hypertension and Editor-in- chief of Hypertension journal is doing commendable job in educating the physicians and encouraging research activities in India.

We at Jayadeva are pleased to offer this special issue of the Hypertension Journal on behalf of our institution. While Jayadeva is widely recognized for it's clinical excellence, a glimpse of our academic dimension is reflected in this dedicated issue of the Journal. We hope that the readers will benefit from the various aspects of clinical hypertension covered by the Jayadeva faculty members.

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Review Article

Blood Pressure Goals in Patients with Coronary Artery Disease

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Abstract

Hypertension is implicated as an independent and strong risk factor, for the occurrence of coronary artery disease (CAD), stroke and renal failure that leads to significant morbidity and mortality throughout the world. Several epidemiological studies show a consistent relationship between high blood pressure (BP) and the risk of CAD. In this review, the BP goals in hypertensives with CAD are discussed. BP targets in accordance to recent guidelines are reviewed and the therapeutic strategies for the management of various presentations of CAD are highlighted. There is a controversy about the lower target range of BP in CAD patients. Some studies support the "J curve" hypothesis, whereas the recent SPRINT trial refutes it. Furthermore, lower BP targets are associated with prescription of multiple drugs, posing a problem of both cost and compliance for patients. Management includes treatment of hypertension along with targeting other comorbidities such as dyslipidemia, obesity, diabetes mellitus, and smoking.

Key words: Hypertension, coronary artery disease, J curve, blood pressure targets

Introduction

Hypertension is implicated as an independent and strong risk factor that leads to significant morbidity and mortality throughout the world. Several observational studies so far, have shown a log-linear and continuous association with the level of blood pressure (BP) and vascular events down to 115/75 mmHg in patients without any baseline major illness.[1] It is noted that there is a 40–50% decrease in death from coronary artery disease (CAD) with every 10 mmHg decrease in systolic blood pressure (SBP).[1]

Hence, in clinical practice, whether BP goals should be guided by this evidence is a question to ponder. Lower BP targets cause adverse events and also escalate treatment costs. However, recent evidence from non-randomized trials in patients with vascular disease, have shown a J-curve association between BP and outcomes.[2] A recent meta-analysis provided evidence that intense BP lowering (SBP <130 mmHg) in high risk patients, reduced cardiovascular (CV) events, although at the risk of causing hypotension.[2]

The recent European Society of Cardiology (ESC) 2018 hypertension guidelines has classified BP into the following categories.[3]

Category	SBP/DBP mmHg
Optimal	<120/<80
Normal	120–129/80–84
High normal	130–139/85–89
Grade 1 hypertension	140–159/90–99
Grade 2 hypertension	160–179/100–109
Grade 3 hypertension	>180/>110
Isolated systolic hypertension	>140/<90

SBP: Systolic blood pressure, DBP: Diastolic blood pressure

Treatment Thresholds

High normal BP: Pharmacological treatment has to be considered if the CV risk is very high, like the presence of any established CV disease, especially CAD.

Grade 1 hypertension (with low risk): These patients have no evidence of target organ damage and therefore antihypertensives are initiated, only after a trial of lifestyle modification.

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Similarly, in older patients (>65 years, not >80 years) antihypertensives and lifestyle modification is recommended in fit older patients who can tolerate the treatment.

Targeting How Much Lower is Better?

"J curve" hypothesis

A non-linear relationship exists, between the level of BP and most CV adverse events, with increased risk noted at low BPs. This is termed the "J curve" relationship.[4] Myocardial perfusion occurs mainly during diastole; hence. diastolic blood pressure (DBP) is considered as the coronary perfusion pressure. The coronary flow is autoregulatory [Figure 1], such that any decrease in the perfusion pressure leads to vasodilation in the coronary vessels that in turn maintains a constant coronary flow. However, the capacity for this autoregulatory response is limited. It is noted that, after a point of maximal vasodilation, any further decrease in coronary perfusion pressure will only result in a further reduction in coronary flow. Therefore, reducing DBP below the autoregulatory limit can compromise coronary flow and lead to adverse coronary events.[5]

The presence of structural CAD influences the pressure-flow inter-relation in the coronary vasculature, causing a decreased tolerance to DBP. The "J curve" relationship is still a controversy. There are some studies which support this hypothesis and some

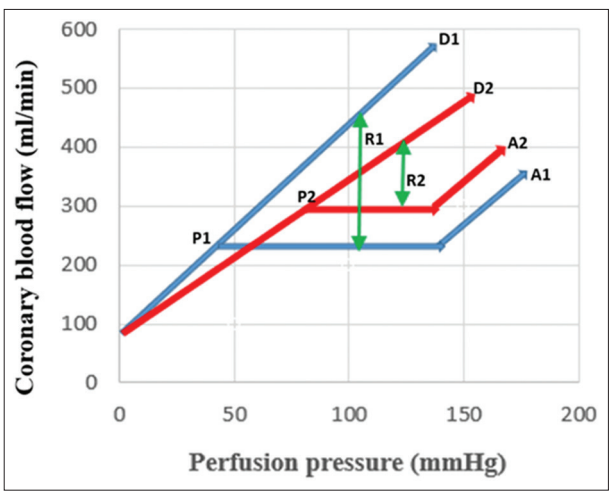

Figure 1: The coronary autoregulation. The coronary flow remains constant because of autoregulation in coronary circulation. With decrease in DBP the coronary vascular bed dilates, so as to maintain constant flow. However, this autoregulatory capacity is limited. P1 marks the lower autoregulatory limit. D1 shows the pressure-flow inter-relation seen with maximal vasodilatation. R1 demonstrates the coronary flow reserve. A2, P 2, and R2 reflect the values in the presence of hypertension or left ventricular (LV) hypertrophy. In these scenarios, there is a shift in the lower autoregulatory limit to the right (P1→P2), thereby making the myocardium vulnerable to drastic dips in diastolic pressure. The coronary flow reserve is also less in patients with hypertensive/hypertrophied hearts (Modified from Rosendorff C).[4]

which argue against it. In the TNT trial, it was noted that a very low arterial pressures (<110–120/<60–70 mmHg) portended a high risk of adverse events.[4] J-curve between DBP and CV outcomes was also noted in CAD subgroup of Cruickshank *et al.* and also in the subgroup analyses from INVEST, ONTARGET, Framingham Heart Study, and ACCORD.[6-10] A meta-analysis by Bangalore *et al.*[2] showed similar outcomes. Similar outcome was also noted in patients who presented with acute coronary syndrome (ACS) in PROVE-IT TIMI 22 trial.[11] The nadir BP here was 136/85 mmHg, while in INVEST trial the nadir systolic BP was ~119 mmHg. On the whole, these analyses noted that the risk of CV events increased at lower systolic pressures (<110 mmHg). The coronary perfusion is driven by the diastolic pressure. Hence, a low DBP in presence of CAD can cause ischemia. Evidence in support comes from the analysis of the TNT trial, where high incidence of angina was noted in patients with lower diastolic pressures.[4] In the INVEST trial, patients were revascularized experienced high event rates at low DBP, compared to those without revascularization.[7] Recently data from the Atherosclerosis in Communities study cohort analyzed by Mc Evoy *et al.* also noted that, low diastolic pressure (<60 mmHg) was associated with sub-clinical myocardial damage and increased CV events.[12] Similar J curve effect was also noted in the data analysis of the Prospective Observational Longitudinal Registry of Patients With Stable CAD (CLARIFY) registry.[13] Hence, studies noted that systolic of <120 mmHg and diastolic of <70 mmHg was associated with poor CV outcomes. However, in the SPRINT trial, treating to a lower target (systolic of <120 mmHg vs. <140 mmHg) in older (≥75 years) patients and also in high-risk hypertensives, reduced the overall CV risk, death, and readmissions for heart failure (HF).[14]

Based on these findings, the current ESC 2018 hypertension guidelines have given the following BP targets [Table 1].

Management of Hypertension in Stable Ischemic Heart Disease (SIHD)[3,15]

The BP goals and therapeutic strategies in hypertensive patients with SIHD are shown in Table 1 and in Figure 2.

Beta-blockers

Beta-blockers are initiated for patients with hypertension and angina. They decrease the heart rate; increase the diastolic filling time and thereby the coronary blood flow. They decrease the oxygen demand of the ischemic myocardium and relieve angina. Metoprolol or bisoprolol, which are cardio selective Beta-1 blockers without intrinsic sympathomimetic activity are recommended.[3,15,16]

RAS blockers

ACE inhibitors are preferred in patients with stable angina. Any associated comorbidities such as hypertension, lower LV ejection fraction ≤40%, diabetes mellitus, and chronic kidney disease further justify their use in them.[3,15] The role of ACEI in

hypertension and angina has been studied in various trials such as HOPE with ramipril, EUROPA with perindopril, and SAVE with captopril.[17-19] Angiotensin receptor blockers (ARB's) are used in patients who do not tolerate ACE inhibitors. In the VALUE trial, there were no differences in CV events, in hypertensives who received valsartan versus amlodipine. Similar observations were noted, in VALIANT trial where patients received valsartan versus captopril.[20,21]

Table 1: BP targets for all and in patients with SIHD[3]

ESC 2018 BP targets	
Recommendations	COR, LOE
Initial objective is to decrease BP to <140/90 mmHg in all and if well tolerated, to achieve a BP of ≤130/80 mmHg	I, A
The target systolic range is 120–129 mmHg for patients who are <65 years	I, A
The target systolic range is 130–139 mmHg for patients who are ≥65 years	I, A
The target systolic range is 130–139 mmHg for patients who are very elderly (>80 years), if tolerated	I, A
To target diastolic pressure of <80 mmHg, and not <70 mmHg (irrespective of the patient's risk level and presence of comorbidities)	I, A
BP goals and therapeutic strategies in patients with hypertension and SIHD	
Recommendations	COR, LOE
Beta-blockers and RAS blockers are the drugs of choice in hypertensives with a prior history of myocardial infarction	I, A
Beta-blockers and/or CCBs are the drugs of choice in hypertensives with angina	I, A

COR: Class of recommendation, LOE: Level of evidence, RAS: Renin Angiotensin System, CCBs: Calcium channel blockers

Calcium channel blockers (CCB's)

Non-dihydropyridine CCBs, such as verapamil, are initiated in hypertensives with stable angina.[3,15] In the INVEST trial (Verapamil vs. Atenolol), there was no difference in CV end points.[7] In the CAMELOT trial amlodipine or enalapril was compared with a placebo. It was noted that the amlodipine arm had less adverse CV events compared to the other two.[22] The ALLHAT trial had three groups, one received a thiazide-type diuretic, the other an ACE inhibitor, while the other used a long-acting dihydropyridine CCB. The trial noted no statistically significant outcome differences among the three groups.[23]

Non-dihydropyridine CCBs are initiated for relief of angina, in the presence of contraindication to the use of beta-blockers. They are not initiated in HF and also along with beta-blockers, as their synergistic effects they can cause profound bradyarrhythmias.[3,15]

Diuretics

The Veterans Administration studies, Survey of Health Experiences of Patients, and Medical Research Council trials

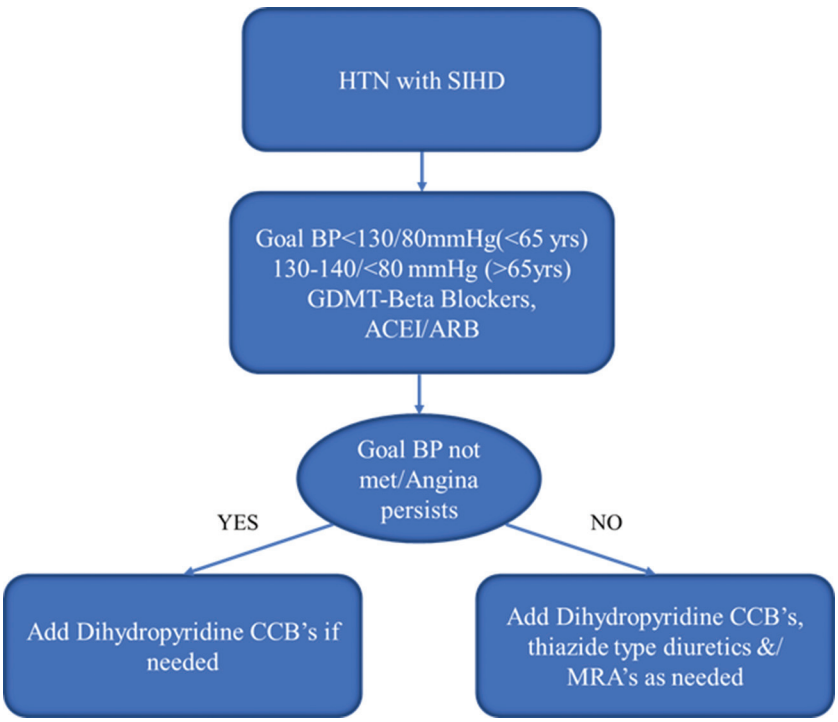

Figure 2: Treatment options in patients with hypertension and SIHD. SIHD: Stable ischemic heart disease, GDMT: Guideline directed medical therapy, ACEI/ARB: Angiotensin converting enzyme inhibitors/angiotensin receptor blockers, CCBs: Calcium channel blockers, MRA: Mineralocorticoid receptor antagonists

which used thiazides showed reduced CV events.[24-26] Similarly, chlorthalidone therapy showed benefit in hypertensives in the ALLHAT trial.[23] Furthermore, the HYVET trial with indapamide showed decreased CV events.[3,15,27]

Management of Hypertension with ACS

The recent ESC 2018 guideline does not address the treatment of hypertension in ACS. According to 2015 ACC/AHA guidelines, in hemodynamically stable ACS patients, the BP is decreased to <140/90 mmHg (Class IIa, C). During discharge, a target of <130/80 mmHg is advised (Class IIb, C). The BP should be lowered slowly and also decrease in diastolic pressure to <60 mmHg should be avoided, as this can compromise coronary perfusion and thereby worsen ischemia.[3,15]

There are no trials that address the treatment of hypertension in the presence of ACS. Drugs that have a role in risk reduction, independent of lowering BP, are preferred.[15] These are beta-blockers, ACE inhibitors (or ARBs), and MRA's [Table 2]. They should be titrated to maximum doses, before other drugs without established evidence are initiated.

Table 2: Therapeutic strategies in patients with ACS

Class of drug	COR, LOE	Recommendation[15,28]
B-blockers	I, A	In hemodynamically stable patients, a short-acting β1-selective agent without intrinsic sympathomimetic activity such as metoprolol tartrate or bisoprolol are initiated in the first 24 h
Nitrates	I, C	To decrease the blood pressure and any pulmonary congestion or to relieve ongoing ischemia
Calcium channel blockers	IIa, B	Non-dihydropyridine CCB such as verapamil or diltiazem are indicated in the presence of ongoing ischemia, in those who are intolerant to beta-blockers Furthermore, along with beta-blockers and ACE inhibitors, in patients who have uncontrolled angina or hypertension
ACE inhibitors	ACEI-I, A	ACE inhibitor or ARB should be added in the presence of anterior wall MI and Persistent hypertension Presence of LV dysfunction or heart failure Presence of diabetes mellitus
ARB	ARB-I, B	
ACEI	IIa, A	In non-diabetic patients who present with ACS and preserved LV ejection fraction.
Aldosterone antagonists	I, A	After MI, along with beta-blockers and ACE inhibitors if there is associated: LV dysfunction Heart failure Diabetes mellitus
Loop diuretics	I, B	In patients with ACS who present in NYHA class III or IV

COR: Class of recommendation, NYHA: New York Heart Association, LOE: Level of evidence

Nitrates

They play an important role in relieving angina, pulmonary edema, or acute hypertension in ACS.[15,28] GISSI-3 and International Study of Infarct Survival (ISIS)-4 trials found no mortality benefit with nitrates.[29,30] Nitrates are contraindicated in hypotension and in presence of right ventricular ischemia. Initial treatment is with sublingual or intravenous nitroglycerin, followed by switch over to longer-acting formulation, if needed.[15,28]

Beta-blockers

These drugs decrease: (1) Myocardial oxygen demand, (2) infarct size, (3) sudden cardiac deaths due to anti-arrhythmic effects. Beta 1 selective agents – metoprolol or bisoprolol are preferred. Carvedilol (β1/β2/α1 adrenergic receptor blocker) is a potent BP-lowering agent and is preferred in ACS with severe hypertension.[15,28,31]

RAS blockers

ACE inhibitors play an important role in ACS.[32] They prevent: (1) Infarct expansion and (2) LV remodeling and dilatation. They also decrease the incidence of arrhythmias, admissions for HF, and cardiac rupture.[15,28,31] The GISSI-3, ISIS-4, and Chinese Cardiac Study-1 trials have demonstrated a clear benefit with early initiation of ACE inhibitors.[29,30,33] ARBs can be used as alternatives for ACE inhibitor-intolerant patients, as noted in the VALIANT trial, with valsartan.[21]

CCB's

Dihydropyridine CCB's decrease BP and may relieve ischemia. Non-dihydropyridine CCB such as verapamil or diltiazem are indicated in the presence of ongoing ischemia, in patients with intolerance to beta-blockers.[15,28]

Mineralocorticoid Receptor Antagonists

In the EPHESUS trial (eplerenone vs. placebo) after myocardial infarction (MI), eplerenone reduced CV mortality and sudden cardiac death.[34] The role of spironolactone in ACS is not known, but it has shown significant mortality benefit in patients with HF in the RALES trial.[35]

Diuretics

In ACS, loop diuretics are initiated in patients with pulmonary edema or HF (New York Heart Association [NYHA] class III or IV). Thiazide diuretics are useful for long-term control of BP.[15,28]

Management of Hypertension and Ischemic HF

Hypertension is implicated as an important risk factor in heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF). The treatment of hypertension reduces the risk of incident HF by around

50%.[36] Several trials have shown that control of BP, delays the development of HF and also prolongs life. Optimization of BP is very important in these patients. Drugs that improve outcomes in patients with HFrEF, generally also lower BP. These drugs are also safe in HFpEF. The target SBP is <130 mmHg. Sodium restriction is important in managing both hypertension and LV dysfunction. The preferred drugs are:

RAS blockers

ACE inhibitors have shown benefit in ischemic heart disease and LV dysfunction.[6,19,37] The AIRE trial supports, ACE inhibition in hypertensives with LV dysfunction after MI.[38] Among ARB's valsartan and candesartan have shown benefit in the Val-Heft and CHARM program, respectively.[39,40]

Beta-blockers

They have emerged as an important group of drugs in the management of HF. Several trials such as MERIT-HF with metoprolol, COPERNICUS with carvedilol, cardiac insufficiency bisoprolol study-II with bisoprolol, and SENIORS with nebivolol have demonstrated decreased mortality in HF.[41-44]

Mineralocorticoid Receptor Antagonists

The RALES and EPHESUS trials have shown the benefit of spironolactone and eplerenone respectively in patients with CAD.[34,35] The subgroup analysis of EMPHASIS trial, demonstrated that hypertensives with chronic HF in NYHA Class II, had a greater improvement in relative risk with eplerenone than normotensives.[45]

Diuretics

Thiazide diuretics prevent HF in hypertensives. They are initiated in patients with mild HF for control of BP. In severe HF, loop diuretics such as furosemide and torsemide are indicated to relieve volume overload.[15,46]

Nitrates and Hydralazine

In HF patients (NYHA Class III or IV), with persistent symptoms and uncontrolled BP, a combination of hydralazine and isosorbide is recommended. The A-heFT trial showed that this combination provided an added benefit in African Americans.[15,46,47]

Thus, ACEI's (or ARB's), beta-blockers, or MRA's (or a combination) are recommended as first-line drugs. A thiazide diuretic is added when hypertension persists despite treatment. Amlodipine or hydralazine is recommended to further reduce BP to optimal levels.

Conclusions

Although we are treating hypertension since several decades, the optimal treatment targets have undergone several revisions, since the JNC-7 guidelines published in 2003. The present evidence shows that intense BP control (≤130/80 mmHg) in patients with CAD reduces MI, HF, and stroke. However, this benefit is noted at the expense of increased risk for hypotension. Randomized trials are needed in these patients to further prove the efficacy and safety of such aggressive treatment. Intensive BP reduction goals should weigh the risk of need for multiple medications versus compromise of compliance. It is prudent to focus on choosing targets that are based on patient's risk profile and their tolerance to antihypertensive medications.

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Review Article

Clinical Diagnosis and Treatment of Hypertensive Emergencies

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Abstract

Hypertensive emergency is a rise in blood pressure (BP) >180/120 mmHg with an associated with end-organ injury, and symptoms and signs are usually dramatic. Complete medical history and quick clinical examination key to treatment. Intravenous antihypertensive medications chosen based on comorbid conditions, type and extent of end-organ injury, pharmacodynamics, and pharmacokinetic property of drugs. Target BP reduction is to reduce 25% of mean arterial pressure in 1st h and further reduce systolic blood pressure to < 160 and diastolic blood pressure < 100 in next 2–6 h, and maintain the same BP for next 24 h, exceptions are aortic dissection, Eclampsia/Preeclampsia, acute stroke, and pheochromocytoma crisis. Labetalol, nitroglycerine, nicardipine, and esmolol cover most of the spectrum of hypertensive emergencies. Over enthusiastic blood pressure correction to be avoided to prevent ischemic effects may arise from rapid reduction in blood pressure.

Key words: Hypertensive emergency, End-organ damage, Compelling conditions, Clevidipine, Nicardipine, Nitroglycerine, Esmolol, Labetalol

Introduction

"Hypertensive Crisis" is an abrupt increase in systolic blood pressure (SBP) >180 mmHg and/or elevation diastolic blood pressure (DBP) >120 mmHg. Based on the presence of acute end-organ damage, a hypertensive crisis can be defined as Hypertensive Emergency or Urgency. Hypertensive urgency defined as "severe blood pressure (BP) elevation in chronic hypertensive patients with no acute target organ injury or dysfunction." Do not require hospital admission, and reduction in blood pressure (BP) can be achieved with oral medication in the emergency room with subsequent outpatient follow-up.[1,2]

"Hypertensive emergency is a critical rise in BP >180/120 mmHg with associated newly developed, progressive, or deteriorating target organ injury."[1,3] In 1928, the term "malignant hypertension" was coined to denote hypertensive emergency, as the patient's outcome was as same as the patient diagnosed with cancer. Because of rapid advancement in the medical field and availability of excellent medications, in-hospital mortality reduced drastically to 2.5%.[4]

Clinical Diagnosis

Symptoms and signs are usually dramatic, and when a patient presents to the emergency room with increased BP of >180/120 mmHg with symptoms and signs suggestive of end-organ damage, hypertensive emergency to be considered.

Patient presenting to the emergency room with a new onset of symptoms along with severely elevated BP, a complete medical history along with a quick physical examination to identify end-organ damage plays an important role. In history, the key points are the duration of hypertension, history of compliance to drugs, list of antihypertensive medications in use, and time of last dose administration.[3] Physical examinations include assessment of peripheral pulses, measurement of BP in both upper limbs; other specific clinical features are summarized Table 1.[5]

Therapeutic Approach

Oral antihypertensive medications are to be discouraged in the management of hypertensive emergencies. Once a patient

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Table 1: Features of end-organ damage and prevalence

Clinical condition	Prevalence	Features of end-organ damage
LVF	22.5%	Dyspnea, palpitations, S3 gallop, rales, b lines in chest X-ray
ACS	12%	Acute chest pain, dyspnea, ST-T changes in ECG, positive cardiac biomarkers, LV dysfunction in echocardiogram
AORTIC DISSECTION	2%	Severe acute tearing retrosternal chest pain radiating to back in the hypertensive patient, unequal pulses. Unequal blood pressures. CT imaging suggestive of dissection
Hypertensive encephalopathy- PRES (posterior reversible encephalopathy syndrome)	16.5%	Occipital headache, visual changes altered sensorium, seizures, papilledema, retinal exudates, No focal deficits
CVA- ICH/ Ischemic strike	4.5/24.5%	Headache, focal neurological deficits. Imaging suggestive of infarct or bleed
Eclampsia/Preeclampsia	4.5%	Pregnant or recently postpartum status hyperreflexia, proteinuria peripheral edema, hemolysis, elevated AST, ALT, decreased platelet counts.
Catecholamine excess	-	Clinical diagnosis in the scenario of sympathomimetic drug use (i.e., cocaine or amphetamines) or pheochromocytoma

ICP: Intracranial pressure, LVF: Left ventricular failure, ACS: Acute coronary syndrome, CVA: Company voluntary arrangements

diagnosed to have hypertensive emergencies, the patient needs to be hospitalized and requires intensive care unit care to treat and assess end-organ damage, and to administer intravenous antihypertensive medications as well as to monitor hemodynamic parameters including intra-arterial pressures.[1,2]

The drugs preferred for the management of hypertensive emergencies are continuous intravenously administered short-acting agents, although no evidence is available which class of drugs gives more benefits.[6] Antihypertensive medications are chosen based on comorbid conditions, extent of end-organ damage, pharmacodynamic, and pharmacokinetic properties of drugs.[7] Excessive and overenthusiastic BP reduction may precipitate ischemia in cerebral, myocardial, and renal tissues.[8]

In the treatment of hypertensive emergencies, few sets of patients require different BP goals, also labeled as compelling conditions due to their unique hemodynamic, for rest of the patients BP goals, are as shown in Table 2.

Table 2: BP treatment goals for hypertensive emergency

Goal time	BP target
1st h	Reduce MAP by 25%
2–6 h	SBP 160 mm Hg and/or DBP 100–110 mmHg
6–24 h	Maintain goal for hours 2–6 during first 24 h
24–48 h	Outpatient BP goals according current guidelines

SBP: Systolic blood pressure, DBP: Diastolic blood pressure, MAP: Mean arterial pressure, BP: Blood pressure

Compelling Conditions

These conditions due to their unique hemodynamic, requires a different set of BP targets in treating a hypertensive emergency.

1. Acute stroke
2. Aortic dissection
3. Severe Preeclampsia/Eclampsia
4. Pheochromocytoma crisis.

Pharmacotherapy

The drugs used in the management of hypertensive emergencies are described in detail as class of drugs and each drug is summarised with respect to, common indications and special consideration, and dose in [Tables 3 and 4].

Calcium channel blockers – dihydropyridines

Nicardipine is short-acting, parenteral, dihydropyridine calcium channel blocker. It is a selective coronary and cerebral vasodilator.[9] One of the special characteristic features is it crosses the blood brain barrier and accumulates in ischemic tissues and causes localized vasodilatation without increasing the intracranial pressure (ICP). The onset of action is 5–15 min and acts for 4–6 h. The initial dose is 5 mg/h infusion, and the dose can be escalated every 5 min with an increment of 2.5 mg/h, and the maximum dose is 15 mg/h. The drug is safe in elders and no need of dose reduction. Nicardipine to be avoided in severe aortic stenosis.[1,2]

Clevidipine is an ultra-short acting calcium channel blocker that belongs to the class of dihydropyridine. It causes vasodilatation by blocking L type calcium channel and consequentially reduces peripheral vascular resistance.[10-12] Clevidipine reduces myocardial infarct size, maintains coronary endothelial function, and protects renal function. Elderly patients require dose adjustments. Clevidipine is contraindicated in patients who have abnormal lipid metabolism, and allergic to egg or soya related products.[13,14]

Nitric Oxide-derived Vasodilators

Nitroglycerine is a venodilator, the mechanism by which reduces BP is by reducing both preload and cardiac output.[8] The initial dose is 5 mcg/min, can be increased in every 3–5 min to a maximum of 20 mcg/min with increments of 5 mcg/min. The commonly encountered adverse effect is a headache, which usually subsides once the dose is reduced. In volume-depleted patients, nitroglycerine known to cause hypotension with to reflect tachycardia.[15] It is an ideal drug while treating

Table 3: Indications and Special consideration[1-3,16]

Drugs	Common indications	Special consideration
Nitroglycerine	LVF, acute coronary syndrome	Headache, Tachyphylaxis
Nitroprusside	LVF-pulmonary edema, aortic dissection	Cyanide accumulation, Increases ICP, coronary steal
Nicardipine	Acute CVA, hypertensive encephalopathy	Avoid in patients allergic to egg/soya
Clevidipine	Acute CVA, hypertensive encephalopathy	Reflex tachycardia, avoid in severe aortic stenosis
Esmolol	Aortic dissection, ACS, perioperative hypertension	Avoid in ADHF, ii and iii degree AV Block, bradycardia
Labetalol	Pregnancy, Acute aortic dissection, ACS, CVA	Avoid in ADHF, ii and iii degrees AV Block, bradycardia
Enalprilat	Acute left ventricular failure	Contraindication-pregnancy
Phentolamine	Catecholamine excess state-pheochromocytoma, cocaine toxicity	Use beta-blockers for rate control after adequate alpha blockade if necessary
Fenoldopam	Most of the conditions	Increases ICP, intraocular pressure

ICP: Intracranial pressure, LVF: Left ventricular failure, ACS: Acute coronary syndrome, CVA: Company voluntary arrangements

Table 4: Drug Dosages

Drugs	Dose	Onset of action
Nitroglycerine	5–100 mcg/min, Titrate by 5–25 mcg/min q5–10 min	2–5 min
Nitroprusside	0.25–10 mcg/kg/min, Titrate by 0.1–0.2 mcg/kg/min q5 min	Seconds
Nicardipine	5–15 mg/h, Titrate by 2.5 mg/h q5–10 min	5–10 min
Clevidipine	IV 1–6 mg/h Titrate by 1–2 mg/h	1-4 min
Esmolol	IV 25–300 mcg/kg/min, Titrate by 25 mcg/kg/min q3–5min	1–2 min
Labetalol	20–80 mg iv bolus every 10 min IV 0.5–10 mg/min, Titrate by 1–2 mg/min q2 h	2–5 min, peak 5–15 min
Enalaprilat	1.25–5 MG 1Vq 6 h, max dose: 5 mg q6h	15–30 min
Hydralazine	IV bolus: 10–20 mg IM: 10–40 mg q30 min	IV: 10 min IM: 20 min
Phentolamine	IV bolus: 1–5 mg, max 15 mg	Seconds
Fenoldopam	0.1–0.3 mcg/kg/min	10–15 min

acute pulmonary edema because of its favorable effects on hemodynamics.

Nitroprusside is a nitric oxide donor. It is a vasodilator known to decrease both preload and after load. The action of drug starts within seconds. Unfavorable pharmacodynamic effects are coronary steal phenomenon, and it known to increase ICP. Patients are prone to cyanide toxicity and thiocyanate toxicity in the presence of hepatic dysfunction and renal dysfunction, respectively.[16]

Direct Vasodilators

Hydralazine is peripheral vasodilator acts by arteriolar smooth muscle relaxation, due to its unpredictable BP response and prolonged action, it is no more the first line of the drug in treating a hypertensive emergency.[17]

Adrenergic Blockers

Esmolol is a short-acting selective beta-blocker and metabolism is independent of the liver and kidney function making it as an ideal drug in critically ill patients. While using esmolol heart rate to be monitored continuously. Esmolol is contraindicated in patients with bradycardia, acute decompensated heart failure, and with concomitant beta-blocker use.[8,16]

Labetalol is a non-selective beta-blocker; it can be used both as intermittent bolus doses or continuous intravenous infusion. The initial dose is 0.3–1.0 mg/kg, slow intravenous injection every 10 min (maximum 20 mg). For intravenous infusion starting dose is 0.4–1.0 mg/kg/h up to 3 mg/kg/h. Contraindications are bradycardia, second degree atrioventricular (AV) blocks, acute decompensated heart failure, chronic obstructive pulmonary disease (COPD), and bronchial asthma.[1,16]

Phentolamine is competitive peripheral alpha-blocker with more affinity for alpha1 receptors causes' direct vasodilation. It reduces BP by reducing systemic vascular resistance with a compensatory increase in heart rate and cardiac output. It is used in the state of catecholamine excess states such as pheochromocytoma, cocaine toxicity, and clonidine withdrawal.[1,16] Phentolamine used as a bolus dose of 5 mg intravenously; the dose can be repeated every 10 min until the target BP achieved.[1,3] Common adverse effects are flushing and headache and rebound tachycardia, this tachycardia can worsen an oxygen supply-and-demand mismatch leading to angina or myocardial infarction in patients with coronary artery disease.[18]

Dopamine 1-Receptor Selective Agonist

Fenoldopam is rapid acting D1 receptor agonist. Fenoldopam reduces BP due to its peripheral vasodilator properties and also increases renal blood flow with diuretic effects. Fenoldopam can cause anaphylactic reactions in patients who are allergic to sulfa drugs as it contains sodium metabisulfite. Other adverse effects are headache, nausea, vomiting, and flushing, and hypokalemia.[19]

Angiotensin Enzyme Converting (ACE) Inhibitors

Enalaprilat is an ACE inhibitor, reduces BP due to its vasodilatory property. The usual dose is 1.25 mg intravenous administration over 5 min. The action starts after 15–30 min, and single bolus dose may last up to 24 h. Unpredictable BP responses making dose adjustment difficult. Enalaprilat contraindicated in bilateral renal artery stenosis, pregnancy, and acute myocardial infarction.[2,20]

Furosemide a loop diuretic, is not recommended as first-line therapy in the management of hypertensive emergencies, though furosemide can be used in conditions such as renal parenchymal disease with fluid overload status.[20,21]

Cardiovascular Emergencies

Acute aortic dissection

The progression of aortic dissection depends on shear stress; therefore, in the management of aortic dissection goal is to reduce both heart rate and BP.[22,23] Within minutes starting treatment, heart rate should be brought down to <60/min. Short-acting beta-blockers esmolol or labetalol are the ideal drugs in aortic dissection.[1] BP to be reduced to below 120 mmHg within the first 20 min. With the adequate dose of beta-blocker use, still BP is elevated nitroglycerine or nitroprusside can be initiated. To avoid reflex tachycardia produced by vasodilators, which further worsens the dissection, Beta-blocker to be used before vasodilator administration.[24]

Acute pulmonary edema

Ideal drugs are nitroglycerin, nitroprusside or clevidipine.[1] BP should be reduced by 25% in first 1 h, followed by reduce to at least 160/100 mmHg in the next 6 h with the target of reaching normal BP values in next 48 h. Beta-blockers are contraindicated in the management of acute pulmonary edema as they are known to cause bronco constriction and impair respiratory function.[25]

Acute coronary syndromes (ACS)

According to the American College of Cardiology/American Heart Association guidelines, ACS with a hypertensive emergency the recommended drugs are nitroglycerin, esmolol, labetalol, and nicardipine.[1] The target BP is <140/90 mmHg in stable patients. Diastolic pressure should not be allowed to drop below 60 mmHg as it reduces coronary blood flow with subsequent worsening of ischemia.[26] Beta-blockers are contraindicated in the presence of left ventricular failure (LVF), hypotension, second- or third-degree AV block, COPD, and bronchial asthma.[20]

Hypertensive Emergencies in Pregnancy

The 2018 European Society of Cardiology Task Force on Cardiovascular Diseases during pregnancy considers an SBP of at least 170 mmHg or DBP of at least 110 mmHg an emergency in a pregnant woman.[27]

While treating pregnant patients sudden or abrupt decrease in BP may lead to the harmful fetal outcome, to avoid these complications, reduce mean arterial pressure (MAP) by 20–25% over first few minutes to hours and further reduce BP to the target of 160/110 mmHg or less over subsequent hours.[28,29] The ideal drugs are labetalol, and nicardipine, which have shown to be safe and effective. Fetal heart rate monitoring is necessary while using labetalol, and cumulative dose should not exceed 800 mg/24 h. Intravenous Urapidil can also be used. When a patient presents with pulmonary edema, intravenous nitroglycerine is the drug of choice. Hydralazine is associated with more perinatal adverse effects compared to other drugs.[30] Angiotensin-converting enzyme inhibitors and nitroprusside are contraindicated in Eclampsia/Pre-eclampsia.[31]

Neurological Emergencies

Acute intracerebral hemorrhage

Ideal drugs for acute intracranial hemorrhage are nicardipine, esmolol, and labetalol. Drugs which increase ICP or reduce cerebral perfusion are contraindicated, for example, nitroprusside, and hydralazine. BP reduction is indicated only when SBP is >220 mmHg. Studies have shown routine immediate BP reduction below 140 mmHg can be harmful.[32,33]

Acute ischemic stroke

Elevated BP seen in ischemic stroke is a physiological response to maintain adequate perfusion pressure, governed by the equation, CPP=MAP-ICP (CPP: Cerebral perfusion pressure, MAP: Mean arterial pressure, ICP: Intracranial pressure). ICP is elevated in ischemic stroke, reducing the MAP may decrease the tissue perfusion with worsening of ischemia. However, the indications to reduce the BP in ischemic stroke are

1. Planning thrombolysis or endovascular management for stroke – Before starting thrombolysis reduce BP to <180/105 mmHg and maintain same BP up to 24 h.
2. Presence of other end organ damage – LVF, ACS, and acute aortic dissection
3. BP >220/120 mmHg.

Severe elevation of BP >220/120 mmHg and presence of other end-organ damage, the goal is to reduce 15% MAP over a period of 24 h.[16] If BP is <220/120 mmHg on presentation, routine BP reduction in first 48–72 h may not be beneficial in these set of patients.[34,35] Drug of choice in ischemic stroke are nicardipine and labetalol.

Hypertensive encephalopathy including press

Once company voluntary arrangements is ruled out, reduce MAP by 25% in 1st h and further reduce the BP to 160/100 mmHg over 2–6 h. Recommended agents include nicardipine, labetalol, and clevidipine.

Perioperative Hypertension

It is defined as an elevation of BP of 160/90 mmHg or higher or an SBP elevation of at least 20% of the pre-operative value, that lasts for more than 15 min. Post-operative hypertension may have significant adverse outcomes in both cardiac and non-cardiac patients. Due to increased sympathetic tone and vascular resistance, hypertensive crises, and hypertension, are very common in the early post-operative period. Post-operative hypertension commonly begins ~10–20 min after surgery and may last up to 4 h, commonly related to increased vascular resistance and sympathetic tone. The best approach to treatment is prevention. Often these complications develop due to stopping or withdrawal of antihypertensive medications in pre-operative period. Administering antihypertensive medicines on the morning of the day of surgery effectively prevents post-operative hypertension. Esmolol, nitroglycerine, clevidipine, or nicardipine are ideal drugs manage perioperative hypertension.[1,36]

States with Excessive Catecholamine Discharge

Pheochromocytoma is a hyperadrenergic status. This condition treated by intravenous infusion of phentolamine, nicardipine, or clevidipine.[1] SBP reduced to 140 mmHg in 1st h using above-mentioned drugs. Alpha-adrenergic blockade is important in controlling BP. For significant tachycardia after alpha-blockade, beta-blockers can be used to control heart rate only after adequate alpha-blockade.[37]

Conclusion

Early diagnosis and quick assessment of end-organ damage in emergency room play a crucial role in the early management of a hypertensive emergency, which avoids further end-organ damage. Drug regimen to be tailored according to patient comorbid condition, extent and type of end-organ damage and should be aware of compelling conditions. Labetalol, nitroglycerine, esmolol, and nicardipine effectively covers most of the spectrum of hypertensive emergencies. Overenthusiastic BP correction to be avoided to prevent cerebral and myocardial hypoperfusion. Treat the patient, not the numbers.

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Review Article

Hypertension and Left Ventricular Hypertrophy

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Abstract

The left ventricular hypertrophy (LVH) in systemic hypertension (HTN) indicates target organ damage and is an independent risk factor for cardiovascular (CV) events. Among various modalities available for LVH assessment, cardiac magnetic resonance imaging has the highest sensitivity and specificity. M-mode echocardiography is the most widely method for LVH assessment currently due to its ease, availability, and reasonably good sensitivity and specificity. LVH is a risk factor for heart failure, stroke, coronary artery disease, and arrhythmias. Variable degree of LVH regression occurs with different antihypertensive medications. LVH regression with treatment has shown a reduction in the risk of CV events.

Key words: Cardiovascular, hypertension, left ventricular hypertrophy

Introduction

The left ventricular hypertrophy (LVH) is an adaptive response by the heart to chronic pressure overload. It indicates hypertension (HTN)-related target organ damage and also shown to be a predictor of heart failure (HF), coronary artery disease, and stroke.[1,2] The development of LVH varies with severity of HTN ranging from <20% in mild HTN to nearly 100% in severe, complicated HTN.[3] The risk of cardiovascular (CV) events increases with increase in the left ventricular (LV) mass.[4] LVH is a potentially reversible risk factor and the regression of LVH with antihypertensive treatment has shown to improve the CV risk, long-term prognosis.

Pathogenesis

Increase in LV mass is a compensatory response to pressure overload. The terminal differentiation of cardiomyocytes occurs soon after birth and hence the increase in mass is secondary to the hypertrophy of existing myocytes rather than hyperplasia.[5] In response to pressure overload, parallel addition of sarcomeres occurs that causes an increase in myocyte width, which leads to increase wall thickness. As a consequence of this remodeling, there is concentric hypertrophy (increase in cardiac mass at the expense of chamber volume). In contrast, predominant volume overload results in eccentric hypertrophy (increase in cardiac mass and chamber volume).[6] Myocyte growth to support an increased mechanical load is associated with increase in the surrounding architecture of connective tissue, ground substance, capillary, and nerve networks. The composition of connective tissue predominantly consists of collagen along with smaller amounts of laminin, elastin, and fibronectin. The complex collagen weave is predominantly responsible for the ventricle's diastolic stiffness.[5]

The inconsistent correlation between blood pressure (BP) and LV mass suggests that the development of LVH is mediated by the mechanical stress of pressure overload alone. Various neurohormonal factors have been implicated in the development of LVH by exerting trophic effect on myocytes and non-myocytes in the heart. Angiotensin II, aldosterone, and norepinephrine have shown to directly increase myocyte hypertrophy and matrix deposition independent of their effects on blood pressure.[7-9] Evidence suggesting a role of renin–angiotensin–aldosterone (RAA) system is also a reduction in LV mass and myocardial fibrosis that occurs by the treatment of BP with drugs that modify the actions of the RAA system.[9,10] Demographic factors such as age, sex, race, and body size also influence the development of LV hypertrophy.[11] Gene polymorphisms of

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various components of the RAA system have also shown to predict the response of LV mass to HTN treatment.[12] Thus, the development of LVH occurs by a combination of hemodynamic and non-hemodynamic factors with genetic and non-genetic influences [Figure 1].

Diagnosis and Measurement

The identification of LVH in hypertensive patients is important for clinical practice and research as it influences treatment and is also a risk factor for CV events. The diagnostic methods currently available are electrocardiogram (ECG), echocardiography, and cardiac magnetic resonance imaging (MRI).[13] The advantages and disadvantages of each are outlined in Table 1.

At present, in clinical practice, ECG is usually the first test performed to evaluate for LVH. Various validated criteria include Romhilt-Estes score, Sokolow–Lyon, Cornell voltage, Cornell voltage QRS duration product criteria, and the Gubner index.[14] ECG criteria have shown to have high specificities and low sensitivity. In the validation studies of LVH ECG criteria, the sensitivity has been reported to range from 6 to 52% and the median specificity ranges from 89 to 99%.[14,15] In view of low sensitivity, a normal ECG will not exclude LVH.

Transthoracic echocardiography is the most common diagnostic tool used for LVH assessment. The important parameters for the assessment of LVH severity by echocardiography are wall thickness, LV mass, and LV geometry. In clinical studies, LVH is often described in terms of LV mass which has shown to be a predictor of CV events. LV mass is indexed to body surface area to enable comparison of various body statures. At present, M-mode echocardiography is the standard clinical diagnostic method used which detects all but the mildest degrees of LVH. Two-dimensional (2-D) echocardiography has the advantage of being more accurate and reproducible than the M-mode method[16] as it takes into account the length of the LV as well as the myocardial wall thickness. However, its use is limited by the lower frame rate and resolution. 2-D echocardiography is less widely used to estimate the LV mass than M-mode echocardiography, in view of the difficulty in obtaining images of suitable quality and is also more time consuming. The upper limits of normal ranges of LV mass as per American Society of Echocardiography chamber quantification update are >95 g/m^2 in women and >115 g/m^2 in men.[17] Three-dimensional (3-D) echocardiography offers the advantage of obviating inaccurate geometric assumptions, inherent to 2-D echocardiography, which is more prominent in remodeled ventricles. The accuracy of 3-D echo is reportedly similar to cardiac MRI for measuring LV mass.[18] However, the limitations of 3-D echo involve difficulties in accurately tracing the LV epicardial border in poor acoustic windows and dilated ventricles resulting in under estimation of LV mass compared to cardiac MRI, but is more accurate than the alternate echocardiographic methods.[19]

LV mass evaluation by cardiac MRI has the advantage of a 3-D high-resolution modeling of the LV, which is free of geometric assumptions, contrast use, dependency on acoustic window, or ionizing radiation. LV mass determined by cardiac MRI is more accurate and precise than M-mode, 2-D echocardiography. It has also shown to have better interstudy reproducibility for normal, dilated, and hypertrophic cardiac chambers.[20] The two methods cannot be used interchangeably for the assessment of LV mass in view of inherent differences in the estimation. However, echocardiography being less expensive, has better versatility, acceptability, and availability compared with MRI making it the most widely used tool in clinical practice for the assessment of LV mass. The use of cardiac MRI at present is limited to areas of research.

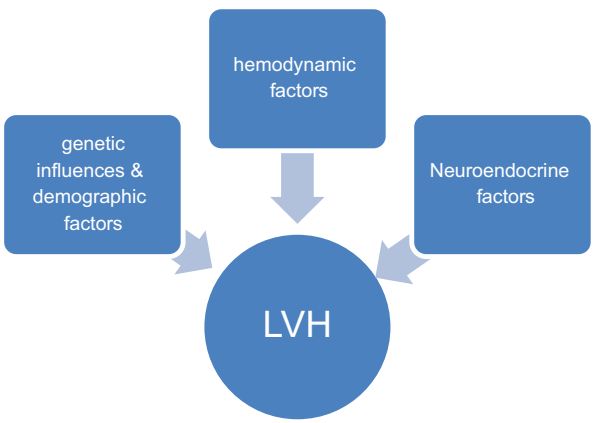

Figure 1: Multifactorial pathogenesis of the left ventricular hypertrophy in hypertension

Table 1: Advantages and disadvantages of various methods for the assessment of LVH

Parameter	ECG	M-mode	2-D echo	3-D echo	Cardiac MRI
Sensitivity	Low	Moderate	High	High	High
Specificity	High	High	High	High	High
Complexity	Low	Low	Moderate	Moderate	Moderate
Cost	Low	Moderate	Moderate	Moderate-High	High

ECG: Electrocardiogram, LVH: Left ventricular hypertrophy, 2-D: Two dimensional, 3-D: Three dimensional, MRI: Magnetic resonance imaging

LVH and Clinical Outcomes

LVH represents HTN-related target organ damage and is an intermediate unfavorable prognostic marker.[3] LVH (diagnosed by ECG or echo) has shown to be an independent risk factor for CV events in patients with HTN [Table 2].[2,21-25] The reason for this association may include a combination of anatomical changes, electrophysiological alterations, and increased activity of RAAS and sympathetic system.[26] The relationship between increasing LV mass and CV morbidity and mortality is linear.[4]

The first discernible manifestation of heart disease in most hypertensive patients is LV diastolic dysfunction.[6] When pressure overload remains sustained, filling of the hypertrophied remodeled LV decreases, diastolic dysfunction progresses,

Table 2: Studies in hypertensives showing the association between LVH and CV outcomes

Study	Study design/inclusion criteria	Key outcomes
Haider *et al.*[22] (1998)	Observational (*n*=3661) >40 years old subjects from Framingham Heart study with LVH followed up for 14 years	LVH independently associated with sudden cardiac death. (HR 1.45 for each 50 g/m^2 increase in LV mass)
Verdecchia *et al.*[23] (PIUMA, 2001)	Cohort (*n*=2363) HTN, mean age 51±12 years	Each 1 SD increase in LV mass (29 g/m^2) associated with an independent 31% increase in the risk for a cerebrovascular events
Verdecchia *et al.*[2] (MAVI, 2001)	Multicenter, prospective (*n*=1033) HTN, age ≥50 years	Each 1 SD increase in LV mass (39 g/m^2) associated with an independent 40% rise in the risk of major CV events
Vakili *et al.*[24] (2001)	Meta-analysis of 20 studies (*n*=48,545)	LVH associated with increased CV morbidity and all-cause mortality across all groups except ESRD
De Simone *et al.*[25] (Cohort derived from Strong Heart Study, 2005)	Cohort (*n*=1026) Inclusions: HTN, No CVD, 47–80 years	Increased LV mass was associated with higher fatal and non-fatal CV events (HR 1.68, *P*<0.05)

HTN: Hypertension, LV: Left ventricular, HR: Heart rate

and HF with preserved ejection fraction (HFpEF) ensues. The end stage of hypertensive heart disease consists of dilated cardiomyopathy with combined diastolic dysfunction and diminished ejection fraction. Hypertensive heart disease can be divided into four stages from a clinical standpoint.[6]

I: LV Diastolic dysfunction without LVH

II: LV Diastolic dysfunction with concentric LVH

III: HFpEF (clinical HF with dyspnea, pulmonary edema)

IV: Dilated cardiomyopathy with reduced EF and HF

The combination of LVH with elevated cardiac biomarkers such as high sensitivity cardiac troponin T, and N-terminal pro-B-type natriuretic peptide (N-T pro-BNP) represents patients with highest risk of developing symptomatic HF, particularly HFrEF.[6] Increased myocardial mass and interstitial fibrosis are associated with a reduced coronary flow reserve leading to an increased risk for myocardial ischemia. The presence of LVH has also shown to be an independent risk factor for the development of coronary events and stroke.[23,24]

LVH has been associated with the development of atrial fibrillation, supraventricular tachycardia (SVT), and ventricular arrhythmias (tachycardia and fibrillation). The exact mechanism of arrhythmogenicity in LVH is not fully understood. The non-uniform propagation of the action potential throughout the myocardium, slowing, and fractionation of ventricular conduction creates a milieu for arrhythmogenesis. Additional factors such as myocardial ischemia, scars, neuroendocrine factors, LV wall stress, and electrolyte imbalances may enhance the pro-arrhythmic risk of LVH.[26,27] In a large meta-analysis of LVH and arrhythmias, patients with LVH had 3.4-fold greater odds of developing SVT and 2.8-fold greater odds of developing ventricular tachycardia and fibrillation.[28] Regression of LVH with antihypertensive treatment has shown to improve CV outcomes.

Antihypertensive Treatment and LVH Regression

BP reduction has shown to reverse LVH. HTN-related LVH is more closely associated with 24 h BP readings than office recordings.[29] Although majority of antihypertensive drugs cause attenuation of LVH, the extent of LVH regression is different with each class. In a large meta-analysis of 80 randomized double-blind antihypertensive trials, the extent of LV mass reduction with various class of antihypertensives was analyzed.[30] The reduction in LV mass index was 13% with angiotensin receptor blockers (ARB), 11% with calcium channel blockers (CCB), 10% with angiotensin-converting enzyme inhibitors (ACEI), 8% with diuretics, and 6% with β-blockers. The reduction in LV mass was significantly more with ARBs, CCBs, and ACEIs compared to β-blockers. Similar findings were noted in a more recent meta-analysis evaluating the aforementioned drugs.[31]

Many studies have shown that LVH regression is associated with better CV outcomes and long-term prognosis [Table 3].[32-35] The Losartan intervention for endpoint reduction study showed that LVH regression (ECG determined) with antihypertension treatment improved prognosis, independent of BP.[28] A meta-analysis of studies reporting LV mass measured by echocardiography before and during HTN treatment, demonstrated that regression of LVH was associated with a significant (59%) reduction in CV events risk when compared to persistence or new development of LVH.[30]

In the real-world setting, there might be many problems in achieving LVH regression in spite of optimal BP control as shown in the subpopulation of Strong Heart Study.[37] Various factors associated with failure of LVH regression include older age, female sex, obesity, higher baseline LV mass index, established vascular disease, and cluster of metabolic abnormalities resembling phenotypic metabolic syndrome.[38-40] Non-pharmacological measures such as weight loss and dietary salt restriction have been linked to the reduction of LV mass independent of BP control.[38,39] However, a clear association is yet to be established. Early initiation of antihypertensive treatment, control of metabolic factors is important in addition to optimal BP control to prevent irreversible LVH.

Table 3: Studies showing improvement in CV outcomes with LVH regression

Study	Study design/inclusion criteria	Key outcomes
Levy *et al.*[32] (1994)	Observational (*n*=524) Subjects from Framingham Heart Study with LVH by ECG were followed.	Improvement in ECG features of LVH resulted in decrease CV risk
Verdecchia *et al.*[33] (2003)	Meta-analysis (*n*=1064) LVM determined by echo, before and during antihypertensive therapy	Regression of LVH was associated with a significant (59%) reduction in CV events risk when compared to persistence or new development of LVH.
Okin *et al.*[34] (LIFE, 2004)	Cohort (*n*=9193) HTN, ECG LVH, 55–80 years	After at least 4 years of follow-up, LVH regression documented by Cornell product associated with decreased MI, CV death, and all-cause mortality
Devereux *et al.*[35] (LIFE echocardiography substudy, 2004)	Cohort (*n*=941) HTN, ECG LVH, 55–80 years	At 1 year follow-up, each 1 SD decrease in LV mass associated with lower CV death, MI, and all-cause mortality independent of baseline LV mass and BP reduction
Verdecchia *et al.*[36] (PIUMIA, 2006)	Cohort (*n*=880) HT, mean age 48 years	Risk of cerebrovascular events was 2.8 times higher in those with lack of LVH regression or new development of LVH

LIFE: Losartan intervention for endpoint, HTN: Hypertension, ECG: Electrocardiogram, LVH: Left ventricular hypertrophy

Conclusions

Assessment of LVH is an important aspect in the management of HTN. It indicates target organ damage, facilitates monitoring of BP control, and also is an independent marker of CV risk. For LVH assessment, ECG, though specific, lacks sensitivity and currently M-mode and 2-D echo are the most widely used tools for LVH assessment with 3-D echo and MRI limited to research purposes. Optimal choice of antihypertensive drugs is essential for achieving LVH regression and also reduces CV events.

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Review Article

Recent Clinical Trials in Hypertension – An Encapsulated Summary

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Abstract

Hypertension (HTN) is a risk factor for cardiovascular (CV) morbidity and mortality. Evidence from studies result in changing strategies for treating HTN. The impact of these trials is evidenced by change in guidelines as well as recommendations for managing HTN with respect to choice of drugs or interventions, as well as goals of treatment.

Key words: Blood pressure, randomized, goal, treatment, cardiovascular risk, intensive

High blood pressure is still a major cause of cardiovascular morbidity and mortality. Management approach of treating hypertension keeps evolving. Hypertension guidelines keep changing based on evidence from trials which influence the changes in recommendation for management of hypertension and the goals of therapy.

HOPE 3 Trial[1-3]

HOPE 3 trial was a landmark primary prevention trial which compared safety and efficacy of cholesterol lowering, blood pressure (BP) lowering, or both.

The trial included males >55 years and females >65 years with at least one CV risk factor. The trial also included women >60 years of age who had ≥2 such risk factors. The patients were randomized to either rosuvastatin 10 mg or placebo in the cholesterol lowering arm, BP lowering arm group received candesartan + hydrochlorothiazide (HCTZ), or placebo. The third group was randomized to receive rosuvastatin + candesartan + HCTZ or placebo.

The highlight of this trial was, enrollment was done based on baseline CV risk irrespective of baseline values of low-density lipoprotein cholesterol (LDL-C) or BP.

The results indicate the benefits of using statins as a primary prevention strategy in moderate risk group irrespective of baseline LDL-C. A fixed-dose combination of all three drugs also showed CV benefits which was mostly driven by rosuvastatin.

The BP arm did not show overall benefit for antihypertensive therapy. However, in normotensives, it caused more harm whereas benefit was noted in patients with high BP. The benefits of statins were seen irrespective of LDL levels.

This shows that all patients at moderate CV risk should be offered statins, but antihypertensive therapy should only be given to those who are hypertensives. In hypertensive patients, benefit is doubled by lowering BP with antihypertensives and also lowering cholesterol simultaneously.

Systolic BP (SBP) Intervention Trial (SPRINT)[4-6]

The SPRINT was a randomized open-label trial. It compared two strategies, one with intensive BP control (SBP <120 mmHg) and other with standard control (SBP <140 mmHg) in non-diabetic individuals with high CV risk. The trial was designed to evaluate the effects of intensive BP control on heart, kidneys, and brain.

The trial was designed to find out whether intensive BP control was better than earlier standard of <140 mmHg.

It included adults age 50 or older who had SBP ≥130 mmHg and at least one other CV disease risk factor (n=9361). Significant number (28%) of patients were elderly with age >75 years of age and also good number of patients who had chronic kidney disease (CKD). Dose adjustment was based on average of three BP readings with unattended automated measurement system.

The results indicate that in high-risk diabetic population with HTN, intensive BP lowering to <120 mmHg is better than

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standard target of <140 mmHg. The above strategy was found to be safe in elderly patients as well. Intensive BP control reduced CV events by 25% and overall mortality by 27%. The same was observed in patients with CKD subgroup. Intensive BP control resulted in greater LVH regression among those who already had LVH and also reduced the risk of developing LVH. Intensive BP control resulted in greater LVH regression among those who already had LVH and also reduced the risk of developing LVH in subjects with no baseline LVH. The trial also suggested that HTN treatment should be tailored according to the CV risk rather than BP measurements alone.

PATHWAY 2 Trial[7]

The goal of the trial was to evaluate treatment with spironolactone compared with doxazosin or bisoprolol or placebo among subjects with resistant HTN.

PATHWAY 2 was designed for the evaluation of better treatment of resistant HTN. This trial is particularly useful as there is high number of patients with resistant HTN leading to high CV risk.

A total of 335 subjects with resistant HTN defined as uncontrolled BP despite three BP medications that also included a diuretic, with mean age of 61 years, who were randomized to receive spironolactone, bisoprolol, doxazosin, or placebo, in addition to their baseline treatment.

Spironolactone was substantially more effective than placebo and also almost 60% of patients had controlled home SBP, and spironolactone was significantly better than doxazosin or bisoprolol. The aldosterone antagonist was well tolerated with no increase in adverse events.

The trial suggested that in patients with resistant HTN, spironolactone was superior add-on drug for improved BP control. Spironolactone should be considered in the management of patients with resistant HTN. Amiloride is also a suitable alternative for resistant HTN, as few patients at study conclusion received it which showed similar reduction in BP. Furthermore, the risk of thiazide-induced glucose intolerance is mitigated when combined with amiloride.[8]

SYMPLICITY HTN 3 Trial[9-11]

The SYMPLICITY HTN-3 study was a randomized, multicenter, prospective, double-blinded study which investigated the safety and efficacy of renal artery denervation (RDN) in refractory HTN. The trial included patients with uncontrolled BP on maximum tolerated doses of three or more drugs, which also included a diuretic. All patients underwent renal angiography and only patients in the treatment group were subjected to RDN with Symplicity renal denervation catheter which used radiofrequency energy.

The trial results did not show any difference in office and ambulatory BP at 6 months between RDN group and medically managed group while at the same time, RDN did not increase the development of new significant renal artery stenosis. The results of this trial are in contrary to the results of smaller trials that did not include a sham control, thus highlighting the usefulness of sham controls in catheter intervention-based trials. The trial also showed that true treatment-resistant HTN is very uncommon than previously thought as only small number of patients from the overall group with apparent treatment-resistant HTN could be recruited. There were few reasons for the failure of this trial. Most operators in the trial had less experience and also some had no previous experience with the procedure. The success of the procedure could not be objectively assessed, as only indirect electrical impedance was utilized to establish contact with the arterial wall. Because of this, incomplete ablation might have happened, irrespective of operator experience.[12,13]

SPYRAL HTN-OFF MED[14]

The trial was designed to find out whether renal sympathetic denervation compared with sham procedure will make a difference in uncontrolled hypertensive patients who are not on any BP drugs. Patients with uncontrolled HTN defined as office SBP ≥150 and <180 mmHg, or ambulatory SBP ≥140 and <170 mmHg, or office diastolic BP ≥90 mmHg and not on treatment were randomized to renal denervation (n = 38) versus sham (n = 42). Mean patient age was 56 years. The primary outcome, improvement in ambulatory SBP control at 3 months, was −5.5 mmHg in the denervation group versus −0.5 mmHg in the sham group (P = 0.04).

This trial among patients with uncontrolled HTN not on treatment showed the efficacy of RDN. There were no excess adverse events from this intervention. A significant difference of this trial was that more ablation attempts were made in the main as well as branch renal arteries as compared to SYMPLICITY HTN-3.

The SPYRAL HTN-ON MED Trial[15]

This trial looked at renal denervation versus sham control in patients with uncontrolled BP on treatment with BP drugs.

Patients with uncontrolled BP (SBP 150–180 mmHg and DBP ≥90 mmHg, and 24 h ambulatory SBP 140–170 mmHg) on treatment were included. Thirty-eight subjects underwent renal denervation and 42 subjects underwent sham procedure. Mean patient age was 54 years.

Renal denervation was performed with the Symplicity Spyral or the Symplicity G3 denervation catheter. Patients in control group underwent a renal angiogram alone.

Renal denervation resulted in 7 mmHg drop in 24 h SBP at 6 months, with no adverse effects. In this trial again, more ablation attempts were made in the main as well as branch renal vessels as compared to SYMPLICITY HTN-3 trial.

This trial showed that renal denervation was superior at improving BP. The study findings are similar to SPYRAL HTN-OFF MED trial.

RADIANCE-HTN SOLO

The normal depth of radiofrequency energy penetration is 3–4 mm.[16] This penetration may not be adequate in the main renal arteries to ablate a large number of sympathetic fibers.[17] This was overcome using a new device that used ultrasound energy which allowed deeper penetration up to 6–7 mm. The Paradise system used in the trial facilitated full circumference cauterization with adequate penetration into the tissue, simultaneously cooling the tissues with a water-filled balloon.[18,19] Deep cauterization will achieve significant denervation of efferent and afferent renal sympathetic nerves in renal artery adventitia.[20] If radiofrequency energy is used to get similar reduction in BP, then many more sites have to be ablated which will prolong procedure time, as energy is delivered from individual electrodes as compared to circumferential energy delivery with ultrasound catheters.

The RADIANCE-HTN SOLO trial[21,22] is a randomized trial comparing renal denervation versus a sham procedure to lower BP.

This trial was done for safety and efficacy assessment of renal denervation for mild-to-moderate HTN.

Patients were randomized to either renal denervation (n = 74) or a sham procedure (n = 72). BP medications were stopped 4 weeks before randomization. Patients in ablation group underwent endovascular ultrasound nerve ablation with Paradise endovascular ultrasound renal denervation system, whereas sham group had only renal angiogram done.

The results show that renal denervation with ultrasound energy resulted in a greater reduction in BP at 2 months. This effect was maintained at 6 months, and also number of medications for controlling BP was also less. The effect of renal denervation appeared reasonably stable.

A Three-arm Randomized Trial of Different Renal Denervation Devices and Techniques in Patients with Resistant HTN (Radiosound-HTN)[23]

This was a randomized head-head comparison trial conducted at a single center which compared three different renal denervation techniques and devices (radiofrequency denervation of main renal arteries [RFM-RDN] vs. denervation of main renal arteries, side branches, and accessory branches [RFM-RDN] vs. endovascular ultrasound [USM-RDN] technique of denervation of main renal artery) in patients with resistant HTN.

Patients with resistant HTN were included. White coat HTN was excluded with ambulatory BP monitoring (ABPM). All patients underwent magnetic resonance imaging (if possible) or duplex scan to rule out renal artery stenosis. Other secondary HTNs were excluded including hyperaldosteronism or obstructive sleep apnea.

Radiofrequency ablation was done with Spyral catheter whereas Paradise catheter was used for ultrasound denervation.

Systolic daytime ABPM significantly decreased with ultrasound denervation group compared with radiofrequency ablation of main renal artery group (13.2 mmHg vs. 6.5 mmHg, P = 0.043), Additional side branch denervation did not show significant difference (8.3 mmHg) either with ultrasound denervation (p-NS) or main branch denervation (p-NS).

This single-center study demonstrated that all three approaches reduce daytime SBP at 3 months of follow-up. Ultrasound denervation was superior in SBP reduction to radiofrequency denervation of main renal arteries alone. However, ultrasound denervation was not found superior, if radiofrequency denervation is done to side branches and accessories along with main branch.

Sympathetic nervous system activation is an important cause of HTN. Percutaneous renal denervation is an option to reduce elevated BP as evidenced from many randomized, sham-controlled trials which demonstrated a convincing and clinically significant reduction of ambulatory BP when compared with sham control groups.[14,15,21]

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Review Article

Renovascular Hypertension

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Abstract

Renovascular hypertension (RVH) constitutes a major cause of secondary hypertension. The most common causes for RVH are atherosclerosis and fibromuscular dysplasia. RVH is an important prognosticator of cardiovascular risk and requires aggressive therapy to reduce the cardiovascular risk. Development of newer antihypertensive drugs and also lifestyle and intense risk factor modification have eased the management and improved outcomes in patients with RVH. Role of revascularization and its benefits in patients with renovascular disease has shown a conflicting result in the various randomized trials. Individual patient-based approach by the treating physician is advised for the enhanced management of the patient with RVH.

Key words: Renovascular hypertension, secondary hypertension, cardiovascular risk

Introduction

"Renovascular hypertension" is defined as systemic hypertension occurring due to the occlusion of the main renal arteries. RVH constitutes approximately 5–10% of the hypertension cases.[1] The most common causes are atherosclerosis in 90% of the cases and fibromuscular dysplasia (FMD) in remaining 10% of cases.[2] Rare causes include vasculitis, embolic disease, dissection, posttraumatic occlusion, and external compression of a renal artery or of a kidney.[3]

Evolution of vascular imaging, especially non-invasive techniques, has resulted in correct and early diagnosis of RVH. Expansion of newer effective antihypertensive drugs targeting the various pathogenic mechanisms of RVH has improved the management outcome in patients with RVH. The role of revascularization either by endovascular techniques or surgery has not shown clear benefits in the various randomized trials.[4] These conflicting data leads to uncertainty among the treating physician in choosing either the endovascular or surgical intervention. This chapter gives the complete review of renovascular hypertension (RVH) with regard to prevalence, etiopathogenesis clinical features, and recent evidence-based management of RVH.

Prevalence

The renal artery stenosis (RAS) is prevalent in 1–5% of patients with hypertension and its prevalence increases with age and with known cardiovascular risk factors. RAS is seen in 14–25% of patients undergoing renal replacement therapy.[5] RAS is associated with coronary artery disease in 67%, cerebrovascular disease in 37%, and peripheral vascular disease in 56% of cases. RAS is seen in 33–39% of patients undergoing angiography for peripheral vascular diseases.[6] The prevalence of RAS is approximately 30% and hemodynamically significant stenosis >50% seen in nearly 50% of patients undergoing coronary angiography. Bilateral RAS is seen in approximately 46%.[7]

Etiology

Most common causes of RAS are atherosclerosis and FMD. Less common causes are large artery vasculitis, trauma, aortic dissection, antiphospholipid syndrome, and mid-aortic syndrome. RAS is present in 26% of patients with Takayasu arteritis.[4] In India, non-specific aortoarteritis is commonly seen, especially in young patients [Table 1].

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Atherosclerosis is seen in approximately 90% of cases. It commonly involves the ostium and proximal third of the main renal artery and the perirenal aorta. Recent studies have shown the prevalence of atherosclerosis in 84% of patients diagnosed with RAS.

FMD is idiopathic, segmental, non-atherosclerotic vascular disease commonly affecting women aged around 15–50 years.[3] It involves all the three layers (intima, media, and adventitia) of the vascular wall. It is seen in 5% of normotensive and 16% of resistant hypertensive patients.[2] Characteristic angiographic feature is "string of beads" appearance due medial fibroplasia.

Pathophysiology

Renin–angiotensin system activation plays a central role in the development of RVH. This has been studied in animal studies and shown that prior treatment with angiotensin-converting enzyme (ACE) inhibitors delayed the development of hypertension. Furthermore, transplantation studies demonstrated the role of angiotensin receptors in both the systemic and renal vasculature.[8] The most important factor determining the renin activation is the presence of significant gradient of more than 20 mmHg between the aorta and the post-stenotic segments of the renal artery.[9]

Clinical Features

The presence of RVH is suspected in patients with

1. HTN onset before age 30 years (without a family history) or after 55 years
2. An abdominal bruit
3. Presenting with accelerated or resistant hypertension
4. Recurrent flash pulmonary edema
5. Renal failure of uncertain cause, with normal urinary sediment
6. Associated with diffuse atherosclerotic vascular disease elsewhere
7. Acute kidney failure precipitated by ACEI or ARBs.[10]

Patients with RVH have paradoxical high nocturnal pressures with absent nocturnal fall in arterial pressure (therefore are classified as "non-dippers").[11] The presence of end-organ damage such as left ventricular hypertrophy, impairment of kidney function, and other manifestations of vascular disease is increased and more severe in such patients. Endothelial dysfunction leading to impaired vascular relaxation is key pathophysiological mechanism seen in patients with RVH.[12] RVH also manifests with flash pulmonary edema characterised by transient episodes of severe hypertension and circulatory congestion leading to left ventricular dysfunction and congestive heart failure.[13]

Table 1: Etiology of renovascular hypertension

1. Atherosclerosis
2. Fibromuscular disease
Medial fibroplasia
Perimedial fibroplasia
Intimal fibroplasia
Medial hyperplasia
3. External fibrous band
4. Trauma
Arterial dissection
Segmental renal infarction
Page kidney (perirenal fibrosis)
5. Dissection of aorta
6. Endograft of aorta obstructing the renal artery
7. Arterial embolism
8. Medical disorders
Hypercoagulable state with renal infarction
Takayasu's arteritis
Radiation induced fibrosis
Tumor encircling the renal artery, for example, pheochromocytoma
Polyarteritis nodosa

Diagnostics of RVH

The key in the diagnosis of RVH is the demonstration of structural and functional occlusion of the renal vessels. The diagnostic tests include studies to assess overall renal function, physiological studies to assess the renin–angiotensin system, assessment of differential renal blood flow by perfusion studies, and non-invasive and invasive imaging studies to assess the degree, location, and significance of RAS. Due to limitation of physiological studies and more cumbersome in nature, imaging techniques mainly non-invasive have replaced these studies.

Duplex ultrasonography

The duplex ultrasonography remains the first line investigation in the diagnosis of RVH. It is most widely available, less

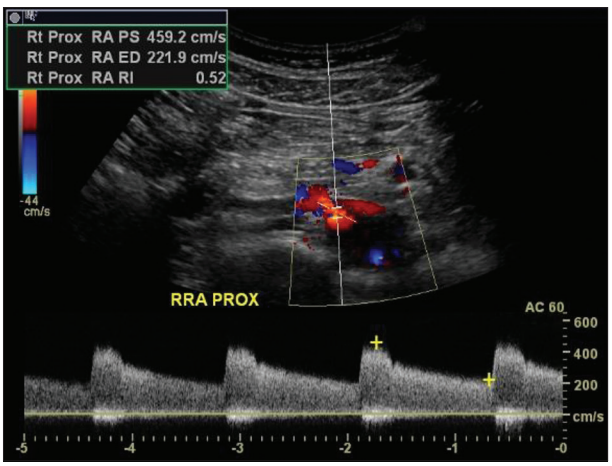

Figure 1: Ultrasound Doppler showing renal artery resistive index of 0.52 suggestive of significant renal artery stenosis

expensive, and non-invasive in nature and gives both structural and functional assessment of RVH. The two commonly used parameters are peak systolic velocity (PSV) in the main renal artery and renal artery to aortic systolic ratio (RAR), in a stenotic segment of the renal artery. Various studies showed PSV ranging from 180 cm/s to 300 cm/s suggest significant stenosis. PSV value above 180–200 cm/s generally correlates with stenosis above 60% with sensitivity of 73–91% and specificity of 75–96%.[14] Other parameters suggestive of significant stenosis include RAR cutoff value of 3.5 and presence of parvus tardus intrarenal waveform, with a small peak and a slow upstroke (highly suggestive of a proximal stenosis).[15]

The elevated resistive index (RI) defined as (PSV – end-diastolic velocity)/PSV, non-specific indicator and the RI >0.80 is used as a negative prognostic sign for response to revascularization [Figure 1].[16,17] However, its use in decision of revascularization is argued against in various other studies.[18]

CT angiography

CT angiography provides excellent vascular and parenchymal imaging of the renal tissue at the cost of radiation and contrast exposure. It is expensive and provides detailed information of function, blood flow, anatomic variation, and approachability [Figure 2].

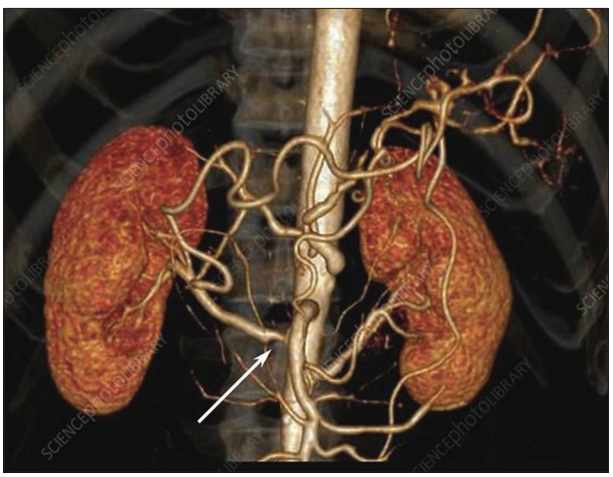

Figure 2: CT renal angiogram arrow demonstrating significant right renal artery stenosis

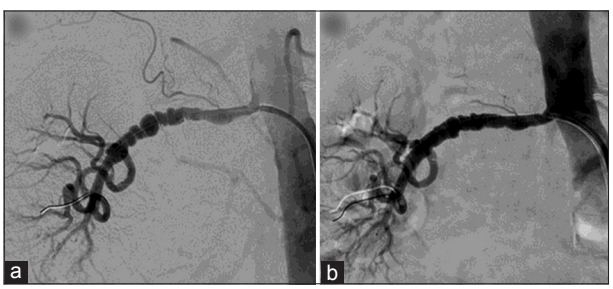

Figure 3: (a and b) Renal angiogram demonstrating classic beaded appearance of renal artery suggestive of fibromuscular dysplasia

MR angiography

MR angiography provides a detailed information of size, structure, and vascular anatomy. It does not carry risk of radiation as CT. The gadolinium-enhanced imaging is less commonly used nowadays due to high risk of nephrogenic systemic fibrosis.

Intra-arterial angiography

Intra-arterial angiograghy is the "gold standard" test for diagnosis of RVH. It accurately identifies the renovascular lesions [Figure 3]. It is usually performed at the time of planned endovascular intervention or when there are discrepancies in diagnosis. Routinely not done in all patients, although some centers include aortic imaging as part of coronary angiography.

Captopril renography

The captopril renography provides the physiological assessment of RVH rather imaging the vasculature directly. It provides the information on functional assessment of overall perfusion and function. It is performed using 99m Tc-DTPA (which largely reflects GFR), immediately before and 60–90 min after the administration of a single 25 mg dose of captopril. Both the uptake and excretion of DTPA on the stenotic side are usually decreased from baseline in patients with unilateral renal arterial disease due to interruption of angiotensin II-mediated vasoconstriction of the post-glomerular efferent arteriole. There will be no consistent decrease in the contralateral uninvolved kidney.

Many biomarkers are used to identify patients likely to have clinical improvement in blood pressure after renal revascularization. These include measurement of renal vein renin levels, brain natriuretic peptide,[19] captopril stimulated renin values, and changes in glomerular filtration after ACE inhibition. The role of these biomarkers remains inconclusive at present. The only strongest predictor of clinical benefit until now remains the short duration of hypertension.

Management of RVH

Management of RVH includes lifestyle changes, adequate treatment of cardiovascular risk factor, and optimal antihypertensive medications with or without revascularization. Option of medical, intervention, and/or surgery depends on the patients characteristics [Table 2]. Algorithm is described below [Figure 4].

The Role of Angiotensin Blockade

Renin–angiotensin system blockade remains the mainstay of treatment in the management of RVH.

Medical therapy is preferred in patients with

a. Adequately controlled blood pressure with stable renal function

b. Stable renal arterial disease without obvious progression
c. Aged patients with limited life expectancy
d. Associated multiple comorbidities.

Table 2: Overview of management of RVH

1. Antihypertensive drug therapy
a. Renin–angiotensin blockade
i. Angiotensin-converting enzyme inhibitors
ii. Angiotensin receptor blockers
iii. Direct renin inhibitors? (Aliskiren)
b. Calcium channel blockers
c. Diuretics
d. Mineralocorticoid receptor blockers
e. Others: Beta-blockade, alpha-receptor blockade, sympatholytic agents, vasodilators
2. Cardiovascular risk factors modification
a. Stop tobacco use
b. Dyslipidemia treatment – medications and lifestyle changes
c. Treatment of obesity and obstructive sleep apnea
d. Strict control of diabetes
3. Renal revascularization: Selected cases
a. Endovascular revascularization
b. PTRA (percutaneous transluminal renal artery angioplasty)
c. PTRA with stenting
d. Surgical techniques such as renal artery bypass/endarterectomy
4. Nephrectomy: Open or laparoscopic removal of pressor kidney, usually non-functional

PTRA: Percutaneous transluminal renal angioplasty

e. High-risk patients or previous atheroembolic disease
f. Presence of concomitant parenchymal renal disease likely to explain renal dysfunction, for example, diabetic nephropathy.

The Role of Renal Revascularization

Endovascular treatment for RAS includes conventional percutaneous transluminal renal angioplasty (PTRA) with or without stenting. PTRA with stenting is treatment of choice in symptomatic patients with hemodynamically significant ARAS [Figure 5]. In FMD with uncontrolled hypertension, PTRA alone is advised and stenting reserved for patients as a bailout procedure. This procedure success rate is around 82–100% and restenosis seen in 10–11%.[20,21] Additional stenting has improved the success rate to 94–100% and restenosis to 11–23% at 1 year.[22]

Indications

The intervention in atherosclerotic RAS is indicated, with a diameter stenosis of greater than 70% on catheter angiogram. Hemodynamically significant is defined by, a translesional systolic pressure gradient of ≥20 mmHg or a mean gradient of ≥10 mmHg.[23] Other indirect signs indicative of significant RAS on angiogram include presence of post-stenotic dilatation and pericapsular or periureteral arterial collaterals.

The American College of Cardiology and American Heart Association guidelines and SCAI AUC recommend.[24]

1. Patients presenting with flash pulmonary edema, unstable angina, or ACS with hypertension with moderate RAS with a resting trans lesional mean gradient of more than 10 mmHg and/or severe RAS (Class I, Level of Evidence: B; Class II a, Level of Evidence: B [unstable angina], Appropriate by SCAI)

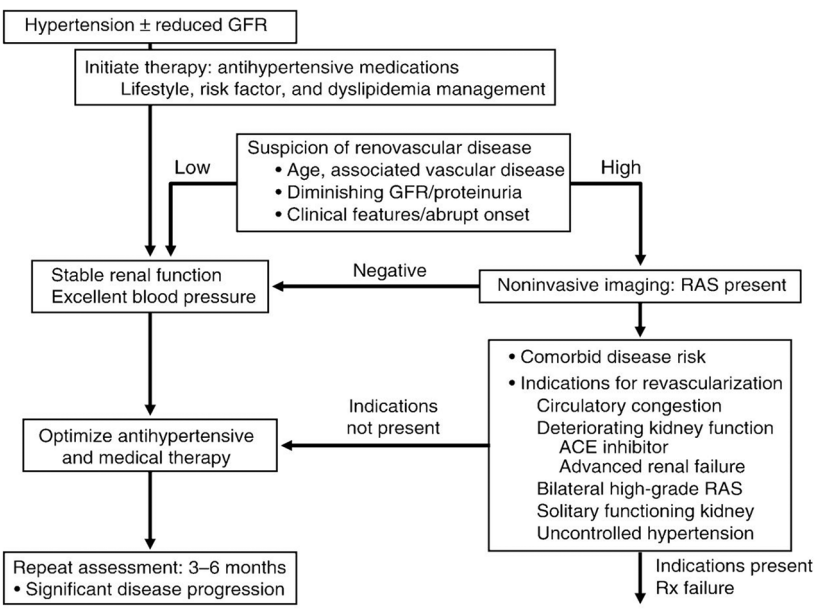

Figure 4: Overview management algorithm for patients with RVH.[31] With permission from American Journal of Hypertension

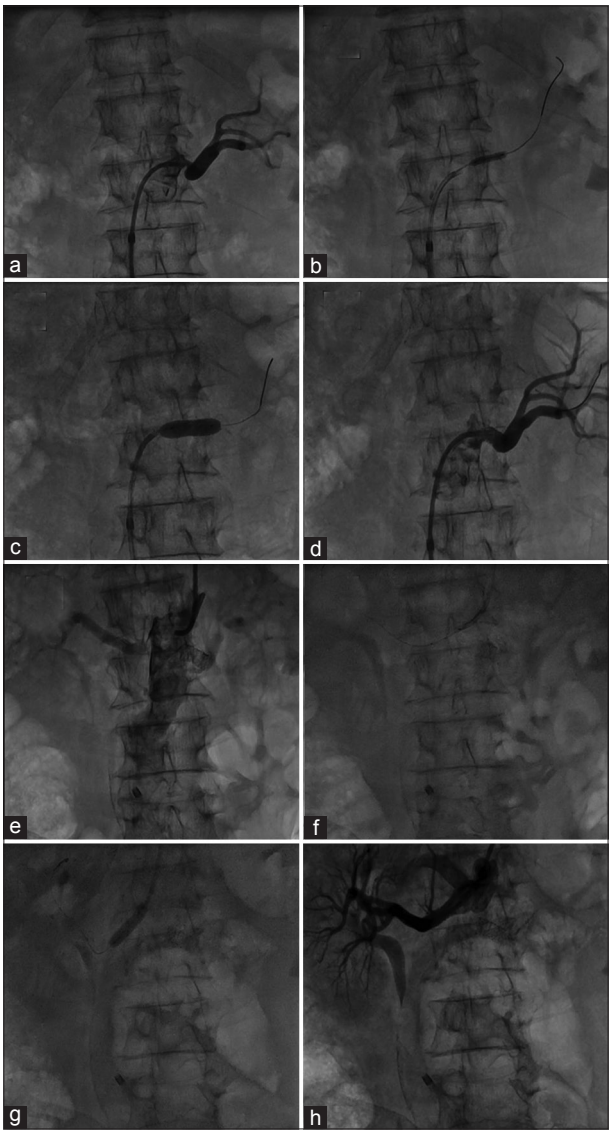

Figure 5: (a-d) The significant left renal artery stenosis (RAS) approached through the right femoral venous approach. (e-h) The right RAS successfully stenting done through the left brachial approach

2. Patients with CKD Stage IV with bilateral moderate RAS with a resting translesional mean gradient of 10 mmHg or more with a kidney size >7 cm in pole-to-pole length (Class IIa, Level of Evidence: B, Appropriate by SCAI)
3. Patients with CKD Stage IV and global renal ischemia (unilateral severe RAS with a single kidney or bilateral severe RAS) without any other cause. (Class IIb, Level of Evidence: B, Appropriate by SCAI)
4. Resistant hypertension and bilateral or single severe RAS. (Class IIa, Level of Evidence: B, Appropriate by SCAI)
5. Patient presenting with recurrent CHF with unilateral moderate RAS with a resting translesional mean gradient of 10 mmHg (Class I, Level of Evidence: B. May be appropriate by SCAI)
6. Resistant hypertension and unilateral severe RAS (Class IIa, Level of Evidence: B. May be appropriate by SCAI)
7. Asymptomatic, unilateral, bilateral, or solitary kidney with hemodynamically significant RAS. (Class IIb, Level of Evidence: C. Rarely appropriate by SCAI).

Contraindications

i. Progressive renal disease with a serum creatinine >3 mg/dl or a kidney size <8 cm
ii. Limited life expectancy
iii. Pregnancy.

Data of Various Trials with Renal Revascularization

Comparison of angioplasty with medical treatment of atherosclerotic RAS

The Essai Multicentrique Medicaments versus Angioplastie and the Dutch RAS Intervention Cooperative trials compared PTRA to medical treatment with more than 6 months of follow-up[25] showed no significant differences between the angioplasty and drug therapy. Meta-analysis involving moderate-to-severe unilateral or bilateral atherosclerotic RAS and poorly controlled hypertension[26] showed better control of blood pressure in patients with atherosclerotic RAS who underwent PTRA. However, no evidence of improved outcomes on renal function noted.

PTRA with stenting versus medical management

The angioplasty and stenting for renal artery lesions, a large randomized trial compared PTRA with stenting combined with medical therapy to medical therapy alone for improvement in renal function.[27] There were no significant differences in renal function, blood pressure, kidney, and cardiovascular events, and mortality between both the groups. The decline in renal function overtime was slightly slower in the revascularization which was not significantly except for medical management group required slightly higher number of antihypertensive medications.

STAR study (the stent placement and blood pressure and lipid lowering for the prevention of progression of renal dysfunction caused by atherosclerotic ostial renal artery disease) also showed no difference in the outcomes.

Drug-eluting stents and distal embolic protection devices (EPDs)

The GREAT (The Palmaz Genesis Peripheral Stainless Steel Balloon Expandable Stent in Renal Artery Treatment) trial[28] done in 102 patients compared sirolimus DES to bare metal stents which showed statistically insignificant angiographic binary renal artery in-stent restenosis. The RESIST (Randomized Study Comparing renal Artery Stenting With or Without Distal Protection) trial demonstrated no improvement in GFR or outcomes with use of glycoprotein IIb/IIIa inhibitors or filter-based distal EPDs. EPDs lead to increased platelet aggregation

or migration of small renal atheroemboli associated with the device.

FMD

PTRA, with or without stent placement, is the treatment of choice. Stenting is routinely not advised in FMD except in bailout situations like vessel dissection. After the intervention, there is successful control of blood pressure alone or with less antihypertensive medications. Recent studies have shown patency over 90% immediate and 87% patency rate during follow-up of 6 years. Repeat procedure was needed in 25% of patients.[29]

Surgical Revascularization

Surgical revascularization is in patients with renal artery disease, renal artery aneurysms, and failed endovascular procedures. Various surgical procedures include renal artery bypass grafting, endarterectomy, or extra-anatomic repair using anastomosis to the hepatic or splenic arteries.

Conclusion

Advances in medical therapy, vascular imaging, and endovascular procedures have changed the management of RVH. Renovascular disease remains an important predictor of cardiovascular risk and warrants intensive therapy to reduce this risk including aspirin, statins, tobacco withdrawal, diabetes, and weight control, in addition to attention to blood pressure. The challenge is to identify patients who would respond and to intervene early to reverse kidney damage. Based on the present evidence, the practice of indiscriminately revascularizing ARAS is no longer accepted. Intervention is not recommended in patients with stable renal function over the past 6–12 months and if hypertension is controlled with medications. The recovery potential for renal function and the long-term outcomes of newer interventional procedures requires further studies.

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Review Article

Medical Management of Hypertensive Heart Failure

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Abstract

Hypertension is an important risk factor of heart failure (HF). HF is a common cardiovascular disease, which carries a poor prognosis. Antecedent hypertension is present in 3/4th of chronic HF patients. The risk of HF increases by 50% with 20 mmHg elevation of systolic blood pressure (BP). Among patients with HF, those with higher levels of systolic and diastolic BP are at greater risk of adverse events. Thus, optimal treatment of hypertension is vital in reducing the risk of incident HF and HF hospitalization.

Key words: Hypertension, heart failure with preserved ejection fraction (HFpEF), heart failure with reduced ejection fraction (HFrEF)

Introduction

Hypertension is an important risk factor of cardiovascular disease (CVD), including heart failure (HF);[1] antecedent hypertension is present in 75% of patients with chronic HF.[2] On the other hand, people with normal blood pressure (BP) at middle age have lower risk of developing HF during the remaining course of life.[3]

HF is a common disease. It carries a poor prognosis, which rivals that of cancer. The 5-year survival rate is 25% in men and 38% in women.[4] The risk of HF increases with age. The annual incidence of HF in men is 3/1000 from 50 to 59 years of age and 27/1000 from 80 to 89 years, whereas in women it is 2/1000 and 22/1000, respectively.[4]

HF is among the most common consequences of hypertensive heart disease (HHD), along with ischemic heart disease and arrhythmias.[5] In the Framingham Heart Study, the risk of HF increased by 50% with 20 mmHg elevation of systolic BP.[6,7]

Hypertension and myocardial infarction (MI) are the two most important risk factors for developing HF.[8-10]

MI confers the greatest risk of developing HF. However, due to its high prevalence, hypertension carries the greatest population-attributable risk, accounting for 39% of cases in men and 59% in women.[11] Among patients with HF, those with higher levels of systolic and diastolic BP are at greater risk of adverse events.[12] Thus, optimal treatment of hypertension is vital in reducing the risk of incident HF and HF hospitalization.[13-15]

Definition

HF is a complex clinical syndrome that results from any structural or functional impairment of ventricular filling (diastolic) or ejection of blood (systolic). The cardinal manifestations of HF are dyspnea and fatigue, which may limit exercise tolerance, and fluid retention, which may lead to pulmonary and/or splanchnic congestion and/or peripheral edema.

The ESC 2016 guidelines classify HF into three types based on the left ventricular ejection fraction (LVEF) [Table 1]. HF with LVEF ≥50% is defined as HF with preserved EF (or diastolic HF). HF with LVEF <40% is defined as HF with reduced EF (or systolic HF). HF with LVEF in the range of 40–49% is defined as HF with mid-range EF (HFmrEF). Patients with HFmrEF have mild systolic dysfunction, along with features of diastolic dysfunction.[16]

Pathophysiology

Long-standing systemic arterial hypertension results in sustained cardiac pressure overload. This results in structural and functional changes in the left ventricular (LV) myocardium as an adaptive response, known as cardiac remodeling. LV diastolic dysfunction is the first abnormal cardiac feature in most cases of hypertension. The other common finding in pressure overload is concentric LV hypertrophy (increase in LV mass at the expense

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of LV volume).[3] On the other hand, in cases of predominant volume overload, cardiac remodeling consists of eccentric hypertrophy (increase in LV mass and volume).[17]

In case of sustained pressure overload, there is progression of diastolic dysfunction of the concentric hypertrophied LV, which results in HF with preserved ejection fraction (HFpEF). Further progression of HFpEF results in LV systolic insufficiency (HF with reduced ejection fraction [HFrEF]), a so-called "burn-out" of LV. Whereas, in case of sustained volume overload, there is progression of LV dilatation, followed by decompensation of the eccentric hypertrophied LV, which results in HFrEF.[3,18]

Based on the pathophysiologic and clinical features, HHD is classified into four categories:

- Degree I: Isolated LV diastolic dysfunction with no LV hypertrophy
- Degree II: LV diastolic dysfunction with concentric LV hypertrophy
- Degree III: Clinical HF (dyspnea and pulmonary edema with preserved ejection fraction)
- Degree IV: Dilated cardiomyopathy with HFrEF.[19]

Based on the development and progression of disease, HF can be classified into various stages:

- Stage A – At high risk for HF but without structural heart disease or symptoms of HF
- Stage B – Structural heart disease but without signs or symptoms of HF
- Stage C – Structural heart disease with prior or current symptoms of HF
- Stage D – Refractory HF requiring specialized interventions.[20]

Investigation in Hypertensive HF

Initial investigation

Plasma natriuretic peptides (NPs)

Plasma concentration of NPs is a useful initial investigation, especially in non-acute patients when echocardiography cannot be done immediately. The other common use lies in the monitoring of HF treatment in the in-patient setting. In acute HF, the upper limit of normal value for B-type NP (BNP) is 100 pg/mL and for N-terminal pro-BNP (NT-proBNP) is 300 pg/mL. In non-acute patients, the upper limit of normal for BNP is 35 pg/mL and for NT-proBNP is 125 pg/mL. Diagnostic values are similar for both HFrEF and HFpEF, although values for HFpEF are usually lower than for HFrEF.[16]

Due to the various cardiovascular and non-cardiovascular causes of elevated NPs apart from HF, including age, atrial fibrillation, and renal failure, the use of NPs is recommended to rule out HF, but not necessarily for establishing the diagnosis.[16]

Electrocardiogram

ECG changes commonly seen in hypertensive HF patients include LV hypertrophy and left atrial enlargement. Atrial fibrillation may be present in some cases since hypertension is a known predisposing factor for AF. In some cases, ECG may provide clue regarding the etiology, like MI. On the other hand, patients with a completely normal ECG are unlikely to have HF (sensitivity 89%).[16]

Echocardiography

Echocardiography is the most useful, widely available test to aid in the diagnosis of HF. It provides important information on ventricular function, chamber volumes, wall thickness, and valve function, which is vital in the diagnosis and treatment of HF.[16]

Chest X-ray

Chest X-ray is more useful to identify an alternative, pulmonary explanation for a patient's clinical findings, rather than for diagnosing HF. In acute HF, chest X-ray shows features of pulmonary venous congestion or edema. The absence of cardiomegaly on X-ray does not exclude significant LV dysfunction.[16]

Further Investigation

HF due to uncontrolled/longstanding hypertension is a manifestation of hypertension-mediated organ damage (HMOD). The presence of extensive HMOD is one of the indications to evaluate the patient for secondary causes of hypertension. Therefore, apart from routine evaluation, the purpose of investigating these groups of patients would be to:

1. Assess the extent of HMOD
2. Look for secondary causes of hypertension.

However, the above rationale might not always be applicable for hypertensive patients who have HF due to other causes, such as MI.

Assessment of HMOD

HMOD refers to structural or functional changes in arteries or end organs (heart, blood vessels, brain, eyes, and kidney) caused by an elevated BP. The presence of HMOD is a marker of pre-clinical or asymptomatic CVD, and indicates an increased cardiovascular risk to the patient.[20,21] Early recognition and treatment of hypertension are important, which may delay the progression of HMOD and will reduce the elevated CV risk of these patients.[22] The various investigations to establish HMOD are shown in Table 2.[23]

Evaluation for Secondary Hypertension

Secondary hypertension is hypertension due to an identifiable cause, which may be treatable with an intervention specific to the cause.[24] The prevalence of secondary hypertension is 5–15% among hypertensive patients.[23]

There are certain patient characteristics that should raise the suspicion of secondary hypertension [Table 3].

HF due to uncontrolled hypertension is a manifestation of HMOD. The presence of extensive HMOD should raise suspicion to rule out secondary causes of hypertension.

The common causes of secondary hypertension and screening tests are described in Table 4.

Table 1: Definition of heart failure with preserved (HFpEF), mid-range (HFmrEF), and reduced ejection fraction (HFrEF)[16]

Type of HF		HFrEF	HFmrEF	HFpEF
Criteria	1	Symptoms±signs	Symptoms±signs	Symptoms±signs
	2	LVEF <40%	LVEF 40-49%	LVEF ≥50%
	3	-	1. Elevated natriuretic peptide levels 2. At-least one additional criterion a. relevant structural heart disease (LVH and/or LAE) b. diastolic dysfunction	1. Elevated natriuretic peptide levels 2. At-least one additional criterion a. relevant structural heart disease (LVH and/or LAE) b. diastolic dysfunction

HF: Heart failure, HFrEF: Heart failure with reduced ejection fraction, HFmrEF: Heart failure with mid-range ejection fraction, HFpEF: Heart failure with preserved ejection fraction, LVEF: Left ventricular ejection fraction, LVH: Left ventricular hypertrophy, LAE: Left atrial enlargement

Table 2: Assessment of hypertension-mediated organ damage[23]

Basic screening tests for hypertension-mediated organ damage
12-lead ECG
Urine albumin: creatinine ratio
Blood creatinine and eGFR
Fundoscopy
More detailed screening for hypertension-mediated organ damage
Echocardiography
Carotid ultrasound
Abdominal ultrasound and Doppler studies
Ankle-brachial index
Cognitive function testing
Brain imaging

ECG: Electrocardiogram, e-GFR: Estimated glomerular filtration rate

Table 3: Patient characteristics that should raise suspicion of secondary hypertension[23]

Characteristic[28]
Grade 2 hypertension in patients <40 years
Hypertension in childhood
Acute worsening hypertension in previously normotensive patients
Resistant hypertension
Hypertensive emergency
Presence of extensive hypertension-mediated organ damage
Features of endocrine abnormalities which cause hypertension
Obstructive sleep apnea
Symptoms/family history of pheochromocytoma

Other causes of secondary hypertension include drugs such as oral contraceptive pills, nonsteroidal anti-inflammatory drugs, herbal remedies, anabolic steroids, nasal decongestants, CNS stimulants, and immunosuppressive medications; and rarer genetic causes such as Liddle syndrome, Gordon syndrome, Geller syndrome, and Glucocorticoid remediable hypertension.

Prevention

Antihypertensive therapy for HF prevention

Clinical trials have shown that the treatment of hypertension reduces the risk of incident HF by up to 64%.[25] Although all anti-hypertensive drugs act to reduce BP, literature shows that not all classes of these drugs have equal propensity to prevent HF.

Beta-blocker therapy which is a cornerstone in HF treatment and has been shown to reduce the risk of mortality and hospital admission in HFrEF patients, has no better preventive effect on HF compared to other antihypertensive drugs. The analysis of 12 randomized controlled trials showed that beta-blockers reduced BP by 12.6/6.1 mm Hg in comparison to placebo, resulting in a 23% reduction in HF risk.[13] However, when compared with other antihypertensive drugs, beta-blockers showed increased risk of stroke in the elderly by 19%, therefore, should not be considered as first-line drugs in older patients.[3,13]

Calcium-channel blockers (CCBs) were initially shown to increase the risk of HF events when compared to diuretics, ACE inhibitors, and angiotensin receptor blockers (ARBs).[3,13] However, a meta-analysis by Thomopoulos *et al*. observed that the anti-hypertensive effect of CCBs is as effective as that of the other anti-hypertensive drugs in the prevention of HF.[26] In addition, CCBs reduce the risk of stroke compared to ACE inhibitors and ARBs, reduce the risk of MI compared to ARBs.[3,13]

Alpha-blockers are not first-line drugs for the treatment of hypertension. In the ALLHAT study, doxazosin showed an increased risk of stroke and doubling of HF risk when compared with chlorthalidone, therefore, indicating that alpha-blockers be avoided as anti-hypertensive drugs in patients who are at risk for or with HF.[13] However, in the ASCOT study, doxazosin was safe and effective when given as a third-line add-on drug, and did not increase the risk of HF.[27]

Renin-angiotensin system blockers are first-line anti-hypertensive drugs and are effective in HF prevention. Between ACE inhibitors and ARBs, no significant difference in efficacy has been documented till present.[3,28,29] Valsartan/sacubitril is the first-in-class angiotensin II receptor neprilysin inhibitor (ARNI), which has shown significant reduction in cardiovascular mortality and morbidity in HFrEF patients, in the PARADIGM-HF trial.[30] This novel drug also has an anti-hypertensive effect and preferentially acts on systolic BP.[31] The anti-hypertensive effect of valsartan/sacubitril is better than that of ARBs.[3]

Thiazide-like diuretics chlorthalidone and indapamide have been proven beyond doubt, to prevent HF when used as antihypertensive drugs. The SHEP trial[32] and the HYVET

trial[33] observed a markedly significant reduction of HF, both with chlorthalidone and indapamide treatment against placebo. Multiple randomized control trials have established the superiority of diuretics in HF prevention as compared to all other antihypertensives.[26] No data for hydrochlorothiazide are available, either for HF or any other cardiovascular endpoint.[3]

To conclude, not all classes of antihypertensive are equal in their efficacy to decelerate the transition from hypertension to HF. Thiazide-like diuretics chlorthalidone and indapamide are preferable over other antihypertensive agents for HF prevention.[3]

Treatment

Treatment of acute hypertensive HF (hypertensive emergency)

This is a clinical condition in which severe hypertension (Grade 3) is associated with acute HF. It is a life-threatening condition requiring immediate but careful intervention to the lower BP, usually with intravenous (i.v.) therapy. The first-line treatment includes i.v. nitroprusside or nitroglycerine with loop diuretic. Alternatively, i.v. urapidil with loop diuretic may be used. Table 5 shows the doses and characteristics of antihypertensive drugs for the treatment of acute hypertensive HF.[16]

Pharmacological therapy for HFrEF

The goals of treatment in patients with HF are to improve their clinical condition, quality of life, prevent hospital admission, and reduce mortality. The recommended treatment for HFrEF consists of neuro-hormonal antagonists, namely, ACEIs, MRAs, and beta-blockers. All these three classes of drugs have been proven to improve survival in patients with HFrEF and are, therefore, recommended for every patient with HFrEF, unless contraindicated, or not tolerated. ARBs have not been consistently proven to reduce mortality in HFrEF patients. Therefore, their usage should be restricted to patients intolerant to ACEI or those who are on ACEI but do not tolerate an MRA.[16]

Valsartan/sacubitril (ARNI) has been proven to be superior to enalapril (ACEI) in reducing cardiovascular mortality and HF hospitalization in HFrEF patients. It is, therefore, recommended as a replacement to ACEI in ambulatory HFrEF patients who are symptomatic despite optimal medical therapy. Ivabradine reduces the elevated heart rate and has been shown to improve outcomes in HFrEF. Ivabradine is recommended in patients with stable symptomatic HF (NYHA Class II–IV) and an LVEF ≤35%, in sinus rhythm and resting heart rate ≥70 bpm despite guidelines-recommended treatment.[16]

Table 4: Common causes of secondary hypertension[23]

Cause	Prevalence in hypertensive patients	Screening investigations
Obstructive sleep apnea	5–10%	Epworth score and ambulatory polygraphy
Renal parenchymal disease	2–10%	Plasma creatinine and electrolytes, eGFR; urine dipstick for blood and protein, urinary albumin:creatinine ratio; renal ultrasound
Atherosclerotic renovascular disease Aortoarteritis	1–10%	Duplex renal artery Doppler; CT angiography or MR angiography
Fibromuscular dysplasia		
Primary Aldosteronism	5–15%	Plasma aldosterone and renin, and aldosterone:renin ratio; hypokalemia (in a minority)
Pheochromocytoma	<1%	Plasma or 24 h urinary fractionated metanephrines
Cushing's syndrome	<1%	24 h urinary free cortisol
Thyroid disease (hyper- or hypothyroidism)	1–2%	Thyroid function tests
Hyperparathyroidism	<1%	Blood levels of parathyroid hormone, calcium
Coarctation of the aorta	<1%	Echocardiogram

eGFR: Estimated glomerular filtration rate, CT: Computed tomography, MR: Magnetic resonance[23]

Table 5: Doses and characteristics of antihypertensive drugs for the treatment of acute hypertensive heart failure[17]

Drug	Onset of action	Duration of action	Dose	Contraindications	Adverse effects
Nitroglycerine	1–5 min	3–5 min	5–200 μg/min i.v. infusion 5 μg/min increase every 5 min		Headache, reflex tachycardia
Nitroprusside	Immediate	1–2 min	0.3–10 μg/kg/min i.v. infusion, increase by 0.5 μg/kg/min every 5 min until goal blood pressure	Liver/kidney failure (relative)	Cyanide intoxication
Urapidil	3–5 min	4–6 h	12.5–25 mg as bolus injection; 5–40 mg/h as continuous infusion		

Sodium–glucose cotransporter 2 (SGLT2) inhibitors are newer class of anti-diabetic drugs which have gained prominence due to their proven benefit in reducing the risk of cardiovascular mortality and HF hospitalization among patients with type 2 diabetes mellitus. The safety and cardiovascular benefit of this class of drugs has recently been established even in HFrEF patients without diabetes mellitus. The DAPA-HF trial demonstrated that dapagliflozin significantly reduced the risk of worsening HF and cardiovascular death in HFrEF patients with NYHA Class II–IV symptoms and LVEF ≤40%, compared to placebo, regardless of the presence or absence of type 2 diabetes mellitus.[34]

Diuretics should be used in HFrEF patients with congestion. Their use should be titrated according to the patient's clinical condition and might be discontinued in selected asymptomatic euvolemic/hypovolemic patients at-least temporarily.[16]

Loop diuretics produce a more intense and shorter diuresis than thiazides and are usually the first line of diuretics used for HFrEF. Together they have a synergistic action and can be combined for treating resistant edema. However, their combination should be used cautiously due to high likelihood of adverse effects.[16]

Hydralazine and isosorbide dinitrate combination may be considered in symptomatic HFrEF patients in whom neither ACEI nor ARB is tolerated, or if they are contraindicated, to reduce mortality.[16]

Table 6 shows the recommended doses of disease-modifying HF medications. The dosage of medications is usually increased every 2–4 weeks as tolerated by the patient, and relevant investigations done periodically, until the maximum tolerated/target dose is achieved. Table 7 shows doses of diuretics commonly used for HF.[16]

Table 6: The recommended doses of disease-modifying HF medications.[16]

Drug – generic name	Starting dose (mg)	Target dose (mg)
ACE-I		
Captopril	6.25 t.i.d.	50 t.i.d
Enalapril	2.5 b.i.d.	10–20 b.i.d.
Lisinopril	2.5–5.0 o.d.	20–35 o.d.
Ramipril	2.5 o.d.	10 o.d.
Trandolapril	0.5 o.d.	4 o.d.
Beta-blockers		
Bisoprolol	1.25 o.d.	10 o.d.
Carvedilol	3.125 b.d.	25 b.i.d. (≤85 kg body weight)
		50 b.i.d. (>85 kg body weight)
Metoprolol succinate	12.5-25 o.d.	200 o.d.
Nebivolol	1.25 o.d.	10 o.d.
ARBs		
Candesartan	4-8 o.d.	32 o.d.
Valsartan	40 b.i.d	160 b.i.d.
Losartan	50 o.d.	150 o.d.
MRAs		
Eplerenone	25 o.d.	50 o.d.
Spironolactone	25 o.d.	50 o.d.
ARNI		
Sacubitril/valsartan	49/51 b.i.d.	97/103 b.i.d.
If-channel blocker		
Ivabradine	5 b.i.d.	7.5 b.i.d.

ACE-I: Angiotensin-converting enzyme inhibitor, ARB: Angiotensin receptor blocker, ARNI: Angiotensin receptor neprilysin inhibitor, b.i.d.: bis in die (twice daily), MRA: Mineralocorticoid receptor antagonist, o.d.: Omne in die (once daily); t.i.d.: ter in die (three times a day)

Treatment of HFpEF

HFpEF is usually associated with concomitant cardiovascular and non-cardiovascular comorbidities, such as COPD, obesity, CKD, CAD, arterial hypertension, AF, anemia, and pulmonary hypertension. Patients with HFpEF are more likely to die or be hospitalized due to non-cardiovascular cause than HF. Therefore, the key to managing these patients also includes treating their comorbidities.[16]

Since no drug has emphatically shown to reduce morbidity or mortality in case of HFmrEF and HFpEF, the focus of treatment is to improve the patients' symptoms.[16]

Diuretics have been proven to improve symptoms across the spectrum of HF. Candesartan, an ARB has shown improvement in NYHA class among patients with LVEF >40% in CHARM-Preserved trial, with a trend toward reduced cardiovascular death and HF hospitalization. Spironolactone and nebivolol might reduce hospitalizations due to HF in HFpEF patients with sinus rhythm. Neuro-hormonal antagonists (ACEIs, ARBs, MRAs, and beta-blockers) have not shown reduction in mortality in HFpEF or HFmrEF patients. Nebivolol, however, has shown reduction in combined endpoint of mortality and HF hospitalization in older patients with HFpEF and HFmrEF.

Recently, the novel drug valsartan/sacubitril (ARNI) has been shown to reduce NT-proBNP and left atrial size in patients with HFpEF.[16]

Antihypertensive therapy in HF patients with persisting hypertension

Lifestyle intervention

Lifestyle intervention is important not only in its ability to BP but also in augmenting the effect of anti-hypertensive therapy.[24] Regular physical activity, cessation of smoking, moderate alcohol consumption, adequate intake of fruits and vegetables, dietary salt restriction, and maintaining ideal body weight are recommended.[1]

Secondary hypertension

The key to managing secondary hypertension lies in treating the primary cause. Interventions addressing the primary cause,

when done at a younger age may be curative. (e.g., renal artery stenting for renal artery stenosis, surgical removal of tumor for pheochromocytoma, and withdrawal of drug/substance in drug induced hypertension). Interventions are less likely to be curative if done later in life, but still, are effective in better control of BP with less medication.[24]

Table 7: The doses of diuretics commonly used in HF[16]

Diuretics	Initial dose (mg)		Usual daily dose (mg)	
Loop diuretics				
Furosemide	20–40		40–240	
Bumetanide	0.5–1.0		1–5	
Torsemide	5–10		10–20	
Thiazides				
Bendroflumethiazide	2.5		2.5–10	
Hydrochlorothiazide	25		12.5–100	
Metolazone	2.5		2.5–10	
Indapamide	2.5		2.5–5	
	Potassium-sparing diuretics			
	+ACE-I/ARB	-ACE-I/ARB	+ACE-I/ARB	-ACE-I/ARB
Spironolactone/eplerenone	12.5–25	50	50	100–200
Amiloride	2.5	5	5–10	10–20
Triamterene	25	50	100	200

ACE-I: Angiotensin-converting enzyme inhibitor, ARB: Angiotensin receptor blocker

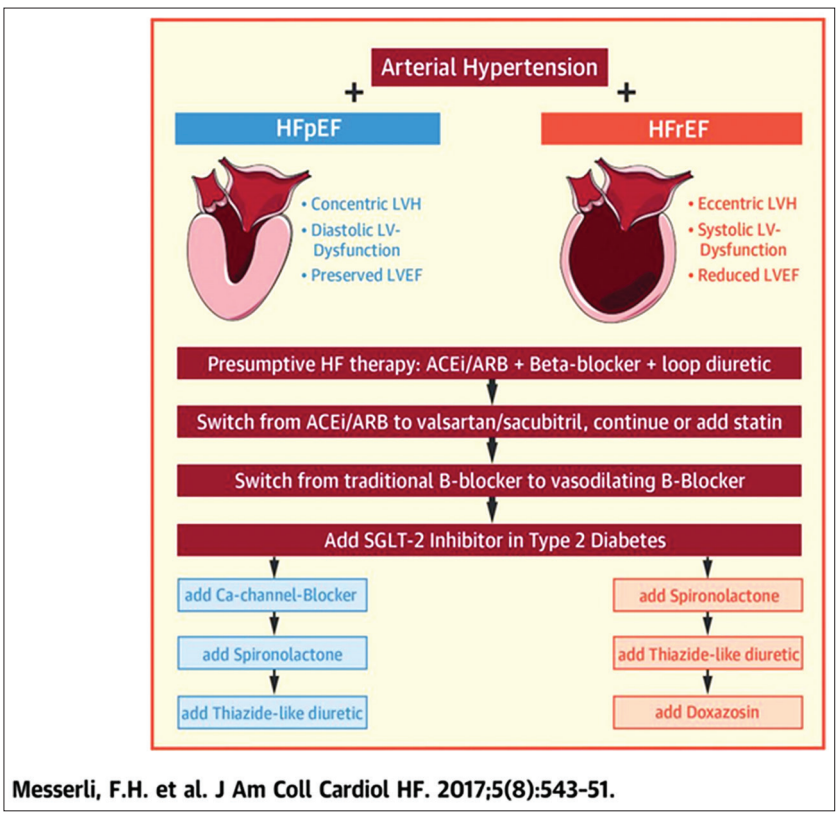

Figure 1: Empirical blood pressure lowering strategy in heart failure with persisting hypertension

Antihypertensive drug therapy

In addition to lowering the BP, the aim of antihypertensive therapy should be to improve systolic function in HFrEF and diastolic function in HFpEF.

If not already initiated, antihypertensive therapy in HFrEF patients should be started when BP is >140/90 mmHg.[24] How low should BP be lowered remains a matter of debate. Due to poor outcomes for HF patients with low BP values, care should be taken so that BP is not actively lowered to <120/70 mmHg.[24] However, patients with the lower BP values should still be continued on guideline-directed HF therapy, as long as it is well tolerated, due to its protective effect.[35]

The recommended drugs for the treatment of hypertension in HFrEF patients include guideline-directed HF medications.[35] They include ACE inhibitors, ARBs, MRAs, and beta-blockers, all of which have been convincingly proven to be effective in improving clinical outcome in HFrEF patients. The benefit of diuretics in HF patients is restricted to alleviating symptoms.[24]

Valsartan/sacubitril lowers BP and improves clinical outcomes in HFrEF patients, and is recommended in the treatment of HFrEF as an alternative to ACE inhibitors or ARBs.[30] As a first step toward better after-load reduction, these patients may be switched to valsartan/sacubitril.

In addition, a vasodilating beta-blocker such as carvedilol or nebivolol may be preferred to other beta-blockers for better BP control.[3] A dihydropyridine CCB may be used if further BP reduction is needed.

Centrally acting agents such as clonidine and non-dihydropyridine CCBs are not to be used.[24]

SGLT2 inhibitors have consistently shown a modest reduction in systolic and diastolic BP.[36] These newer class of drugs exert their BP lowering effect by osmotic diuresis and have been reported to be especially useful in some cases of resistant hypertension in diabetic patients.[37]

In case of HFpEF patients requiring antihypertensive therapy, the same strategy followed for HFrEF patients might be applied.[24] Threshold for starting BP lowering therapy and target BP values for HFpEF patients are same as for HFrEF.[35] Statin therapy is important in HFpEF patients for reducing microvascular dysfunction.[3]

Based on clinical and pathophysiologic features, Messerli *et al*. have suggested the following BP lowering strategy in HF with persisting hypertension [Figure 1].[3]

Conclusion

Hypertensive heart failure is an important manifestation of HMOD and carries a poor prognosis if not treated promptly and adequately. Patients should be investigated for other manifestations of HMOD and secondary causes of hypertension, and treated accordingly. Optimal BP control is vital in prevention of HMOD, including HF. Thiazide-like diuretics namely chlorthalidone and indapamide, and RAAS (renin-angiotensin-aldosterone system) blockade by ACE-I/ARBs are effective in HF prevention compared to other antihypertensive drugs. Acute hypertensive HF is a life threatening emergency which requires immediate treatment with intravenous BP lowering therapy. In chronic and more stable patients, guideline directed HF medical therapy including ACE-I/ARB/ARNI, MRA, beta-blockers are recommended for BP reduction. Dihydropyridine CCBs and thiazide-like diuretics can be used in addition to the above drugs for better BP control. Diuretics are useful for symptomatic relief across the spectrum of HF. Special attention should be paid to management of concomitant cardiovascular and non-cardiovascular comorbidities in HFpEF patients to improve outcomes. SGLT2 inhibitors provide remarkable cardiovascular benefit and modest BP reduction in HFrEF patients with and without diabetes, when given in addition to GDMT.

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Review Article

Cardiovascular Disease in Women

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Abstract

Whereas heart disease is often thought of as a "man's" problem, it is the most common cause of premature mortality in women. A diagnostic hurdle is that women may not present with typical manifestations of coronary artery disease (CAD). However, like men, women should take precautions to reduce the risk of cardiovascular diseases (CVDs). Some women with CAD may not complain of chest pain but present with neck, jaw, or shoulder pain, nausea, dizziness, or unusual fatigue. Women may describe chest pain as merely pressure or tightness. The symptoms of CVD in women may occur even at rest, not on exertion. Moreover, may women tend to downplay their symptoms. The risk factors for CAD in women include – hypertension, hyperlipidemia, diabetes, mental stress, depression, tobacco use, menopause, obesity, and pregnancy-related complications. The risk factors should be identified and controlled aggressively with close follow-up to minimize CV complications. In general, CVD treatment in women is similar to men, but those with a typical feature may derive less benefit from therapeutic and life-saving options. This chapter discusses the pathophysiology, diagnostic work-up, clinical management, and rehabilitation measures in women with CVDs.

Key words: Hypertension, heart disease, women's health, risk factors

Instruction

Cardiovascular disease (CVD is an important cause of premature morbidity and mortality in women. CVD annually claims lives of as many women as the next four to five causes of death. Therefore, CVD (rightly) has emerged as a leading health issue in women. There are some pathophysiological differences between men and women in the context of CVD. The clinical manifestations of CVD in women may differ from that in men; there are critical disparities between women and men in the clinical features, diagnosis, therapy, and outcomes. In comparison to men, women are often underdiagnosed, undertreated, and understudied for CVD.

The global burden of disease study[1] has identified CVD as the most important cause of morbidity, mortality, and disability in women [Figures 1 and 2]. Statistics from India further confirms CVD as a major cause of death in women.[2] Nearly 40% of CVD deaths in India occur in women; and in more than half, the disease occurs prematurely. Consequently, it is essential that women at high risk for CVD receive appropriate diagnostic evaluation and preventive therapeutic options. Our current understanding of CVD in women should instantly dispel the old notion that it is a "man's disease."

Risk Factors for CVD in Women

While there are no population-based studies in India which specifically evaluated women for CVD, studies like INTERHEART[3] indicate that women share the same risk factors as men (except perhaps for cigarette consumption) [Tables 1-3]. Unfortunately, there is a disturbing rise of smoking rates in women of lower socioeconomic and educational background.[4] The National Family Health Survey found an increase in the use of tobacco among Indian women.[5,6]

Family history

Women with family history of CVD demonstrate an aggressive pattern of atherosclerotic plaque formation. Endothelial

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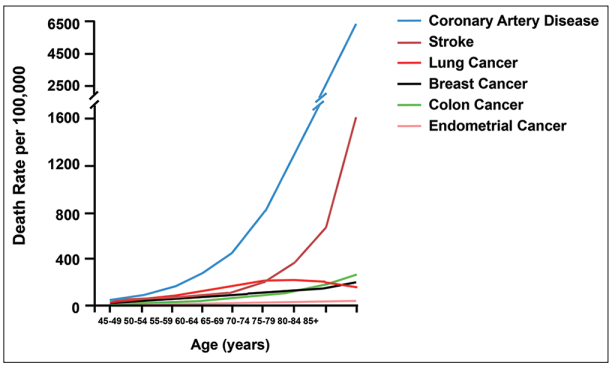

Figure 1: Death rates in women

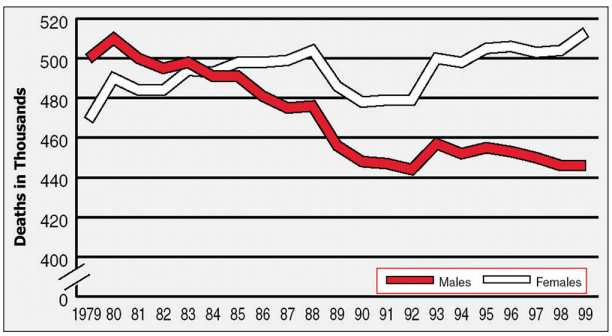

Figure 2: CVD Mortality Trends (1979–1999)

dysfunction (hormone mediated) and altered hemostasis (↑fibrinogen and factor VII levels) may play a pathogenetic role in the inheritance of CVD by women. Women may show genetic alterations in the plaque rupture pathways such as stromelysin-1 and plasminogen activator inhibitor-1.

Hypertension

Hypertension, a risk factor for CVD and cerebrovascular disease (CeVD) to which women are especially susceptible.[7,8] Women experience high CV mortality related to hypertension compared to men, 29% versus 14.9%. By the sixth decade, the prevalence of hypertension in women exceeds that in men. Even borderline blood pressure levels (previously termed "prehypertension") induce excessive CVD and CeVD in women compared to their male counterparts. Estrogen-mediated endothelial dysfunction may provoke vasoconstriction directly or through its stimulatory effects on the renin–angiotensin–aldosterone system (RAAS). In women, hypertension often tends to be severe and poorly controlled which is of great public health concern.

Diabetes

The rates of Type-2 diabetes mellitus are rapidly increasing in Indian women. Moreover, diabetes is a critical risk factor for CVD in women.[9,10] There is a several fold increase in the risk of fatal CVD in women with diabetes compared non-diabetic women. In addition, diabetic women have a higher risk of CVD death compared to diabetic men. This observation calls for a special need to detect, to prevent, and to treat CVD in woman with diabetes. The adverse metabolic and hemodynamic milieu in diabetes is compounded in women compared to men. The direct detrimental consequences of glucose occur at lower thresholds in women. The INTERHEART study concluded that women with diabetes have a greater predisposition to CVD than men with diabetes. It is recognized, based on the evidence, that CVD risk in a diabetic woman is considerably higher than in a man even after adjustment for conventional risk factors. In general, diabetes exerts a greater CV risk in women than in men, 19.1% versus 10.1%. Diabetic women have 40% higher risk for CAD and 25% excess risk for stroke. In fact, the correlation with CVD mortality in diabetes is greater in women compared to men. It is not clear whether this is related to an increase in adiposity, insulin resistance, or, yet, unidentified factors.

Table 1: Risk factors for coronary heart disease

Men and women
Smoking
Diabetes
High cholesterol (in particular high LDL and/or low HDL)
High blood pressure
Obesity
Sedentary lifestyle
Women
Menopause
Birth control pills in combination with smoking

Table 2: Major risk factors for heart disease

Modifiable	Nonmodifiable	Emerging risk factors
High blood pressure	Family history	Homocysteine
Abnormal cholesterol levels	Age	Elevated lipoprotein (a) levels
Diabetes	Gender	Clotting factors
Cigarette smoking		Markers of inflammation (CRP)
Obesity		
Physical inactivity		

Table 3: Overweight as compared with physical activity in predicting death from heart disease among women

Body mass index	<25	25–30	>30
Age-adjusted RR active (>3.5 h)	1.00	1.58	2.87
Age-adjusted RR 1.0–3.5 h	1.51	2.06	4.26
Age-adjusted RR inactive (<1 h)	1.89	2.52	4.73

Dyslipidemia

Dyslipidemia bestows a high CV risk in women than in men.[11,12] When compared to men, low-density lipoprotein (LDL) level is

lower in women and high-density lipoprotein (HDL) is higher, more so in premenopausal years. Postmenopause, however, LDL rises and HDL declines. In women (compared to men), a low HDL to high triglycerides (TGs) ratio has an immense predictive value for CVD. Fortunately, on the other hand, increased HDL levels in women may provide greater protection for CVD than for men.

An elevated TG level is a potent risk factor for CVD in women; meta-analyses have revealed 37% increased risk of CVD in women compared to 14% increased risk in men. At present, outcome data are not available to recommend gender-specific therapeutic approaches to treat dyslipidemia. Guidelines suggest that more women are candidates for lipid-lowering therapy than men. It is possible that advanced lipid testing to predict CVD may refine gender-based tailored therapeutic approach to dyslipidemia. Ironically, despite comparable lipid-lowering benefits, women are less likely to be treated with statins than men after acute myocardial infarction (MI). It is reasonable to conclude that lipid-lowering therapy in women should be intensified.

Metabolic syndrome

Metabolic syndrome, obesity, and physical inactivity contribute to CVD in general but more so in women. Studies suggest metabolic syndrome confers >30% higher CV risk in women compared to men. Women also have higher rates of physical inactivity and obesity. A high level of physical activity reduces the risk of CVD both in men and women. The adverse impact of obesity on CVD is greater in women than in men. Weight gain at any age is a significant risk factor for CVD in women. These established data dictate precautionary measures to manage metabolic syndrome and to prevent CVD in women.

Non-traditional CVD Risk Factors in Women

Depression

An important component of CVD risk assessment in women is the recognition of non-traditional risk factors. For example, auto-immune disorders such as systemic lupus and rheumatoid arthritis which affect women are known to be associated with increased CV risk. Although these mechanisms are thought to be mediated by chronic inflammation, the exact causal connection is not established. Patients with lupus and rheumatoid arthritis have an increased risk for CVD, congestive heart failure (CHF), and also stroke.

Depression, a common psychological disorder, is a known risk factor for CVD. Depression is twice as common in women compared to men. Furthermore, CVD coupled with depression has poor prognosis. Younger women have higher risk of depression and it remains to be seen if it predisposes to CVD.[13] It also is unclear whether the lack of decline in CVD in young women is due to depression. Depression may indirectly increase the risk of CVD through factors such as non-adherence to therapy, poor diet, lack of physical activity, and tobacco use. Depression after acute MI is greater in women compared to men. Anxiety is associated with increased risk of CAD in women. Future CVD prevention trials should include the utility of antidepressant therapies. Furthermore, cultural taboos are a hindrance for psychosocial assessment of women at risk for CVD.

Pregnancy-induced CV risk

There is emerging evidence to suggest that CVD increases in women beyond the affected pregnancy period.[14,15] Even prompt resolution of pregnancy associated hypertension results in residual long-term risk of CVD in the later years. In a large meta-analysis of nearly 200,000 pre-eclampsia women compared to normotensive pregnancies, the future risk of CVD, CeVD, and venous embolism increased significantly. Severe and early onset of pre-eclampsia increase the lifetime risk of CVD several fold. It is of note that pregnancy-induced CV risk is not included in any CVD risk scoring systems. Pregnancy is an area of considerable intrigue for the study of CVD in women. Both gestational diabetes and hypertension are clearly linked to "long-term" risk of CVD in women. Interestingly, the CV status of women before and during pregnancy influences the development of CVD in their offspring – so-called "CV circle of life."

Menopause

It is generally accepted that premenopausal women are relatively protected against CVD in comparison to age-matched men. This advantage, however, vanishes after menopause.[16-18] Whether estrogen is cardioprotective during premenopausal years is not firmly proven. Estrogen exerts vasculoprotective actions on endothelial function and insulin resistance leading to the concept of menopausal hormonal therapy. Early menopause is a potential risk factor for CVD in women as they are exposed to a longer period of hormonal imbalance [Figures 3 and 4]. The role of hormone replacement therapy (HRT) to decrease the CVD risk has not been proven uniformly. Women with vasomotor manifestations of menopause have a higher prevalence of traditional CVD risk factors. The therapeutic role of HRT (for CV protection) remains controversial. In the Women's Health

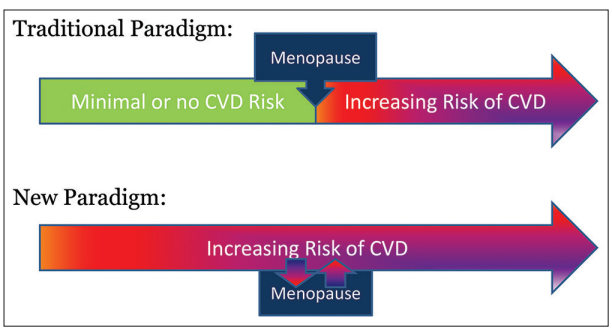

Figure 3: Relationship between early menopause and premature CVD

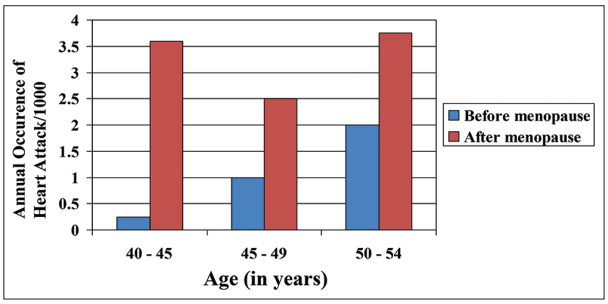

Figure 4: Menopause and the risk of coronary heart disease (modified data from "Menopausal status as a risk for coronary artery disease" Arch Intern Med 1995;155:57-61

Initiative study, surprisingly, HRT exerted CVD protection in younger but not older women. Other observations concluded that HRT reduces CVD risk in women under 60 years of age but not older. In spite of these inconsistent results, HRT is indicated to treat (early) menopausal symptoms but not for CVD prevention. Menopause (surgical) increases the CVD risk compared to natural menopause.

Polycystic ovary syndrome (PCOS)

PCOS is an increasingly recognized endocrine disorder in women of reproductive age which puts them at a high risk for metabolic syndrome. Interestingly, women with PCOS have higher coronary artery calcium content scores. PCOS is associated with premature atherosclerosis. The clustering of traditional CV risk factors (hypertension, dyslipidemia, and diabetes) is widely prevalent in women with PCOS.[19,20] Women with PCOS are vulnerable to develop stroke. Obstructive sleep apnea, a possible risk factor for CVD, is commonly associated with POCS.

Cardiovascular Risk Assessment in Women

While we have indeed made some advances in the diagnosis and treatment of CVD in women, the area of a major gap has been in risk assessment.[21-24] Historically, the Framingham Risk Score (FRS) has been widely advocated to estimate the probability of a coronary artery disease (CAD) event during a 10-year period. A FRS >20% can identify women at high risk, a lower score may under represent a women's future risk for CAD. Age-dependent FRS predictions would eliminate younger women from CVD prevention therapy who would actually benefit from early pharmacotherapy. Another disadvantage of FRS applicability to women is that weight is not given to hysterectomy status, ethnicity, family history, and metabolic syndrome. Thus, FRS significantly underestimates risk in women by (mis)classifying most women as having a low risk for CVD.

Ironically, the FRS (designed to predict CVD events) may be quite inaccurate to estimate CAD risk in women affected by CHF, angina, and stroke. The first manifestation of CAD in 44% of women is acute MI. Thus, the clinicians should be aware of limitations of FRS in women. In the Framingham Heart Study (FHS), the lifetime risk of CVD for healthy women at age 40 is 32% and at age 50 is 39%. This lifetime CVD risk exceeds that of breast carcinoma, lung, and colorectal cancers combined! Although more men than women experience sudden cardiac death, nearly two-thirds of women who die suddenly have no previous symptoms of CAD.

In contrast to FHS, the American Heart Association (AHA) primary prevention of CVD in women guidelines[22] provides a better method of predicting CAD in women. These guidelines overcome the disadvantage of FRS for women and propose aggressive preventive measures. Smoking is the only lifestyle risk factor identified in the FRS system. Thus, a middle-aged woman with multiple unhealthy lifestyle habits may get a low predictive value according to FRS. Thus, the AHA risk assessment model overcomes the limitations of FRS as far as women are concerned. The AHA guidelines provide lifetime risk in contrast to the 10-year risk offered by the FRS. The AHA model places women into one of the three lifetime risk categories – optimal, high, and "at risk." The AHA guidelines thus provide a good estimate of a women's CVD risk based on lifestyle factors, premature CVD, family history, and subclinical evidence of vascular disease. The AHA categories (for women) offer flexibility to aggressively treat CV risk factors in women to reduce lifetime risk. Ideal CV health in women is predicted by an (untreated) blood pressure <120/80 mmHg, a fasting blood glucose <100 mg/dL (untreated), a total cholesterol of <200 mg/dL (untreated), a BMI <25 kg/m^2, abstinence from smoking, and a healthy diet. The Reynolds Risk Score considered more than 30 risk factors to predict CVD in women.[25] Thus, risk factors/indices – hsCRP and family history, were added to the risk algorithm and therefore identifying more women who might be at risk for premature CVD. The Reynolds model (like the FRS) only predicts 10-year risk. A major disadvantage of the Reynolds Score is that it is not applicable to women with different ethnic groups.

CAD Presentation among Women

Multifaceted and complex presentations of CAD among women often lead to misdiagnosis, confusion, and delayed management.[26-28] For example, men frequently present with ST-segment elevation MI, whereas women may present with non-ST segment elevation acute coronary syndrome (ACS).[29,30] In general, as a group, women have a high incidence of silent or missed MI than in men. Women (compared to men) are less likely to present with typical angina. Women may experience angina not only with physical exertion but also with rest and during sleep [Figures 5 and 6; Table 4]. CV symptoms expressed in women with normal coronary angiogram may be related to endothelial dysfunction and vasospasm. Both men and women with ACS present with chest pain. However, women are more likely demonstrate atypical symptoms such as dyspnea, indigestion, back pain, nausea, sudden weakness, and fatigue [Tables 5-7]. Failure to recognize these atypical clinical

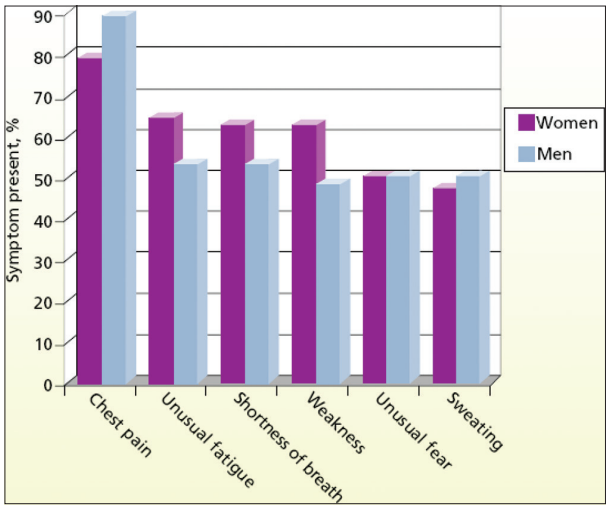

Figure 5: CVD symptoms in men and women

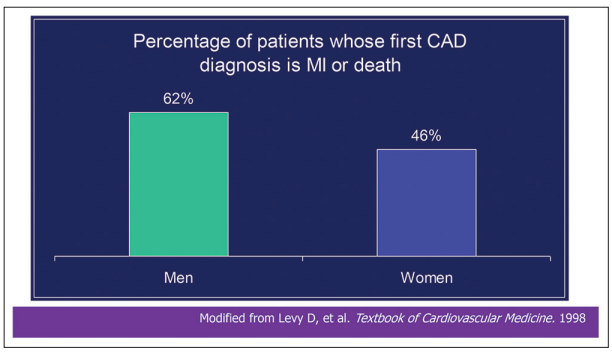

Figure 6: MI or death often first sign of CAD

features delays the diagnostic and therapeutic steps which could result in avoidable complications and even death. Women also tend to attribute their symptoms to non-cardiac causes as there is much misinformation that CAD is a "man-centric" disease! Compounding these factors lead to the delay in seeking medical attention. Sadly, even on arrival to the hospital with CAD complaints, men get faster attention and more medical care than women. It is important to remember that women have a higher prevalence of angina and lower burden of obstructive CAD on angiography and poorer outcomes compared to men. Studies have shown that women with ACS are less likely to receive myocardial reperfusion therapy and coronary artery interventions compared to men.

CAD in Women: Anatomical and Physiological Attributes

CAD in women is characterized by structural and functional differences compared to men. Women may have diffuse and non-obstructive coronary artery lesions.[31,32] Findings from the women's ischemia syndrome evaluation (WISE)[21] indicate that a substantial number of women with angina had non-obstructive CAD. Despite this anatomical finding, women fared poorly compared to men – a fact further warranting aggressive evaluation

Table 4: Less common heart attack symptoms in women

Milder symptoms without accompanying chest pain
Sudden onset of weakness, shortness of breath, fatigue, body aches, overall feeling of illness
Burning sensation in the chest, may be mistaken as heartburn
An "unusual" feeling or mild discomfort in the back, chest, arm, neck, or jaw

Table 5: Gender differences in heart attack symptoms

Typical in both genders	Typical in women
Pain, pressure, squeezing, or stabbing pain in the chest	Milder symptoms (without chest pain)
Pain radiating to neck, shoulder, back, arm, or jaw	Sudden onset of weakness, shortness of breath, fatigue, body aches, or overall feeling of illness (without chest pain)
Pounding heart, change in rhythm	Unusual feeling or mild discomfort in the back, chest, arm, neck, or jaw (without chest pain)
Difficulty breathing	
Heartburn, nausea, vomiting, abdominal pain	
Cold sweats or clammy skin	
Dizziness	

Table 6: Chest pain features in men and women

Location of chest pain		
Location	Women (%)	Men (%)
Central chest	75	81
Left chest	57	56
Left arm	40	42
Neck*	37	22
Right chest	37	34
Upper back	34	26
Jaw*	24	12

*Indicates statistically significant difference. Adapted from Devon *et al.* Amer J Critical Care 2008:17(1):14-24

Table 7: Quality of chest pain

Location	Women (%)	Men (%)
Pressure	77	74
Tightness	66	72
Heaviness	58	57
Dull	45	43
Sharp	40	44

No differences were statistically significant. Adapted from Devon, *et al.* Amer J Critical Care 2008:17(1): 14-24. In both men and women, the discomfort of a heart attack tends not to be sharp, but rather a pressure sensation, tightness or heaviness

and management of women with CAD manifestations. Women are more prone to plaque erosion and demonstrate intramural atherosclerosis than the usual protrusion of the plaque into the arterial lumen. Endothelial dysfunction, microvascular disease, and pro-inflammatory atherosclerosis are important anatomical distinguishing features of CAD in women. Future research should further identify the anatomical and physiological differences in coronary circulation between women and men. Further understanding of this difference will allow for rapid diagnosis and immediate management of CAD syndromes in women.

Spontaneous Coronary Artery Dissection in Women

A vast majority of patients with spontaneous CAD dissection (SCAD) are women.[33-35] Young women are more likely to present with SCAD and peripartum period is especially vulnerable. Occult fibromuscular dysplasia of coronary arteries may be a contributing factor, but the exact pathophysiology of SCAD is not conclusively known. Moreover, there may be a genetic basis. It is important to distinguish SCAD from ACS because the management strategies are different. One reason not to miss SCAD is that response to percutaneous coronary intervention (PCI) is inferior in SCAD compared to the usual atherosclerotic ACS. In contrast with ACS, conservative management of SCAD yields satisfactory long-term results. Careful in-patient observation of SCAD is mandated to detect progression of dissection and to determine the need for interventional therapy.

Diagnostic Testing for CAD in Women

The options for non-invasive tests to uncover CAD are similar in men and women.[36,37] The tests should be chosen based on the index of suspicion and appropriateness. In women with limited physical fitness, pharmacological stress test is an acceptable method. Stress imaging provides additional information about perfusion and wall motion abnormalities. When indicated, functional tests such as exercise treadmill testing, stress echocardiography, nuclear imaging, PET, SPECT, CT perfusion, and Doppler flow reserve measurements can by utilized in the order of clinical suspicion. CT angiography and coronary artery calcium scores provide useful information on the presence and severity of CAD. The validity of these and other diagnostic tests is similar both in men and women.

As in men, coronary angiography establishes the presence or absence of obstructive CAD in women. Despite the standard and proven diagnostic tools (invasive and non-invasive), women are treated less aggressively and are subjected to fewer catheter-based interventions, fibrinolytic and bypass procedures resulting in less favorable clinical outcomes, higher mortality, and impaired quality of life. Women may be more prone to bleeding complications which can be reduced by dose adjustments of anti-thrombotic therapies and alternate technical approaches such as radial access. It is extremely crucial to recognize and acknowledge that women and men with ACS derive comparable benefits from early invasive treatment strategies.

CVD in Women: Prevention Guidelines

In the recent years, substantial progress has been made in our awareness about the importance of recognizing and preventing CVD in women.[38-40] CVD is no longer a curse on the men but does not spare women. Guidelines are available for the diagnosis and prevention of CVD in women. Evidence exists to advocate primary and secondary prevention of CVD in women [Tables 8-10]. The translation from clinical research and population sciences to clinical practice is a critical path to prevent CVD in women. Studies such as the Nurses' Health Study have provided valuable information on the lifestyle modification as the foundation to prevent CVD in women. We can now say with certainty that a majority of CVD events in women can be prevented by consumption of healthy diet, maintenance of desired body weight, limiting alcohol intake, and by regular vigorous physical activity. The INTERHEART study has shown that CVD risk factors are similar between men and women, but the impact of preventive measures is greater in women. Thus, evidence-based guidelines and longitudinal studies affirm that lifestyle modifications can prevent and delay CVD in women substantially.

Table 8: Prevention of coronary heart disease

No gender difference
No smoking
Weight reduction/maintenance
Regular exercise
Control of high blood pressure
Reduction in high cholesterol

Table 9: High blood pressure

Optimal blood pressure <120/80 mmHg
Medication are indicated when blood pressure >140/90 mmHg or >130/80 mmHg in the setting of diabetes

Slide Information Source: Mosca *et al.* Evidence-based guidelines for cardiovascular disease prevention in women. Circulation 2004;109:672-693

Table 10: Lipids (cholesterol and triglycerides)

Optimal levels of lipids and lipoproteins in women
LDL <100 mg/dL
HDL >50 mg/dL
Triglycerides <150 mg/d
(total cholesterol not that important)

Slide Information Source: Mosca *et al.* Evidence-based guidelines for cardiovascular disease prevention in women. Circulation 2004;109:672-693

Statins

Statins are effective for secondary preventive of CVD both in men and in women.[11,12,41] Various studies have confirmed that statin therapy reduces the CVD burden (irrespective of baseline risk) both in men and in women; there may be subtle differences in the magnitude of clinical outcomes between men and women, but the guidelines for statin therapy are similar for both genders. Guidelines recommend statin therapy in adults between the ages of 40 and 75 years who have – LDL cholesterol >189 mg/dL, LDL cholesterol of 70–189 mg/dL in patients with diabetes, and estimated 10-year CVD risk of >7.5%.

A report from the center for disease control noted that nearly 33% of women are eligible for statin therapy, but in only 58% were statins prescribed reflecting a gap between theory and practice of preventive cardiology. The safety and benefits of statin therapy are similar for men and women. In the JUPITER trial (which enrolled substantial number of women), statin associated myopathy was similar in women and men. However, new-onset diabetes development was more in women; a majority of women with incident (new onset) diabetes had impaired fasting glucose at the baseline. It is fair to conclude, however, that the benefits of statin therapy exceed possible adverse effects on glucose metabolism.

Aspirin

Aspirin (ASA) is a proven therapy for secondary prevention of CVD for both men and women and in the management of acute MI.[42] The data for women, however, for primary prevention of CVD are not strong. In the Women's Health Study, 40,000 healthy women were treated with ASA (100 mg) or a placebo for a decade. The study showed only a trend and a statistically non-significant reduction of CVD events. However, the risk of stroke was substantially reduced. As in men, ASA increased the chances of gastrointestinal bleeding. In women over the age of 65 years, ASA reduced the risk of CAD as well as stroke. Based on this outcome, AHA recommends ASA therapy (81 mg/day) for women >65 years with well-controlled hypertension. ASA may be beneficial in women <65 years for stroke prevention. The US Preventive Services Task Force suggests ASA (81 mg/day) for both men and women (<69 years) who have a calculated 10-year CVD risk of >10%. It is prudent to conclude that adult women with no CVD risk would not benefit from ASA therapy.

Management of CAD in Women: Treatment Disparities

Coronary artery bypass graft (CABG)

Women account for nearly a third of patients who need CABG surgery.[43] Studies suggest that certain procedural and other factors influence the graft patency and survival in women; these include but not limited to off-pump procedures and use of internal thoracic artery graft. Women historically have been reported to have a high risk for CABG compared to men. The influence of gender on CABG outcomes should be further studied in detail. There is a tendency for women to experience higher readmission rates than men and for lower rates of cardiac rehabilitation care. The precise reasons for lower cardiac rehabilitation rates among women may be multifactorial – referral pattern, medical care structure, facilities, and personal preferences. Nevertheless, cardiac rehabilitation programs should be offered consistently to all women with CAD.

PCI

A common observation is the underutilization of indicated PCI in women. Not only PCI but also medical therapy of CAD is less in women compared to men. Women benefit as much as men from PCI and surgical therapies for CAD.[44] Women are at a high risk for bleeding and other complications of PCI. Therefore, it is extremely important to weigh the benefits and risks before PCI are undertaken in women.[45,46] The benefit of PCI among women is greater if there is elevated troponin concentration. PCI therapy for low-risk women should be avoided but should be strongly considered for high-risk patients (with positive biomarkers).

Drug Therapy of CAD

Women with ACS are less likely to receive proven pharmacotherapy compared to men. Before the advent of PCI, women were unlikely to receive fibrinolytic therapy. Moreover, when they were given (indicated) fibrinolytic treatment, women experienced adverse effects. Studies have demonstrated that women with ACS are less likely to be considered for indicated pharmacotherapy even in the setting of elevated troponin levels. This trend exists despite the benefits of drug therapy in women with ACS. Furthermore, women with CAD events are less likely (than men) to be prescribed antiplatelet drugs, anticoagulants, β-blockers, and RAAS blockers.

Despite the high risk for recurrent CVD events, women with chronic stable angina are under prescribed pharmacotherapy. A substantially lower utilization of ASA, statins, and β-blockers exists in women with known CAD. We should increase the awareness of this disparity and undertake remedial therapeutic actions to improve the survival of women with CVD. Even after adjusting for all the confounding factors, women experience recurrent non-fatal and fatal events at follow-up after an acute event. Thus, it is imperative to apply evidence-based therapies aggressively for the primary and secondary prevention of CVD in women.

Conclusions

The full spectrum of CVD is pervasive among women. The lifetime risk of experiencing CVD in women older than 50 years is high, especially in the presence of risk factors. It is of paramount importance to reduce the CVD burden in women by early diagnosis, aggressive therapy, and follow-up evaluation. Risk factors such as obesity, hypertension, diabetes, smoking,

dyslipidemia, and physical activity should be tackled without any delay. The traditional risk factors for CVD are increasing at alarming rates among young women; this trend should be checked, halted, and reversed. Future research should take into consideration possible differential CVD risk pattern in women and gender-dependent clinical outcomes. CVD risk factors (such as hypertension and diabetes) identified during reproductive years should be followed carefully in the long term. Surveillance and timely therapeutic interventions will likely reduce the extent and severity of CVD in women. Menopausal transition is yet another opportunity to consider CVD assessment and prevention measures.

CVD in women is underappreciated, understudied, underdiagnosed, underprevented, and undertreated. Moreover, this trend requires urgent attention of the medical and lays communities, public policy-makers, research organizations, scientists, and drug/device companies. Unless, we embark on this wholesome pathway, CVD in women will continue to pose a public health challenge.

A multidisciplinary approach (including obstetricians and gynecologists) is needed for the early detection and treatment of CVD in women. Ironically, even for women who are already under medical care, gender-centric risk assessment is lacking. There is not only a need to recognize risk assessment in women but also to look for CVD screening and rehabilitation opportunities.[47,48] One would think that obstetrics and gynecology clinics would be an ideal base for the detection, management, and referral of patients with high CVD risk profile. It is of immense importance to identify traditional as well as gender-specific CV risk factors in women so that appropriate and timely preventive and therapeutic interventions are applied to reduce chronic CVD burden. Incorporating the available scientific evidence into current risk assessment tools for women's health is mandated as a societal obligation.

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