IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

A REVIEW ON: PHARMACOTHERAPY OF HYPERTENSION

Treatment & Combination Pharmacotherapy in Pulmonary Hypertension and Angina

[1]Mr. Amol Shinde, [2]Mrs. Pooja Bhonde, [3]Dr. Gajanan Sanap, [4]Mr. Aniket Bankar, [5]Mr. Sudarshan Chavan

[1]Student, [2]Assistant Professor, [3]Principal, [4]Student, [5]Student

[1]Department of Pharmacy,

[1]Late Bhagirathi Yashwantrao Pathrikar College of Pharmacy, Pathri, Aurangabad, 431001. Maharashtra, India.

Abstract: Hypertension will increase with growing age. Optimal remedy of high blood pressure is critical to lessen cardiovascular disease. Recent pointers for high blood pressure have made pointers for older adults however are supported through proof that consists of more youthful individuals. This systematic evaluation evaluates the harms of antihypertensive marketers in adults elderly C65 years. Eligible research covered contributors elderly C65 years with high blood pressure. Eligible research had truly described remedy assignments, blood pressure (BP) targets, and evaluated endpoints of cardiovascular morbidity, mortality, and/or harms of antihypertensive medications. We abstracted take a look at characteristics, cardiovascular blessings, and harms. Most studies as compared distinctive antihypertensive agents and/or placebo groups. These research constantly confirmed decreased cardiovascular morbidity and mortality as compared with out a treatment. Seven research tested optimal BP targets. Strict manipulate [systolic BP (SBP) 140 mmHg] became not constantly higher than mild manipulate (SBP 150 mmHg) for adults aged C65 years. Mild SBP manipulate benefitted topics in all age levels over 65 years. Few research assessed and explicitly reported harms. Hypertensive issues of pregnancy (HDP) constitute a primary purpose of maternal, fetal and neonatal morbidity and mortality and identifies women at risk for cardiovascular and different continual sicknesses later in life. When antihypertensive drugs are used during pregnancy, their benefit and damage to each mother and fetus should be evaluated.

Keywords **- Hypertension, Circadian Rhythm, Pulmonary Arterial Hypertension, Prostanoids, Anticoagulants, etc.**

I. INTRODUCTION

Despite impressive development in the closing half of the 20th century closer to the manipulate and prevention of cardiovascular disease, this disorder accounts for greater deaths international than every other non-communicable sickness[1]. Many of those deaths are premature, happening earlier than the age of sixty five years. Coronary heart disease and stroke account for almost all of cardiovascular disease–associated death, and hypertension is a main chance issue for each of those conditions. A latest record from the Centers for Disease Control and Prevention[2] shows a fashion closer to a lower in suggest blood pressure stages in the US and an boom with inside the quantity of handled sufferers with high blood pressure whose blood stress stages are managed.[2] However, about 70% of patients with hypertension do not have blood stress controlled to the aim of <140mmHg Furthermore, stroke mortality has leveled off in comparison with the last decades, and, due to the fact growing numbers of sufferers are surviving hypertension-associated diseases, consisting of myocardial infarction, heart failure is becoming a more vital health concern.[2]

These epidemiologic facts assist the want for persisted efforts in the direction of more expertise of disorder procedures so as to layout extra useful cardiovascular treatments. Chronobiology, the observe of biologic rhythms, may provide a useful alternative to traditional homeostatic therapy of high blood pressure and coronary artery disease.[3]

II. CHRONOBIOLOGY AND CIRCADIAN RHYTHM

Most bodily tactics aren't static however alternatively are in a state of flux. When those dynamics arise in 24-hour, repeating cycles, they may be termed circadian rhythms. Circadian rhythms deliver rise to prominent day–night time styles or oscillations in the concentrations of neurotransmitters, hormones, 2d messengers, and different biologic markers, and hence have an effect on the sample of ailment interest.[4-9] Figure 1 illustrates individual height physiologic variables as a characteristic of time in a regular sleep–wake cycle.[10]These versions in human physiochemical states are related to the environmental light– darkish cycle and with one's sleep– wake routine. For instance, for people with a regular sample of sunlight hours interest and middle of the night sleeping, plasma cortisol concentrations height round 0700, whereas night time-shift employees enjoy height plasma cortisol concentrations in the afternoon (corresponding to the time of awakening from daytime sleep).[11] Cardiovascular hemodynamics comply with a circadian pattern. Heart rate and blood pressure are lowest at some point of sleep and start to upward push towards the end of the sleep cycle.[12]

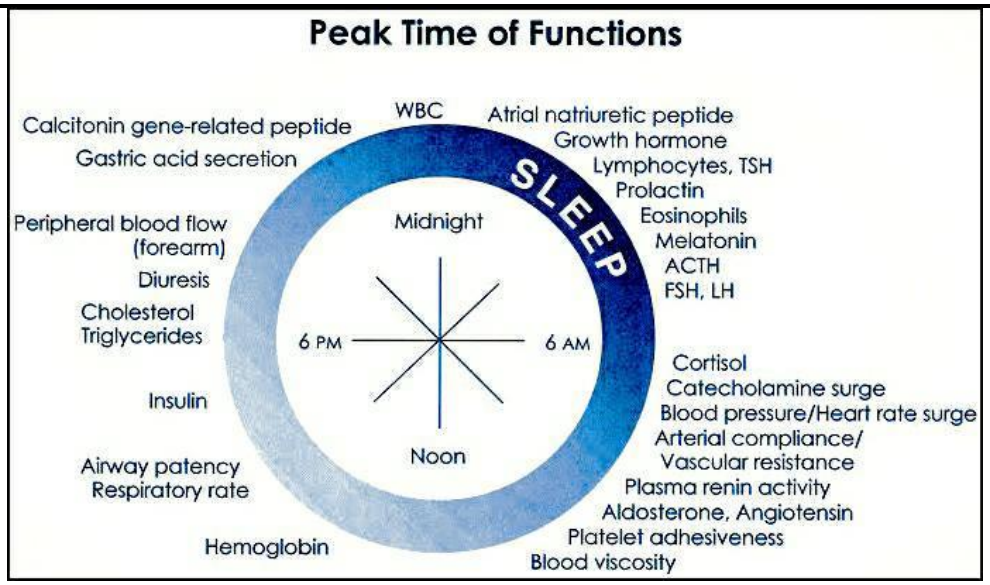

Fig. 1: - The normal 24-hour cycle of human physiologic circadian rhythms; this chronogram shows the timing of peaks of physiologic variables in people who are active during the day and sleep at night.

The rise will become exacerbated after awakening, on assuming an upright posture, and peaks in the late morning hours. These hemodynamic adjustments comply with changes in systemic concentrations of catecholamine's, cortisol, and plasma renin.[13-15] Moreover, sensitivity to such changes can be extra prominent in the early morning hours, as verified through decrease concentrations of epinephrine had to result in platelet aggregation.[13] The early-morning rise in blood pressure, heart rate, and catecholamine concentrations may disrupt the equilibrium among myocardial oxygen demand and supply. This disequilibrium may result in myocardial ischemia, with an multiplied susceptibility to cardiovascular events[16]

III. The Issue of Hypertension and It's Treatment

Hypertension stays one of the maximum crucial modifiable risk factors for cardiovascular and renal mortality and morbidity in the industrialized world [17-19]. There is indisputable evidence from large, population-primarily based totally studies showing a non-stop affiliation among the upward thrust in blood strain and the upward thrust in the hazard of cardiovascular activities and end-stage renal disease [20, 21]. Even a small rise in blood pressure is related to a proportional and widespread effect on risk of loss of life from coronary heart disorder or stroke [4]. A latest meta-analysis of 61 potential observational research trials concerning 1,000,000 topics elderly 40– 69 years clearly showed an immediate dating between blood pressure and the cardiovascular risk, beginning from blood pressure levels as little as 115/ 75 mm Hg (systolic/diastolic) and doubling for every incremental rise in blood strain by 20/ 10 mm Hg [20]. Physicians should be proud of the development that has been made in scientific hypertension research, due to the fact the proof base that confirmed the benefits of antihypertensive treatment in preventing cardiovascular activities is one of the most powerful in medicine. In the closing four many years a complete of 17 prospective randomized final results trials that protected 47,653 hypertensive subjects as compared antihypertensive drug treatment towards placebo or occasionally rare remedy [21, 22]. Metaanalyses of trials in systolic–diastolic and isolated systolic hypertension showed a marked reduction with inside the risk of stroke and coronary heart activities and of cardiovascular and all-reason death (Table 1) [6–10].

Furthermore, numerous potential randomized managed trials evaluated the results of various antihypertensive drug regimens on primary cardiovascular activities and additionally proven incredible protection (Table 2) [21–25]. On the premise of this incredible database of trials, all hypertension societies and country wide groups withinside the US, Europe and some other place suggest that, in all hypertensive adults, blood strain ought to be decreased with treatment to the extent of< 140mmHg. (systolic/diastolic).The hypertension can also be treated by using the indian ancient system of medicine like unani medicines, but they cannot be used in emergency cases. Although, the researchers also proven that, there are some essential effect of polyunsaturated fatty acids (PUFA'S) on prevention of hypertension in human's.[55,56]

IV. The Issue of Hypertension Control

Hypertension remains an increasingly critical and unresolved clinical and public-health issue international [17-18]. A current evaluate confirmed that during 2000 the prevalence of hypertension in the grownup population worldwide become approximately 25% (972 million subjects) and that in 2025 this proportion is expected to increase to 29.2% (1.56 billion subjects) [27].Unfortunately, countrywide surveys in numerous international locations continually confirmed negative stages of awareness, remedy and manipulate of high blood pressure with inside the fashionable population [28]. Studies in number one care have proven negative overall performance of practitioners in achieving the encouraged blood strain goals [29, 30]. A huge examine in number one care in France (PRATIK) [29], which evaluated using antihypertensive pharmacotherapy in sufferers with out of control high blood pressure, confirmed that manipulate charges had been in fashionable negative, and had been worse in high-threat sufferers (27% controlled) compared to moderate-threat (31%) or low-threat sufferers (43%). In the Aggressive Blood Pressure Control in General Practice Study (ABC-GP) in Greece [21], after 6 months of intervention to govern high blood pressure the bulk of sufferers (85%) had reached the encouraged diastolic blood strain goal, while simplest 50% the systolic, and no in addition development on top of things charges changed into accomplished at nine months. Clinical inertia is appeared as one of the most important motives for the negative charges of high blood pressure manipulate [17]. Several research counseled that physicians might. now no longer be competitive sufficient in treating high blood pressure, specifically concerning the systolic blood strain [29–34]. It appears that there's nevertheless a few uncertainty amongst number one care physicians approximately the significance of lowering expanded blood strain, specifically systolic, which might also additionally explain, as a minimum in part, the negative stages of high blood pressure manipulate with

inside the population [35]. Physician-associated obstacles may not be the only purpose for the ineffective control of hypertension. This is usually recommended through a meta-evaluation of managed outcome trials of antihypertensive treatment that confirmed performed common blood pressure to be nicely above the encouraged goal, in particular for systolic blood pressure [35]. The authors of this evaluate concluded that even in the context of final results trials, in which patients' compliance and physicians' expertise are ensured, systolic blood pressure manage is neither regularly nor effortlessly achieved.

Table 1: - Lipid: Cardiovascular Endpoint's

LIPID: Cardiovascular Endpoints
Post-MI or Unstable Angina Patients with Average/raised Cholesterol

Outcomes	Number of events			
	placebo (*n=4502*)	pravastatin (*n=4512*)	Risk reduction (%)	*p*-value
CHD death*	373	287	24	<0.001
CVD death	433	331	25	<0.001
All-cause mortality	633	498	22	<0.001
CHD death or non-fatal MI	715	557	24	<0.001
Any MI	463	336	29	<0.001
PCTA or CABG	708	585	20	<0.001
Hosp. for unstable angina	1106	1005	12	0.005
Stroke	204	169	19	0.048

* primary endpoint

V. The Choice of Antihypertensive Drugs

In the last 30 years a lot of discussion has been raised and extensive attempt targeting the problem of the ''quality antihypertensive drug''. Using an proof based-method that requires the selection of antihypertensive therapy to be based solely on final results trial data, in 2003 the 7th record of America. A Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) [17], the European Society of Hypertension–European Society of Cardiology (ESH/ESC) guidelines [18] and the World Health Organization/International Society of Hypertension (WHO/ISH) guidelines [19], all advocated using diuretics, beta-blockers, angiotensin changing enzyme (ACE) inhibitors, calcium antagonists and angiotensin receptor blockers as first line treatment in the control of hypertension [28]. However, in the JNC-7 record, diuretics had been located one step forward and had been advocated as first therapy ''for the most'' whilst there are no compelling indications for different drug classes [17]. This role of the JNC-7 is stated to be in large part based at the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) [36]. However, in the ALLHAT no distinction become observed among the diuretic arm and the ACE inhibitor or the calcium antagonist arms concerning the primary endpoint (coronary events) on the basis of which the observe become designed [36]. Although diuretics regarded to be advanced to the opposite drugs in regard to numerous secondary endpoints, those findings had been confounded by variations in executed blood pressure and different factors [36]. Although diuretics regarded to be advanced to the alternative drugs in regard to numerous secondary endpoints, those findings had been confounded through variations in achieved blood pressure and different factors [36]. are drawbacks in the use of those drugs, which remain controversial. Their damaging metabolic effects, which includes hyperglycemia, won't translate right into a medical circumstance in the context of a trial that lasts best 3–five years [36]. However, in the long-time period they may have a significant effect at the risk of death [37].

There are critical motives why in lots of sufferers the selection of the preliminary antihypertensive drug is probably of secondary importance. First, meta-analysis of the final results studies in hypertension furnished convincing proof that the benefits of antihypertensive treatment are in large part attributed to the discount of the raised blood stress according to se as an alternative that to specific drug class effects [24]. Second, which will manage hypertension, combination pharmacotherapy is needed in the majority of hypertensive sufferers [33, 34]. Therefore, for almost all of patients without a compelling indication for a particular class of drug, the selection have to be most of the 5 essential classes and be stimulated by the individuals' cardiovascular risk profile, presence of target organ damage, related medical situations and cost [17-19]. Every attempt have to be made in order to acquire most efficient blood pressure manipulate by systematic and in depth titration of treatment and effective use of combination pharmacotherapy in the majority of hypertensive patients. The presence of cardiovascular disease allows the selection of antihypertensive drugs due to installed specific useful properties of numerous drug classes [17-19]. On the idea of final results trial data, there are compelling indicators for specific antihypertensive drug classes, inclusive of the usage of beta-blockers and ACE inhibitors after myocardial infarction and in heart failure (ACE inhibitors also in left ventricular dysfunction) and of ACE inhibitors and angiotensin receptor blockers in persistent kidney disorder [17-19]. By immediately translating final results data into exercise guidelines, the ESH–ESC [18] and the WHO–ISH [19] recommended in diabetic nephropathy a preference for ACE inhibitors in type-1 and for angiotensin

receptor blockers in type-2 diabetes. The JNC-7 [17] took a extra liberal position with the aid of using recommending the usage of both an ACE inhibitor or an angiotensin receptor blocker in diabetic nephropathy, regardless of the form of diabetes. It have to be referred to that, at present, none of the guidelines recommends a particular class of antihypertensive drugs in diabetic sufferers with everyday renal function. In sufferers with a history of stroke diuretics and ACE inhibitors is probably the first choice [19], while in those with left ventricular hypertrophy angiotensin receptor blockers is probably preferred [18]

VI. Current Drugs for Pulmonary Arterial Hypertension

The current treatments for iPAH target signal pathways tested to be concerned with inside the disease's pathophysiology (Box 2). Ultimately, everyday life expectancy and everyday quality of life are the objectives of therapy. Realistically, transferring sufferers to a low risk of mortality with, at worst, moderate useful limitation (NYHA Class IeII) is the existing target of therapy.24 Patients whose PH can be Group 1 or Group four in aetiology should be stated a specialized PH centre for diagnosis and treatment. Patient education and use of professional centre guide are crucial for most suitable consequences and minimum side effects the use of presently available drug treatments[38]

1. Calcium Channel Blockers

There is a small institution of sufferers with iPAH (6%) who appear to reply nicely to excessive doses of dihydropyridine calcium channel blockers and who may also have long lasting advantage from this therapy.25 These sufferers are recognized the use of a vasodilator challenge on the time of proper heart catheterization. Patients with out a acute vasodilator response must not be dealt with excessive dose calcium channel blockers.

2. Endothelin Receptor Antagonists

The oral endothelin receptor antagonists (ERAs) bosentan and ambrisentan (and the more recent ERA macitentan) inhibit the sign pathway by blocking endothelin receptors. Monotherapy with bosentan and ambrisentan has produced upgrades in 6MWD, PVR and time to scientific deterioration.[39,40]

3. Phosphodiesterase Type 5 Inhibitors

Phosphodiesterase type 5 (PDE5) breaks down cyclic guanosine monophosphate (cGMP) and consequently decreases the vasodilator outcomes of nitric oxide. The oral PDE5 inhibitors sildenafil and tadalafil lower cGMP degradation, which will increase the interest of the nitric oxide system and clinically improves 6MWD inpatients with iPAH.[41,42] Tadalafil also will increase time to scientific deterioration as compared with placebo.[43]

4. Prostanoids

The main prostanoids used in Australia are epoprostenol and iloprost. Epoprostenol is the only single agent for remedy of PAH, however it calls for shipping of a non-stop intravenous infusion via a central venous catheter. It has been proven to enhance 6MWD, hemodynamics, quality of existence and survival.[44] Recently, a extra thermostable components of epoprostenol has become available, which can be extra convenient to use because it eliminates the want for a cold percent to keep the drug's temperature at the required level. Inhaled iloprost improves functional class, 6MWD and time to scientific deterioration,[45] however requires up to 9 inhalations per day.

5. Anticoagulants

Early pathological studies confirmed thrombosis inside small lung vessels in sufferers with PAH,[46] main to treatment with anticoagulants turning into a part of general therapy. Anticoagulation in sufferers with iPAH can be of benefit, with a few observational collection indicating enhancements in survival, however uncertainty persists because of the low stage of evidence.[47] Use of anticoagulation in sufferers with PAH and scleroderma is greater controversial.[48] Recent suggestions for the treatment of iPAH state that oral anticoagulation with warfarin can be considered in treatment algorithms.

VII. New Drugs for Pulmonary Arterial Hypertension

While calcium channel blockers, intravenous epoprostenol, the oral ERAs bosentan and ambrisentan, and PDE5 inhibitors sildenafil and tadalafil are properly mounted within the treatment of iPAH in Australia, new pills have these days been added or will quickly to be had. Direct contrast with presently to be had remedies is hard, as maximum present day remedies had been examined in especially small trials of brief duration, the usage of surrogate endpoints primarily based totally in large part on hemodynamic or useful measures. In contrast, trials of more recent retailers had been large and in lots of instances have used mortality and morbidity endpoints, together with time to scientific deterioration, to illustrate efficacy. Direct contrast is likewise hard because of the extensive use of history PAH cures in current studies.[49]

Macitentan

Macitentan is a these days delivered non-selective ERA advanced with the aims of enhancing effectiveness and lowering the side effects, toxicities and drug interactions related to in advance ERAs. Macitentan has been assessed in the SERAPHIN trial, the most important RCT of ERAs, wherein macitentan doses (3 mg and 10 mg) have been as compared with placebo in 742 patients with Group 1 PH over a mean treatment duration of a hundred and fifteen weeks.[50] Occurrence of the primary outcome (first incidence of a composite of death, lung transplantation, atrial septostomy, initiation of intravenous or subcutaneous prostanoids, or worsening of PAH) become decreased by 30% (P ¼ 0.01) with three mg and by 45% (P < 0.001) with 10 mg of macitentan. This become in general pushed by a discount in incidence of worsening of PAH. Worsening of PAH become described as a lower in 6MWD of at the least 15%, worsening of PAH signs and the want for added PAH treatment. Reductions in hospitalization were also visible with macitentan treatment. About -thirds of sufferers on this study have been already taking different PAH treatments, predominantly PDE5 inhibitors, with the final 1/3 taking the study drug as monotherapy. Improved results with macitentan have been visible in each the treatment-naive sufferers and people the usage of mixture therapy.[50]

Riociguat

The effectiveness of PDE5 inhibitors can be restricted because PAH is a state of nitric oxide deficiency, and inhibiting breakdown of the already decreased tiers of cGMP won't be the simplest strategy. Riociguat acts immediately to stimulate soluble guanylate cyclase and accordingly growth cGMP impartial of nitric oxide tiers.[51] Riociguat has been examined in patients with Group 1 PH in the PATENT-1 trial.[52] This take a look at as compared doses of riociguat with placebo in 443 sufferers, of whom 1/2 of had been remedy naive. Most of these taking the energetic drug had been dealt with with 2.five mg 3 instances a day (254 sufferers). Riociguat led to a placebo-corrected growth in 6MWD of 36 m after 12 weeks of treatment ($P < 0.001$). In addition, upgrades had been visible in PVR, time to medical deterioration, practical class, N-terminal pro-mind natriuretic peptide levels and quality of existence with riociguat treatment.[52]

Selexipag

Although intravenous epoprostenol is a highly powerful treatment for PAH, the logistics and infective complications related to continual intravenous management restrict its use.[44] Other intravenous, oral and subcutaneous prostanoids were constrained by problems of their management or insupportable facet effects.[45,53] More recently, a non-prostanoid prostacyclin receptor agonist, selexipag, has been studied in sufferers with PAH. The 1152 sufferers with Group 1 PH withinside the event-pushed GRIPHON trial have been randomly allotted to obtain selexipag or placebo and observed for an average of 70.7 and 63.7 weeks, respectively. About 80% have been already the use of particular PAH therapies, and the last 20% have been treatment naive. Selexipag changed into uptitrated to 1600 mg two times every day or the very best tolerated dose. Selexipag treatment changed into related to a 40% decrease hazard of the primary composite endpoint of death, hospitalization for PAH, disorder progression, initiation of parenteral prostanoid or long time oxygen therapy, or lung transplantation. The importance of advantage did now no longer vary throughout one of a kind performed doses, suggesting that the most tolerated dose is the correct dose for the patient. Several side effects, which includes jaw pain, nausea, diarrhoea, vomiting and myalgia, have been extra common in the ones handled with selexipag

Combination therapy

In diseases consisting of cancer, human immunodeficiency virus, systemic hypertension and heart failure, treatment with mixtures of medication has demonstrated to be extra effective than treatment with a single agent. There is now proof that combining precise therapies for PAH is extra effective than monotherapy. Combination remedy can be used both sequentially or as preliminary remedy on the time of diagnosis. The most powerful proof for preliminary aggregate therapy comes from the AMBITION trial, which confirmed that an preliminary aggregate of ambrisentan and tadalafil turned into advanced to both agent alone, with a 50% discount in the incidence of a primary endpoint occasion (first occasion of medical failure) for the ones taking aggregate therapy in comparison with the monotherapy group.[54] There have been additionally useful consequences on secondary endpoints.

VIII. CONCLUSION

Uncontrolled hypertension stays a prime fitness problem with negative levels of optimal manipulate worldwide. In order to attain the presently recommended blood pressure goals, mixture pharmacotherapy with or greater drugs is needed in the majority of hypertensive patients, mainly those with a goal of<130mmHg Further to the potentiation of the antihypertensive results, benefits of aggregate therapy consist of the ability of fewer adverse affects and of development of sufferers' compliance. Current guidelines recommend that aggregate pharmacotherapy may additionally be considered for treatment initiation in sufferers with considerable elevation of blood pressure and proof of complications. Several powerful and well-tolerated antihypertensive drug classes to be had these days provide more than one alternatives for aggregate remedy. The preference of antihypertensive agents ought to be made on the basis of current tips concerning first line drugs and compelling indications. Specific drug combinations might have extra useful or adverse long-time period metabolic results, past their results on blood pressure. However, greater final results data evaluating antihypertensive drug mixtures are required. The beyond 10 years have seen the introduction into routine scientific exercise of recent oral and intravenous healing procedures for PAH.

REFERENCES

[1] World Health Organization. The world health report: 1999: making a difference. World Health Organization; 1999.

[2] Centers for Disease Control and Prevention (CDC. Decline in deaths from heart disease and stroke--United States, 1900-1999. MMWR. Morbidity and mortality weekly report. 1999 Aug 6;48(30):649-56.

[3] Joint National Committee on Detection, Treatment of High Blood Pressure, National High Blood Pressure Education Program. Coordinating Committee. Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. National Heart, Lung, and Blood Institute, National High Blood Pressure Education Program.; 1995.

[4] Smolensky MH. Chronobiology and chronotherapeutics applications to cardiovascular medicine. American journal of hypertension. 1996 Apr 1;9(4):11S-21S.

[5] Lemmer B. Chronopharmacology: time, a key in drug treatment. InAnnales de biologie clinique 1994 Jan 1 (Vol. 52, No. 1, pp. 1-8). Paris, Expansion scientifique francaise..

[6] LEMMER B. The clinical relevance of chronopharmacology in therapeutics. Pharmacological research. 1996 Feb 1;33(2):107-15.

[7] Reinberg AE. Concepts of circadian chronopharmacology. Annals of the New York Academy of Sciences. 1991 Jan 1;618:102-15.

[8] Tamura K. Chronobiologic evaluation of drug efficacy in hypertension. Chronobiology international. 1991 Jan 1;8(6):511-25.

[9] Cooke HM, Lynch A. Biorhythms and chronotherapy in cardiovascular disease. American Journal of Health-System Pharmacy. 1994 Oct 15;51(20):2569-80.

[10] Smolensky MH, D'Alonzo GE, Portman R. Chronobiology and chronotherapeutics: new concepts in cardiovascular medicine. J Am Osteopath Assoc. 1998;98:S6-16.

[11] Smolensky MH, D'alonzo GE. Medical chronobiology: concepts and applications. American Review of Respiratory Disease. 1993 Jun 1;147:S2-.

[12] Millar-Craig M, Bishop C, Raftery EB. Circadian variation of blood-pressure. The Lancet. 1978 Apr 15;311(8068):795-7.

[13] Tofler GH, Brezinski D, Schafer AI, Czeisler CA, Rutherford JD, Willich SN, Gleason RE, Williams GH, Muller JE. Concurrent morning increase in platelet aggregability and the risk of myocardial infarction and sudden cardiac death. New England Journal of Medicine. 1987 Jun 11;316(24):1514-8.

[14] Weitzman ED, Fukushima D, Nogeire C, Roffwarg H, Gallagher TF, Hellman L. Twenty-four hour pattern of the episodic secretion of cortisol in normal subjects. The Journal of Clinical Endocrinology & Metabolism. 1971 Jul 1;33(1):14-22.

[15] Gordon RD, Wolfe LK, Island DP, Liddle GW. A diurnal rhythm in plasma renin activity in man. The Journal of clinical investigation. 1966 Oct 1;45(10):1587-92.

[16] Rocco MB, Nabel EG, Selwyn AP. Circadian rhythms and coronary artery disease. The American Journal of Cardiology. 1987 Mar 9;59(7):C13-7.

[17] Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo Jr JL, Jones DW, Materson BJ, Oparil S, Wright Jr JT, Roccella EJ. Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. hypertension. 2003 Dec 1;42(6):1206-52.

[18] Mancia G, Grassi G. The new European society of hypertension/European society of cardiology (ESH/ESC) guidelines. Therapeutic advances in cardiovascular disease. 2008 Feb;2(1):5-12.

[19] World Health Organization, International Society of Hypertension Writing Group. 2003 World Health Organization (WHO)/International Society of Hypertension (ISH) statement on management of hypertension. Journal of hypertension. 2003 Nov 1;21(11):1983-92.

[20] Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. The Lancet. 2002 Dec 14;360(9349):1903-13.

[21] Klag MJ, Whelton PK, Randall BL, Neaton JD, Brancati FL, Ford CE, Shulman NB, Stamler J. Blood pressure and end-stage renal disease in men. New England Journal of Medicine. 1996 Jan 4;334(1):13-8.

[22] Collins R, MacMahon S. Blood pressure, antihypertensive drug treatment and the risks of stroke and of coronary heart disease. British medical bulletin. 1994 Jan 1;50(2):272-98.

[23] Staessen JA, Gasowski J, Wang JG, Thijs L, Den Hond E, Boissel JP, Coope J, Ekbom T, Gueyffier F, Liu L, Kerlikowske K. Risks of untreated and treated isolated systolic hypertension in the elderly: meta-analysis of outcome trials. The Lancet. 2000 Mar 11;355(9207):865-72.

[24] Staessen JA, Wang JG, Thijs L. Cardiovascular prevention and blood pressure reduction: a quantitative overview updated until 1 March 2003. Journal of hypertension. 2003 Jun 1;21(6):1055-76.

[25] Zanchetti A. Evidence-based medicine in hypertension: what type of evidence?. Journal of hypertension. 2005 Jun 1;23(6):1113-20.

[26] Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. The Lancet. 2003 Nov 8;362(9395):1527-35.

[27] Julius S, Kjeldsen SE, Weber M, Brunner HR, Ekman S, Hansson L, Hua T, Laragh J, McInnes GT, Mitchell L, Plat F. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. The Lancet. 2004 Jun 19;363(9426):2022-31.

[28] Powrie RO. Tentative de conception d'une femme de 30 ans avec hypertension chronique. JAMA-français. 2007 Oct 3;298(13):1548.

[29] Hansson L, Zanchetti A, Carruthers SG, Dahlöf B, Elmfeldt D, Julius S, Ménard J, Rahn KH, Wedel H, Westerling S, HOT Study Group. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. The Lancet. 1998 Jun 13;351(9118):1755-62.

[30] UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. Bmj. 1998 Sep 12;317(7160):703-13.

[31] Bakris GL. National Kidney Foundation Hypertension and Diabetes Executive Committees Working Group. Preserving renal function in adults with hypertension and diabetes: a consensus approach. Am J Kidney Dis. 2000;36:646-61.

[32] Nissen SE. CAMELOT Investigators. Effect of antihypertensive agents on cardiovascular events in patients with coronary disease and normal blood pressure: The CAMELOT study: A randomized control trial. Jama. 2004;292:2217-25.

[33] Zanchetti A, Grassi G, Mancia G. When should antihypertensive drug treatment be initiated and to what levels should systolic blood pressure be lowered? A critical reappraisal. Journal of hypertension. 2009 May 1;27(5):923-34.

[34] Mancia G, Grassi G. Systolic and diastolic blood pressure control in antihypertensive drug trials. Journal of hypertension. 2002 Aug 1;20(8):1461-4.

[35] Appel LJ. The verdict from ALLHAT—thiazide diuretics are the preferred initial therapy for hypertension. Jama. 2002 Dec 18;288(23):3039-42.

[36] Verdecchia P, Reboldi G, Angeli F, Borgioni C, Gattobigio R, Filippucci L, Norgiolini S, Bracco C, Porcellati C. Adverse prognostic significance of new diabetes in treated hypertensive subjects. Hypertension. 2004 May 1;43(5):963-9.

[37] LEE RE, SELIGMANN AM, GOEBEL D, FULTON LA, CLARK MA. RESERPINE-HYDRALAZINE COMBINATION THERAPY OF HYPERTENSIVE DISEASE, WITH HYDRALAZINE IN DOSES GENERALLY BELOW THE" TOXIC RANGE". Annals of internal medicine. 1956 Mar 1;44(3):456-65.

[38] McLaughlin VV, Gaine SP, Howard LS, Leuchte HH, Mathier MA, Mehta S, Palazzini M, Park MH, Tapson VF, Sitbon O. Treatment goals of pulmonary hypertension. Journal of the American College of Cardiology. 2013 Dec 24;62(25S):D73-81.

[39] Rich S, Kaufmann E, Levy PS. The effect of high doses of calcium-channel blockers on survival in primary pulmonary hypertension. New England Journal of Medicine. 1992 Jul 9;327(2):76-81.

[40] Rubin LJ, Badesch DB, Barst RJ, Galiè N, Black CM, Keogh A, Pulido T, Frost A, Roux S, Leconte I, Landzberg M. Bosentan therapy for pulmonary arterial hypertension. New England Journal of Medicine. 2002 Mar 21;346(12):896-903.

[41] Galiè N, Olschewski H, Oudiz RJ, Torres F, Frost A, Ghofrani HA, Badesch DB, McGoon MD, McLaughlin VV, Roecker EB, Gerber MJ. Ambrisentan for the treatment of pulmonary arterial hypertension: results of the ambrisentan in pulmonary arterial hypertension, randomized, double-blind, placebo-controlled, multicenter, efficacy (ARIES) study 1 and 2. Circulation. 2008 Jun 10;117(23):3010-9.

[42] Galiè N, Ghofrani HA, Torbicki A, Barst RJ, Rubin LJ, Badesch D, Fleming T, Parpia T, Burgess G, Branzi A, Grimminger F. Sildenafil citrate therapy for pulmonary arterial hypertension. New England Journal of Medicine. 2005 Nov 17;353(20):2148-57.

[43] Galiè N, Brundage BH, Ghofrani HA, Oudiz RJ, Simonneau G, Safdar Z, Shapiro S, White RJ, Chan M, Beardsworth A, Frumkin L. Tadalafil therapy for pulmonary arterial hypertension. Circulation. 2009 Jun 9;119(22):2894-903.

[44] Barst RJ, Rubin LJ, Long WA, McGoon MD, Rich S, Badesch DB, Groves BM, Tapson VF, Bourge RC, Brundage BH, Koerner SK. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. New England Journal of Medicine. 1996 Feb 1;334(5):296-301.

[45] Olschewski H, Simonneau G, Galiè N, Higenbottam T, Naeije R, Rubin LJ, Nikkho S, Speich R, Hoeper MM, Behr J, Winkler J. Inhaled iloprost for severe pulmonary hypertension. New England Journal of Medicine. 2002 Aug 1;347(5):322-9.

[46] Wagenvoort CA, WAGENVOORT N. Primary pulmonary hypertension: a pathologic study of the lung vessels in 156 clinically diagnosed cases. Circulation. 1970 Dec;42(6):1163-84.

[47] Olsson KM, Delcroix M, Ghofrani HA, Tiede H, Huscher D, Speich R, Grünig E, Staehler G, Rosenkranz S, Halank M, Held M. Anticoagulation and survival in pulmonary arterial hypertension: results from the Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA). Circulation. 2014 Jan 7;129(1):57-65.

[48] Nikpour M, Stevens W, Proudman SM, Buchbinder R, Prior D, Zochling J, Williams T, Gabbay E, Nandurkar H. Should patients with systemic sclerosis-related pulmonary arterial hypertension be anticoagulated?. Internal Medicine Journal. 2013 May;43(5):599-603.

[49] Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk Noordegraaf A, Beghetti M, Ghofrani A. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: the joint task force for the diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). European heart journal. 2016 Jan 1;37(1):67-119.

[50] Pulido T, Adzerikho I, Channick RN, Delcroix M, Galiè N, Ghofrani HA, Jansa P, Jing ZC, Le Brun FO, Mehta S, Mittelholzer CM. Macitentan and morbidity and mortality in pulmonary arterial hypertension. N engl j med. 2013 Aug 29;369:809-18.

[51] Grimminger F, Weimann G, Frey R, Voswinckel R, Thamm M, Bölkow D, Weissmann N, Mück W, Unger S, Wensing G, Schermuly RT. First acute haemodynamic study of soluble guanylate cyclase stimulator riociguat in pulmonary hypertension. European Respiratory Journal. 2009 Apr 1;33(4):785-92.

[52] Ghofrani HA, Galiè N, Grimminger F, Grünig E, Humbert M, Jing ZC, Keogh AM, Langleben D, Kilama MO, Fritsch A, Neuser D. Riociguat for the treatment of pulmonary arterial hypertension. N Engl J Med. 2013 Jul 25;369:330-40..

[53] Galiè N, Corris PA, Frost A, Girgis RE, Granton J, Jing ZC, Klepetko W, McGoon MD, McLaughlin VV, Preston IR, Rubin LJ. Updated treatment algorithm of pulmonary arterial hypertension. Journal of the American College of Cardiology. 2013 Dec 24;62(25S):D60-72.

[54] Galiè N, Barberà JA, Frost AE, Ghofrani HA, Hoeper MM, McLaughlin VV, Peacock AJ, Simonneau G, Vachiery JL, Grünig E, Oudiz RJ. Initial use of ambrisentan plus tadalafil in pulmonary arterial hypertension. New England Journal of Medicine. 2015 Aug 27;373(9):834-44.

[55] Joshi U, Chishty E, Sanap G. A detail on unani system of medicine. International Journal of Creative Research Thoughts (IJCRT). 2021 Dec 12;9:c785-c796.

[56] Mali AA, Chavan SA, Sanap G. A review on edible fats & oils. International Journal of Creative Research Thoughts (IJCRT). 2022 Feb 2;10:a852-a859.