A REVIEW ON: PHARMACOTHERAPY OF HYPERTENSION

Treatment & Combination Pharmacotherapy in Pulmonary Hypertension and Angina

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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]
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 indubitable 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 withinside 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 ≤140/90 Hg, (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

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Number of events</th>
<th>Placebo (n=4502)</th>
<th>Pravastin (n=4512)</th>
<th>Risk reduction (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD death*</td>
<td>373</td>
<td>287</td>
<td>24</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>CVD death</td>
<td>433</td>
<td>331</td>
<td>25</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>633</td>
<td>468</td>
<td>22</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>CHD death or non-fatal MI</td>
<td>715</td>
<td>657</td>
<td>24</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Any MI</td>
<td>463</td>
<td>336</td>
<td>29</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>PCTA or CABG</td>
<td>708</td>
<td>585</td>
<td>20</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Hosp. for unstable angina</td>
<td>1106</td>
<td>1003</td>
<td>12</td>
<td>0.005</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>204</td>
<td>169</td>
<td>19</td>
<td>0.048</td>
<td></td>
</tr>
</tbody>
</table>

* 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 alternative 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 alternate 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 3–5 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 see 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 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 every day 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, every day 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 receptor blockers. 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 examin...
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 2.5 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 remedy 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, benefi of PAH. 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 2.5 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]

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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


