Treatment in Hypertension: Non-Pharmacologic and Pharmacologic Approach

Amanda Tiksnadi, MD

Abstract

The goal of hypertension treatment is to lower high blood pressure and protects important organs, like the brain, heart, and kidneys from damage. Many researches revealed that treatment for hypertension has been associated with reductions in stroke (35-40%), heart attack (20-25%), and heart failure (> 50%).

In general, either non-pharmacological or pharmacological approach or both is used to treat hypertension, depends on the initial level of risk. Non-pharmacological approach is all about lifestyle changes, which includes maintain a healthy diet and weight, physical exercise, and reduce sodium and alcohol intake, smoking cessation, etc. It is recommended for all groups of CV risk stratification: low, moderate, high, and very high risk.

Pharmacological approach needs more special medical consideration, e.g. when to initiate drug treatment, blood pressure target treatment, which drug to start, use of combination treatment, etc.

The decision on when to start pharmacological treatment strategies all importantly depends on the initial level of risk. Blood pressure target treatment should consider co-existing diabetic and other associated clinical conditions such as stroke, myocardial infarction, renal dysfunction, and proteinuria. There are conditions favoring use of some antihypertensive drugs versus others. There are also some possible combinations between some classes of antihypertensive that proven to be beneficial in treating hypertension.

EXTENDED ABSTRACT

Blood Pressure Variability : The Importance in Hypertension and How to Control It.

Arieska Ann Soenarta,MD,FIHA

Recommendations of major guidelines in hypertension(HT) diagnosis and managementare still based on isolated clinical bloodpressure (BP) measurements. The evaluation of BP relatedcardiovascular (CV) risk is based to the assessment of mean BP values.(1)

Mean BP has indeed been proven to be a powerful risk factor for CV events, but data collected these years from many studies have shown that instability,fluctuation,variability in BP is of utmost important in the progression of organ damage and in triggering CV events.(1-8)

These findings were made possible thanks to the introduction of the Ambulatory BP Monitoring (ABPM).There are many advantages of this technique. More measurements than with the conventional BP measurement can be obtained,it provides a profile of BP over 24-h period, allowing identificationof BP fluctuations and informing the efficacy of anti-HT medications over 24-hperiod.(2,3.4)

BP variability is a multifaceted phenomenon.BP values may vary by more than 50-60 mmHg over 24-h.These variations originate from short-lasting pressor - and depressor episodes,from regular occurrence of higher day-time and lower night-time values, the day- night BP differences being usually around 15-20 mm Hg.(5)

BP variability (BPV) has been assessed by calculation of the standard deviation (s.d) of 24-h systolic,diastolic and mean arterial pressures. Other indices for BPV are BPV among half-hours,BPV within half-hours. BP vary also between months and seasons (*Pamela Study).*These studies also show that BPVincrease with increasing age of the subjects:studies in essential HT have shown that the s.d for 24-h rises progressively with increasing levels of BP.(5)

The mechanism of BPV is not fully known,several evidences have however showed that behavioral,neural,reflex,humoral factors,compliance to anti-HT treatment influence this phenomenon.BPV and sympathetic activity becomes progressively greater from normotensive to mild- and more severe essential HT.(5)

A recent large study have shown that BPV(the difference between BP measured at various visits) is a strong predictor of stroke and to a lesser extent to coronary events, heart failure. RothwellPM has done many studies .He concluded that BPV, whether measured on clinic visits or on ABPM, is a strong predictor of stroke and that Calcium Channel Blockers (CCB) and to a lesser extent Thiazide diuretics aresuperior to other drugs in reducing BPV,

the older beta blockers (BB) increase BPV and should only be used if there are compelling indications like Ischemic Heart Disease.(6-10)
The X-CELLENT study has shown that age,BP,heart rate variability were the major determinants of BPV. Amlodipine and IndapamideSR were the only effective anti-HT agents in reducing BPV.The mechanism underlying the reduced BPV is notyet clear. Results of the recent ASCOT-BPLA substudy (2010) showed that Amlodipine/Perindopril was more effective in reducing variability in SBP (both clinic and ABPM) than B-blocker/Thiazide in Hypertensive patients. In both treatment groups with well controlled mean BP,a five fold increased risk of vascular events was detected if their visit-to-visit variability in systolic BP was high. The better reduction in BPV explained the differences in stroke and cardiovascular events between Amlodipine/Perindopril and B-blocker/thiazide in this sub study (12)

Despite the many researches regarding BPV,there is still a need to study the mechanisms of BPV, its accurate detection and the means to reduce it. We need a readily applicable measure of variability which might be achieved by ABPM.Improved methods of collecting data to detect trends in BP in the office and home must be as well achieved, so that data could be obtained from prospective studies.

In Summary : The value of office and out-of-office BP have been demonstrated and established.Lowering mean BP, as is common in our daily practice is still of importance and should continue.Evidences have shown that long-term average of BP as well as long-term variability of BP, both provide complimentary prognostic implications.

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THE COLLABORATION IN FIGHTING HYPERTENSION AND ITS COMPLICATIONS
Cardiologist's Perspective

Anna Ulfah Rahajoe
President of Indonesian Heart Association

Introduction.

In 2008, cardiovascular disease (CVD) are responsible for over 17.3 million deaths per year (31% of the total of all annual deaths), and are the leading causes of death in the world.Deaths due to heart attacks, strokes and other types of CVDs as a proportion of total cardiovascular deaths for males and females are shown in Figures 1A and 1B, respectively.

In 2011 WHO reported in Global Atlas on Cardiovascular Disease Prevention and Control thathypertension is estimated to cause 7.5 million deaths worldwide (12.8% of the total of all annual deaths). This accounts for 57 million DALYS or 3.7% of total DALYS.

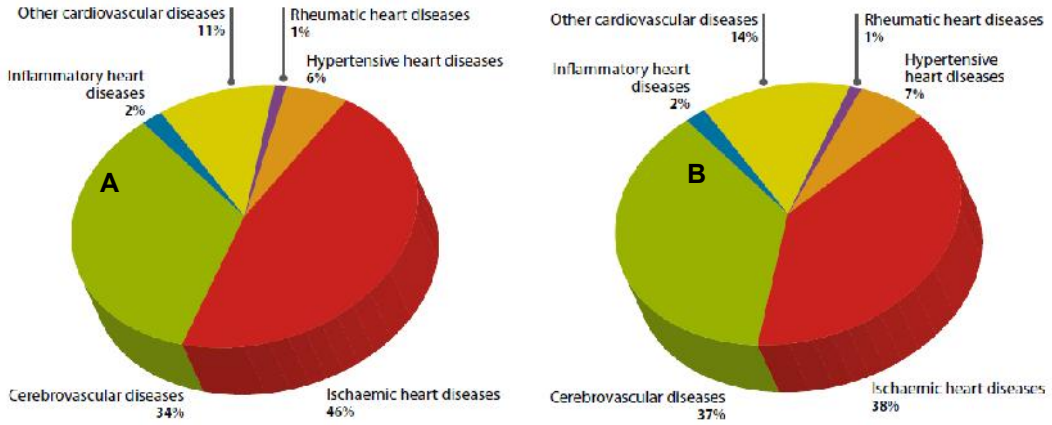

Figure 1.Distribution of cardiocerebrovascular disease deaths due to heartattacks, strokes and other types of cardiovasculardiseases in males(A) and females (B)(Adopted from : Causes of death 2008, World Health Organization)

Hypertension Complications

Hypertension places stress on several organs (called target organs), including the kidneys, eyes, brain and heart, causing them to deteriorate over time. High blood pressure contributes to 75% of all strokes and heart attacks.

Risk of complications or rapid progression of hypertension become more likely in the presence of other risk factors, including significant elevation of blood pressure, increasing age, smoking, abnormal cholesterol, family history of premature heart disease, obesity, diabetes, coronary artery disease, and other evidence of vascular disease. Hypertension must be monitored, treated and controlled by medication, lifestyle changes, or a combination of both.

Heart Complications

High blood pressure is a major risk factor for hypertensive heart disease, the leading cause of illness and death from high blood pressure. Hypertensive heart disease is a group of complications that include :

- *Coronary Artery Disease (CAD).*High blood pressure contributes to the thickening of the blood vessel walls, which can cause or worsen atherosclerosis. The end result is CAD, also called ischemic heart disease, which increases the risk for heart attack and death.

- *Heart Failure.* High blood pressure increases the heart's workload. Over time, this can cause the heart muscle to thicken. As the heart pumps against elevated pressure in the blood vessels, the left ventricle becomes enlarged and the amount of blood pumped by the heart each minute (cardiac output) goes down, a condition called left ventricular hypertrophy (LVH). Without treatment, this can lead to heart failure.

- *Cardiac Arrythmias.*High blood pressure increases the risk for cardiac arrhythmias (atrial fibrillation, premature ventricular contractions, and ventricular tachycardia).

Stroke

About two-thirds of people who suffer a first stroke have moderate elevated blood pressure ($\geq$160/95 mm Hg). Hypertensive people have up to 10 times the normal risk of stroke, depending on the severity of the blood pressure in the presence of other risk factors. Hypertension is also an important cause of so-called silent cerebral infarcts, or blockages, in the blood vessels in the brain (mini-strokes) that may predict major stroke or progress to dementia over time.

Kidney Disease

Cardiorenal syndrome (CRS) defines a condition due to combined cardiac and renal dysfunction leading to the amplification of the progression of failure of the individual organs and a bad prognosis. Hypertension causes 30% of all cases of end-stage kidney disease, leads to more cases of kidney failure. Women with GFR 30-44 ml/min/1.73m^2 and men with GFR 30-50 ml/min/1.73m^2 but without history of CVD had a hazard ratio for CVD of 1.51 that increased to 2.39 in those with CVD history. Worsening of renal function is also an independent predictor of mortality in acute decompensated heart failure (ADHF). Between 27 and 45% of subjects admitted for acute heart failure suffered an acute worsening of renal function, with an increase in serum creatinine level (0.3 mg/dl) during hospitalization. The aging of the population, the amelioration of cardiac invasive procedures leading to a better prognosis of diseases that historically had a poor outcome have resulted in increasing number of patients with combined heart and kidney failure.

Hypertensive heart disease and HF with a normal ejection fraction are common among individuals with advanced and end-stage renal disease. One study showed that there is echocardiographic evidence of left ventricular hypertrophy (LVH) in 45% of individuals with creatinine

clearance < 24 mL/min. Renal disease patients with LVH have accelerated rates of coronary events and markers of uremia compared with those with normal left ventricular mass, and a high proportion of these individuals develop clinical HF.

In patients with HF, renal dysfunction can result from intrinsic renal disease, hemodynamic abnormalities, or their combination. Cardiac pump failure leads to low cardiac output and hypotension, responsible of neurohormonal activation producing both fluid retention and vasoconstriction. However, the cardiorenal relationship is more complex than the hemodynamic model alone; activation of the renin-angiotensin system, nitric oxide, reactive oxygen species, inflammation, anemia and the sympathetic nervous system should also be taken into account.

In a recent study, found that patients with elevated intra abdominal pressure (IAP) had significantly lower baseline GFR compared with those with normal IAP, and the degree of reduction in IAP after diuresis predicted an improvement in renal function. Other initial hemodynamic parameters such as pulmonary capillary wedge pressure and cardiac index were not different between patients with elevated IAP and those with normal IAP. The concept that venous congestion, not arterial blood flow, is an important mediator of cardiorenal failure is supported by the findings of the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization. The mechanisms underlying the relationship between heart failure (HF) and renal dysfunction is shown in Figure 2.

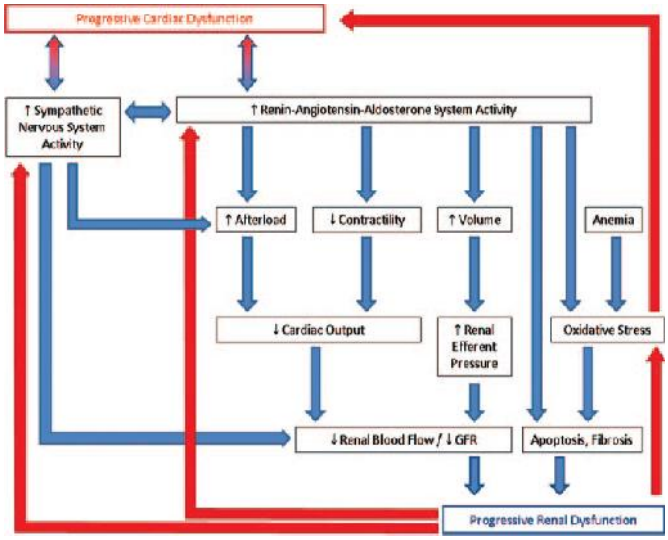

Figure 2.Postulated mechanisms underlying the relationship between heart failure (HF) and renal dysfunction. Blue arrows indicate pathways by which HF may lead to renal failure. Red arrows indicate pathways by which renal failure may lead to HF.

Cardiorenal syndrome patients were classified into 5 groups: type 1 was defined as acute cardiac decompensation leading to kidney injury, type 2 as congestive heart failure (CHF) leading to worsening renal function, type 3 as acute kidney injury leading to cardiac dysfunction, type 4 as chronic kidney disease (CKD) leading to CHF, and type 5 as systemic conditions leading to both cardiac and renal dysfunction.

Diabetes

High blood pressure, and some of the medications used to treat it, can increase the risk for developing diabetes. There are strong biologic links between insulin resistance (with or without diabetes) and hypertension. Up to 75% of cardiovascular problems in people with diabetes may be due to hypertension.The United States Preventive Services Task Force recommends screening for type 2 diabetes in all patients with blood pressure higher than 135/80 mm Hg.

People with diabetes or chronic kidney disease need to reduce their blood pressure to 130/80 mm Hg or lower to protect the heart and help prevent other complications common to both diseases.

Eye Damage

High blood pressure can injure the blood vessels in the eye's retina, causing a condition called retinopathy.

Sexual Dysfunction

Sexual dysfunction is more common and more severe in men with hypertension and in smokers than it is in the general population.

Summary

Hypertension, widespread atherosclerotic vascular damage and diabetes are significant risk factors for stroke, heart attack, heart failure and renal failure. Heart failure leads to low cardiac output and hypotension, responsible of neurohormonal activation (renin-angiotensin system, nitric oxide, reactive oxygen species, inflammation, anemia and the sympathetic nervous system) - producing fluid retention, venous congestionand vasoconstriction - important mediators of cardiorenalsyndrome.

Collaboration of multidisciplinary experts especially Cardiologist, Neurologist, Nephrologistand Diabetologistis important in prevention and control of stroke, heart attack, heart failureand renal failure because they share common risk factors and pathophysiology.

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Abstract

HYPERTENSION SYNDROME : Challenge for Better Outcomes

Dr Arieska Ann Soenarta

The guidelines in hypertension (HT) define hypertension as an elevation of arm cuff blood pressures (BP) exceeding 140/90 mmHg. Consequently to reduce Cardiovascular (CV) morbidity mortality related to HT, BP must be reduced to less than 140/90 mmHg.

Data from Framingham Study however, have shown that BP is directly related to CV events, even at levels below the definition of Hypertension by JNC-7. (1) High normal BP was associated with 7 fold increased of CV diseases. Lowering BP in the normotensive population reduces morbidity and mortality.

A meta analysis of large scale interventional studies found that a reduction in BP, decreases the risk of both fatal and non fatal stroke, but less than expected reduction was found in fatal and non fatal CV disease events. High BP is not the only cause of high CV morbidity mortality rates associated with HT. Indeed BP reduction is of utmost importance in reducing CV morbidity mortality but there are other factors contributing to the risk of CV events and death.(2)

HT is a heterogeneous complex syndrome, comprising many abnormalities. The other factors than BP is also of importance regarding the adverse outcomes of HT. These factors are : intermittent HT, BP variability, pathophysiologic heterogeneity of sustained HT, relationship between ages, systolic BP and pulse pressure, differences between cuff BP and Central Systolic Pressure in the prediction of CV events, the need to consider global CV risk in the BP management. (3)

Literatures from the past few decades show that the definition of HT has changed. The American Society of Hypertension in a paper *"Expanding the definition and classification of HT"*, stated that there is more to HT than just BP.

The JNC-6 agree that the degree of BP elevation has to be coupled to the presence or absence of other risk factors as a guide to treatment, but the JNC-7 decided to use BP cut points (>140/90mmHg) combined with a set of compelling indications. The proposed new definition of HT from the HT Writing Group is : *HT is a progressive CV syndrome arising from complex and interrelated etiologies. Early markers of the syndrome are often present before BP elevation is observed, therefore, HT can not be classified solely by BP thresholds. Progression is associated with functional and structural cardiac - and vascular abnormalities that damage the heart, kidneys, brain, vasculature, and other organs, and leads to premature morbidity and death.*(4)

Studies have shown that vascular remodeling and left ventricular hypertrophy are independent with the degree of elevated BP and may even precede increased BP, suggesting they are not in response to that elevation.

They appear to result from genetic – and environmental factors that also contribute to high BP. (5-6) The combination of elements of the HT syndrome can determine the impact of elevated BP for an individual patient. Regarding HT as a syndrome, the American Heart Association and The American College of Cardiology have stated four categories of variables to classify patients : BP, CV risk factors, early diseases markers, and target organ damage. The 2007 European Society Hypertension (ESH) Guideline for the management of arterial HT and the 2009 Updated ESH guidelines recognize the importance of the assessment of total CV risk in the management of HT to make the decision for treatment initiation.(7)

It seems that in the evaluation and treatment of hypertensive patients, we have to go beyond BP, besides still regarding the primacy of BP.

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Vascular Biology in Hypertension: Impact on Hemorheology

Ario Soeryo Kuncoro,MD

Hypertension is a one of the disease which causing significant impact to mortality and morbidity. Hypertension has been one of the common problem anywhere in the world struggling to lower the cardiovascular disease, the number one cause of mortality in the world. The number of population is clearly increasing even in the developing countries as well as Asian countries. Although hypertension not consider stand alone in increasing cardiovascular event, by improving understanding, pathophysiology of hypertension it is with big hopes that the impact to mortality will be lessened.

The understanding of hypertension process has been quite changed in the recent years. It is now believed that hypertension is part of heterogenous condition that is best described as atherosclerotic syndrome or hypertension syndrome with genetic and acquired structural and metabolic syndrome. It is estimated that around 70% of patients with genetic hypertension have one or more of the coexisting metabolic or functional disorders increasing the risk of vascular damage, atherosclerosis and target organ damage.

The deterioration of endothelial function has been discovered as the culprit of the disease. As this process will impact to the balance of vasoconstriction-vasorelaxation function as well as hemorheology role of endothelial. Endothel dysfunction has been related to increase vascular tone, increase thrombogenicity, and acceleration of atherosclerosis process in the vascular. Increase wall stress to the vascular causing remodeling process in the vascular, heightening endothelial constriction signal and worsened the disease process.

The abnormalities in coagulation and fibrinolytic pathways associated with hypertension may lead to an increased risk of thrombotic events due to enhanced coagulability and impaired fibrinolysis. The association betweeb rising blood pressure and impaired fibrinoysis in hypertensive patients is obvious. The increase level of D-dimer was found in such patients. Another prove showed by higher level of plasma fibrinogen (prothrombotic factors) in patient with left ventricle hypertrophy.

Platelets in hypertensive patients differ in terms of size, shape , volume and life span, they also demonstrate an increased tendency to aggregate. Biochemical indices released from platelets such as beta-thromboglobulin and soluble P-selectin, where these agents will increase platelet activation. Many commonly associated conditions with hypertension such as diabetes, atrial fibrillation and congestive heart failure are recognized to activate platelet aggregation.

Key words : hypertension, endothelial dysfunction, platelet aggregation, thrombogenicity

NEW INSIGHT AND RESULTS FROM RE-LY TRIAL AND NEW TREATMENT GUIDELINES FOR ANTICOAGULATION IN SPAF : THE FUTURE IS NOW

Bambang Budiono, MD
Heart & Vascular Center- Awal Bros Hospital Makassar

For more than 5 decades, warfarin has been the best, and pretty much only, oral anticoagulant for stroke prevention in atrial fibrillation (AF). Managing patients who require chronic anticoagulation is a cumbersome task, and until a few years ago, warfarin, a vitamin K antagonist, has been the only available oral anticoagulant. Warfarin treatment requires regular monitoring with prothrombin time testing, and, since it has multiple interactions with food and drugs, frequent dose adjustments are necessary. Despite regular monitoring by either patient self-management or hospital-based anticoagulation clinics, patients fall outside the desired therapeutic range about one-third of the time.

Dabigatran is going to be one of very important drugs in stroke patients with atrial fibrillation. Dabigatran will replace warfarin in a number of patients, because of its ease of use and lower rates of intracranial hemorrhage. Unlike warfarin, dabigatran, an oral reversible direct thrombin inhibitor, can be taken as a fixed daily dose regardless of age, sex, or body mass index. Only for patients with renal failure does the dose need to be adapted.

A large, open label, randomized trial, The RE-LY trial, addressed the efficacy of dabigatran versus warfarin to prevent stroke or systemic embolism in moderate- to high-risk patients with atrial fibrillation. Dabigatran dosed at 110 mg twice daily is equivalent to warfarin in efficacy but is associated with lower rates of major hemorrhage (2.7 % vs. 3.4 % per year), while dosing at 150 mg twice daily has a reduced stroke and systemic embolism rate (1.1 percent vs. 1.7 percent), with similar major hemorrhage rates. The FDA has approved dabigatran for this indication. Based on this corner stone trial, several reputable societies like, ESC, Canadian Cardiovascular Society, ACCF/AHA/HRS, had published new guidelines focus on the use of oral anticoagulant for thromboprophylaxis and recommended the use of Dabigatran as a class I (Level of evidence B) indication for stroke prevention in atrial fibrillation.

Which group of Patients will Benefit Most in Hypertension Management with Beta Blockers

Budi Yuli Setianto, MD, FIHA, FINASIM, FAsCC
Department of Cardiology and Vascular Medicine Faculty of Medicine Gadjah Mada University – Sardjito Hospital Yogyakarta

ABSTRACT.

After 2006, the use of β-blockers as first-line therapy in hypertensive patients has been somewhat controversial. Anyway, a recent review of the European Society of Hypertension guidelines shows that these agents show off similar BP lowering efficacy to other classes of agents, prompting a crosscheck of the utility of these agents in various patient populations.

Moreover to their use as a potential first-line therapy in uncomplicated hypertension, β-blockers have a particular role in patients with hypertension and comorbidities such as heart failure or coronary artery disease, hypertensive patients with increased sympathetic activity, diabetic patients with hypertension, hypertensive patients with atrial fibrillation with a rapid ventricular rate, hypertension in pregnancy. One advantage which β-blockers give is the additional protective effects in patients with prior cardiovascular events.

Some of the disadvantages associated with β-blockers appear more related to the older drugs in this class and further appraisal of the efficacy and safety profile of newer β-blockers will give support to the current guideline recommendations in in selected patient populations.

Keywords : selected patient populations – hypertension - first-line therapy - β-blockers

ACHIEVING BETTER BP CONTROL WITH BETTER ADHERENCE

EkaHarmeiwaty
National Cardiovascular Center, Harapan Kita Hospital, Jakarta

Although effective control of BP reduces the risk of cardiovascular even in patients with hypertension BP control rate (< 140/(90 mmHg) among treated patients in actual clinical practice are less optimal . According most recent result from the National Health and Nutrition Examination Survey (NHANES) 2005-2006 th estimate BP control rate among all hypertension patients is 44 % and among treated patients is 64 %.Typically about 50 % of patients discontinued antihypertension therapy after 1 year and one study assumed the median time to overall discontinuation of antihypertension drug was 3,07 years.

Non-adherence is thought to be a factor in lack of control of blood pressure and may lead to unnecessary adjustments of drug regimens and increased health care costs.Studies suggest that a treatment's efficacy is attenuated by patient non-adherence with medication and lifestyle advice.

Recognizing patient nonadherence to medical therapy as a factor leading to poor blood pressure control and adverse outcomes remains a key challenge for clinicians caring for patients with hypertension. Factors contributing to lack of adherence and persistence with antihypertension therapy have been grouped into 5 categories, ie patient related, condition related, therapy related, health system related and socioeconomic factor. Most patients need 2 or more antihypertension drug to achieving BP control and may have 1 or more comorbidities such as type 2 DM that necessitate the use of additional medication. Simplifying regimen can be accomplished by using combination therapy. Drug cost also provider another barrier to adherence to medical therapy.

To achieve better BP control need the strategy to improve the adherence and persistence to treatment ie a)prescribed drug(s) like placebo tolerability, b)use long acting drugs, c)simplifying dose regimen that can taken once daily, d) prescribe low dose combination drugs,and e)improving patient monitoring , increase acces to support and enchance patient educational

METODE PENGUKURAN TEKANAN DARAH YANG BAIK ?

Ekawati Dani yulianti

ABSTRAK

Latar Belakang : Hipertensi berdasarkan *Joint National Committee* (JNC) VII merupakan tekanan darah sistol yang sama atau melebihi 140 mmHg (≥ 140) dan atau sama atau diastol melebihi 90 mmHg (≥ 90). Berbagai faktor dapat mempengaruhi hasil pengukuran seperti faktor pasien, alat dan tempat pengukuran. Sering terjadi kesalahan pengukuran tekanan darah yang diakibatkan oleh metode yang tidak akurat, variabilitas tekanan darah yang *inherent* dan pengaruh kondisi pemeriksa.

Tujuan **:** Untuk memperoleh kontrol tekanan darah yang baik diperlukan pengukuran yang akurat dengan berbagai macam metode yang telah direkomendasi, lokasi dan persiapan pengukuran.

Metode **:** Pengukuran darah dapat menggunakan metode The Auscultatory – Mercury, Aneroid, sfigmomanometer hibrid, pemeriksaan dengan ambulatory. Lokasi pengukuran yang sering dilakukan adalah di daerah: lengan atas, pergelangan tangan yang dipengaruhi oleh tekanan hidrostatik dan jari tangan yang tidak direkomendasikan. Persiapan pengukuran dipengaruhi oleh faktor pasien, posisi tubuh, ukuran *cuff*.

Kesimpulan **:** Untuk memperoleh kontrol tekanan darah yang baik harus diperhatikan metode yang direkomendasi, lokasi dan persiapan pengukuran.

Kata Kunci : Hipertensi – Metode pengukuran– Kontrol tekanan darah yang akurat.

Ischemic Preconditioning in Diabetic Patients

Erwinanto MD
Department of Cardiology and Vascular Medicine
Division of Cardiovascular, Department of Internal Medicine
Universitas Padjadjaran School of Medicine/Hasan Sadikin Hospital
Bandung

Ischemic preconditioning (IPC) is referred to the ability of short periods of ischemia to limit infarct size. It is now evidence that IPC can lead to enhanced recovery of contractile function of the myocardial region at risk. The protective effect of IPC can last as soon as less than 2 hour or prolong for about 48 hours. Unfortunately, in human, for both logistic and ethical reasons, no clinical study can meet the strict conditions of experimental studies on IPC in which infarct size is the end-point. Thus, surrogate endpoints have been used, including contractile function, electrocardiographic ischemic changes, or biochemical evidence of cell damage.

The mechanism by which intermittent reperfusion prevents cumulative injury is not known with certainty. It has been found that the rate of ATP depletion was actually slowed in subsequent ischemic episodes compared with the first. At least 3 mechanisms by which IPC slows ATP depletion include metabolic effect, ionic effect, and activation of signaling pathway.

The effect of diabetes on ischemic preconditioning has been inconsistent due to the difference in experimental conditions. However, it is still noteworthy that the cardioprotective effects of prodromal angina were lost even in patients with diabetes who had been treated without oral hypoglycemic drugs. The altered nature of KATP channel is one of the possible mechanisms that may explain the loss of IPC in diabetics. The association between diabetes and IPC especially became a focus of discussion about 25 years ago when it was observed that patients taking sulfonylurea had increased cardiovascular mortality. The ability of sulfonyl urea to inhibit adenosine triphosphate (ATP)-sensitive potassium channels has been associated with the risk of the drug to inhibit ischemic preconditioning. However, neither experimental nor clinical data suggest a uniform effect of different sulfonylureas on the cardiovascular system.

Analysis of 1310 diabetics included in the nationwide French Registry of Acute ST-Elevation and Non-ST-Elevation Myocardial Infarction showed no hazard was associated with the use of sulfonylureas before the acute episode. Patients previously receiving gliclazide/glimepiride had improved in-hospital outcomes, compared with those on glibenclamide.

Optimising Blood Pressure Control To Protect Microvascular Involvement

A. Fauzi Yahya
Department of Cardiology and Vascular Medicine
Medical School of Padjadjaran University

Badan kesehatan dunia (WHO) menyebutkan bahwa hipertensi bertanggung jawab terhadap 62% kejadian stroke dan 49% serangan jantung. Hipertensi yang menyebabkan 7,1 juta kematian prematur.Setiap peningkatan tekanan sistolik sebesar 20 mmHg dan tekanan diastolik 10 mg dari tekanan dasar 115/75 mmHg maka angka mortalitasi penyakit jantung iskemi meningkat dua kali lipat.

Problem hipertensi di dunia diperkirakan terus meningkat. Pada tahun 2000 terdapat 972 juta warga dunia yang menderita hipertensi dan sebagian besar bermukim di negara sedang berkembang. Proyeksi penderita hipertensi pada 2025 akan meningkat menjadi 1,56 milyar.

Dalam mengatasi hipertensi , sebagaimana hasil penelitian yang melibatkan 7 studi besar tersamar ganda, seringkali diperlukan lebih dari satu jenis obat untuk mengendalikan hipertensi. Pada hasil United Kingdom Prospective Diabetes Study (UKPDS), 29% pasien membutuhkan tiga atau lebih jenis obat hipertensi untuk mencapai tekanan rata-rata 144/82 dalam kurun 9 tahun *follow up.*

Selain manfaat efektifitas terapi kombinasi anti hipertensi menurunkan risiko efek samping dan meningkatkan kepatuhan berobat. Salah satu dari berbagai jenis kombinasi anti hipertensi yang tersedia adalah irbesartan dan hidrochlorthiazide (HCTZ). Kombinasi kedua jenis terapi ini adalah pilihan logis karena kedua jenis obat ini bekerja via mekanisme tersendiri. Irbesartan termasuk jenis obat penghambat reseptor angiotensin (ARB) yang bekerja dengan menghambat aktivasi reseptor angiotensin II tipe 1 sehingga terjadi vasodilatasi dan menurunkan sekresi vasopressin dan aldosteron.

Irbesartan tidak hanya bermanfaat menurunkan tekanan darah namun juga dapat mereduksi laju ekskresi albumin urine dan juga memperbaiki mikrovaskular pembuluh koroner penderita hipertensi.

Adapun HCTZ bekerja dengan menghambat reabsorpsi Na^+/Cl^- dari tubulus distal ginjal. Melalui reduksi tekanan osmotik maka HCTZ menurunkan reabsorpsi air dari tubulus distal ginjal sehingga mengurangi volume plasma dan curah jantung.

Keamanan dan efektifitas penurunan tekanan darah kombinasi irbesartan plus HCTZ telah teruji dalam berbagai studi klinis.Tidak terdapat laporan efek samping serius pada kombinasi kedua jenis obat ini. Pada studi INCLUSIVE (The Irbesartan/HCTZ blood pressure reductions in diverse populations) yang merupakan studi prospektif terbuka dan multisenter membuktikan bahwa kombinasi terapi ini dapat ditoleransi dan secara bermakna dapat menurunkan tekanan darah pada berbagai populasi

termasuk orang tua, ras afrika-amerika, ras hispanik, pasien DM tipe 2 dan pasien dengan sindrom metabolic.

Kombinas irbesartan/HCTZ memperlihatkan efikasi yang lebih baik dibanding kombinasi ARB/HCT yang lain pada sejumlah studi perbandingan. Hasil studi COSIMA (The Comparative Study of Efficacy of Irbesartan/HCT with Valsartan/HCTZ Using Home Blood Pressure Monitoring in the Treatment of Mild-to-Moderate Hypertension) memperlihatkan keunggulan Irbesartan/HCT dalam menurunkan tekanan darah yang lebih baik. Demikian pula studi perbandingan Irbesartan/HCTZ dengan Losartan/HCTZ yang secara bermakna memperlihatkan efek penurunan TD irbesartan/HCTZ secara bermakna lebih baik.

Kombinasi terapi Irbesartan/HCTZ merupakan opsi pilihan yang dapat dipertimbangkan dalam mengatasi hipertensi

Stroke Prevention in Atrial Fibrillation : Where are we now ?

Hendro Susilo

Dept of Neurology
Airlangga School of Medicine
Dr. Soetomo Hospital
Surabaya

Approximately one fifth of ischemic stroke subtype are considered cardioembolic with Atrial Fibrillation (AF) represents the most common cause of cardoembolic stroke and is a major cause of stroke in the elderly. The risk of a cardioembolic event rises with age with elderly women are particularly affected.

Atrial fibrillation is present in 1% of the US population of which around 5% is in the older than 70 years and it is found in up to 50% of all cardioembolic strokes. The lifetime risk of developing AF is 1-4 for adults older than 40 years. AF conveys a 5 –fold increase risk of stroke. Formerly associated with rheumatic valvular disease and AF is now related most frequently to hypertension and ischemic heart disease (nonvalvular AF). Stasis secondary to decreased contractility of the left atrium leading to thrombus formation in its appendage is the possible mechanism of cardioembolic stroke .

Several clinical risk stratification have been proposed to identify AF at high, moderate or low risk for selecting which patients would benefit most and least from anticoagulation. The $CHADS_2$ (congestive heart failure (CHF) , hypertension, age >75 yrs, diabetes, stroke aor TIA) classification scheme is the most validated system and accurately stratifies stroke risk.

Anticoagulant and antiplatelet therapies are the mainstay in the prevention of cardioembolic stroke with the management of anticoagulation at a specialized clinic is recommended based on the results of several studies. Patients need cardiac evaluation for arrythmia and structural abnormality of the heart as well as hematological evaluation when the possibility of prothrombotic state is suspected.

Warfarin is the first line anticoagulant treatment for most causes of cardioembolic stroke. Among antiplatelet agents aspirin has been proved in clinical trials to reduce the risk of stroke. However clopidogrel plus aspirin did not show efficacy compared with warfarin in patients with AF (ACTIVE W trial) although in patients who were not candidates for vitamin K antagonists, the combination of clopidogrel plus low dose aspirin was superior to low dose aspirin alone albeit with a slightly higher risk of bleeding (ACTVE A trial). Randomized trials have demonstrated that the efficacy of VKA warfarin is related directly to how carefully it is used. With inadequate anticoagulation procedure provide minimal or no protection, whereas supratherapeutic anticoagulation may increase the risk of serious hemorrhagic complication. To optimize the level of anticoagulation , interaction with concomitant medications known to potentiate or inhibit the

anticoagulant effect should be considered. Patient under warfarin therapy should be provided with the list of vitamin K containing foods that inhibit warfarin's anticoagulant effects. In addition most clinicians severely limit consumption of alcoholic beverages in patients taking warfarin.

The new direct thrombine inhibitor dabigatran was approve by US FDA for prevention of stroke and thromboembolism associated with nonvalvular AF. The efficacy and safety of 2 different doses of dabigatran was reported in RE-LY study with the 110 mg bid dose of dabigatran was noninferior to warfarin for the primary efficacy end point of stroke and thromboembolism while dabigatran 150 mg was significantly more effective than warfarin or dabigatran 110 mg . Major bleeding occurred significantly less often with dabigatran 110 mg than warfarin and 150 mg dose had similar bleeding to warfarin. The new Guideline from ACCF/AHA/HRS on AF have been updated to include the use of oral direct thrombine inhibitor (dabigatran) as an alternative to warfarin for the prevention of stroke and systemic thromboembolism in patients with paroxysmal to permanent AF and risk factors for stroke or systemic embolization.

Risk Assessment of Thromboembolism in Atrial Fibrillation

Iwan Dakota MD, FIHA, FACC, FESC, FSCAI
Dept. Cardiology and Vascular Medicine, Faculty of Medicine – University of Indonesia
National Cardiovascular Center Harapan Kita Hospital

Atrial fibrillation (AF) is said to be an epidemic, affecting 1%-1.5% of the population in the developed world. The clinical significance of AF lies predominantly in a 5-fold increased risk of stroke. Strokes associated with AF are usually more severe and confer increased risk of morbidity, mortality, and poor functional outcome.. It is responsible for nearly one-third of all strokes and is the leading cause of embolic stroke. Without preventive treatment, approximately 1 in 20 patients with AF will have a stroke each year. AF has also been associated with poorer clinical outcomes in patients suffering a myocardial infarction and in patients with acute coronary syndromes.

Assessment of the risk of a thromboembolic complication in a patient with atrial fibrillation is no easy task and the decision to initiate anticoagulation, albeit a common every day problem, often remains a dilemma for the clinician. Guidelines have been published by different organizations to help the physician make the optimal decision in each individual case. Some of these guidelines are precise and direc; other recommendations sound, to say the least, much more pruden. The statistics on the prescription of anticoagulants for patients with atrial fibrillation reflect some uncertainties among the medical community. The general consensus, however, is that one should focus on the individual patient's risk profile, taking into account age and coexisting conditions representing either a risk for stroke or a risk for major bleeding should anticoagulation be applied. It is generally agreed, for example, that it would not be reasonable to anticoagulate young patients with atrial fibrillation and no evidence of coexisting cardiac disease. But, even that statement which sounds so simple deserves a clearer definition of the terms 'young' and 'with no evidence of cardiac disease'.

The definition used in the often quoted paper by Kopecki *et al* seems acceptable. Their low risk group (1·3% cumulative incidence of stroke in 15 years) consisted of patients under the age of 60 without evidence of valvular or structural heart disease, hypertension, diabetes, coronary heart disease or thyrotoxicosis. These patients need no anticoagulation.

At the other end of the scale, the patient with a history of prior stroke or ischaemic transient attack is at very high risk of recurrent thromboembolic ischaemic events. The annual stroke rate in this subgroup approximates 12%. Such patients should be anticoagulated unless there is some unquestionable contraindication to this kind of therapy. Patients aged 75 years or more are also at very high risk (8·1%) and the American College of Chest Physicians recommend anticoagulation in this age group regardless of the presence or absence of other risk factor. One should keep in mind, however, that those older than 75 are also those in whom the dangers of antivitamin K are most threatening. In this age group, the

contraindications to anticoagulants should be scrupulously followed. They extend far beyond strictly medical reasons and encompass psychosocial factors, the likely compliance to therapy and the possible inability to monitor carefully the INR value (target : 2–3). Let us mention, by the way, that the dangers of anticoagulation were probably underestimated in the large clinical trials of anticoagulation in atrial fibrillation; other studies, reflecting more closely the real life situation than the best case scenario showed cumulative major bleeding rates that reached more than 5% at 1 year and more than 10% at 2 years.

The major problem is with the patient aged more than 60 and less than 75. The cohorts of controls enrolled in the large atrial fibrillation trials identified clinical characteristics which designate high risk individuals for whom anticoagulation is warranted (mitral stenosis, mitral annular calcification, increasing age, arterial hypertension, chronic cardiac failure, apparent coronary artery disease, diabetes mellitus, hyperthyroidism).

It is agreed, however, that these clinical features have a weak sensitivity and specificity. Therefore, echocardiographic findings such as left ventricular dysfunction, left atrial enlargement, left atrial spontaneous echoes (and particularly thrombi) have been added; they represent independent predictors of thromboembolism and help stratification. Thus, in the SPAF (Stroke Prevention in Atrial Fibrillation). cohort the group at low risk by clinical criteria alone had an annual stroke rate of 2·5%. Those within that subgroup who had none of the echocardiographic findings cited above had, according to the prediction model, an annual risk of 1%.

Abstract

The Pathophysiology of Hypertension

Januar Wibawa Martha
Department of Cardiology and Vascular Medicine, Padjadjaran University, Bandung

High blood pressure remains one of the most prevalent health problems facing humans. Among the causes of hypertension, more than 90% are essential which implies no clear identifiable etiology. Althogh several genehas been identified as a hypertensinogenic, there is still no single gene or group of genes responsible for hypertension. Essential hypertension has been extensively researched but there are no single cause and no single mechanism underlying the increased blood pressure.

Therefore it is multifactorial and multimechanism. Blood pressure may increase as a result of an increase in cardiac output and or elevation in systemic vascular resistance. These two component of blood pressure have their own causes and factors that contribute to increase in blood pressure. Interaction between cardiac output and systemic vascular resistance to increase in blood pressure is exceedingly complex.

The interplay involves many systems including local (vascular) and systemic factors. Renal sodium handling, sympathetic nervous system, renin angiotensin pathway are among the major player in high blood pressure. To make the matter more complex, environmental factors such as dietary habit, psychological stress, drug interactions may influence the rise in blood pressure. Pharmacological agents had been developed to block the suspected pathways of hypertension. Current pharmacological treatment for hypertension should be tailored according to known pathophysiological nature of high blood pressure.

Keywords: essential hypertension - pathophysiology

Neurologic Aspects in the Treatment of Hypertensive Crisis

Mursyid Bustami,MD
Neurology Department
University of Indonesia

Abstract.

The appropriate and timely evaluation and treatment of patients with severely elevated blood pressure is essential to avoid serious adverse outcomes. Most importantly, the distinction between a hypertensive emergency (crisis) and urgency needs to be made. A sudden elevation in systolic (SBP) and/or diastolic blood pressure (DBP) that is associated with acute end organ damage (cardiovascular, cerebrovascular, or renal) is defined as a hypertensive crisis or emergency. In contrast, acute elevation in SBP and/or DBP not associated with evidence of end organ damage is defined as hypertensive urgency. In patients with a hypertensive emergency, blood pressure control should be attained as expeditiously as possible with parenteral medications to prevent ongoing and potentially permanent end organ damage. In contrast, with hypertensive urgency, blood pressure control can be achieved with the use of oral medications within 24–48 hours.

Common neurologic emergencies in the setting of hypertensive crisis include hypertensive encephalopathy, intracerebral hemorrhage, and acute ischemic stroke. Severe hypertension is very common in the setting of acute stroke, and there is controversy surrounding the goal blood pressure. In intracerebral hemorrhage, there is typically disruption of the cerebral autoregulation of blood flow in the area of the bleed, and blood flow and oxygen delivery are dependent on systemic perfusion pressure. The American Heart Association recommends treating hypertension in the setting of an intracerebral bleed only when blood pressure is more than 180/ 105 mm Hg. Mean arterial pressure should be maintained below 130 mm Hg.

In patients with ischemic stroke, perfusion pressure distal to the obstructed vessel is low, and compensatory vasodilatation of these blood vessels occurs to maintain adequate blood flow. A higher systemic pressure is required to maintain perfusion in these dilated blood vessels. Most patients, irrespective of pre-ischemic blood pressure control, experience a sustained rise in blood pressure during cerebral ischemia, including transient ischemic attack. Therefore, in patients with ischemic stroke, blood pressure should be carefully observed for the first 1 to 2 hours to determine if it will spontaneously decrease. Only a persistently mean arterial pressure over 130 mm Hg or a systolic blood pressure over 220 mm Hg should be carefully treated. In this setting, mean arterial pressure should be lowered by 15% to 20%.

Hypertensive encephalopathy is a severe end-organ manifestation of the hypertensive process. Gradual lowering of the blood pressure frequently leads to rapid improvement of neurologic symptoms. If patients do not

improve within 6 to 12 hours, evaluation for other causes of the encephalopathic process should be undertaken.

Generally, the therapeutic approach is dictated by the particular presentation and end-organ complications. The ideal pharmacologic agent for the management of hypertensive emergency would be fast-acting, rapidly reversible, and titratable without significant effect. The appropriate therapeutic approach in each patient will depend on the clinical presentation of the acute end-organ damage. The preferred agents include nitroprusside, nicardipine, esmolol, labetalol, fenoldopam, and nitroglycerine. Parenteral therapy is generally preferred, and strategies include use of sodium nitroprusside, beta-blockers, labetalol, or calcium-channel antagonists.

In acute neurological cases, labetalol and calcium-channel antagonist is also recommended, because of both experimental and human data have indicated that may increase CBF, however it has a little effect on ICP while lowering blood pressure.

Cardiorenal Anemia Syndrome : a cardiologist's perspective

Nani Hersunarti, MD, FIHA
Clinical Cardiology and Critical Care Division National Cardiovascular Center Harapan Kita
Department of Cardiology and Vascular Medicine
Faculty of Medicine Universitas Indonesia

The interaction between chronic heart failure (CHF), chronic kidney insufficiency (CKI) and anemia, form a vicious cycle, termed as the cardiorenal anemia syndrome. The interaction between these three conditions causes deterioration of the cardiac and renal function and increases anemia. Each of the three can cause or be caused by the others. Anemia can increase the severity of CHF and is associated with a rise in mortality, hospitalization and malnutrition. Anemia can also further worsen renal function and cause a more rapid progression to dialysis than is found in patients without anemia. Uncontrolled CHF can cause rapid deterioration of renal function and anemia.

CKI can also cause anemia, as well as worsen the severity of CHF, and is associated with increased mortality and hospitalization in patients with CHF. Aggresive therapy againts CHF with all the conventional medications at the accepted doses often fails to improve the CHF if anemia is also present but is not treated.Therefore, regardless of the level of left ventricular dysfunction, the cardiorenal anemia syndrome might be viewed as a stage of HF where the progression rate of biochemical, cellular, and neurohormonal alterations leading to unfavourable outcomes is accelerated.

Moreover, owing to the lack of population-specific treatment effect data, current guidelines do not provide specific recommendations for the management of CHF patients with anaemia, renal dysfunction, or both, with consequent difficulties in clinical practice. The cardiorenal anemia syndrome, though of particular interest, has not been thoroughly characterized. In this review we explained the mechanism involved in the pathophysiology and therapy of this new syndrome from cardiologist perspective.

PENGGUNAAN STATIN PADA PENYAKIT GINJAL KRONIK : APAKAH AMAN ?

Dr.dr. Parlindungan Siregar SpPD.KGH

PENDAHULUAN

Penyakit Ginjal Kronik atau PGK didefinisikan sebagai 1) Gangguan struktur ginjal lebih dari tiga bulan yang dapat disertai penurunan atau tanpa penurunan Laju Filtrasi Glomerulus (LFG). Gangguan struktur ginjal dapat diketahui berdasarkan hasil pemeriksaan laboratorium urin, hasil pemeriksaan imejing ginjal dari foto ronsen, ultrasonografi, atau *CT-Scan*, dan gambaran histopatologi ginjal. 2) Penurunan Laju Filtrasi Glomerulus (LFG) kurang dari 60 mL/menit lebih dari tiga bulan.

PGK merupakan perjalanan penyakit yang secara terus menerus hingga mencapai stadium terminal, sehingga dalam perjalanannnya ini PGK digradasikan menjadi stadium-I hingga stadium-V. Disebut stadium-I bila LFG lebih dari 90 mL/menit, stadium-II bila LFG antara 90-60 mL/menit, stadium-III bila LFG antara 60-30 mL/menit, stadium-IV bila LFG antara 30-15 mL/menit, dan stadium-V atau tahap akhir bila LFG kurang dari 15 mL/menit. Stadium-II disebut sebagai PGK-ringan, stadium-III disebut sebagai PGK-sedang, stadium-IV disebut sebagai PGK-berat, sedang stadium-V adalah tahap terminal atau tahap dialisis.[1,2,3] Kekerapan PGK dalam populasi usia antara 30-63 tahun berkisar pada angka 7,2%, sedang pada usia 64 tahun ke atas berkisar antara 23,4-35,8%.[4]

Penelitian ini menunjukkan bahwa kekerapan PGK dalam populasi di dunia cukup tinggi. Komplikasi maupun angka kematian pada PGK makin meningkat sesuai dengan peningkatan stadium pada PGK ini juga.[5] Angka kematian oleh penyebab apapun meningkat mulai dari 1,08% per tahun pada LFG 45-59 mL/menit, 4,76% per tahun pada LFG 30-44 m>/menit, 11,36% pertahun pada LFG 15-29 mL/menit, hingga 14,14% per tahun pada LFG < 15 mL/menit.

Angka kejadian komplikasi kardiovaskuler meningkat mulai dari 3,65% per tahun pada LFG 45-59 mL/menit, 11,29% per tahun pada LFG 30-44 m>/menit, 21,80% pertahun pada LFG 15-29 mL/menit, hingga 36,60% per tahun pada LFG < 15 mL/menit. Angka kejadian rawat inap di rumah sakit meningkat mulai dari 17,22% per tahun pada LFG 45-59 mL/menit, 45,26% per tahun pada LFG 30-44 m>/menit, 86,27% pertahun pada LFG 15-29 mL/menit, hingga 144,61% per tahun pada LFG < 15 mL/menit. Dua faktor yang berpengaruh terhadap kejadian kardiovaskuler pada PGK adalah apa yang disebut dengan faktor tradisional dan faktor non-tradisional.

Sesuai dengan penelitian oleh kelompok *ARIC Study* menunjukkan faktor tradisional yang bermakna memberi pengaruh adalah merokok, obesitas, aktifitas fisik rendah, hipertensi, diabetes melitus, dan kolesterol, sedang faktor non-tradisional yang bermakna berpengaruh adalah lingkar pinggang, anemia, albumin serum, dan fibrinogen.[6] Banyaknya faktor yang berpengaruh pada PGK terhadap kejadian komplikasi kardiovaskuler, kadar kolesterol merupakan salah satu yang penting untuk dikendalikan.

Pengendalian ini dilakukan melalui jalur pengaturan diit dan pemakaian obat penurun kolesterol. Target kadar kolesterol yang harus dicapai untuk mencegah komplikasi kardiovaskuler menurut NKF (National Kidney Foundation), K/DOQI pada tahun 2003 adalah sebagai berikut : 1) Kolesterol-LDL kurang dari 100 mg/dL; 2) Kolesterol non-HDL merupakan selisih antara Kolesterol total dengan Kolesterol-HDL (*non-HDL = TC – HDL*) harus kurang dari 130 mg/dL.[7] Pada pasien yang menjalani dialisis, pemeriksaan kolesterol tanpa didahului puasa ternyata mempunyai nilai prognostik yang sama dengan pemeriksaan kolesterol dengan didahului puasa.

Pemeriksaan kolesterol tanpa puasa dapat dilakukan tanpa merubah nilai prognostik.[8] Khususnya pada PGK, apakah semua obat penurun kolesterol aman untuk dipakai? Kelompok statin yang saat ini dikenal sebagai obat penurun kolesterol yang kuat, penting untuk dibahas apakah seluruh statin aman dipakai pada kelompok PGK.

STATIN

Beberapa obat golongan statin yang saat ini beredar adalah Rosuvastatin, Atorvastatin, Simvastatin, Lovastatin, Pravastatin, dan Fluvastatin. Tidak semua jenis statin ini aman pada PGK stadium III-V. Ekskresi melalui urin obat statin diatas berturutan; Rosuvastatin 10%, Atorvastatin < 2%, Simvastatin 13%, Lovastatin 10%, Prvastatin 20%, dan Fluvastatin 6%.

Disamping faktor ekskresi melalui urin, faktor metabolisme melalui cytochrome P450-3A4 system (CYP-3A4) juga berperan, karena statin yang dimetabolisme melalui jalur ini memberi efek samping khususnya bila dikombinasi dengan obat yang menghambat cytochrome P450-3A4 seperti obat-obat berikut, Atazanavir, Boceprevir, Clarithromycin, Isoniazid, Ketoconazol, Nicardipine, Voriconazole dan lain lain. Obat golongan statin yang dimetabolisme melalui jalur ini adalah Lovastatin, Simvastatin, dan yang paling minimal ialah Atorvastatin. Pravastatin, Fluvastatin, dan Rosuvastatin tidak dimetabolisme melalui jalur ini.[9,10]

Pengaruh Statin terhadap progresi PGK.

Proteinuria merupakan salah satu faktor risiko independen yang mempengaruhi progresifitas perburukan PGK. Satu penelitian memperlihatkan ada beberapa obat golongan statin yang menimbulkan proteinuria lebih dari tinggi seperti simvastatin dan rosuvastatin dibanding dengan pravastatin dan atorvastatin. Penelitian lain menunjukkan hal yang berbeda-beda, ada yang mengatakan statin tertentu menimbulkan proteinuria, akan tetapi penelitian lain mengatakan justru mengurangi proteinuria. Walaupun statin oleh dua penelitian meta-analisis menyatakan terjadi reduksi proteinuria, akan tetapi tidak berani mengambil kesimpulan bahwa statin bersifat renoprotektif.[11,12]

Penelitian prospektif dengan kontrol, berskala kecil yang dilakukan, menunjukkan bahwa Atorvastatin dapat menghambat progresi PGK dan reduksi proteinuria.[13] Analisis pasca pemasaran (*Postmarketing Analysis*) yang dilakukan, dengan membandingkan beberapa jenis statin terhadap kejadian rabdomiolisis, proteinuria, nefropati, dan gagal ginjal, diperoleh bahwa untuk progresi PGK, rosuvastatin menunjukkan progresi ke arah

perburukan tertinggi sedang atorvastatin menunjukkan progresi ke arah perburukan terendah bermakna. Secara berurutan mulai dari tertinggi hingga terendah adalah rosuvastatin, simvastatin, pravastatin, dan atorvastatin dimana masing-masing simvastatin, pravastatin, dan atorvastatin berbeda bermakna dibanding dengan rosuvastatin.[14]

Dosis Statin pada PGK

Target kadar kolesterol yang harus dicapai untuk mencegah komplikasi kardiovaskuler menurut NKF (National Kidney Foundation), K/DOQI pada tahun 2003 dan 2007 adalah sebagai berikut: 1) Kolesterol-LDL kurang dari 100 mg/dL; 2) Kolesterol non-HDL harus kurang dari 130 mg/dL.[7] NKF-K/DOQI 2007 mengeluarkan panduan dosis obat golongan statin yang beredar saat itu antara lain : 1) Atorvastatin dan Pravastatin tidak memerlukan penyesuaian dosis mulai dari PGK stadium 1-5; 2) Semua golongan statin tidak memerlukan penyesuaian dosis pada PGK stadium 1-3; 3) Simvastatin dianjurkan menggunakan dosis 5 mg pada PGK stadium 4-5; 4) Lovastatin tidak dianjurkan memakai dosis lebih dari 20 mg/hari pada PGK stadium 4-5; 5) Fluvastatin tidak dianjurkan pada PGK stadium 4-5; 6) Rosuvastatin tidak dianjurkan memakai dosis lebih dari 10 mg pada PGK stadium 4-5.

SIMPULAN

1. Kelompok Statin dapat menurunkan proteinuria pada PGK, akan tetapi belum cukup bukti sebagai renoprotektif.

2. Hanya Atorvastatin dan Pravastatin yang tidak memerlukan penyesuaian dosis pada PGK stadium 1 s/d 5.

3. Simvastatin, Lovastatin, Fluvastatin, dan Rosuvastatin memerlukan penyesuaian dosis pada PGK stadium 4 dan stadium 5.

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CLASSIFICATION AND CARDIOVASCULAR RISK ASSESSMENT IN HYPERTENSION

Pringgodigdo Nugroho
Nephrology and Hypertension Division, Departmen of Internal Medicine
Dr. Cipto Mangunkusumo Hospital, Faculty of Medicine University of Indonesia

Blood pressure has a continuous relationship with cardiovascular risk. It makes the word hypertension scientifically questionable and its classification based on cutoff values arbitrary. However, changes of a widely known and accepted terminology may generate confusion while use of cutoff values simplifies diagnostic and treatment approaches in daily practice.

International guidelines have all adopted almost the same blood pressure classification of hypertension based on findings on risk of cardiovascular outcomes associated with blood pressure. There are minor differences in classification of hypertension in different guidelines. The United State of America Joint National Committee Guidelines (JNC 7) on hypertension published in 2003 unified the normal and high normal blood pressure categories into a single entity termed 'prehypertension'. This was based on the evidence from the Framingham study that in such individuals the chance of developing hypertension is higher than in those with a blood pressure 120/80 mmHg (termed 'normal' blood pressure) at all ages. The following classification was suggested in JNC 7 based upon the average of two or more properly measured readings at each of two or more visits after an initial screen : normal blood pressure (<120/80 mmHg); prehypertension (120-139/80-89 mmHg); hypertension stage 1 (140-159/90-99 mmHg); hypertension stage 2 (≥160/≥100mmHg).

Isolated systolic hypertension is considered to be present when the blood pressure is ≥140/≤90 mmHg and isolated diastolic hypertension is considered to be present when the blood pressure is <140/≥90 mmHg. These classification apply to adults on no antihypertensive medications and who are not acutely ill. If there is a disparity in category between the systolic and diastolic pressures, the higher value determines the severity of the hypertension. The systolic pressure is the greater predictor of risk in patients over the age of 50-60.

Similar but not identical classification was suggested in the 2007 European Societies of Hypertension and Cardiology (ESH/ESC) guidelines for the management of arterial hypertension. The major difference is that the European guidelines divide blood pressures below 140/90 mmHg into three categories ("optimal" <120/80mmHg, "normal" 120-129/80-84mmHg, and "high normal" 130-139/85-89) instead of the two categories ("normal" and "prehypertension") defined by JNC 7. Hypertension was classified as three categories: grade 1 hypertension (140-159/90-99mmHg), grade 2 hypertension (160-179/100-109mmHg), and grade 3 hypertension (≥180/≥110mmHg).

Although JNC 7 Guidelines focused on blood pressure values as the only or main variables determining the need and the type of treatment,

ESH/ESC Guidelines emphasized that diagnosis and management of hypertension should be related to quantification of total or global cardiovascular risk. This concept is based on the fact that only a small fraction of the hypertensive population has an elevation of blood pressure alone, with the great majority exhibiting additional cardiovascular risk factors, with a relationship between the severity of the blood pressure elevation and that of alterations in glucose and lipid metabolism.

More over, when concomitantly present blood pressure and metabolic risk factors potentiate each other, leading to a total cardiovascular risk which is greater than the sum of its individual components. Finally, evidence is available that in high risk individuals thresholds and goals for antihypertensive treatment, as well as other treatment strategies, should be different from those to be implemented in lower risk individuals. In order to maximize cost-efficacy of the management of hypertension the intensity of the therapeutic approach should be graded as a function of total cardiovascular risk.

The ESH/ESC Guidelines classified the total cardiovascular risk based on the scheme proposed by the 1999 WHO/ISH Guidelines on hypertension with the extension to subjects with 'normal' or 'high normal' blood pressure. The terms 'low', 'moderate', 'high' and 'very high' risk are used to indicate an approximate risk of cardiovascular morbidity and mortality in the coming 10 years, which is somewhat analogous to the increasing level of total cardiovascular risk estimated by the Framingham or the SCORE models. The term 'added' is used to emphasize that in all categories relative risk is greater than average risk. The ESH/ESC Guideline illustrates how total cardiovascular risk evaluation influences the definition of hypertension when this is correctly considered as the blood pressure value above which treatment does more good than harm.

There are common clinical variables that should be used to stratify the risk. They are based on risk factors (demographics, anthropometrics, family history of premature cardiovascular disease, blood pressure, smoking habits, glucose and lipid variables), measures of target organ damage, and diagnosis of diabetes and associated clinical conditions.

KESEIMBANGAN AIR DAN NATRIUM

Parlindungan Siregar

Pendahuluan

60% dari berat badan manusia dewasa terdiri dari cairan, sehingga perlu pengaturan agar kehidupan manusia tersebut berada dalam keadaan yang baik (*steady state*). Cairan tubuh terdapat di dalam dua kompartemen besar yaitu cairan intraseluler dan cairan ekstraseluler. Cairan intraseluler memiliki volume yang lebih besar dari cairan ekstraseluler, masing-masing 36% dan 24% berat badan berturutan. Air dari cairan intraseluler bebas bergerak masuk ke dalam cairan ekstraseluler, demikian juga sebaliknya.

Pergerakan air ini dimungkinkan oleh adanya perbedaan osmolalitas efektif di kedua kompartemen ini. Osmolalitas efektif atau disebut juga tonisitas adalah rasio antara solut yang impermeabel dengan air. Solut yang impermeabel atau disebut juga sebagai solut yang efektif adalah natrium, kalium, glukosa, mannitol, dan sorbitol. Solut inilah yang mempengaruhi besaran tonisitas. Natrium merupakan solut yang dominan di ekstraseluler, sedang kalium merupakan solut yang dominan di intraseluler. Air akan bergerak dari tonisitas yang rendah ke arah tonisitas yang tinggi.

Pergerakan air ini tujuannya adalah untuk menyeimbangkan osmolalitas di antara kedua kompartemen tersebut. Kompartemen ekstraseluler dibagi menjadi dua subkompartemen yaitu cairan interstisial dan cairan intravaskuler. Antara interstisium dan intravaskuler dibatasi oleh membran yang permeabel, sehingga baik air maupun solut bebas berpindah di antara kedua subkompartemen ini kecuali albumin tidak dapat berpindah dari intravaskuler ke interstisium dan dengan demikian tidak akan ada perbedaan tonisitas di antara kedua subkompartemen cairan ekstraseluler ini.

Air dan Natrium merupakan dua komponen cairan tubuh yang sangat erat kaitannya, sehingga keseimbangan air juga menyangkut keseimbangan natrium atau sebaliknya. Keseimbangan akan terganggu bila salah salah komponen pengatur keseimbangan tidak berjalan sebagaimana seharusnya.

Pengaturan Keseimbangan Air dan Natrium

Pengaturan keseimbangan ini dilakukan oleh dua regulator yaitu regulator osmotik dan regulator volume. Regulator osmotik bertugas mengatur ekskresi air melalui ginjal, sedang regulator volume bertugas mengatur ekskresi natrium melalui ginjal.

Pemicu regulator osmotik adalah osmolalitas plasma. Perubahan osmolalitas plasma akan dirasakan oleh reseptor osmotik atau osmoreseptor dan pusat rasa haus di hipotalamus. Peningkatan osmolalitas plasma akan merangsang osmoreseptor mengeluarkan hormon anti diuretik atau ADH dan membangkitkan rasa haus. ADH akan menyebabkan reabsorpsi air di duktus koligentes ginjal meningkat. Disamping itu peningkatan rasa haus akan menyebabkan keinginan untuk minum. Kedua hal ini menyebabkan

penambahan volume air dalam cairan ekstraseluler yang akan mengembalikan osmolalitas plasma ke arah normal. Penurunan osmolalitas plasma akan meredam osmoreseptor untuk tidak mengeluarkan ADH sehingga banyak air yang dikeluarkan ginjal dari tubuh dalam bentuk urin, dan rasa haus juga diredam. Kedua hal ini akan mengembalikan osmolalitas plasma ke arah normal.

Pemicu regulator volume adalah volume sirkulasi efektif atau volume arteri efektif. Volume arteri efektif merupakan bagian dari cairan ekstraseluler yang berada dalam sistem arteri untuk memberikan perfusi jaringan yang efektif. Volume sirkulasi efektif, besarannya tak dapat diukur, akan tetapi kaitannya erat secara langsung dengan volume cairan ekstraseluler. Dalam keadaan tertentu besaran volme arteri efektif tidak berkaitan dengan volume cairan ekstraseluler, misalnya pada gagal jantung, volume cairan ekstraseluler meningkat, akan tetapi volume arteri efektif menurun akibat curah jantung yang turun. Besaran volume sirkulasi efektif ini dirasakan oleh sensor yang disebut sebagai baroreseptor (reseptor penanda volume atau tekanan) berlokasi di arteri karotis, atrium dan ventrikel kanan jantung, arteri aferen ginjal, dan hipotalamus.

Baroreseptor di arteri karotis akan mengaktifasi atau meredam sistem simpatis pada pengurangan atau peningkatan volume sirkulasi efektif berturutan. Pengaktifan sistem simpatis akan meningkatkan sekresi angiotensin-II dan konstriksi pembuluh darah dan demikian juga sebaliknya. Sebagai contoh bila ada hipovolemia, sistem simpatis teraktifasi, sehingga angiotensin-II meningkat yang kemudian akan meningkatkan hormon aldosteron yang hasil akhirnya terjadi penghambatan ekskresi natrium melalui duktus koligen ginjal, terjadi retensi natrium dan sekaligus air dengan tujuan untuk mengembalikan volume sirkulasi ke arah normal. Baroreseptor di atrium/ventrikel kanan akan teraktifasi pada keadaan hipervolemia atau terjadi peregangan dinding jantung. Aktifasi ini akan merangsang pengeluaran hormon *atrial natriuretic peptide* atau ANP oleh sel atrium/ventrikel kanan. ANP yang meningkat ini akan bekerja di duktus koligentes ginjal untuk merangsang ekskresi natrium. Disamping itu, ANP juga menghambat kerja aldosteron dan ADH.

Kesemuanya ini akan meningkatkan eksresi natrium melalui ginjal dan sekaligus ekskresi urin sehingga keadaan hipervolemia dapat kembali ke arah normovolemia. Baroreseptor di arteri aferen ginjal akan teraktifasi pada keadaan penurunan volume sirkulasi efektif. Aktifasi ini akan mengaktifkan sistem renin-angiotensin-aldosteron, yang hasil akhirnya akan terjadi penghambatan ekskresi natrium di duktus koligentes ginjal, sehingga volume sirkulasi efektif kembali ke arah normal. Baroreseptor di hipotalamus akan teraktifasi pada keadaan penurunan volume sirkulasi efektif yang mengakibatkan peningkatan sekresi ADH sehingga volume sirkulasi efektif kembali ke arah normal.

Dalam kehidupan sehari-hari, kedua regulator yang mengatur keseimbangan air dan natrium akan bekerja secara simultan untuk mengembalikan keseimbangan ke arah normal.

Gangguan Keseimbangan Air dan Natrium

Gangguan ini meliputi: 1) Hipovolemia; 2) Dehidrasi; 3) Hipervolemia; 4) Edema; 5) Hiponatremia; 6) Hipernatremia.

Hipovolemia adalah keadaan berkurangnya volume cairan ekstraseluler.

Hipovolemia dapat disebabkan pengeluaran cairan ekstraseluler yang isoosmolal atau isotonik misalnya pada perdarahan, diare, muntah, pemakaian diuretik. Dalam keadaan ini volume cairan intraseluler tidak berkurang, karena osmolalitas cairan ekstraseluler tidak berubah sehingga air dari intraseluler tidak bergerak ke dalam cairan ekstraseluler. Hipovolemia dapat juga disebabkan pengeluaran cairan hipotonik atau hipoosmolal, akan tetapi dibutuhkan kehilangan volume cairan tubuh 2,5 kali lipat dari pada hipovolemia akibat pengeluaran cairan isoosmolal, oleh karena volume cairan ekstraseluler hanya 40% dari total cairan tubuh.

Bila yang keluar dari cairan ekstraseluler adalah cairan hipoosmolal (proporsi air lebih besar dari pada proporsi solut), maka tonisitas cairan ekstrasel akan meningkat, menyebabkan air dari intrasel bergerak ke dalam ekstrasel, keadaan ini yang menyebabkan dibutuhkannya pengeluaran cairan 2,5 kali lipat. Contoh klasik terjadinya hipovolemia pada pengeluaran cairan ekstrasel yang hipoosmolal adalah diabetes insipidus. Akibat ADH yang kadarnya mendekati nol pada diabetes insipidus, maka cairan hipoosmolal dari ekstraseluler banyak dikeluarkan melalui ginjal berupa urin dengan osmolalitas rendah, kurang dari 100 mosm/kg H2O. Bila volume cairan ekstrasel sebesar 24% dari Berat Badan (Kg), maka berkurangnya volume cairan ekstrasel akibat hipovolemia pada tingkat yang ringan (< 5% volume cairan ekstraseluler), menimbulkan rasa lemah, cepat lelah, haus, keram otot, dan melihat gelap pada posisi berdiri lama.

Pada tingkat yang lebih berat, volume turun sebesar 10-15% volume cairan ekstraseluler, menimbulkan nyeri perut akibat iskemia arteri mesenterika, nyeri dada akibat iskemia arteri koroner, dan letargia, rasa bingung akibat iskemia pembuluh serebral. Penurunan volume lebih dari 15% volume cairan ekstraseluler, bersifat fatal, timbul penurunan tekanan darah atau syok. Hipovolemia akibat pengeluaran cairan hipoosmolal, seperti pada diabetes insipidus, disamping gejala akibat hipovolemia, akan timbul juga gejala karena hipernatremia. Gejala biasanya timbul pada keadaan hipernatremia akut, kejadian kurang dari 24 jam, dengan kadar natrium lebih dari 158 meq/L antara lain kelemahan tubuh, gelisah, dan berlanjut menjadi kejang kemudian jatuh dalam koma. Kematian dapat timbul bila kadar natrium darah lebih dari 180 meq/L.

Dehidrasi adalah berkurangnya volume cairan intraseluler.

Dehidrasi dapat disebabkan oleh pengeluaran cairan ekstraseluler yang hipoosmolal, tetapi tidak menyebabkan hipovolemia. Misalnya pada keadaan pengeluaran cairan hipoosmolal melalui keringat, penguapan kulit, atau pernafasan. Dehidrasi dapat juga disebabkan oleh penambahan NaCl hipertonik yang berlebihan sehingga osmolalitas atau tonisitas cairan ekstraseluler menjadi meningkat sehingga air dari cairan intraseluler bergerak masuk ke dalam cairan ekstraseluler. Secara klinis, gejala dehidrasi adalah gejala yang ditimbulkan akibat hipernatremia.

Gejala yang ditimbulkan dapat berupa letargia, kelemahan tubuh, dan lebih peka terhadap rangsangan. Bila berlanjut dapat menimbulkan kejang dan koma. Gejala yang berat biasanya timbul bila terjadi kenaikan natrium yang cepat, kurang dari 48 jam, mencapai lebih dari 158 meq/L. Kenaikan cepat lebih dari 180 meq/L akan menimbulkan kematian.

Hipervolemia adalah peningkatan volume cairan ekstraseluler.

Peningkatan ini ditandai dengan adanya edema paru, asites, dan edema umum. Keadaan ini dapat ditemukan pada kasus dengan gagal jantung, sirosis hati, sindrom nefrotik, dan Penyakit Ginjal Kronik (PGK) stadium 4-5.

Edema adalah peningkatan volume cairan interstisium.

Edema secara patofisiologi disebabkan oleh dua hal yaitu 1) Perubahan hemodinamik dalam kapiler sehingga terjadi perpindahan cairan dari intrakapiler ke interstisium; 2) Retensi natrium dan air oleh ginjal, yang berasal dari makanan atau berasal dari cairan masuk melalui intravena. Kedua hal di atas dapat berupa peningkatan tekanan hidrostatik akibat peningkatan volume plasma oleh karena ada retensi natrium, obstruksi vena, penurunan resistensi arteriol, hipoalbuminemia, peningkatan permeabilitas kapiler, obstruksi pembuluh lemfe, dan peningkatan tekanan onkotik interstisium. Peningkatan volume plasma dapat disebabkan oleh gagal jantung, retensi natrium primer oleh ginjal, kehamilan, premenstruasi, edema idiopatik yang diinduksi oleh diuretik.

Obstruksi vena dapat terjadi pada sirosis hati, edema paru, obstruksi vena lokal. Penurunan resistensi arteriol dapat terjadi pada pemberian CCB (*calcium channel blocker*) dan edema idiopatik. Hipoalbimunemia dapat ditemukan pada sirosis hati, sindrom nefrotik, malnutrisi. Peningkatan permeabilitas kapiler dapat ditemukan pada luka bakar, trauma, sepsis, reaksi alergi, diabetes melitus, malignansi, edema idiopatik, dan terapi dengan interleukin-2. Obstruksi pembuluh limfe misalnya keganasan sistem limfatik. Peningkatan tekanan onkotik interstisium dapat terjadi pada hipotiroid dan keganasan.

Hiponatremia adalah berkurangnya kadar natrium dalam plasma yaitu kurang dari 135 meq/L.

Natrium merupakan solut utama dalam cairan ekstraseluler sehingga dalam keadaan normal merupakan komponen utama penentu osmolalitas plasma. Kita ketahui osmolalitas adalah rasio antara air dengan solut, dalam hal natrium dapat kita katakan bahwa hiponatremia menimbulkan penurunan osmolalitas plasma. Penurunan osmolalitas plasma akibat hiponatremia dapat terjadi oleh dua hal : 1) Volume air dalam cairan ekstraseluler meningkat atau 2) Natrium banyak terbuang dari cairan ekstraseluler. Disamping itu, hiponatremia dapat diklasifikasikan kepada Hiponatremia Sungguhan (*True Hyponatremia*) dan Hiponatremia Palsu (*False Hyponatremia*). Disebut hiponatremia sungguhan bila hiponatremia disertai dengan hipoosmolalitas plasma dan hiponatremia palsu bila hiponatremia disertai dengan normoosmolalitas plasma atau hiperosmolalitas plasma.

Hiponatremia disertai dengan normoosmolalitas plasma dapat ditemukan pada keadaan hipertrigliseridemia atau pada penyakit paraprotein.

Hiponatremia disertai dengan hiperosmolalitas plasma dapat ditemukan pada keadaan hiperglikemia, pemberian manitol atau gliserol. Penetapan osmolalitas plasma dalam hal ini harus dengan cara diukur dengan osmometer, bukan dihitung dengan rumus. Seperti tertulis diatas maka hiponatremia sungguhan dapat disebabkan peningkatan volume air dalam cairan ekstraseluler seperti pada polidipsia primer, penyakit ginjal kronik, gagal jantung, sirosis hati, sindrom nefrotik, dan SIADH (*Syndrome of Inappropriate of ADH secretion*). Penyebab yang lain adalah natrium dari cairan ekstraseluler banyak terbuang melalui ginjal seperti pada pemberian diuretik, adanya diuresis osmotik, gangguan reabsorpsi natrium di tubulus ginjal (*salt losing nephropathy*), RTA tipe-II, dan penyakit Addison. Atau natrium banyak terbuang melalui saluran cerna seperti pada keadaan muntah berat dan diare.

Hipernatremia adalah meningkatnya kadar natrium dalam plasma lebih dari 140 meq/L.

Seperti pada hiponatremia, maka pada hipernatremia akan terjadi peningkatan osmolalitas plasma. Peningkatan natrium dalam plasma ini dapat disebabkan terbuangnya air dalam jumlah proporsi yang lebih besar dari natrium melalui ginjal, saluran cerna, atau kulit. Peningkatan natrium dalam plasma dapat juga disebabkan penambahan natrium melalui oral atau parenteral. Pembuangan air dalam proporsi yang lebih besar melalui ginjal ditemukan pada diabetes insipidus, melalui saluran cerna pada enteritis berat, dan melalui kulit pada keadaan hiperhidrosis berat.

Gejala yang ditimbulkan dapat berupa letargia, kelemahan tubuh, dan lebih peka terhadap rangsangan pada kenaikan yang kronik, lebih dari 48 jam. Hipernatremia menimbulkan gejala yang berat bila peningkatan terjadi secara akut atau kurang dari 48 jam berupa kejang dan koma bila mencapai lebih dari 158 meq/L. Kenaikan yang aku lebih dari 180 meq/L akan menimbulkan kematian.

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Beta Blockers in the Management of Hypertension: An Asian Perspective

Ria Bandiara
Div of Nephrology & Hypertension, Internal Medicine Department
Faculty of Medicine Unpad/ Hasan Sadikin Hospital Bandung

Abstract

The Asia Pacific region accounts for approximately half of the worldwide burden of cardiovascular disease. High blood pressure is an important contributor to this burden, with a population-attributable fraction of hypertension for cardiovascuar disease reported to be as 66% in Asia countries. It is anticipated that by 2025, the number of hypertensive individuals in China and India alone will increase to >500 million.

Rates of hypertension control remain low in most Asian countries. In China, for example, 18.8 percent of the population had hypertension. However, only 30.2 percent oh the hypertensive patients were aware of their condition, 24.7 percent were treted, and 6.1 percent achieved blood pressure control. It is clear that an increased awareness and effective treatment of hypertension will be crucial to reducing the burden of cardiovascular disease within the region.

Following publication of the National Institute of Clinical Excellence (NICE) Guidelines in 2006, the use of β-blockers as first-line therapy in hypertension has been somewhat controversial. However, a recent reappraisal of the European Society of Hypertension guidelines highlights that these agents exhibit similar BP lowering efficacy to other classes of agents, prompting a re-examination of the utility of these agents in various patient populations.

That is important to address this controversy and provide an Asian perspective on the place of β-blockers in current clinical practice and the benefits of β-blockade in selected patient populations. In addition to their use as a potential first-line therapy in uncomplicated hypertension, β-blockers have a particular role in patients with hypertension and comorbidities such as heart failure or coronary artery disease, including those who had a myocardial infarction. One advantage which β-blockers offer is the additional protective effects in patients with prior cardiovascular events. Some of the disadvantages attributed to β-blockers appear more related to the older drugs in this class and further appraisal of the efficacy and safety profile of newer β-blockers will lend support to the current guideline recommendations in Asian countries and encourage increased appropriate use of β-blockade in current clinical practice within Asia.

"Resistant Hypertension"

Resistant hypertension requires special consideration in terms of evaluation & treatment. It is important to determine that a person's condition truly resistant and we have to differenciate it with "uncontroled" hypertension.

It is called resistant hypertension if a person's blood pressure remains above goal despite taking three or more medications included diuretic.

People with resistant hypertension have a high cardiovascular risk and often multiple conditions that complicated their blood pressure management. Resistant hypertension is almost always multifactorial in etiology. Treatment is prediated on identification & reversal of lifestyle factors contributing to treatment resistance; accurate diagnosis and appropiate treatment of secondary causes of hypertension and use of multidrugs regimen.

"Resistant Hypertension" untuk How to session
Rossana Barack

EVOLVING THE FUTURE OF SINGLE PILL COMBINATION IN ANTIHYPERTENSION THERAPY

Rubin Surachno
Nephrology and Hypertension Sub.Div. Department of Internal Medicine Dr Hasan Sadikin General Hospital Padjadjaran University Bandung

The goal of antihypertensive therapy is to abolish the risks associated with blood pressure (BP) elevation without adversely affecting quality of life. Drug selection is based on efficacy in lowering BP and reducing cardiovascular (CV) end points including stroke, myocardial infarction, and heart and kidney failure. Available data suggest that at least 75% of patients will require combination therapy to achieve contemporary BP targets. Clinical trials document that achieving BP target is usually not possible with a single agent. In the ALLHAT study only 26% of patients achieved goal BP with monotherapy. In the HOT trial 33% of patients achieved their BP target with monotherapy, 45% required two drugs, and 22% needed three or more agents. There are seven major classes of antihypertensive drugs and multiple members of each class; therefore the number of possible combinations is quite large.

Clinical application and initial therapy consider several questions such as: should treatment be started with monotherapy or a combination? If two drugs are initiated, should they be administered as single entities or an single pill combination (SPC)? And which combination is appropriate or effective on the basis of efficacy, safety and tolerability? SPC may be used: as initial treatment in a patient in whom multidrug therapy is likely to be needed, as the second step in a patient partially controlled on monotherapy, or as a substitute for independently titrated doses of individual components. Convenience is the major advantage of using an SPC. It is easier for the patient to comply with a regimen that includes fewer pills. It also takes less time to achieve BP control.

The preferred two-drug combinations are ACE/diuretics, ARB/diuretics, ACEI/CCB or ARB/CCB. The combination of an ARB and DHP-CCB results in fully additive BP reduction. ARBs significantly improve the tolerability profile of the CCB. Through their antisympathetic effects, ARBs blunt the increase in heart rate that may accompany treatment with a DHP-CCB. In addition ARBs partially neutralize the peripheral edema, which is a dose-limiting side effect of CCB. ARBs will counteract this edema through venodilation. ARBs reduced vasoconstriction, aldosteron secretion and catecholamine release. And CCB causes arterial dilatation. Fixed dose combination therapy with ARBs/CCB on clinical outcomes in high-risk hypertensive patients such as diabetics gave comparable BP reduction.

ARB/CCB combination reduced the combined end point of cardiovascular death, myocardial infarction and stroke by 20% Of the available ARBs, telmisartan has a unique pharmacokinetic profile with the longest plasma elimination half-life (approximately 24 hours) and longest dissociation half-life from AT1 receptor and the strongest binding affinity to the AT1 receptor. Telmisartan has been shown to provide long-acting BP reduction throughout the 24 –hours dosing period, including during critical early

morning hours when compared with other ARBs. Amlodipine is a potent antihypertensive drugs also with a long half-life (approximately 30-50 hours). So these two antihypertensive fixed dose combination will significantly increase the antihypertensive efficacy and reduced of edema and suited to provide the additional BP reduction needed to reach BP treatment targets.

ARB IN BP LOWERING: ARE THERE ANY ANY PLEIOTROPIC EFFECTS ?

Santoso Karo Karo

Prospective analysis of the 36-year follow-up data from the Framingham Heart Study demonstrates that hypertension (BP >140/90 mmHg) predisposes powerfully to all major atherosclerotic cardiovascular (CV) disease outcomes, including coronary heart disease (CHD), stroke, peripheral artery disease and cardiac failure. Hypertension imparts a 2- to 4-fold increase in the risk for major CV events. This increased risk occurs among both men and women.

While there are already a large number of antihypertensive agents in use, many of which are effective at controlling blood pressure (BP), it is now recognized that some antihypertensive medications are associated with cardiovascular (CV) benefits beyond those of effective BP control.Angiotensin II promotes oxidative stress, vascular remodelling, inflammation, and the formation of atherosclerotic lesions. These actions, which are mediated almost exclusively by the angiotensin II type 1 (AT_1) receptor, can be blocked by administration of angiotensin II type 1 receptor antagonists (angiotensin receptor blockers [ARBs]). Olmesartan represents the newest drug in the angiotensin II receptor antagonist (or angiotensin II receptor blocker; ARB) class and has a unique tolerability and efficacy profile to support its use in hypertension.

However, the potential advantage beyond antihypertensive efficacy for plaque modification has not been well-clarified in atherosclerotic human coronary arteries. The impact of administration of olmesartan, an ARB, on the progression of coronary atherosclerosis as assessed by serial IVUS interrogation. In OLIVUS Study for the first time ARB showed regression of atherosclerotic plaque in patients who received olmesartan.

In a preliminary study Olmesartan, can prevent and reverse atherosclerotic processes including: oxidative stress, endothelial inflammation, remodelling of cardiac vascular tissues, development of atherosclerotic lesions and reduction of large plaques.These additional vascular protective effects appear to be independent of olmesartan's blood-pressure-reducing function. EUTOPIA showed that olmesartan produced significantly greater reductions in inflammatory atherosclerosis markers after 6 weeks compared with placebo.VIOS showed that olmesartan can reverse the hypertension-associated changes in small vascular structure compared with atenolol. After one year of treatment, olmesartan reduced the wall:lumen ratio of small resistance arteries from baseline (14.9%) to a value (11.1%) similar to that seen in a group of normotensive control patients (11.0%).

In a 2-year study involving hypertensive patients with carotid atherosclerosis (the MORE [Multicentre Olmesartan atherosclerosis Regression Evaluation] trial), olmesartan reduced the intima-media thickness of the carotid artery and significantly reduced the volume of large atherosclerotic plaques. These data suggest that olmesartan may reduce cardiovascular risk by simultaneously normalizing BP and reversing the

proatherogenic effects of angiotensin II. This might suggest the potential manifold action of olmesartan, apart from the antihypertensive effect, that might be beneficial, such as activity leading to atheroma stabilization and reduction.

The ROADMAP trial, randomized some 4447 diabetic patients with normoalbuminuria to daily olmesartan or placebo. In addition, participants' blood pressures were treated to maintain values under 130/80 mm Hg. After a median 3-year follow-up, the olmesartan group showed a significant advantage over placebo in delaying time to onset of microalbuminuria (the primary outcome). However, fatal cardiovascular events were more common with olmesartan. This result was seen in patients with preexisting CV disease who achieved lower BP. *(The ESC/ECC also recommends since 2010 that BP BP should not be lowered to < 120/70 mmHg in coronary heart disease).*

According to FDA, The benefits of olmesartan "continue to outweigh its potential risks when used for the treatment of patients with high blood pressure according to the drug label".The agency began a safety review of the angiotensin-receptor blocker in June 2010 after two studies showed a higher rate of cardiovascular death among patients taking olmesartan, compared with those taking placebo. The agency advises that clinicians "follow the recommendations in the drug label" when prescribing the drug.

As a BP lowering agent Olmesartan has been combined with diuretics or amlodipine to treat hypertensve patients not responsive to monotherapy. Data from a number of small clinical studies indicated that olmesartan medoxomil + amlodipine + HCTZ triple combination therapy provides antihypertensive efficacy in patients whose BP is not adequately controlled with olmesartan medoxomil + amlodipine. Olmesartan medoxomil + amlodipine + HCTZ was generally well tolerated in the TRINITY study, with adverse events usually being mild or moderate . OSCAR (Olmesartan and Calcium Antagonists Randomized Study) in 1164 Japanese elderly hypertensive provides the first evidence that olmesartan standard dose combination with CCB is superior to high dose olmesartan in reducing adverse events in elderly hypertensive patients with CV disease.

Hypertension in CKD patients

Tunggul Diapari Situmorang MD
Cikini CCI Hospital, MRCC Hospital - Jakarta

Hypertension is present in approximately 80 to 85 percent of patients with CKD and is a risk factor for faster progression of kidney disease and development and worsening of CVD.Only small proportion of patients with CKD stage 1-4 can reach ESRD. Cardio-vasculer (CV) morbidity and mortality is markedly increased at all stages of renal dysfunction.Data from the MDRD in Renal Disease Study, showed that the prevalence of hypertension rose progressively from 65 to 95 percent as the GFR rate fell from 85 to 15 mL/min per 1.73 m2.The contribute factors include sodium retention as a primary importance,increased activity of the renin-angiotensin system,enhanced activity of the sympathetic nervous system and secondary hyperparathyroidism.

Treatment with erythropoietin,impaired nitric oxide synthesis and endothelium-mediated vasodilatation has been demonstrated in patients with CKD.Treatment of even mild hypertension is important in patients with chronic CKD to protect against both progressive renal function loss and cardiovascular disease.Some antihypertensive agents also slow the progression of kidney disease by mechanisms in addition to their antihypertensive effect.

The goal of blood pressure treatment is depends upon the degree of **proteinuria** (the 2011 KDIGO guideline). In patients with proteinuric positif (≥ 500 mg/day),the blood pressure should be lowered to less than 130/80 mmHg,while in proteinuric negative patients,(≤ 500 mg/day),the blood pressure should be lowered to less than 140/90 mmHg.Specific goals related to a reduction in urinary protein excretion have been formulated to slow the rate of progression of proteinuric CKD patients. ACE inhibitor or angiotensin II receptor blocker (ARB) is the first-line therapy in CKD patients with proteinuric.If further antihypertensive therapy is required, diuretic and a non-dihydropyridine calcium channel blocker as second line and third line. In non proteinuric CKD patients ,diuretic and dihydropyridine channel blockers can be added as a second and third line treatment.

Key word : ckd, anti hypertensive, proteinuria, goal

Hypertension in elderly

Yuda Turana
Dept of Neurology ,Medical Faculty of Atma Jaya Indonesia Catholic University, Jakarta/
Center of Health Research, Atma Jaya Indonesia Catholic University, Jakarta

Hypertension has become a challenging disease to control and treat in elderly. As the elderly population rises, the prevalence of hypertension also increases.

Hypertension in the elderly must be treated with special caution, taking comorbid diseases and physiology alteration as considerations. Drug treatment should be tailored according to the risk factors, target organ damage and associated cardiovascular and non-cardiovascular conditions that frequently found in the elderly. Because of the increased risk of postural hypotension, BP should always be measured also in the erect posture.

Initial doses and subsequent dose titration should be more gradual because of a greater chance of undesirable effects, especially in very old and frail subjects. BP goal is similar with younger patients, i.e. <140/90mmHg or below, if tolerated. Many elderly patients need two or more drugs to achieve blood pressure control.

Drug treatment can be initiated with thiazide, calcium antagonists, angiotensin receptor antagonists, ACE inhibitors, and b-blockers, in line with general guidelines. Trials specifically addressing treatment of isolated systolic hypertension have shown the benefit of thiazides and calcium antagonists but subanalysis of other trials also show efficacy of angiotensin receptor antagonists.

Key words : hypertension - elderly

Treating Hypertensive Diabetic Patients: What Should We Know ?

Zulkhair Ali
Div. Nephrology & Hypertension, Dept. Medicine, Medical Faculty
Sriwijaya University, Moh. Hoesin Hospital Palembang

T2DM and hypertension are common across all populations and frequently coexist. Data showing that patients with diabetes have, on average, a 2-fold greater risk of renal disease and a 3-fold greater risk of CVD in comparison with subjects without diabetes. An early aggressive approach is recommends in the management of hypertension as part of overall risk factor reduction.

Because angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) areassociated with favorable effects on renal function and may improve insulin sensitivity, they are ideal first choices in the treatment of patients with both diabetes and hypertension (*grade A*). Diuretics have also been shown to be effective in the treatment of hypertension, both alone and in combination therapy, and likely are even more effective in patients with excess sodium intake or impaired sodium excretion.β-Adrenergic blocking agents (BBs) may likewise precipitate or exacerbate T2DM. The use of calcium channel blockers (CCBs) has been associated with both benefits and adverse outcomes in a variety of study populations with diabetes. The nondihydropyridine CCBs (diltiazem and verapamil) mayreduce microalbuminuria, whereas dihydropyridine CCBs mayincrease it. CCBs have proved safe and effective in combination regimens with ACEIs, diuretics, and BBs.

The target of glycemic control is A1C less than 7%. The treatment including lifestyle modification, insulin therapy, and oral hypoglycemic agent.At the time of diagnosis, the treatment with metformin in combination with lifestyle changes and continuing timely augmentation of therapy with additional agents (including early initiation of insulin therapy) as a means of achieving and maintaining recommended levels of glycemic control. Intensive diabetes management with the goal of achieving near-normoglycemiahas been shown in large prospectiverandomized studies to delay the onset ofmicroalbuminuria and the progression ofmicro- to macroalbuminuria in patientswith T1DM and T2DM. When renal function decrease, the hypoglycemic agent wichis eliminated via renal excretion and accumulation in renal impairment increases the risk for severe side-effects, such ashypoglicemia and lactic acidosis. The DPP-4 inhibitor, Linagliptin, is an alternative choice for T2DM patients with declining renal function, because its predominantly excreted via the enterohepatic system.

Keywords : Hypertension; Diabetes Mellitus;

Blood Pressure Lowering or Cardiovascular Protection : Which One Will You Choose?

Yudi Her Oktaviono

Management of hypertension should be based on the considerations of the strength of available evidence on the benefits associated with antihypertensive treatment as well as on the comparative benefits of the various classes of drugs. With regard to cause-specific events antihypertensive treatment is associated with a major reduction in the risk of fatal or non-fatal stroke (about 30–40%), but, coronary events are reduced as well, though to a lesser degree (20%).

In addition, treatment also appears to cause a large reduction in the incidence of heart failure. The Blood Pressure Lowering Treatment Trialists' (BPLTT) collaboration metaanalyses, included about 22,000 hypertensive patients, showed significant benefits from a more intense blood pressure reduction on stroke and major cardiovascular events.

The demonstration of the beneficial effects of blood pressure lowering has made it ethically unacceptable to perform placebo controlled trials i.e. with an untreated placebo group. This has provided additional evidence on the beneficial effect of various antihypertensive drugs also documenting that the benefit may be substantial even when blood pressure reductions are small and the initial blood pressure is below the traditional cutoff defining hypertension. These studies provide important information on the relative efficacy of the various classes of antihypertensive agents, but their straightforward interpretation is often made difficult by the failure to achieve comparable blood pressure values with the different treatments.

Even small blood pressure differences may be accompanied by large differences in outcome. Finally, trials comparing different agents actually compare regimens only initiated on different agents, since the majority of randomized subjects ends up with combination therapy including agents similarly distributed in the comparison groups.

Comparative randomized trials show that for similar blood pressure reductions, differences in the incidence of cardiovascular morbidity and mortality between different drug classes are small, thus strengthening the conclusion that their benefit largely depends on blood pressure lowering per se. All recent meta-regression analyses underline the important role of blood pressure lowering for all cause-specific events, with the exception of heart failure: whenever systolic blood pressure is reduced by 10 mmHg, independent of the agent used, both stroke and coronary events are markedly reduced.

Calcium antagonists showed less protection compared with diuretics/beta - blockers, ACEIs and ARBs with respect to prevention of new onset heart failure. Meta-regression analyses also suggest that some antihypertensive agents may exert some cause-specific beneficial effects that are blood pressure independent. This effect, however, is definitively smaller than the

dominant protective effect exerted by lowering blood pressure. Because in many patients more than one drug is needed, emphasis on identification of the first class of drugs to be used is often futile. Nevertheless, there are many conditions for which there is evidence in favour of some drugs versus others either as initial treatment or as part of a combination.

Keywords: Hypertension, ARB, CV Protection, Combination Therapy

THE NEUROPROTECTIVE EFFECTS OF CALCIUM CHANNEL BLOCKERS IN STROKE

Moh Hasan Machfoed
Department of Neurology
Medical Faculty of Airlangga University/
Dr. Soetomo Hospital – Surabaya

Stroke is a leading cause of death and disability worldwide. The importance of lowering blood pressure for reducing the risk of stroke is well established. There are a lot of drugs that are in experimental stage for treatment of stroke. Among them are calcium channel blockers (CCBs) that have, in animal models, different effectiveness in healing of ischemic damage in brain.

Mechanism of CCBs action in cerebral ischemia is still unclear, but antioxidative property is supposed to be implicated. Prevention of neuronal damage by CCBs with antioxidative effects after transient focal ischemia were shown in rats.

However, not all the benefits of antihypertensive treatments in stroke can be accounted for by reductions in BP and there may be differences between antihypertensive classes as to which provides optimal protection. Dihydropyridine calcium channel blockers, such as amlodipine represent the antihypertensive drug class with the strongest supportive data for the prevention of stroke.

Abstrak

PERAN ANTIHIPERTENSI KOMBINASI DALAM MENINGKATKAN EFEKTIFITAS TERAPI
Fokus pada kombinasi Olmesartan dan Amlodipin

Ketut Suwitra,
Divisi Ginjal dan Hipertensi bagian SMF Ilmu Penyakit Dalam
FK Unud/RSUP Sanglah Denpasar

Joint Committee National (JNC) 7 2003 dan *European Society of Hypertension (ESH)/ European Society of Cardiology (ESC) 2007,* keduanya merekomendasikan pemakaian obat antihipertensi kombinasi dalam terapi hipertensi dengan kondisi-kondisi tertentu. JNC 7 2003 mengatakan bahwa, 1) kebanyakan pasien hipertensi membutuhkan dua atau lebih obat antihipertensi untuk mencapai sasaran tekanan darah <140/90 mmHg atau <130/80 mmHg bagi yang diabetes atau mengalami penyakit ginjal kronik; 2) bila tekanan darah >20/10 mmHg di atas sasaran, dianjurkan untuk memulai terapi dengan obat antihipertensi kombinasi, salah satu di antaranya adalah diuretik.

ESH/ESC 2007 dalam statemennya mengatakan, 1) kebanyakan pasien hipertensi membutuhkan dua atau lebih obat antihipertensi untuk mencapai tekanan darah sasaran, 2) kombinasi obat antihipertesi dosis rendah seharusnya dipilih sebagai langkah pertama pada terapi hipertensi grade 2 atau 3, atau pasien dengan risiko kardiovaskuler tinggi atau sangat tinggi.

Rekomendasi-rekomendasi di atas didasarkan atas berbagai studi yang sudah membuktikan bahwa, 1) terapi hipertensi dengan obat antihipertensi kombinasi lebih efektif dibandingkan dengan monoterapi, 2) kepatuhan pasien menjadi lebih tingi, 3) frekuensi efek samping obat menjadi lebih rendah.

Beberapa studi juga sudah merekomendasikan jenis-jenis obat anti hipertensi apa saja yang dapat dikombinasikan di antaranya, 1) diuretik dengan *Angiotensin Converting Enzyme(ACE) inhibitor, Calcium Channel Blocker (CCB) dan Angiotensin Receptor Blocker (ARB,* 2) *ACE inhibitor* dengan *CCB,* 3) *ARB* dengan *CCB.* Sedangkan kombinasi antara ACE inhibitor dan ARB hanya dipergunakan pada kondisi tertentu yaitu hipertensi dengan proteinuria yang berat (ONTARGET *study* 2009*).* Studi-studi di atas juga membuktikan bahwa kombinasi dalam tablet tunggal (*fixed dose*) lebih menguntungkan dibandingkan tablet terpisah.

Kombinasi Olmesartan (mewakili ARB) dan Amlodipin (mewakili CCB), dalam berbagai studi juga meperlihatkan efektifitas yang baik. Hal ini disebabkan karena 1) kedua klas obat tersebut bekerja pada titik tangkap yang berbeda yaitu, ARB pada resistensi perifer sedangkan CCB pada otot polos arteriol, 2) pada ginjal, ARB mendilatasi vas eferen sedangkan CCB mendilatasi vas aferen. Kombinasi kedua klas obat tersebut juga mengurangi efek samping oedem yang sering ditimbulkan oleh CCB yang diberikan tersendiri.

Kata kunci : anti hipertensi kombinasi, olmesartan dan amlodipin.

SODIUM DAN HIPERTENSI
ASPEK PATOGENESIS DAN TATALAKSANA

Ketut Suwitra
Divisi Ginjal dan Hipertensi Bagian SMF Ilmu Penyakit Dalam
FK Unud/RSUP Sanglah Denpasas

Studi-studi epidemiologis menunjukan dugaan kuat, bahwa asupan sodium pada makanan berperan terhadap terjadinya peningkatan tekanan darah dan prevalensi hipertensi di masyarakat. Pada negara-negara yang belum berkembang, dimana masyarakatnya tidak banyak mengkonsumsi sodium, prevalensi hipertensi lebih rendah dibandingkan negara-negara yang sudah maju. Dalam beberapa ratus tahun saja, telah terjadi peningkatan konsumsi sodium pada negara maju dari 0,5 gr menjadi 10 – 12 gr NaCl perhari, diiringi dengan peningkatan prevalensi hipertensi menjadi sekitar 20 – 30 orang perjuta penduduk pertahun. Sumber sodium bukan semata-mata dari makanan/minuman yang kaya sodium, tapi juga berasal dari proses penyajian makanan itu sendiri (*food processing*).

Patofisiologi peran sodium terhadap kejadian hipertensi masih belum pasti, tapi diduga erat kaitannya dengan retensi sodium di cairan ekstraseselular akibat penurunan ekskresinya oleh ginjal. Retensi sodium mengakibatkan peningkatan volume plasma (*volume dependent mechanism*), yang selanjutnya diikuti oleh peningkatan *cardiac out put*, memicu respon autoregulasi, dan diakhiri dengan peningkatan resistensi perifer. Ion sodium juga dapat memperkuat kontraksi otot polos vascular yang ditimbulkan oleh substansi vasokonstriktor endogen. Tapi diduga juga ada peran lain di luar peningkatan volume plasma (*volume independent mechanism*).

Pembatasan asupan sodium (*sodium restriction*) telah menjadi kesepakatan (*guide line*) dalam terapi hipertensi. *Randomized controlled clinical trial* pada penderita hipertensi membuktikan bahwa, pengurangan asupan sodium menjadi 80 – 100 mmol yang setara dengan 4,7 – 5,8 gr NaCl perhari, dari sebelumnya sebanyak 180 mmol yang setara dengan 10,5 gr NaCl perhari; telah menurunkan tekanan darah sistolik sebesar 4 – 8 mmHg. Pengaruh ini terlihat sangat nyata pada kulit hitam (*blacks*), usia lanjut dan hipertensi yang disertai diabetes atau penyakit ginjal kronik. Penderita dianjurkan untuk mengurangi asupan sodium dengan mengurangi makan garam dan menghindari makanan yang sudah diproses (*processed food*). Asupan sodium dianjurkan 80 – 100 mmol, setara dengan kurang dari 5 gr NaCl perhari.

Kata kunci : sodium retensi, sodium restriksi

Are All Calcium Channel Blockers (CCBs) the same ? Lercanidipine and Renoprotection

Mohammad Yogiantoro
Sub Departemen Ginjal & Hipertensi,
Departemen – SMF Ilmu Penyakit Dalam
FK UNAIR – RSUD Dr. Soetomo

ABSTRAK

Kalsium antagonis (CCB) dihidropiridin sering dilaporkan menimbulkan efek samping sehingga kita harus menghentikan penggunaannya atau mengganti dengan obat lain yang berbeda kelas. Lercanidipine (suatu CCB dihidropiridin) merupakan kalsium antagonis baru dengan sifat lipofilik dan selektifitas pembuluh darah yang tinggi, akibatnya dapat memberi efek anti hipertensi yang bertahap dan berlangsung lama, karena juga memiliki tolerabilitas yang baik dibandingkan dengan CCB dihidropiridin yang lain.

Walaupun, masih banyak bahasan kontroversi tentang efek renoproteksi kalsium antagonis, namun juga terbukti semakin banyak manfaat yang diperoleh. Akhirnya disarankan untuk menambah kalsium antagonis untuk dapat memperbaiki fungsi ginjal pada penderita yang sebelumnya sudah diobati dengan *ACE inhibitor* maupun *Angiotensine Receptor Blocker* (ARB).

Pada **Zafra Study** (the Zanidip en Funcion Renal Alterada) suatu studi untuk menguji efek lercanidipine (suatu CCB dihidropiridin baru yang unik) dalam kemampuannya memperbaiki fungsi ginjal penderita CKD dengan proteinuria. Ternyata terbukti lercanidipine dapat memperbaiki klirens kreatinin dan menurunkan proteinuria secara bermakna. Jadi lercanidpine adalah CCB dihidropiridin yang renoprotektif.

Maka lercanidipine menjadi satu-satunya CCB dihidropiridin yang mempunyai sifat anti proteinuria, karena CCB dihidropiridin yang lain justru meningkatkan proteinuria. Hal ini berbeda dengan CCB non dihidropiridin yang memang sudah terbukti mempunyai sifat anti proteinuria misalnya diltiazem dan verapamil.

Lercanidipine, the unique dyhidropiridine CCB, adalah generasi baru lipofilik CCB, rumus molekulnya yang khusus membuat lercanidipine ini berebda dengan CCB dihidropiridin yang lain. Gugus *"protonated amin group"* membuat lercanidipine cepat hilang dari plasma sehingga membuat lercanidipine ini bersifat *short plasma half life*.

Gugus *"lipophilic anchor group"* membuat lercanidipine tersebut melekat kuat di membran sel dan bertahan lama di sini sehingga lercanidipine bersifat *long duration of action*.

	Lercanidipine	Amlodipine	Felodipine
Renal arterial Tree			
larger and medium	Dilatation	Dilatation	Dilatation
small arterioles	Dilatation	no effect	no effect
Glomeruli			
Mesangial cell	⇓	⇓	n.a
Afferent arterioles	**Dilatation**	**Dilatation**	**Dilatation**
Efferent arterioles	**Dilatation**	**Less effect**	**Less effect**
Glomerular pressure	**Normalized**	Increased	Increased
Renal regulation Block	n.a	completely	completely
Time-dependent Renal Injury	**Less**	More	More

Ginjal dan Hipertensi V.V

RP Sidabutar Memorial Lecture.

Harun Rasyid Lubis.
Divisi Nefrologi dan Hipertensi
Departemen Ilmu Penyakit Dalam
FK-USU Medan.

Ginjal- Hipertensi.

Guyton dan Coleman pada tahun 1967 menulis mengenai regulasi jangka panjang sirkulasi dan interrelasi antara volume berbagai cairan tubuh. Didalam menjaga keseimbangan cairan dan elektrolit tubuh maka ada mekanisme yang melibatkan tekanan filtrasi glomerulus dengan banyaknya exkresi air dan elektrolit yang, dalam keseimbangan, selalu sama dengan asupan keduanya. Konsep ini dinamakan Pressure-Natriuresis. Konsep ini menerangkan bagaimana peningkatan tekanan darah dibutuhkan apabila kemampuan glomeruli, dalam mengeluarkan air dan elektrolit, mengalami kemunduran. Keadaan seperti ini didapati pada hipertensi primer[1], dan juga oleh Kimura et al [2] ditunjukkan pada hipertensi sekunder.

Adanya konsep ini menimbulkan gagasan bahwa hipertensi primer berawal dari ketidak mampuan ginjal/glomeruli dalam menjaga keseimbangan air dan elektrolit. Untuk tetap memelihara keseimbangan ini maka diperlukan peningkatan tekanan filtrasi di glomeruli, yang berarti juga peningkatan tekanan darah secara sistemik. Dan ini adalah hipertensi primer. Adakah bukti bahwa pada hipertensi primer glomeruli tidak utuh? Uraian berikut memberi beberapa fakta. Memang sejak abad ke 17 Richard Bright sudah menduga bahwa peningkatan tekanan darah, yang menyebabkan pembesaran dan kelemahan jantung, timbul dari ginjal yang rusak.

Selanjutnya penemuan **renin** oleh Tigerstedt dan Bergmann pada tahun 1898 dan experimen Goldblatt pada tahun 1934 yang menunjukkan terjadinya hipertensi dengan konstriksi partial dari a. renalis, memantapkan peran ginjal dalam terbentuknya hipertensi. Bukti bukti dari binatang percobaan juga jelas. Dahl dan Heine pada tahun 1975 melaporkan hasil transplantasi silang pada tikus percobaan. Bila pada tikus hypertensive prone (s) strain yang hipertensi, dicangkokkan ginjal tikus dari strain yang sama maka tekanan darahnya akan meningkat sedikit saja. Bila ginjal yang dicangkok berasal dari hypertensive resistent ® strain, maka tekanan darah akan turun dengan tajam.

Sebaliknya pula bila pada tikus R-strain mendapat ginjal dari R-strain maka tekanan darah akan menetap, sedangkan bila ginjal berasal dari S-strain maka hipertensi akan muncul. Ini disimpulkan sebagai bukti bahwa faktor genetik didalam ginjal dapat mengendalikan tekanan darah jangka panjang[3]. Penelitian pada kelompok tikus yang dibiakkan secara khusus dan ginjalnya dicangkokkan kepada SHR di Greifswald, Jerman menunjukkan bahwa hipertensi pada SHR yang mendapat cangkok, tergantung dari latar belakang genetik dari ginjal yang dicangkokkan[4].

Beberapa peneliti Inggeris, pada tahun 1987, Barker et al, mempublikasikan suatu studi epidemiologis yang mendapatkan bahwa tingginya tekanan darah pada dewasa berbanding terbalik dengan berat badan lahir. Korelasi ini tidak berhubungan dengan usia gestasi, sehingga diyakini korrelasi ini terkait dengan pertumbuhan in utero[5]. Hubungan ini juga telah ditunjukkan pada bayi lahir dengan berat badan sangat rendah (<1500 mg) dan bayi yang pre-term[6].

Konsep ini juga disebut sebagai "fetal programming" dari hipertensi essensial. Selanjutnya Brenner mengemukakan konsepnya yang terkenal sebagai "low nephron number" sebagai awal dari mekanisme patofisiologis timbulnya hipertensi primer[7].

Timbullah pertanyaan, apakah benar pasien hipertensi primer mempunyai defek pada nefron nya? Sealey dkk melakukan biopsy ginjal pada banyak pasien hipertensi dan mendapatkan bahwa banyak diantara glomeruli memang mempunyai defek, sehingga secara keseluruhan nampak *heterogeneity* dari glomeruli tersebut. Hai ini tidak dijumpai pada ginjal orang yang normotensi[8]. Kemudian, pada tahun 2003, kelompok dari Heidelberg menemukan metode penghitungan jumlah glomeruli pada ginjal dan selanjutnya melakukan penelitian pada pasien yang mengalami kecelakaan lalu lintas dengan autopsy dan penghitungan jumlah glomeruli pada setiap ginjal.

Mereka menjumpai bahwa dari 10 korban yang mempunyai riwayat hipertensi, dengan kriteria inklusi dan eksklusi yang jelas, jumlah rata rata glomeruli pada setiap ginjal adalah 703,379, sedang pada 10 korban dengan riwayat normotensi jumlahnya 1 429 200 ($p<0.001$). Disamping itu kelihatan bahwa volume masing masing glomerulus $6{,}5.10^{-3}$ mm^3 vs $2{,}79.10^{-3}$ mm^3 (p,0.001). Besarnya volume dari glomeruli subjek hipertensi menunjukkan adanya hipertrofi dan hiperplasi dari glomeruli tersebut[9].

Dengan adanya temuan maka sempurnalah pembuktian bahwa hipertensi primer berawal dari defek glomeruli dan sudah bermula dari sejak pertumbuhan in utero (fetal programming). Mekanisme yang berlaku pada hipertensi ini adalah terjadinya mekanisme Pressure –Natriuresis di ginjal. Didalam terapi mekanisme ini juga berperan, seperti ditunjukkan oleh banyak penelitian bahwa terapi hipertensi yang berhasil, meningkatkan natriuresis dan menurunkan tekanan darah[10].

Hipertensi – ginjal.

Disisi lain dari spektrum Hipertensi dan Ginjal Vice-Versa ini adalah temuan dari USRDS yang menunjukkan bahwa 27 % dari End Stage Renal Disease (ESRD), atau Penyakit Ginjal Tahap Akhir (PGTA), yang menjalani RRT, berasal dari hipertensi, menyusul DM yang memberi kontribusi terbanyak, 50,1% [11]. Pada tahun 1996 Klag sudah menghitung risiko terjadinya PGTA dari setiap klassifikasi hipertensi yang tertera pada JNC VI. Terlihat bahwa makin tinggi kelasnya maka makin tinggi pula risiko untuk sampai kepada PGTA[12]. Sementara itu terapi terhadap hipertensi telah pula ditunjukkan mengurangi risiko tersebut[13,14].

Suatu penelitian secara kohort retrospektif, di desa Blahbatuh, Gianyar di Bali, mengukur tekanan darah dan kreatinin serum penduduk pada tahun

2005 dan pada tahun 2011. Populasi dengan eGFR >60 ml/mnt pada awalnya ada sebanyak 302 orang, dan setelah 6 tahun yang masih survive dan dapat diperiksa ulang adalah 136 orang dan yang memenuhi criteria inklusi sebanyak 99 orang. Dari jumlah ini didapati bahwa mereka yang mempunyai e-GFR >60 ml/mnt mengalami peningkatan TDS 5,6 mmHg, sedang pada mereka yang e-GFR nya <60 ml/mnt dijumpai peningkatan 10,7 mmHG. Untuk tekanan diastolic angka angka ini masing masing adalah 0.1 mmHg dan 4,4 mmHg.

Artinya adalah bahwa pada mereka yang setelah 6 tahun menunjukkan penurunan fungsi ginjal hingga mencapai grade PGK stad 3, dengan eGFR <60 ml/mnt, kenaikan tekanan darahnya cendrung lebih tinggi, baik sistolik maupun diastolik, dibanding mereka yang eGFR nya menetap >60 ml/mnt[15] Suatu studi terbaru yang dilakukan di Norwegia, dimana diukur tekanan darah secara ABPM dan GFR dengan metode Iohexal clearance, mendapatkan hubungan yang bermakna antara penaikan tekanan darah dengan penurunan GFR, baik pada tekanan darah yang masih normal maupun pada tekanan darah yang tinggi[16].

Vice-versa

Seluruh uraian diatas menunjukkan bagaimana eratnya keterkaitan ginjal dan hipertensi, sehingga cendrung kausatif, pada kedua arah (vice-versa), sehingga sangat beralasan bagi perintis pengembangan pelayanan penyakit ginjal dan hipertensi di Indonesia, Alm Prof. RP Sidabutar SpPD-KGH menyatukan keduanya dibawah satu nama yaitu Poliklinik Ginjal dan Hipertensi di RSCM, dibawah asuhan Departemen Ilmu Penyakit Dalam pada tahun 1970, yang selanjutnya diikuti oleh seluruh RS Pendidikan diseluruh Indonesia.

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NEUROLOGIST'S PERSPECTIVE ON THE COLLABORATION IN FIGHTING HYPERTENSION AND ITS COMPLICATIONS

Moh Hasan Machfoed
Department of Neurology
Medical Faculty of Airlangga University/
Dr. Soetomo Hospital – Surabaya

Complications of hypertension are clinical outcomes that result from persistent elevation of blood pressure. Hypertension is a risk factor for all clinical manifestations of atherosclerosis since it is a risk factor for atherosclerosis itself.

It is an important risk factor for brain infarction and hemorrhage. Approximately 85% of strokes are due to infarction and the remainder are due to hemorrhage, either intracerebral hemorrhage or subarachnoid hemorrhage. Hypertension is also associated with impaired cognition in an aging population, and causes hypertensive encephalopathy.

Multi discipline collaborative work in fighting hypertension and its complication is very important. It can be performed by several ways. It includes promotion the awareness of cerebrovascular diseases, service and training.

Erythropoiesis Stimulating Agents (ESA) and Hypertension

Suhardjono
Div of Nephrology and Hypertension,
Dept of Medicine
Faculty of Medicine University of Indonesia,
RS DrCiptoMangunkusumo

Kidney has an important role in renal anemia through production of erythropoietin hormone (EPO) which stimulates bone marrow. As chronic kidney disease (CKD) progress, EPO response to anemia will decrease. Erythropoiesis-stimulating agents or ESA is a group of medications that increase the production of red blood cells. ESAs stimulate body's bone marrow for producing more red blood cells. Recently therehas beenexpanding increased in the clinical use of ESA, from initial use in severely anemic hemodialysis patients to predialysis patients and to patients with tumor- and/or chemotherapy-induced decreases in red blood cell mass. Unfortunately this drug has been reported to be used illegally as a doping in sport games.

But as other drugs ESAs have limitations. There aremany evidences from clinicalstudies that ESA treatment induces significant and sustainedincreases in mean arterial BP in both normal subjects andpatients with CKD. Recently the FDA issued a warning that more conservative dosing guidelines should be used for ESAs when they are used to treat anemia in patients with chronic kidney disease because of an increased risk of cardiovascular events, including stroke, thrombosis and death. The mechanisms responsible for these excess cardiovascularand mortality events are not fully elucidated, but ESA-inducedarterial hypertension is a leading candidate. CHOIR predialysisCKD trial showed that onlyincreased ESA dose was significantly associated with the compositeendpoint of death, coronary heart failure, stroke, ormyocardial infarction.

How EPO therapy may raise the blood pressure is not well understood. Several factors that may contribute to the hypertensive response have been identified. These include; high dose, prior personal or family history of hypertension, diminished production of nitric oxide, marked increase in intracytosolic calcium levels, enhanced vascular alpha adrenergic sensitivity, increased plasma endothelin levels, arterial remodeling through stimulation of vascular cell growth, activation of the renin-angiotensin system, elevation of the thromboxane prostacyclin ratio in vascular tissue.

Therapy of EPO-induced hypertension begins with prevention. To prevent hypertension, blood pressure must be closely monitored in all patients with chronic kidney disease, particularly during ESA initial treatment. The risk of hypertension can be ameliorated by raising the hematocrit slowly.If there has been a rapid rise in the hemoglobin levels, there may be a reduction in the EPO dose.In CKD patients, the risk may also be lessened by aiming for the current target levels for hemoglobin, which are 10 to 11 g/dL. A meta-analysis on nine studies, which included the CREATE study, also reported a higher risk of poorly-controlled blood pressure in patients targeted to higher

hemoglobin levels. Administration route of ESA also influence blood pressure. Approximately 20 to 30 percent of patients who receive ESA intravenously for the anemia of chronic kidney disease may develop an elevation in diastolic pressure of 10 mmHg or more. In comparison, the blood pressure (BP) is less likely to rise after subcutaneous administration.Patients who still become hypertensive can be treated with fluid removal (via dialysis or, if the patient has only CKD, diuretics) and the administration of antihypertensive agents.

In conclusion, ESA is a new drug group for correcting anemia in CKD which can induces high blood pressure and fatal cardiovascular complications. The cause of hypertension is multifactorialsnot related to Hbincrement. Many complications can be preventedif we aware of it,therefore we must follow the evidence based guideline, including indications, doses, Hb target, etc.Closed monitoring of patient's blood pressure as well as Hb level is a must to prevent hypertension.

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