SAFETY AND EFFICACY OF LOSARTAN (50 MG) IN POST DIALYSIS EUVOLEMIC HYPERTENSIVE PATIENTS: A SINGLE-BLIND RANDOMIZED CONTROL TRIAL

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by

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To

My precious grandparents, parents, uncles and my wife

who gave me inspiration, unconditional sacrifice and love for completing

this scholastic work

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LIST OF ACRONYMS AND ABBREVIATIONS

Adverse drug reaction	ADR
Angiotensin-converting enzyme	ACE
Angiotensin receptor blocker	ARB
Angiotensin converting enzyme inhibitor	ACE inhibitor
Asymmetric di-methyl-arginine	ADMA
Bioimpedance spectroscopy	BIS
Body composition monitor	BCM
Brain natriuretic peptide	BNP
Blood pressure	BP
Chronic kidney disease	CKD
Chronic kidney disease-Mineral and Bone Disorder	CKD-BMD
Glomerular filtration rate	GFR
C-reactive protein	CRP
Congestive heart failure	CHF
Coronary artery disease	CAD
Cockroft Gault	CG
Estimated glomerular filtration rate	eGFR
End stage renal disease	ESRD
Extracellular water	ECW
Erythropoietin	EPO
Fluid overload	FO
Haemodialysis	HD
Hydrochlorothiazide	HCTZ

Intracellular water	ICW
Joint National committee	JNC
Kidney Disease: Improving Global Outcome	KDIGO
Left ventricular hypertrophy	LVH
Malnutrition-inflammation complex syndrome	MICS
Modification of Diet in renal disease	MRDRD
National kidney foundation-Kidney Disease Outcomes Quality Initiative	NKF-KDOQI
N-terminal pro brain natriuretic peptide	NT-pro BNP
Over hydration	OH
Once daily	OD
Prostaglandin E_2	PGE2
Peritoneal Dialysis	PD
Per million population	PMP
Randomized control trial	RCT
Renin angiotensin aldosterone system	RAAS
Systolic blood pressure	SBP
Total body water	TBW
United States	US
Upper respiratory tract infection	UPTI
United States Renal Data System	USRD
World Health Organisation	WHO

KESELAMATAN DAN KECEKAPAN LOSARTAN (50MG) KEPADA PESAKIT EUVOLEMIC TEKANAN DARAH TINGGI SELEPAS DIALISIS: SINGLE BLIND PERCUBAAN KAWALAN RAWAK

ABSTRAK

Pesakit buah pinggang peringkat akhir (ESRD) memerlukan terapi penggantian cecair sepanjang hayat atau pemindahan buah pinggang. Hampir 60-90% pesakit hemodialisis adalah hipertensi. Kajian ini bertujuan untuk membuktikan patofisiologi hipertensi dalam kalangan pesakit hemodialisis menyimpulkan bahawa 90% kes disebabkan oleh lebihan natrium dan isipadu (bergantung kepada isi padu), manakala majoriti kes selebihnya mempunyai aktiviti renin (renin dependent), yang membawa kepada renin tekan darah tinggi yang bergantung kepada renin. Oleh sebab terdapat perubahan isipadu pemalar semasa rawatan dialisis, kemungkinan besar pengaktifan sistem renin angiotensin aldosterone (RAAS) berlaku semasa dialisis. Pengaktifan RAAS akan menyebabkan vasoconstriction arteri dan kenaikan tekanan darah walaupun tahap penghidratan pesakit adalah normal. Oleh itu, di akhir sesi dialisis, pesakit akan memperoleh kadar normal cecair di dalam badan walaupun masih hipertensi. Monitor komposisi badan (BCM) membantu menganggarkan tahap penghidratan pesakit dan berat kering dengan tepat. Memandangkan kepentingan sistem RAAS, satu kajian telah dirancang untuk menilai keselamatan dan keberkesanan losartan 50 mg (dos losartan yang disyorkan oleh Garis Panduan Klinikal K/DOQI) untuk mengurangkan tekanan darah dalam kalangan pesakit hipertensi euvolemik pasca dialisis dan memerhatikan kelangsungan hidup mereka Trend. Percubaan pelbagai pusat, prospektif, rawak, single-blind dilakukan untuk menilai kesan kehilangan 50 mg setiap hari (EOD) sekali sehari (OM) dalam

kalangan pesakit hipertensi euvolemik selepas dialisis. Penilaian euvolemik pasca dialisis dilakukan oleh monitor komposisi badan (BCM). Covariate Adaptive Randomization digunakan oleh peserta ke atas lengan standard atau tangan intervensi, dan digunakan selama dua belas bulan. Ujian tekanan darah di peringkat awal, intra dan pasca-dialisis (BP) direkodkan, dan sebarang kesan buruk disahkan menggunakan skala Naranjo. Trend survival dianalisis menggunakan analisis Kaplan-Meier, dan ujian statistik Wilcoxon dilakukan untuk memerhatikan perbezaan tekanan darah dari awal hingga 12 bulan menggunakan SPSS versi 20. Daripada 229 pesakit yang dianalisis melalui monitor komposisi badan, 96 pesakit (41.9 %) dikenalpasti sebagai hipertensi euvolemik post-dialisis. Sampel akhir 88 pesakit (40.1%) telah dipilih secara rawak kepada kumpulan standard dan intervensi. Sejumlah 21 pesakit (47.8%) ialah lelaki dan 23 pesakit (52.2%) ialah perempuan telah dipilih secara rawak kepada lengan standard, berbanding 24 pesakit (54.5%) lelaki dan 20 pesakit (45.5%) wanita kepada lengan intervensi. Selepas susulan systolic pra-dialisis selama 12 bulan dan diastolic, diastolic intradialisis dan diastolic tekanan darah berkurangan dari garis dasar dalam kalangan pesakit-pesakit intervensin. Walau bagaimanapun, penurunan tekanan darah sistolic pra-dialisis yang ketara selepas 12 bulan susulan hanya dilihat untuk pesakit lengan standard. Sebanyak enam kematian dilaporkan di kalangan pesakit lengan standard berbanding 2 kematian di kalangan lengan intervensi. Antara lengan intervensi, dua kes hyperkalemia dilaporkan telah mengakibatkan mereka terkeluar dari kumpulan intervensi. Bukan sahaja penggunaan Losartan 50 mg mencapai penurunan tekanan darah yang signifikan di kalangan pesakit hipertensi euvolemik pasca dialisis, tetapi pesakit-pesakit ini juga mempunyai kadar kematian yang lebih rendah. Selain itu, losartan 50mg dapat diterima dengan baik di kalangan peserta kajian

SAFETY AND EFFICACY OF LOSARTAN (50 MG) IN POST DIALYSIS EUVOLEMIC HYPERTENSIVE PATIENTS: A SINGLE-BLIND RANDOMIZED CONTROL TRIAL

ABSTRACT

Patients with End Stage Renal Disease (ESRD) require lifelong fluid replacement therapy or renal transplant. Almost 60-90 % haemodialysis patients are hypertensive**. S**tudies aimed at elucidating the pathophysiology of hypertension among haemodialysis patients concluded that 90% cases resulted from sodium and volume overload (volume-dependent), while the majority of the remaining cases have elevated renin activity (renin dependent), leading to renin dependent high blood pressure. Since there is a constant volume variation during dialysis session, there is a strong possibility for activation of Renin Angiotensin Aldosterone System (RAAS) during dialysis that causes high blood pressure even if they are post dialysis euvolemic. Keeping in view the importance of RAAS system, current study was designed to assess the safety and effectiveness of losartan 50 mg (losartan dose recommended by K/DOQI Clinical Practice Guidelines) in reducing blood pressure among post-dialysis euvolemic hypertensive patients and observing their survival trends. A single centre, prospective, randomised, single-blind trial was conducted to assess the effect of losartan 50mg every other day (EOD), once a morning (OM) among post-dialysis euvolemic hypertensive patients. Post-dialysis euvolemic assessment was done by a Body Composition Monitor (BCM). Covariate Adaptive Randomization was used for allocation of participants to the standard or intervention arm, and these participants were followed up for twelve months. Pre-, intra- and post-dialysis session blood-pressure (BP) measurements were recorded, and any

adverse events were confirmed using Naranjo scale. Survival trends were analysed using Kaplan-Meier analysis, and a Wilcoxon statistical test was performed to note the difference in blood pressure from baseline up to 12 months using SPSS version 20. Of the total 229 patients analysed via a body composition monitor, 96 (41.9%) were identified as post-dialysis euvolemic hypertensive. Final samples of 88 (40.1%) patients were randomized into standard and intervention arms. A total of 21 (47.8%) male and 23 (52.2%) females were randomized to the standard arm, compared to 24 (54.5%) male and 20 (45.5%) females to the intervention arm. After follow-up of 12 months' pre-dialysis systolic (Cohen's d 0.94, p <0.001) and diastolic (Cohen's d 0.45, p 0.01), intradialysis diastolic (Cohen's d 0.34, p 0.02), post-dialysis systolic (Cohen's d 1.19, <0.001) and diastolic (Cohen's d 0.95, p <0.001) blood pressure was reduced from the baseline among intervention-arm patients. However, a significant decline in pre-dialysis systolic blood pressure (Cohen's d 0.54, p 0.003) after 12 months of follow-up was only observed for standard-arm patients. A total of six deaths were reported among standard-arm patients compared to 2 deaths among the intervention arm. Among the intervention arm, two confirmed cesses of Hyperkalemia were reported that resulted in their drop out. Not only did use of Losartan 50 mg achieve an overall significant decline in blood pressure among post-dialysis euvolemic hypertensive patients, but lower mortality rates were also observed. Apart from 2 hyperkalemia cases among intervention arm patients, losartan 50mg was well tolerated.

CHAPTER 1

INTRODUCTION

1.1 Losartan

Losartan was the first approved by FDA by 1995 as an antihypertensive agent and was scheduled for generic release in 2010 [1]. Although many benefits of losartan represents a class effect of ARB however losartan has pharmacokinetic and pharmacodynamic characteristics and effects that are unique and are not classes effects. Benefits of losartan include decreasing proteinuria, slowing the progression of diabetic nephropathy, controlling hypertension and decreasing risk of stroke in patients with left ventricular hypertrophy [1].

Losartan is a non peptide molecule that is a competitive antagonist with selective binding to AT1 receptor. Losartan has an oral bioavailability of 33% and has significant first pass metabolism using the cytochrome P450. The metabolites appear to be a reversible, non competitive inhibitor of the AT1 receptor. Elimination of losartan is approximately 40% in urine and 60% in faeces. Losartan and its metabolites are highly protein bound, mainly to albumin, but other plasma proteins bind them leaving only 1.3% and 0.2% free respectively. The half life of losartan is 2 hours with the terminal half life of metabolites being longer at 6-9 hours [1]. Losartan has FDA approval for the treatment of hypertension either alone or in combination with other antihypertensive including diuretics [1].

The concentration of angiotensin type II receptor (ATII) is about 1,000 times higher in the kidney than in the circulation. All the key elements of the RAS system have

been demonstrated with in various portions of the kidney and its action have shown both paracrine and autocrine regulation. The angiotensin type I receptor (AT1) have been detected in almost all parts of nephron [2]. The activation of the AT1 receptor leads to up regulation of angiotensinogen, renin and angiotensin converting enzyme (ACE). Thus losartan by blocking the AT1 receptor leads to decreased intra renal ATII by blocking this up regulation [3]. AII causes the concentration of mesangial cells leading to decrease in GFR which can be blocked by losartan. However the overall effect of losartan on GFR can be variable, depending on the blood pressure is within this range, losartan is associated with an increase GFR . However, with low blood pressure, it may be associated with decrease, increased or unchanged GFR [4].

One of the unique effects of losartan compared to other AT1 receptor blockers is to reduce proximal tubular reabsorption of uric acid that increases uric acid excretion and decreases serum uric acid concentration [1]. The changes in uric acid levels have been variable in studies where losartan is used as antihypertensive [5, 6]. Reduction of proteinuria is associated with stabilization of renal failure and slows its progression. This is common in both diabetic and non diabetic nephropathy and is both dependent and independent of blood pressure lowering [7]. Losartan have shown to decrease proteinuria in non diabetic nephropathies [8].

Blood pressure reduction is associated with renal protection and slowing of progression of CKD. Losartan, in combination with other antihypertensive lowers blood pressure [9]. ARBs have shown to provide antihypertensive and reno protective effects similar to that of ACE inhibitors. The Renoprotection of Optimal Antiproteniuric Dose (ROAD) trial demonstrated that titration to maximal anti proteinuric effect of benazeril or losartan beyond usual antihypertensive dose did not show increased blood pressure reduction but was associated with significant

reduction of doubling the serum creatinine by 49% and 50% respectively. The combination of ACE inhibitor and ARB has shown to have a significant reduction of proteinuria [9, 10]. The combination of angiotensin II receptor blocker and ACE inhibitor and ACE inhibitor in a non diabetic renal disease (COOPERATE) study was thought to show this benefit; however due to significant questions regarding this study, it was later retracted [11]2]. Blockage of RAS has shown improvements on survival and hospitalization in heart failure patients. Higher dose of losartan are associated with further decrease in blood pressure and with up to 150mg of losartan, there is increasing renin levels and circulating AII[12]. The effect of high dose versus low dose losartan on clinical outcomes in patients with heart failure was studied in a randomized control trial that compared losartan 50mg with losartan 150mg. With intent to treat analysis, there was no difference in deaths, but there was a significant decrease in hospitalization for heart failure with higher dose. Renal impairment, hypotension and hyperkalemia were also observed in higher dose group [13].

Losartan intervention for endpoint reduction (LIFE) trail was conducted among 9,193 hypertensive patients. The study participants were randomly assigned to losartan or atenolol. Doses were increased and hydrochlorthazide along with other antihypertensive therapy were added to obtain a target blood pressure of <140/90mmHg. Both medications were started with 50mg and titrated to 100mg as needed. The primary endpoint was occurrence of cardiovascular death, myocardial infarction or stroke and the composite end point was any of these. The study demonstrated that losartan was associated with a significant decline in incidence of primary composite end point. Sub studies of LIFE study has provided additional advantage for example , losartan treated individuals had a significant regression of

LVH hypertrophy [14], decreased left atrial size[15, 16] and decreased BNP [17]. Moreover losartan was also associated with decreased platelet aggression and serum uric acid [18]. Clinically significant findings were decreased incidence of atrial fibrillation and new onset of diabetes[19, 20]. LIFE study has proven losartan to be useful to patients with chronic kidney disease [21]

1.2 End stage renal disease

End stage renal disease is a condition where GFR levels <15 ml/min/1.73m^2 which is usually accompanied with signs and symptoms of uremia. End stage renal disease patients needs initiation of renal replacement therapy either in form of dialysis or transplant [22].

Creatinine is the bi product of protein metabolism. When kidney function diminishes and clearance from kidney is reduced, this leads to elevation in serum creatinine , urea and uric acid[23]. Patients in stage 4 may also need dialysis based on their kidney function and clinical scenario. The main purpose of dialysis is to act as an artificial kidney and eliminate nitrogenous products, urea, excessive electrolytes and other waste products from blood. In general two type of dialysis are in practice

1. Haemodialysis
2. Peritoneal dialysis

Haemodialysis procedure involves filtration of blood through different filters and dialysis solution. Before initiation of haemodialysis, a vascular access is created through which a blood is drawn into dialysis machine where it passes through membrane filters. Alongside, dialysis solution is pumped on other side of membrane filter thereby aiding in ion exchange. In this way, the waste products that are higher

in concentration in blood are drawn to the dialysis solution based on concentration gradient. Once this exchange happens the dialysis solution containing waste products is pumped out of machine and blood is pumped back in body. On average this procedure requires 4 hours to complete [24]. However, in peritoneal dialysis (PD) instead if making vascular access, a catheter is placed in the peritoneal cavity (PC) instead of making vascular access, a catheter is placed in peritoneal cavity. The same dialysis solution is used to fill the peritoneal cavity and is removed on a periodic basis to eliminate waste products

1.3 Prevalence of End stage renal disease

An estimated 2 million people are suffering from ESRD whereas there is a rise in 5-7% per year new diagnosed cases with ESRD. Taiwan, Japan, Mexico, US and Belgium are the highest prevalent countries with ESRD. According to mortality data in 2007, ESRD patients in US are on 15 % higher risk of mortality compared to Europe and 33% higher risk of mortality compared to Japan on comparable treatment modalities [25].

US renal data system annual data report more than 660,000 American being treated for renal failure. Of 660,000 end stage renal disease patients , 468,000 patients are on dialysis and more than 193,000 have a functioning kidney transplant [26]. In 2013 only, newly reported kidney failure cases occurred in approximately 117,000 Americans. Of these patients, 57.3% were male and 42.69% were female patients. Altogether 44.3% of patient aged between 45 to 64 years. Diabetes (37.4 %) and hypertension (25.2%) made up the majority of primary cause for end stage renal disease [26].

According to Global burden of disease report 2010, chronic kidney disease is ranked 27th in the list of cases of death in 1990 that rose up to 18th place by 2010. Over 2 million end stage renal disease patients worldwide receive treatment in form of dialysis or kidney transplant. Yet this number only represents 10% of people that actually needed treatment to live. In middle income counter, end stage renal disease treatment that include dialysis or kidney transplant, creates a financial burden to the people who need it. Many people cannot afford it resulting in a death of over 1 million people annually from untreated kidney failure.

Europe represents an estimated 13 % of overall ESRD prevalence worldwide. The countries with highest prevalence in Europe include Portugal, Germany Cyprus, Spain and Italy. In Europe, of 552,000 patients, 575 are treated with haemodialysis, 5% with peritoneal dialysis whereas 39% are living with kidney transplant. Kidney transplant in Europe is the fastest growing ESRD treatment in Europe representing an average 3% increase every year [27]. Reports from England suggest that cost associated with chronic kidney disease is higher as compared to breast, lung, colon and skin cancer combined. Whereas cost associated with ESRD is estimated to be $ 12 billion by 2020. In Uruguay, annual cost associated with haemodialysis is close to $ 23 million representing a total of 30% of overall budget for National resources fund for specialized therapies. Finally, china estimated to lose up to $558 billion over nest decade due to effects of disability and death related to heart disease and kidney failure [28].

1.4 Prevalence of end stage renal disease in Malaysia

The prevalence of stage 1 CKD in Malaysia is estimated as 4.16%, stage 2 as 2.05%, stage 3 as 2.26% , stage 4 has 0.24% whereas prevalence of end stage renal disease

in Malaysia was reported as 0.36% [29] . According to 22 renal registry 2014, Malaysia continues to note an increase linear in new patients on dialysis over 10 years from 3167 cases in 2005 to 6985 cases in 2015 and at least 7055 cases in 2014 [30]. A steeper linear rise from 13 thousand in 2005 to almost 35 thousand in 2014 was observed among number of prevalent dialysis patients. New kidney transplantation rate decreased by 50 % over last 10 years to about 3 pmp in 2014 owing to decreasing trend of live related transplantation due to easy availability of dialysis treatment

In 2014, a total of 6107 new haemodialysis cases were reported representing an acceptance rate of 203 pmp whereas 948 new peritoneal dialysis cases were reported giving an acceptance rate of 31 pmp. The total number of haemodialysis and peritoneal dialysis patients increased to 31,497 and 3270 in 2014 thereby giving a prevalence rate of 1046 and 109 pmp respectively. Over last 10 years, the male to female ratio for incident and prevalent dialysis patients remains the same as about 55 to 45%. A total of 58% of new dialysis cases were 55 years or older at the onset of dialysis. The dialysis treatment rate exceeded 100 per million populations in all states of Malaysia by year 2014 (except Sabah) with the lowest rates in Perlis, Kelantan and Sabah [30].

1.5 Complications associated with end stage renal failure patients on haemodialysis

A normal kidney helps in removal of waste products from human body, maintain body fluids, helps regulate hypertension by releasing hormones, produces activated form of vitamin D known as calcitrol maintain acid base electrolyte imbalances and importantly produces urine. In addition, the kidney is also responsible for production

of erythropoietin that plays an important role in red blood cell formation. Once kidney function starts to deteriorate, the equilibrium that is maintained by a healthy kidney is disturbed that leads to variety of disorders. A summary of common occurring complications associated with end stage renal disease are as follows

1.5.1 Cardiovascular disease as a complication of end stage renal disease patients on haemodialysis

Cardiovascular disease is one of the most frequent complications associated with end stage renal disease. Overall, mortality associated with cardiovascular events among end stage renal disease accounts for 44% annually [31]. According to national kidney foundation task force on cardiovascular events, mortality rates among general population when compared to haemodialysis patients with respect to cardiovascular events are higher in latter despite stratification for gender, ethnicity or even age group. Young dialysis patients report an approximate 500 times higher cardiovascular mortality rates compared to their counterparts in general population [32]. Herzog et al in their study observes outcomes among 34, 189 haemodialysis patients using US renal data base system report poor prognosis among haemodialysis patients with acute infarction. The author reports that cardiac related mortality rates were 51.8% at 2 years and 70.2% at 5 years [31].

It is important to mention that prevalence of cardiovascular events is increasing among all patients with CKD, not only with end stage renal disease. The prevalence of left ventricular hypertrophy increases as glomerular filtration declines thereby as many as 30% of patients reaching end stage renal disease already have clinical evidence of ischemic heart disease or heat failure. Moreover, it is important to note that patients with reduced glomerular filtration rate are more likely to die of cardiovascular event than they are to develop end stage renal disease [33].

The relationship between cardiovascular events and end stage renal disease includes common pathological links that includes higher prevalence of conventional and non conventional factors. Conventional factors to cardiovascular events among haemodialysis patients includes hypertension, dyslipidemia, anaemia, electrolyte imbalances, acid base and mineral disorders while non conventional factors include fluid overload , inflammation and oxidative stress [34]. Increase in parathyroid hormone as a result of CKD-BMD increase cardiac mortality and contribute to the development of left ventricular hypertrophy since parathyroid receptors are also present in heart [35]. Moreover, parathyroid hormone causes artheroscleosis and increases vascular tone that leads to hypertension leading to increase risk for cardiovascular disease. Malnutrition is also associated with releases of pro-inflammatory cytokines that aggregates existing inflammation and acceleration of arthrosclerosis[36]. Similarly, fluid overload is strongly associated with hypertension among end stage renal disease patients and independently influences vascular and endothelial function causing arterial stiffness, artheroscleosis and left ventricular hypertrophy.

Interestingly, another possible explanation for high association between both diseases includes “reverse causation”. i.e CKD is a risk factor risk factor for CVD and vice versa [37]. This association between CKD and CVD is commonly termed as “cardio-renal syndrome” and is defines as a “disorder of heart or kidney whereby any acute or chronic dysfunction in one organ induces acute or chronic dysfunction of the other organ [37].

1.5.2 Hypertension as complication of end stage renal disease patients on haemodialysis

Hypertension is common among patients with end stage renal disease. The prevalence of hypertension among end stage renal disease patients is up to 90% [29]. The prevalence of hypertension in pre dialysis stages of CKD depends upon nature of underlying renal disease. The prevalence of CKD related hypertension increases linearly with decline of kidney function. Pathogenesis of hypertension among haemodialysis patients is multilayered and still not completely elucidated however; hypervolemic, increased sympathetic activity, renin angiotensin receptor blocker and altered endothelial cell function are few of many reasons.

1.5.2 (a) Increased extracellular volume/volume overload among end stage renal disease patients on haemodialysis

Among haemodialysis patients, an excretory function of kidney is largely replaced by haemodialysis. Absorption of salt and water among haemodialysis patients takes place in same manner as among normal people however their excretion require haemodialysis procedure. Approximately 1-3 litters of extracellular water is gained between each dialysis procedure. These constant fluctuations in volume put cardiovascular system under pressure and is also responsible for rise in blood pressure among haemodialysis patients [38].

Thirst is the main drive behind fluid intake that is dependent on osmolality [39] where plasma osmolality is determined by sodium concentration. Among haemodialysis patients plasma osmolality depends upon dietary salt intake and net sodium gained or lost during dialysis. Individuals with normal renal function experience a small rise in plasma concentration after high salt diet that draws fluid from fluid from intracellular to extracellular space and simultaneously stimulating

hypothalamus and pituitary gland resulting in thirst thereby diluting plasma sodium back to normal. Sodium excretion from kidney occurs within 1 hour [40]. An exact same mechanism is involved among kidney failure patients except that they are unable to excrete sodium thereby resulting in plasma sodium to stay longer and induce thirst for longer duration of period. All this causes an higher intake of fluids resulting in volume overload that induces high blood pressure among haemodialysis patients [41]. Thereby limiting salt intake is absolute vital in reducing thirst and interdialytic weight gains.

Over hydration and sodium retention not only plays an important role in volume overload but also by non hemodynamic effects on vascular system. Patients those begin dialysis with low pre dialyses blood pressure are at greater risk of cardiac failure because of vicious cycle (fluid overload leading to problem in removing fluid leading to further overload). Prognosis of such patients is poor as fluid removal is slow. To further aggregate this scenario, dialysis patients often have diastolic dysfunction. In these patients, a small decrease in filling pressure following dialysis procedure may result in decreased cardiac output and hypotension [29].

Estimation of excess volume is dependent upon estimation of dry weight. In haemodialysis patients, dry weight is that weight that at the end of dialysis at which the patient can remain normotensive until next dialysis despite retention of salt water. At dry weight, the extracellular volume is approximately at normal [42] . Incorrect assessments of dry weight will either lead to chronic fluid overload or chronic under hydration. The clinical assessment of fluid overload is relatively difficult and it is asses on the basis of high blood pressure, cardiovascular complication and physical signs of edema in routine clinical setting. Although edema can roughly estimate excess extracellular volume but it of limited value in assessing excess intravascular

volume. Moreover, several litters of water should be retained before physical signs of edema becoming visible [43]. Other techniques in assessing fluid status include ultrasonic evaluation of inferior vena cava diameter but it is subjected to inter patient and inter operator variability. Biomarkers such as brain natriuretic peptide (BNP) and N-terminal pro brain natriuretic peptide (NT-pro BNP) can reflect changes in fluid status but both are induced by presence of cardiovascular disease. And are also accumulated in CKD patients , rendering these methods inappropriate for evaluation of fluid status [44]. Recently, bioimpedance spectroscopy (BIS) has been used for assessment for fluid status and dry weight among end stage renal disease patients.

1.5.2(a)(i) Dry weight among end stage renal disease patients on haemodialysis

Sinha and agarwal define dry weight as lowest tolerated post dialysis weight achieved via gradual change in post dialysis weight at which there are minimal signs or symptoms of either hypovolemic or hypervolemia [44].

1.5.2(a)(ii) Benefits of probing dry weight among end stage renal disease patients on haemodialysis

Observational studies support the practice of probing dry weight. Vertes et al, reported that 35 of 40 patients became normotensive by achieving dry weight [45]. Other report from kayikcioglu et al compared the benefits of non pharmacological therapy very pharmacologic therapy control of left ventricular mass among HD patients[46]. In a case control study, patients who had been treated at one centre with salt restriction and dry weight reduction were compared with patients at another centre where antihypertensive based therapy was the primary method of managing hypertension. The centre using dry weight and salt restriction as a primary strategy had lower antihypertensive drugs usage, lower interdialytic weight gain, lower left ventricular mass, better diastolic and systolic left ventricular function and fewer

episodes of intradialytic hypotension. These observations are important and clinical relevance; they suggest that probing for dry weight as opposed to adding more antihypertensive drugs perhaps diminishes the risk of cardiac remodelling and mitigates LVH and preserves systolic and diastolic left ventricular function. Although a case control study cannot asset causation, the results support the use of non pharmacological therapy in the management of ESRD patients could be beneficial.

1.5.2(a)(iii) Assessment of dry weight among end stage renal disease patients on haemodialysis

The physical assessment of dry weight is unreliable for example, pedal edema does not correlate with dry weight very well. In a case control study, Agarwal et al, found that inferior vena cava diameter, blood volume monitoring, plasma volume makers, and inflammation markers were not determinants of edema [47]. For the most part, the assessment and achievement of dry weight is an iterative process that often provokes uncomfortable intradialytic symptoms such as hypotension, dizziness, cramps etc. These symptoms often lead to interventions such as cessation of ultrafilteration, administration of saline, premature cessation of dialysis, or placing the patient in the head-down position. Interestingly, placing the patients in the head down position does little to protect the BP and this practice is questionable [48]; raising the leg passively without lowering the head can, however, be effective to rise ventricular filling pressure [49]. Often , if dry weight is reduced gently either by setting the ultrafiltration goal to just a little above the previous achieved post dialysis weight either without changing the dialysis time or better still by prolonging the dialysis time to allow for slower ultrafilteration with dialysis , dry weight can be

successfully achieved. However a body composition monitor using bio impedance technology provides an accurate estimation of patient dry weight

1.5.2(b) Body composition monitor

Body composition monitor that utilizes bioimpedance spectroscopy is a unique approach that is used to assess fluid distribution in both healthy and diseased population. This device has been intensively validated against different gold standards in general and haemodialysis population [43, 50]. However in the past decade, few studies have shown its validation in NDD-CKD population[51, 52]

Body composition monitoring (BCM) is a painless and non-invasive method that is used to determine amount of body fluids and body composition in terms of lean tissue mass and fat tissue mass. It not only measures total body water (TBW) but also differentiates between intracellular water (ICW) and extracellular water (ECW) [53]. TBW is the sum of ECW and ICW. The ECW consist of interstitial water, plasma water and transcellular water. The ICW comprises of water inside cell and these cells are protected by membranes [54].

A whole body impedance spectroscopy method is used to assess fluid distribution by using multi-frequency (5-100 kHz) low amplitude current. At high frequency, current passes through the TBW while at low frequency, the current only passes through extracellular water as is is unable to penetrate through cell membranes [55, 56]. BIS is based on principle that when multi-frequency current is applied through the body, every compartment of body offers resistance that is proportional to the TBW and electrolytes present in that compartment. Based on these assumptions, the highest conductors of electric current are lean tissue due to large amount of water and electrolytes and thus offering a very low resistance to current flow. On the contrary,

fat and bones offer high resistance to current flow due to low water and electrolytes current [57].

The value of fluid overload (FO) or over hydration (OH) is defined in term of ECW and is expressed in litres [72]. OH is the difference between the amounts of extracellular water (ECW) in the tissue that is predicted by using physiological models under normal circumstances. Therefore, the OH value obtained from BCM can be compared directly with the value for the normal population [56]

1.5.2(c) Assessment of fluid status using Body composition monitor

The person under observation lies flat on the back and with hands palms facing downwards. A total of four electrodes are attached to one hand (2 electrodes) and one foot (2 electrodes) at the ipsilateral side. A cable is attached to both electrodes at hand and feet. A patient card having information regarding patient height, weight, blood pressure is added into BCM equipment. Measurement is initiated and results are displayed within 2 minutes. All results are stored in patient card. The card is then inserted in the laptop and all results are analysed with fluid management tool software.

1.5.2(d) Clinical uses of body composition monitor

BCM is an important tool for healthcare professional that helps in determine individual hydration status and differentiate clearly between ECW and ICW. Due to assessment of lean tissue and fat mass, this technique is extensively used by nutritionist in clinics as well as weight management centres. With the help of appropriate assessment of total body water and blood pressure, this device helps in management of hypertension as well as maintenance of fluid status according to patient needs. One of the most common uses of BCM is for haemodialysis patients.

BCM helps in determining urea distribution volume for the dialysis prescription does which is the amount of fluid volume needed to be removed during haemodialysis.

1.5.2(e) Limitations of body composition monitor

The assessment of body composition with BIS has been extensively explored in both healthy and diseased population over the last decade. Despite easy handling and quick interpretation of results, this technique offers some limitation. BIS cannot be used among pregnant females, patients with amputations or pacemakers, patients with burns or skin infections due to difficulty of placement of electrodes. The result of interpretation are less precise is any condition that makes patient susceptible to water retention (congestive heart failure and liver cirrhosis) or where water-electrolyte balance is disturbed. Lastly, the results are also affected with heavy meal, intense physical exercise, dehydration and menstrual cycle [57].

1.5.3 Renin angiotensin aldosterone system (RAAS) induced hypertension among end stage renal disease patients on haemodialysis

1.5.3(a) Renin angiotensin aldosterone system pathway

The renin-angiotensin-aldosterone system (RAAS) is a signalling pathway that is responsible for regulating the blood pressure. Stimulated by low blood pressure or certain nerve impulses (e.g. in stressful situations), the kidneys release an enzyme called renin, that triggers a signal transduction pathway. This renin splits the protein angiotensinogen, producing angiotensin I that is converted by another enzyme, the angiotensin-converting enzyme (ACE), into angiotensin II [58].

Angiotensin II not only causes blood vessels to narrow (vasoconstriction), it also simultaneously stimulates the secretion of the water-retaining hormone vasopressin in the pituitary gland (hypophysis) as well as the release of adrenaline, nor adrenaline and aldosterone in the adrenal gland.

Adrenaline and noradrenaline enhance vasoconstriction, aldosterone influences the filtration function of the kidneys. The kidneys retain more sodium and water in the body and excrete more potassium. The vasopressin from the pituitary gland prevents the excretion of water without affecting the electrolytes sodium and potassium. In this way, the overall volume of blood in the body is increased: more blood is pumped through constricted arteries, which increases the pressure exerted on the artery walls known as blood pressure.

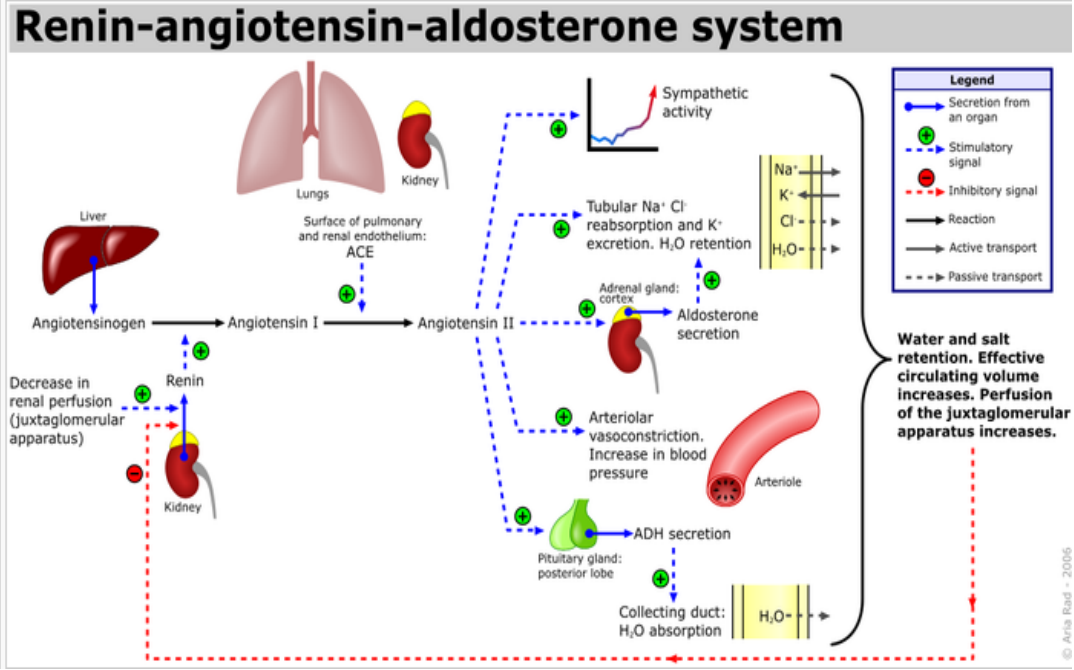

Figure 1.1: Renin angiotensin aldosterone system pathway [59]

1.5.3(b) Effect of RAAS system in kidney

The renin-angiotensin-aldosterone system amends intravascular volume and cellular proliferation in the nephron, whereas activation of AT_1 receptors in the kidney contributes to hypertension through sodium retention. Effects of angiotensin II on intrearenal hemodynamic are critical in blood pressure control. Constriction of efferent arterioles by angiotensin II reduces renal blood flow and amends glomerular filtration by reducing glomerular capillary pressure. Changes in peritubular pressure

promote movement of sodium and fluid from proximal tubules to interstitium and systemic circulation through renal vessels. Moreover, angiotensin II reduces medullary blood flow and reducing renal intertital blood pressure thereby decreasing sodium and water excretion. The RAAS also increases sodium and water reabsorption through direct actions on renal transport function.

Apart from hemodynamic effects, RAAS also promotes other processes in the kidney. Angiotensin II maintain production of nephron-toxic reactive oxygen species and stimulates cell proliferation and tissue remodelling [60]. Collagen deposition is also enhanced through inhibition of proteases, normally functioning to degrade abnormal tissue protein [60]. Similarly studies indicates aldosterone has mitogenic and profibrotic properties that directly increases production of the profibrotic cytokine transforming growth factor β. Aldosterone synthesis is increased in experimental renal ablation models that suggest that it has been associated with increased renal fibrosis and progressive loss of renal function. It is proposed that both aldosterone-induced hypertensive effects as well as direct mitogenic actions synergistically act to promote renal damage.

1.5.3(c) Role of RAAS in kidney injury

Based on the homeostatic effects of RAAS of kidney, its importance cannot be over emphasised. Excessive activation of RAAS cascade promotes and exacerbates pathological changes in kidney. Excessive production of angiotensin II and aldosterone is associated with progression of kidney damage. Animal models suggests that combination of glomerular capillary hypertension, profibrotic effects and proteinuria contributes to kidney damage that is associated with RAAS [61]

1.5.3(c)(i) Glomerular capillary hypertension

The basis of any kidney disease is the injury to nephron and loss of functioning units that results in hyper-filtration and glomerular capillary hypertension. This adaptive change is detrimental over time to renal function. The hyper-filtration state associated with glomerular capillary hypertension up regulates expression of RAAS. Stimulation of RAAS cascade causes further glomerular injury by rising glomerular capillary pressure through angiotensin II driven efferent arteriolar vasoconstriction. Experimentally, hyperglycaemia also stimulates angiotensin II production in mesangial cells that leads to mesangial matrix expansion, an effect reversed by use of losartan [62]

1.5.3(c)(ii) Profibrotic Effect

Elevated glomerular capillary pressure may induce glomerulosclerosis, other factors may directly induce RAAS cascade that induces kidney injury. Renal fibrosis is also associated with pro inflammatory and profibrotic effects of angiotensin II and aldosterone. The RAAS promotes kidney fibrosis through multiple untoward effects that include toxic oxygen radical formation, enhanced cellular proliferation and collagen deposition in the kidney.

1.5.3(c)(iii) Proteinuria

Activation of RAAS exacerbates proteinuria. Glomerular capillary hypertension leads to increased glomerular permeability and excessive protein filtration. The RAAS may also lead to proteinuria through renal expression. Although proteinuria is a biomarker of renal disease however proteinuria itself contributes to renal injury. Protein in urine are toxic to tubules and can result in tubulointerstitial inflammation and scaring [63]. Literature suggests that reduction of proteinuria is associated with nephro-protection [61].

1.5.3(d) Blockage of RAAS in kidney injury

Blockage of RAAS results in antagonism of renal pro-fibrotic effects and reduces proteinuria. Moreover, interpretation in RAAS reduces the progression of renal injury in both diabetic and non-diabetic forms of nephropathy. Animal studies have demonstrated that inhibition of RAAS is associated with kidney protection. However, another aspect of antagonism effect of RAAS in these animal studies is also related to better blood pressure control [64]. Literature suggests that reno-protection afforded by inhibition of RAAS is blood pressure dependent. Whereby using radiotelemetry to measure blood pressure continuously, excellent correlation between histological renal damage and blood pressure was demonstrated in rats when treated with RAAS inhibitors and untreated control [64]

1.5.3(e) Over activity of RAAS among hypertensive end stage renal disease patients on haemodialysis

Plasma renin levels are twice as higher in hypertensive haemodialysis patients compared to normotensive patients [65]. Similarly higher plasma angiotensin II level are also observed in chronic kidney failure [66]. Patients with higher plasma renin and angiotensin II levels prior to haemolysis procedure have been associated with rise in blood pressure. With dialysis, despite removing excess volume that contributes to volume dependent hypertension, Plasma renin levels tend to rise higher with minor changes in blood pressure. Saralasin (partial angiotensin II receptor agonist) lowered pre-dialysis blood pressure and to an extent post dialysis blood pressure thereby demonstrating interaction in individuals between level of angiotensin II and volume dependent high blood pressure [67]. Moreover, Textor et al, measuring pre and post dialysis blood pressure with response to plasma renin and blood pressure identifies and classify patients based on responses to saralasin as

volume dependent hypertensive patients and renin dependent hypertension. The latter population of patients responded to reduction in blood pressure with infusion of saralasin post dialysis whereas no or non significant effect was observed among volume dependent hypertensive patients despite high levels of plasma renin or angiotensin II levels [68].

Perhaps one of the most vivid explanation of increased RAAS was observed among hypertensive end stage renal disease patients is observed in anephric patients where both kidney are removed. As Plasma renin levels are very low among these patients as both kidney are removed, their blood pressure is entirely volume dependent and is sensitive to volume changes moreover, introduction of sarasalin to these patients have no change in blood pressure. In addition, anephric patients require considerable amount of blood volume in order to maintain blood pressure at the same level as dialysis patients with intact kidneys [38]. In past, bilateral nephrectomy was performed in patients with high level of renin however with greater understanding of mechanism of blood pressure in renin dependent individuals, bilateral nephrectomy was abandoned as drugs that block RAAS activity were effective in controlling blood pressure.

1.5.4 Increased sympathetic activity associated hypertension among end stage renal disease patients on haemodialysis

Sympathetic activity induced vascular resistance and hypertension is common among end stage renal disease. Studies indicate that an increased sympathetic activity is observed among chronic haemodialysis patients [69]. In addition, sympathetic activity was found to be normal among haemodialysis patients with bilateral nephrectomy, leading to hypothesis of sympathetic activity is related to neurogenic signal carried by renal afferents arising in the failing kidney [70]. Patients with

chronic kidney disease and renin dependent hypertension, sympathetic over activity were normalized by chronic angiotensin converting enzyme inhibitor but not by calcium channel blockage, implicating a central neural action of angiotensin II. Other factors that may contribute towards increased sympathetic activity include oxidative stress, obesity , chronic inflammation, nocturnal hypoxia and elevated levels of asymmetric di-methyl-arginine (ADMA) [71].

1.5.5 Parathyroid hormone associated hypertension among end stage renal disease patients on haemodialysis

Intracellular calcium levels induced by parathyroid hormone are associated with hypertension among end stage renal disease. Entry of calcium in smooth muscles cells of blood vessels leads to vasoconstriction thereby leading o hypertension. Correction of hyperparathyroidism by either vitamin D administration or parathyroidectomy in chronic dialysis patients have resulted in low blood pressure [72].

1.5.6 Reduced production of prostaglandins/ bradykinins associated hypertension among end stage renal disease patients on haemodialysis

Kidney produces several vasodilating chemicals including kinins, prostaglandins antihypertensive neural renomedullary lipids. Fluctuations in production of these chemicals lead to hypertension among haemodialysis patients. Decreased levels of prostaglandin E_2 (PGE2) is observed in hypertensive ESRD patients whereas a negative correlation is observed between prostacyclin metabolite 6-keto-PgF1α and blood pressure among end stage renal disease patients [29]

1.5.7 Management of hypertension among haemodialysis patients

The management of hypertension in dialysis patients is frequently challenging and requires the knowledge of pharmacokinetics and pharmacodynamic properties of all the agents used. Life style modification is the first and integral part of management of hypertension among CKD patients. The importance of salt restriction cannot be over emphasised. Achievement of dry weight and reduction of extracellular fluid should not be neglected.

In case of lifestyle modifications are not successful, antihypertensive therapy should be initiated. The first line of antihypertensive therapeutic agents recommended by NKF KDOQI guidelines are ACE inhibitors or ARBs. The latter reduces LVH in haemodialysis patients and may be more potent than ACE inhibitors [73-75]. Calcium channel blockers and alpha anti-adrenergic drugs should be an integral part of management of hypertension to achieve control if necessary. In most several forms of hypertension, multiple antihypertensive therapies are required. If full dose of one agent are ineffective, a second or a third drug should be added. If blood pressure is not controlled with dialyses and three antihypertensive agents of different classes, patient should be evaluated for a potential secondary cause[76] .

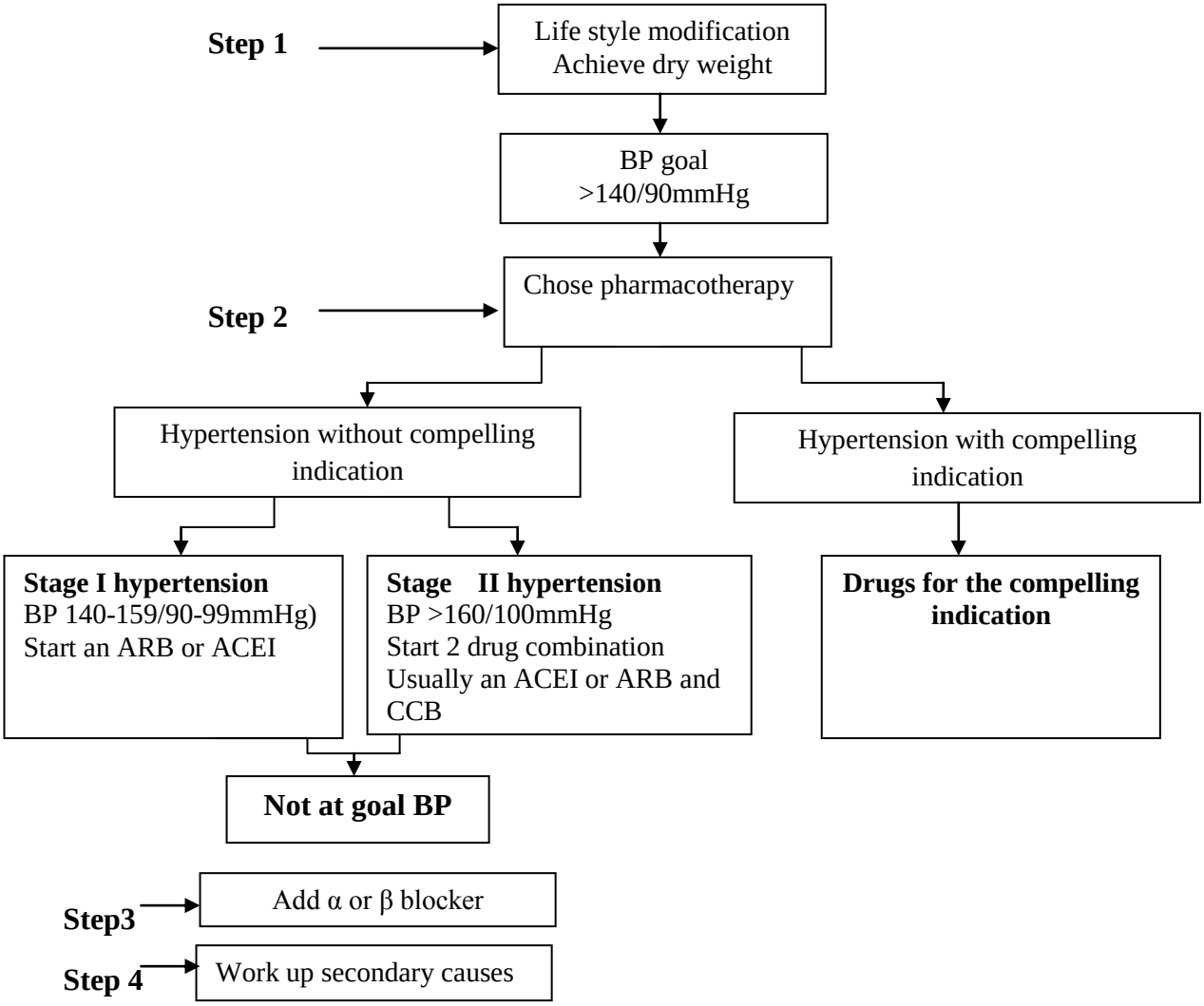

Figure 1.2 : Algorithmic approach to the management of hypertension among haemodialysis patients [76]