



Treatment of Hypertension in Chronic Kidney Disease

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US Trends in Prevalence, Awareness, Treatment and Control of Hypertension, 1988-2008.

(Egan, BM, etal. JAMA, 2010; 303(20): 2043-2050)

- NHANES sampled the US population between 1988-1994 and 1999-2008.
- Hypertension rates increased from about 24% to 28.5%.
- Hypertension controlled to $< 140/90$ increased from 27.3% to 50.1%.



Importance of Hypertension In CKD

- Controlling blood pressure is one thing we can do to prevent progression of kidney disease and life diminishing cardiovascular events.
- Antihypertensive therapy in patients with CKD can have significant negative impacts on the patient's health and quality of life.
- Evidence based guidelines are critical in helping the provider tailor a treatment program for individuals



Goals of Presentation

- Discuss the evaluation of hypertension using ambulatory blood pressure monitoring (ABPM) and mention tools to assess aortic stiffness.
- Consider newest guidelines on blood pressure targets in subgroups of patients with CKD.
 - Age
 - Diabetes
 - Proteinuria
 - Stages of CKD



Goals of Presentation

- Non pharmacological management of blood pressure
 - Sodium restriction
 - Obesity management
 - Renal Denervation
 - Carotid baroreceptor stimulation
 - Dialysis
- Pharmacological management of hypertension in CKD



Ambulatory Blood Pressure Monitoring

- A typical profile of daily blood pressure includes higher levels during the day, dipping during rest at night and then resurgence in the early morning prior to waking up.
- Office blood pressure readings provide a snap shot of the process and are usually higher than those obtained with ambulatory monitoring.
- False + hypertension diagnoses can occur in as many as 20-35% patients with “white coat” induced elevation of the blood pressure.



Suggested Indications for ABPM (7th JNC Report)

- Suspected white coat hypertension in patients with no evidence of end organ damage
- Drug resistance based on office readings
- Symptoms suggesting over control of the blood pressure not supported by office readings
- Suspected episodic hypertension
- Autonomic dysfunction



ABPM in patients with CKD

- Blood pressure readings detected by ABPM are more likely to predict bad outcomes in CKD patients than those obtained in the office or dialysis unit.



Home Blood Pressures are of Greater Value than Hemodialysis Unit Recordings

(Alborzi P, et al, Clin J Am Soc Nephrol, 2007; 2:1228-1234)

- Blood pressure was measured by ABPM, scheduled home BP readings and BP in the dialysis center in 150 hemodialysis patients
- 46 patients died with 26 deaths due to cardiovascular events in 24 months of follow up
- BP measured in the dialysis unit did not predict mortality, but ABPM and home BP readings did

Prognostic role of ABPM in patients with non-dialysis chronic kidney disease.


Minitolo R, et al. Arch Int Med, 2011; 171:1090-1098

- 436 patients with CKD 3 were followed for 4 years
 - 155 required dialysis or died from renal disease
 - 103 had cardiovascular events including 52 deaths
- ABPM readings were predictive of progressive renal failure and cardiovascular events while office blood pressure readings were not.



Measures of Arterial Function

- Aortic stiffness is associated with aging, diabetes, hypertension and CKD.
 - Widening of the pulse pressure (systolic – diastolic)
 - Increased pulse wave velocity (from carotid to femoral artery)
 - Earlier, increased pulse wave reflection that raises central pulse pressure (tonometry at radial artery)
- These measures of aortic stiffness may be better predictors of progression of CKD than standard blood pressure



Increased pulse pressure predicts risk of progression of diabetic nephropathy

- RENAAL study (*Bakris GL, et al. Arch Intern Med, 2003;163(3):1555*)
 - 1513 patients with diabetic nephropathy and hypertension randomized to placebo or losartan
 - Patients with the highest baseline pulse pressure had the highest risk for progression of nephropathy

Guidelines for Management of Blood Pressure in Patients with CKD

- KDIGO (Kidney Disease-Improving Global Outcomes) Work Group Updated KDOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Management (2012)
- Sub-grouped their recommendations:
 - CKD not on dialysis without diabetes
 - CKD not on dialysis with diabetes
 - CKD in the elderly
 - CKD in children
 - CKD with transplant
 - CKD on dialysis (published separately)



Measurement of Blood Pressure- KDIGO

- Workgroup recognized the superiority of ABPM in determining prognosis but wrote guidelines based on office BP readings since most randomized control trials (RCTs) used this measure.
- Considered use of pulse pressure or pulse wave velocity measures but too little data.
- Workgroup recommends that management decisions be based on repeated measurements and used the term “consistently” in their guidelines for emphasis.



KDIGO: CKD not on dialysis without diabetes

- If the daily urine albumin excretion is < 30 mg, goal BP is ≤ 140 systolic and ≤ 90 diastolic.
 - Previous guidelines set the target for each 10 mmHg lower
 - Randomized control trials have not shown benefit of lower BP targets in this group



KDIGO: CKD not on dialysis without diabetes

- Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease. Results from the AASK Trial (*Wright JT, JAMA, 2002; 288:2421-2431*).
- About 1000 African-American patients with CKD 3 and 4 were followed for 3-6 years
- Randomized to lower (128/78) or higher blood pressure (141/85) targets
- No effect of different BP targets on rate of loss of GFR, ESRD or death.



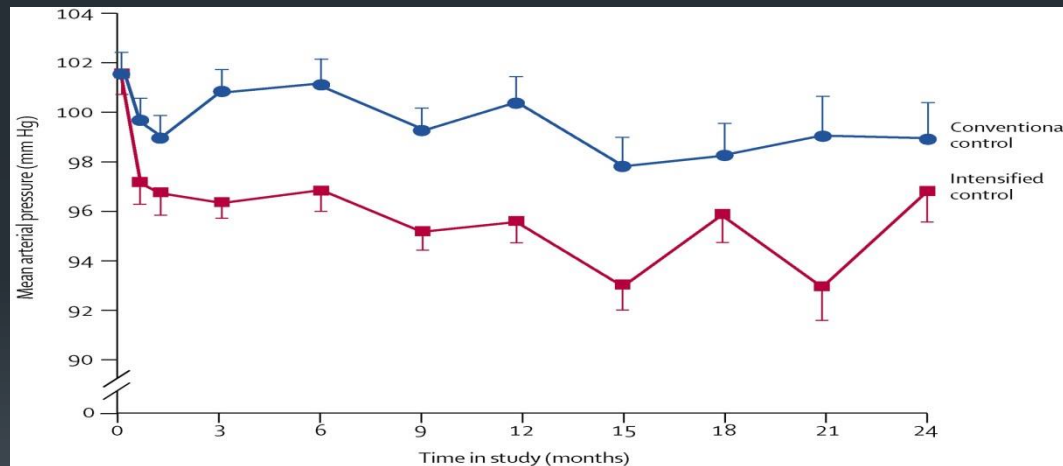
KDIGO: CKD not on dialysis without diabetes

- Workgroup recommended that if patients in this group have urine albumin excretion of 30-300 mg or > 300 mg per 24 hours that the BP target should be lowered to $\leq 130/80$ mm Hg
 - MDRD data showed that patients with proteinuria had slower loss of GFR with a BP target of 120/75 compared to a higher target (140/90) (*Klahr S et al, New Eng J Med, 1994;330(13): 877-884*)
 - Follow up of these proteinuric MDRD patients 7 years later showed that those in the low BP group had slower progression to ESRD than those in the higher BP group. (*Sarnak MJ, et al. Ann of Int Med, 2005;142:342-351*)

Blood pressure control for renoprotection in patients with nondiabetic chronic renal disease (REIN-2)

Ruggenti P, et al. Lancet, 2005;365:939-946

- 338 patients with proteinuric non diabetic CKD treated with ACEI were randomized to usual control or intensified treatment to $< 130/80$




- After 19 months the rate of progression to ESRD was the same.




KDIGO- CKD not on dialysis without diabetes

- Workgroup recommended that an ACEI or ARB be used in non diabetic adults with CKD and albuminuria when treatment with a BP lowering drug is indicated




Angiotensin-converting enzyme inhibitors and progression of nondiabetic renal disease. A Meta-analysis of patient-level data. Jafar, et al. *Ann Int Med.* 2001;135:73-67

- Review of 11 RCTs comparing the efficacy of antihypertensive regimens including ACEI with regimens without ACEI.
- ACEI slowed progression of non diabetic renal disease and the effect is greater in patients with proteinuria.




KDIGO: CKD not on dialysis with diabetes

- CKD patients with diabetes and < 30 mg albumin excretion per day should have their blood pressure lowered to $< 140/90$ mmHg
 - About 25% of CKD patients with diabetes will not have albuminuria
 - RCTs have consistently shown that lowering BP below this target prevents major cardiovascular events and reduces risk of progressive CKD
 - Evidence for benefit of further lowering of the BP target is mixed.




KDIGO: CKD not on dialysis with diabetes

- Effects of Intensive Blood Pressure Control in Type 2 Diabetes Mellitus. (*ACCORD study group, N Engl J Med, 2010;362(17):1575-1585*)
 - 4700 patients with Type II Diabetes were randomized to a goal systolic BP of 140 or 120 mmHg and followed for 4.7 years
 - There was no difference in the composite outcome of non fatal stroke, myocardial infarction or death from a cardiovascular event
 - Patients in the intensive BP group were more likely to have adverse events




KDIGO: CKD not on dialysis with diabetes

- ACCORD renal outcomes
 - The number of patients who had albuminuria at the last visit was lower in the intensive group versus controls
 - The final mean GFR was also lower in the intensive group
 - More patients in the intensive group had their GFR drop below 30 ml/min
 - There was no difference in the number of patients developing ESRD




KDIGO: CKD not on dialysis with diabetes

- Work group did not believe evidence strong enough to suggest BP targets lower than 140/90 mmHg for all patients with diabetes and CKD



KDIGO: CKD not on dialysis with diabetes

- The workgroup recommends that patients with CKD and diabetes who have albuminuria have their BP lowered to < 130/80
 - Multifactorial intervention and cardiovascular disease in patients with Type 2 diabetes. (*Gaede, et al. N Engl J Med, 2003;348:383-393*)
 - Patients with microalbuminuria treated to lower the blood pressure to < 130/80 mm Hg had a reduced risk of development of nephropathy ($p = 0.003$)



KDIGO: CKD not on dialysis with diabetes

- Workgroup recommended that patients with CKD and diabetes who have albuminuria be treated with ACE-I or ARB
 - Many studies support this recommendation in patients with diabetes and hypertension
 - Only one major study supports treating normotensive diabetic patients with albuminuria (*Ravid M, et al. Ann Int Med 1993; 118:557*)



KDIGO: Elderly with CKD

- Elderly referred to > 65 years
- 37.8% of patients > 70 years had a GFR < 60 ml/min/1.73 m²
- Age related loss of GFR can accelerate to 4-8 ml/min per year if systolic BP is uncontrolled



KDIGO: Elderly with CKD

- Problems with BP assessment
 - Widening pulse pressure due to arterial stiffening results in systolic hypertension
 - Atrial fibrillation
 - Orthostatic hypotension
- Problems with BP management
 - Elderly often have vascular causes of CKD that increase risk of complications from ACE-I and ARB
 - Co-morbidities influence drug choices
 - Pharmacology of drugs is altered with aging
- Individualized care paramount in the elderly



KDIGO: Elderly with CKD

- BP targets
 - Review of 15 RCTS in persons > 60 years indicated that treatment of patients with BP > 140/90 mmHg reduced overall mortality (*Mussini VM, et al. Cochrane Database Syst Rev 2008:CD000028*)
 - Meta-analysis of 8 RCTs of BP lowering in persons > 80 years (*Bejan-Angalvount T, et al. J Hypertens, 2010;28:1366-1372*)
 - BP lowering reduced risk of stroke and cardiovascular events but not overall mortality
 - Reduction in mortality was noted in the studies with the least blood pressure reduction and lowest intensity therapy



KDIGO: Elderly with CKD

- Over control of BP increases risk of adverse outcomes in elderly hypertensives
 - Post hoc analysis of INVEST trial of the association between level of blood pressure control and risk of MI, stroke or death from any cause.
 - Lowering systolic pressure in those over 70 years old below 120 increased the risk for MI, stroke or death.

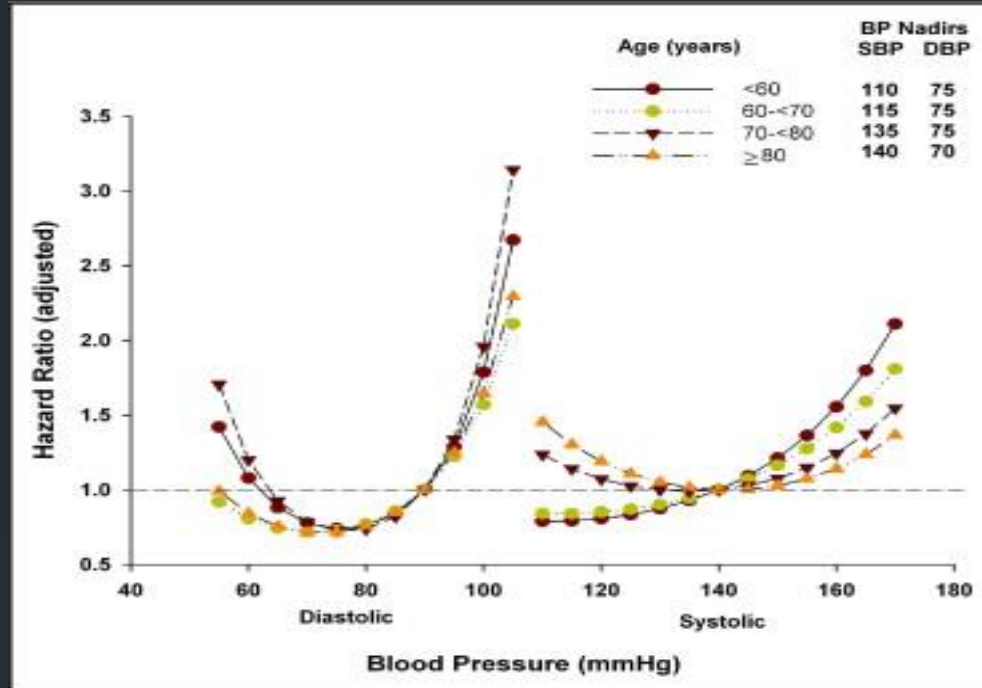


Figure 5 Adjusted hazard ratio as a function of age (in 10-year increments), systolic and diastolic blood pressure. Reference systolic and diastolic blood pressure for hazard ratio: 140 and 90 mm Hg, respectively.

Scott J. Denardo , Yan Gong , Wilmer W. Nichols , Franz H. Messerli , Anthony A. Bavry , Rhonda M. Cooper-DeHoff , ...

Blood Pressure and Outcomes in Very Old Hypertensive Coronary Artery Disease Patients: An INVEST Substudy

The American Journal of Medicine, Volume 123, Issue 8, 2010, 719 - 726

<http://dx.doi.org/10.1016/j.amjmed.2010.02.014>



KDIGO: Elderly with CKD

- Work group decided that it could not specify BP targets in the elderly with CKD, and found it was even more difficult in patients over 80 years
- A reasonable approach:
 - Use BP targets recommended for younger patients with CKD
 - Reach targets gradually with careful attention to potential adverse effects like orthostatic hypotension



KDIGO: CKD on dialysis

- The pathophysiology of BP assessment and management is complex
 - Many patients have underlying cardiac disease
 - Arterial stiffness increases
 - Variables relating to the effect of ultrafiltration and plasma volume refilling
 - Variables relating altered pharmacology and clearance of drugs with dialysis



KDIGO: CKD on dialysis

- How and when should blood pressure be measured?
 - Pre and post dialysis BP measurements are less accurate predictors of negative cardiovascular outcomes than interdialytic ABPM or home BP levels
 - But most clinical decisions are made by necessity using BP measurements at dialysis

KDIGO: CKD on dialysis

- What are treatment goals for BP in patients with CKD on hemodialysis?
 - A U shaped association with adverse cardiovascular events has been identified

BP method	BP level	CV Events or Death	Reference
Pre HD systolic	> 200	Increased mortality	Li et al, AJKD, 2006
Pre HD systolic	> 150	Increased mortality	Zocalli, NDT, 2003
Pre HD systolic	< 115	Increased mortality	Klassen, et al JAMA, 2002
Pre HD systolic	< 110	Increased mortality	Zager, et al Kid Int, 1998



KDIGO: CKD on dialysis

- KDOQI recommendation was $< 140/90$ pre dialysis and $< 130/80$ post dialysis (*Am J Kid Dis, 2005*) and was based on expert judgement rather than strong evidence.

BP Targets in Patients with CKD

Group	KDIGO (2012)	JNC 8 (2014)
General Population < 60 years		< 140/90
General Population > 60 years		< 150/90
CKD ND without diabetes and no albuminuria	<140/90	< 140/90
CKD ND without diabetes and with albuminuria	<130/80	<140/90
CKD ND with diabetes without albuminuria	<140/90	<140/90
CKD ND with diabetes with albuminuria	< 130/80	< 140/90



Management of BP in CKD

- Non pharmacological management of blood pressure
 - Sodium restriction
 - Treatment of obesity
 - Renal Denervation
 - Carotid baroreceptor stimulation
 - Dialysis




Dietary sodium restriction

- KDIGO recommends lowering Na intake to < 2 g per day (NaCl of 5 g per day)
- JNC 8 recommended following the guidelines provided by American Heart Association and American College of Cardiology
 - No more than 2.4 g of Na per day and shoot for 1.5 g per day (*Eckel, RH, et al. Circulation, 2013*).

Controversies in dietary sodium restriction

- Recent prospective population study linked lower urine sodium excretion to higher cardiovascular mortality. (*Stolarz-Skrzypek, et al. JAMA, 2011;305:1777-1785*)
- Meta analysis of 7 RCTS suggested that sodium restriction did not reduce mortality or cardiovascular morbidity in normotensive or hypertensive adults. (*Taylor et al., Cochrane Database Syst Rev 2011;7:CD009217.*)
- Re analysis of same question refuted the conclusions of Taylor et al. (*He et al, Lancet, 2011;378:380-382*)



Controversies in dietary sodium restriction

- Both meta-analyses reviewed in Nephsoap, 2012. Conclusion of the authors was that for now it seems reasonable for clinicians to advise the American Heart Association guidelines.



Sodium in dialysis population

KDIGO

- Salt and water overload play a major role in hypertension in patients on dialysis
 - Ultrafiltration rate
 - Dialysate sodium
 - Dietary sodium



Sodium in dialysis population

KDIGO

- Dry weight reduction in hypertensive hemodialysis patients (DRIP) (*Agarwal, et al, Hypertens, 2009;53:500-507*).
 - Long term hypertensive hemodialysis patients were assigned to an ultrafiltration group (n=100) or control group (n=50).
 - The ultrafiltration group had the target dry weight systematically lowered and the control group had dry weight adjustments based on routine physician visits.
 - After eight weeks, the ultrafiltration group had a mean decrease in EDW of 1 kg compared to no change in the controls. This corresponded to a decrease in systolic BP was 7 mmHg and diastolic BP of 3 mmHg.

Sodium in dialysis population

KDIGO

- Adjusting the dialysate sodium to match the patient's predialysis sodium level reduced BP in hypertensive hemodialysis patients compared to controls undergoing dialysis with a standard level (138 meq/L). (*de Paula, FM, et al. Kidney Int, 2004;66:1232-1238*).



Obesity

- Mechanisms of hypertension
 - Impaired sodium excretion
 - Endothelial dysfunction
 - Increased activity of the sympathetic nervous system



Obesity in Hypertensive Patients with CKD

- Weight loss interventions in CKD: A systematic review and meta-analysis (*Navaneethan SD, et al. Clin J Am Soc Nephrol 2009; 4: 1565-1574*)
 - 13 studies were included
 - Weight loss with non surgical interventions in patients with CKD was associated with a significant decrease in systolic BP, proteinuria and stabilization of GFR

Renal Denervation

- Sympathetic nervous system contributes to the pathogenesis of essential hypertension.
- Catheter placed in renal artery via femoral artery and attached to radiofrequency generator. Four to six discrete low power radiofrequency treatments are applied along the length of both main renal arteries. Some patients experience visceral pain during the energy delivery.



Renal Denervation

- Renal sympathetic denervation in patients with treatment resistant hypertension. (*Symplicity HTN-2 Trial, Lancet, 2010;376:1903-1908*).
 - Patients with uncontrolled HTN taking 3 or more drugs randomized to denervation or continued drug therapy alone.
 - Renal denervation reduced mean BP by 32/12 mmHg (SD 23/11) at 6 months whereas the control group remained unchanged
 - 84% of treated patients had a 10 mmHg reduction in systolic BP compared to 35% of controls ($p < 0.001$).
 - No serious complications related to the procedure were noted
 - There was no effect on GFR



Carotid Baroreceptor Stimulation

- Surgical placement of an electrode on each carotid artery bulb and electrical stimulation of the baroreceptor (Baroreflex Activation Therapy or BAT).
- 265 patients with resistant hypertension underwent BAT therapy. 50% of patients achieved a systolic BP < 140 mmHg after 12 months. (*Bisognano, JD, et al. J Am Coll Cardiol 58:765-773, 2011*)



Pharmacologic Treatment of Hypertension-JNC 8

- Main objective is to attain and maintain goal BP
- Initial Rx should be a thiazide diuretic, calcium channel blocker (CCB), ACEI, or ARB
 - In black patients, initial therapy should include a thiazide diuretic or CCB
- Do not use ACEI and ARB together in the same patient



Pharmacologic Treatment of Hypertension-JNC 8

- Patients 18 years or older with CKD and hypertension (with or without diabetes), initial therapy should include an ACEI or ARB



Pharmacologic Treatment of Hypertension-KDIGO

- ARB or ACEI should be used in CKD patients in whom treatment with BP lowering drug is indicated
 - diabetic or non diabetic with albuminuria
- ARB or ACEI should be used in CKD patients with diabetes and albuminuria irrespective of pre-treatment BP



KDOQI Update on Guidelines for Management of Diabetes (*Am J Kidney Disease, 2012*)

- KDOQI also recommends ACEI or ARB for diabetic patients with albuminuria regardless of pre treatment blood pressure
- Also recommends NOT using ACEI, ARBs or direct renin inhibitor (Aliskiren) together



ONTARGET Study

(Mann, JFE, et al. Lancet, 2008)

- 2500 people with or without diabetes with baseline GFR around 75 ml/min randomized to treatment with ramipril, or telmisartan or both and followed for a mean of 56 months
 - Renal composite outcome (dialysis, doubling of serum creatinine or death) were similar with ACEI or ARB but worse with the combination of ACEI + ARB

ACEI and ARBs: When to stop in CKD?

- Efficacy and safety of benazepril for advanced chronic renal insufficiency. (*Hou, FF, et al. New Engl J Med, 2006, 354: 131-140*)
 - 224 patients with serum creatinine ranging from 3.1 to 5 mg/dl assigned to receive 20 mg of benazepril or placebo
 - Treatment with benazepril reduced the risk of a composite outcome (doubling of serum creatinine, dialysis or death) by 43%
 - Similar incidence of adverse events, including hyperkalemia

ACEI and ARBs: When to stop in CKD?

- Renoprotective effect of renin-angiotensin-aldosterone system (RAAS) blockade in patients with predialysis advanced chronic kidney disease, hypertension and anemia. (*Hsu, T, et al. JAMA, 2013*).
 - Prospective study of 28,497 patients with serum creatinine > 6 mg/dl, hematocrit < 28% being treated with erythrocyte stimulating agents.
 - 14,117 were treated with RAAS blockers and 14,380 were not
 - Median follow up was 7 months
 - 70.7% required starting dialysis
 - 20% died before starting dialysis
 - Use of RAAS blockers reduced the risk of starting dialysis or of composite outcome of dialysis or death
 - Use of RAAS blocker users had a higher hyperkalemia associated hospitalization rate but the risk of predialysis mortality due to hyperkalemia was not significantly increased.



Treatment of Hypertension in Dialysis Patients-KDIGO

- Sound BP management requires information on cardiac structure and function
- Accurate assessment of dry weight remains difficult but critical
- The evidence to guide practitioners in BP management of dialysis patients is poor
- The use of RAAS blockers, β adrenergic blockers and CCBs should be strongly considered in HD patients on the basis of studies in the general population.



Take Away Points

- Consider using ABPM in challenging patients
- Pay attention to over-control of blood pressure, particularly in the elderly
- Include the dieticians in BP management at all stages of CKD
- Carefully lower target weight and dialysate sodium in hemodialysis patients with uncontrolled hypertension
- Try to keep the ACEI or ARB on board at all stages of CKD
- Consider referral of patients with resistant hypertension to a research group for consideration of renal denervation or BAT