SECTION 6. BLOOD PRESSURE MANAGEMENT

6.0.1 Blood Pressures

A. For All Visits

Note: Section 6.0.1 describes general procedures, and Section 6.0.2 describes specific details and goals with regard to adjustments in medications. Section 6.0.3 provides action plans. Section 6.0.4 lists action items. Section 6.0.5 describes the stop point.

Each visit should include the following procedures listed below. Further management will be guided by the nature of the visit and the blood pressure.

Protocol and Rx Compliance Assessment:

Confirm intake of BP medications:

Type, amount, time (Form #4).

Document time last BP medication were taken (Form #10).

Pill count (Form #05) post-randomization.

Record new or change of medication (Form #40 at time of randomization and follow-up visits).

Complete Adherence Review (Form #16) at all post-randomization visits.

Assess adverse reactions/symptoms (Form #11).

Assess edema (Form 11).

Review home blood pressures if available.

Query participant about any problems, stressful events, change in sodium intake, etc., if needed.

Follow MOP and Protocol for Blood Pressure Measurement:

Comfortable room with consistent room temperature. Consistent appointment times.

Equipment calibrated and checked.

No smoking or caffeine or heavy exercise 30 minutes before measurement.

Patient relaxed.

Feet on floor.

Patient seated with back on chair.

B. For Screening, Baseline, and Back Titration Visits

Adjustment of antihypertensive agents during screening will be dependent on two factors: 1) medication status at screening and 2) level of blood pressure as measured by the RZ at SV2..

Screening: Documentation of diastolic BP of $\geq$ 95 mm Hg.

Titration Visits: Titrate either back (withdraw) or forward (increase) antihypertensive medicine to achieve desired blood pressure goal. **Back titrate, if possible, the three initial randomized drug classes (BB, CCB, CEI) and forward titrate the non randomized initial drugs to achieve BP control.**

A diastolic BP of $\geq$ 95 mm Hg must be documented before proceeding through Baseline. If necessary, participants who are on antihypertensive therapy will have their medications back titrated (antihypertensives withdrawn) if necessary to achieve a $\geq$ 95 mm Hg diastolic BP. During forward titration, blood pressure management will be directed toward achieving $\leq$ 140/90 mm Hg either by using agents which the participant is currently receiving or by prescribing a regimen which excludes the three initial randomized drug classes (BB, CCB, CEI), if possible. If participants are currently receiving any initial randomized drug class, an effort will be made to reduce or discontinue these agents if satisfactory control of BP can be rapidly achieved and maintained with other agents.

FOR PATIENTS NOT ON ANTIHYPERTENSIVE THERAPY:

Patients are eligible if mean diastolic BP is $\geq$ 95 mm Hg as measured by RZ on two occasions. If patients are JNC Stage IV (SBP $\geq$ 210 or DBP $\geq$ 120 mm Hg), they are eligible after one measure at Screening Visit 2 and will be eligible for initiation of drug therapy during Baseline. Therapy can include diuretics, alpha blockers, central alpha agonist, and vasodilators, sequentially added as needed. These medications will be provided free.

FOR PATIENTS ALREADY ON ANTIHYPERTENSIVE THERAPY:

Patients are eligible if <u>any</u> of the average sitting diastolic BP are $\geq$ 95 mm Hg (Form #10). During Baseline, attempts will be made whenever possible to decrease or discontinue any of the initial drugs which belong to any of the classes of agents to which they will initially be randomized. B-Blockers, CCB, or CEI can be used short-term to control pre-biopsy blood pressure. To enhance BP control, participants will have the option of receiving BP medications free-of-charge or continuing/augmenting their own therapy at their own cost but under the supervision of clinic center staff.

BACK TITRATION VISITS:

Patients with diastolic BP < 95 mm Hg at the first visit will have medications back titrated or stopped until BP increases to qualifying range of $\geq$ 95 mm Hg. **If participants are taking medications that belong to the classes that include the randomized drugs, these agents will be the first ones back-titrated or replaced if possible by other classes of drugs.**

If participants are on BB, taper off to avoid a rebound effect unmasking previously occult angina. Participants will be seen weekly or at more frequent intervals as deemed necessary by the investigators to check BP, vital signs, weight, compliance (by questioning and pill counts), the presence of adverse drug reactions or intercurrent illness, and for a limited history and physical examination. As soon as the BP increases into the qualifying range, the first GFR will be scheduled.

Once hypertension is confirmed, a regimen <u>excluding</u> BB, CCB, or CEI will be implemented if possible.

C. Randomization:

It is anticipated that at the time of randomization, participants will be on a variety of antihypertensives agents with varying degrees of blood pressure control.

Day of Randomization:

Begin randomized drug:

amlodipine (CCB)	5mg, 10 mg (once/day)?
ramipril (ACE)	2.5mg, 5mg, 10mg (once/day)?
metoprolol (BB)	50mg, 10mg, 200mg

The dose selected will be prescribed once-a-day.

At the discretion of the PI and based on the participant's blood pressure at the time of randomization, any of the three dosage levels of the blinded randomized drug may be selected.

If at randomization in the PI's judgment, the <u>maximum</u> dosage of the randomized drug alone will not be adequate to control safely the participant's BP, the PI may begin post-randomization therapy with several levels of the subsequently outlined Level II - V drugs. (At training, Dr. Wright seemed to be discouraging them from starting out at the max due to potential side effects.)

Antihypertensive agents not provided by the study will be tapered and withdrawn as safely as possible as study medications are titrated over the next two months.

D.Post-Randomization Titration Visits:

It is anticipated that after randomization there will be a time period of two months during which the participant's antihypertensive regimen will need to be titrated to achieve BP goal.

Monitoring for drug adverse effects will need to be done more frequently during the first few weeks of therapy.

Participants must be instructed to call the investigator if there are any changes or additions made in their medications between Follow-up visits. If new medications are prescribed, the PI will assess the need and ensure the medication is not contraindicated.

If necessary for control, the randomized drug will be titrated to the maximally tolerated dose within 2 months of randomization.

Recommendations are that additional antihypertensive agents will be added in the following order:

Level I - Blinded randomized drugs

Level II - Loop Diuretic (furosemide)
Tablets: 20mg, 40mg, 80mg

The exact dosage and the use of it as a once-or-twice per day drug as well as time intervals between dosage change will be determined by the PI. Furosemide may be added before the randomized drug is titrated to maximum dosage if more rapid BP control is needed, or if it is needed for volume control. The randomized drug will be titrated to the maximally tolerated dose within two months of randomization and the furosemide dose decreased to the minimum dose to achieve and maintain MAP goal.

Level III - Long Acting Alpha Blocker (doxazosin)
Tablets: 1mg, 2mg, 4mg, 8mg

The starting dosage and timing of dose increases will be determined by the PI, however compliance with the package insert for the agent is recommended to avoid first dose orthostatic hypotension.

Level IV - Central Acting Alpha 2 Antagonist (clonidine)
Tablets: 0.1mg, 0.2mg, 0.3mg

Transdermal Patch(es): TTS-1 (0.1mg/24 hours)
TTS-2 (0.2mg/24 hours)
TTS-3 (0.3mg/24 hours)

The PI can use clonidine in either oral or patch form. If the drug is used in the oral form, it will be administered BID. The starting dose and intervals between changing drug doses will be determined by the PI.

Participants will be instructed about how to place patches as well as be cautioned about suddenly stopping the medication.

Level V - Arteriolar Vasodilator (minoxidil or hydralazine)
minoxidil tablets: 2.5 mg, 5 mg, 10mg
hydralazine tablets: 10mg, 25mg, 50mg, 100mg
Minoxidil can be used QD or BID at the discretion of the PI. Hydralazine will be prescribed on a BID schedule. The starting dose and the time intervals between dose changes will be determined by the PI.

Antihypertensive agents not provided by the study will be tapered and withdrawn as safely as possible as study medications are titrated over the next two months.

Level II - V agents will usually be added sequentially and each agent should be titrated to the maximally tolerated dose (see exception for furosemide). However, at the discretion of the PI, if more rapid lowering of BP is needed, multiple levels may be initiated at a time. Then, in order to simplify the regimen, back titration of higher level agents is recommended as the dose of lower level agents is increased.

It is anticipated that after randomization there will be a time period of two months during which the participant's antihypertensive regimen will be titrated. During this titration period, drugs will be altered and increased frequency of visits will occur to achieve BP goal rapidly. Following the two month's titration phase, it is anticipated that the participant will enter a maintenance phase of blood pressure control during which infrequent alterations and non-protocol visits will not be required.

It is recognized that any one of these additional antihypertensive agents may be contraindicated, may produce unacceptable adverse effects, or may not be efficacious. However, where feasible, all attempts will be made to add additional antihypertensive medications in the above sequence and to maximize the dose of medication at one level before progressing to a new agent to enhance uniformity in the additional antihypertensives utilized.

Check serum potassium and creatinine, centrally 5 to 7 days the FV0-0 visit.

6.0.2 Antihypertensive Drug Management in AASK

Goal of Adjustments in Antihypertensives

•During qualification, to safely withdraw meds until DBP >95 (if possible get off antihypertensives belonging to randomized classes of agents)

•Postrandomization, to get and maintain participants at Goal MAP and on randomized meds.

Medication Adjustments During BP Qualification

•Participants on antihypertensives with mean DBP >95, no medication withdrawal required.

-Add open label antihypertensives (e.g. furosemide, doxazosin, clonidine, hydralazine/minoxidil) to maintain BP in safe range until randomization. The patient also may elect to continue their own antihypertensives until randomized.

-Should try to withdraw or at least taper to lowest dose all antihypertensives belonging to randomized class(es) of drug(s). This is especially true if patient is on beta blockers.

•Participants with controlled BP (DBP 90 mm Hg)

-Taper antihypertensives until DBP >95 mm Hg

-Taper antihypertensives belonging to randomized class 1st

-Must be able to discontinue all antihypertensives belonging to randomized class before you can randomize a patient

Medication Adjustments Post Randomization

NOTE: Anticipate very few participants will be able to be controlled on monotherapy. Most patients at time of randomization will be on more than one medication.

•Can leave patient on all non-randomized class antihypertensives

•Add dose level 1 or higher dose of randomized medication plus any dose level of open label antihypertensive to safely achieve or maintain goal blood pressure

Principles of Dosage Titration

•At randomization, MUST stop all BB, CaCB, ACEI

•Start randomized medication, at starting dose

-If need additional blood pressure lowering and BP too high to start at initial dose,

consider

-adding or increasing dose of open label antihypertensives
-starting at higher dose level of randomized medication (should be last resort in order to minimize risk of intolerance due to ADR)

-Open label antihypertensives usually should be added sequentially in following order and each agent titrated to maximally tolerated dose before adding another agent:

-Furosemide on QD or BID regimen (Level 2)
-Doxazosin starting 1 mg QD (Level 3)
-Clonidine starting at 0.1 BID po (Level 4) (can use patch but is more expensive and cost is borne by the clinical centers)
-Either Hydralazine starting at 25 mg BID or Minoxidil starting at 5 mg QD or BID (Level 5)

•However, multiple levels and/or higher doses of the open label medication can be prescribed if in judgement of the PI, more rapid lowering of BP is required.

•Then in order to simplify the regimen, back titration of higher level agents is recommended as the dose of the lower level agents is increased.

•The order of use of open label agents can be altered, if any of open label medications are contraindicated or produce ADR. However, where feasible, all attempts should be made to add antihypertensives in sequence and maximize the dose of one agent before adding another.

•Should achieve goal MAP before 3-month visit.

6.0.3 Action Plans

ACTION AND PLAN: IN-CENTER MAP WITHIN RANGE
Moderate MAP Goal: 102 - 107 mm Hg
Low MAP Goal: $\leq$ 92 mm Hg without symptoms

Assess protocol and prescription compliance as per "all visits/all levels" instructions.

If compliance is confirmed:
Participant to return for next monthly visit.

If non-compliance is identified:

Determine cause (e.g., problems with local M.D., family members).
Advise and instruct.
If adverse reaction caused non-compliance, attempt to modify regimen.
Consider home BP monitoring to involve participant in achieving BP goal.

ACTION AND PLAN: IN-CENTER MAP BELOW GOAL

Moderate MAP: < 102 mm Hg
Low MAP: < 92 mm Hg if symptomatic only

Assess protocol and prescription compliance as per "all visits/all levels" instructions.

If compliance is confirmed:

Decrease or discontinue most recently prescribed drug. Drugs other than the randomized drugs will be the first agents to be decreased or discontinued. The last agent of the sequential levels will be the first agent to be reduced or discontinued.

Home BP and/or non-protocol clinic visits within one week will be used to determine if BP goal is reached.

If participant is only receiving the lowest dose of a randomized drug and has symptoms of hypotension, BP will be repeated in-center at weekly intervals without any change in medication. If BP remains below goal with symptoms for two consecutive weeks, the clinical center will confer with the DCC or their designee to determine if a stop point (adverse event) has been reached.

If MAP is $\leq$ 92 mm Hg in a participant randomized to higher MAP, they should continue in an intention to treat study.

If non-compliance is identified:

Determine cause (e.g., concerns of local M.D., family members).
Advise/instruct.
Attempt to modify regimen
(excluding the discontinuation of randomized drugs).

Encourage home blood pressure monitoring or other forms of compliance enhancement measures.

Follow up by phone within one week and with a clinic visit within two weeks of any intervention or when clinic and home BP differ.

ACTION AND PLAN: MAP IS ABOVE GOAL

Moderate MAP: > 107 mm Hg
Low MAP: > 92 mm Hg

Assess protocol and prescription compliance as per "all visits/all levels" instructions.

If compliance is confirmed:

Increase dosage of randomized drug if not at maximum level. If maximum dosage is current, then move to next level drug. Increase dosage of medication at each level to its maximum dose or until an adverse reaction occurs.

Check serum potassium and creatinine in 5 - 7 days if randomized drug is increased. Recheck in-center MAP within one week.

If repeat in-center MAP is still above goal, increase dosage as per protocol or move to next level drug, whichever is appropriate per protocol. Follow up with phone call in one week and have patient return in one week for next monthly visit.

If protocol and prescription non-compliance is identified:

Advise and instruct.
If adverse reaction caused non-compliance, attempt to modify regimen.
Consider home BP monitoring to involve participant in achieving BP goal.
Follow up by phone in one week and with a clinic visit in two weeks of any intervention or when clinic and home MAPs differ.

MAINTENANCE PHASE:

For participants whose BP level remains out of range for two consecutive months or more during maintenance phase or after titration to maximum doses of medications, a standing committee will be available to work with the PI at each center.

Home blood pressure monitor may be provided at the investigators discretion to any participant with difficult to control BP.

Follow up the patient by phone within one week and with a clinic visit within two weeks of any intervention or when clinic and home BP differ.

Sodium intake should be assessed by 24-hour urinary sodium excretion. Excessive intake should be modified by counseling. Recommend and encourage additional lifestyle modifications to lower BP.

ACTION AND PLAN: IN-CENTER MAP WITHIN RANGE
Moderate MAP Goal: 102 - 107 mm Hg
Low MAP Goal: $\leq$ 92 mm Hg without symptoms

Assess protocol and prescription compliance as per "all visits/all levels" instructions.

If compliance is confirmed:
Participant to return for next monthly visit.

If non-compliance is identified:
Advise and instruct.
If adverse reaction caused non-compliance, attempt to modify regimen.
Consider home BP monitoring to involve participant in achieving BP goal.
If MAP is not within goal range, follow up with a phone call within one week and a clinic visit within two weeks.

ACTION AND PLAN: IN-CENTER MAP 1 - 4 mm Hg ABOVE OR BELOW GOAL
Moderate MAP below range: 98 - 101 mm Hg
Moderate MAP above range: 108 - 111 mm Hg
Low MAP above range: 93 - 96 mm Hg

Assess protocol and prescription compliance as per "all visits/all levels" instructions.

If compliance is confirmed:
Do not change medication.
Have participant return for in-center BP check in two weeks.
Encourage home BP monitoring if desired.
Encourage lifestyle modification if appropriate.

If in-center BP is still 1 - 4 mm Hg above or below goal range after two weeks, change medication per protocol. Follow up with phone call in one week. Have participant return for next scheduled monthly visit.

If non-compliance is identified:
Determine cause.
Advise and instruct.
If adverse reaction caused non-compliance, attempt to modify regimen.

Consider home BP monitoring to involve participant in achieving BP goal.
Follow up with phone call in one week.
Have participant return for BP check within two weeks of previous visit.

ACTION AND PLAN: IN-CENTER MAP $\geq$ 5 mm Hg ABOVE OR BELOW ACCEPTABLE RANGE

Moderate MAP: < 96 mm Hg or > 112 mm Hg
Low MAP: Symptoms with MAP < 92 mm Hg or > 98 mm Hg

Assess protocol and prescription compliance as per "all visits/all levels" instructions.

If compliance is confirmed:
If BP is above goal, change medication as per protocol, increasing medication at each level to its maximum dose until an adverse reaction occurs.

Follow up with phone call within one week.
Have participant return for in-center BP check within two weeks of visit.
Encourage home BP monitoring if desired.
Encourage lifestyle modification if appropriate.

If BP is below goal, reduce or discontinue antihypertensive agents per titration or maintenance protocols in order to achieve BP goal. Drugs other than randomized drugs will be the first agents to be reduced or discontinued. Home BP and/or non-protocol visits within one week will be used to see if BP is at goal. If participant is only receiving lowest dose of a randomized drug and has symptoms of hypotension, the BP will be repeated at weekly intervals without any change in medication. If BP remains below goal for two consecutive weeks, the clinical center will confer with the DCC to determine if a stop point has been reached.

If non-compliance is identified:
Determine cause (e.g., concerns of local M.D., family members)
Advise and instruct.
Consider home BP monitoring to involve participant in achieving BP goal.
Follow up with phone call in one week.
Have participant return for BP check within two weeks of previous visit.

6.0.4 Actions Items During Follow-Up Related to BP Management:
New onset of Nephrotic Range Proteinuria
High Blood Pressure
Randomized Drug Noncompliance
Visit Noncompliance
Low Blood Pressure with or Without Symptoms

Persistent Symptoms of Low Blood Pressure
Low Serum Potassium
High Serum Potassium
Leukopenia
Randomized Drug-Specific Adverse Effects

See Protocol for DEFINITIONS AND ACTION.

6.0.5 Stop Points Related to BP Management

Blood Pressure - A diastolic BP that remains at or above 100 mm Hg or a systolic BP that remains at or above 160 mm Hg on two or more consecutive post-randomization visits following maximally tolerated doses of multiple drug regimen specified by the protocol in spite of documented compliance.