SUPPLEMENTARY DATA

Blood Pressure Management and Control Protocol

BP Management:

A) BP goal: Achieve blood pressure values less than 130/80mmHg.

B) Process:

- Have participants measure their blood pressure daily at a standard time for two weeks.
- Obtain BP values from participant (fax, call, email, mail).
- Contact participant every 2 weeks to review blood pressure results.
- Ideally would like to obtain 14 readings prior to antihypertensive regiment change (if less than 4 are obtained for two-week period prior to planned nurse call-no medication change will be made).
- If patient is at a milestone time period (defined below) the case manager will add a new medication to their current regimen, if needed. If not at a milestone only a change in dose can be made to a previously prescribed medication.
- Contact will occur biweekly until 4 weeks of controlled blood pressure are achieved. At that point the nurse may decrease frequency of blood pressure measurement and telephone contact in a graded manner (i.e., increase to q 4 weeks for 8 weeks then q 8 weeks for 16 weeks, etc).

C) Pharmacological Protocol:

- No changes to antihypertensive drugs will be made at baseline visit unless BP>200/110mmHg. If BP>200/110mmHg call study physician.
- If an individual is not at BP goal a new antihypertensive medication must be added at milestone time periods defined as weeks 2, 8, 14, 20, or 26 after randomization.
- New antihypertensive drugs are added in the order outlined in Tables 1 and 2.
- Non-milestone time periods are weeks not defined above, during these weeks only dosage changes can be made to existing medications.
- Participants will continue on their baseline hypertensive throughout the course of trial unless provider specifies otherwise.
- If protocol requires addition of a drug class that an individual is already taking at baseline, the dosage will be increased if it had been prescribed at a sub-maximal dose. Otherwise that drug class will be skipped in the protocol and the next drug will be utilized.

Table 1. Baseline blood pressure < 150/100

Step	Drug	Dose 1	Dose 2	Dose 3
1	HCTZ	12.5mg	25mg	NA
2a	Lisinopril	10mg	20mg	40mg
2b[2]	Losartan	25mg	50mg	100mg
3	Metoprolol	12.5mg bid	25mg bid	50mg bid
4	Felodipine[3]	2.5mg	5mg	10mg
5	Clonidine	0.1 mg bid	0.2mg bid	0.3mg bid
6	Hydralazine	25 mg bid	50 mg bid	100 mg bid
7	Minoxidil + furosemide	2.5mg+20mg[4]	5mg +40mg[4]	NA

Table 2. Baseline blood pressure > 150/100

Step	Drug	Dose 1	Dose 2	Dose 3
1a	HCTZ/ Lisinopril	12.5 mg/20 mg	25 mg /20 mg	25mg/40 mg
1b[5]	HCTZ + Losartan	12.5 mg + 25 mg	12.5 mg + 50 mg	25mg + 100 mg
2	Metoprolol	12.5mg bid	25mg bid	50mg bid
3	Felodipine[3]	2.5mg	5mg	10mg
4	Clonidine	0.1 mg bid	0.2mg bid	0.3mg bid
5	Hydralazine	25 mg bid	50 mg bid	100 mg bid
6	Minoxidil + furosemide	2.5mg+20mg[4]	5mg +40mg[4]	NA

1) All medications are dosed on a daily basis unless otherwise stated

2) Only to be used if an individual develops or has a history of either angioedema or cough on an ACE inhibitor

3) Amlodipine should be substituted for felodipine for individuals with an EF < 35% (Can use the same dose titration)

4) If patient is already taking furosemide, when minoxidil is added then the dose will be increased by 20mg

5) Every attempt should be made to use combination therapy specifically hctz/lisinopril for individuals who are on lisinopril and a thiazide diuretic.

D) Drug Intolerance or Allergy:

If individual has history of drug intolerance or allergy to scheduled drugs, a substitution will be made. If previous adverse event was determined to be due to a class effect, that class will be excluded. If individual develops or has history of angioedema or cough on an ACE inhibitor, the angiotensin receptor blocker losartan may be utilized. If individual demonstrates intolerance for a medication prescribed, the offending medication will be discontinued and a new medication of a different class will be initiated.

E) Laboratory monitoring:

Electrolytes and creatinine will be monitored 3-4 weeks after dose or medication change of ACE inhibitor or diuretic.

F) Adverse Events Protocol

Contact participant two weeks after medication or dose change to determine through open-ended questions whether they experienced any adverse effects.

a) Hypotension:

If the average home systolic blood pressure is <110 mmHg and the individual is symptomatic, discontinue or decrease medication dosage until symptom free. If blood pressure subsequently rises to above 130/80 mmHg then restart on the antihypertensive algorithm, but at slower rate milestone visits every 8-10 weeks, dose increments every 4 weeks instead of every 2 weeks.

b) Hyperkalemia

Serum potassium 5.0 – 5.5 meq/L: Patient will be educated on a low potassium diet. Case managers will consult dietitian or a dietitian will see or call the patient that day to review a low potassium diet. Potassium will be repeated within a week. If potassium remains high and blood pressure is above goal, diuretic (HCTZ) will be initiated. Weekly potassium measurements will

be obtained and if hyperkalemia not resolved dose of ACE inhibitor/ARB will be reduced or discontinued.

Serum potassium 5.5 – 6.0 meq/L: Obtain EKG if no evidence of hyperkalemia changes then hold ACE/ARB and consult dietitian or a dietitian will see or call the patient that day to review a low potassium diet. May rechallenge once potassium is below 5.5meq/L with a blood draw 2-3 weeks after.

Serum potassium > 6.0 meq/L: Obtain EKG if no evidence of hyperkalemic changes then stop ACE/ARB and list as an allergy in CPRS no further attempts at use.

If EKG ever shows evidence of hyperkalemia changes than contact the study physician for possible admission.

c) Hypokalemia

Serum potassium 3.0-3.5meq/L: Patients will be encouraged to follow a high potassium diet. Case managers will consult dietitian or a dietitian will see or call the patient that day to review a high potassium diet. Serum potassium rechecked within 2-3 days of lab result documenting hypokalemia. If <3.5 meq/L potassium supplementation will be initiated to maintain serum potassium at 4.0 meq/L.

Serum potassium < 3.0 meq/L: The study physician will be contacted.

d) Worsening renal function:

Defined as a new decline of eGFR > 30% compared to the baseline value. Worsening renal function will result in discontinuation of ACE inhibitor/ARB. (Primary care provider notified and encouraged to evaluate renal artery stenosis).

G) Non-pharmacological Treatment:

a) **Weight loss:** For participants who are overweight or obese, lose weight, ideally attaining a BMI<30kg/m^2; for nonoverweight participants, maintain desirable BMI<25kg/m^2

b) **Reduced salt intake:** Participants will lower salt intake as much as possible, ideally to 2g/d of sodium.

c) **DASH-type dietary patterns:** Participants will be encouraged to consume a diet rich in fruits and vegetables (8-10 servings a day), rich in low fat dairy products (2-3servings/d) and reduced in saturated fat (less than 10% of total daily caloric intake) and cholesterol (less than 300mg/d).

d) **Moderation of alcohol intake:** For those who drink alcohol, consume 2 or less alcoholic drinks/d (men) and one or less alcoholic drink/d (women).

e) **Exercise:** Instruct participants to have regular exercise adapted to complications and co-morbidities. Optimal is 30-60 minutes of walking/day.

SUPPLEMENTARY DATA

LIPID MANAGEMENT PROTOCOL

Lipid Management

1. MEDICATIONS:

If the patient has isolated LDL elevation:

Start with simvastatin (unless otherwise specified by the provider)

1) Initial dose: 40 mg po q HS. (Unless provider specifies a different dose). RN will lower simvastatin dose if patient is on a medication that increases serum simvastatin concentration such as amiodarone, diltiazem or verapamil. Recheck lipids in 6 weeks.

2) At 6 weeks if goal is not achieved on simvastatin of 40mg start rosuvastatin 10mg po q day. Recheck lipids in 6 weeks. In Asians, in patients with chronic kidney disease with a ClCr less than 30ml/min and in patients who are on interacting drugs such as cyclosporine or gemfibrozil initial rosuvastatin dose will be 5mg.

3) If goal is not achieved by rosuvastatin 10mg, titrate dose to 20mg. Recheck lipids in 6 weeks.

4) If goal is not achieved on rosuvastatin 20mg RN may either:

    a) titrate dose up to 40mg (if well tolerated) and monitor side effects including proteinuria closely. Recheck lipids at 6 weeks

    or

    b) add ezetimibe 5mg po q day. Recheck lipids in 2 weeks. If not at goal increase ezetimibe to 10mg. Recheck lipids in 4 weeks.

5) If patient is intolerant of rosuvastatin and failed 40mg of simvastatin then start simvastatin 80mg + ezetimibe 10mg combination. Recheck lipids in 2 weeks. If goal is not achieved by simvastatin + ezetimibe change medication to atorvastatin 80mg and ezetimibe 10mg. Recheck lipids in 6 weeks.

6) If goal is not achieved on rosuvastatin/atorvastatin + ezetimibe add niacin (as described below).

7) If goal is not achieved add colestipol 4g po tid.

8) Patient can add psyllium 1 teaspoonful tid or oat cereals.

If the patient has LDL+ Triglyceride (less than 500mg/dl) elevation:

Start with simvastatin and maximize dose as above until LDL goal is achieved.

If patient not at goal for LDL on maximum dose simvastatin add niacin SR 500mg po q hs (only if patient is on insulin or glycohemoglobin equal to or less than 7 on oral hypoglycemics). Alert provider when niacin is initiated. RN to assess drug tolerance in 2 weeks and if patient tolerates niacin SR well then increase dose to 1000mg po q hs. Recheck lipids in 6 weeks. Increase niacin dose to 2000mg po q hs if goal is not achieved. Patients on niacin will have glycohemoglobins rechecked q 2 months and will be instructed to call RN if self blood glucose recordings increase above baseline.

If LDL is at goal but triglycerides remain elevated on simvastatin + niacin combination then discontinue niacin, decrease simvastatin to 20mg and add gemfibrozil 600mg po bid. Recheck lipids in 6 weeks. Simvastatin may be increased to 40mg po q day if well tolerated and if LDL increases above goal. When gemfibrozil is added to simvastatin baseline CK will be obtained and monitored every 6-8 weeks. Patient will be instructed to call with muscle pain. Medications will be discontinued if CK increases >10x baseline or if the patient cannot tolerate.

Nonpharmacological therapy (diet and exercise) needs to be reemphasized.

If the patient has isolated triglyceride (greater than 500mg/dl) elevation:

Reinforce optimal diabetes control. Review chart to see if secondary causes of dyslipidemia such as hypothyroidism, kidney failure, nephrotic syndrome, liver disease have been addressed. If not, discuss with primary provider.

Start with gemfibrozil as above. If not at goal in 6 weeks add omega 3 fatty acids with a goal dose of 3-4g per day. If not at goal in 2 months then add niacin SR as above.

If the patient has low HDL (less than 40mg/dl):

Recommend regular exercise, stop smoking and weight loss. If triglycerides are elevated (150 >TG <500mg/dl) start gemfibrozil and subsequently fish oil (if needed) as outlined above. If not at goal in 6 weeks then discontinue gemfibrozil and start niacin as above.

If the patient has LDL+ Triglyceride (more than 500mg/dl) elevation:

Reinforce optimal diabetes control. Review chart to see if secondary causes of dyslipidemia such as hypothyroidism, kidney failure, nephrotic syndrome, liver disease have been addressed. If not, discuss with primary provider.

RN will contact provider to discuss treatment options. Niacin or gemfibrozil + simvastatin 20mg may be started and simvastatin dose titrated as described above. In addition baseline CK will be obtained and monitored every 6-8 weeks. Patient will be instructed to call with muscle pain. Medications will be discontinued if CK increases >10x baseline.

Instruct patient on medication side effects when new medications are started.

Evaluate medication tolerance when medication doses are adjusted.

Labs:

a) Recheck lipids every 6 weeks until above goal achieved.

b) Recheck LFT and CK at 3 months, 6 months and yearly thereafter.

c) If there is an increase of greater than 3 fold in liver function tests (LFTs) while patient is on simvastatin, discontinue the medication and follow up LFTs in 1 week. If LFTs normalize change simvastatin to fluvastatin. Start fluvastatin at 20mg po qhs. Recheck LFTs and lipids in 6 weeks. Increase dose to 40mg (and then 80mg SA tablet) po qhs if not at goal and if well tolerated.

d) If another ADR occurs to any of these medications alert and discuss with provider.

Alert provider if lipid goal has not been achieved.

Drug Intolerance or Allergy:

If individual has history of drug intolerance or allergy to scheduled drugs, a substitution will be made. If individual demonstrates intolerance for a medication prescribed, the offending medication will be discontinued and a new medication will be initiated.

2. NON-PHARMACOLOGICAL TREATMENT: (patient should already have received information about diet, weight loss and exercise from provider and/or dietitian before enrolling in this program)

Emphasize diet (low in starches and in saturated fat as described below) and exercise, use of plant stanols/sterols (2g/day) and increased fiber (>20g/day) and refer to dietitian again as

needed. Encourage increased consumption of omega-3 fatty acids in the form of fish or in capsule form (1-4g/day) for risk reduction.

1. **DIET:**

   If isolated LDL elevation: Participants will be instructed on low fat diet (saturated fat intake less than 10% of total caloric intake in a day and less than 7% if at very high risk as defined before).

   If LDL + Triglycerides(less than 500) are elevated: Instruct on

   - Diet low on saturated fat (as above) and high in monounsaturated fat (more than 10% of total caloric intake).
   - Diet low on starches (e.g. less than 200g carbohydrate a day). Consult with dietitian to teach carbohydrate counting if total carbohydrate intake is reduced.
   - Instruct to increase fruit and vegetable intake (Referral to Dietitian; Reinforcement by RPh).

   If isolated triglycerides (greater than 500) elevation: Instruct on a diet low in fat. Patients need to refrain from alcohol. Consult dietitian if needed.

2. **EXERCISE:**

   Instruct patient to have regular exercise adapted to complications and co-morbidities. Optimal is 30-60 minutes of walking/day.

3. **WEIGHT LOSS:**

Patients will be instructed about ideal weight and weight loss. Patients will be referred to the MOVE program if they are willing and able to participate.

Diabetes Management Protocol

1. **Treatment:**

   a. **Diet:** Instruct on carbohydrates, starches vs. sugars. Teach carbohydrate counting if on Aspart Insulin. Instruct to increase fruit and vegetable intake (Referral to Dietitian; Reinforcement by case manager).

   b. **Hemoglobin A1C**: Order and monitor every 2 months until goal is achieved, and every 6 months thereafter.

c. **Exercise**: Instruct patient to have regular exercise adapted to complications and co-morbidities. Optimal is 30-60 minutes of walking per day. If patient is on insulin, encourage patient to exercise at the same time each day.

2. **Self-Monitoring of Blood Glucose**

a. **Oral hypoglycemics:** twice a week

b. **Insulin**: Fasting, before meals and bedtime. If pre-prandial glucose is at goal (90-130 mg/dl), but hemoglobin A1C is above goal, then instruct patient to check postprandial glucoses (2 hour post-meal) once a day. All patients on Aspart or Regular Insulin should check postprandial glucoses at least one meal per day, on a rotating basis.

3. **Medications**.

a. **Metformin:** First choice for most patients. Dosage: Metformin 500 mg twice a day (BID). Increase by 500mg every 2-4 weeks to 1,000mg BID. (Maximum dose is 850mg three times a day) Instruct to take with meals. For intolerable gastrointestinal side effects provider can consider Metformin SA. Labs: Check serum creatinine (SCr) yearly. If SCr is greater than 1.4, notify principal investigator.

b. **Glyburide or Glipizide:** Added if Metformin does not achieve the hemoglobin A1C goal. Dosage:

i. Initial: Glyburide 2.5 mg. once a day. Adjust in increments of 2.5 mg every 2-4 weeks based on BG to maximum dose of Glyburide 10 mg BID (start adjusting morning dose first).

ii. Initial: Glipizide 5mg once a day. Adjust in increments of 5mg every 2-4 weeks based on BG to a max dose of glipizide 20 mg BID. (Start adjusting morning dose first).

c. **Pioglitazone:** Discuss with principal investigator if this is an option, ideal for nonobese patients or patients who refuse or are unable to use insulin. Contraindicated in patients with coronary artery disease (CAD), congestive heart failure (CHF). Major side effect is weight gain.

i. Dosage: Initial 15 mg qday. (Maximum dose 45 mg.) To be used if hemoglobin A1C is greater than 8.5. Discontinue if there are no improvements (0.5% drop in HbgA1C) in 6 months Labs: A baseline liver

function assessment is required before glitazone therapy can be initiated. When used for patients who are unable draw-up and/or inject insulin, document assessment in the medical record.

d. Aspirin: Instruct patient to take 81 mg Aspirin once a day. Alert provider if the patient is not on aspirin.

4. **Monitoring of Medications and dosage adjustment**

a. The patient is instructed to call the case manager every 2-4 weeks to review fingerstick glucoses (goal: 90-130). If the patient does not call, the case manager will attempt to call the patient twice at 5 weeks.

b. Dosage adjustments are made based on the hemoglobin A1C check (every 2 months), if the patient is not at the glycemic goal

c. ** If all oral agents fail add BASAL Insulin****

5. **Basal or Long acting INSULIN:**

a. NPH Insulin: Usual Initial dose: 8-10 units. In the morning or at bedtime. Instruct patient that NPH insulin has duration of 8-16 hours (dose dependent). Increase by 2 units every 3-5 days until the morning (Insulin given QHS) or in the evening (Insulin given in the morning) Blood Sugar Goal of 90-130 is achieved **OR**

b. Glargine (Detemir-second line) Insulin: Usual initial dose: 5-8 units in the morning or at bedtime. Instruct patient that glargine insulin has duration of 20-26 hours Increase by 1-2 units every week until the morning (Insulin given at bedtime) or in the evening (Insulin given in the morning) BG of 90-130 is achieved.

i. *Patients are instructed to call 3-7 days during initial insulin adjustment. If patient does not call, case manager will attempt to call patient.*

ii. *If the glycemic goals) are achieved, but the hemoglobin A1C is elevated after 2 months (labs every 2 months), change NPH to BID (Initial dose determined by provider).*

iii. *If glycemic goals are not achieved by BID Insulin, contact provider to determine if TID NPH is appropriate.*

iv. *If overnight hypoglycemia occurs for Type 1 or Type 2 with beta cell failure NPH can be switched to glargine, as determined by the provider.*

c. Switching from NPH to Glargine or Detemir: Dosage: 80% of total daily NPH dosage at bedtime. Increase by 1-2 units every week until the morning blood glucoses are within goal.

   i. *Patients are instructed to call 3-7 days during initial insulin adjustment. If patient does not call, case manager will attempt to call patient.*

   ii. *If the glycemic goals (as determined by provider) are achieved, but the hemoglobin A1C is elevated after 2 months (labs every 2 months) consider meal time insulin (short or rapid acting).*

d. Meal time insulin: Short acting insulin: ASPART OR REGULAR: If the hemoglobin A1C goal is not achieved on long acting insulin add Aspart Insulin before meals.

   i. The case manager will initiate a dietitian consult for carbohydrate counting and the use of carbohydrate sheets. The case manager will also mail this information and reinforce this teaching.

   ii. Instruct patient to check postprandial glucoses (2-hours after meal).

      1. *Insulin to Carb Ratio determined by provider. (General guideline: 10-15g. Carbohydrate (CHO)= 1 unit short acting insulin. It is easier to calculate for patients if 1/10 ratio is used initially).*

      2. *.If postprandial glucose levels remain elevated (>180mg/dl, 2 hours after the meal, or greater than premeal value), despite accurate carbohydrate counting, then contact provider to check whether supplemental insulin before meals is appropriate.*

      3. *Guidelines for supplemental aspart/regular insulin coverage: The dose of short-acting insulin is calculated based on the carbohydrate content of the meal. Then if before the meal*,

         BG 120-160 = add 1 unit

         BG 160-200 = add 2 units

         BG 200-240 = add 3 units.

         (Rule of thumb = add 1 unit for every 40 mg/dl greater than BG 120). For example: if the patient's blood sugar before lunch is 187 and he is planning to consume 40 grams of carbohydrates, then he needs 4 units based on carb content (insulin to carb ratio 1 to 10) and 2 units based on his correction scale. Thus, he should inject a total of 6 units of short acting insulin before lunch.

      4. *If the postprandial(pp) glucose goals (pp glucose 140-180) are not met, contact the provider to change the ratio. If all blood sugars before meals are high, the long-acting insulin needs adjustment, not Aspart.*

e. Exercise Adjustment: Instruct patient to monitor glucose to determine the effect of exercise on the glycemic level. (Guidelines: Take 15grams of carbohydrate containing food before and every 30 minutes during exercise or decrease insulin by 2 units for every 30 minutes of exercise. Check fingersticks every 60 minutes for 2 hours after exercise.)

6. Hypoglycemia Treatment:

Instruct patient to treat with 15 grams of carbohydrates.

Adjustment: Determine TIMING (night time versus before/after meals). Etiology: Increased exercise, excess insulin, mismatching aspart/carb ratio. If due to increased exercise instruct patient to: Take in additional CHO before exercise OR decrease Aspart insulin before meal.