Appendix 1. IMA HTN Medication Titration Algorithm

Table 1: Antihypertensive Medication Dosing, Considerations, and monitoring[1]			
Drug	**Dose**	**Considerations**	**Monitoring Parameters**
Thiazide/Thiazide-like diuretics: Inhibit sodium reabsorption in the distal convoluted tubules causing increased excretion of sodium, water, and potassium			
Chlorthalidone	12.5-25mg once daily	- Chlorthalidone preferred due to prolonged t ½ - Caution in patients with a history of gout - Administer in the morning to prevent nocturnal diuresis	Electrolytes, glucose, renal function within 1-2 weeks of initiation and again in 6 to 12 months
Hydrochlorothiazide	25-50mg once daily		
Indapamide	1.25-2.5mg once daily		
Metolazone	2.5-5mg once daily		
ACE Inhibitors: block the conversion of angiotensin I to angiotensin II, resulting in decreased vasoconstriction and decreased aldosterone secretion			
Benazepril	10-40mg once or twice daily	- Do not use in combination with ARBs or direct renin inhibitor - Do not use if patient has a history of angioedema with ACE inhibitors - Avoid in pregnancy - Increased risk of hyperkalemia - Increased risk of AKI in patients with severe bilateral renal artery stenosis - Consider dose adjustment in patients with pre-existing renal insufficiency - Monitor for cough and hyperkalemia	SCr and potassium within 2-4 weeks of initiation or increase in dose
Captopril	12.5-150mg 2 to 3 times daily		
Enalapril	5-40 mg 1-2 times daily		
Fosinopril	10-40 mg once daily		
Lisinopril	10-40mg once daily		
Quinapril	10-80 mg once or twice daily		
Ramipril	2.5-20 mg once or twice daily		

Table 1: Antihypertensive Medication Dosing, Considerations, and monitoring[1]			
Drug	**Dose**	**Considerations**	**Monitoring Parameters**
ARBs: block angiotensin II from binding to the angiotensin II type 1 receptor on vascular smooth muscle thereby preventing vasoconstriction			
Candesartan	8-32 mg once daily	Same as ACE inhibitors - May use in patients who develop cough or angioedema to ACE inhibitors	SCr and potassium within 2-4 weeks of initiation or increase in dose
Irbesartan	150-300 mg once daily		
Losartan	50-100mg once or twice daily		
Olmesartan	20-40mg once daily		
Telmisartan	20-80mg once daily		
Valsartan	80-320mg once daily		
Calcium Channel Blockers: dihydropyridines- inhibit calcium ions from entering vascular smooth muscle and myocardial cells, resulting in peripheral arterial vasodilation thereby decreasing systemic vascular resistance and blood pressure			
Amlodipine	2.5-10mg once daily	Dose related pedal edema	
Felodipine	2.5-10mg once daily		
Nifedipine LA	30-90mg once daily		
Secondary Agents			
Loop Diuretics			
Bumetanide	0.5-2mg twice daily	- Preferred in symptomatic HF - Preferred over thiazides in moderate-severe CKD	Electrolytes, glucose, renal function within 1-2 weeks of initiation, frequently during first few months (loops), then at least yearly.
Furosemide	20-80mg twice daily		
Torsemide	5-10mg once daily		

Table 1: Antihypertensive Medication Dosing, Considerations, and monitoring[1]			
Drug	**Dose**	**Considerations**	**Monitoring Parameters**
		Furosemide 40 mg = bumetanide 1 mg = torsemide 20 mg	Repeat potassium within 4 weeks of initiation or dose increase
Potassium Sparing Diuretics: compete with aldosterone at receptor sites in the distal convoluted tubule and collecting ducts of the nephron, increasing sodium and water excretion and conserving potassium			
Eplerenone	50-100mg once or twice daily	- Preferred agents in primary aldosteronism and resistant hypertension - Avoid use with K+ supplements, other K sparing diuretics, or significant renal dysfunction - Spironolactone: non-selective; gynecomastia, breast tenderness, impotence	eGFR and potassium 2 weeks after initiation or dose titration May need dose adjustment in renal impairment
Spironolactone	25-100mg once daily		
Beta Blockers: Cardioselective- competitively block beta-1 receptors, decreasing heart rate and myocardial contractility			
Atenolol	25-100mg once daily	- Abrupt discontinuation may result in rebound hypertension and tachycardia - Selectivity lost at higher doses	
Bisoprolol	2.5-10mg once daily		
Metoprolol	Tartrate: 100-400mg twice daily Succinate: 50-200mg once daily		
Beta Blockers: Mixed alpha and beta blockers: decrease BP by reducing heart rate, myocardial contractility, and vasoconstriction			
Carvedilol	12.5-50mg twice daily	- Abrupt discontinuation may result in rebound	

Table 1: Antihypertensive Medication Dosing, Considerations, and monitoring[1]			
Drug	**Dose**	**Considerations**	**Monitoring Parameters**
Labetalol	200-800mg twice daily	hypertension and tachycardia - alpha blockade causes more vasodilation and orthostasis	
Central alpha-agonists: stimulate alpha-2 receptors in the brain, reducing sympathetic outflow of norepinephrine, decreasing SVR and HR			
Clonidine oral	0.1-0.8mg twice daily	- Last line due to CNS side effects, especially in older adults - avoid abrupt d/c due to rebound hypertension	
Clonidine patch	0.1-0.3mg weekly		
Methyldopa	250-1000mg twice daily		
Direct Vasodilators: cause direct vasodilation of arterioles, resulting in a decrease in SVR and BP			
Hydralazine	100-200mg 2-3 times daily	- Water retention and reflex tachycardia - Hydralazine associated with drug induced lupus like syndrome at higher doses - Minoxidil associated with hirsutism, and requires loop diuretic	
Minoxidil	5-100mg 1-3 times daily		

Table 2: Drugs and Other Substances With Potential to Induce or Exacerbate Elevated BP and Hypertension[1]
NSAIDs
Oral contraceptives
Sympathomimetic including decongestants
Cyclosporine, tacrolimus
Erythropoietin
VEGF inhibitors
Alcohol
Cocaine
Amphetamines
Antidepressants
Glucocorticoids, mineralocorticoids

Table 3: Features of Secondary Hypertension[2]

2020 International Society of Hypertension Global Hypertension Practice Guidelines. *Hypertension*. 2020;75(6):1334-1357.

Secondary Hypertension	Clinical History and Physical Examination	Basic Biochemistry and Urine Analysis	Further Diagnostic Tests
Renal parenchymal disease	• Personal/familial history of CKD	• Proteinuria, hematuria, leukocyturia on dipstick urine analysis • Decreased estimated GFR	• Kidney ultrasound
Primary aldosteronism	• Symptoms of hypokalemia (muscle weakness, muscle cramps, tetany)	• Spontaneous hypokalemia or diuretic-induced hypokalemia on blood biochemistry (50%–60% of patients are normokalemic). • Elevated plasma aldosterone-renin activity ratio	• Confirmatory testing (eg, intravenous saline suppression test) • Imaging of adrenals (adrenal computed tomography) • Adrenal vein sampling
Renal artery stenosis	• Abdominal bruit • Bruits over other arteries (ie, carotid and femoral arteries) • Drop in estimated GFR >30% after exposure to ACE-inhibitors/ARBs • For suspected atherosclerotic RAS, history of flash pulmonary edema or history of atherosclerotic disease or presence of cardiovascular risk factors • For suspected fibromuscular dysplasia, young women with onset of hypertension <30 years	• Decrease in estimated GFR	• Imaging of renal arteries (duplex ultrasound, abdominal computed tomography or magnetic resonance angiograms depending on availability and patient's level of renal function)

Table 3: Features of Secondary Hypertension[2]

2020 International Society of Hypertension Global Hypertension Practice Guidelines. *Hypertension*. 2020;75(6):1334-1357.

Secondary Hypertension	Clinical History and Physical Examination	Basic Biochemistry and Urine Analysis	Further Diagnostic Tests
Pheochromocytoma	• Headaches • Palpitations • Perspiration • Pallor • History of labile hypertension	• Increased plasma levels of metanephrines • Increased 24-hour urinary fractional excretion of metanephrines and catecholamines	• Abdominal/pelvic computational tomography or MRI
Cushing's syndrome and disease	• Central obesity • Purple striae • Facial rubor • Signs of skin atrophy • Easy bruising • Dorsal and supraclavicular fat pad • Proximal muscle weakness	• Hypokalemia • Increased late-night salivary cortisol	• Dexamethasone suppression tests • 24 hour urinary free cortisol • Abdominal/pituitary imaging
Coarctation of the aorta	• Higher blood pressure in upper than lower extremities • Delayed or absent femoral pulses		• Echocardiogram • Computational tomography angiogram • Magnetic resonance angiogram
Obstructive sleep apnea	• Increased BMI • Snoring • Daytime sleepiness • Gasping or choking at night • Witnessed apneas during sleep • Nocturia		• Home sleep apnea testing (eg, level 3 sleep study) • Overnight polysomnography testing
Thyroid disease	• Symptoms of hyperthyroidism: heat intolerance, weight loss, tremor, palpitations • Symptoms of hypothyroidism: cold intolerance, weight gain, dry brittle hair	• TSH, Free T4	

Table 4: Single Pill Combination Tablets
ACE Inhibitor or ARB + Diuretic
Losartan-HCTZ Lisinopril-HCTZ Olmesartan-HCTZ Valsartan-HCTZ Azilsartan-Chlorthalidone Benazepril-HCTZ Candesartan-HCTZ Captopril-HCTZ Enalapril-HCTZ Fosinopril-HCTZ Irbesartan-HCTZ Telmisartan-HCTZ
ACE Inhibitor or ARB + CCB
Benazepril-Amlodipine Olmesartan-Amlodipine Valsartan-Amlodipine Telmisartan-Amlodipine
Direct Renin Inhibitor + Diuretic
Aliskerin-HCTZ
Alpha Agonist + Diuretic
Clonidine-Chlorthalidone
Beta Blocker + Diuretic
Atenolol-Chlorthalidone Bisoprolol-HCTZ Metoprolol Tartrate-HCTZ Metoprolol Succinate-HCTZ
Beta Blocker + ARB
Nebivalol-Valsartan
K-Sparing Diuretic + Thiazide Diutetic
Triameterene-HCTZ Amiloride-HCTZ Spironolactone-HCTZ
Triple Combinations
Olmesartan-Amlodipine-HCTZ Valsartan-Amlodpine-HCTZ

Table 5: 2022 Healthfirst Medicare Formulary for Combination Pills
ACE or ARB + Diuretic
Benazepril-HCTZ Enalapril-HCTZ Fosinopril-HCTZ Lisinopril-HCTZ Quinapril-HCTZ Amlodipine-Valsartan-HCTZ Irbesartan-HCTZ Losartan-HCTZ Olmesartan-HCTZ Valsartan-HCTZ
ACE or ARB + CCB
Amlodipine-Benazepril Amlodipine-Olmesartan Amlodipine-Valsartan
Triple Combinations
Amlodipine-Valsartan-HCTZ Olmesartan-Amlodipine-HCTZ
Beta-Blocker + Diuretic
Atenolol-Chlorthalidone Bisoprolol-HCTZ Metoprolol-HCTZ

Appendix 2: IMA HTN Medication Titration Algorithm Rationale:

One Pill Once a Day (BP >130/80 and 10 year ASCVD risk score >10%)[1]; Most patient's will require 2 agents for adequate control:

- Starting with CCB is in line with guidelines for black and non-black patients, more effective in lowering BP and stroke risk compared to ACE/ARB

Two Pills Once A Day - Add Second Agent

- When adding second agent, consider ARB for most patients given lower risk of angioedema, less cough
- Single pill combination tablets should be prioritized
- Optimize dosing prior to adding a third agent
- Once doses are optimized, add a diuretic.
- Chlorthalidone superior to HCTZ given prolonged half-life, proven trial reduction of CVD.
- Decision between chlorthalidone vs HCTZ should be based on how far patient is from goal as well as renal function and potassium level.
- Optimize dosing then consider additional agent. If on HCTZ, may also consider switching to more potent diuretic (chlorthalidone) if still above goal, considering renal function and potassium.

Three Pills Once A Day – Add Third Agent and Maximize Third Agent, Think about Secondary causes of HTN.

- Guidelines recommend initiating mineralocorticoid first, though may not be an option in patients with impaired renal function or prone to hyperkalemia- eGFR <45, baseline serum potassium >4.5[1]
  - ASCOT Trial[5]: Included 1411 patients whose blood pressure was not controlled on three antihypertensive drugs (mean blood pressure 157/85 mmHg). The addition of spironolactone

(median dose 25 mg/daily) as a fourth drug was associated with a mean 22/10 mmHg reduction in blood pressure at one-year follow-up. The mean rise in serum potassium was 0.4 mEq/L, with hyperkalemia (serum potassium >5.5 mEq/L) occurring in 4 percent.

- PATHWAY-2 Trial[6]: Compared spironolactone, doxazosin, bisoprolol and placebo. Double-blind, placebo-controlled, crossover trial, enrolled patients aged 18–79 years with seated clinic systolic blood pressure 140 mm Hg or greater (or ≥135 mm Hg for patients with diabetes) and home systolic blood pressure (18 readings over 4 days) 130 mm Hg or greater, despite treatment for at least 3 months with maximally tolerated doses of three drugs. Patients rotated, in a preassigned, randomised order, through 12 weeks of once daily treatment with each of spironolactone (25–50 mg), bisoprolol (5–10 mg), doxazosin modified release (4–8 mg), and placebo, in addition to their baseline blood pressure drugs. Spironolactone was superior to each of: placebo (–8·70 mm Hg [95% CI −9·72 to −7·69]; p<0·0001); the mean of the other two active treatments (doxazosin and bisoprolol, −4·26 [–5·13 to 3·38]; p<0·0001); and each of the other individual treatments; doxazosin (–4·03 [–5·04 to 3·02]; p<0·0001) and bisoprolol (–4·48 [–5·50 to −3·46]; p<0·0001)
- If patient is not a candidate for treatment with spironolactone, consider a beta blocker with alpha blocking activity- Labetalol or carvedilol. Initiate beta blocker only if HR >70.
- Labetalol or carvedilol may be less favorable given multiple daily doses.
- Beta-1 selective agents (metoprolol) will have a greater impact on heart rate and cardiac contractility. May combine beta blocker with doxazosin to gain similar impact of combined alpha-beta therapy.
- Choice of beta blocker may be dependent on comorbid conditions (CHF, SIHD)

Four Pills Once A Day - Add Fourth Agent, Think About Secondary causes of HTN

- Would prioritize adding on spironolactone or BB, whichever was NOT started in step 3
- Other options
    - Doxazosin
    - Clonidine: Considered last line. Use limited by side effects- somnolence and dry mouth. Must be tapered off. Not great for patients with adherence issues due to rebound hypertension
    - Direct vasodilators (hydralazine, minoxidil): Use requires concomitant therapy with a loop diuretic due to risk of fluid retention, as well as beta blocker due to reflex tachycardia

References:

1. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines [published correction appears in Hypertension. 2018 Jun;71(6):e140-e144]. *Hypertension*. 2018;71(6):e13-e115. doi:10.1161/HYP.0000000000000065

2. Unger T, Borghi C, Charchar F, et al. 2020 International Society of Hypertension Global Hypertension Practice Guidelines. *Hypertension*. 2020;75(6):1334-1357. doi:10.1161/HYPERTENSIONAHA.120.15026

3. Carey RM, Calhoun DA, Bakris GL, et al. Resistant Hypertension: Detection, Evaluation, and Management: A Scientific Statement From the American Heart Association. *Hypertension*. 2018;72(5):e53-e90. doi:10.1161/HYP.0000000000000084

4. Zidek W, Spiecker C, Knaup G, Steindl L, Breuer HW. Comparison of the efficacy and safety of nifedipine coat-core versus amlodipine in the treatment of patients with mild-to-moderate essential hypertension. Hypertension Study Group. Clin Ther. 1995 Jul-Aug;17(4):686-700. doi: 10.1016/0149-2918(95)80045-x. PMID: 8565032.

5. Chapman N, Dobson J, Wilson S, et al. Effect of spironolactone on blood pressure in subjects with resistant hypertension. Hypertension. 2007;49(4):839-845. doi:10.1161/01.HYP.0000259805.18468.8c

6. Williams B, MacDonald TM, Morant S, et al. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial. *Lancet*. 2015;386(10008):2059-2068. doi:10.1016/S0140-6736(15)00257-3

7. Wong GW, Boyda HN, Wright JM. Blood pressure lowering efficacy of beta-1 selective beta blockers for primary hypertension. *Cochrane Database Syst Rev*. 2016;3(3):CD007451. Published 2016 Mar 10. doi:10.1002/14651858.CD007451.pub2

8. Wong GW, Laugerotte A, Wright JM. Blood pressure lowering efficacy of dual alpha and beta blockers for primary hypertension. *Cochrane Database Syst Rev*. 2015;2015(8):CD007449. Published 2015 Aug 26. doi:10.1002/14651858.CD007449.pub2

9. Townsend RR, DiPette DJ, Goodman R, et al. Combined alpha/beta-blockade versus beta 1-selective blockade in essential hypertension in black and white patients. *Clin Pharmacol Ther*. 1990;48(6):665-675. doi:10.1038/clpt.1990.210

10. Franz IW, Agrawal B, Wiewel D, Ketelhut R. Comparison of the antihypertensive effects of carvedilol and metoprolol on resting and exercise blood pressure. *Clin Investig*. 1992;70 Suppl 1:S53-S57. doi:10.1007/BF00207612