

Pharmaceutical Treatment of Hypertension and Dyslipidemia in People With Diabetes: An Educator's Perspective

Part I: Hypertension

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Case Presentation

M.J. is a 50-year-old white man who has had type 1 diabetes since age 20. He also has known retinopathy that has required laser treatment. He has no microalbuminuria. Treatment for depression was initiated more than 1 year ago. He has erectile dysfunction.

M.J. presents for his routine quarterly follow-up appointment with a blood pressure of 142/92 mmHg. He is on a four-shot insulin regimen using glargine and aspart. On physical exam, he has noted peripheral neuropathy. His family history includes hypothyroidism in his mother and hypertension in his father.

Physical examination and laboratory assays yield the following data:

- Height: 72 inches
- Weight: 171 lb
- BMI: 23 kg/m²

- Random capillary blood glucose: 126 mg/dl
- Triglycerides: 105 mg/dl
- Total cholesterol: 170 mg/dl
- HDL cholesterol: 69 mg/dl
- LDL cholesterol: 95 mg/dl
- Creatinine: 1.2 mg/dl
- Hemoglobin A_{1c}: 7.5%
- Electrocardiogram: normal
- Stress thalium: normal

The patient's current medications and supplements include:

- ramipril, 5 mg daily initially (renal protection)
- insulin: glargine, 16 units a.m. and 20 units p.m.; aspart, 2 units/15 g carbohydrate for breakfast and 1 unit/15 g carbohydrate for lunch, dinner, and snacks
- simvastatin, 40 mg daily
- aspirin, 325 mg daily

- sertraline hydrochloride, 100 mg daily
- alpha lipoic acid, 300 mg three times a day

M.J. does not have a regular physical activity program and eats most of his lunches in restaurants. He consumes one to four alcoholic beverages in the evening and does not smoke. Diet history reveals that the carbohydrate content of his lunches and dinners varies greatly from meal to meal. Snacks are usually from the vending machine at work. His diet is estimated to include a daily average of 2,400 calories made up of 35% total fat, 12% saturated fat, 13% protein, and 52% carbohydrate.

He bases his insulin doses on a sliding scale and not by anticipating his carbohydrate intake using a carbohydrate-to-insulin ratio.

Discussion

Hypertension, a common comorbid condition in diabetes, is defined as a blood pressure \geq 140/90 mmHg and increases the risk of both macrovascular and microvascular complications. M.J. has microvascular disease as evidenced by retinopathy and erectile dysfunction, presumably secondary to diabetic neuropathy. For people with diabetes, it is recommended that the target for blood pressure—lowering should be $<$ 130/80 mmHg.¹

The U.K. Prospective Diabetes Study² and the Hypertension Optimal Treatment (HOT) study³ both demonstrated improved outcomes, especially in preventing stroke, in patients assigned to lower blood pressure targets. In the HOT study, the epidemiological analysis showed that blood pressures \geq 120/70 mmHg are associ-

ated with increased cardiovascular event rates and mortality in people with diabetes. There is no threshold value for blood pressure, and risk continues to decrease well into the normal range.

For treatment of high blood pressure, the American Diabetes Association recommends therapeutic lifestyle change (TLC) for a maximum of 3 months if blood pressure is 130–139 mmHg systolic or 80–89 mmHg diastolic. Medication should be initiated after 3 months if TLC does not decrease the blood pressure. However, in instances in which the systolic is \geq 140 mmHg or the diastolic is \geq 90 mmHg (as in the case above), medication should be started immediately in conjunction with TLC.¹

Lifestyle modifications to manage hypertension recommended in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) include weight reduction in individuals who are overweight or obese, dietary sodium reduction, physical activity, and moderate alcohol consumption.⁴ Table 1 lists lifestyle modifications to manage hypertension. Note the column that quantifies the benefit on systolic blood pressure of each lifestyle modification.⁴

In the case above, M.J. needs to modify his cardiovascular risk factors. His diet is high in fat and sodium as noted by his eating restaurant lunches and vending machine snacks. Strategies to improve the quality of

Table 1. Lifestyle Modifications to Manage Hypertension With Approximate Reduction in Systolic Pressure⁴

Modification	Recommendation	Approximate reduction in systolic blood pressure (range)
Weight reduction	Maintain normal body weight	5–20 mmHg/10 kg weight loss
Adopt DASH eating plan	A diet rich in fruits, vegetables, and low-fat dairy products, with a reduced content of saturated and total fat	8–14 mmHg
Dietary sodium restriction	No more than 2,400 mg/day	2–8 mmHg
Physical activity	Regular aerobic activity, such as brisk walking, for at least 30 minutes per day, most days of the week	4–9 mmHg
Moderation of alcohol consumption	Limit alcohol to no more than two daily drinks for men, or one daily drink for women	2–4 mmHg

his food intake should include reduction in fats and sodium and an increase in the number of fruits and vegetables eaten daily. Referral to a dietitian for medical nutrition therapy would be appropriate. Instruction on the Dietary Approaches to Stop Hypertension (DASH) meal plan would be beneficial.⁴ Information on the DASH meal plan is available at the referenced Web site.

M.J.'s alcohol intake is of concern because of his neuropathy, as well as the effect of alcohol on his triglycerides and hypertension. His provider would also need to quantify how much alcohol he is taking in.

According to JNC 7, moderate consumption of alcohol means no more than two drinks (24 oz. of beer, 10 oz. of wine, or 3 oz. of 80-proof whiskey) per day in most men and no more than one drink per day in women and lighter individuals.

Encouraging physical activity (at least 30 minutes per day, most days of the week) would be ideal for this patient. However, his provider would need to further investigate whether his peripheral neuropathy is the reason behind his lack of physical activity.

Because M.J.'s blood pressure is > 140/90 mmHg, medication to treat his hypertension should be started immediately. For pharmacological management of hypertension in individuals with diabetes, most patients will require more than one medication to achieve adequate hypertension control. First-line therapy will likely be an angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor blockers (ARBs). M.J. has

already been started on an ACE inhibitor because studies have shown that, in people with type 1 diabetes, ACE inhibition will delay the progression of nephropathy with or without hypertension.⁵ In addition, patients who are 55 years of age or older and have an additional cardiovascular risk factor should be started on an ACE inhibitor regardless of their blood pressure, because this has been shown to reduce cardiovascular mortality.⁴ However, his current reno-protective dose will need to be increased to a therapeutic dose for lowering his blood pressure.

By blocking ACE, ACE inhibitors prevent the formation of angiotensin II. This action results in arteriolar and venous dilation, reducing total peripheral resistance and arterial blood pressure. ACE inhibitors also suppress aldosterone secretion, increase renal blood flow, and increase circulating levels of vasodilating cytokine, bradykinin.

The ARBs act by blocking the effect of angiotensin II on specific tissue receptors. Unlike ACE inhibitors, these drugs do not inhibit the enzyme that catalyzes the conversion of angiotensin I to angiotensin II, nor do they bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation. If ACE inhibitors or ARBs are used, monitor renal function and serum potassium levels.

Other strategies include the use of diuretics or β -blockers. Both have been repeatedly shown to be beneficial in reducing cardiovascular disease events during the treatment of

uncomplicated hypertension and are therefore preferred agents for initial therapy. The ALLHAT study⁶ concluded that thiazide-type diuretics are comparable in most instances to ACE inhibitors or calcium channel-blockers in preventing one or more major forms of cardiovascular disease.

The hypotensive effect of this drug class is mediated by decreased plasma volume and arteriolar vasodilation. Thiazides had been avoided in the past in people with diabetes, but hyperglycemia is not a significant issue at lower doses (< 25 mg daily).

β -blockers decrease heart rate, force of heart contractions, cardiac output, and renin excretion. They also have the potential to mask symptoms of hypoglycemia (at higher doses) and some may worsen lipid panels (although carvedilol has favorable effects on HDL cholesterol and triglycerides). Table 2 provides a complete listing of antihypertensives with dosing recommendations, possible side effects, and other useful information.

Finally, because M.J. may need multiple drugs from different classes to control his hypertension, there are combination medications that usually contain a diuretic along with an ACE inhibitor, ARB, or β -blocker. These are also listed in Table 2.

Regular blood pressure monitoring should occur to verify that the goals for therapy are being achieved. Home monitoring devices may be prescribed, but clinicians should verify that patients are using the correct size of cuff and are using the equipment

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Table 2. Medications for Hypertension

BRAND NAME	GENERIC NAME	STARTING DOSE	MAXIMUM DOSE	PEARLS
ANGIOTENSIN-CONVERTING ENZYME (ACE) INHIBITORS				
<i>Class side effects: hyperkalemia, dry nonproductive cough, decrease in renal function</i>				
<i>Time to increase dose: 1–2 weeks</i>				
Lotensin	benazepril	5–10 mg once a day	40 mg/day (may be divided)	For all ACE inhibitors: Neutral metabolic effects Does not increase lipids Does not increase orthostatic hypertension Does not aggravate coronary peripheral vascular disease Preserves renal function
Capoten	captopril	25 mg twice daily	50 mg 2- or 3-times daily	
Vasotec	enalapril	2.5–5 mg once a day	40 mg/day (may be divided)	
Monopril	fosinopril	10 mg once a day	80 mg/day (may be divided)	
Prinivil, Zestril	lisinopril	5–10 mg once a day	80 mg/day	
Univasc	moexipril	7.5 mg once a day, 1 hour before meals	30 mg/day (may be divided)	
Aceon	perindopril	4 mg once a day	16 mg/day (may be divided)	
Accupril	quinapril	5–10 mg once a day	80 mg/day (may be divided)	
Altace	ramipril	1.25–2.5 mg once a day	20 mg/day (may be divided)	
Mavik	trandolapril	1 mg once a day (2 mg if African American)	4 mg/day	
ANGIOTENSIN RECEPTOR BLOCKERS (ARBs)				
<i>Class side effects: dizziness, cough (less than ACE inhibitors)</i>				
<i>Time to increase dose: 1–2 weeks</i>				
Atacand	candesartan	16 mg once a day	> 32 mg/day no benefit	Nausea may be reduced by taking with food
Teveten	eprosartan	600 mg/day (may be divided)	> 800 mg/day no experience	
Avapro	irbesartan	150 mg once a day	300 mg once a day	For all ARBs: Similar effects as ACE inhibitors for kidneys
Cozaar	losartan	25–50 mg once a day	100 mg/day (may be divided)	
Micardis	telmisartan	40 mg once a day	80 mg/day	
Diovan	valsartan	80 mg once a day	320 mg once a day	Take on an empty stomach
Benicar	olmesartan	20 mg once a day	40 mg once a day	Titration is 2–4 weeks
β-BLOCKERS				
<i>Class side effects: increased triglycerides, decreased HDL cholesterol, masks symptoms of hypoglycemia, hyperglycemia/hypoglycemia (inhibits insulin secretion, generates insulin resistance)</i>				
<i>ISA (intrinsic sympathomimetic activity): do not decrease cardiac output, do not induce glucose intolerance</i>				
<i>b1 (β-1 receptor selectivity): do not provoke bronchospasms, do not reduce insulin secretion and glycogenolysis, selectivity diminishes at higher doses</i>				
<i>Time to increase dose: 1–2 weeks</i>				
Sectral	acebutolol (b1, ISA)	200–400 mg daily (may be divided)	800 mg/day	For all β-blockers: Documented increased survival in diabetes and coronary artery disease UKPDS: decreased stroke, heart failure Hypoglycemic symptoms masked
Tenormin	atenolol (b1)	25–50 mg once a day	> 100 mg/day no benefit	
Kerlone	betaxolol (b1)	5–10 mg once a day	> 20 mg/day no benefit	
Zebeta	bisoprolol (b1)	2.5–5 mg once a day	20 mg once a day	
Cartrol	carteolol (ISA)	2.5 mg once a day	> 10 mg/day no benefit	
Lopressor, Toprol	metoprolol (b1)	50–100 mg daily (may be divided)	400 mg/day	
Corgard	nadolol	20–40 mg once a day	320 mg/day	
Levatol	penbutolol (ISA)	10–20 mg once a day	80 mg/day no benefit	
Visken	pindolol (ISA)	5 mg twice daily	60 mg/day	
Inderal	propranolol	40 mg twice daily or 80 mg once a day (suspended release)	640 mg/day	
Blocadren	timolol	10 mg twice daily	60 mg/day	Carvedilol only is approved by the Food and Drug Administration for heart failure. 3.125 mg twice daily for heart failure
Coreg	carvedilol	6.25 mg twice daily for hypertension	50 mg/day	

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Table 2. Medications for Hypertension, cont'd from p. 62

BRAND NAME	GENERIC NAME	STARTING DOSE	MAXIMUM DOSE	PEARLS
DIURETICS				
<i>Thiazide</i>				
<i>Class side effects: hyperglycemia (insulin resistance) at higher doses, hyperlipidemia, hypercalcemia, hypokalemia, hypomagnesemia, hyperuricemia, hyponatremia, sexual dysfunction</i>				
Diuril	chlorothiazide	0.5–1 g/day (may be divided)	2 g/day	For all thiazide diuretics: Low doses have additive effect Under 25 mg should not cause increased insulin resistance May increase lipids
Hygroton	chlorthalidone	12.5–25 mg/day in the morning with food	> 25 mg/day no benefit	
Hydrodiuril	hydrochlorothiazide	12.5–25 mg/day (may be divided)	> 50 mg/day no benefit	
Diurcardin	hydroflumethiazide	25–50 mg once or twice daily	200 mg/day	
Lozol	indapamide	1.25 mg in the morning; can double dose to increase	5 mg/day	
Enduron	methyclothiazide	2.5–5 mg once a day	5 mg/day	
Zaroxolyn	metolazone	2.5–5 mg once a day	5 mg/day	
Hydromox	quinethazone	50–100 mg once a day	150–200 mg/day	
<i>Loop</i>				
<i>Class side effects: no glucose or lipid changes, hypocalcemia, hypokalemia, hypomagnesemia, hyperuricemia, hyponatremia, sexual dysfunction</i>				
Lasix	furosemide	40 mg twice daily, reduce dose of other agents at least 50%	240 mg/day	
Demadex	toremide	5 mg once a day	10 mg once a day	
CALCIUM CHANNEL-BLOCKERS				
<i>Dihydropyridines</i> <i>Class side effects: reflex tachycardia, edema, palpitations, HA, dizziness</i>				
<i>Time to increase dose: 10–14 days</i>				
Norvasc	amlodipine	2.5–5 mg once a day	10 mg once a day	For all dihydropyridine calcium channel-blockers: Often used as second agent with ACE inhibitor Metabolically neutral Not recommended if congestive heart failure, edema, tachycardia Avoid taking with high-fat meal and grapefruit
Plendil	felodipine	5 mg once a day	10 mg/day	
DynaCirc	isradipine	2.5 mg twice daily, increase by 5 mg/day increments	> 10 mg/day no benefit	
Procardia XL, Adalat CC	nifedipine	30–60 mg once a day, take Adalat CC on an empty stomach	> 120 mg/day (Procardia XL), > 90 mg/day (Adalat CC)	
Sular	nisoldipine	20 mg once a day, increase by 10 mg increments	60 mg once a day	
<i>Non-dihydropyridines</i>				
<i>Class side effects: dizziness, headache, decrease heart rate</i>				
<i>Time to increase dose: 10–14 days</i>				
Dilacor XR	diltiazem	180–240 mg once a day	540 mg/day	
Cardizem CD	diltiazem	180–240 mg once a day	> 360 mg/day no experience	
Cardizem SR	diltiazem	60–120 mg twice daily	360 mg/day	
Calan, Isoptin, Covera, Verelan	verapamil	120–240 mg/day (may be divided)	> 360 mg/day no benefit	Take slow release with food
COMBINATIONS				
Aldoril	methyldopa/hydrochlorothiazide		Maxzide, Dyazide	hydrochlorothiazide/triamterene
Avalide	irbesartan/hydrochlorothiazide		Moduretic	amiloride/hydrochlorothiazide
Diovan HCT	valsartan/hydrochlorothiazide		Prinzide	lisinopril/hydrochlorothiazide
Hyzaar	losartan/hydrochlorothiazide		Tarka	trandolapril/verapamil ER
Inderide	propranolol/hydrochlorothiazide		Tenoretic	atenolol/chlorthalidone
Lexxel	enalapril/felodipine ER		Uniretic	moexipril/hydrochlorothiazide
Lopressor HCT	metoprolol/hydrochlorothiazide		Vaseretic	enalapril/hydrochlorothiazide
Lotensin	benazepril/hydrochlorothiazide		Zestoretic	lisinopril/hydrochlorothiazide
Lotrel	amlodipine/benazepril		Ziac	bisoprolol/hydrochlorothiazide

Reasonable steps have been taken to ensure the accuracy of the information presented. However, the American Diabetes Association cannot ensure the safety or efficacy of any product described in this table.

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correctly. Lying and standing blood pressures should be monitored in the medical office to verify that patients are not experiencing orthostatic hypotension. Titration should be done carefully, especially in the elderly, to prevent hypotension and potential falls.

Hypertension substantially increases the risk of both macrovascular and microvascular complications including stroke, coronary artery disease, peripheral vascular disease, retinopathy, nephropathy, and possibly neuropathy. For M.J., it is imperative that adequate blood pressure control be achieved through medication and therapeutic lifestyle change. He already has retinopathy and neuropathy. It is crucial that he achieve acceptable blood pressure control to prevent further damage.

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References

- ¹American Diabetes Association: Treatment of hypertension in adults with diabetes (Position Statement). *Diabetes Care* 26 (Suppl 1.):S80-S82, 2003
- ²U.K. Prospective Diabetes Study Group: Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes (UKPDS 38). *BMJ* 317:703-713, 1998
- ³Hansson L, Zanchetti A, Carruthers SG, Dahlöf B, Elmfeldt JS, Menard J, Rahn KH, Wedel H, Westerling S: Effects of intensive blood pressure lowering and low dose aspirin in patients with hypertension: principal result of the Hypertension Optimal Treatment (HOT) randomized trial. *Lancet* 351:1755-1762, 1998
- ⁴U.S. Department of Health and Human Services: The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. NIH Publication No. 03-5233, 2003 (available at <http://www.nhlbi.nih.gov/guidelines/hypertension/express.pdf>)

⁵Lewis EJ, Hunsicker LG, Bain RP, Rhode RD: The effect of angiotensin-converting enzyme inhibition on diabetic nephropathy. *N Engl J Med* 329:1456-1462, 1993

⁶ALLHAT Collaborative Research Group: Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic. *JAMA* 288:2981-2997, 2002

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