MANAGEMENT OF HYPERTENSION IN DIABETES - 2005

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Mr. M.M.

- 56 yr-old white male CPA from SLC: "check-up"
- Past Hx:
  - Type 2 DM for 5 yr: "diet-controlled"
  - Hypertension for 5 yr: "diet-controlled"
  - "Mild kidney disease for?: "diet-controlled"
- ROS: pedal paresthesias for 1 yr

Mr. M.M.

- BP = 154-158/80-84 X3, both arms, sit-stand
  5'11"; 222 lbs; central obesity; HR = 88, reg
  Fundoscopy: no microaneurysms, exudates
  Cardiac: sustained PMI; S_4; nl JVP and pulses
  Lungs: clear to auscultation
  Abd: no bruits; obese; otherwise OK
  Feet: pulses present; no deformity; insensate 10-g MF

Mr. M.M.

- Labs:
  - FBG = 190 mg% HbA1c = 8.6%
  - BUN = 32 Cr = 1.7 K = 4.8 eGFR = 45ml/min/1/73m^2
  - UA = trace protein
  - Albumin/creatinine X2 = 74 - 92 mg/g
  - TC = 234 LDL = 140 HDL = 38 TG = 282
  - ECG = LVH by voltage, ST-T△'s

MULTIPLE ISSUES FOR Mr. M.M.

Glycemia	Lipids	Feet	Eyes	Kidneys	BP↑
Wt. Loss	Repeat(?)	Education	Ophthal	PVR	RX
Exercise	Statin	Podiatry		US	
SU RX					

ED
?

HYPERTENSION IN DIABETES - 2005

	% with BP ≥ 140/90
General population	29%
All patients with DM	65%
Type 1 DM, normal AER	≥ 30%
Type 2 DM:	
At Dx	50%
Microalbuminuria	83%
Macroalbuminuria	96%

Am J Kid Dis 2004; 43 (May Suppl): S142

EFFECTS OF ↑ BP ON DM COMPLICATIONS

- **CVD**: 75% of all DM deaths
  - 3X ↑ in CAD
  - 2X ↑ in stroke
  - 2X ↑ in mortality
- **Microvascular complications**
  - ↑ retinopathy, nephropathy, ? neuropathy

JAMA 2002; 287:2570 Hypertension 2001; 37:1053

FOCUS ON SYSTOLIC BP IN DIABETES

- **Isolated ↑ SBP - ≥ 140 and < 90 – in 65%**
- **↑ SBP strongest predictor of risk:**
  - CVD
    - Each 20 mm Hg ↑ SBP > 115 → ↑ 2X CVD death
  - Progression of renal disease
- **↑ SBP more difficult to control**
  - 50% more drugs with DM than non-DM

Diabetes Care 1994; 17:1247 Lancet 2002; 360:1903 Hypertension 2003; 42:1206

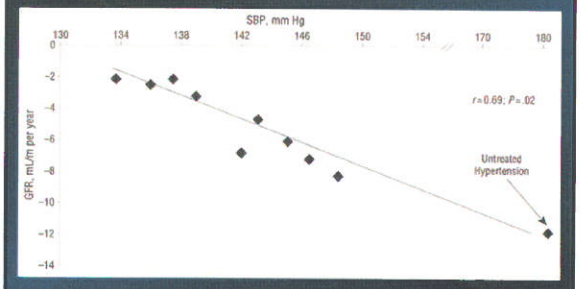
LOWER ↑BP : ↓ DM CVD

	Placebo BP	Rx BP	△BP	CVD RRR, %
SHEP, 1996: Thiazides, ± B-Blocker ± Reserpine	155/72	145/70	10/2	34%
Syst-EUR, 1999: DHP-CCB, ± ACE-I ± Diuretic	161/84	151/79	10/5	63%*

*CVD RRR in nondiabetics = 30%

JAMA 1996; 276: 1886 NEJM 1999; 340: 677

LOWER ↑BP : ↓ DM NEPHROPATHY



OPTIMAL BP IN DIABETES

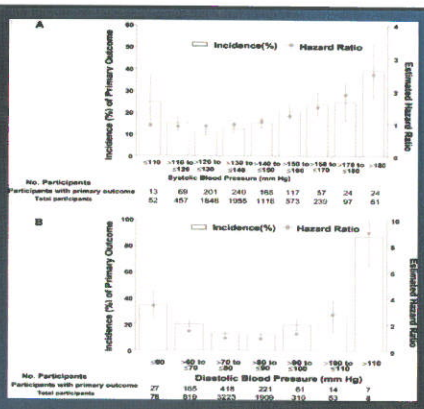
- **DBP < 80 mm Hg:**

	Achieved DBP	RRR%
HOT, 1998	85 vs 81 mm Hg	51% ↓ CVD events
UKPDS, 1998	87 vs 82 mm Hg	24% ↓ DM comp.

- **SBP < 130 mm Hg:** observational data
  - UKPDS: each 10 mm Hg ↓ SBP to < 120 decreased DM comp. by 10-15%
  - INVEST 2004: ↓ CVD risk to 110/60
    - BB vs non-DHP CCB in 6400 pts with DM ⊕ CAD ⊕ ↑BP

Hypertension 2004; 44:637 BMJ 2000; 321:412

BP Control and CVD Events in DM: INVEST



Hypertension 2004; 44:637

ABCD NORMOTENSIVE TRIAL
(Kidney International 2002: 61:1086)

- RCT, 480 Type 2 DM pts, 5.3 yr FU

	Placebo	ACE-I or CCB-DHP
• Baseline BP	136/84	137/84
• FU BP	137/81	128/75

- ↓ CVA 70% (p = 0.03)
- ↓ retinopathy 26% (p = 0.019)
- ↓ onset microalbuminuria 33%
- ↓ progression to macroalbuminuria 46%
- No diff ACE-I's vs CCB-DHP

TARGET BP IN DIABETES - 2005

	Office Target BP, mm Hg
• ADA (2005), JNC-7 (2003)	< 130/80
CHS (2004), ESH-WHO (2003)	
BHS (2004)	
• NKF (2004)	< 130/80
– Urine TP/Cr > 500 mg/g	< 125/80
• ACP (2003)	< 135/80

* Home Target BP: subtract 5-10/5 mm Hg

↓ RISK IN DIABETES (8Y)

	△ Parameters	
	Conventional Rx	Intensive Rx
HbA1c	- 0.2%	- 0.5%
LDL-C	- 13.0 mg%	- 47.0 mg%
SBP	- 3.0 mm Hg	- 14.0 mm Hg

CVD Risk	↓ 53%
Nephropathy Progression	↓ 61%
Retinopathy Progression	↓ 58%
Autonomic Neuropathy Progression	↓ 63%

NEJM 2003; 348: 383

COST-EFFECTIVENESS OF RISK FACTOR CONTROL IN TYPE 2 DM

↓ HbA1c	↓ BP	↓ Cholesterol
↓ Nephropathy	↓ CHD	↓ CHD
↓ Retinopathy	↓ Stroke	↓ Stroke
↓ Neuropathy	↓ Nephropathy	? Nephropathy
? Effect on CVD	↓ Retinopathy	
	? ↓ Neuropathy	

- **CVD → 75% of DM deaths**

COST-EFFECTIVENESS OF RISK FACTOR CONTROL IN TYPE 2 DM

	Total Cost/Quality Adjusted Life Year
Intensive BP control including ACE-I	- $1959/QALY
Intensive ↓ HbA1c SU ± insulin	$41,384/QALY
Intensive ↓ LDL-C with statin	$51,889 QALY*

- **↓ BP reduces costs, improves outcomes**
- **↓ HbA1c and ↓ LDL-C increase costs and improve outcomes**

*↓ with advancing age

JAMA 2002; 287:2542

CONTROL OF RISK FACTORS IN DIABETES
1999-2000 NHANES

	% Meeting ADA Targets
• BP < 130/80	36%*
• HbA1c < 7.0	37%
• Total cholesterol < 200 mg% (LDL ≅ < 130mg%)	48%
• BP < 130/80, HbA1c < 7.0%, (TC < 200 mg%)	7%

*? overestimates BP control – home measurement

JAMA 2004; 291:335

POOR BP CONTROL IN DIABETES

Setting	Goal BP	% ≤ Goal
NHANES – home (2000)	< 130/80	36%
Clinical practice (2004)	< 130/80	22%
Clinical practice (2002)	< 130/85	27%
INVEST RCT (2003)	< 130/85	44%
GEMINI RCT (2004)	**< 130/80**	**68%**

JAMA 2004; 291:355

Hypertension 2004; 44:637

2004; 292:2227

Hypertension 2004; 43:198

Diabetes Care 2002; 25:718

WHY POOR BP CONTROL IN DM?

- **SBP more difficult to control in DM**
  - 50% more drugs required in RCTs
- **Poorly invested patients 2° to ↓ knowledge**
  - 60%: CVD not a complication of DM
  - 55%: not "personally at risk" of CVD
  - 95%: unaware of BP-CVD link

J Am Coll Cardiol 2002; 40: 1877

WHY POOR BP CONTROL IN DM?

- **Low clinician knowledge in 2002:**
  - 63%: glycemic control top priority to ↓ CVD
  - 22%: BP control top priority to ↓ CVD
- **Clinician inertia:**
  - DM patients receive fewer BP drugs
  - DM patients receive fewer dose increments
    - 30% with SBP > goal had ↑ dose # drugs over next 12 mo!

J Am Coll Cardiol 2002; 40: 1877 Diabetic Medicine 2004; 21: 150

ADA, 2005: INDICATIONS TO RX ↑ BP IN DM

SBP	DBP	Intervention
< 130	< 80	1. At goal: ✓ BP q visit
130-139 or	80-89	1. Nonpharm Rx for 3 mo 2. Add pharm Rx if still ≥ 130/80
≥ 140 or or TOD	≥ 90	1. Pharm Rx and Nonpharm Rx

Diabetes Care 2004; 27:S65

LIFESTYLE MODIFICATION TO REDUCE BP

Modifications	↓ SBP/DBP in Hypertension (mmHg)	↓ SBP/DBP in Pre-Hypertension (mmHg)
Wt loss ≥ 10lbs	7/6	5/7
DASH Diet (feeding study)	11.4/5.5	6/3
ETOH - ≤ 2d/day men ≤ 1d/day women	3.9/2.4	3.6/1.8
↓ Dietary Na - 1.8-2.4 gm/d	3.4/1.9	2.1/--
Exercise – 120 min/wk	4.9/3.7	4.0/2.3

JAMA 2002; 288:1882

LIFESTYLE MODIFICATION OFFICE TOOLS

- Your Guide to Lowering Blood Pressure:
  www.nhlbi.nih.gov/health/public/heart/hbp/hbp_low/index.htm
- DASH Diet Update, May 2003:
  www.nhlbi.nih.gov/health/public/heart/hbp/dash/index.htm
- Low sodium diet:
  www.nhlbi.nih.gov/hbp/prevent/sodium/tips.htm
- Exercise and lowering BP:
  www.nhlbi.nih.gov/hbp/prevent/p_active/start.htm
- Alcohol and lowering BP:
  www.nhlbi.nih.gov/hbp/prevent/1_alcohol/1_alcohol.htm
- Weight control:
  www.nhlbi.nih.gov/health/public/heart/hbp/hbp_low/weight.htm

CAVEATS RE- LIFESTYLE MODIFICATION

- **Exercise**:
  - ? Age > 35y, ? walking ——→ ETT
  - Neuropathy/foot deformity
    - Caution/avoid walking
    - Favor cycling, swimming

Diabetes Care 2004; 27 (Suppl 1): S58

EFFECTIVE BP DRUGS IN DM RCTs

	↓ CVD	↓ Microvascular Events
Thiazides	Yes	Yes
ACE-Is	Yes	Yes
ARBs	Yes	Yes
Non-DHP-CCBs	Yes	Yes
DHP-CCBs	Yes	Yes
B-Blockers	Yes	Yes

- BP reduction of 9-11/2-9 mm Hg over 2-5 y
  - ↓ CVD 34-70%
  - ↓ Microvascular disease 26-46%

Hypertension 2003; 42: 1206 Am J Kid Dis 2004; 43 (May Suppl): S142

RCTs WITH DIABETES

CVD Outcomes:

ALLHAT, 2002	D vs ACE-I or CCB or alpha-B
- (12,163 patients)	
CONVINCE, 2003	D or BB vs CCB
INVEST, 2003	BB ⊕ D vs CCB ⊕ ACE-I
LIFE, 2002	BB vs ARB

Renal Outcomes:

RENAAL, 2001	ARB vs Others
IDNT, 2001	ARB vs Others
Collaborative, 1993	ACE-I vs Others

ALLHAT: ALPHA-BLOCKER vs DIURETIC

Diabetes Subgroup. 8749 patients:

	Relative Risk* Doxazosin vs Chlorthalidone
Fatal CHD/Nonfatal MI	No difference
Combined CVD events	1.22
CHF	1.85

*Numbers > 1.00 favor chlorthalidone

Hypertension 2003; 42:239

ALLHAT Diabetes Patients

Amlodipine/Chlorthalidone	Relative Risk
Nonfatal MI + CHD death	0.99 (0.87-1.13)
All-cause mortality	0.96 (0.87-1.07)
Stroke	0.90 (0.75-1.08)
Combined CHD	1.04 (0.94-1.14)
Combined CVD	1.06 (0.98-1.15)
Heart failure	1.42 (1.23-1.64)

Lisinopril/Chlorthalidone	
Nonfatal MI + CHD death	1.00 (0.87-1.14)
All-cause mortality	1.02 (0.91-1.13)
Stroke	1.07 (0.90-1.28)
Combined CHD	1.03 (0.93-1.14)
Combined CVD	1.08 (1.00-1.17)
Heart failure	1.22 (1.05-1.42)

ALLHAT Collaborative Research Group. *JAMA*. 2002;288:2981-2997.

RECENT RCTs: CVD OUTCOMES IN DM

Trial	Drugs Compared	% RRR for Major CVD Events
CONVINCE • 3239 DM pts	BB or D vs COER-Verapamil	No difference
INVEST • 6400 DM pts with CAD	BB ⊕ D vs Verapamil ⊕ ACE-I	No difference
LIFE • 1195 DM pts with LVH	BB vs ARB	Favor ARB: RRR = 24% for CVD

JAMA 2003; 289:2073 JAMA 2003; 290:2805 Lancet 2002; 359:1004

RECENT RCTS: RENAL OUTCOMES

Trial	Drugs Compared	RRR% for ESRD
IDNT • Type 2 DM • CRI	ARB vs Others	Favor ARB: 23% (NS)
RENAAL • Type 2 DM • CRI	ARB vs Others	Favor ARB: 28%
Collab. Study • Type 1 DM • CRI	ACE-I vs Others	Favor ACE-I: 50% (death, ESRD)

NEJM 2001; 345:851, 861 NEJM 1993; 329:1456

RECENT RCTS: RENAL OUTCOMES

DETAIL (2004) • Type 2 DM • Microalbuminuria (82%) Macroalbuminuria (18%)	Telmisartan Vs Enalapril	Telmisartan not inferior to enalapril for slowing loss of GFR
BENEDICT (2004) • Type 2 DM • Normoalbuminuria	Trandolapril Vs Trandolapril ⊕ Verapamil Vs Verapamil	Trandolapril ↓ progress to microalbuminuria by 47% (10.9% → 5.8%) over 4 yrs

NEJM 2004; 352:1952 NEJM 2004; 351:1941

BEST DRUG FOR ↑ BP IN DM?

No albuminuria:

- Thiazide = ACE-I = ARB to ↓ CVD events
  - CCBs less able to ↓ CHF
- ACE-I superior to CCB to prevent microalbuminuria
- Less desirable monoRx drugs:
  - Alpha-blockers (ALLHAT)
  - Beta-blockers (LIFE)
- Most DM patients need 2-3 drugs
- **Outcomes ∝ ↓ SBP: lower SBP < 130 mm Hg**

Hypertension 2003; 42: 1206 Ann Intern Med 2003; 138:587

INITIAL DRUG TO ↓ BP IN DM

No albuminuria:

- ADA (2005):
  - ACE-I or ARB
- JNC-7 (2003), CHS (2004), BHS (2004):
  - Thiazide, ACE-I, or ARB
  - Begin 2 drugs if BP ≥ 150/90
- ACP (2003)
  - Thiazides or ACE-I
    - Favor thiazide if African-American

BEST DRUG FOR ↑ BP IN DM?

Albuminuria:

- ACE-I or ARB essential to ↓ renal events
  - Choice according to available evidence base
- Most DM patients need 3-4 drugs
  - Diuretic as 1st add-on ---- volume expansion
  - Other add-ons according to comorbidity

Am J Kid Disease 2004; 43 (May Suppl): S142

ACE-I vs ARB FOR ↑ BP IN DM

- **2005 ADA and 2004 NKF recommendations:**

	Option 1	Option 2
Type 1 DM	ACE-I	ARB
Type 2 DM with/without micro-albuminuria	ACE-I or ARB	-----
Type 2 DM with nephropathy	ARB	ACE-I

Diabetes Care 2005; 28(Suppl 1): S14-15 Am J Kid Dis 2004; 43 (May Suppl): S142

RAS-BLOCKERS IN DIABETES

- Special **cardioprotection**? Not confirmed in RCTs
- Special **renoprotection**? Confirmed in RCTs
  - ∝ Cr = 1.4-3.0 and ↑ albuminuria
  - Lost with Cr > 3.0?
  - **Safety monitoring essential**
    - FU ≠ baseline SBP, eGFR, △ eGFR, K
    - See attached NKF guideline
- ACE-I vs ARB?
  - Same in type 2 DM with microalbuminuria

NEJM 2004; 352:1952 Am J Kid Dis 2004; 43 (May Suppl): S142

RAS-BLOCKERS IN DIABETES

- **Titrate to ≥ clinical trial dose, if tolerated, in CKD:**

ACE-I*	ARB*
Lisinopril, 20 mg	Irbesartan, 300 mg
Benazepril, 30 mg	Candesartan, 16-32 mg
Ramipril, 10 mg	Valsartan, 160-320 mg
Perindopril, 4-8 mg	
Trandolapril, 3 mg	

*QD dosing

Am J Kid Dis 2004; 43 (May Suppl): S142

ACE-I ⊕ ARB IN DIABETES?

Limited data:

- No renal outcome studies in DM
  - Favorable short-term RCT in non-DM CKD
- Additive ↓ in albuminuria = 20-25%
- Variable further ↓ BP
- **Safety uncertain**: ↑ K^+, ↓ GFR?
- Indications??
  - BP ≥ 130/80 on 3-4 drugs?
  - Heavy proteinuria on ACE-I or ARB?
    - Urine total protein/Cr ? 500-1000 mg/g?

Am J Kid Dis 2004; 43 (May Suppl): S142

DIURETICS FOR ↑ BP IN DM

- **Thiazides**
  - RCT efficacy for HCTZ, chlorthalidone, indapamide
  - Potentiate ACE-I, ARB: AA's, obese, elderly
  - ↓ K^+ may prevent CVD benefits: SHEP Trial
  - ↓ efficacy with eGFR < 30-45 ml/min/1.73 m^2
    - Cr = 1.8-2.0 mg%
    - www.kidney.org/professionals/kdqi/gfr_page.cfm

Hypertension 2003; 42:1206 Am J Kid Dis 2004; 43 (May Suppl): S142

DIURETICS FOR ↑ BP IN DM

- **Loop diuretics:**
  - No RCT outcome data
  - Favored if eGFR < 30-45 ml/min/1.73 m2
  - Short-acting required bid-tid dosing
    - Furosemide, bumetanide
  - Long-acting OK for qd dosing
    - Torsemide
  - ? Efficacy if no volume overload

Am J Kid Dis 2004; 43 (May Suppl): S142

CCBs FOR ↑ BP IN DIABETES

- ↓ CVD events in DM in RCTs
- Most effective drug class to ↓ SBP
  - **Non-DHP CCBs** – verapamil, diltiazem
    - ↓ albuminuria consistently
  - **DHP CCBs** – amlodipine, others
    - Inconsistent effect on albuminuria
- **Metabolically neutral**

CCBs FOR ↑ BP IN DIABETES

- Useful Step 3 agents to ACE-I/ARB ⊕ D
  - **No albuminuria:**
    - Non-DHP or DHP CCB
  - **Albuminuria:**
    - Favor non-DHP CCB
      - Step 1 if intolerant to ACE-I and ARB
    - DHP-CCB safe, effective if added to ACE-I or ARB
- Non-DHP CCB ⊕ DHP-CCB often effective

Am J Kid Dis 2004; 43 (May Suppl): S142 Arch Intern Med 2003; 163: 1555

BETA-BLOCKERS FOR ↑ BP IN DM

- **Lesser ↓ CVD events than other agents**
  - Meta-analysis: less effective than thiazides
  - LIFE: less effective than ARB in DM
  - CONVINCE, INVEST: no more effective than non-DHP CCB, even in stable CAD
- **Least effective drug class to ↓ SBP**
  - Not additive to ACE-I if HR<84 beats/min
- **Inconsistent effects on albuminuria**

Am J Hypertens 2001; 14: 241 Am J Kid Dis 204; 43 (May Suppl): S142

BETA-BLOCKERS FOR ↑ BP IN DM

- **Carvedilol optimizes CVD risks/glycemia vs metoprolol**

GEMINI TRIAL (2004)
1235 Type 2 DM with ↑ BP on RAS-blocker

	Carvedilol	Metoprolol
↑ HbA1c > 0.5%	22%	30%
↑ HbA1c > 1.0%	7%	14%
↑ TG	2%	13%
Onset microalbuminuria	6%	10%

JAMA 2004; 292:2227

BETA-BLOCKERS FOR ↑ BP IN DM

- 1st line Rx with ACE-I if post-MI, CHF
- Step 3 or 4 in other DM patients
- Carvedilol optimizes short-term CVD risks and glycemia vs metoprolol

JAMA 2004; 292:2227 Hypertension 2003; 42:1206

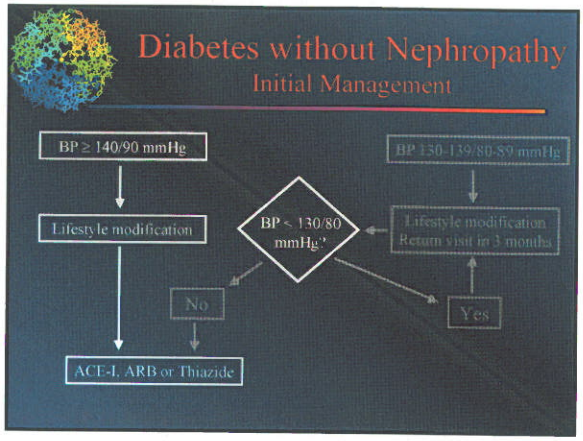
Blood Pressure Targets

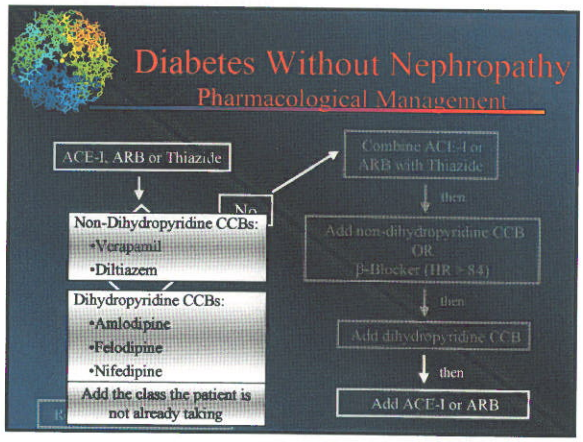
<130/80 mmHg

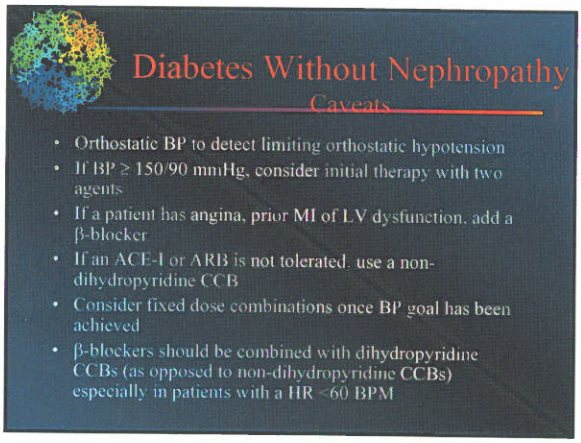
<125/75 mmHg (suggested by some for nephropathy)

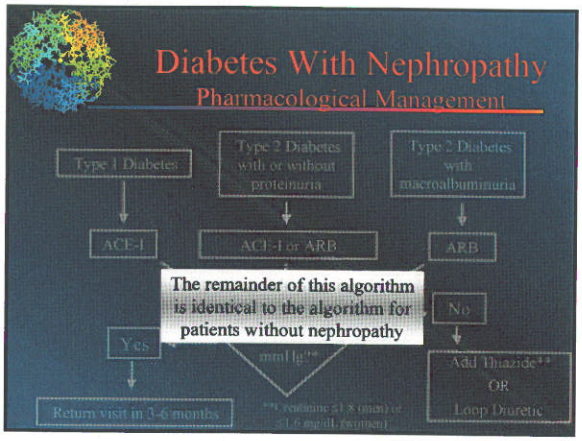
Blood Pressure Control

- Guidelines reviewed:
  - American Diabetes Association, 2005
  - Canadian Hypertension Education Program, 2004
  - British Hypertension Society, 2004
  - National Kidney Foundation, 2004
  - Joint National Committee-7, 2003
  - American College of Physicians, 2004
  - European Society of Hypertension and Cardiology, 2003


Diabetes without Nephropathy
Initial Management
BP ≥ 140/90 mmHg
Lifestyle modification
BP 130-139/80-89 mmHg
Lifestyle modification
Return visit in 3 months
BP < 130/80 mmHg*
No
Yes
ACE-I, ARB or Thiazide


Diabetes Without Nephropathy
Pharmacological Management
ACE-I, ARB or Thiazide
No
Combine ACE-I or ARB with Thiazide
then
Non-Dihydropyridine CCBs:
•Verapamil
•Diltiazem
Add non-dihydropyridine CCB
OR
β-Blocker (HR > 84)
then
Dihydropyridine CCBs:
•Amlodipine
•Felodipine
•Nifedipine
Add dihydropyridine CCB
then
Add the class the patient is not already taking
Add ACE-I or ARB


Diabetes Without Nephropathy
Caveats
• Orthostatic BP to detect limiting orthostatic hypotension
• If BP ≥ 150/90 mmHg, consider initial therapy with two agents
• If a patient has angina, prior MI of LV dysfunction, add a β-blocker
• If an ACE-I or ARB is not tolerated, use a non-dihydropyridine CCB
• Consider fixed dose combinations once BP goal has been achieved
• β-blockers should be combined with dihydropyridine CCBs (as opposed to non-dihydropyridine CCBs) especially in patients with a HR <60 BPM



Diabetes With Nephropathy
Caveats

- In addition to the caveats mentioned under diabetes without nephropathy, the following comments apply:
- Renal function and serum potassium must be monitored in patients with renal insufficiency.
  - If renal function deteriorates significantly (> 25-30%) while on an ACE-I or ARB, consider evaluating for renal artery stenosis
- Any albuminuria is an indication for treatment with an ACE-I or ARB without regard to BP measurement
- Combining ACE-I and ARBs may lower BP and reduce proteinuria

Mr. M.M.

- Poorly controlled Type 2 DM
- Systolic hypertension: 156/82
- Renal insufficiency
  - Cr = 1.7 and eGFR = 45 ml/min/1.73 m^2
- Microalbuminuria
- LVH