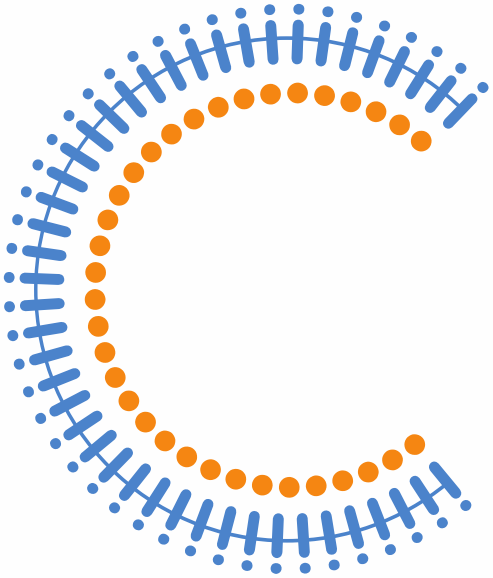

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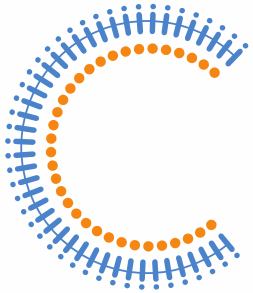

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The Complex Patient
Case Module 1:
Management of Patients with Diabetes and Hypertension

Case Development & Disclosures

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Case Authors

- Dr. Martin Dawes, MB.BS. MD, FRCGP, Head, Dept. Family Practice, University of British Columbia
- Dr. Onil Bhattacharayya, MD, PhD University of Toronto.
- Dr. Neil Heron; MBChB, Mphil, MFSEM, Queen's University, Belfast, UK.

Executive Editor: Dr. Sheldon W. Tobe, MD, MScCH (HPTE), FRCPC, FACP, FASH

Editorial Project Manager: Diane Hua, MPH

Case Development & Disclosures

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Continuing Education Committee

- Richard A. Ward, MD CCFP
- Steven Goluboff, MD CCFP
- David Dannenbaum, MD CCFP
- Sol Stern, MD CCFP
- John Hickey MD CCFP
- Karen Mann, BN, MSc, PhD

Outline of Today's Activity

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- Introduction
- Case Presentation
- Key Learnings & Questions
- Wrap Up

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CEPD
continuing education and professional development

Faculty/Presenter Disclosure Slide 1

- **Presenter:**

- **Relationships with commercial interests:**
  - **Grants/Research Support:**
  - **Speakers Bureau/Honoraria:**
  - **Consulting Fees:**

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CEPD
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Disclosure of Commercial Support Slide 2

- **This program has received financial support from** Public Health Agency of Canada, Ontario Ministry of Health and Long-Term Care **in the form of** educational grants.
- **This program has received in-kind support from** C-CHANGE and Elsevier Canada **in the form of** content management, logistical and project support.

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- Altering control over content: information and recommendations given in the program are evidence based and sourced from multiple clinical practice guidelines/scientific professional associations.
- Program material is peer reviewed by a committee with members representative of the target audience.

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Case 1:
Management of Patients with Diabetes and Hypertension

Tom

A white 55 year old man with diabetes presents to your office for routine review with an upper respiratory tract infection.

Learning Objectives

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Upon completion of this activity, participants should be able to:

1. Identify the Canadian blood pressure targets for patients with diabetes.
2. Formulate a treatment plan for patients with diabetes and hypertension using the C-CHANGE recommendations.
3. Assess the risks associated with diabetes in patients with hypertension and the evidence supporting the use of RAAS blockers; and the risks of RAAS blockers use in diabetic nephropathy

Statement of Need

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"My greatest challenge as a health care professional in the management of patients with ***multiple morbidities*** *is _____"*

History of Present Illness

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- Tom is a white 55 year old man with diabetes.
- He presents to your office for routine review with an upper respiratory tract infection.

Past History

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- Tom has been living with type 2 diabetes for 3 years.
- His diabetes is currently controlled with lifestyle interventions.
- He cycles to his work as an accountant on most days.
- He is a non-smoker, with occasional alcohol use.
- Married with 2 children.
- No history of CV disease.

Family History

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- Father
  - diabetes at age 45, controlled with insulin
- Grandfather
  - diabetes at age 51, controlled with insulin
- No Siblings
- No history of cardiovascular disease.

Current Medications

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What are his current medications?

- Diabetes currently diet controlled.
- ASA, 81mg, od (patient started on own, buys over the counter)

Physical Examination

- Height: 170 cm
- Weight: 83.9 kg
- Waist: 104 cm
- BMI: 29 kg/m^2
- BP (left arm, seated): 148/92 mmHg using an approved automated device

- Funduscopic: - normal
- Neck-Thyroid palpable, no nodule
- Heart: Normal
- Lungs: Normal
- Abdomen: no murmurs
- Arteries: Normal
- Ankle edema: nil
- Neuro: normal

Question 1

After addressing the initial complaint of an URTI, you turn to Tom's blood pressure.

Tom's current blood pressure is 148/92 mmHg. What is the target BP for Tom?

Question 1. This patient has hypertension and diabetes, what is his target BP?

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a) <140/90 mmHg

b) <135/85 mmHg

c) <130/80 mmHg

d) <120/80 mmHg

Question 1. This patient has hypertension and diabetes, what is his target BP?

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a) < 140/90 Incorrect for Canada

- Other guidelines groups had moved their target up to < 140 systolic based on the ACCORD study
- And even <90 diastolic

Question 1. This patient has hypertension and diabetes, what is his target BP?

C•CHANGE

c) <130/80 mmHg

Treatment Targets: Hypertension

- Persons with diabetes mellitus should be treated to attain systolic blood pressures of <130 mm Hg and diastolic blood pressures of <80 mm Hg. (These target blood pressure levels are the same as the blood pressure treatment thresholds.)

Usual Office BP Threshold Values for Initiation of Pharmacological Treatment

Population	SBP	DBP
High Risk (SPRINT population)	≥130	NA
Diabetes	≥130	≥80
Moderate-to-high risk (TOD or CV risk factors)*	≥140	≥90
Low risk (no TOD or CV risk factors)	≥160	≥100

TOD = target organ damage

***AOBP threshold ≥135/85**

Recommended Office BP Treatment Targets

Treatment consists of health behaviour ± pharmacological management

Population	SBP	DBP
High Risk	≤120	NA
Diabetes	< 130	< 80
All others*	< 140	< 90

* Target BP with AOBP < 135/85

Reasons that Canada has Kept <130/80 as the BP target for People with DM

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- ACCORD was underpowered for the main outcome (event rate in control arm 2% vs 4% predicted)
- Stroke reduced by 47% in the < 120/80 group
- The HOT study 50% reduction of major CV events in < 80 diastolic group compared to <90
- ACCORD did not test the current recommendation of < 130 systolic.
- Meta-analyses demonstrate an increased risk of stroke when moving the BP target to < 140 from < 130

ACCORD: NEJM 2010
HOT: L Hansson,L. Lancet 1998
Meta-analyses: Bangalore et al. Circ 2011; Reboldi et al. J Hyperten 2011

Increased Risk of Stroke with Higher Achieved BP in People with Diabetes

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- Reboldi meta-regression showed the risk of stroke decreased by 13% for each 5-mmHg reduction in SBP
- Bangalore meta-analysis showed 48% lower risk of stroke (.82% vs 1.6%) for systolic BP < 130 vs < 140

Meta-analyses: Bangalore et al. Circ 2011; Reboldi et al. J Hyperten 2011

New thresholds/targets for the high risk patient post-SPRINT: *who does this NOT apply to??*

Limited or No Evidence:

- Heart failure (EF <35%) or recent MI (within last 3 months)
- Indication for, but not currently receiving a beta-blocker
- Frail or institutionalized elderly

Inconclusive Evidence:

- **Diabetes mellitus**
- Prior stroke
- eGFR < 20 ml/min/1.73m2

Contraindications:

- Patient unwilling or unable to adhere to multiple medications
- Standing SBP <110 mmHg
- Inability to measure SBP accurately
- Known secondary cause(s) of hypertension

Question 2

This patient has diabetes and hypertension, what investigations are appropriate?

IV ROUTINE AND OPTIONAL LABORATORY TESTS FOR THE INVESTIGATION OF PATIENTS WITH HYPERTENSION

1) Routine laboratory tests that should be performed for the investigation of all patients with hypertension include:

   i) urinalysis (Grade D);

   ii) blood chemistry (potassium, sodium, and creatinine) (Grade D);

   iii) fasting blood glucose and/or glycated hemoglobin (A1c) (Grade D);

   iv) fasting serum total cholesterol and high density lipoprotein cholesterol, low density lipoprotein cholesterol and triglycerides (Grade D); and

   v) standard 12-lead electrocardiography (Grade C).

While you have Tom in the room,
you decide to carry out these tests.
Please review the results.

Laboratory Investigations

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Test	Results	Normal Values
Glucose	6.6 mmol/L	4.0-8.0 mmol/L
Urea	5.2 mmol/L	3.0-7.0 mmol/L
Creatinine	97 µmol/L eGFR 88 ml/min	44-106 µmol/L
K	4.3 mmol/L	3.5-5.0 mmol/L
Na	136 mmol	135-145 mmol/l

- *Note that labs are done prior to the next visit*

Laboratory Investigations

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Test	Results	Target values
LDL	4.2 mmol/L	<2.0 mmol/L
Total chol	6.8 mmol/L	<5.20 mmol/L
TG	3.6 mmol/L	<1.70 mmol/L
HDL	0.8 mmol/L	>0.99 mmol/L
TC:HDL	8.5	

Laboratory Investigations

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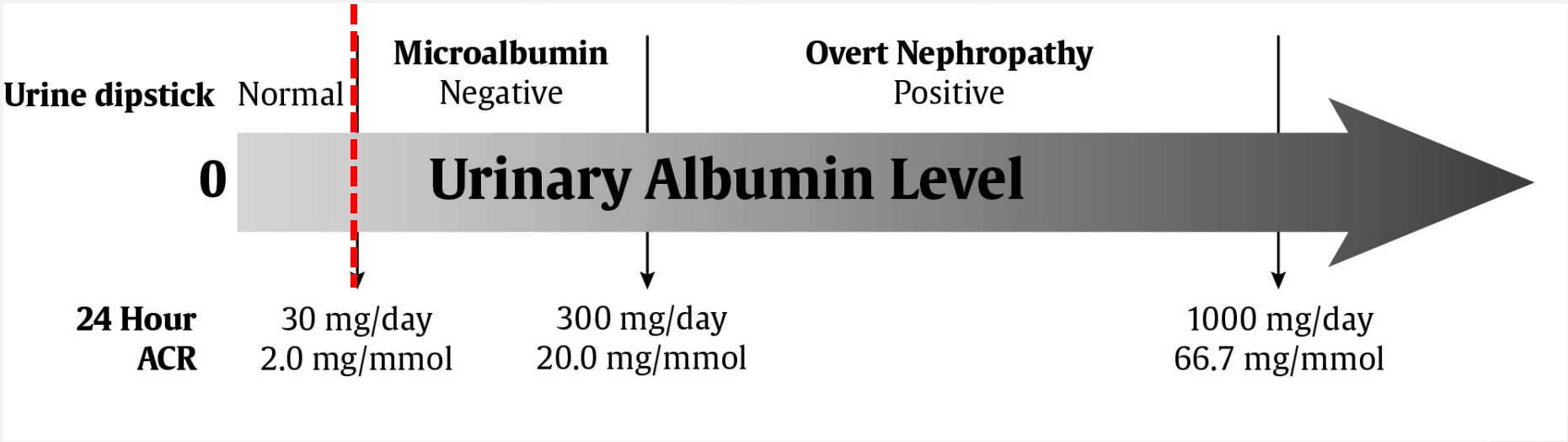
Test	Results	Normal Values
HbA1c	0.074	0.045 - 0.057 mmol/L
Urinalysis	Negative for proteinuria	Neg
Alb/creat	4.1 mg/mmol	< 2.0 mg/mmol

Tom's annual assessment confirms microalbuminuria.

- *Note that labs are done prior to the next visit*

Stages of Diabetic Nephropathy



Note: change in definition of microalbuminuria

2013

ACR ≥2.0 mg/mmol

Canadian Diabetes Association

Question 3

You have confirmed hypertension **(last BP was 148/92 mmHg)**, what would be your first choice of anti-hypertensive?

Question 3) What would be your first-line anti-hypertensive in this patient?

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a) Treatment with ACEi or ARB

b) Treatment with an ACEi/ARB combination

c) Treatment with a calcium channel blocker such as amlodipine

Question 3) What would be your first-line anti-hypertensive in this patient?

C•CHANGE

a) Treatment with ACEi or ARB

- Correct

Pharmacological Therapy/ Procedural Therapy

Hypertension:

For persons with cardiovascular or kidney disease, including microalbuminuria or with cardiovascular risk factors in addition to diabetes and hypertension, an ACE inhibitor or an ARB is recommended as initial therapy.

Question 3) What would be your first-line anti-hypertensive in this patient?

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b) Treatment with an ACEi/ARB combination

Pharmacological Therapy

For patients with stroke treatment with an ACE inhibitor and thiazide/thiazide-like diuretic combination is preferred The combination of an ACE inhibitor and ARB is not recommended.

Question 3) What would be your first-line anti-hypertensive in this patient?

C•CHANGE

c) Treatment with a calcium channel blocker such as amlodipine

- In the absence of microalbuminuria this is reasonable, if there is a reason not to use an ACEi or an ARB
- Adding a CCB to an ACEi or an ARB is an excellent second step for controlling BP

XII. Treatment of Hypertension in association with Diabetes Mellitus

Threshold equal or over 130/80 mmHg and Target below 130/80 mmHg

Diabetes

with Nephropathy*

***Urinary albumin to creatinine ratio ≥ 2.0 mg/mmol**

without Nephropathy**

Systolic-diastolic Hypertension

Isolated Systolic Hypertension

A combination of 2 first line drugs may be considered as initial therapy if the blood pressure is ≥20 mmHg systolic or ≥10 mmHg diastolic above target

Combinations of an ACEI with an ARB are specifically not recommended in the absence of proteinuria

*** based on at least 2 of 3 measurements**

XII. Treatment of Hypertension in association with Diabetic Nephropathy

THRESHOLD equal or over 130/80 mmHg and TARGET below 130/80 mmHg

DIABETES with Nephropathy

→ **ACE Inhibitor or ARB**

IF ACEi and ARB are contraindicated or not tolerated, SUBSTITUTE
- **Long-acting CCB or**
- **Thiazide diuretic**

→ **Addition of one or more of** Long-acting CCB or Thiazide diuretic

3 - 4 drugs combination may be needed

If Creatinine over 150 µmol/L or creatinine clearance below 30 ml/min (0.5 ml/sec), a loop diuretic should be substituted for a thiazide diuretic if control of volume is desired

Monitor serum potassium and creatinine carefully in patients with CKD prescribed an ACEi or ARB

CHEP

Hypertension Canada (2015). Part 2: Recommendations for Hypertension Treatment [PowerPoint slides]. Retrieved from Hypertension Canada Website: http://hypertension.ca/chep-recommendations.

Hypertension CANADA

Counsel all Patients About

Sick Day Medication List

Instructions for Healthcare Professionals:
If patients become ill and are unable to maintain adequate fluid intake, or have an acute decline in renal function (e.g. due to gastrointestinal upset or dehydration), they should be instructed to hold medications which will:

A) Increase risk for a decline in kidney function:
- Angiotensin-converting enzyme inhibitor
- Angiotensin receptor blockers
- Direct renin inhibitors
- Non-steroidal anti-inflammatory drugs
- Diuretics
- SGLT2 inhibitors

B) Have reduced clearance and increase risk for adverse effects:
- Metformin
- Sulfonylureas (gliclazide, glimepiride, glyburide)

S sulfonylureas
A ACE-inhibitors
D diuretics, direct renin inhibitors

M metformin
A angiotensin receptor blockers
N non-steroidal anti-inflammatory
S SGLT2 inhibitors

Please complete the following card and give it to your patient.

Patients should be instructed that increased frequency of self blood glucose monitoring will be required and adjustments to their doses of insulin or oral antihyperglycemic agents may be necessary.

Case progression

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After confirmation of hypertension, you discuss starting an ACE inhibitor with Tom. He is not keen on starting a “pill”. He prefers a natural alternative or any way to avoid taking medication. He says he feels well and asks how starting an ACE inhibitor will make him better.

Question 4

C•CHANGE

a) What would you say to him about the efficacy of an ACE inhibitor, particularly in someone with diabetes, hypertension and evidence of diabetic nephropathy?

b) What common side-effects of an ACE inhibitor should you discuss with Tom before you prescribe it?

Question 4 a) Efficacy of RAAS blockade in Diabetes and Hypertension

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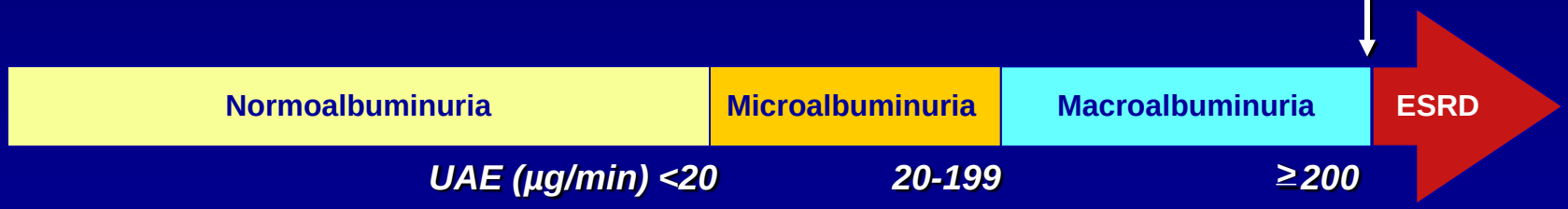
- Blood pressure lowering in people with diabetes and hypertension prevents both microvascular and macrovascular disease (UKPDS, HOT)
- Adding a RAAS blocker for patients with diabetic nephropathy helps to both lower the blood pressure and to prevent renal complications IDNT, RENAAL) and in the HOPE study was associated with improved cardiovascular outcomes.

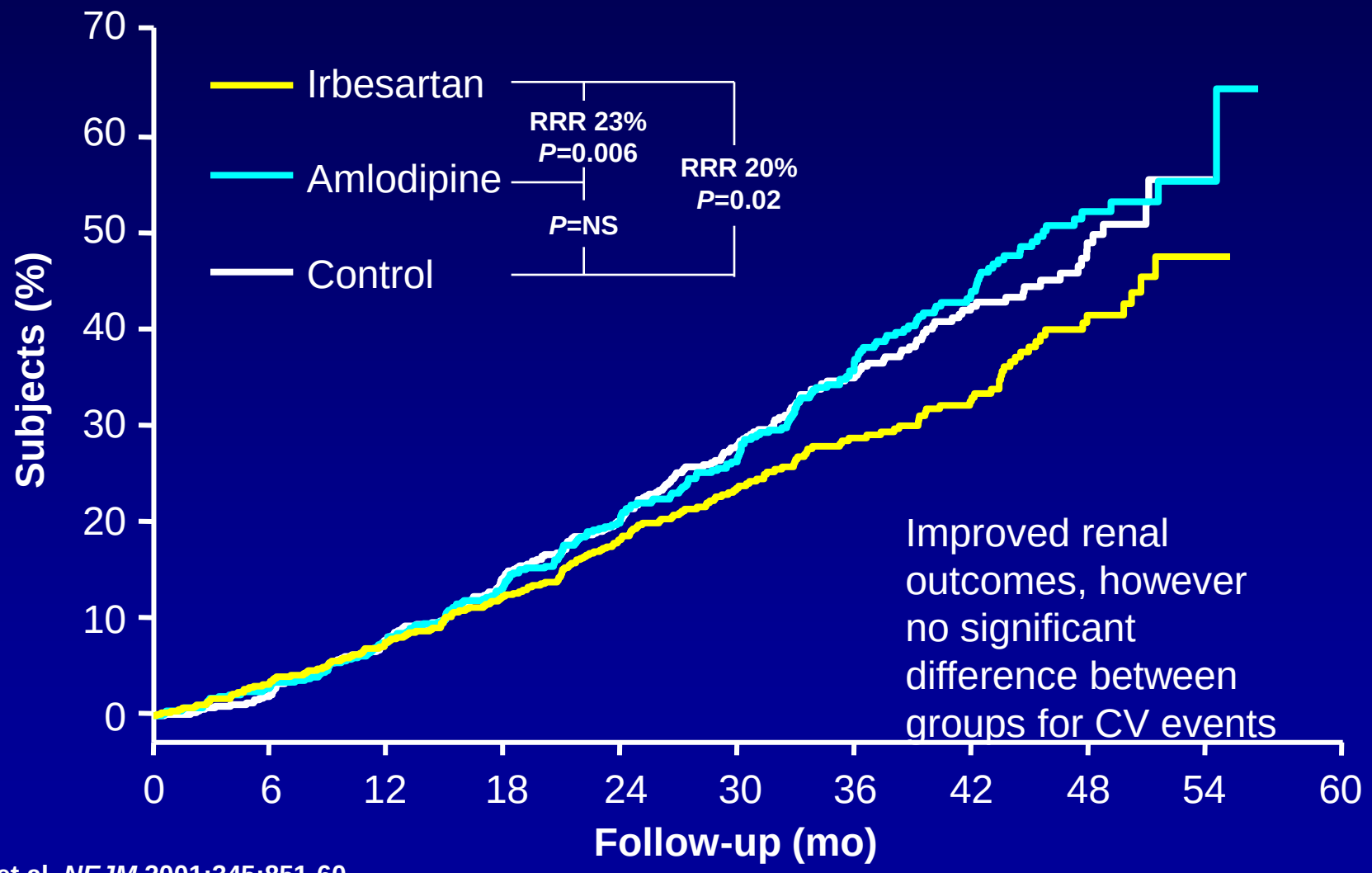
Lewis 1, RENAAL and IDNT have shown prevention of progression to ESRD for ACE and ARB

Lewis 1 T1DM
RENAAL T2DM
IDNT T2DM



Brenner BM, *et al*. *N Engl J Med* 2001; **345**: 861-9.
Lewis EJ, *et al*. *N Engl J Med* 2001; **345**: 851-60.
Lewis EJ, et al. N Engl J Med 1993;329:1456–1462.

IDNT: Primary Endpoint (Time to Doubling of Serum Creatinine, ESRD, or Death)



Lewis et al. *NEJM* 2001;345:851-60.

Impact of RAAS blockade on Cardiovascular Events in Participants With and Without Baseline Microalbuminuria

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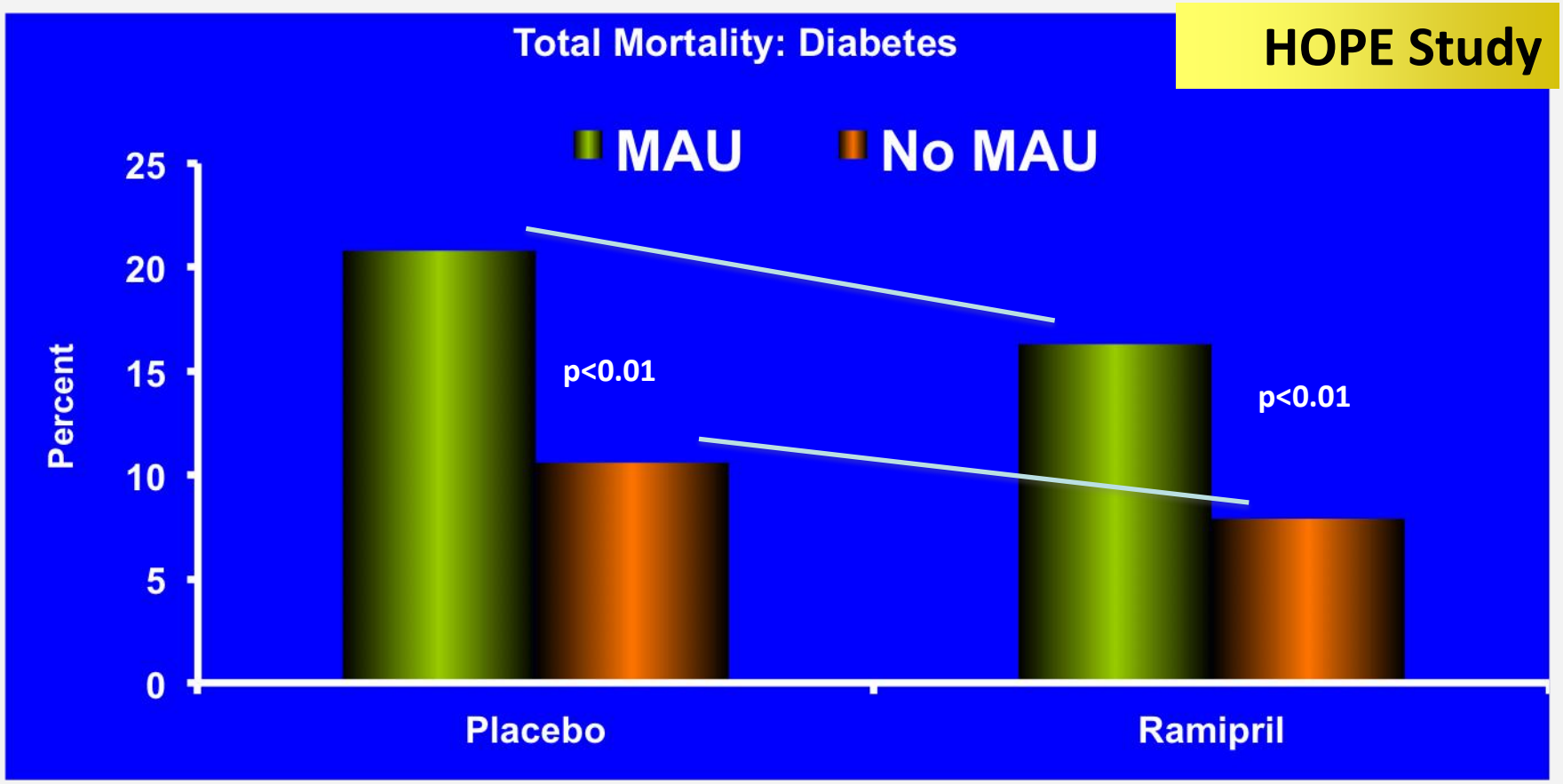
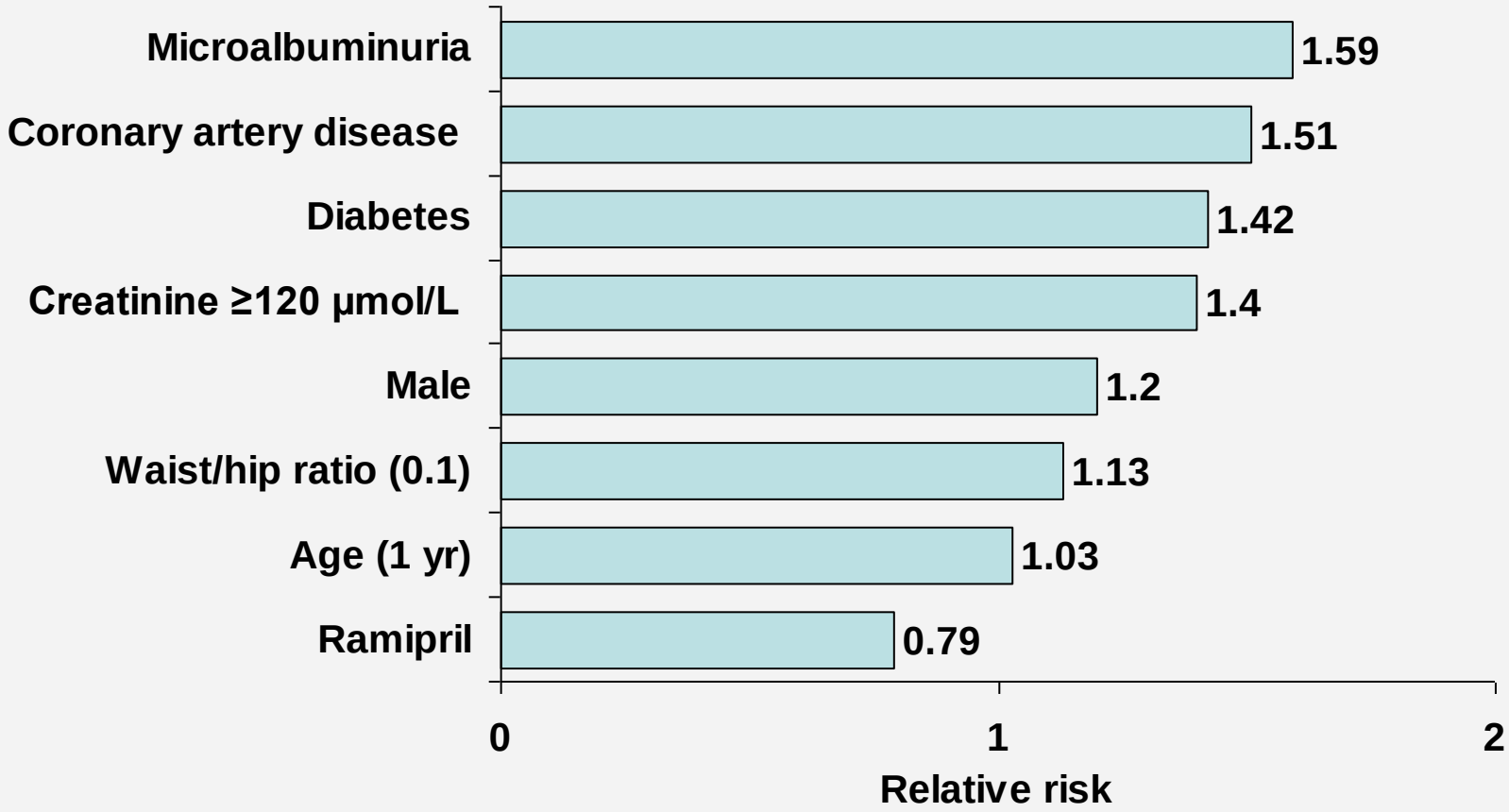


Gerstein. JAMA. 2001;286:421-26.

Multivariate Relative Risks for Primary Outcomes in the HOPE Study



Mann et al. Ann Intern Med 2001;134:629-36

4b) What common side-effects of an ACE inhibitor and other RAAS blockers should you discuss with Tom before you prescribe it?

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- Ensure no known drug allergies and drug interactions.
- Dry cough (5-15% of people) with ACEi's– alternatives available (ARBs).
- Acute Kidney Injury if the patient has a sudden volume depletion event
  - Counsel about sick day medication (i.e. when patient can not take oral fluids)
- Rising creatinine in patients with bilateral renal artery stenosis is rare unless patient is vasculopathic
- Hyperkalaemia – monitor serum potassium 1-2 weeks after start in high risk patients

Question 5

If the 1st line anti-hypertensive drug didn't achieve BP control, what additional drug would you use in this patient?

Question 4) If the 1st line anti-hypertensive drug didn't achieve BP control, what additional drug would you use in this patient?

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Pharmacological Therapy – Hypertension and Diabetes

- Additional antihypertensive drugs should be used if target blood pressure levels are not achieved with standard dose monotherapy. Add-on drugs should be chosen from first line choices. Useful choices include a thiazide diuretic or CCB with an ACE inhibitor, ARB or a β-blocker. Caution should be exercised in combining a nondihydropyridine CCB and a β-blocker. The combination of an ACE inhibitor and ARB is not recommended.

ACCOMPLISH Study: ACEi + CCB vs ACEi + HCTZ

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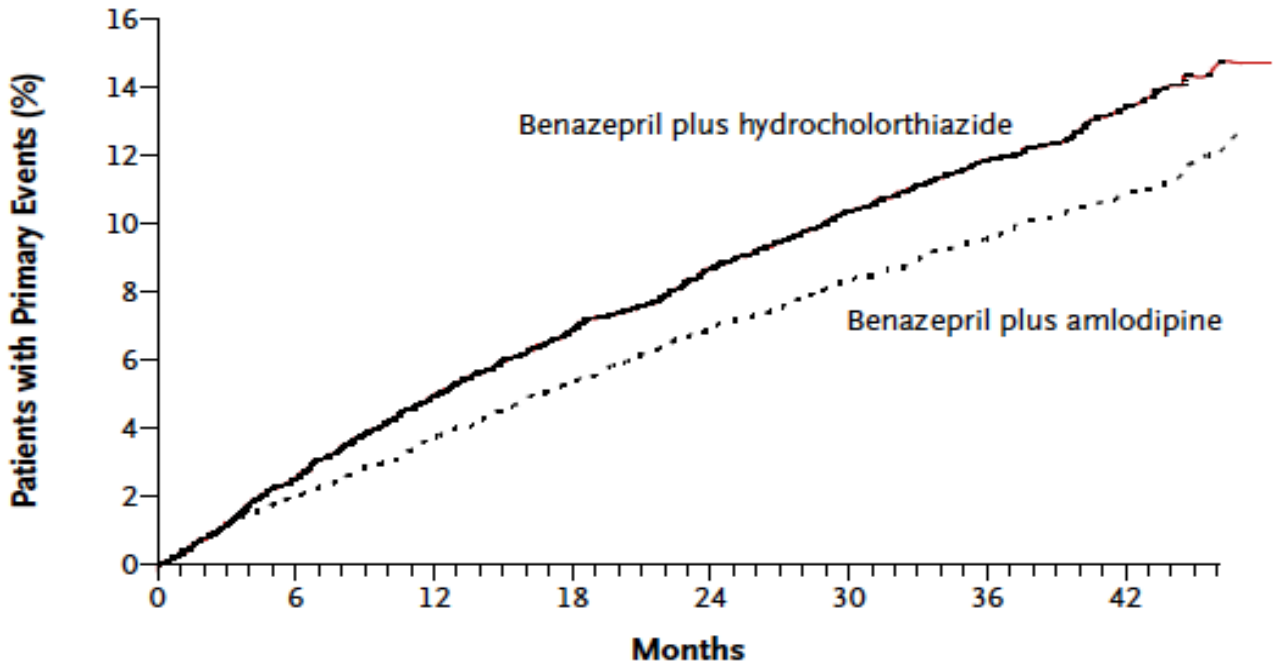

No. at Risk							
Benazepril plus amlodipine	5512	5317	5141	4959	4739	2826	1447
Benazepril plus hydrochlorothiazide	5483	5274	5082	4892	4655	2749	1390

Figure 2. Kaplan–Meier Curves for Time to First Primary Composite End Point.

There were 552 patients with events (9.6%) in the benazepril–amlodipine group, as compared with 679 patients with events (11.8%) in the benazepril–hydrochlorothiazide group. The relative risk reduction was 20% (hazard ratio, 0.80; 95% CI, 0.72 to 0.90; P<0.001).

Jamerson K et al. NEJM 2008; 359 (23)

Guideline based on ACCOMPLISH Study

- In high risk patients, when combination therapy is being used, the combination of an ACE inhibitor and a dihydropyridine CCB is preferable to an ACE inhibitor and a diuretic

Question 6

What other modifiable risk factors can you start to address in Tom?

Question 6) What other modifiable risk factors can you start to address in Tom?

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a) Body habitus/diet

b) LDL - Statins

c) Blood glucose lowering:

Oral hypoglycaemic with CV Risk Reduction

Question 6) What other modifiable risk factors can you start to address in Tom?

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Body Habitus: All

Maintenance of a healthy body weight (BMI 18.5 to 24.9 kg/m2, and waist circumference <102 cm for men and <88 cm for women) is recommended for nonhypertensive individuals to prevent hypertension and for hypertensive patients to reduce blood pressure. All overweight hypertensive individuals should be advised to lose weight.

Question 6 b) What other modifiable risk factors can you start to address in Tom?

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- The beneficial effects of lowering low-density lipoprotein cholesterol (LDL-C) with statin therapy applies equally well to people with diabetes as to those without the disease.
- The primary treatment goal for people with diabetes is LDL-C ≤2.0 mmol/L, which is generally achievable with statin monotherapy. (CDA, 2013)

Pharmacological Therapy – Dyslipidemia

- We recommend a target LDL-C ≤ 2.0 mmol/L or ≥ 50% reduction of LDL-C for high risk individuals in whom treatment is initiated.

Question 6 c) Blood Glucose Control, CV Risk Reduction

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At diagnosis of type 2 diabetes

Start lifestyle intervention (nutrition therapy and physical activity) +/- Metformin

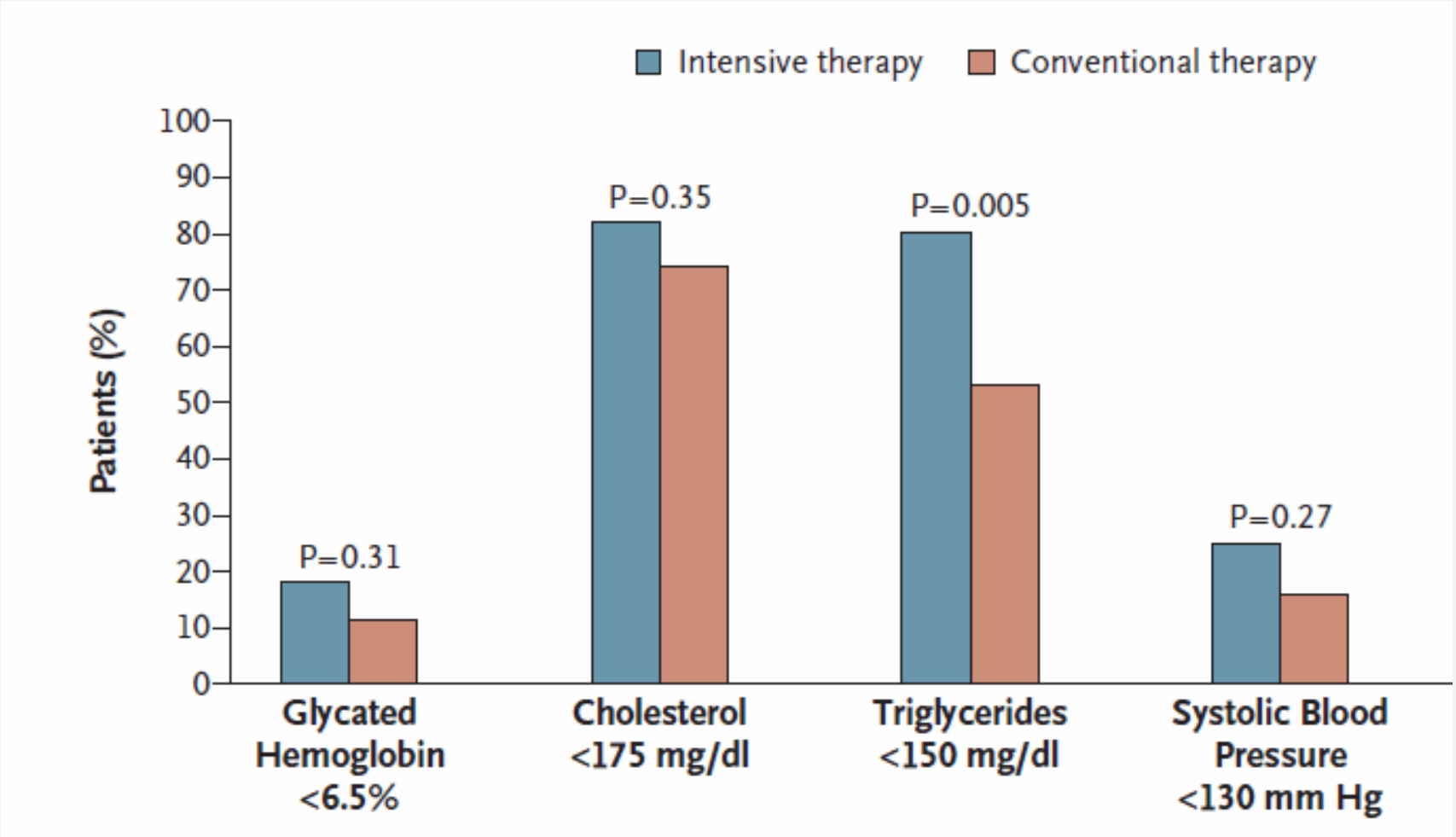
A1C <8.5%	A1C ≥8.5%	Symptomatic hyperglycemia with metabolic decompensation
If not at glycemic target (2-3 mos)	Start metformin immediately. Consider initial combination with another antihyperglycemic agent.	Initiate insulin +/- metformin
Start/Increase metformin	If not at glycemic targets	

Add another agent best suited to the individual by prioritizing patient characteristics:

PATIENT CHARACTERISTIC	CHOICE OF AGENT
Priority: Clinical cardiovascular disease	Antihyperglycemic agent with demonstrated CV outcome benefit (empagliflozin, liraglutide)
• Degree of hyperglycemia • Risk of hypoglycemia • Overweight or obesity • Cardiovascular disease or multiple risk factors • Comorbidities (renal, CHF, hepatic) • Preferences & access to treatment	• Consider relative A1C lowering • Rare hypoglycemia • Weight loss or weight neutral • Effect on cardiovascular outcome • See therapeutic considerations, consider eGFR • See cost column; consider access

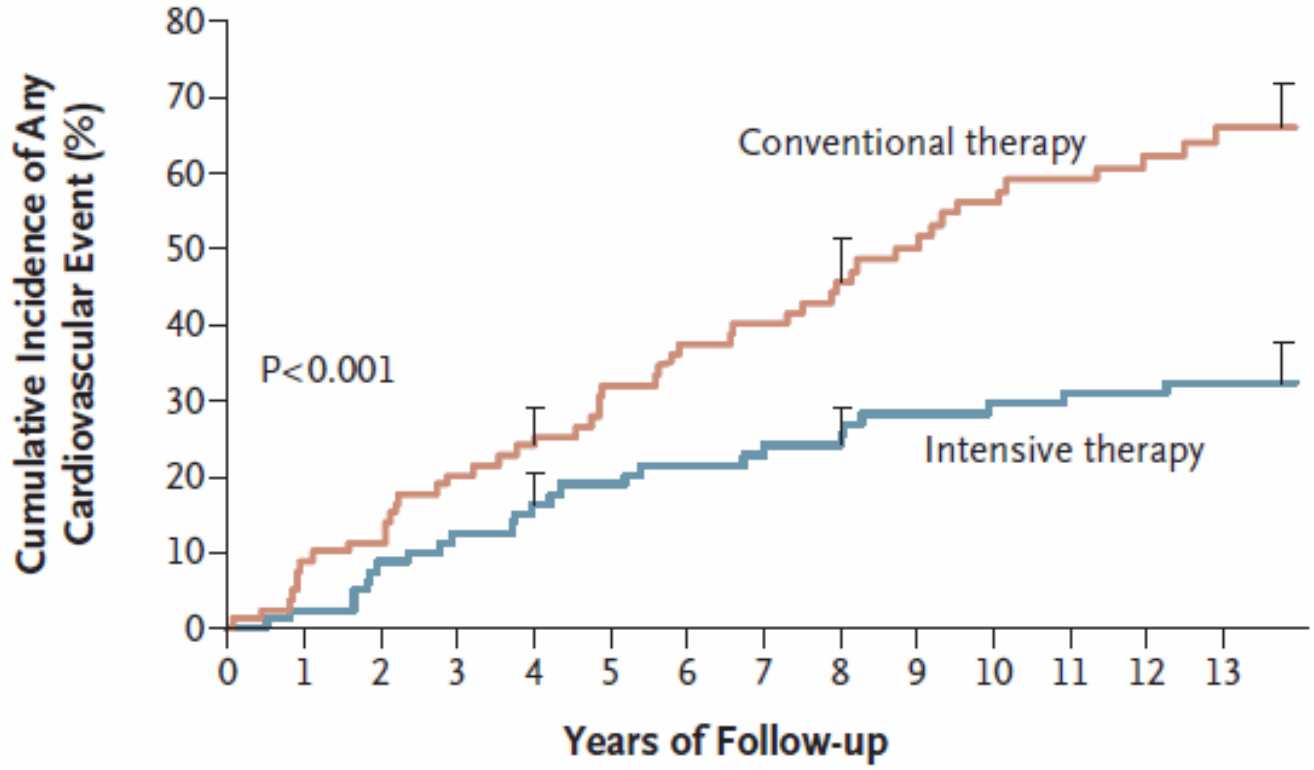
Booth G, Can J Diabetes 40 (2016) 484–486

STENO-2 Long Term 12 year Follow-up
Effect of a Multifactorial Intervention on Mortality in Type 2 Diabetes



Gaede P, NEJM; 2008; 358:580-91

STENO-2 Long Term 12 year Follow-up
Effect of a Multifactorial Intervention on Mortality in Type 2 Diabetes



No. at Risk

Intensive therapy	80	72	65	61	56	50	47	31
Conventional therapy	80	70	60	46	38	29	25	14

Gaede P, NEJM; 2008; 358:580-91

Case progression

Tom agrees to taking an ACEi after your discussion with him. You see him 4 weeks later and his BP is better but still not < 130/80 mmHg. You start him on amlodipine 5 mg/d and his BP is now controlled at 126/78. He feels well but complains of having to take the two medications. He will consider starting a statin on future visits. He has stopped ASA.

Summary

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- Tom presented with a respiratory infection and was found to have hypertension and microalbuminuria
- His BP was controlled to target < 130/80 mm Hg
- He was started on a RAAS blocker and a CCB
- Target LDL of < 2.0 mmol/L was discussed and must still be completed
- Lifestyle issues were discussed

Discussion & Reflection

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1. Do you need to change your current practice to implement any of these recommendations?
2. How do you engage patients and their families in therapy and manage expectations?
3. What are some other adherence strategies that were discussed or not discussed that could work for your practice?
4. Who are some agents of change who can help you implement the recs?

Key Learnings:

- Patients with diabetes are at high cardiovascular risk. Target BP <130/80mmHg.
- 1st line antihypertensive for diabetic patients is an ACE-I or an ARB.
- If BP is not controlled with ACE-I or ARB, then a dihydropyridine CCB is generally initiated next.
- It is important to educate patients about the common side-effects of ACEi or ARB as well as monitoring their use in family practice.
- Multifactorial intervention has a significant impact on mortality in Type 2 diabetes.

Systolic blood Pressure INtervention Trial SPRINT

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- Compares < 120 vs < 140 mmHg
- NHLBI RCT
  - Age 50+
  - SBP 130-180
  - High CV risk (other than stroke)
    - CKD (eGFR 20 - <60)
    - 10 Year Framingham risk of 15%+
    - Age 75+
- Excludes: **DM** and prior stroke

Learning Objectives

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Upon completion of this activity, participants should be able to:

- ✓ 1. Identify the Canadian blood pressure targets for patients with diabetes.
- ✓ 2. Formulate a treatment plan for patients with diabetes and hypertension using the C-CHANGE recommendations.
- ✓ 3. Assess the risks associated with diabetes in patients with hypertension and the evidence supporting the use of RAAS blockers; and the risks of RAAS blocker use in diabetic nephropathy