Hypertension Management in Diabetic Patients

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Contents
(Treatment of 2 Cases)

- Type 2 Diabetes Mellitus
- Hypertension

Case 1

- Male /58 years old
- 15 years history of hypertension and diabetes
- Ex-smoker; quit 15 years ago(daily 0.5 pack)

Physical Exam

- BWt 72 kg, Height 167 cm
- BMI 25.8 kg/m2,
- Waist circumference 98cm
- Blood pressure :194/128 mmHg

Laboratory results

- **HbA1c: 10.1 %, FBS: 198mg/dl**
- **Lipid profile (mg/dl)**
  - **TC:218, LDLc:143, TG :282, HDLc :44**
- **Echo:**
  - **LVH 14.3/13.3 mm**
  - **EF :60-65%**
- **U/A :proteinuria 1+**
- **Micro-albumin :16.26mg/dL**

Medication

- **Exforge**

  (amlodipine/valsartan 5/80 mg) od

- **Rosuvastatin 10 mg od**
- **Metformin 500mg od**

Two weeks later

- Blood pressure :138/96 mmHg
- PP2: 256mg/dl,HbA1c: 10.6 %

- Medication
  - Exforge 5/80 mg od
  - Rosuvastatin 10 mg od
  - Metformin 500mg bid
  - Indapamide 1.5mg bid
  - Galvus 50mg bid

Two month later

- Blood Pressure : 122/76mmHg
- HbA1c: 6.8 %
- PP2:173 mg/dl

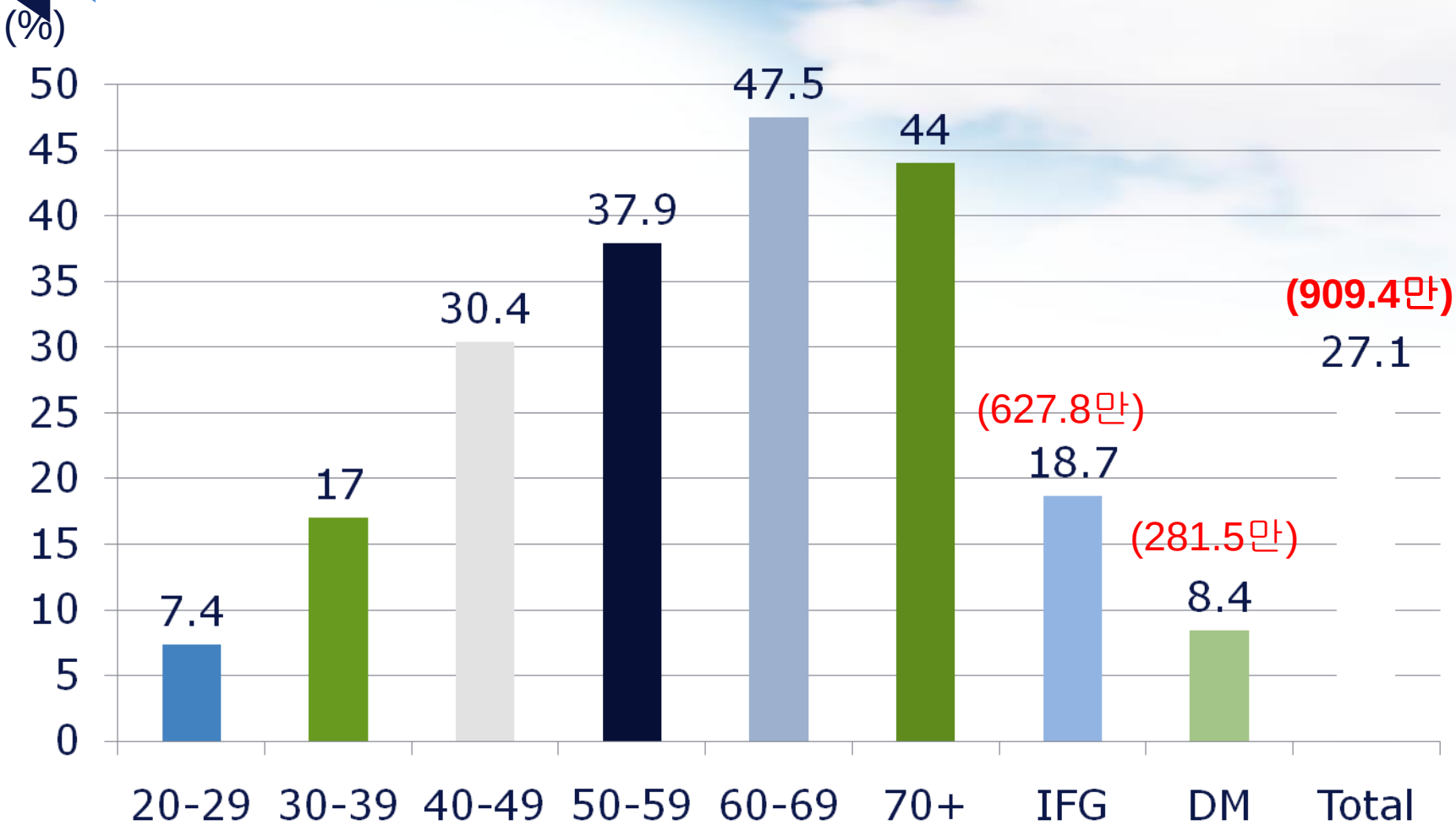
Diabetes vs. Dysglycemia

- **Diagnostic criteria of Diabetes (ADA,2011)**
  - FPG ≥ 126 mg/dl
  - PP2hr glucose ≥ 200 mg/dl after OGTT
  - Random glucose ≥ 200 mg/dl with 3P's Sx
  - HbA1C ≥ 6.5%
  - IFG : 100-125 / IGT : PP2h of 140-199 mg/dl

Prevalence of diabetes

- 6.2 % of total population
- 20% of persons over 65
- Highest in ethnic groups
  - African American (up to 12%)
  - Asian American (up to 22%)
  - Latin American (up to 20%)
  - Native American (up to 60%)

Prevalence of Dysglycemia in General Population, KNHANES 2008, >20 yo

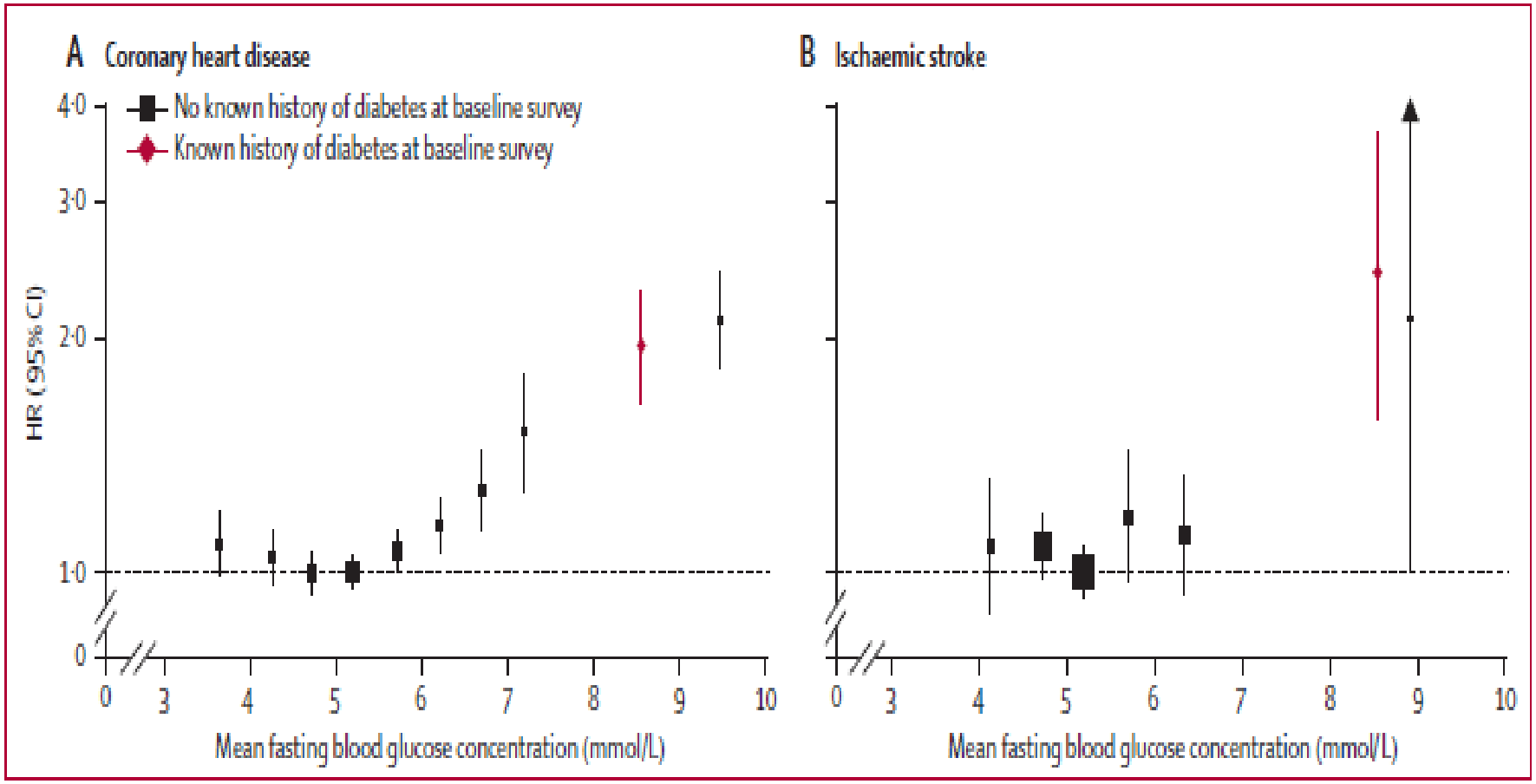


가중치 적용

Hypertension Diabetes

- People with both diabetes and hypertension have approximately twice the risk of cardiovascular disease as non-diabetic people with hypertension
- In the UKPDS epidemiological study, each 10-mmHg decrease in mean SBP was associated with reductions in risk of 12% for any complication related to diabetes, 15% for deaths related to diabetes, 11% for myocardial infarction, and 13% for microvascular complications.

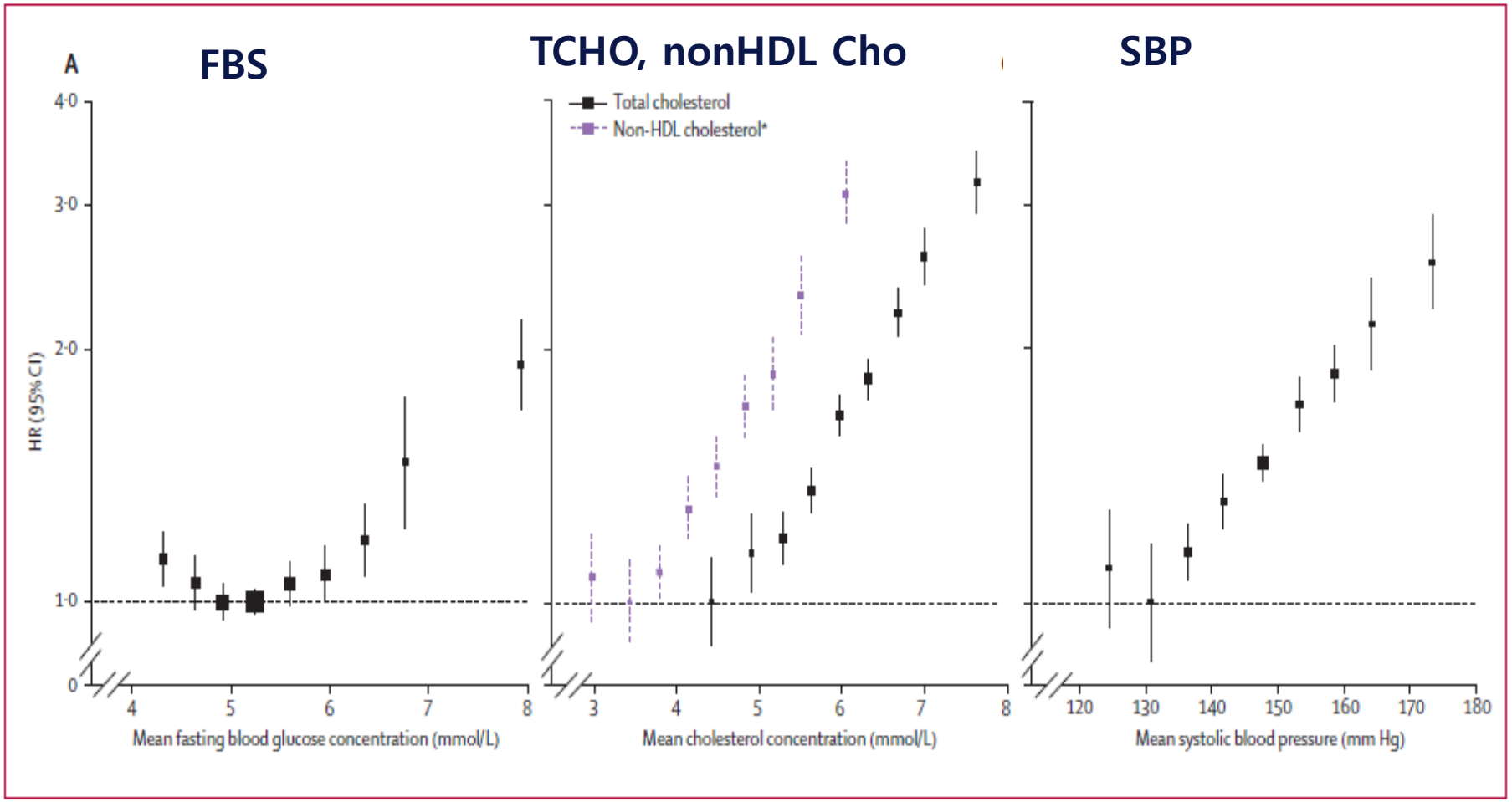
HRs for vascular outcomes by Fasting Glucose



* CHD (n=279,290), Ischemic stroke (n=175,542)
* Reference group : 5.0-5.5 mmol/L (90-99 mg/dL)

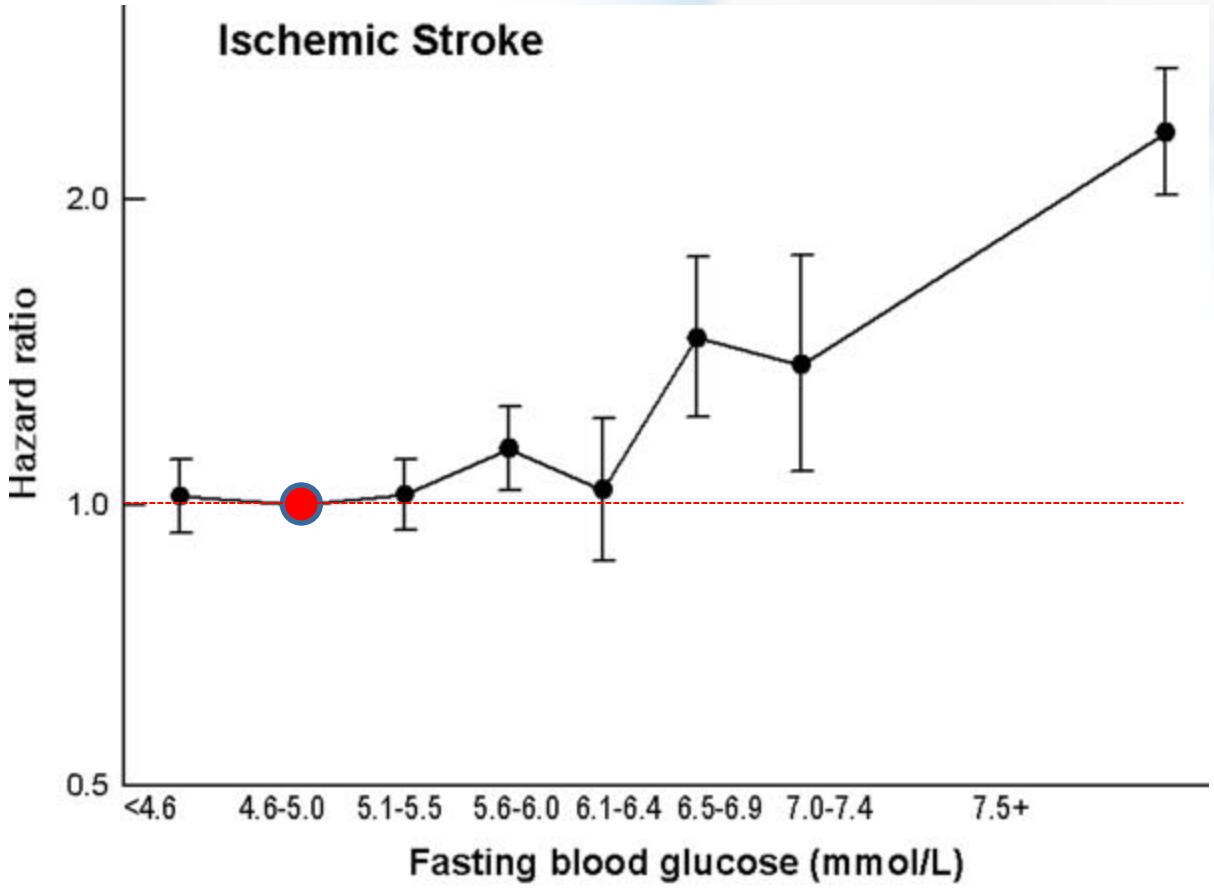
Lancet 2010;375:2215-22

HRs for vascular outcomes by Glucose, Cholesterol and BP



Lancet 2010;375:2215-22

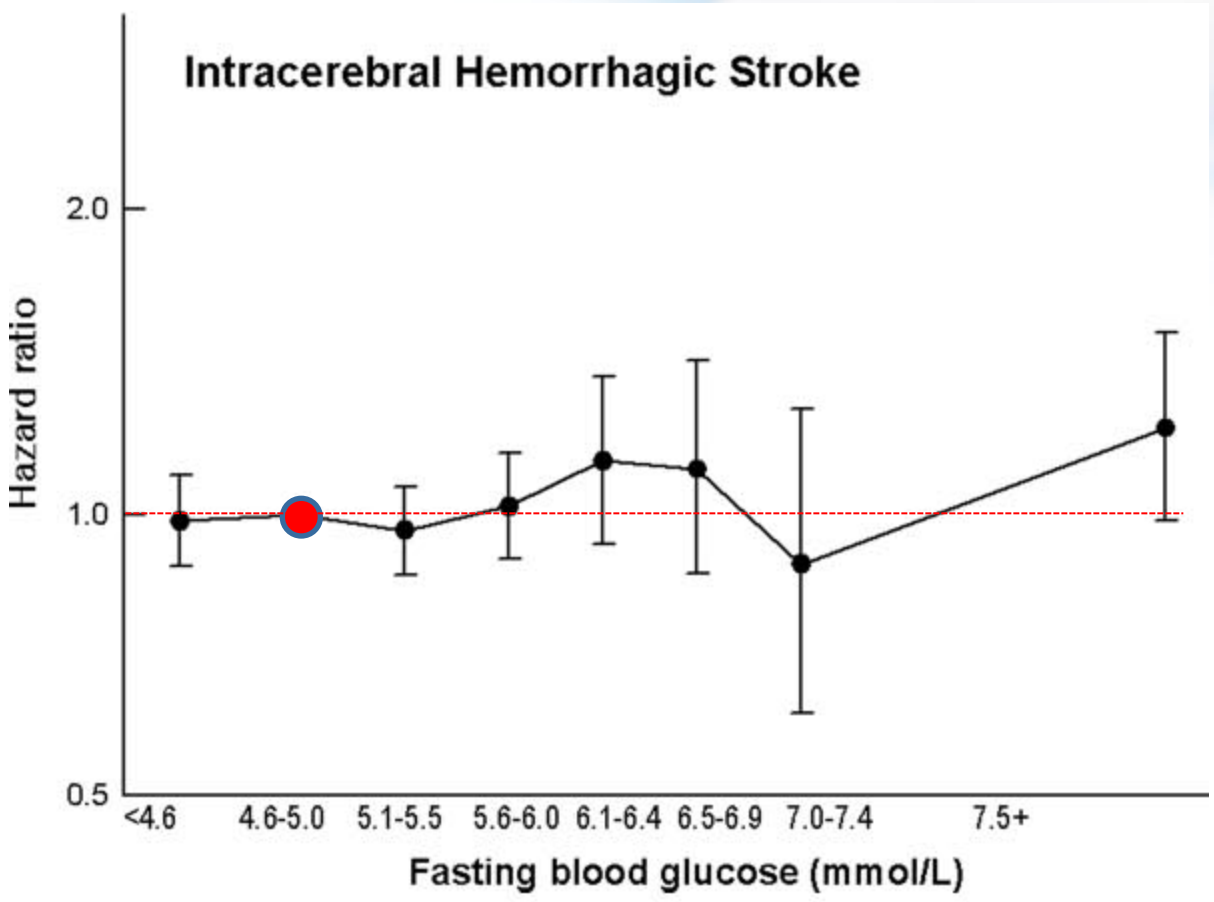
Fasting Blood Glucose and Risk of Ischemic Stroke



*after excluding diabetes,
*adjusted for age, height, BP, TC, BMI, smoking, alcohol, regular exercise, salary, and area of residence

Circulation 2009;119;812-819

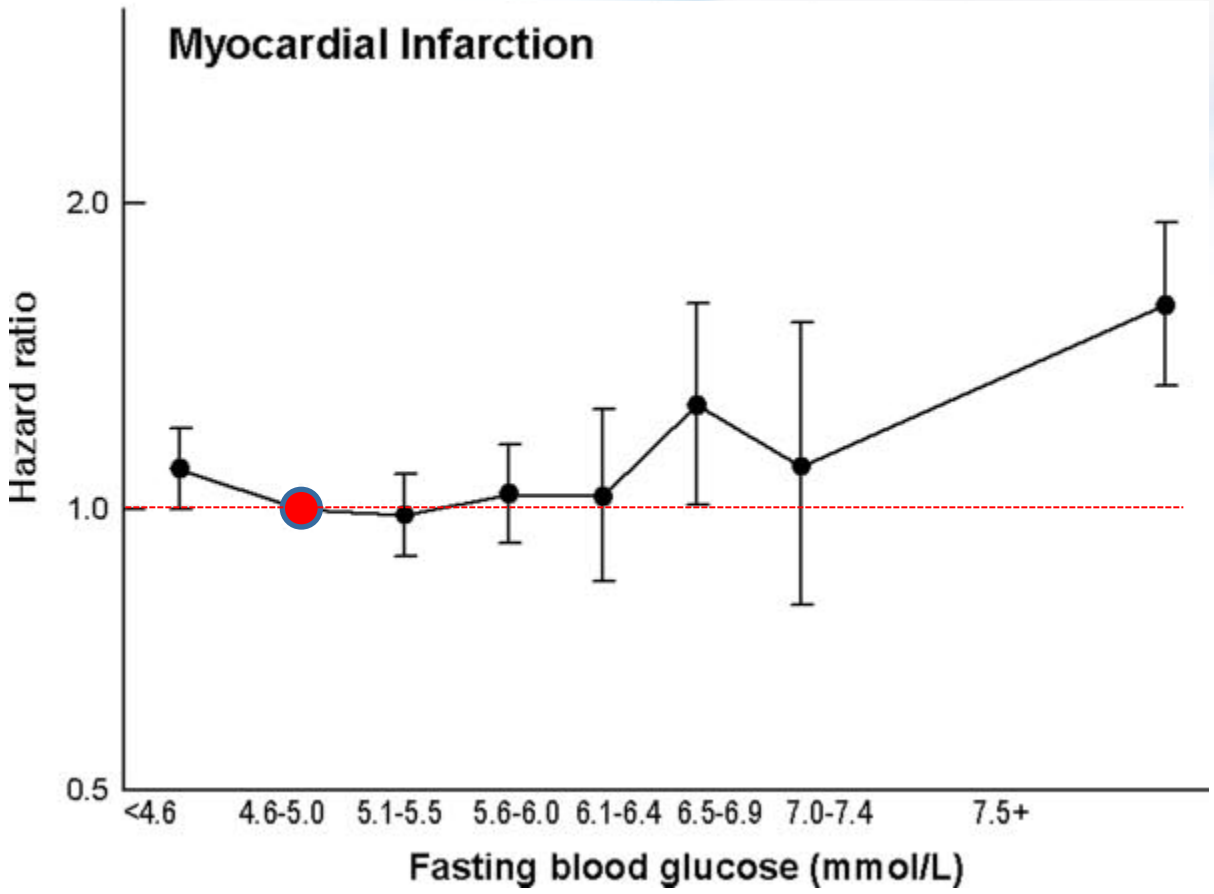
Fasting Blood Glucose and Risk of Hemorrhagic Stroke



*after excluding diabetes,
*adjusted for age, height, BP, TC, BMI, smoking, alcohol, regular exercise, salary, and area of residence

Circulation 2009;119;812-819

Fasting Blood Glucose and Risk of Myocardial Infarction

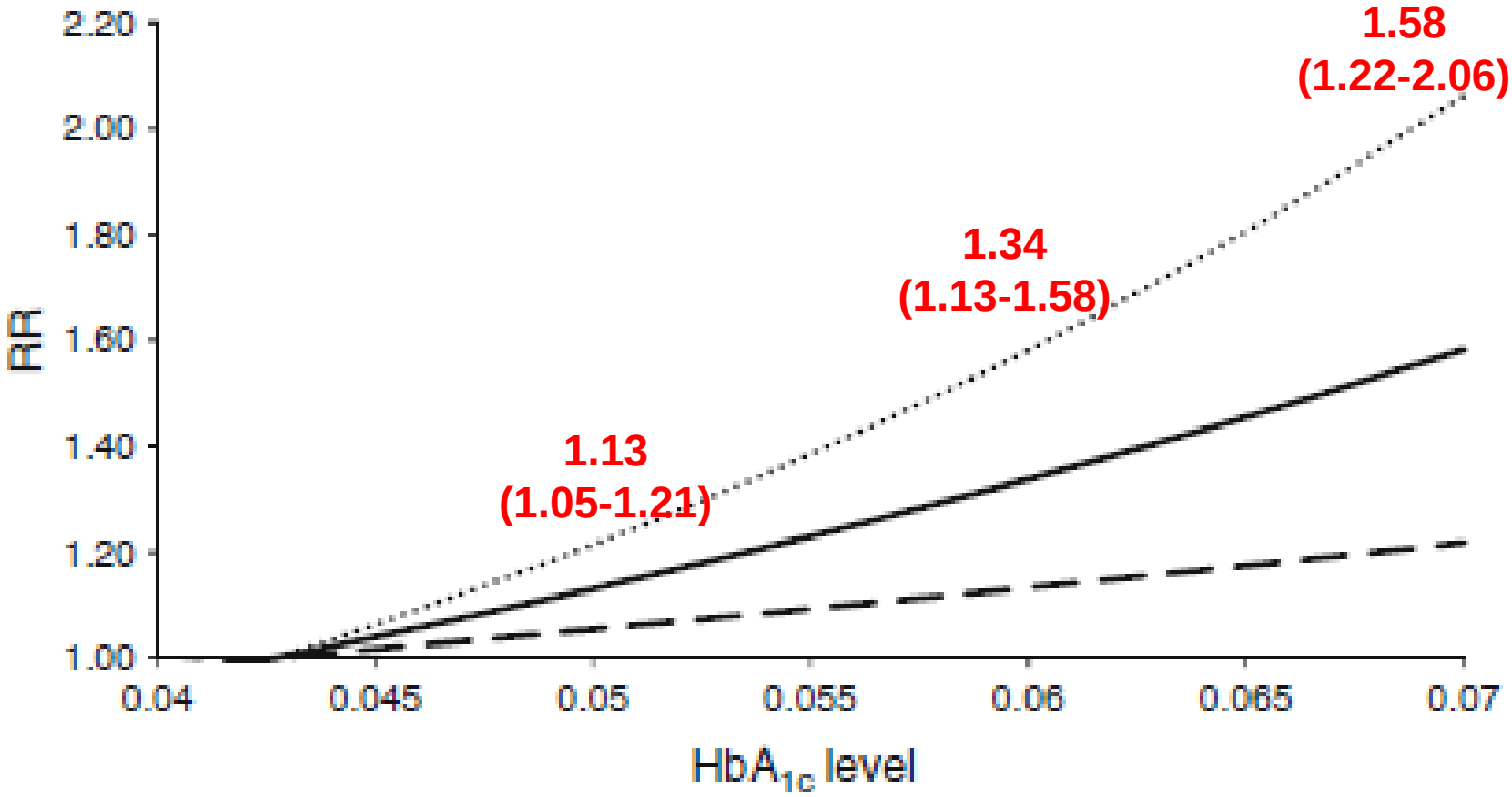


*after excluding diabetes,

*adjusted for age, height, BP, TC, BMI, smoking, alcohol, regular exercise, salary, and area of residence

Circulation 2009;119;812-819

HbA1C and Cardiovascular Death in non-DM



Reference : 0.0427 (4.27%)

Results for **total CV events** were similar

Diabetologia. 2011 Feb

HbA1C and CVD in non-DM : meta-analysis

- **HbA1c was significantly associated with cardiovascular events and deaths in persons without diabetes**

Diabetologia. 2011 Feb

Glycemic control and CVD in Diabetes

Study	Microvascular		CVD		Mortality	
UKPDS	↓	↓	↔	↓	↔	↓
DCCT/EDIC	↓	↓	↔	↓	↔	↔
ACCORD	↓		↔		↑	
ADVANCE	↓		↔		↔	
VADT	↓		↔		↔	

Initial Trial

Long-term F/U

Clinical trials of glucose-lowering therapies in people with dysglycemia

- Intensive versus standard glycemic control in people with well-established diabetes have not proved whether either strategy has cardiovascular benefit (ACCORD, VADT, ADVANCE)
- Intensive glycemic control in people with newly diagnosed diabetes reduces their long-term risk of cardiovascular disease (UKPDS, UKPDS-FU)

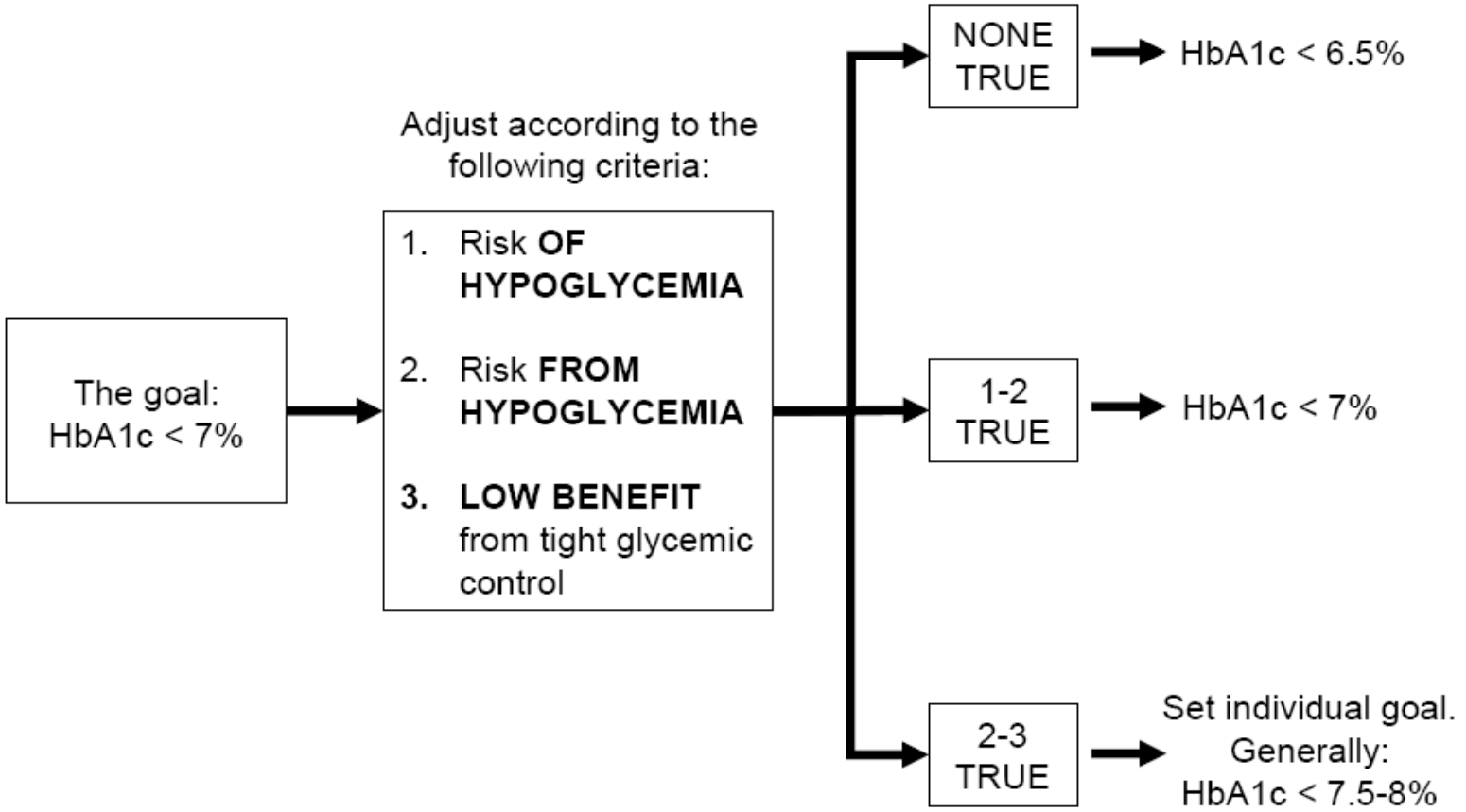
Gerstein, H. C. Nat. Rev. Endocrinol. 5, 270–275 (2009)

Current Targets for Glycemic Control

	ADA	ACE	IDF
HbA1C (%)	**<7.0**	**≤6.5**	**≤6.5**
Fasting(mg/dL)	**90-130**	**<110**	**<100**
Postprandial (mg/dL)	**<180***	**<140**	**<135**

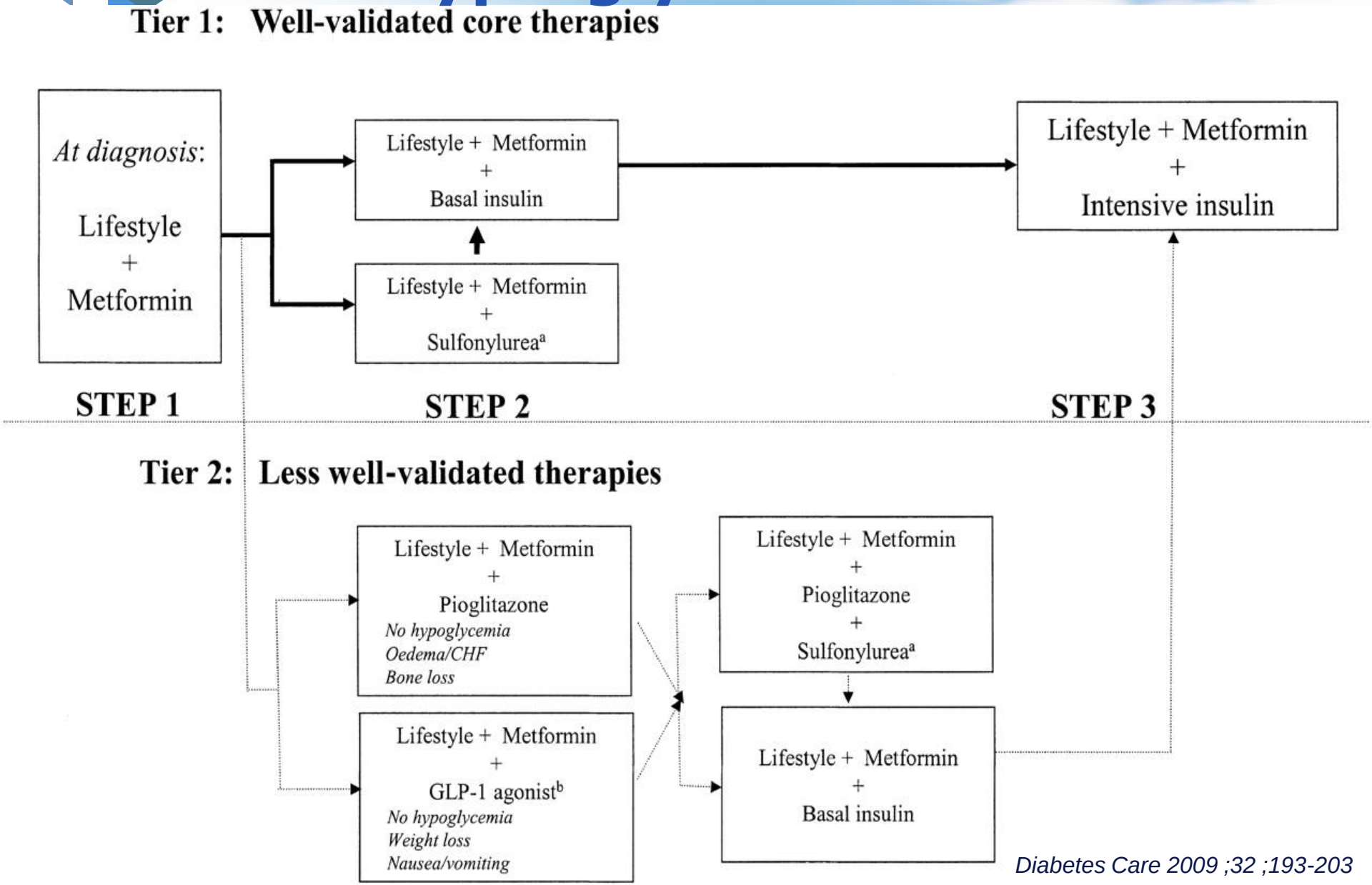
American Diabetes Association. *Diabetes Care*. 2004,27:S15-S35.
The American Association of Clinical Endocrinologists. *Endocr Pract.* 2002; 8(suppl. 1):40-82.
IDF (Europe) European Diabetes Policy Group. *Diabet Med.* 1999;16:716-730.

Determining the optimal HbA1c goal



Rev Diabet Stud 2009; 6:6-12

Medical Management of Hyperglycemia in T2 DM



Diabetes Care 2009 ;32 ;193-203

Recently Diagnosed Patients with Type 2 Diabetes

Age(years)	Young 15-40		Middle 40-70		Elderly >70	
Complications, Duration of disease > 10Yrs	-	+	-	+	-	+
HbA1c(%)	<6	<6.5	<6.5	6.5-7	<7	7-8

DIABETES/METABOLISM RESEARCH AND REVIEWS
Diabetes Metab Res Rev 2010; **26**: 239–244.

당화혈색소 목표치 개별화의 예

당화혈색소(%)	위험요소
< 6.0	40세 이하, 당뇨병 초기, 합병증 없는 경우
< 6.5	65세 이하, 당뇨병 10년 이하, 합병증이 없는 경우
7.0 –	65세 이상, 당뇨병 10년 이상, 합병증을 동반 경우

Case 2

- F / 53 yo
- Long hypertension history since 15 yo
- Treat hypertension with short acting nifedipine since 43 yo
- Diagnose T2 DM at 3 years ago

P/Ex

(1) 165cm, 82Kg, BMI 30.1

(2) W/H ratio: 1.1

(3) BP 150/95mmHg

Lab

(1) CBC, Elecrolyte, LFT, BUN/Cr : WNL

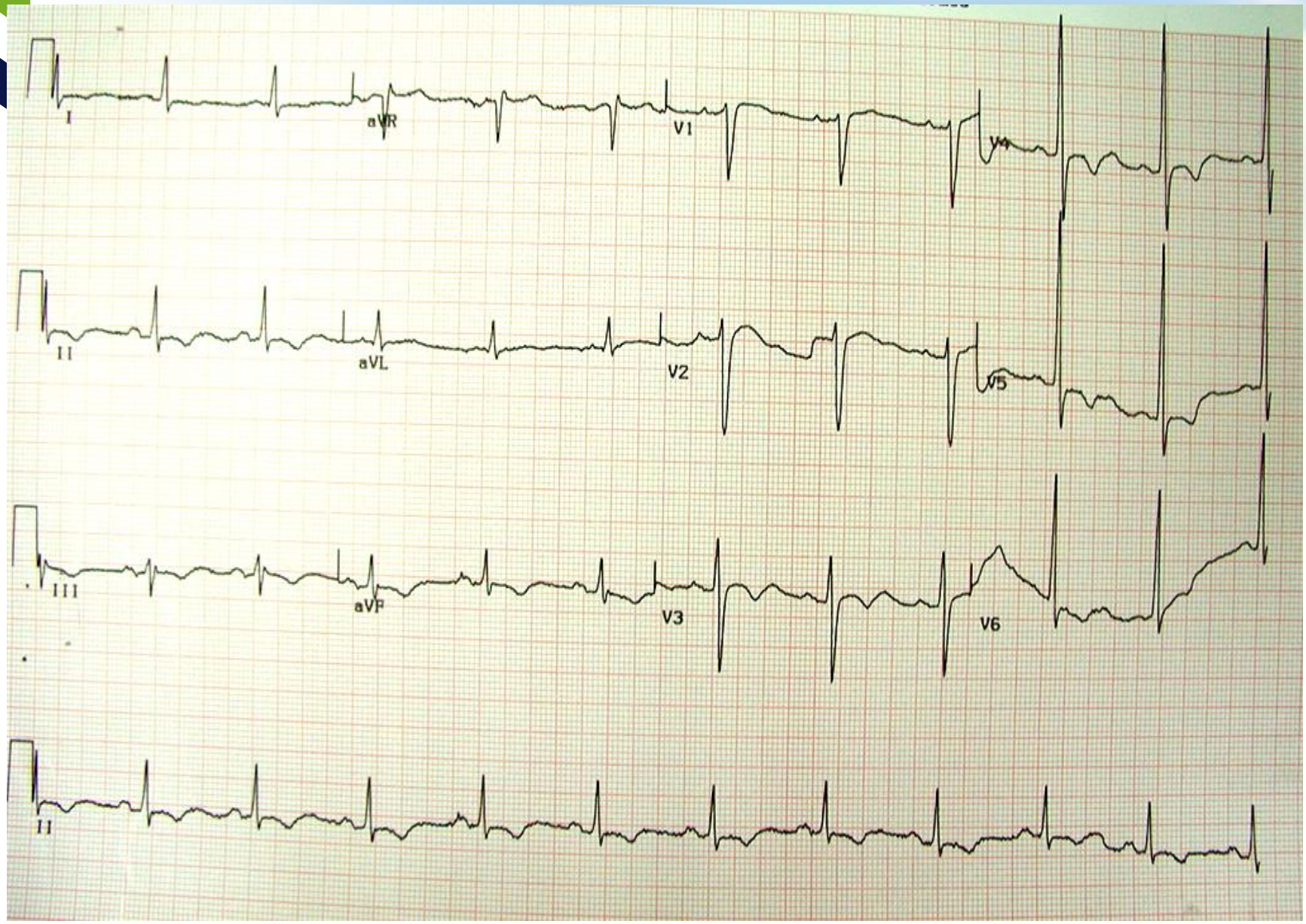
(2) HbA1c: 7.3 %, FBS: 138mg/dl

(3) T-Cho 257 mg/dl, TG 204 mg/dl, HDL 42mg/dl, LDL 198 mg/dl

(4) CK-MB 7.8 mg/dl, Troponin-I 0.07 mg/dl

(5) Microalbuminuria: 55mg/min

ECG

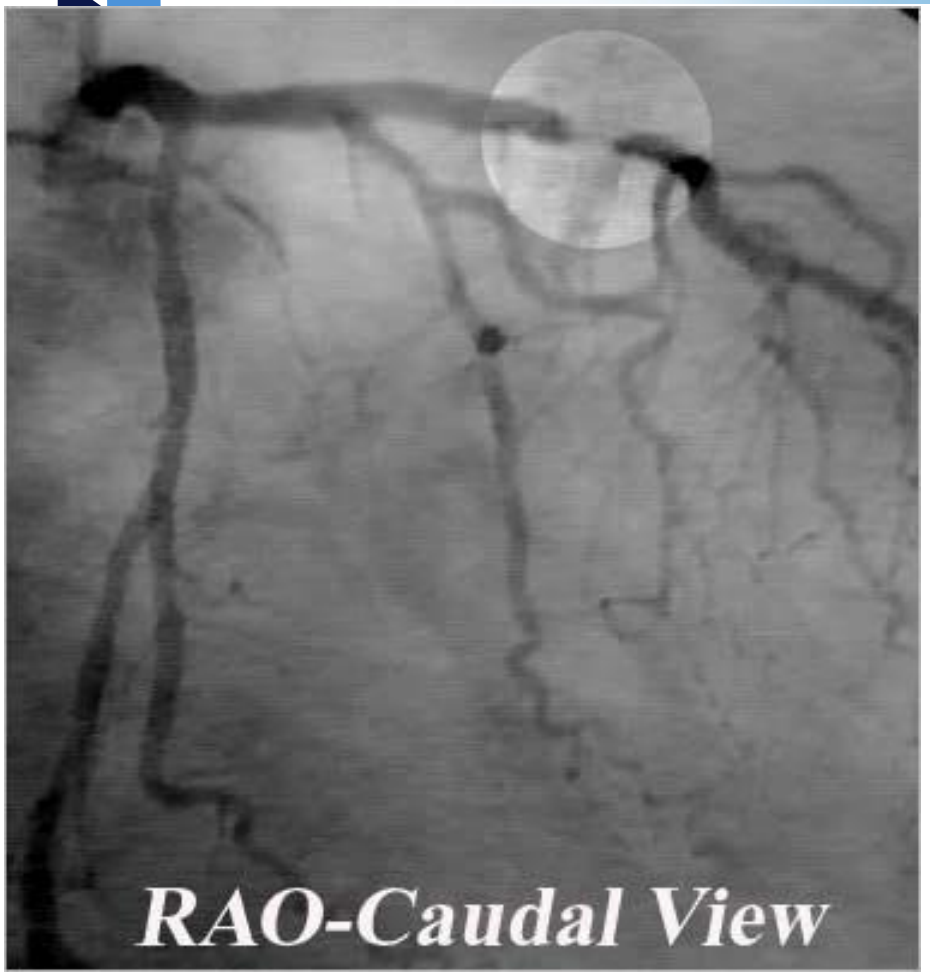


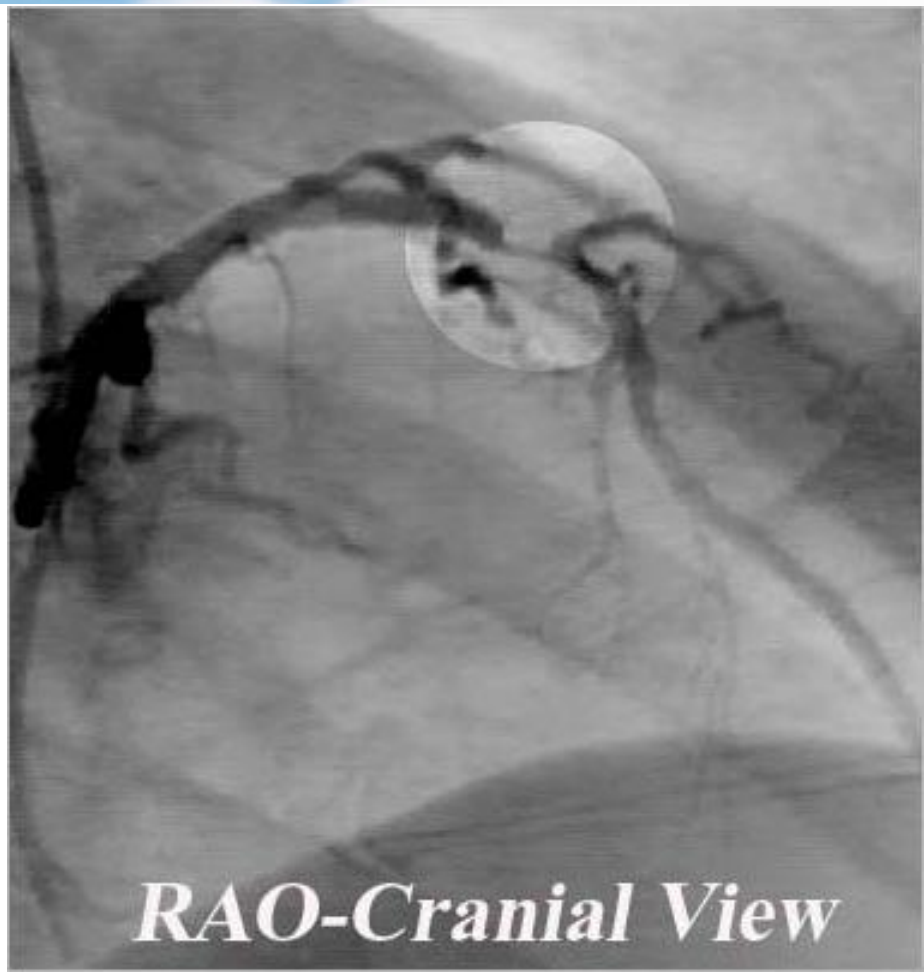
Echocardiography

(1) normal LVwall motion (EF=65%)

(2) No valvular abnormality

(3) mild LVH


RAO-Caudal View


RAO-Cranial View

What is the clinical diagnosis ?

Multiple choice

① Hypertension

② T2 DM with nephropathy

③ Dyslipidemia; high TG 204, low HDL 43

④ Abdominal obesity

⑤ Metabolic syndrome

⑥ Coronary heart disease

What is the choice of antihypertensive drugs? Multiple choice

① Diuretic

② B -blocker

③ CCB

④ ACEI

② ARB

First choice of antihypertensive drug (JNC-7)

Comorbidities	Diuretic	B -blocker	ACEI	ARB	CCB
IHD	○	○	○		○
CHF	○	○	○	△	
Post MI	○(antialdosterone)	○			
DM	○	○	○	○	○
Stroke				○	
CKD			○	○	

Table 1

Recommended Target Blood Pressure and Drugs in Patients With Diabetes Mellitus and Nephropathy

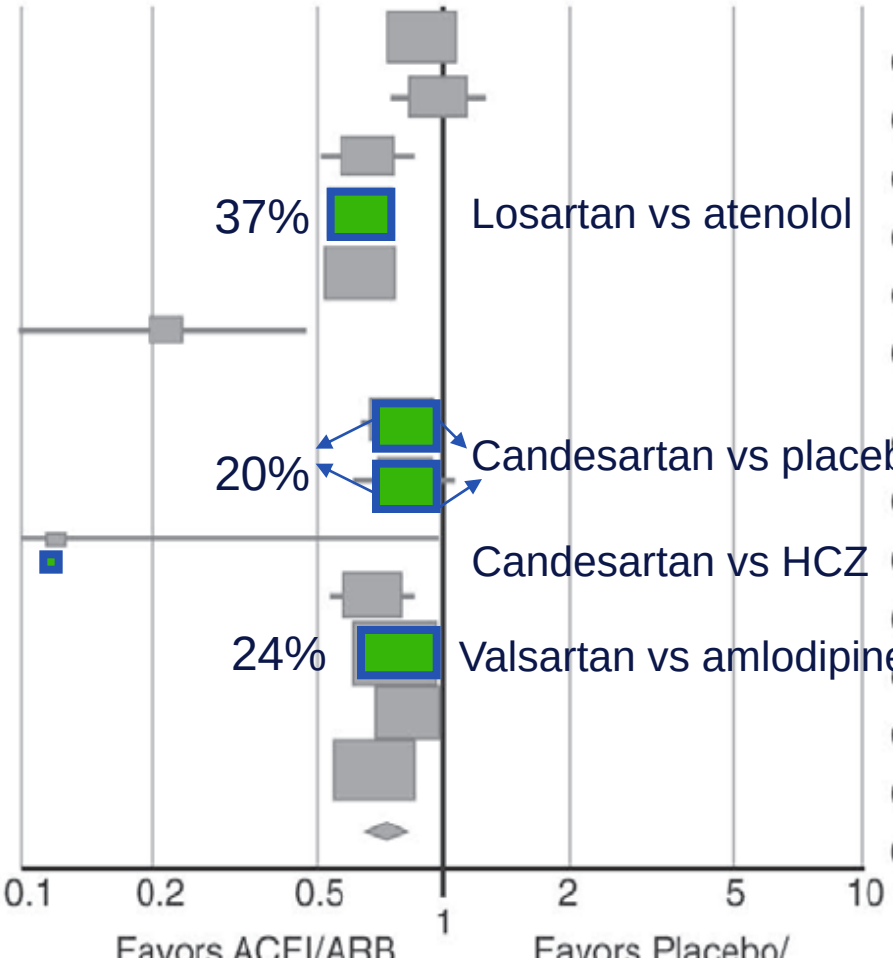
Organization	Year	Blood Pressure Goal, mm Hg	Recommended Agent		
			Hypertension	Type 1 Diabetic Nephropathy	Type 2 Diabetic Nephropathy
JNC VII[1]	2004	<130/85, 125/75 if proteinuria present	ACE, ARB, β-blockers, CA, diuretic	ACE/ARB	ACE/ARB
American Diabetes Association[8]	2002	<130/80	ACE, ARB, β-blockers, CA, diuretic	ACE/ARB	ACE/ARB
National Kidney Foundation[5]	2002	<130/80, 125/75 if proteinuria present	—	ACE/ARB	ACE/ARB
European Society of Hypertension[4]	2003	<130/80	ACE, ARB, β-blockers, CA, diuretic	ACE/ARB	ACE/ARB
British Hypertension Society[7]	2004	<130/80	ARB, diuretic	ACE	ACE

JNC VII = Joint National Committee on Prevention, Detection, Valuation, and Treatment of High Blood Pressure; ACE = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; CA = calcium antagonist.

Navaneethan et al Diabetes Educator 32(4): 596-602, 2006

Incidence of Diabetes Mellitus – All Trials

Study (reference)	Treated (n/n)	Control (n/n)	OR (95% CI)
CAPP (28)	337/5183	380/5230	0.888 (0.762-1.033)
STOP-2 (29)	93/1969	192/3926	0.964 (0.748-1.243)
HOPE (30)	102/2837	155/2883	0.656 (0.508-0.847)
LIFE	241/4605	319/3979	0.634 (0.533-0.753)
ALLHAT (32)	220/4096	883/10720	0.632 (0.543-0.736)
SOLVD Montreal Substudy (33)	9/153	31/138	0.216 (0.099-0.472)
CHARM overall	163/2718	202/2721	0.796 (0.643-0.985)
SCOPE	93/2167	115/2175	0.803 (0.607-1.063)
ALPINE	1/196	8/196	0.121 (0.015-0.973)
ANBP-2 (37)	138/3044	200/3039	0.674 (0.539-0.842)
VALUE	690/5308	845/5152	0.762 (0.683-0.849)
PEACE (39)	335/3432	399/3472	0.833 (0.714-0.971)
ASCOT-BPLA (40)	567/7072	799/7040	0.681 (0.608-0.762)
Total	**2989/42780**	**4528/50671**	**0.730 (0.662-0.805)**



DM developed in 8.2% with ARBs, compared with 10.5% with placebo or other agents (OR 0.73, 95% CI 0.64 to 0.84, p< 0.001)

The mechanism of prevention of DM by inhibition of the RAS

- **Hemodynamic benefits**

  - antagonizing the Ang II–mediated hypoperfusion of skeletal muscle or pancreatic islet cells.

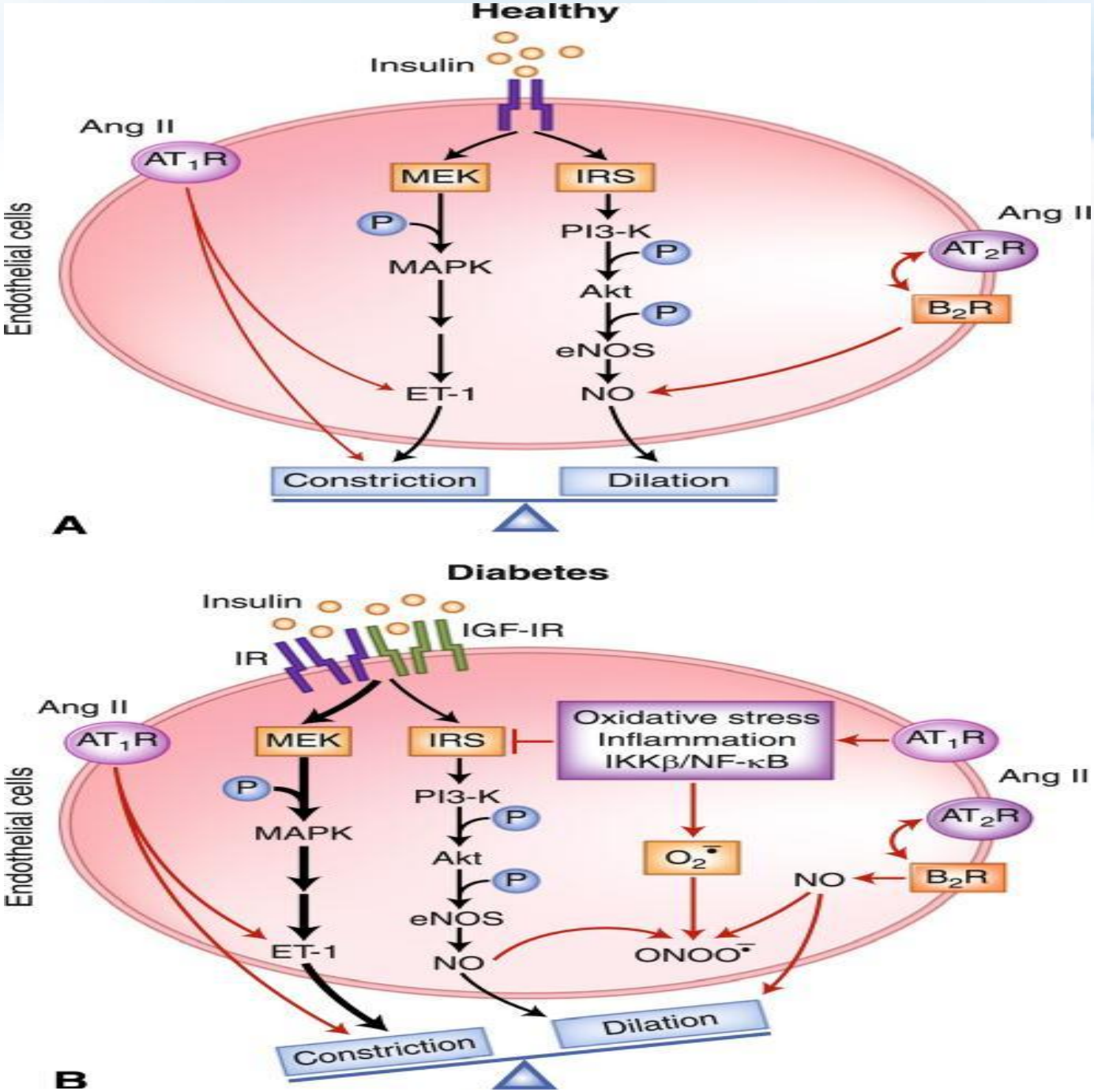
*Circulation 2004;110:*1507–1512

- **Direct inhibitory effects of angiotensin II on insulin signaling and glucose transport**

Am J Cardiol 2003;91(suppl):30H–37H

- **Reduction in islet fibrosis and increased B-cell mass, by decreasing oxidative stress, apoptosis, and profibrotic pathways**

J Hypertens 2005;23:463– 473.


Healthy
Insulin
Ang II
AT1R
MEK
IRS
P
MAPK
PI3-K
P
Akt
P
eNOS
NO
ET-1
Ang II
AT2R
B2R
Endothelial cells
Constriction
Dilation
A
Diabetes
Insulin
IGF-IR
IR
Ang II
AT1R
MEK
IRS
Oxidative stress
Inflammation
IKKβ/NF-κB
AT1R
Ang II
P
MAPK
PI3-K
P
Akt
P
eNOS
NO
ET-1
O2•−
AT2R
B2R
NO
ONOO•−
Endothelial cells
Constriction
Dilation
B

Clinical course

- LAD stenosis → PTCA and stenting
- 100mg ASA, 75mg Clopidogrel
- 10mg Lipitor
- 2.5mg bisoprolol
- 8mg perindopril

BP 120~130/80~90mmHg

No chest pain

Good lipid and glucose level

Controversy for target BP in diabetic patients

Major guidelines in patients with diabetes or a history of CV or renal disease ;ESH 2007, JNC 7 and ADA 2010

- Recommend drug treatment to be initiated within a lower BP range
  - a SBP between 130 and 139 mmHg and
  - a DBP between 85 and 89 mmHg,
- aiming at achieving SBP/DBP values 130/80 mmHg.

Classic diagram for antihypertensive management in diabetes

BP > 130/80 mmHg

↓

Start ACEI or ARB titrate upwards

↓

If BP still not 130/80 mmHg

↓

Add thiazide or long-acting CCB

↓

If BP still not 130/80 mmHg

HR > 84 bpm

Add low-dose β-blocker or αβ-blocker

HR < 84 bpm

Add other subgroup of long-acting CCB

ACCORD Blood Pressure Trial

Effects of Intensive Blood Pressure Control on Cardiovascular Events in Type 2 Diabetes Mellitus

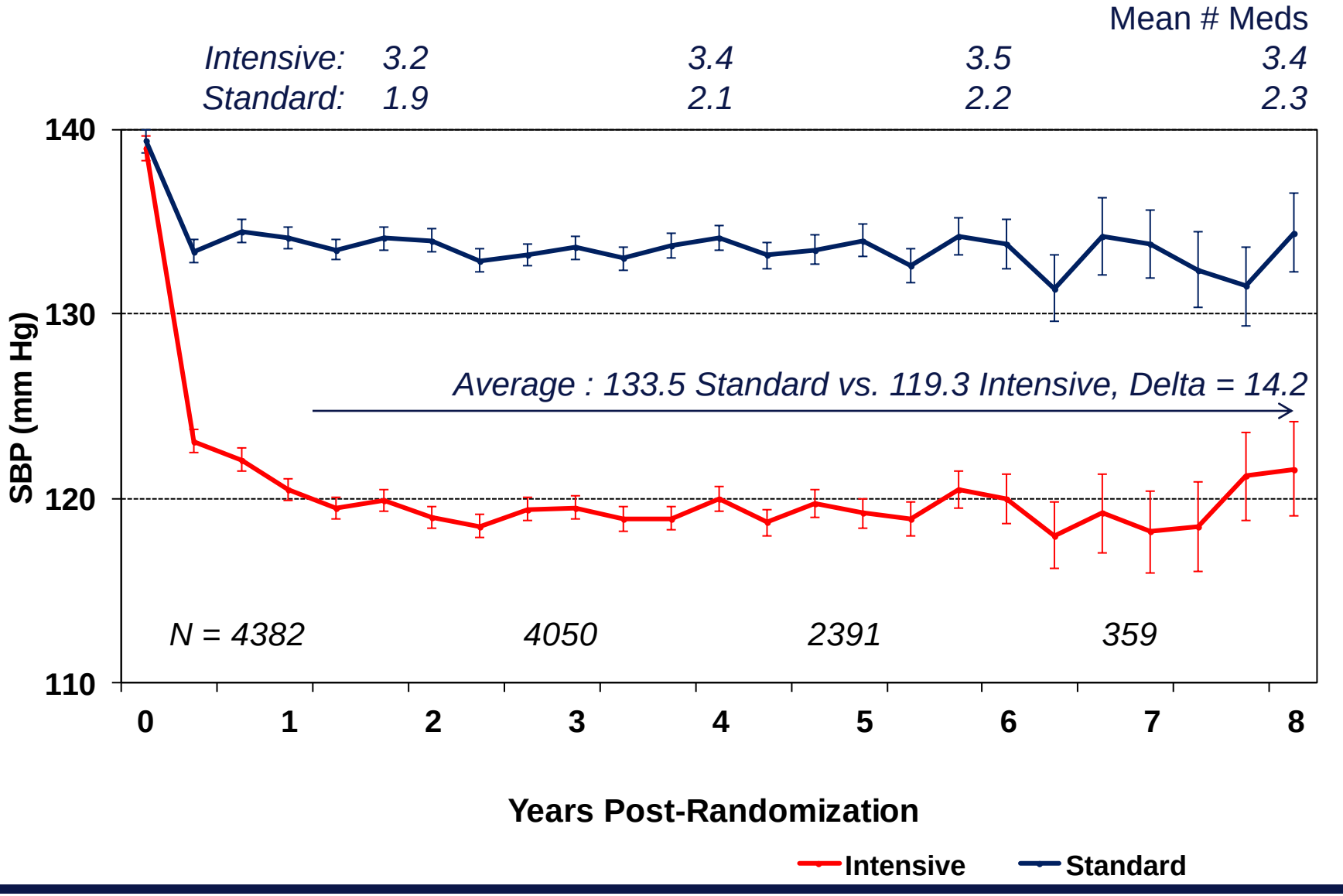
N Engl J Med. 2010 Apr 29;362:1575-85

ACCORD Study Design

Designed to independently test three medical strategies to reduce CVD in diabetic patients

- BP question: does a therapeutic strategy targeting SBP <120 mmHg reduce CVD events compared to a strategy targeting SBP <140 mmHg in patients with type 2 diabetes at high risk for CVD events

Systolic Pressures (mean ± 95% CI)

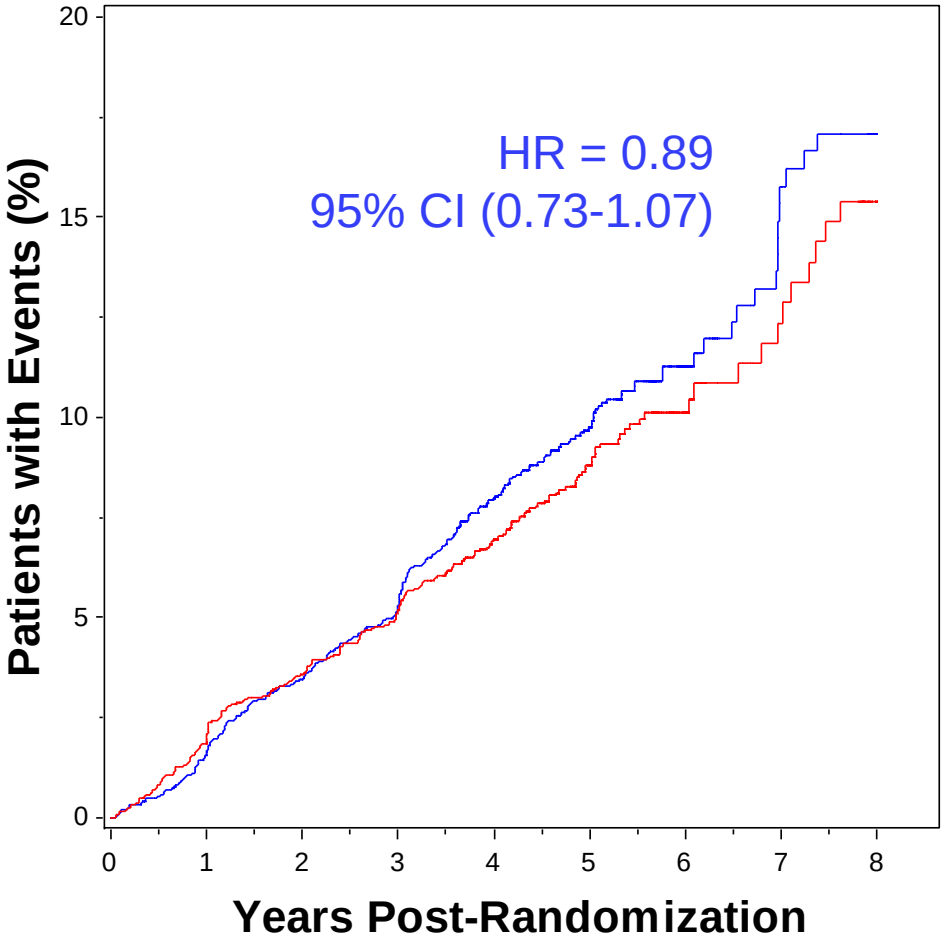


Primary & Secondary Outcomes

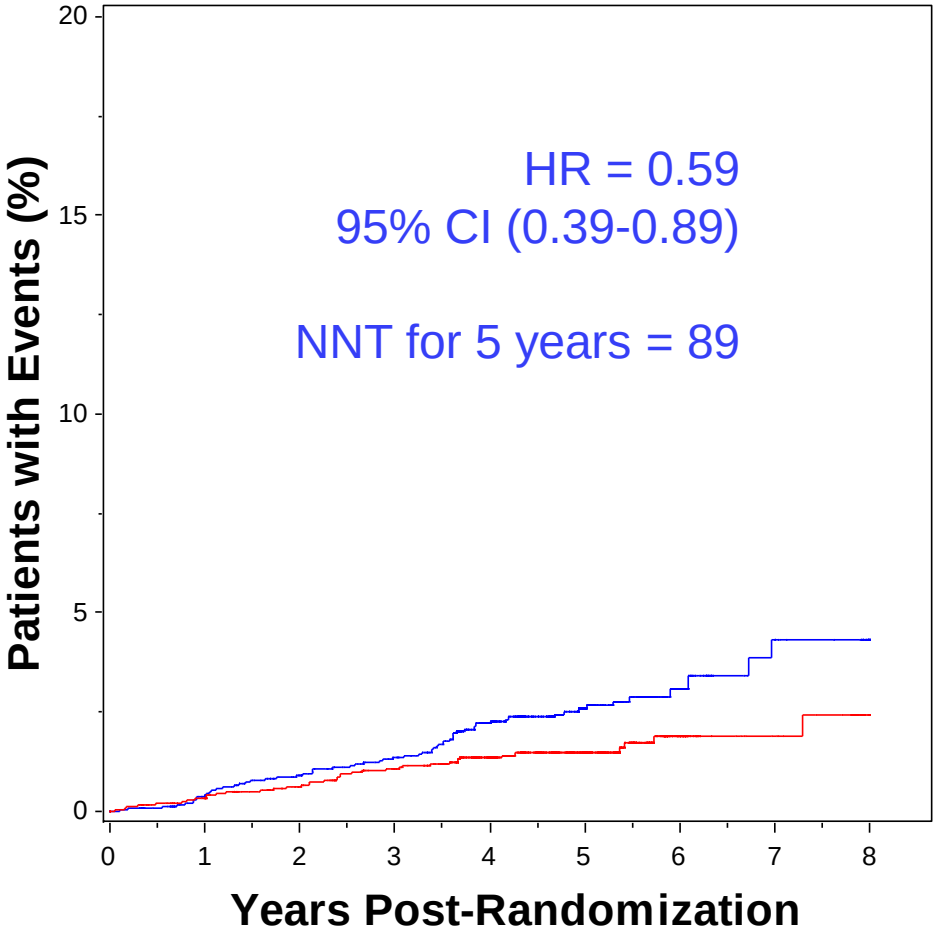
	Intensive Events (%/yr)	Standard Events (%/yr)	HR (95% CI)	P
Primary	208 (1.87)	237 (2.09)	0.89 (0.73-1.07)	0.20
Total Mortality	150 (1.28)	144 (1.19)	1.07 (0.85-1.35)	0.55
Cardiovascular Deaths	60 (0.52)	58 (0.49)	1.06 (0.74-1.52)	0.74
Nonfatal MI	126 (1.13)	146 (1.28)	0.87 (0.68-1.10)	0.25
Nonfatal Stroke	34 (0.30)	55 (0.47)	0.63 (0.41-0.97)	0.03
Total Stroke	36 (0.32)	62 (0.53)	0.59 (0.39-0.89)	0.01

Also examined Fatal/Nonfatal HF (HR=0.94, p=0.67), a composite of fatal coronary events, nonfatal MI and unstable angina (HR=0.94, p=0.50) and a composite of the primary outcome, revascularization and unstable angina (HR=0.95, p=0.40)

Primary Outcome
Nonfatal MI, Nonfatal Stroke or CVD Death



Total Stroke



Intensive Standard

Adverse Events

	Intensive N (%)	Standard N (%)	P
Serious AE	77 (3.3)	30 (1.3)	<0.0001
Hypotension	17 (0.7)	1 (0.04)	<0.0001
Syncope	12 (0.5)	5 (0.2)	0.10
Bradycardia or Arrhythmia	12 (0.5)	3 (0.1)	0.02
Hyperkalemia	9 (0.4)	1 (0.04)	0.01
Renal Failure	5 (0.2)	1 (0.04)	0.12
eGFR ever <30 mL/min/1.73m^2	99 (4.2)	52 (2.2)	<0.001
Any Dialysis or ESRD	59 (1.2)	58 (1.2)	0.91
Dizziness on Standing†	217 (44)	188 (41)	0.39

† Symptom experienced over past 30 days from HRQL sample of N=943 participants assessed at 12 and 48 months post-randomization

Clinical Parameters assessed at last clinic visit

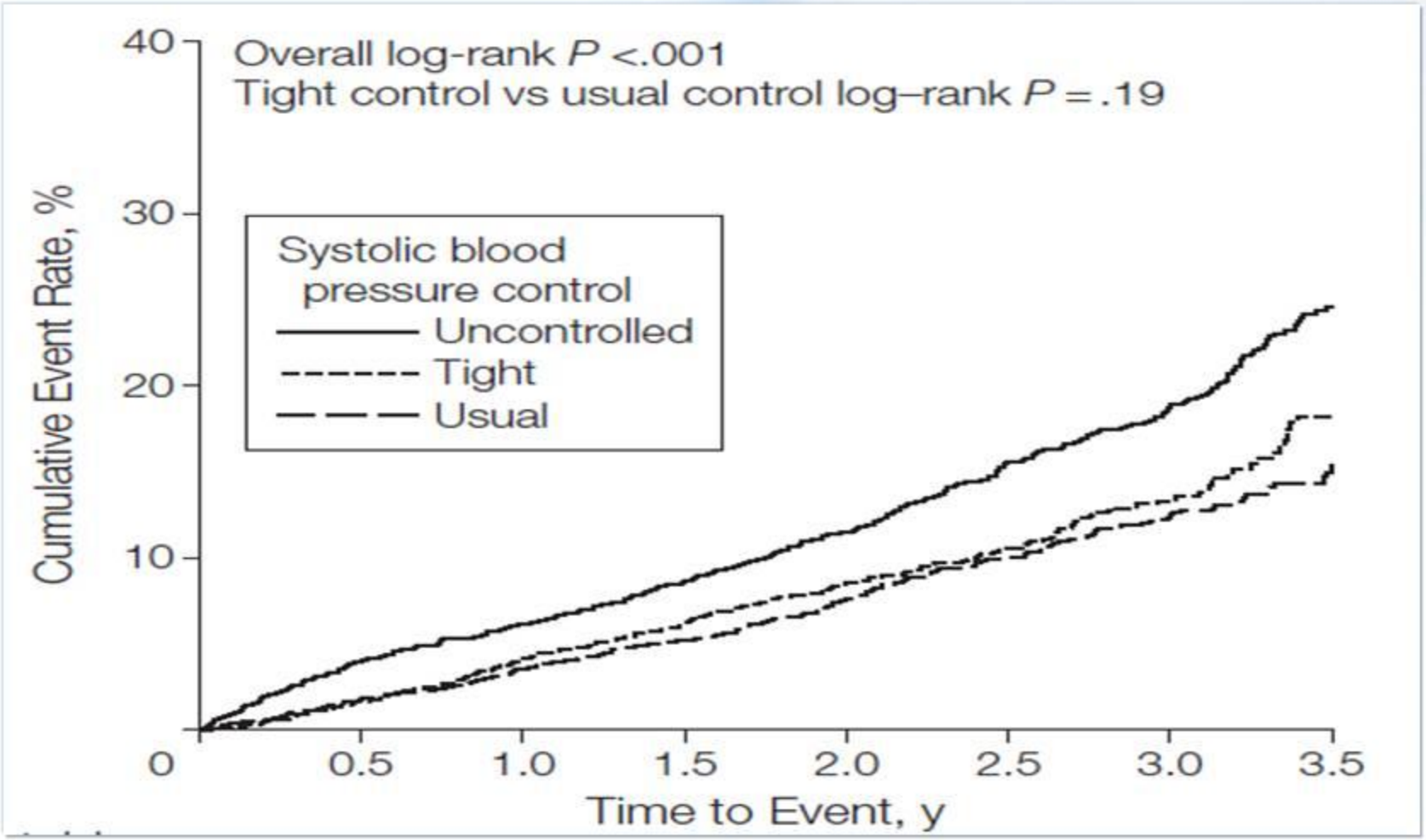
	Intensive	Standard	P
Potassium (mean mg/dl)	4.3	4.4	0.17
Serum Creatinine (mean mg/dl)	1.1	1.0	<0.0001
Estimated GFR (mean mL/min/1.73m^2)	74.8	80.6	<0.0001
Urinary Alb/Cr (median mg/g)	11.0	13.3	<0.0001
Macroalbuminuria (%)	6.6	8.7	0.009

Tight Blood Pressure Control and Cardiovascular Outcomes Among Hypertensive Patients With Diabetes and Coronary Artery Disease

JAMA. 2010;304:61-68

Primary Outcome

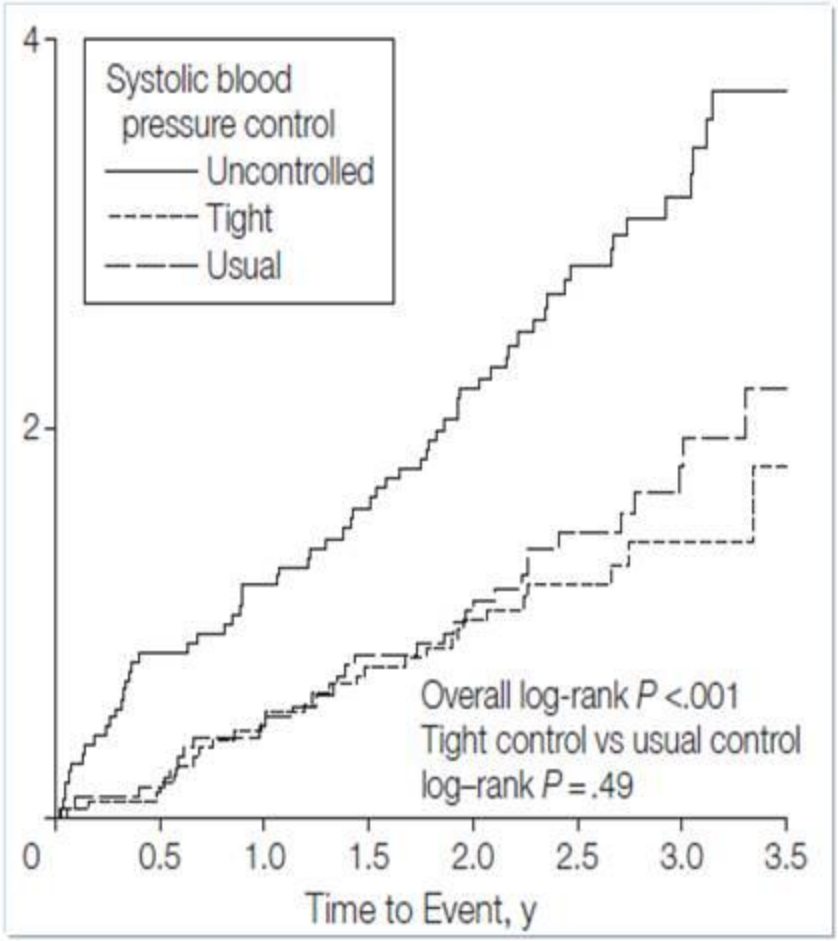
Composite endpoint of all-cause death, nonfatal myocardial infarction, or nonfatal stroke



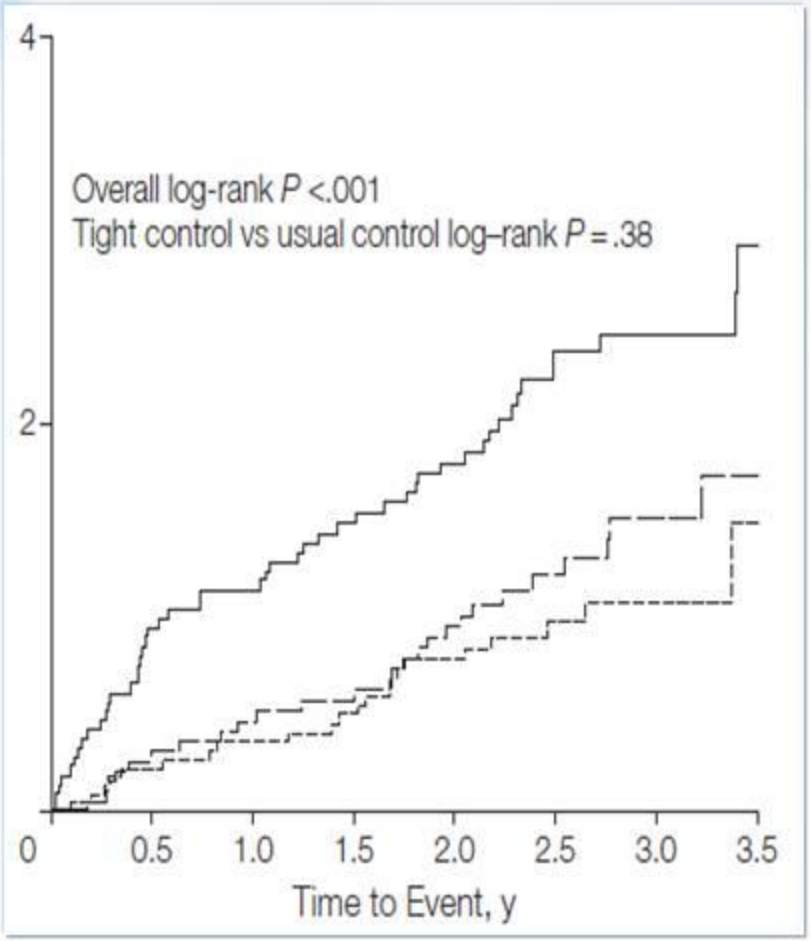
JAMA. 2010;304:61-68

Cumulative Event Rates

Nonfatal myocardial infarction

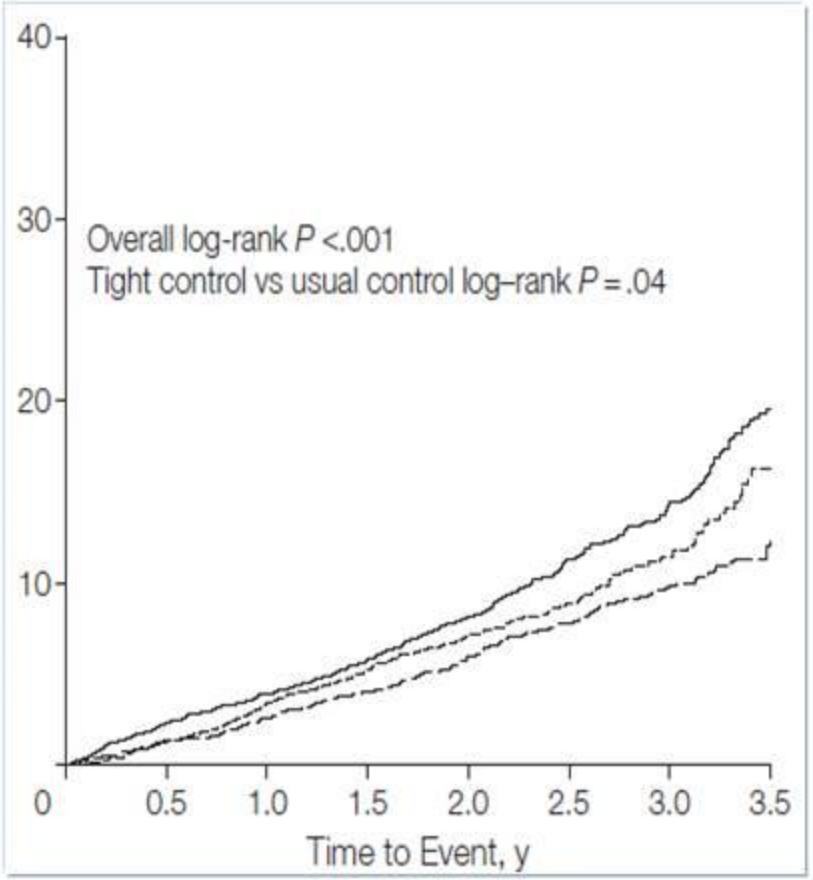


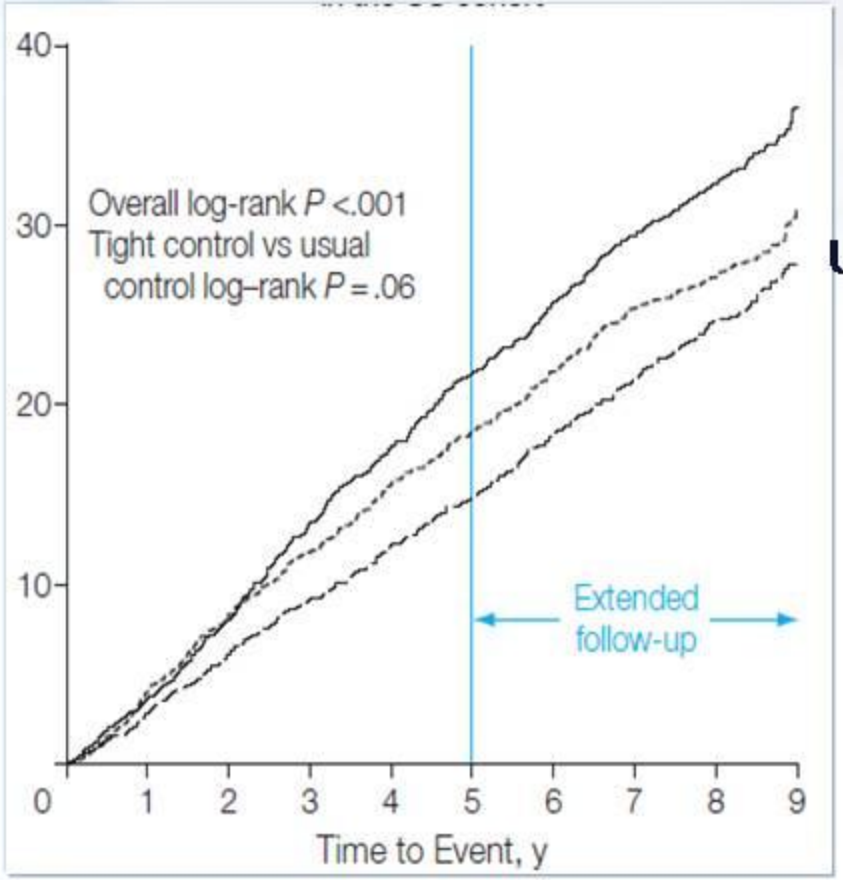
Nonfatal stroke



JAMA. 2010;304(1):61-68

All-cause mortality





tight
Usual

JAMA. 2010;304(1):61-68

2009 Reappraisal of ESH guidelines :hypertension treatment initiation

- **Initiation of antihypertensive drug therapy in diabetic patients with high normal BP is presently unsupported by prospective trial evidence**.
- For the time being, it appears prudent to recommend treatment initiationin high normal BP diabetic patients if subclinical organ damage (particularly microalbuminuria or proteinuria) is present.

Strategy for management of Hypertensive Diabetic patients

- Proper blood sugar control .
- Achieve target level of BP control for diabetic patients
- Early Detection of both diabetes and hypertension complications & manage them as well as delay their progression
- Improve patient's quality of life .


Thanks for your attention !