Diabetes and Hypertension

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20-8-96
Hypertension

- Common DM comorbidity
- Prevalence depends on diabetes type, age, BMI, ethnicity
- Major risk factor for ASCVD & microvascular complications
- In T1DM, HTN often results from underlying kidney disease.
- In T2DM, HTN coexists with other cardiometabolic risk factors.
Achieved SBP $<140$ Lowered risk of
- All-cause mortality
- CVD events
- CHD events
- Stroke
- Retinopathy
- Albuminuria (but not ESRD)

Emdin CA. JAMA. 2015;313(6):603-615
Diabetes and hypertension are leading causes of kidney failure

Incident ESRD rates, by primary diagnosis, adjusted for age, gender, & race.
Primary Diagnoses for Patients Who Start Dialysis

- Diabetes: 50%
- Hypertension: 27%
- Glomerulonephritis: 13%
- Other: 10%

United States Renal Data System (USRDS)
2000 Annual Data Report • WWW.USRDS.ORG

www.hypertensiononline.org
### 2016 BMJ DM-HTN Meta-analysis

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Relative Risk (95% CI)</th>
<th>Favors</th>
<th>Favors</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV Mortality</td>
<td></td>
<td>Treatment</td>
<td>Control</td>
</tr>
<tr>
<td>&gt;150</td>
<td>0.75 (0.57-0.99)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>140-150</td>
<td>0.87 (0.71-1.05)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;140</td>
<td>1.15 (1.00-1.32)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

“If SBP is already less than 140 mm Hg, however, adding additional agents might be harmful.”

Brunström M. *BMJ* 2016;352:i717 January 2016
2016 BMJ DM-HTN Meta-analysis

49 trials, 73,738 subjects

- Treatment when SBP > 140 reduced mortality and cardiovascular morbidity
- Treatment when SBP < 140 increased cardiovascular mortality without observed benefit

Brunström M. *BMJ* 2016;352:i717 January 2016
4733 subjects with DM2
4.7 yr duration
SBP goal <120 mm Hg vs <140 mm Hg

No difference in composite of nonfatal MI, nonfatal stroke, or CV death

# ACCORD - SBP 120 vs 140 in DM

<table>
<thead>
<tr>
<th>Condition</th>
<th>Total</th>
<th>Hypotension</th>
<th>Bradycardia</th>
<th>Hyperkalemia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3.3 v 1.27%</td>
<td>0.7 v 0.4%</td>
<td>0.5 v 0.13%</td>
<td>0.4 v 0.04%</td>
</tr>
</tbody>
</table>

Reduction in nonfatal stroke
0.21% per year, ARR 1.1% at 5 years,
NNT 89

Achievement of ABC targets alone or in combination in patients with type 2 diabetes with and without CVD

<table>
<thead>
<tr>
<th></th>
<th>CVD + (n=323)</th>
<th>CVD – (n=1706)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbA1c ≤ 7</td>
<td>25.3%</td>
<td>30.0%</td>
<td>0.336</td>
</tr>
<tr>
<td>7 &lt; HbA1c &lt; 8</td>
<td>32.3%</td>
<td>29.3%</td>
<td>0.329</td>
</tr>
<tr>
<td>HbA1c ≥ 8</td>
<td>42.4%</td>
<td>40.7%</td>
<td>0.286</td>
</tr>
<tr>
<td>B</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BP ≤ 140/90</td>
<td>53.2%</td>
<td>52.8%</td>
<td>0.274</td>
</tr>
<tr>
<td>C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL ≤ 100</td>
<td>58.4%</td>
<td>48.1%</td>
<td>0.003</td>
</tr>
<tr>
<td>A &amp; B &amp; C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbA1c ≤ 7 and BP ≤ 140/90 and LDL ≤ 100</td>
<td>7.7%</td>
<td>7.4%</td>
<td>0.733</td>
</tr>
</tbody>
</table>

Rabizadeh et al. Primary and secondary cardiovascular prevention status. Among patients with type 2 diabetes referred to a tertiary diabetes clinic. Under publication.
Automated office blood pressure measurement in the management of hypertension

• The use of mercury in healthcare settings in the European Community and elsewhere is now severely curtailed.

J European Society Cardiology Vol.13,N°15 - 10 Mar 2015
Automated office blood pressure measurement in the management of hypertension

• More importantly is the recognition that manual BP measurement, regardless of the type of sphygmomanometer used, is inferior because it is subject to multiple sources of error in routine clinical practice.

J European Society Cardiology Vol.13,N°15 - 10 Mar 2015
Studies comparing semi-automated BP readings with awake ambulatory or home BP

<table>
<thead>
<tr>
<th>Study</th>
<th># patients</th>
<th>Semi-automated BP</th>
<th>Awake Ambulatory BP</th>
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</thead>
<tbody>
<tr>
<td>Myers et al (8)</td>
<td>27</td>
<td>157/83</td>
<td>145/78</td>
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<tr>
<td>Myers et al (9)</td>
<td>139</td>
<td>146/86</td>
<td>142/81</td>
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<tr>
<td>Stergiou et al (10)</td>
<td>30</td>
<td>137/88</td>
<td>128/83</td>
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<tr>
<td>Al-Karkhi et al (11)</td>
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<td>140/86</td>
<td>133/83</td>
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</table>

J European Society Cardiology Vol.13, N°15 - 10 Mar 2015
Studies comparing automated office BP with awake ambulatory BP

<table>
<thead>
<tr>
<th>Study</th>
<th># Subjects</th>
<th>Settings</th>
<th>AOBP</th>
<th>Awake ABP</th>
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</thead>
<tbody>
<tr>
<td>Beckett and Godwin (14)</td>
<td>481</td>
<td>Family practice</td>
<td>140/80</td>
<td>142/80</td>
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<tr>
<td>Myers et al (15)</td>
<td>309</td>
<td>ABPM</td>
<td>132/75</td>
<td>134/77</td>
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<tr>
<td>Myers et al (16)</td>
<td>62</td>
<td>Hypertension Clinic</td>
<td>140/77</td>
<td>141/77</td>
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<tr>
<td>Myers et al (16)</td>
<td>254</td>
<td>ABPM</td>
<td>133/80</td>
<td>135/81</td>
</tr>
<tr>
<td>Godwin et al (17)</td>
<td>654</td>
<td>Family Practice</td>
<td>139/80</td>
<td>141/80</td>
</tr>
<tr>
<td>Myers et al (9)</td>
<td>139</td>
<td>ABPM</td>
<td>141/82</td>
<td>142/81</td>
</tr>
<tr>
<td>Myers et al (18)</td>
<td>303</td>
<td>Family Practice</td>
<td>136/78</td>
<td>133/74</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td></td>
<td>138/79</td>
<td>139/79</td>
</tr>
</tbody>
</table>

J European Society Cardiology Vol.13,N°15 - 10 Mar 2015
Studies comparing automated office BP with awake ambulatory BP
Effect of Blood Pressure on Progression of Nephropathy

Case Question 1

A 50-year-old female was diagnosed with type 2 diabetes at age 30. She has taken medications as prescribed since diagnosis. The fact that she has confirmed diabetes puts this patient at:

A. Higher risk for kidney failure and CVD
B. Higher risk for kidney failure only
C. Higher risk for CVD only
D. None of the above
Primary Care Providers – First Line of Defense Against CKD

- Primary care professionals can play a significant role in early diagnosis, treatment, and patient education
- A greater emphasis on detecting CKD, and managing it prior to referral, can improve patient outcomes

CKD is Part of Primary Care
CKD Risk Factors

**Modifiable**
- Diabetes
- Hypertension
- History of AKI
- Frequent NSAID use

**Non-Modifiable**
- Family history of kidney disease, diabetes, or hypertension
- Age 60 or older (GFR declines normally with age)
- Race/U.S. ethnic minority status
Hypertension is defined as a sustained blood pressure => 140/mmHg. This threshold are strongly associated with ASCVD, death, disability, and microvascular complications.
Blood pressure should be measured at every routine visit. Patients found to have elevated blood pressure should have blood pressure confirmed on a separate day, within a month to confirm diagnosis of hypertension.
Hypertension/Blood Pressure Control Screening and Diagnosis

• At the initial visit blood pressure should be measured in both arms. Pressure should have blood pressure confirmed on a separate day.
The “sustained” aspect of the hypertension definition is important, as blood pressure has considerable normal variation.
• All hypertensive patients with diabetes should have home blood pressure monitored to identify white-coat hypertension.
Hypertension/Blood Pressure Control
Screening and Diagnosis

• White-coat hypertension is elevated office blood pressure (=> 140/mmHg) and normal untreated home blood pressure (<135/85 mmHg).
Hypertension/Blood Pressure Control
Screening and Diagnosis

• The correct cuff size such that encircles 80% of the arm is very important.
• Too small a cuff will give higher and too large a cuff will give lower values.
Hypertension/Blood Pressure Control

**Goals**

- Most patients with diabetes and hypertension should be treated to a systolic blood pressure goal of 140 mmHg and a diastolic blood pressure goal of 90 mmHg. A
Hypertension/Blood Pressure Control

Goals

• Lower systolic and diastolic blood pressure targets, such as 130/80 mmHg, may be appropriate for individuals at high risk of cardiovascular disease, if they can be achieved without undue treatment burden. C
SBP <130 mmHg/DBP <80 may be appropriate
- if younger
- albuminuria
- 1 or more ASCVD risk factors

if it can be achieved without undue treatment burden.

ADA Standards of Care 2016
Hypertension/Blood Pressure Control

Goals

• In pregnant patients with diabetes and chronic hypertension, blood pressure targets of 120–160/80–105 mmHg are suggested in the interest of optimizing long-term maternal health and minimizing impaired fetal growth. E
Hypertension/Blood Pressure Control Treatment

• Patients with confirmed office-based blood pressure 140/90 mmHg should, in addition to lifestyle therapy, have prompt initiation and timely titration of pharmacologic therapy to achieve blood pressure goals. A
Blood Pressure Control & T2DM

Action to Control Cardiovascular Risk in Diabetes (ACCORD):

• Does SBP <120 provide better cardiovascular protection than SBP 130-140? **No.**

ADVANCE-BP:

• Significant risk reduction
Recommendations: Hypertension/ Blood Pressure Control (2)

**Systolic Targets:**

- People with diabetes and hypertension should be treated to a systolic blood pressure goal of $<140 \text{ mmHg}$. A

- Lower systolic targets, such as $<130 \text{ mmHg}$, may be appropriate for certain individuals at high risk of CVD, if they can be achieved without undue treatment burden. C
Diastolic Targets:

• Patients with diabetes should be treated to a diastolic blood pressure <90 mmHg. A

• Lower diastolic targets, such as <80 mmHg, may be appropriate for certain individuals at high risk for CVD if they can be achieved without undue treatment burden. C
Clinical Pearls

- Blood pressure <140/90 mmHg in diabetes are recommended to reduce CVD mortality and slow CKD progression.
- Avoid diastolic blood pressure levels <60-70 mmHg.
Pregnant patients:

- In pregnant patients with diabetes and chronic hypertension, blood pressure targets of 120–160/80–105 mmHg are suggested in the interest of optimizing long-term maternal health and minimizing impaired fetal growth.
Recommendations: Hypertension/ Blood Pressure Treatment

• Patients with BP >120/80 should be advised on lifestyle changes to reduce BP. B

• Patients with confirmed BP >140/90 should, in addition to lifestyle therapy, have prompt initiation and timely subsequent titration of pharmacological therapy to achieve blood pressure goals. A
Recommendations: Hypertension/ Blood Pressure Treatment (2)

• Lifestyle intervention including:
  – Weight loss if overweight
  – DASH-style diet
  – Moderation of alcohol intake
  – Increased physical activity

American Diabetes Association Standards of Medical Care in Diabetes. Cardiovascular disease and risk management. Diabetes Care 2017; 40 (Suppl. 1): S75–S87
Hypertension/Blood Pressure Control
Treatment

- Patients with confirmed office-based blood pressure 160/100 mmHg should, in addition to lifestyle therapy, have prompt initiation and timely titration of two drugs or a single pill combination of drugs demonstrated to reduce cardiovascular events in patients with diabetes. A
Treatment for hypertension should include drug classes demonstrated to **reduce cardiovascular events** in patients with diabetes (ACE inhibitors, angiotensin receptor blockers, thiazide-like diuretics, or dihydropyridine calcium channel blockers). Multiple drug therapy is generally required to achieve blood pressure targets (but not a combination of ACE inhibitors and angiotensin receptor blockers).
Recommendations: Hypertension/ Blood Pressure Treatment (3)

• Treatment for hypertension should include A
  – ACE inhibitor
  – Angiotensin II receptor blocker (ARB)
  – Thiazide-like diuretic
  – Dihydropyridine calcium channel blockers

• Multiple drug therapy (two or more agents at maximal doses) generally required to achieve BP targets.
Hypertension/Blood Pressure Control
Treatment

- An ACE inhibitor or angiotensin receptor blocker, at the maximum tolerated dose indicated for blood pressure treatment, is the recommended first-line treatment for hypertension in patients with diabetes and urinary albumin-to-creatinine ratio => 300 mg/g creatinine (A) or 30–299 mg/g creatinine (B). If one class is not tolerated, the other should be substituted. B
Recommendations: Hypertension/ Blood Pressure Treatment (4)

• An ACE inhibitor or angiotensin receptor blocker, at the maximum tolerated dose indicated for blood pressure treatment, is the recommended first-line treatment for hypertension in patients with diabetes and urinary albumin–to–creatinine ratio ≥300 mg/g creatinine (A) or 30–299 mg/g creatinine (B). If one class is not tolerated, the other should be substituted. B
Recommendations: Hypertension/ Blood Pressure Treatment (5)

- If using ACE inhibitors, ARBs, or diuretics, monitor serum creatinine / eGFR & potassium levels. B
Hypertension/Blood Pressure Control Treatment

- For patients with blood pressure 120/80 mmHg, lifestyle intervention consists of weight loss if overweight or obese. A
- Dietary Approaches to Stop Hypertension–style dietary pattern including reducing sodium and increasing potassium intake; moderation of alcohol intake; and increased physical activity. B
Antihypertensive Treatment in the Absence of Hypertension

- For people with diabetes and untreated blood pressure <140/90 mmHg, there is little evidence that antihypertensive treatment improves health outcomes.
Case Study 1

• R.C. is a 57-year-old man with type 2 diabetes first diagnosed 2 years ago. Other medical problems include obesity and hypothyroidism. He presents now for routine follow-up and is noted to have a blood pressure of 168/100 mmHg. He is asymptomatic.
Case Study 1

• Physical exam reveals a height of 170 cm, weight of 98 kg, blood pressure of 160/100 mmHg, and a regular pulse of 84 beats/min. There is no retinopathy or thyromegaly. There is no clinical evidence of congestive heart failure or peripheral vascular disease.
Case Study 1

Laboratory evaluation reveals

• Blood urea nitrogen of 14 mg/dl, serum creatinine of 1.2 mg/dl
• Random Serum glucose of 169 mg/dl
• Normal electrolytes
• Normal thyroid-stimulating hormone levels.
• Trace protein on urinalysis
• A 24-h urine collection reveals a urinary albumin excretion rate of 250 mg/day.
Case Study 1

• Questions
• Should his blood pressure be treated?
• What treatment strategy should be used?
• Does this patient have renal disease?
Confirmed Hypertension in People With Diabetes

Initial BP between 140/90 mmHg and 160/100 mmHg

Start one agent

Albuminuria*

No

Start one drug:
- ACEi
- ARB
- CCB***
- Diuretic**

Yes

Start: ACEi or ARB

Initial BP ≥ 160/100 mmHg

Lifestyle management

Start two agents

Albuminuria*

No

Start drug from 2 of 3 options:
- ACEi or ARB
- CCB***
- Diuretic**

Yes

Start:
- ACEi or ARB
- CCB*** or Diuretic**

Assess BP Control and Adverse Effects
Assess BP Control and Adverse Effects

- Treatment tolerated and target achieved
  - Continue therapy

- Not meeting target on two agents
  - Add agent from complementary drug class:
    - ACEi or ARB
    - CCB**
    - Diuretic**

- Adverse effects
  - Consider change to alternative medication:
    - ACEi or ARB
    - CCB**
    - Diuretic**

- Not meeting target or adverse effects using a drug from each of three classes
  - Consider Addition of Mineralocorticoid Receptor Antagonist; Refer to Specialist With Expertise in BP Management
Pharmacotherapy of Hypertension with Nephropathy, CVD or CV Risk Factors

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

- **Diabetes with Nephropathy or CVD or CV risk factors**
  - ACE Inhibitor or ARB
  - **If ACEI and ARB are contraindicated or not tolerated, substitute**
    - Long-acting CCB or
    - Thiazide diuretic
  - Addition of a Dihydropyridine CCB is preferable to HCTZ
  - 3 - 4 drugs in 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.
Pharmacotherapy of Hypertension in Diabetes without Nephropathy, CVD or CV Risk Factors

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

DIABETES without Nephropathy, CVD or CV risk factors

1. ACE Inhibitor or ARB or
2. Dihydropyridine CCB or Thiazide diuretic

Combination of first line agents

IF ACE Inhibitor, ARB, DHP-CCB and Thiazide are contraindicated or not tolerated, SUBSTITUTE
- Cardioselective BB* or
- Long-acting NON DHP-CCB

Addition of one or more of:
- Cardioselective BB or Long-acting CCB

Combinations of an ACE Inhibitor with an ARB are specifically not recommended in the absence of proteinuria
Threshold equal or over 130/80 mmHg and Target below 130/80 mmHg

With Nephropathy, CVD or CV risk factors

ACE Inhibitor or ARB

With Nephropathy, CVD or CV risk factors

Without the above

1. ACE Inhibitor or ARB or
2. Thiazide diuretic or DHP-CCB

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

> 2-drug combinations

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

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

More than 3 drugs may be needed to reach target values

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
Case Study 1 continued

• Early detection and treatment of albuminuria is essential in diabetes. A normal urinary albumin excretion rate (UAER) ranges from 0 to 30 mg/day. Overt albuminuria or macroalbuminuria is defined as a UAER $\geq 300$ mg/day.
Case Study 1 continued

• Many studies have shown that a UAER \( >30 \text{ mg/day} \) is abnormal and can be used to predict the development of overt albuminuria or diabetic nephropathy and both microvascular and macrovascular disease.
Case Study 1
Screening for Albuminuria

• Many organizations, including the American Diabetes Association, recommend regular screening for albuminuria. Type 1 diabetic patients should be screened 5 years after diagnosis of diabetes and after puberty.
Case Study 1
Screening for Albuminuria

• People with type 2 diabetes should be screened from the time of diagnosis, since many type 2 diabetic patients have had undiagnosed disease for some time. If the initial screening is negative, then annual screenings are indicated.
Case Study 1
Detection of Albuminuria

• Traditional urinary dipsticks are insensitive at detecting albuminuria <300 mg/day. Spot urine samples may be assayed for albuminuria and creatinine and a ratio ≥30 µg/mg or mg/g is abnormal.
Case Study 1
Detection of Albuminuria

• Newer methods, such as Micral-Test II test strips (Boehringer Mannheim, Mannheim, Germany), permit reliable semiquantitative determination of albuminuria and can be used in the office for dipstick screening of diabetic patients.
Case Study 1
Variability in Albuminuria

• Transient elevations in urinary albumin excretion may be associated with marked hyperglycemia, acute febrile illness, exercise, hypertension, heart failure, and urinary tract infection. If the initial test is elevated, these and other potential causes of renal disease should be considered and ruled out.
Case Study 1
Variability in Albuminuria

• Because there is also marked day-to-day variability in urinary albumin excretion, a positive test should be confirmed on a subsequent occasion before designating a patient as having persistent albuminuria.
Case Study 1

• Patients identified with persistent albuminuria should be aggressively treated both with respect to glycemic and blood pressure control. Patients are considered to be hypertensive if their blood pressure is $\geq 140/90$ mmHg. The goal for the management of hypertensive diabetic patients is to keep the blood pressure $<130/85$ mmHg.
Case Study 1

• In addition to aggressively managing blood pressure, attempts need to be made toward lifestyle modifications. These include meticulous control of blood glucose, seeking counseling to stop smoking, maintaining optimal body weight, following an appropriate diet, and exercising regularly.
Case Study 1: Diabetic Kidney Disease

• Diabetic nephropathy is a clinical syndrome characterized by albuminuria, hypertension, and progressive renal insufficiency.
Case Study 1: Diabetic Kidney Disease

• Diabetic nephropathy is the most common cause of end-stage renal disease (ESRD) in Western countries, accounting for ~35% of all new ESRD cases in the United States. The life expectancy of patients with diabetic ESRD is <50% at 3 years, despite improvements in dialysis and renal transplantation.
Clinical Pearls

• Blood pressure <140/90 mmHg in diabetes are recommended to reduce CVD mortality and slow CKD progression.
• Avoid diastolic blood pressure levels <60-70 mmHg.
Clinical Pearls

- ACE inhibitors or ARBs are the preferred first line agent for BP treatment among patients with diabetes, HTN, eGFR<60 mL/min/1.73m², and UACR >= 300 mg/g Cr
Clinical Pearls

• Screen diabetic patients for albuminuria.
• Recognize hypertension in diabetic patients with a blood pressure $>140/90$ mmHg.
• ACE inhibition is the preferred treatment of albuminuria and/or hypertension.
• Counsel diabetic patients on lifestyle modifications, including blood glucose control, weight control, smoking cessation, diet, and exercise.
Study time line of DCCT/EDIC Study

- National Commission
- RFA
- DCCT Planning
- Feasibility
- Recruitment
- DCCT
  1978
  1982
  1983
  1989
  1993
  1994
- EDIC
  2005
  2013

DCCT 10 years

EDIC 20 years
DCCT: Results Summary

Improved control of blood glucose reduces the risk of clinically meaningful complications.

- Retinopathy: 76% ($P \leq 0.002$)
- Nephropathy: 54% ($P < 0.04$)
- Neuropathy: 60% ($P \leq 0.002$)

Progression to Vision-Threatening Proliferative Diabetic Retinopathy Over 10 Years (WESDR)

P<0.0001

Total glycosylated hemoglobin (HbA$_{1c}$) quartiles (%)

- 5.4-8.5
- 8.6-10.0
- 10.1-11.5
- 11.6-20.8