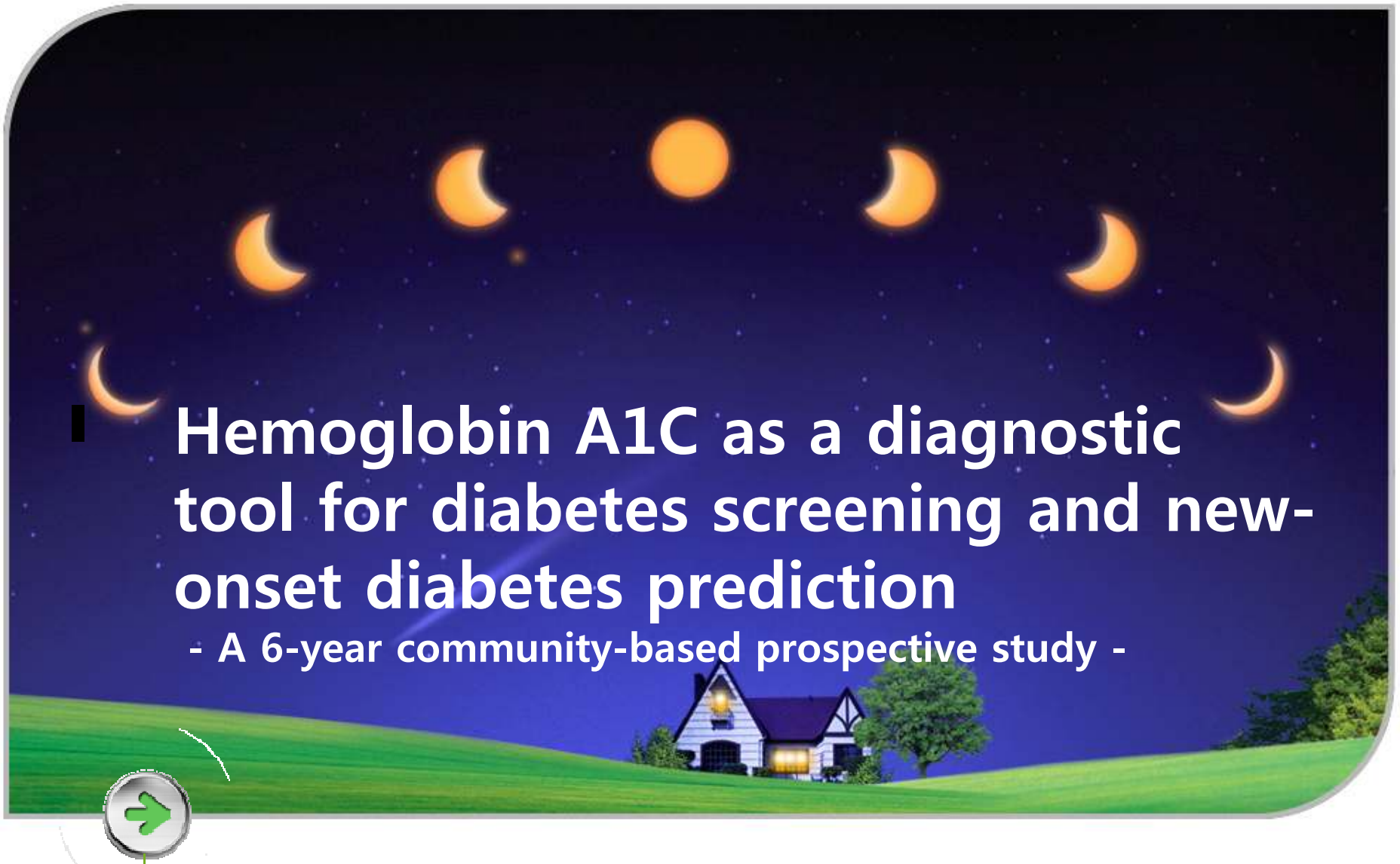


Hemoglobin A1C as a diagnostic tool for diabetes screening and new-onset diabetes prediction

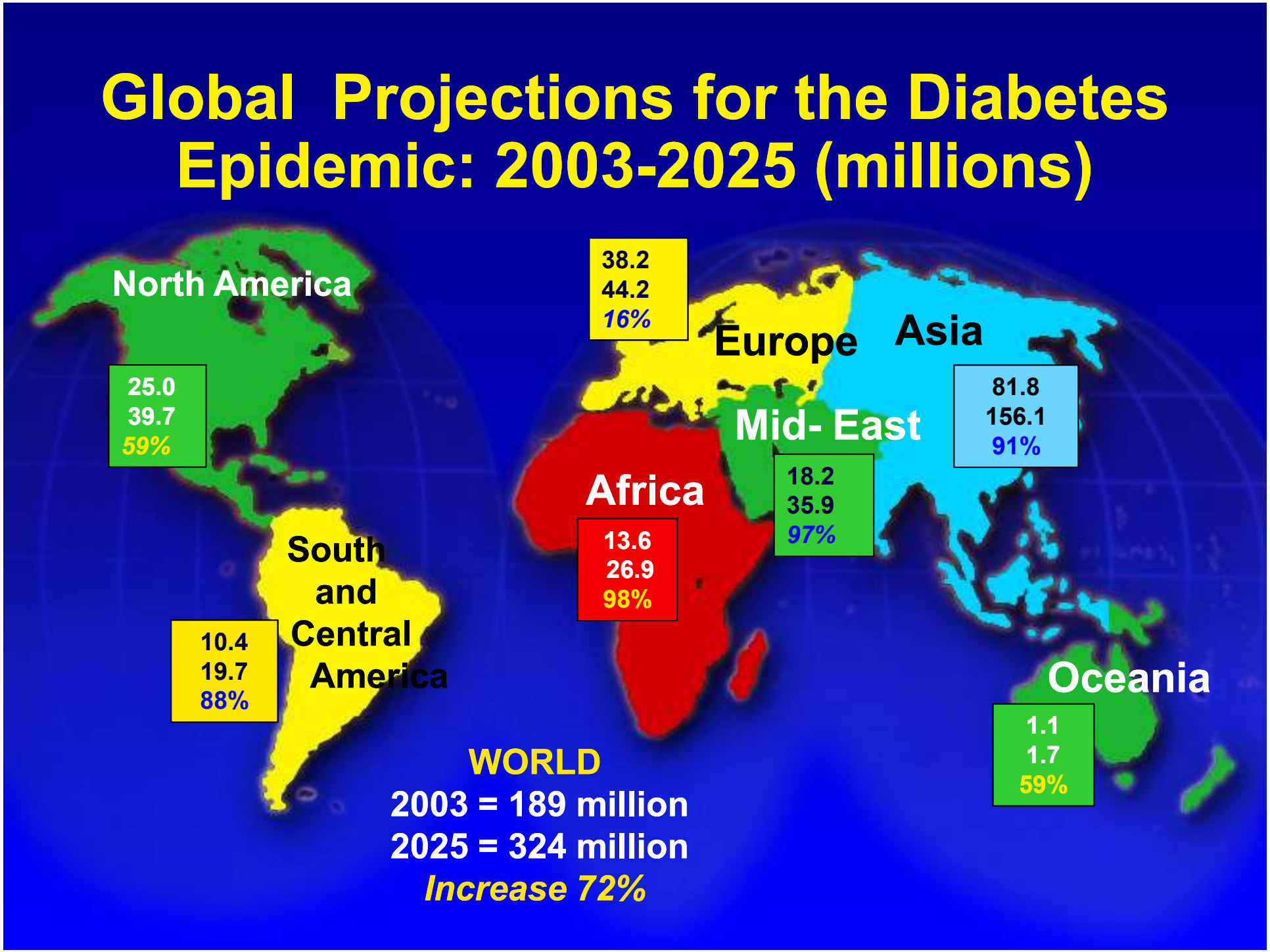
- A 6-year community-based prospective study -

임 수 MD, MPH, PHD, Dr.PH

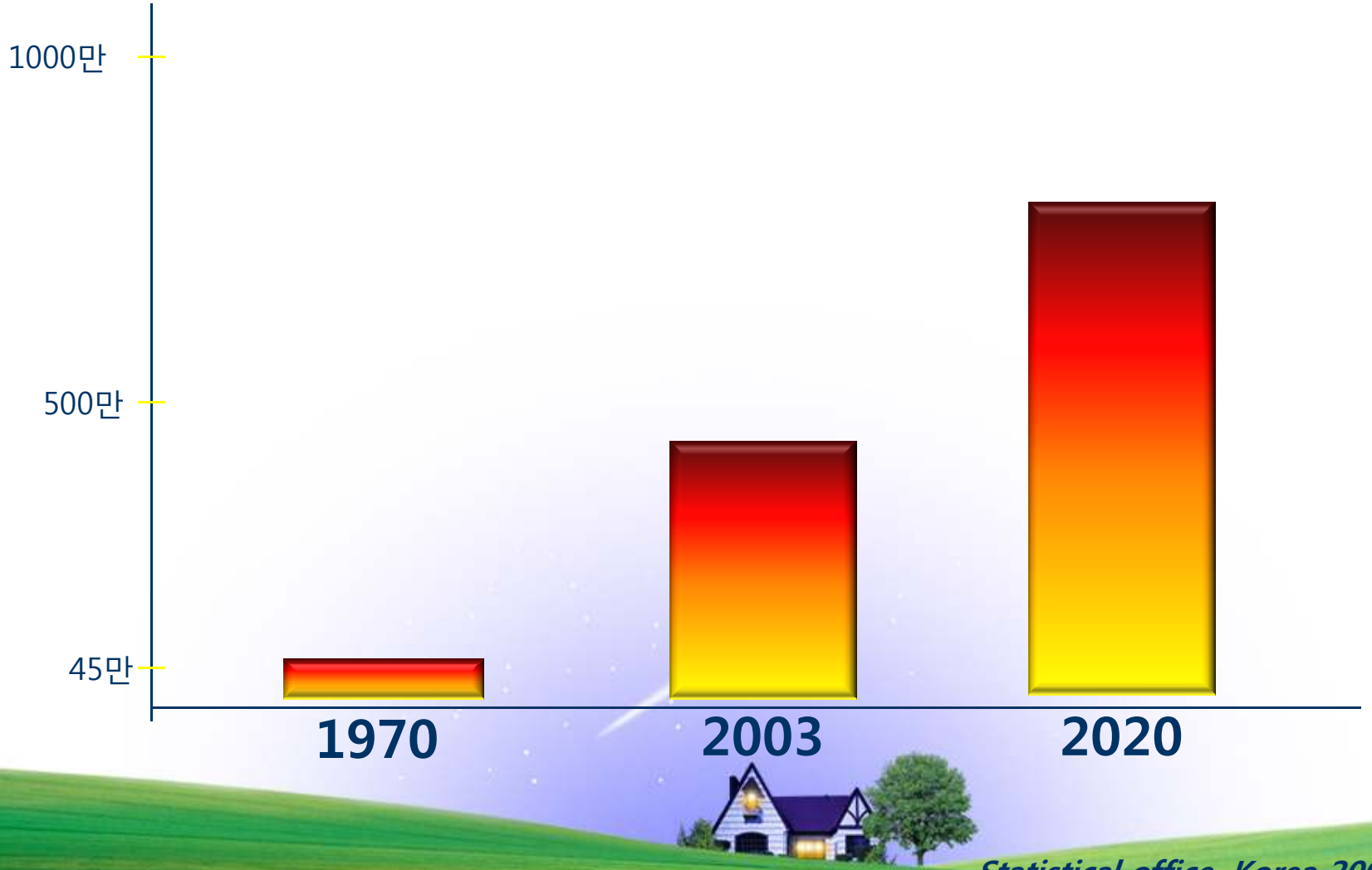
Seoul National University College of Medicine

Seoul National University Bundang Hospital

Global Projections for the Diabetes Epidemic: 2003-2025 (millions)



Type 2 Diabetes Prevalence Is Projected to Reach 7 Million by 2020 in KOREA



Statistical office, Korea 2005

Background

- The prevalence of type 2 diabetes is increasing rapidly throughout the world.
- However, a lot of patients with diabetes are not diagnosed timely.
- Up to 25% of newly diagnosed diabetic patients already have established microvascular complications.

=> This finding suggests that there is a 6- to 7-year time lag between the onset and the diagnosis of type 2 diabetes.

American Diabetes Association (ADA)

- **Recommends screening asymptomatic people**
  - at age 45 years
  - in those of any age who are overweight or obese (BMI ≥25 kg/m^2) using (1) a fasting plasma glucose test or (2) 2 h oral glucose tolerance test (OGTT).
- **However, it is not easy to perform the OGTT in clinical practice.**
- **Fasting glucose alone does not provide an accurate diagnosis of diabetes.**

Diabetes Care 2009

ADA clinical recommendation 2010

- Diagnosis of diabetes: A1C ≥ 6.5%

- The A1C level provides a reliable measure of chronic glycemic control over the previous 2 to 3 months without the need for a fasting or timed sample.

The hemoglobin A1C (A1C) level

- Several population-based studies suggested the potential to use the A1C level as a useful screening tools for type 2 diabetes.

Ann Intern Med 2004

Diabetes Care 2008

- The A1C level correlates well with the risk of long-term diabetic complications and mortality.

Diabetes Care 2007

DRCP 2007

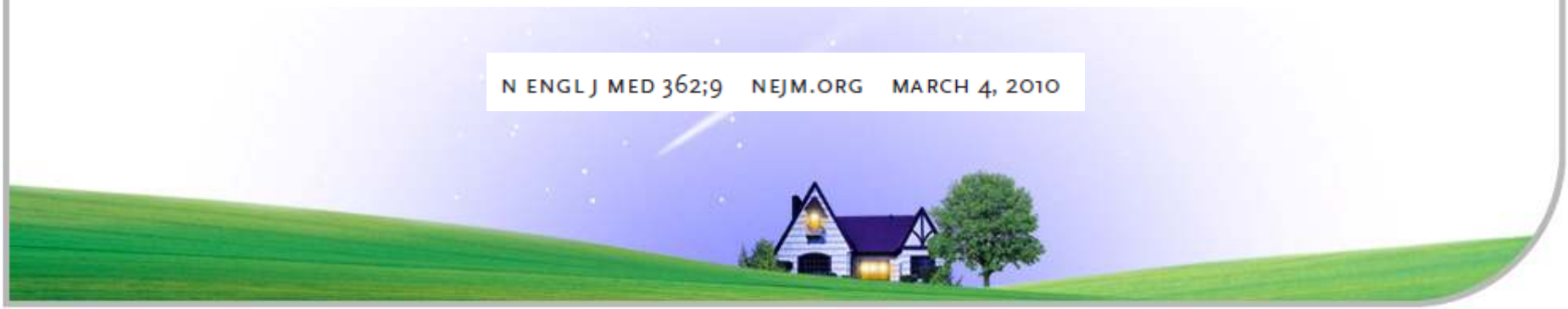
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Glycated Hemoglobin, Diabetes, and Cardiovascular Risk in Nondiabetic Adults

Elizabeth Selvin, Ph.D., M.P.H., Michael W. Steffes, M.D., Ph.D., Hong Zhu, B.S., Kunihiro Matsushita, M.D., Ph.D., Lynne Wagenknecht, Dr.P.H., James Pankow, Ph.D., M.P.H., Josef Coresh, M.D., Ph.D., and Frederick L. Brancati, M.D., M.H.S.

N ENGL J MED 362;9 NEJM.ORG MARCH 4, 2010



Background

- Fasting glucose is the standard measure used for the diagnosis of diabetes in the United States.
- Glycated hemoglobin (A1c) has been recommended only for the determination of glucose control.
- New clinical practice recommendations from the American Diabetes Association advocate the use of A1c in the diagnosis of diabetes.

Objective

- To compare the prognostic value of A1c and fasting glucose for identifying adults at risk for (1) diabetes, (2) coronary heart disease, (3) ischemic stroke, and (4) death from any cause in a large community-based cohort of middle-aged adults who did not have a history of diabetes.

Study Population

- The Atherosclerosis Risk in Communities (ARIC) study

  :community-based prospective cohort study of 15,792 middle-aged adults from four U.S. communities.

- The baseline visit
  - attended by 14,348 participants
  - during 1990–1992
  - stored whole-blood samples were available for measurement of A1c

Study Population

Exclusion criteria

- other than white or black
- self-reported diabetes
- use of diabetes medication
- history of cardiovascular disease
- a validated cardiovascular event between visit 1 and visit 2
- nonfasting state
- missing data

11,092 patients

Assessment of Diabetes and CHD

- **Two definitions of newly identified diabetes:**
  - Visit-based diabetes :
    - elevated fasting glucose levels (≥126 mg/dL)
    - diabetes medication use during the first 6 years of follow-up
  - Interview-based diabetes:
    - a self-reported diagnosed diabetes
    - diabetes medication use during 15 years of follow-up.

- **Newly diagnosed coronary heart disease**
  - a definite or probable myocardial infarction
  - a death from coronary heart disease
  - a cardiac procedure
  - ECG evidence of a silent myocardial infarction

Methods

- Statistical Analysis

- **Categories of glycated hemoglobin values**

  (<5.0%, 5.0 to <5.5%, 5.5 to <6.0%, 6.0 to <6.5%, and ≥6.5%)

- **Standard fasting glucose categories**

  (<100, 100 to <126, and ≥126 mg/dL)

- **Hazard ratios, 95% confidence intervals :**

  Cox proportional-hazards models

Methods

- Statistical Analysis

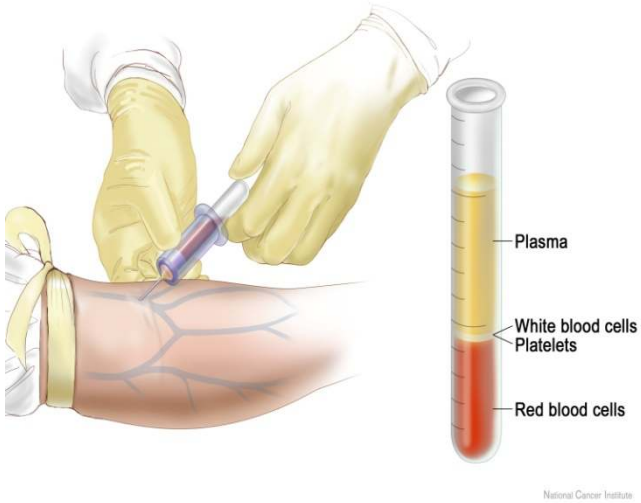
- **three core models :**
  - **Model 1** was adjusted for age, sex, and race.
  - **Model 2** was adjusted for age, sex, race, low-density and high-density cholesterol levels, triglyceride level, BMI, waist-to-hip ratio, hypertension, family history of diabetes, education level, alcohol use, physical activity, and smoking status.
  - Glycated hemoglobin categories (called models 1a and 2a)
  - standard fasting glucose categories (called models 1b and 2b)
  - Model 3 was adjusted for all the variables in model 2 plus either the **baseline fasting glucose level (model 3a)** or the **baseline glycated hemoglobin value (model 3b).**

- **glycated hemoglobin category of 5.0 to less than 5.5% : largest number of participants (4950) → reference category**

- **Model discrimination was assessed with the use of Harrell's C statistic.**

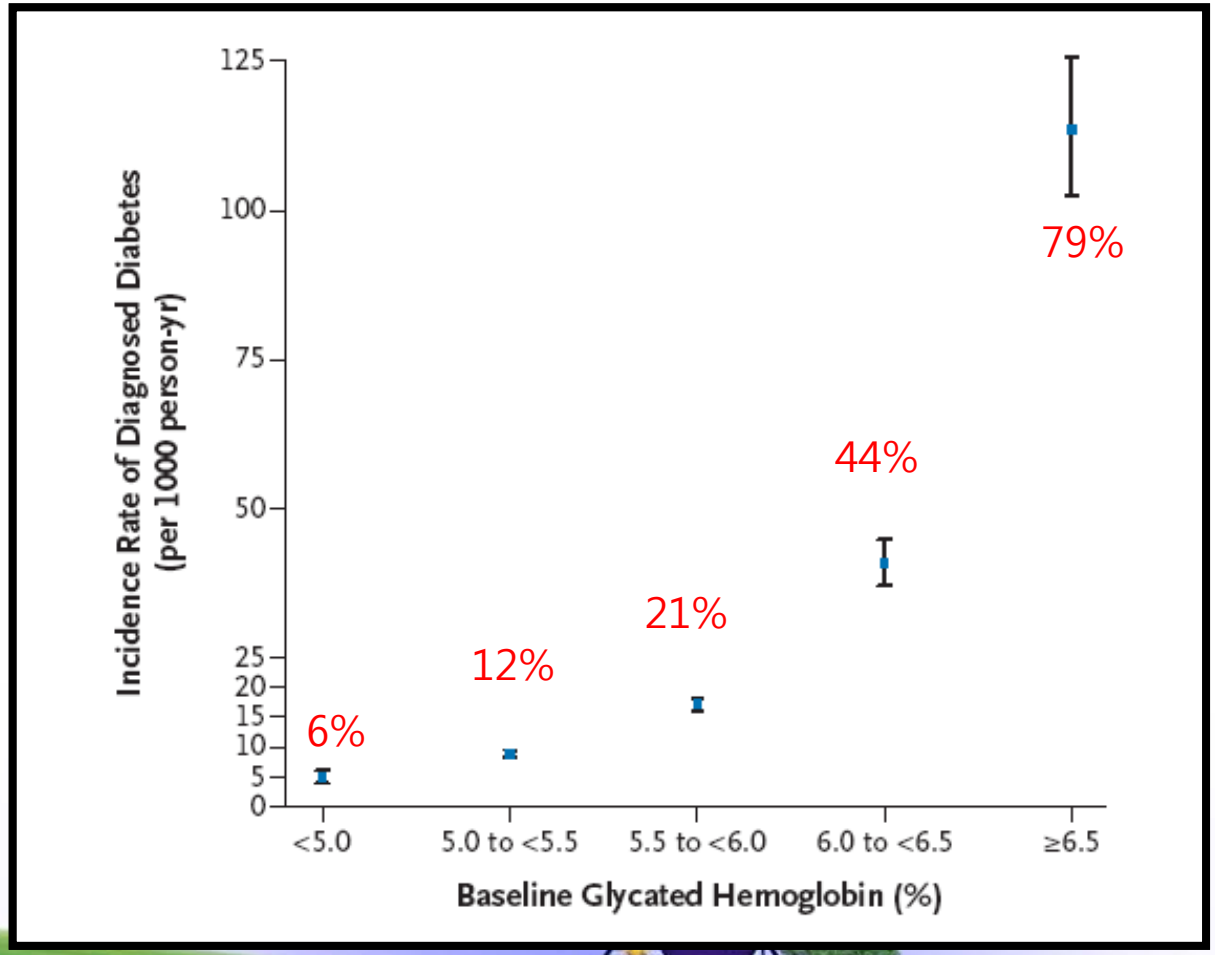
Table 1. Selected Characteristics of the Study Participants, According to the Glycated Hemoglobin Value at Baseline.*

Value	Any (N=11,092)	Glycated Hemoglobin Category <5.0% (N=949)	5.0 to <5.5% (N=4950)	5.5 to <6.0% (N=3683)	6.0 to <6.5% (N=1031)	≥6.5% (N=479)
Glycated hemoglobin (%)	5.5±0.6	4.8±0.2	5.2±0.1	5.7±0.1	6.1±0.1	7.4±1.4
Fasting glucose (mg/dl)	104.7±18.6	98.0±8.8	99.7±9.4	104.5±10.6	113.4±15.5	153.1±51.7
Fasting glucose category (%)						
<100 mg/dl	41.3	60.5	53.2	32.8	14.9	1.7
100 to <126 mg/dl	52.4	38.7	45.7	64.2	67.2	27.8
≥126 mg/dl†	6.3	0.8	1.1	3.0	17.9	70.6
Age (yr)	56.7±5.7	55.3±5.5	56.1±5.6	57.3±5.7	58.0±5.7	57.6±5.7
Sex (%)						
Female	57.7	55.2	58.8	56.8	55.8	61.8
Male	42.3	44.8	42.2	43.2	44.2	38.2
Race (%)‡						
Black	22.4	15.5	11.9	27.0	49.1	52.2
White	77.6	84.5	88.1	73.0	50.9	47.8
Fasting cholesterol (mg/dl)						
LDL	133.0±36.4	122.8±34.7	130.0±34.9	136.6±37.0	138.6±37.5	143.6±39.0
HDL	50.9±16.7	53.2±18.5	52.5±17.0	50.1±16.2	47.0±14.7	43.9±13.6
Fasting triglycerides (mg/dl)						
Median	110	101	105	111	121	139
Interquartile range	80–154	73–136	78–150	81–155	88–164	99–190
Body-mass index§	27.7±5.3	26.5±4.7	26.7±4.6	28.0±5.3	30.0±6.0	32.5±6.3
Waist-to-hip ratio	0.9±0.1	0.9±0.1	0.9±0.1	0.9±0.1	0.9±0.1	1.0±0.1
Hypertension (%)	32.0	26.9	26.7	33.8	49.4	56.8
Family history of diabetes (%)	22.7	19.5	20.4	23.9	27.1	33.8
Education (%)						
Less than high school	19.2	13.0	14.0	22.6	31.7	33.2
High school or equivalent	42.0	40.6	44.5	41.1	37.3	36.1
College or above	38.8	46.4	41.5	36.3	31.0	30.7


Plasma
White blood cells
Platelets
Red blood cells
National Cancer Institute

RESULTS

The incidence of diabetes



Results

Table 2. Adjusted Hazard Ratios for Selected Clinical Outcomes in the Study Population during the 15-Year Study Period, According to the Glycated Hemoglobin Category at Baseline and the Model.*

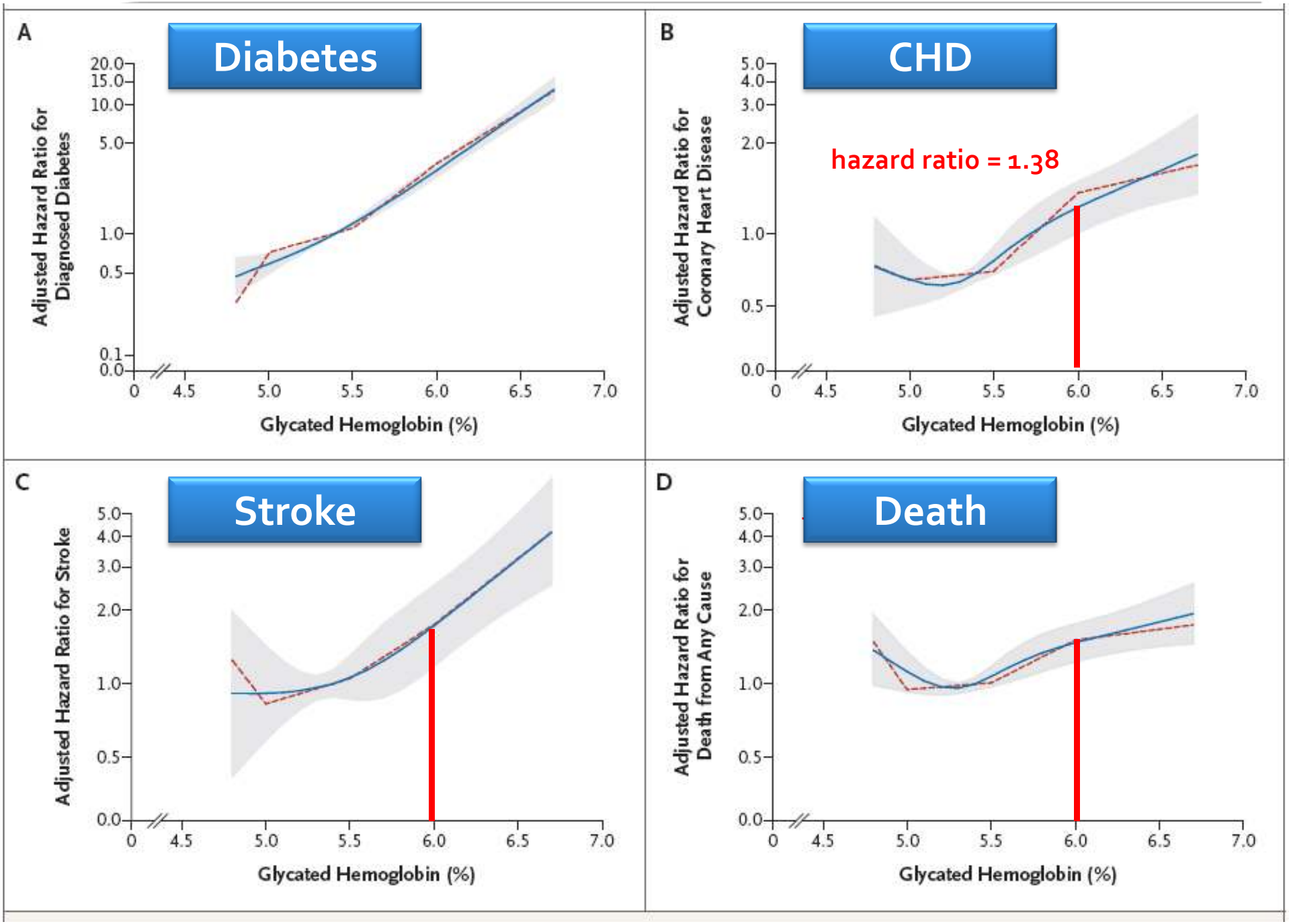
Outcome	Model 1a	Model 2a	Model 3a
Visit-based diabetes†			
Glycated hemoglobin category — hazard ratio (95% CI)			
<5.0%	0.49 (0.27–0.89)	0.50 (0.28–0.90)	0.57 (0.31–1.03)
5.0 to <5.5% (reference)	1.00	1.00	1.00
5.5 to <6.0%	2.91 (2.33–3.63)	2.44 (1.95–3.05)	1.77 (1.41–2.22)
6.0 to <6.5%	13.38 (10.51–17.03)	9.20 (7.18–11.78)	5.08 (3.93–6.56)
≥6.5%	50.73 (37.44–68.74)	32.77 (23.96–44.82)	14.53 (10.53–20.04)
P value for trend	<0.001	<0.001	<0.001
Glycated hemoglobin value — hazard ratio (95% CI)	2.73 (2.56–2.91)	2.75 (2.55–2.96)	2.57 (2.35–2.81)
C statistic	0.7771	0.8258	0.8695
Diagnosed diabetes‡			
Glycated hemoglobin category — hazard ratio (95% CI)			
<5.0%	0.51 (0.39–0.67)	0.52 (0.40–0.69)	0.53 (0.40–0.69)
5.0 to <5.5% (reference)	1.00	1.00	1.00
5.5 to <6.0%	2.12 (1.90–2.37)	1.86 (1.67–2.08)	1.80 (1.61–2.01)
6.0 to <6.5%	6.29 (5.52–7.17)	4.48 (3.92–5.13)	4.03 (3.52–4.61)
≥6.5%	27.19 (23.61–31.31)	16.47 (14.22–19.08)	10.40 (8.80–12.28)
P value for trend	<0.001	<0.001	<0.001
Glycated hemoglobin value — hazard ratio (95% CI)	1.97 (1.92–2.03)	1.80 (1.75–1.86)	1.44 (1.35–1.55)
C statistic	0.7458	0.7766	0.7816

Result

Coronary heart disease			
Glycated hemoglobin category — hazard ratio (95% CI)			
<5.0%	0.89 (0.69–1.15)	0.96 (0.74–1.24)	0.95 (0.73–1.22)
5.0 to <5.5% (reference)	1.00	1.00	1.00
5.5 to <6.0%	1.45 (1.27–1.66)	1.23 (1.07–1.41)	1.25 (1.09–1.44)
6.0 to <6.5%	2.37 (1.98–2.84)	1.78 (1.48–2.15)	1.88 (1.55–2.28)
≥6.5%	2.91 (2.31–3.67)	1.95 (1.53–2.48)	2.46 (1.84–3.28)
P value for trend	<0.001	<0.001	<0.001
Glycated hemoglobin value — hazard ratio (95% CI)	1.34 (1.27–1.42)	1.19 (1.11–1.27)	1.50 (1.33–1.68)
C statistic	0.6888	0.7351	0.7383
Ischemic stroke			
Glycated hemoglobin category — hazard ratio (95% CI)			
<5.0%	1.06 (0.65–1.71)	1.09 (0.67–1.76)	1.09 (0.68–1.77)
5.0 to <5.5% (reference)	1.00	1.00	1.00
5.5 to <6.0%	1.27 (0.97–1.67)	1.17 (0.89–1.53)	1.16 (0.89–1.53)
6.0 to <6.5%	2.63 (1.92–3.61)	2.22 (1.60–3.08)	2.19 (1.58–3.05)
≥6.5%	3.68 (2.56–5.30)	3.16 (2.15–4.64)	2.96 (1.87–4.67)
P value for trend	<0.001	<0.001	<0.001
Glycated hemoglobin value — hazard ratio (95% CI)	1.41 (1.30–1.54)	1.34 (1.22–1.48)	1.55 (1.28–1.88)
C statistic	0.7229	0.7581	0.7594

Table 2. (Continued.)

Outcome	Model 1a	Model 2a	Model 3a
Death from any cause			
Glycated hemoglobin category — hazard ratio (95% CI)			
<5.0%	1.43 (1.17–1.74)	1.48 (1.21–1.82)	1.48 (1.21–1.81)
5.0 to <5.5% (reference)	1.00	1.00	1.00
5.5 to <6.0%	1.34 (1.18–1.52)	1.18 (1.04–1.35)	1.19 (1.05–1.35)
6.0 to <6.5%	1.92 (1.63–2.27)	1.59 (1.34–1.89)	1.61 (1.35–1.91)
≥6.5%	1.92 (1.54–2.40)	1.65 (1.31–2.08)	1.71 (1.30–2.25)
P value for trend§	—	—	—
Glycated hemoglobin value — hazard ratio (95% CI)	1.21 (1.13–1.28)	1.12 (1.05–1.21)	1.18 (1.05–1.32)
C statistic	0.6885	0.7316	0.7314


A
Diabetes
Adjusted Hazard Ratio for Diagnosed Diabetes
20.0
15.0
10.0
5.0
1.0
0.5
0.1
0.0
0
4.5
5.0
5.5
6.0
6.5
7.0
Glycated Hemoglobin (%)
B
CHD
hazard ratio = 1.38
Adjusted Hazard Ratio for Coronary Heart Disease
5.0
4.0
3.0
2.0
1.0
0.5
0.0
0
4.5
5.0
5.5
6.0
6.5
7.0
Glycated Hemoglobin (%)
C
Stroke
Adjusted Hazard Ratio for Stroke
5.0
4.0
3.0
2.0
1.0
0.5
0.0
0
4.5
5.0
5.5
6.0
6.5
7.0
Glycated Hemoglobin (%)
D
Death
Adjusted Hazard Ratio for Death from Any Cause
5.0
4.0
3.0
2.0
1.0
0.5
0.0
0
4.5
5.0
5.5
6.0
6.5
7.0
Glycated Hemoglobin (%)

Results

Table 3. Adjusted Hazard Ratios for Selected Clinical Outcomes in the Study Population during the 15-Year Study Period, According to the Fasting Glucose Category at Baseline and the Model.*

Outcome	Model 1b	Model 2b	Model 3b
Diagnosed diabetes†			
Fasting glucose category — hazard ratio (95% CI)			
<100 mg/dl (reference)	1.00	1.00	1.00
100 to <126 mg/dl	3.01 (2.69–3.37)	2.31 (2.06–2.59)	2.19 (1.95–2.45)
≥126 mg/dl	21.5 (18.7–24.6)	12.3 (10.7–14.2)	8.07 (6.92–9.42)
P value for trend	<0.001	<0.001	<0.001
Fasting glucose — hazard ratio (95% CI) per 10 mg/dl increase	1.244 (1.233–1.254)	1.202 (1.191–1.214)	1.088 (1.063–1.112)
C statistic	0.7546	0.7749	0.7816
Coronary heart disease			
Fasting glucose category — hazard ratio (95% CI)			
<100 mg/dl (reference)	1.00	1.00	1.00
100 to <126 mg/dl	1.19 (1.05–1.35)	1.03 (0.91–1.18)	1.01 (0.88–1.14)
≥126 mg/dl	1.80 (1.46–2.22)	1.29 (1.04–1.61)	1.00 (0.77–1.30)
P value for trend	<0.001	0.09	0.97
Fasting glucose — hazard ratio (95% CI) per 10 mg/dl increase	1.058 (1.034–1.082)	1.013 (0.986–1.041)	0.913 (0.877–0.950)
C statistic	0.6761	0.7329	0.7383
Ischemic stroke			
Fasting glucose category — hazard ratio (95% CI)			
<100 mg/dl (reference)	1.00	1.00	1.00
100 to <126 mg/dl	1.06 (0.84–1.34)	0.97 (0.76–1.23)	0.93 (0.73–1.18)
≥126 mg/dl	2.33 (1.68–3.24)	1.89 (1.33–2.69)	1.30 (0.85–1.98)
P value for trend	<0.001	0.02	0.63
Fasting glucose — hazard ratio (95% CI) per 10 mg/dl increase	1.089 (1.057–1.121)	1.068 (1.034–1.104)	0.950 (0.893–1.012)
C statistic	0.7109	0.7506	0.7594
Death from any cause			
Fasting glucose category — hazard ratio (95% CI)			
<100 mg/dl (reference)	1.00	1.00	1.00
100 to <126 mg/dl	1.11 (0.99–1.24)	1.07 (0.96–1.21)	1.06 (0.94–1.19)
≥126 mg/dl	1.42 (1.17–1.73)	1.31 (1.07–1.61)	1.16 (0.91–1.47)
P value for trend	0.001	0.03	0.20
Fasting glucose — hazard ratio (95% CI) per 10 mg/dl increase	1.035 (1.012–1.058)	1.021 (0.997–1.045)	0.980 (0.945–1.018)
C statistic	0.6865	0.7313	0.7314

Results

- no significant interaction between sex and glycated hemoglobin category for any of the clinical outcomes (P>0.20 for all interactions).
- no significant interaction between race and glycated hemoglobin value regarding the risk of coronary heart disease, ischemic stroke, or death from any cause (P>0.80 for all interactions).
- Blacks had lower hazard ratios for reporting a diagnosis of diabetes during the 15 years of follow-up.

Summary

- **A1c value ≥ 6.0%** : clinically useful marker for the development of
  - (1) Diabetes
  - (2) Cardiovascular disease and death.

- A1c remained associated with cardiovascular disease and death even after adjustment for the baseline fasting glucose levels

- A1c values have low intra-individual variability.

Conclusion

- A1c may be superior to fasting glucose for long term macrovascular risk stratification.

- The prognostic data may add to the evidence supporting the use of A1c as a diagnostic test for diabetes.

Discussion

- **limitations of this study:**
  - The reliance on single glycated hemoglobin and glucose measurements at baseline
  - a limited number of fasting glucose measurements during the follow-up period
  - lack of validation of self reported diabetes for the 15-year analyses

The recent ADA redefinition

- Considers many aspects of diagnostic testing and the economic burden, raises concerns about the possible delay in diagnosing diabetes, the ADA redefined the diagnosis of diabetes using **an A1c level $\geq$ 6.5%.**
- However, there are many debates about the appropriate A1C cut-off value for diagnosing diabetes throughout the world.

Hemoglobin A1C as a diagnostic tool for diabetes screening in Korea

최성희, 김태혁, 임 수, 장학철, 조남한
Seoul National University College of Medicine
Ajou University School of Medicine

Objective

- Recently, various levels of A1c have been suggested when screening for diabetes.
- However, there needs more consensus about the best level for screening especially for different ethnicities.
- We evaluated the usefulness of A1C level as a predictor of incident diabetes in a prospective, population-based cohort study.

Korean Genome Epidemiology Study (KoGES)

-Research Design and Methods-

- **Ansung cohort**
  - Population: 135,000
  - Farming area
  - Age: 40-69 yr
  - Subject: 5,018
- **Ansan cohort**
  - Population: 550,000
  - Industrial area
  - Age: 40-69 yr
  - Subject: 5,020

*** Eligibility criteria**

- 40-69 years,
- residence within the borders of the survey area for at least 6 months
- mental and physical ability to participate.

Measurements

Biochemical parameters

75g OGTT, fasting plasma glucose, total cholesterol, triglyceride, HDL- & LDL-cholesterol

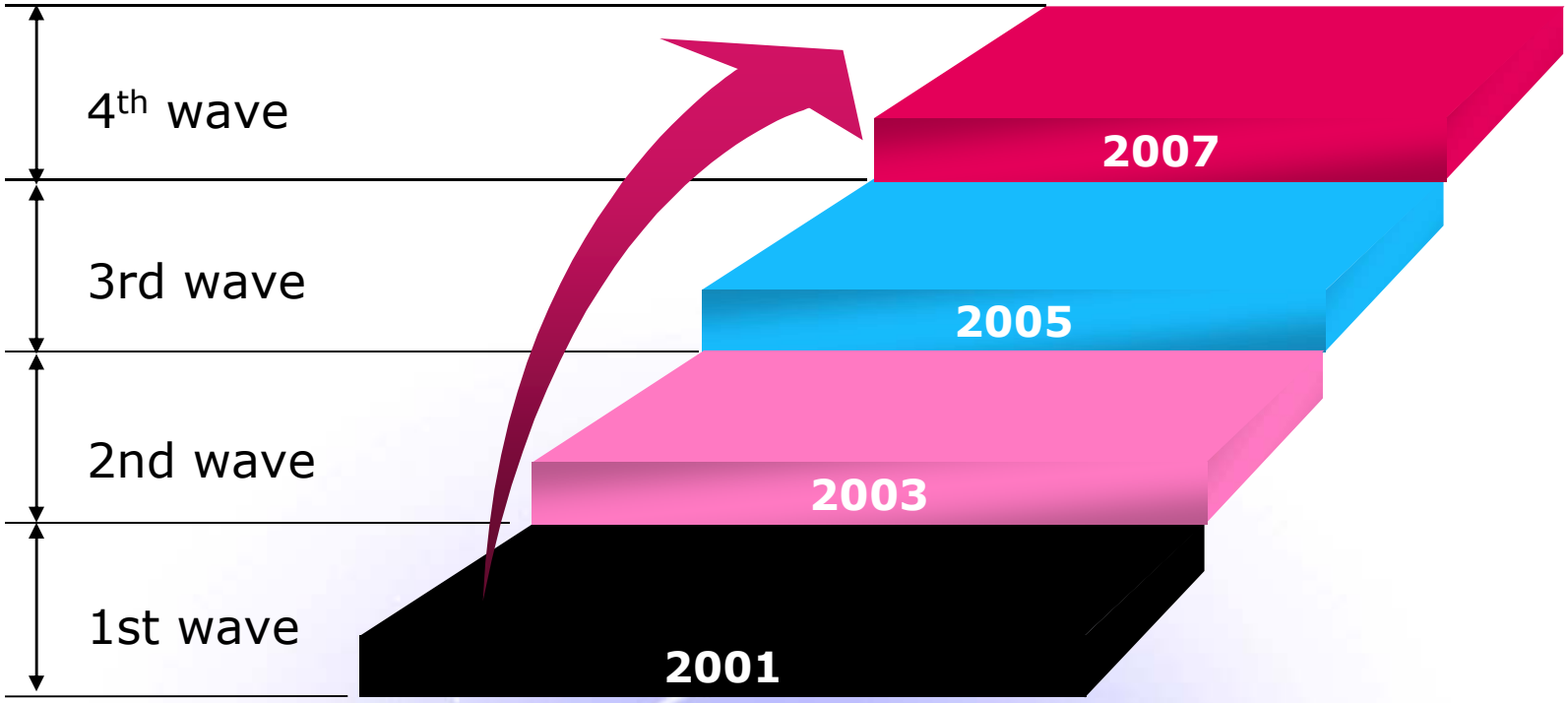
Demographic information

Age, gender, smoking and alcohol status, education, PMHx., FMHx., drug usage, & physical activity

Obesity index

Body weight, waist and hip circumference, body composition

Follow-up schedule



Research Design

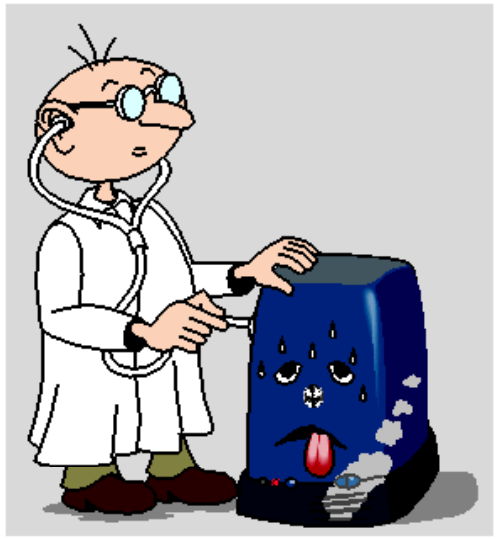
- From the Korean Genome Epidemiology Study , 10,038 participants aged 40–69 years were recruited.
- All subjects underwent a 75 g oral glucose tolerance test at baseline and at each biennial follow-up.
- HbA1c was measured by HPLC method (Rio-Rad, CA, USA).

Methods

- Subjects with prior history of diabetes (n=572) were excluded.

- The receiver operating characteristic (ROC) curve was used to evaluate the diagnostic accuracy of the A1C cut-off.

- The Cox proportional hazard model was used to predict diabetes at 6 years.

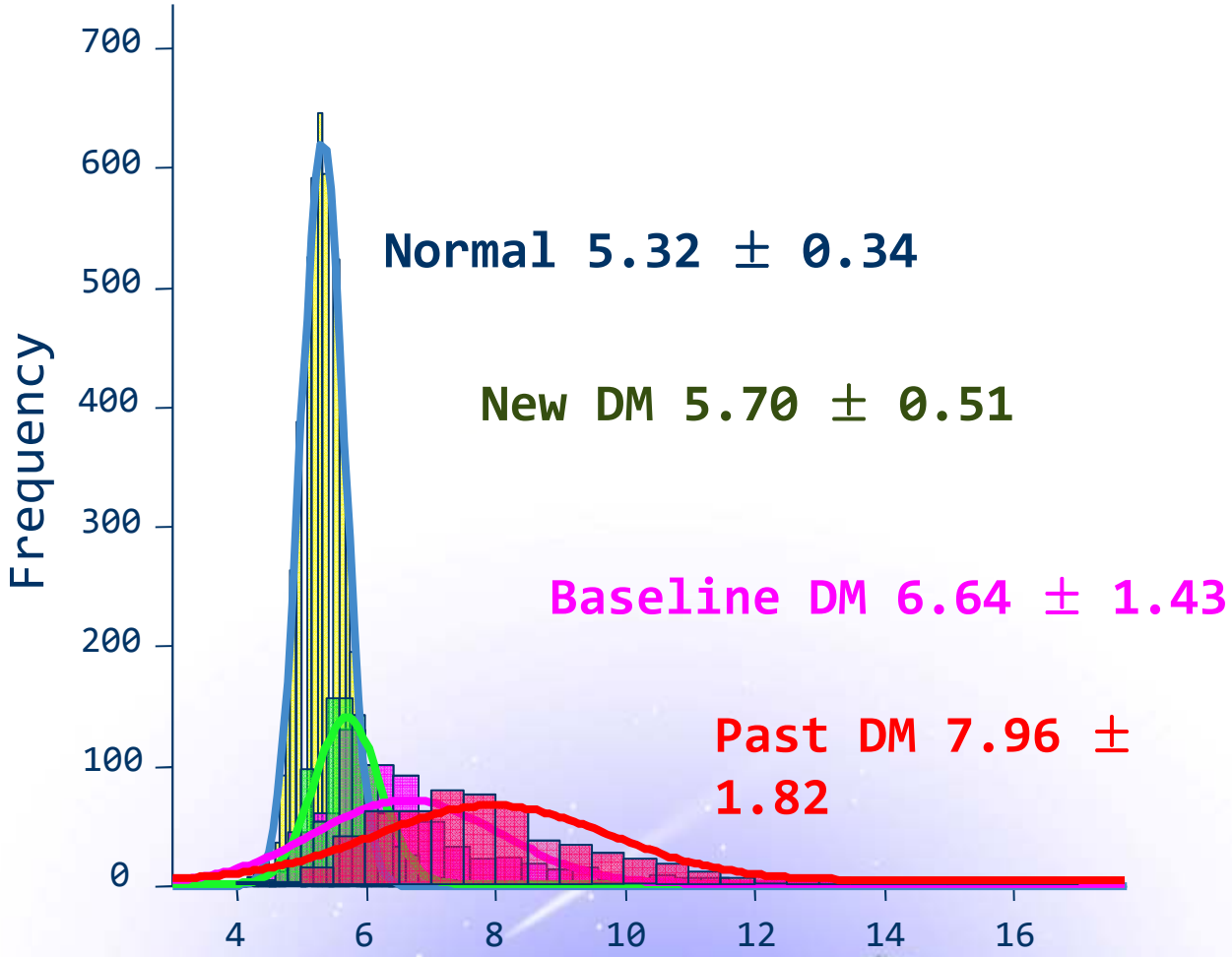


RESULTS

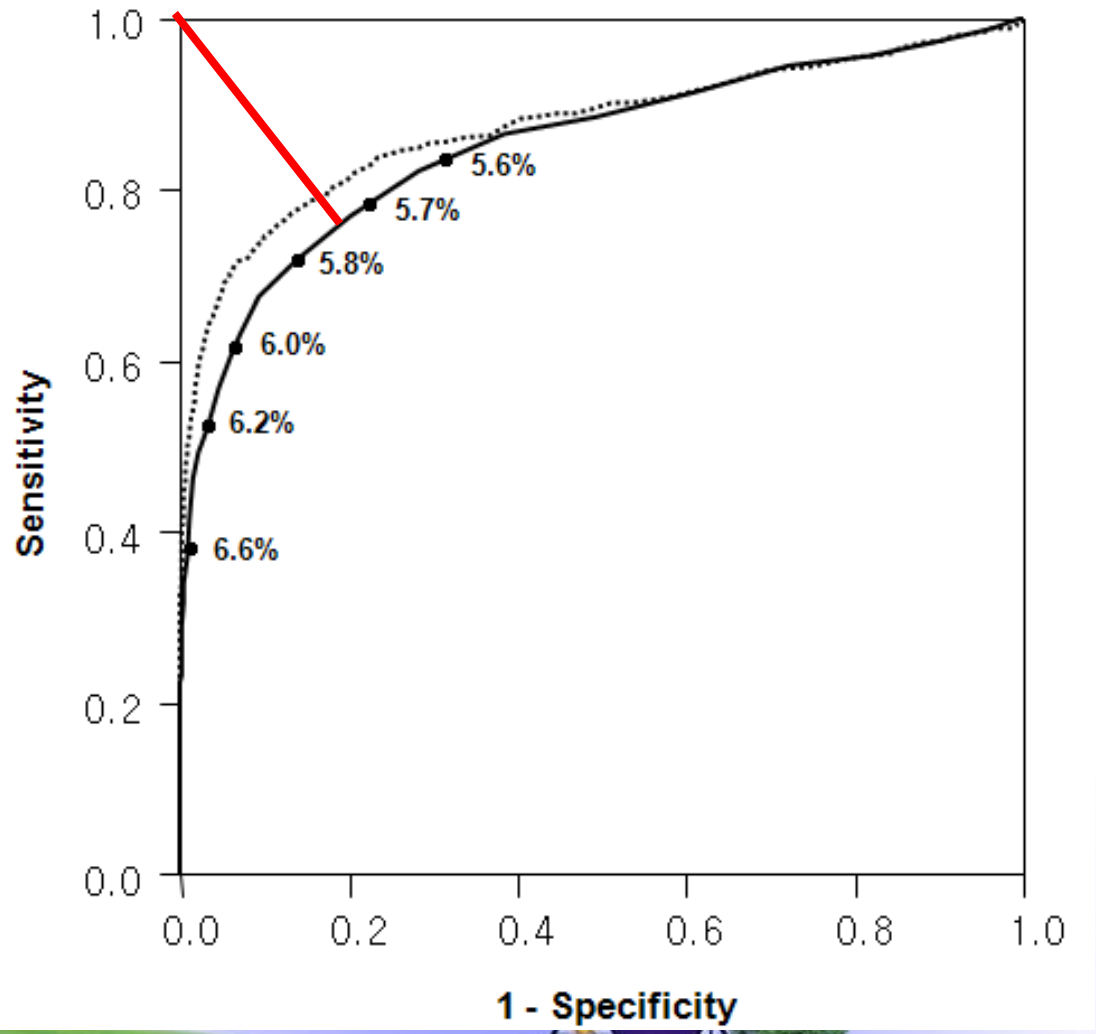
Baseline characteristics of subjects who developed (n=895) or did not develop diabetes at 6 years

	Men			Women		
	Nondiabetic (n = 2,328)	Diabetic (n = 478)	P	Nondiabetic (n = 2,722)	Diabetic (n = 417)	P
Age (years)	51.1 ± 8.4	52.5 ± 8.7		51.6 ± 8.7	54.1 ± 8.8	
BMI (kg/m^2)	24.1 ± 2.8	24.8 ± 3.1	< 0.001	24.6 ± 3.1	26.0 ± 3.3	< 0.001
Waist circumference (cm)	83 ± 7	85 ± 8	< 0.001	81 ± 9	85 ± 10	< 0.001
SBP (mmHg)	116 ± 16	121 ± 17	< 0.001	115 ± 18	123 ± 20	< 0.001
DBP (mmHg)	76 ± 11	78 ± 11	< 0.001	73 ± 11	77 ± 12	< 0.001
Fasting plasma glucose (mmol/l)	4.7 ± 0.5	5.1 ± 0.6	< 0.001	4.6 ± 0.4	4.9 ± 0.6	< 0.001
2-h glucose (mmol/l)	6.1 ± 1.6	8.0 ± 1.9	< 0.001	6.6 ± 1.5	8.4 ± 1.6	< 0.001
A1C(%)	5.3 ± 0.3	5.6 ± 0.5	< 0.001	5.3 ± 0.3	5.8 ± 0.5	< 0.001
Fasting insulin (pmol/l)	35.8 ± 25.4	38.3 ± 28.1	0.016	41.1 ± 30.6	46.1 ± 27.2	< 0.001
HOMA-IR	1.2 ± 0.9	1.4 ± 1.1	< 0.001	1.4 ± 1.1	1.7 ± 1.0	< 0.001
HOMA-B	105.3 ± 123.4	84.5 ± 223.2	< 0.001	139.6 ± 142.2	120.9 ± 150.0	<0.001
Fhx . of diabetes (%)	9.2	14.0	< 0.001	10.9	17.5	< 0.001
Smoker (%)	46.1	48.2	0.319	2.4	5.6	0.001

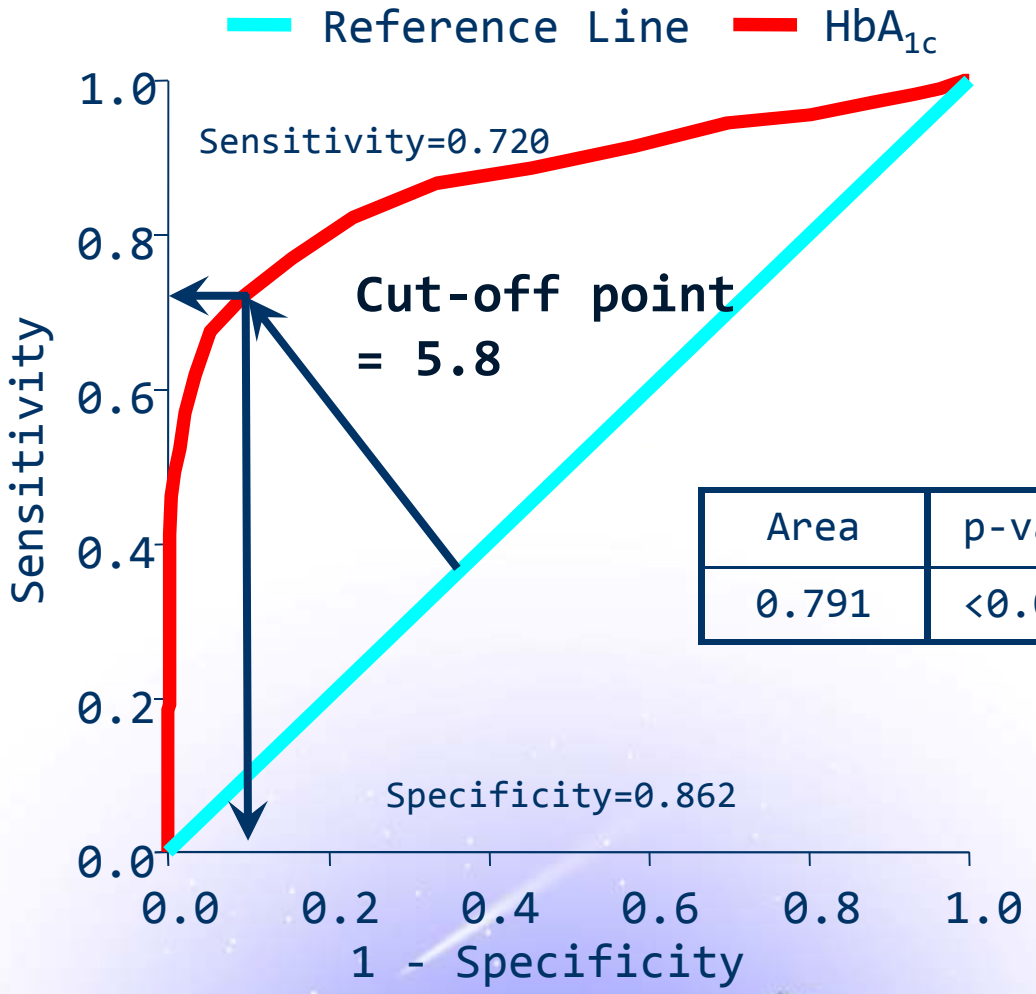
Hba1c level according to diagnosis of DM



ROC curves for A1C level corresponding undiagnosed diabetes at baseline

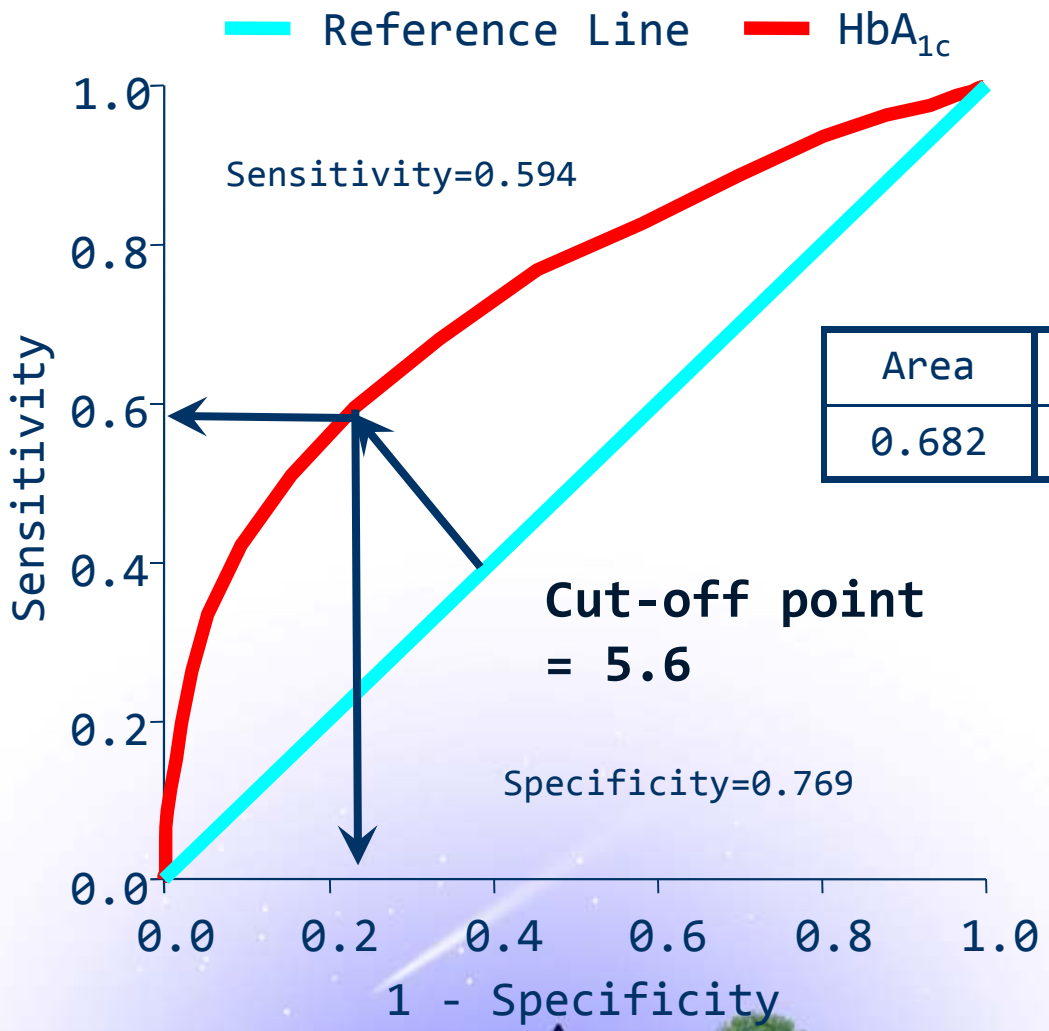


HbA1c of baseline DM



Area	p-value
0.791	<0.0001

HbA1c of new DM



Area	p-value
0.682	<0.0001

Cut-off point = 5.6

A1C cutoff for detecting type 2 diabetes

A1C cutoff (%)	Baseline undiagnosed diabetes					Incident diabetes in 6 year follow up				
			Predictive Value		Area under ROC curve			Predictive value		Area under ROC curve
	Sensitivity	Specificity	Positive	Negative		Sensitivity	Specificity	Positive	Negative	
5.6	0.822	0.717	0.174	0.982	0.770	0.594	0.769	0.313	0.914	0.682
5.7	0.770	0.797	0.216	0.979	0.784	0.508	0.847	0.370	0.907	0.678
5.8	0.720	0.862	0.274	0.977	0.791	0.420	0.908	0.448	0.898	0.664
6.0	0.619	0.935	0.411	0.971	0.777	0.263	0.967	0.586	0.881	0.615
6.2	0.523	0.968	0.544	0.965	0.746	0.152	0.987	0.677	0.868	0.570
6.6	0.372	0.992	0.771	0.956	0.682	0.051	0.999	0.885	0.856	0.525

The relative risk of 6 year incidence of type 2 diabetes according to A1C status

- Cox-proportional hazard model -

	Men			Women		
	RR	95% CI	P-value	RR	95% CI	P-value
A1C ≥ 5.8% (*vs* < 5.8%) in entire study population						
Model A*	4.6	(3.81-5.54)	< 0.001	5.5	(4.54-6.75)	< 0.001
Model B†	4.3	(3.53-5.20)	< 0.001	4.9	(3.96-5.99)	< 0.001
Model C‡	**3.0**	(2.48-3.74)	< 0.001	**3.6**	(2.89-4.44)	< 0.001

*Age adjusted. †Model A + Waist circumference, family history of diabetes, living in urban area, hypertension, smoking and alcohol intake adjusted. ‡Model B + Triglycerides (log), HDL cholesterol, HOMA-IR (log), HOMA-B (log) and hs CRP (log) adjusted.

The relative risk of 6 year incidence of type 2 diabetes according to A1C status

- Cox-proportional hazard model -

	Men			Women		
	RR	95% CI	P-value	RR	95% CI	P-value
A1C ≥5.8% (*vs* <5.8%) in entire study population						
Model A*	4.60	(3.81-5.54)	< 0.001	5.54	(4.54-6.75)	< 0.001
Model B†	4.28	(3.53-5.20)	< 0.001	4.87	(3.96-5.99)	< 0.001
Model C‡	3.04	(2.48-3.74)	< 0.001	3.58	(2.89-4.44)	< 0.001
A1C ≥5.8% (*vs* <5.8%) in subjects with IFG						
Model A*	3.15	(2.13-4.64)	< 0.001	6.29	(3.03-13.05)	< 0.001
Model B†	3.57	(2.36-5.41)	< 0.001	5.99	(2.83-12.66)	< 0.001
Model C‡	3.47	(2.27-5.29)	< 0.001	5.15	(2.39-11.11)	< 0.001

*Age adjusted. †Model A + Waist circumference, family history of diabetes, living in urban area, hypertension, smoking and alcohol intake adjusted. ‡Model B + Triglycerides (log), HDL cholesterol, HOMA-IR (log), HOMA-B (log) and hs CRP (log) adjusted.

Summary

- At 6 years, 895 (10.2%) had developed incident diabetes (annual incidence rate = 1.7).
- The cut-off A1C of 5.8% was the most accurate for predicting 6-year incident diabetes.
- After multivariate adjustment, men with baseline A1C ≥5.8% had a 3.0-fold increased risk and women had a 3.6-fold increased risk of new-onset diabetes compared with those with A1C<5.8%.

Consideration points

- All participants were enrolled from a Korean rural and urban community of homogeneous ethnic background.
- At present, the significant differences in A1c level is not clear in different races.
- The use of different A1C values according to ethnicity is not currently recommended.

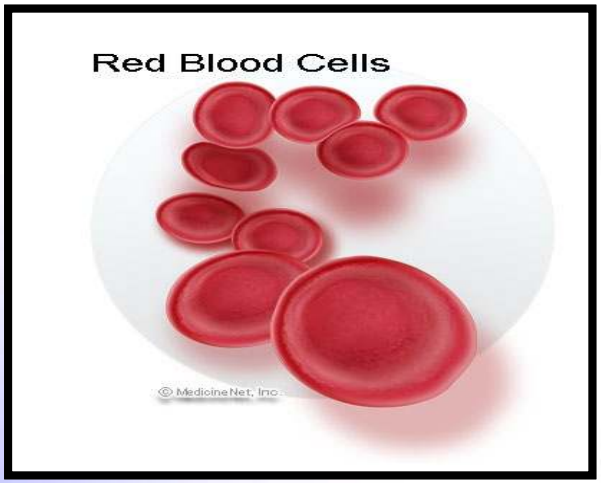
A1c

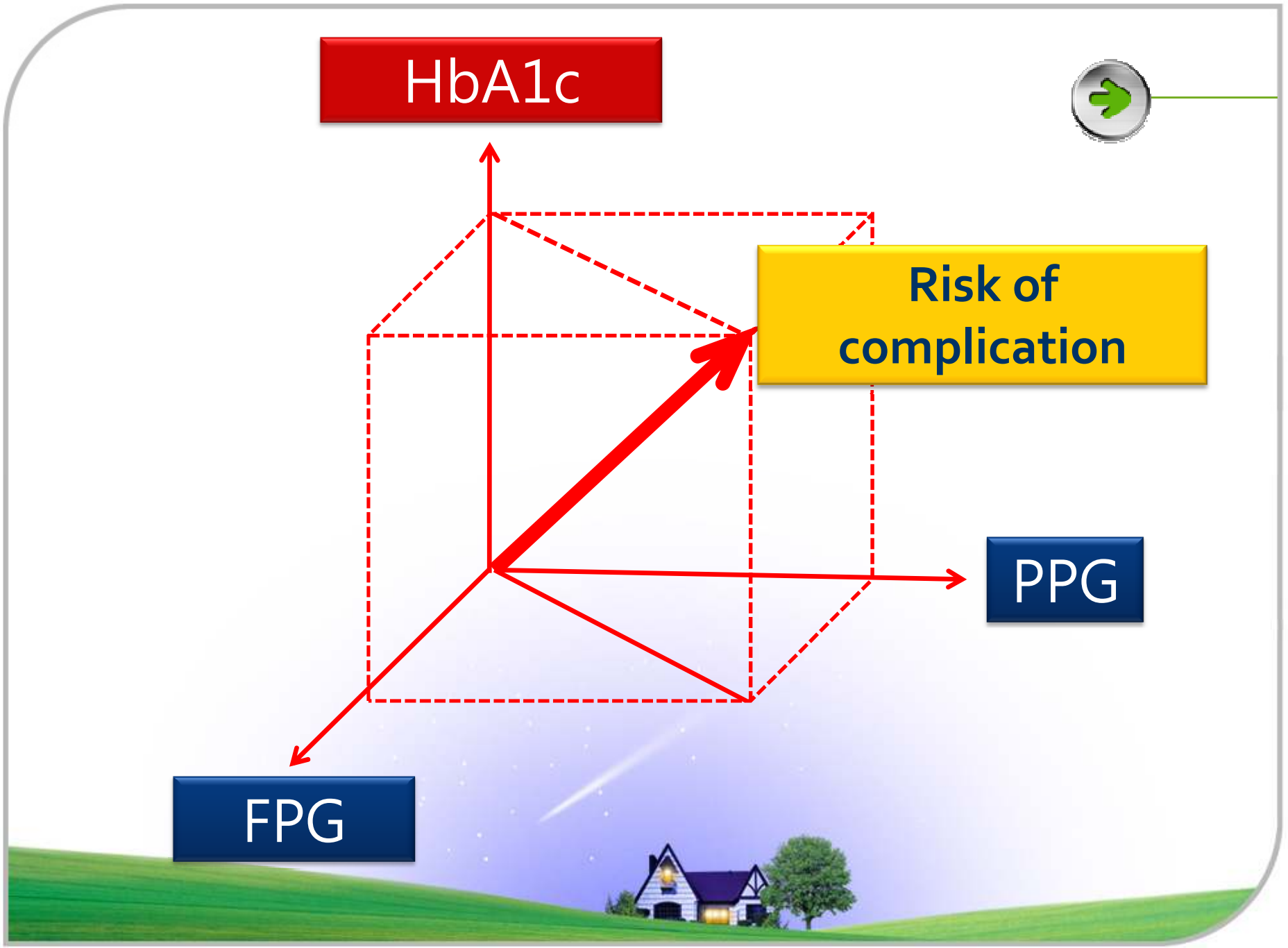
Several advantages as a diagnostic test

- High repeatability
- Can be assessed in the nonfasting state
- Preferred test for monitoring glucose control

Some limitations

- Standardization
- Cost
- Discrepancy with glucose level
- Hemoglobinopathy




HbA1c
Risk of complication
PPG
FPG

Conclusions

- A1C is an effective and convenient method for diabetes screening.
- An A1C cut-off of 5.8% may identify subjects with undiagnosed diabetes and with high risk of future diabetes in Korean.
- This value may possibly be used to identify individuals for early intervention.

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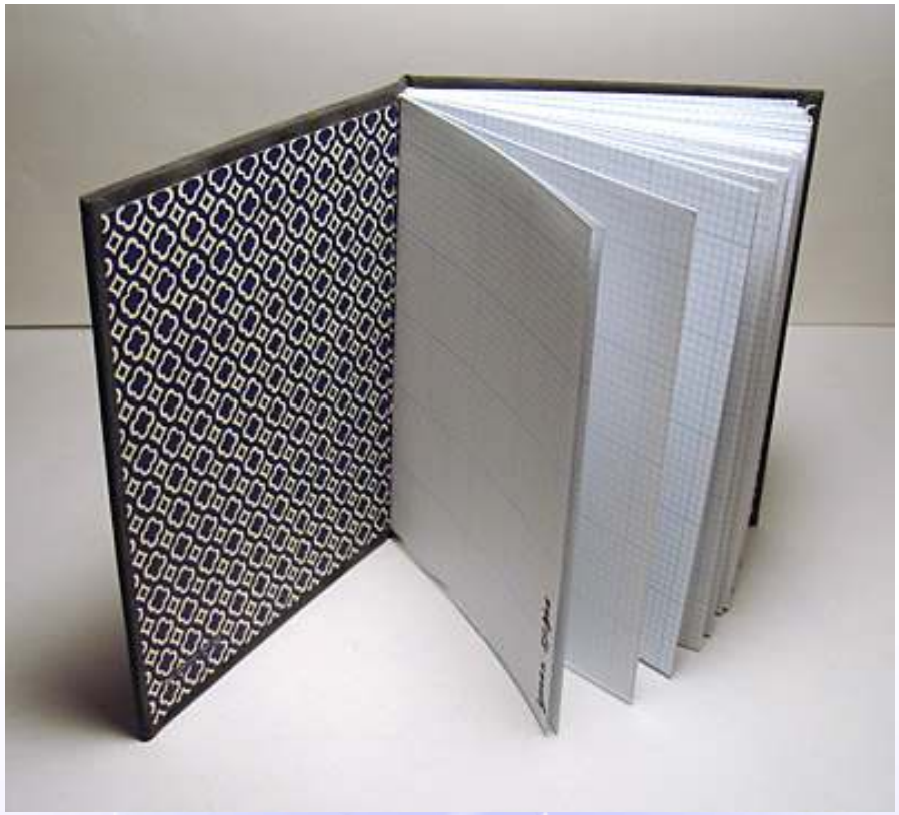
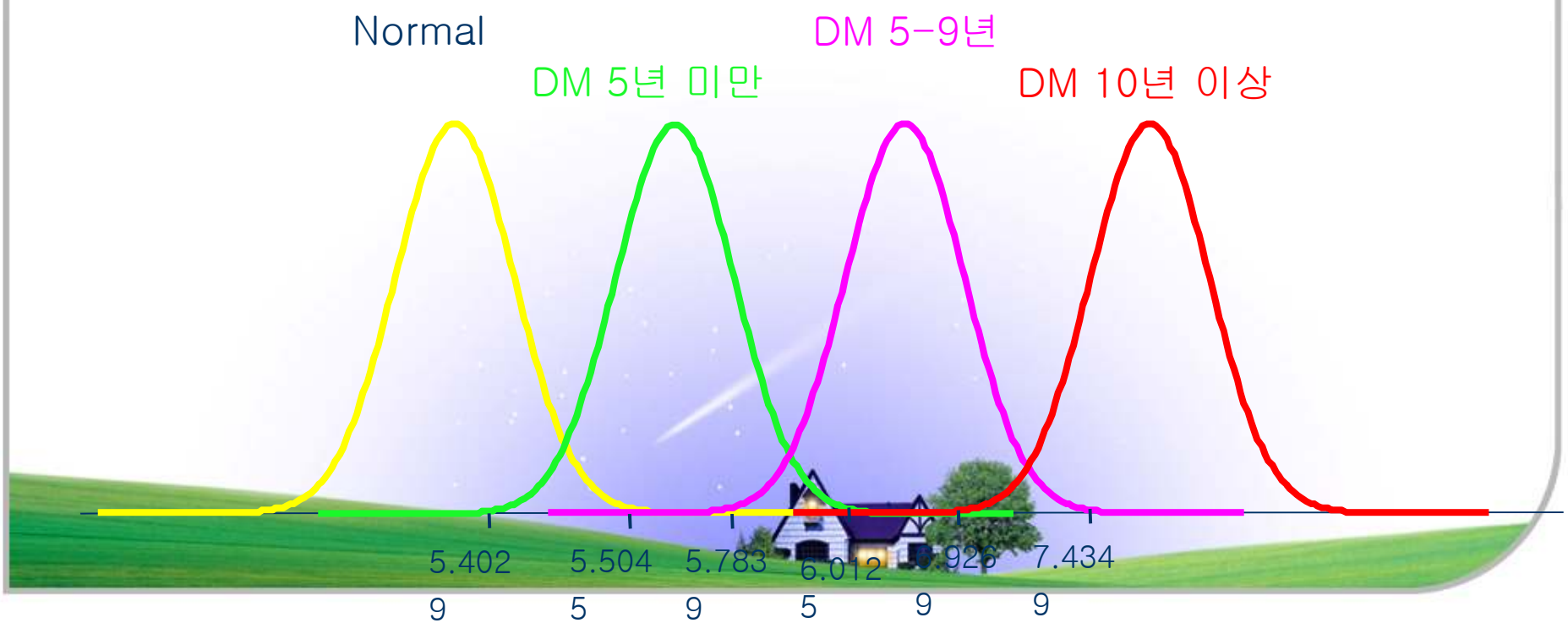
  - Seoul National University College of Medicine, Department of Internal Medicine

Many thanks for your attention



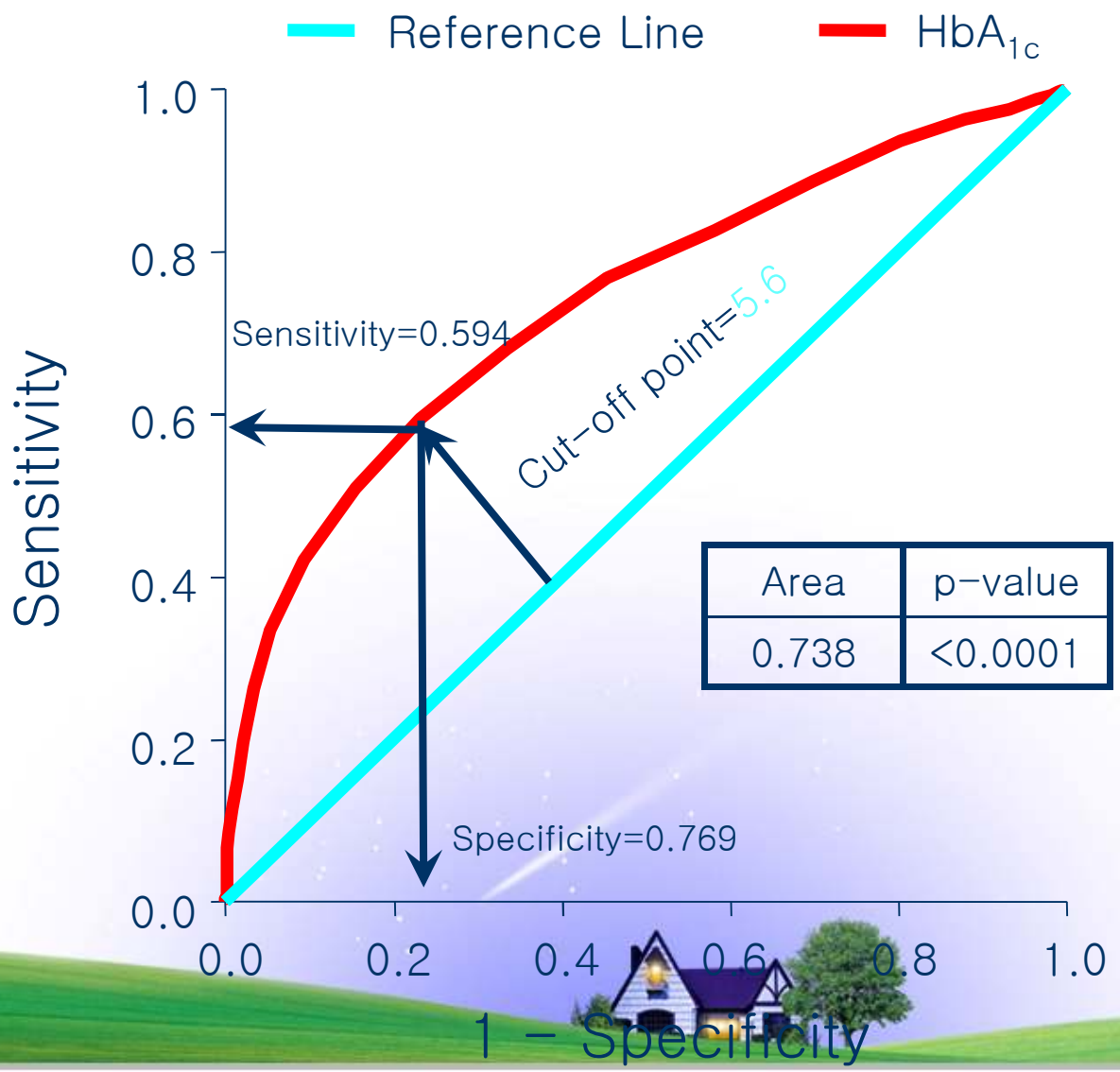
당뇨병 발병 기간별 Hba1c 분포



당뇨병 진단별 망막증 상태

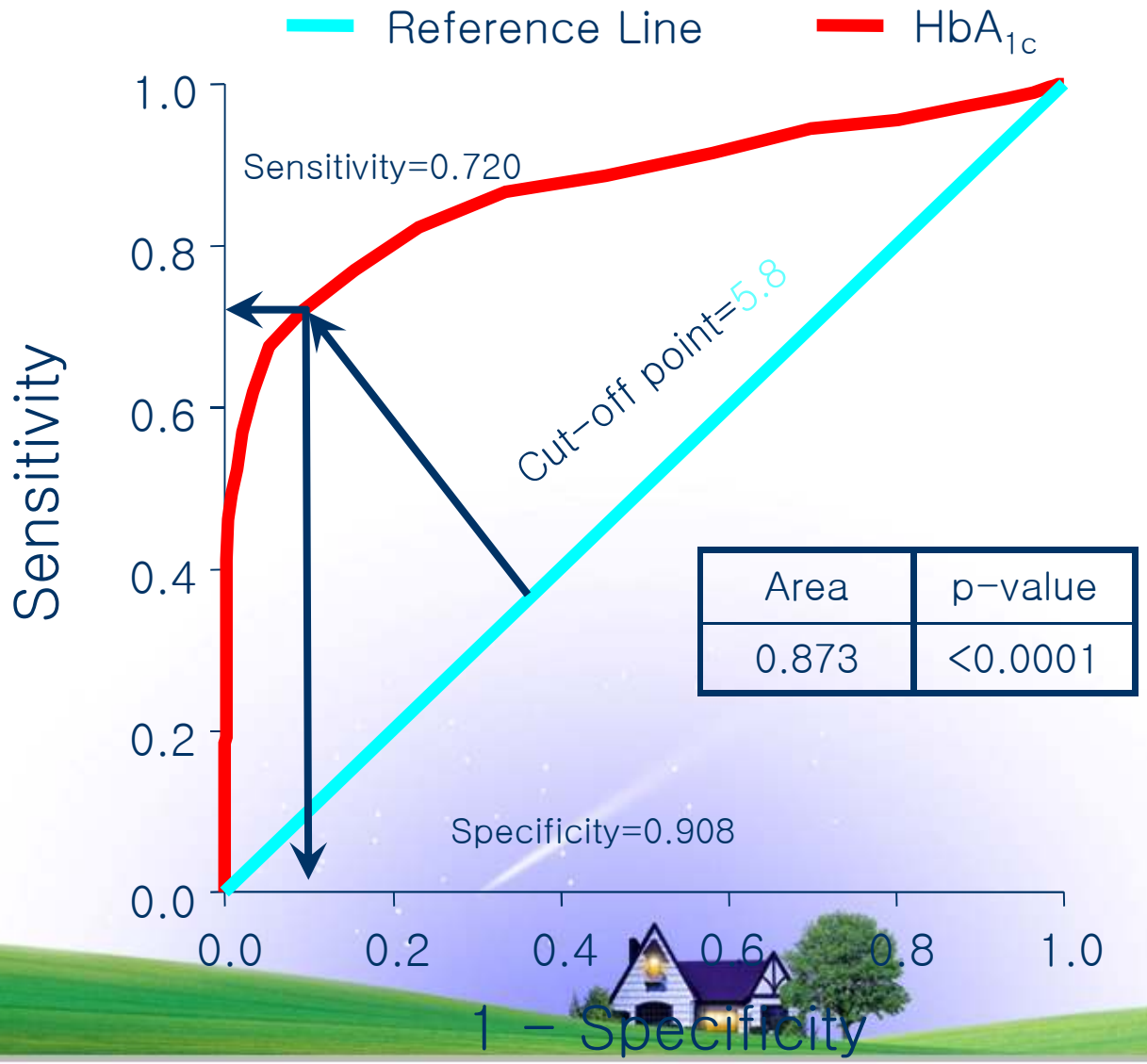
	당뇨병 구분				p-value
	Normal	New DM	Base DM	DM(past)	
NDR	2,631(79.6%)	322(9.7%)	182(5.5%)	171(5.2%)	<0.001
NPDR	1(2.2%)	5(10.9%)	7(15.2%)	33(71.7%)	
PDR	0(0.0%)	0(0.0%)	0(0.0%)	8(1000.0%)	
Total	2,632(78.3%)	327(9.7%)	189(5.6%)	212(6.3%)	

New DM for HbA_{1c}



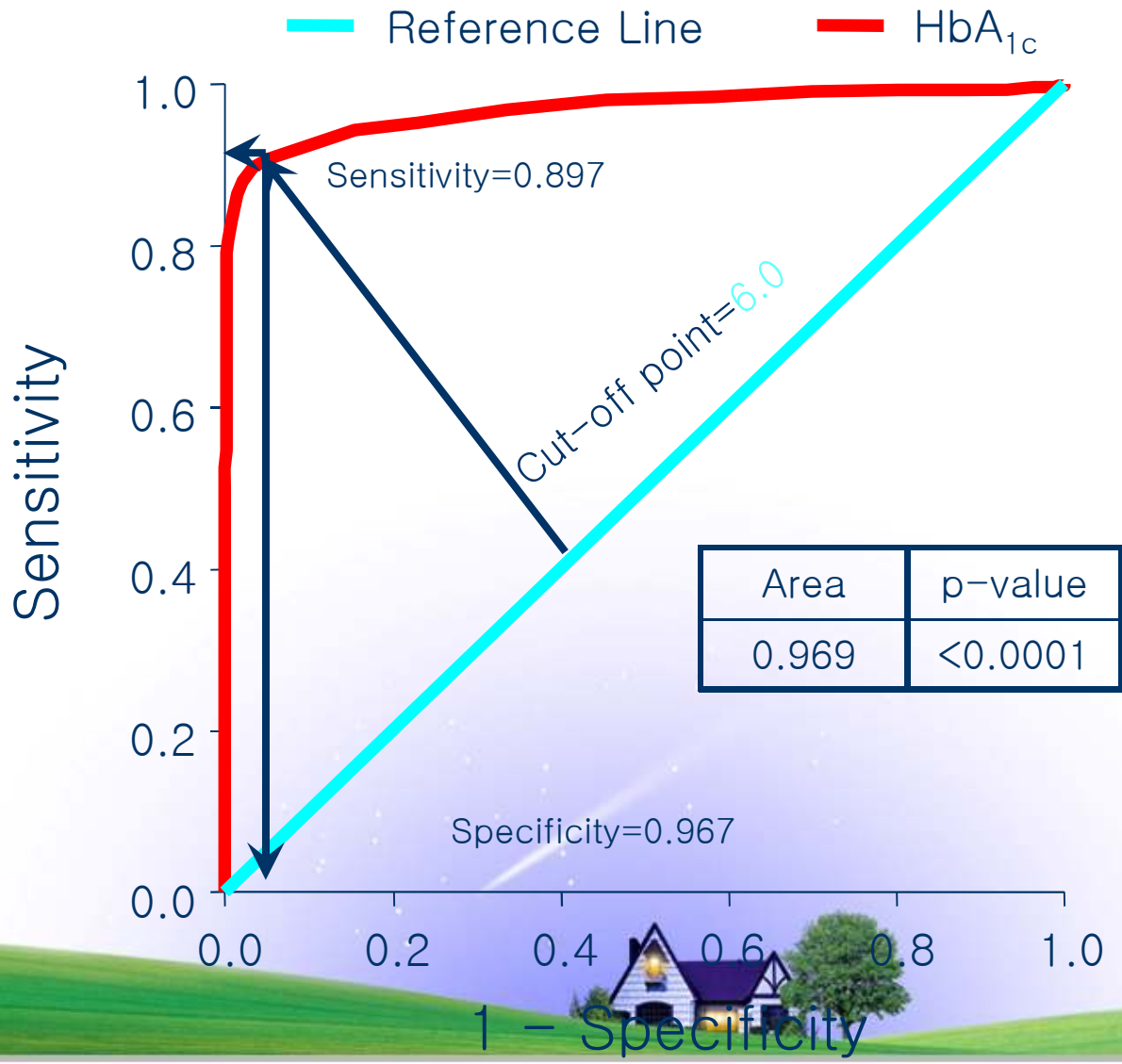
Area	p-value
0.738	<0.0001

Base DM for HbA_{1c}



Area	p-value
0.873	<0.0001

DM(past) for HbA_{1c}



Area	p-value
0.969	<0.0001

SURVIVAL AS A FUNCTION OF HBA1C IN PEOPLE WITH TYPE 2 DIABETES: A RETROSPECTIVE COHORT STUDY

Craig J Currie, John R Peters, Aodan Tynan, Marc Evans, Robert J Heine, Oswaldo L Bracco, Tony Zagar, Chris D Poole

Lancet 2010; 375: 481–89

Introduction

- **The main objective for care of patients with DM**
  - → Risk of microvasular & macrovascular complications
- **Control of glycemia**
  - Reduce risk of longterm microvascular complications
  - → Potentially raised mortality rates associated with intensive glycaemic control
- **Intensive glycemic control**

  → Positive effects on cardiovascular endpoints ?
- **To assess the association between all-cause mortality and HbA1c in patients with type 2 diabetes**

Methods

- General Practice Research Database (GPRD)
- 1986.11~2008.11
  - Demographic information, medical history, test results, and additional health-related data (smoking, drug, mortality)

DM
Age ≥ 50

- **Cohort 1** : Monotherapy → Combination(SU + metformin)
- **Cohort 2** : Initiated on insulin (+ - OAD)

- Post-index mean HbA1c (glycaemic control)
- → Death or Large-vessel disease
  - Myocardial infarction, stroke, coronary revascularisation,
  - carotid or peripheral arterial revascularisation, or angina of cardiac origin

Methods

- **Primary outcome**
  - All-cause mortality
- **Secondary outcome**
  - First major cardiovascular event
- **Statistical methods**
  - Cox proportional hazards models
  - Covariates: Age, sex, smoking, post-index chol, BMI, comorbidity

Baseline charateristics

Cohort 1, 27965 Pts, baseline HbA1c 9.0%

	HbA_{1c} deciles										All (n=27965)
	1 (n=3513)	2 (n=3501)	3 (n=3374)	4 (n=3136)	5 (n=2884)	6 (n=2684)	7 (n=2437)	8 (n=2334)	9 (n=2133)	10 (n=1969)	
HbA_{1c} post index* (% total haemoglobin)	6·42% (3·30–6·72)	6·94% (6·73–7·11)	7·27% (7·12–7·40)	7·54% (7·41–7·68)	7·82% (7·69–7·96)	8·11% (7·97–8·26)	8·44% (8·27–8·63)	8·85% (8·64–9·11)	9·41% (9·12–9·84)	10·47% (9·85–16·20)	7·73% (3·30–16·20)
Men	1973 (56%)	1939 (55%)	1928 (57%)	1824 (58%)	1699 (59%)	1596 (60%)	1410 (58%)	1370 (59%)	1254 (59%)	1055 (54%)	16048 (57%)
Age† (years)	67·4	66·3	65·5	64·7	64·0	63·7	62·7	62·1	61·0	59·7	64·1
Previous SBP‡ (mm Hg)	145 (17)	144 (16)	144 (16)	144 (16)	144 (17)	143 (17)	144 (17)	144 (17)	144 (17)	145 (18)	144 (17)
Smoked ever (%)	2178 (62%)	2240 (64%)	2159 (64%)	1976 (63%)	1846 (64%)	1745 (65%)	1487 (61%)	1447 (62%)	1322 (62%)	1201 (61%)	17618 (63%)
Previous total cholesterol‡ (mmol/L)	5·2 (1·0)	5·3 (1·0)	5·3 (1·0)	5·4 (1·1)	5·4 (1·0)	5·5 (1·1)	5·6 (1·1)	5·6 (1·1)	5·7 (1·2)	5·8 (1·3)	5·4 (1·1)
Male weight (kg)	90 (16)	89 (16)	88 (15)	89 (16)	90 (16)	90 (16)	91 (17)	91 (17)	92 (18)	93 (19)	90 (16)
Female weight (kg)	79 (17)	79 (16)	78 (16)	78 (16)	78 (16)	79 (17)	79 (17)	81 (17)	81 (18)	84 (19)	79 (17)
Previous LVD§	892 (25%)	846 (24%)	760 (23%)	702 (22%)	629 (22%)	620 (23%)	552 (23%)	466 (20%)	403 (19%)	360 (18%)	6230 (22%)
Diabetes duration¶ (years)											
Mean (SD)	5·3 (4·2)	5·3 (4·1)	5·5 (4·1)	5·4 (3·9)	5·4 (3·9)	5·6 (4·1)	5·6 (4·0)	5·5 (4·0)	5·2 (3·7)	5·4 (3·9)	5·4 (4·0)
Median (IQR)	4·2 (2·2–7·3)	4·2 (2·3–7·1)	4·5 (2·4–7·4)	4·5 (2·4–7·4)	4·4 (2·4–7·4)	4·6 (2·4–7·4)	4·8 (2·5–7·8)	4·6 (2·5–7·5)	4·3 (2·4–7·0)	4·4 (2·3–7·6)	4·4 (2·4–7·4)
Previous vision problem	502 (14%)	486 (14%)	509 (15%)	424 (14%)	351 (12%)	343 (13%)	278 (11%)	246 (11%)	253 (12%)	212 (11%)	3604 (13%)
Creatinine >130 µmol/L‖	243 (7%)	204 (6%)	184 (6%)	167 (5%)	133 (5%)	111 (4%)	110 (5%)	86 (4%)	71 (3%)	57 (3%)	1366 (5%)
Deaths	301 (9%)	238 (7%)	231 (7%)	207 (7%)	190 (7%)	179 (7%)	175 (7·%)	168 (7%)	161 (8%)	185 (9%)	2035 (7%)

Achieved HbA_{1c} was the mean of any values recorded between the index date and death or censor. Data are median (range), n (%), mean (SD), or median (IQR) unless otherwise stated. HbA_{1c}=glycated haemoglobin. SBP=systolic blood pressure. LVD=large-vessel disease. *Mean HbA_{1c} recorded between study index date and event or censor date. †At index date. ‡Mean of all observations in year before index date. §Clinically emergent large-vessel disease before index date (defined by ACCORD[6] trial criteria). ¶Duration of diabetes before index date from first relevant clinical event. ‖Any record of serum creatinine test result >130 µmol/L before index date.

Table 1: **Baseline characteristics of cohort 1 (oral hypoglycaemic agents) by baseline, stratified by mean HbA_{1c} decile group**

Baseline charateristics

Cohort 2, 20005 Pts, baseline HbA1c 10.0%

	HbA_{1c} deciles										All (n=20 005)
	1 (n=1289)	2 (n=1291)	3 (n=1424)	4 (n=1661)	5 (n=1878)	6 (n=2148)	7 (n=2354)	8 (n=2463)	9 (n=2660)	10 (n=2837)	
HbA_{1c} post index* (% total haemoglobin)	6·38% (3·97–6·72)	6·95% (6·73–7·11)	7·28% (7·12–7·40)	7·55% (7·41–7·68)	7·83% (7·69–7·96)	8·11% (7·97–8·26)	8·45% (8·27–8·63)	8·87% (8·64–9·11)	9·42% (9·12–9·84)	10·56% (9·85–18·80)	8·31% (3·97–18·80)
Men	680 (53%)	726 (56%)	780 (55%)	911 (55%)	1035 (55%)	1128 (53%)	1262 (54%)	1315 (53)	1320 (50%)	1409 (50%)	10 566 (53%)
Age† (years)	65·9 (11·2)	66·3 (10·3)	65·5 (10·0)	64·9 (10·5)	64·4 (10·5)	64·7 (10·5)	63·4 (10·6)	63·1 (10·9)	62·3 (11·3)	60·3 (11·5)	63·6 (11·0)
Previoius SBP‡ (mmHg)	145 (19)	145 (18)	145 (18)	144 (18)	144 (18)	144 (18)	143 (17)	143 (18)	143 (18)	142 (18)	143 (18)
Smoked ever (%)	786 (61%)	852 (66%)	897 (63%)	1030 (62%)	1202 (64%)	1332 (62%)	1483 (63%)	1527 (62%)	1649 (62%)	1731 (61%)	12603 (63%)
Total cholesterol‡ (mmol/L)	5·3 (1·2)	5·3 (1·1)	5·3 (1·1)	5·3 (1·0)	5·4 (1·1)	5·4 (1·1)	5·4 (1·1)	5·5 (1·2)	5·6 (1·2)	5·6 (1·2)	5·5 (1·2)
Male weight‡ (kg)	88 (17)	87 (16)	86 (16)	88 (16)	86 (16)	86 (16)	87 (16)	87 (17)	88 (17)	90 (19)	88 (17)
Female weight‡ (kg)	77 (18)	79 (17)	79 (18)	77 (17)	79 (17)	77 (16)	78 (17)	79 (17)	79 (19)	81 (19)	79 (18)
Previous LVD§	459 (36%)	435 (34%)	411 (29%)	505 (30%)	569 (30%)	625 (29%)	733 (31%)	711 (29%)	766 (29%)	723 (26%)	5937 (30%)
Diabetes duration¶ (years)											
Mean (SD)	6·8 (5·2)	7·5 (5·1)	8·1 (5·4)	7·8 (5·3)	8·0 (5·1)	8·2 (5·1)	8·0 (5·0)	7·9 (5·1)	7·9 (5·0)	7·3 (4·9)	7·8 (5·1)
Median (IQR)	5·9 (2·6–9·9)	6·9 (3·4–10·8)	7·4 (3·8–11·5)	7·1 (3·5–11·1)	7·2 (4·0–11·3)	7·4 (4·3–11·4)	7·4 (4·0–11·2)	7·2 (3·8–11·2)	7·2 (4·0–11·2)	6·5 (3·4–10·4)	7·1 (3·7–11·0)
Previous vision problems	251 (20%)	272 (21%)	320 (23%)	341 (21%)	380 (20%)	501 (23%)	524 (22%)	523 (21%)	557 (21%)	556 (20%)	4225 (21%)
Creatinine >130 µmol/L‖	205 (16%)	185 (14%)	182 (13%)	215 (13%)	203 (11%)	248 (12%)	213 (9%)	251 (10%)	257 (10%)	250 (9%)	2209 (11%)
Deaths	232 (18%)	204 (16%)	209 (15%)	192 (12%)	211 (11%)	271 (13%)	305 (13%)	334 (14%)	404 (15%)	472 (17%)	2834 (14%)

Achieved HbA_{1c} was the mean of any values recorded between the index date and death or censor. Data are median (range), n (%), mean (SD), or median (IQR). HbA_{1c}=glycated haemoglobin. SBP=systolic blood pressure. LVD=large-vessel disease. *Mean HbA_{1c} recorded between study index date and event date or censor date. †At index date. ‡Mean of all observations in year before index date. §Clinically emergent large-vessel disease before index date (defined by ACCORD[6] trial criteria). ¶Duration of diabetes before index date from first relevant clinical event. ‖Any record of serum creatinine test result >130 µmol/L before index date.

Table 2: **Baseline characteristics of cohort 2 (insulin treated) at baseline, stratified by mean HbA_{1c} decile group**

Results

- **Mean follow-up** **Unadjusted mortality**
  - Cohort 1: 4.5yrs → 16.2 death/1000person/yrs
  - Cohort 2: 5.2yrs → 27.2 death/1000person/yrs

- **Increased unadjusted mortality in the lowest and highest HbA1c deciles**

- **Patients included in decile 4 (HbA1c 7.5%) had the lowest hazard of death across the range of HbA1c deciles**

	Model 1: all patients		Model 2: cohort 1 (met plus sulph)		Model 3: cohort 2 (insulin-based regimens)	
	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
Age at baseline (years)	1·08 (1·08–1·09)	<0·0001	1·10 (1·09–1·11)	<0·0001	1·07 (1·07–1·08)	<0·0001
Sex (men *vs* women)	1·34 (1·26–1·43)	<0·0001	1·25 (1·12–1·38)	<0·0001	1·41 (1·29–1·54)	<0·0001
Smoking status (ever *vs* never)	1·10 (1·03–1·18)	0·0063	1·18 (1·06–1·31)	0·0019	1·05 (0·96–1·15)	0·2760
Mean total cholesterol (mmol/L)	1·30 (1·26–1·35)	<0·0001	1·40 (1·33–1·47)	<0·0001	1·23 (1·17–1·28)	<0·0001
Previous LVD (yes *vs* no)	1·21 (1·13–1·30)	<0·0001	1·28 (1·15–1·43)	<0·0001	1·18 (1·08–1·29)	<0·004
Cohort (insulin *vs* OHA combination)	1·49 (1·39–1·59)	<0·0001		NA		NA
Age adjusted Charlson (C) index, C 1 (reference)						
C 2	1·52 (1·40–1·64)	<0·0001	1·55 (1·38–1·74)	<0·0001	1·51 (1·35–1·68)	<0·0001
C 3	2·06 (1·88–2·26)	<0·0001	1·86 (1·61–2·15)	<0·0001	2·17 (1·92–2·45)	<0·0001
C 4	2·79 (2·48–3·14)	<0·0001	2·57 (2·12–3·13)	<0·0001	2·88 (2·48–3·34)	<0·0001
C 5	3·66 (3·11–4·3)	<0·0001	2·15 (1·52–3·03)	<0·0001	4·31 (3·57–5·21)	<0·0001
C 6	3·16 (2·42–4·13)	<0·0001	1·83 (1·03–3·26)	0·0405	3·72 (2·74–5·04)	<0·0001
C 7	4·71 (3·28–6·76)	<0·0001	5·67 (2·34–13·75)	<0·0001	4·62 (3·10–6·88)	<0·0001
C 8	8·17 (4·61–14·49)	<0·0001	7·39 (2·36–23·09)	0·0006	8·97 (4·61–17·45)	<0·0001
C 9	3·10 (1·29–7·46)	0·0117	7·06 (2·27–22·01)	0·0007	1·95 (0·49–7·81)	0·3480
HbA_{1c} as mean of values by decile*						
D 1 (mp 6·4%)	1·52 (1·32–1·76)	<0·0001	1·30 (1·07–1·58)	0·0072	1·79 (1·45–2·22)	<0·0001
D 2 (mp 6·9%)	1·24 (1·07–1·44)	0·0036	1·07 (0·88–1·31)	0·4882	1·45 (1·17–1·80)	0·0007
D 3 (mp 7·3%)	1·18 (1·02–1·37)	0·0234	1·03 (0·85–1·26)	0·7716	1·35 (1·09–1·67)	0·0001
Reference D 4 (mp 7·5%)	..	..	..	..	..	..
D 5 (mp 7·8%)	1·01 (0·87–1·17)	0·8809	1·06 (0·86–1·3)	0·5872	0·98 (0·79–1·21)	0·8564
D 6 (mp 8·1%)	1·07 (0·93–1·24)	0·3586	0·99 (0·80–1·23)	0·9162	1·15 (0·95–1·41)	0·1608
D 7 (mp 8·4%)	1·17 (1·01–1·35)	0·0349	1·12 (0·90–1·39)	0·3067	1·21 (1·00–1·48)	0·0544
D 8 (mp 8·9%)	1·14 (0·99–1·32)	0·0707	1·09 (0·87–1·37)	0·4368	1·21 (0·99–1·47)	0·0577
D 9 (mp 9·4%)	1·36 (1·18–1·57)	<0·0001	1·23 (0·98–1·55)	0·0733	1·46 (1·21–1·77)	<0·0001
D 10 (mp 10·6%)	1·79 (1·56–2·06)	<0·0001	1·93 (1·55–2·42)	<0·0001	1·80 (1·49–2·17)	<0·0001

Results

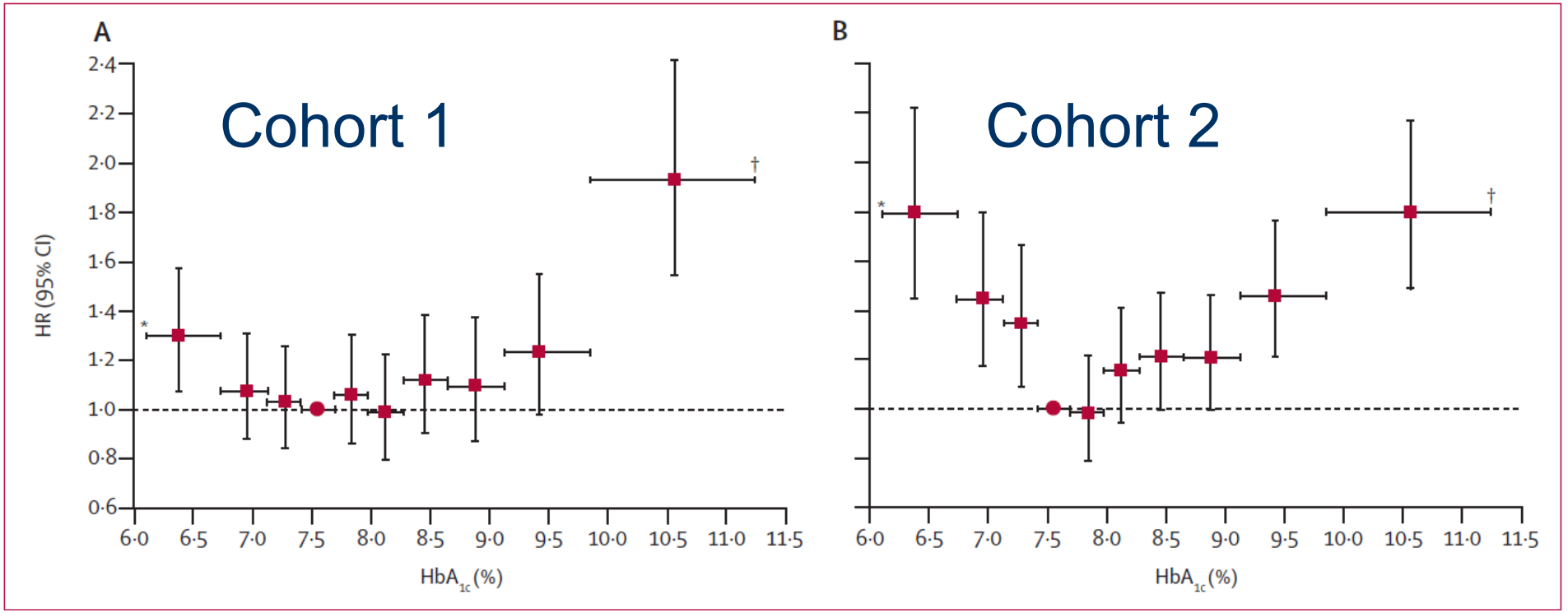


Figure 1: Adjusted hazard ratios for all-cause mortality by HbA_{1c} deciles in people given oral combination and insulin-based therapies

Cox proportional hazards model as a time fixed or time dependent covariate

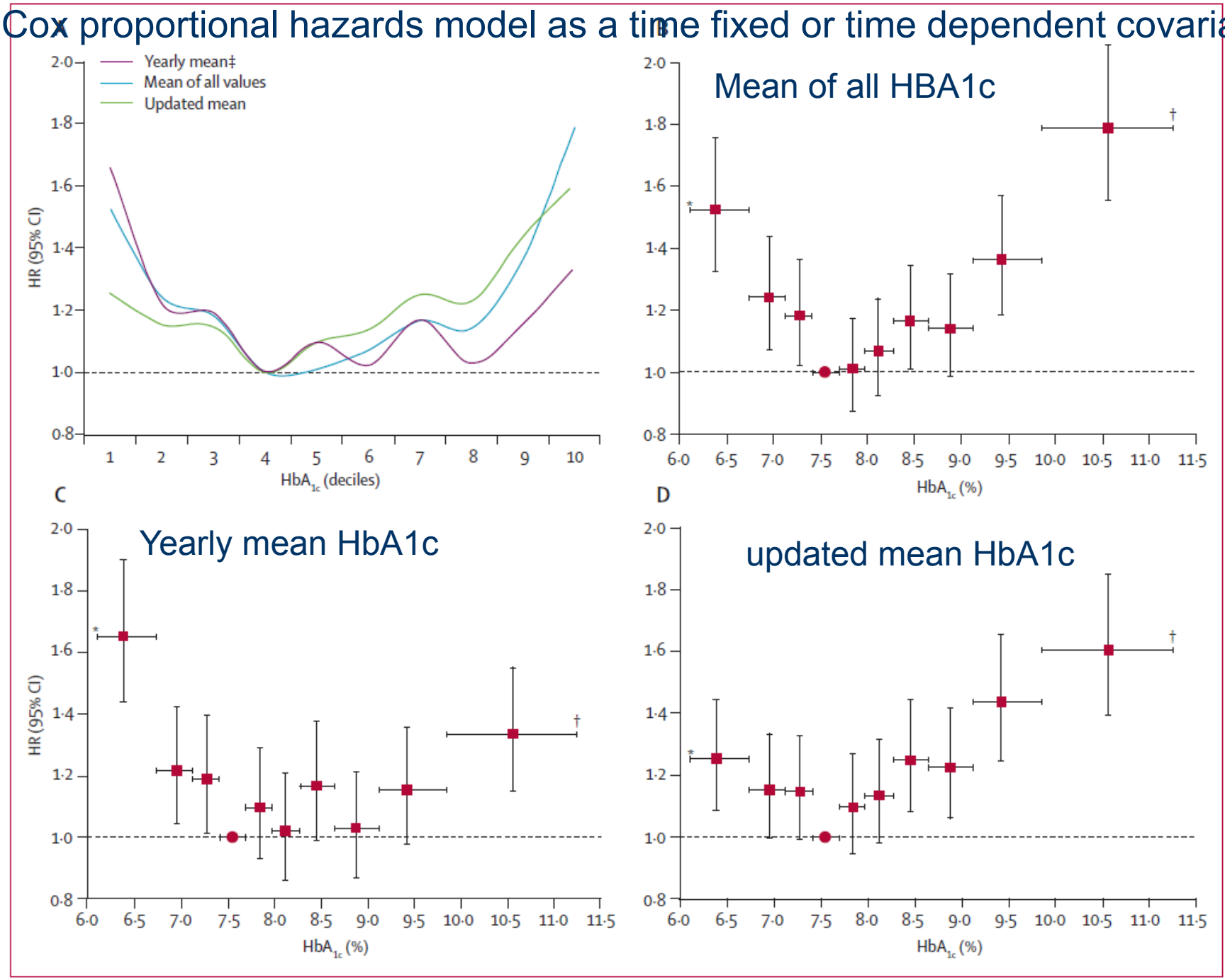


Figure 2: Adjusted hazard ratios for all-cause mortality introducing HbA_{1c} (%) into Cox proportional hazards model as a time-fixed or time-dependent covariate

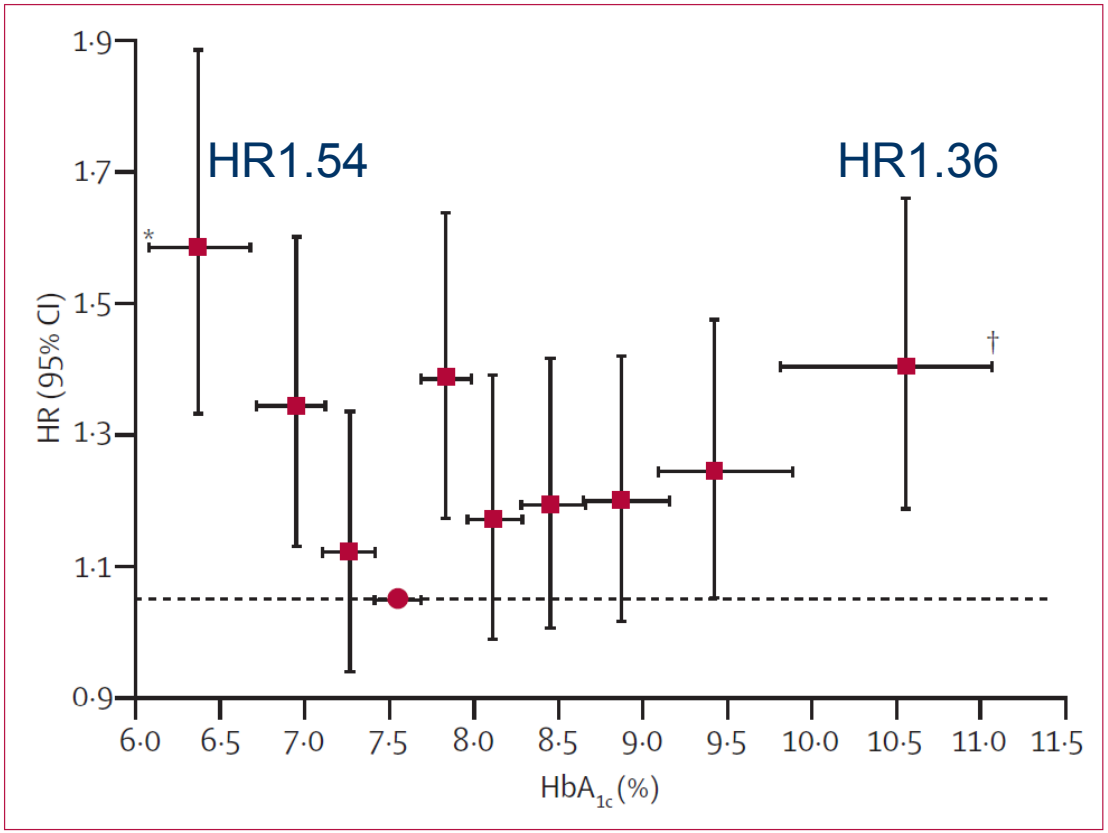


Figure 3: Hazard ratios for progression to first large-vessel disease event by HbA_{1c} decile, with Cox proportional hazards model

- First large-vessel disease events
  - Cohort 1 → 18.8 death/1000person/yrs
  - Cohort 2 → 24.1 death/1000person/yrs
- Same general U-shaped assocation

Discussion

- Low and high mean HbA1c values were associated with increased all-cause mortality and cardiac events

- HbA1c of approximately 7.5% was associated with lowest all-cause mortality and lowest progression to large-vessel disease events

→ Support to findings of the ACCORD trial

- Hypoglycaemia is associated with various sequelae that could increase mortality

Discussion

- **Insulin might heighten mortality risk**
  - Old, comorbidities, diabetes duration
  - Direct cardiotoxic effect in type 2 diabetes ?

- **Limitations**
  - Missing data
  - HbA1c standardization
  - Not randomised

- At baseline, 635 participants (6.8%) had previously undiagnosed diabetes.
- An A1C cut-off of 5.8% produced the highest sensitivity (72%) and specificity (86%).

Incretin based therapy

DDP-4 Inhibitors

- GLP-1 enhanced
- Superior tolerability
- Weight neutral
- Oral

GLP-1 agonists

- Pure GLP-1 effect
- Nausea, vomiting
- Weight loss
- Injection

Agenda of today's talk

1. Glucose fluctuation
2. Overall Adverse Events
3. Hypoglycemia
4. Hepatic safety EASD
5. Pancreatitis, Immune system EASD
6. Cardiovascular safety data EASD

Vildagliptin vs. sitagliptin

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Effects of vildagliptin twice daily vs. sitagliptin once daily on 24-hour acute glucose fluctuations

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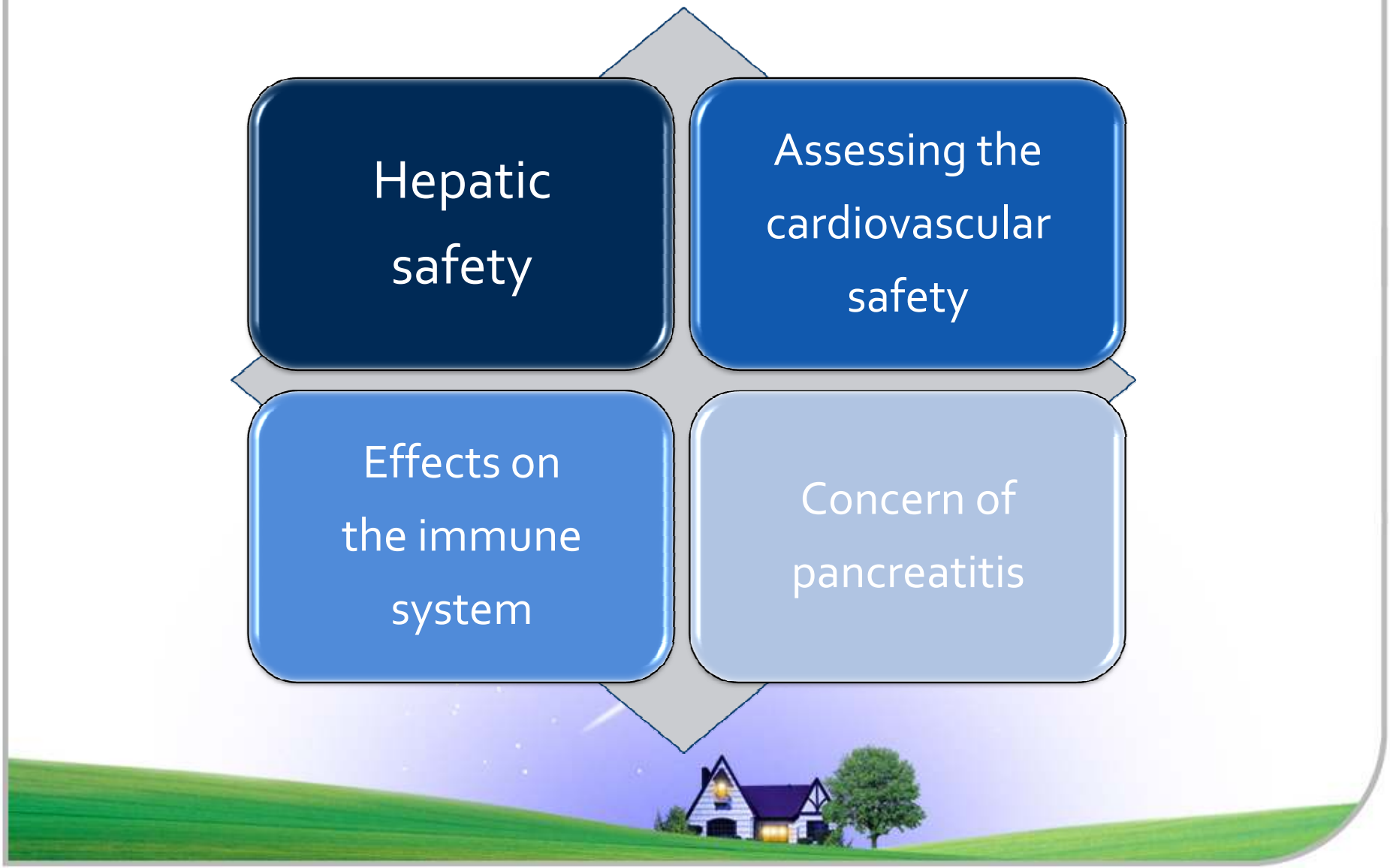
Key information before review of data

- *Glycemic disorders such as rapid glucose fluctuations over a da ily period might play an important role on diabetic complications .*
- *Not company sponsored trial.*
- *First published article about head to head study of Vildagliptin vs. Sitagliptin*
- *Using 48H continuous glucose monitoring system (CGMS)*

Vildaglitin in 45th EASD



Hepatic Safety

Are there any concerns for hepatic safety?

Hepatic safety profile of vildagliptin, a new DPP-4 inhibitor for the treatment of type 2 diabetes" (Kothny et al.)

Summary

- Galvus & Hypoglycemia: no increased relative to all comparators
- Galvus & Hepatic safety: similar risk for Galvus and comparators
- Galvus & Pancreatitis: no increased relative to all comparators
- Galvus & Immune system: no increased relative to all comparators
- Galvus & Cardiovascular safety: no increased relative to all comparators