Arterial stiffness and diabetes

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당뇨병은 얼마나 많은가?

전 세계인의 문제

우리나라

366 million people have diabetes in 2011;
by 2030 this will have risen to 552 million

자료 출처 : EGDM

IDF Diabetes Atlas, http://www.diabetesatlas.org/map


현재 보이는 당뇨병 환자 및
당뇨병 고위험군
진단되지 않은 당뇨병 환자,
앞으로 당뇨병이 될 위험군,
당뇨병으로 인한 합병증의 부담

Contents

- 당뇨병의 병리기전
- Arterial stiffness의 측정
- 당뇨병에서의 arterial stiffness가 오는 원인
- 당뇨병에서의 arterial stiffness – 실제 임상
- 치료 방법

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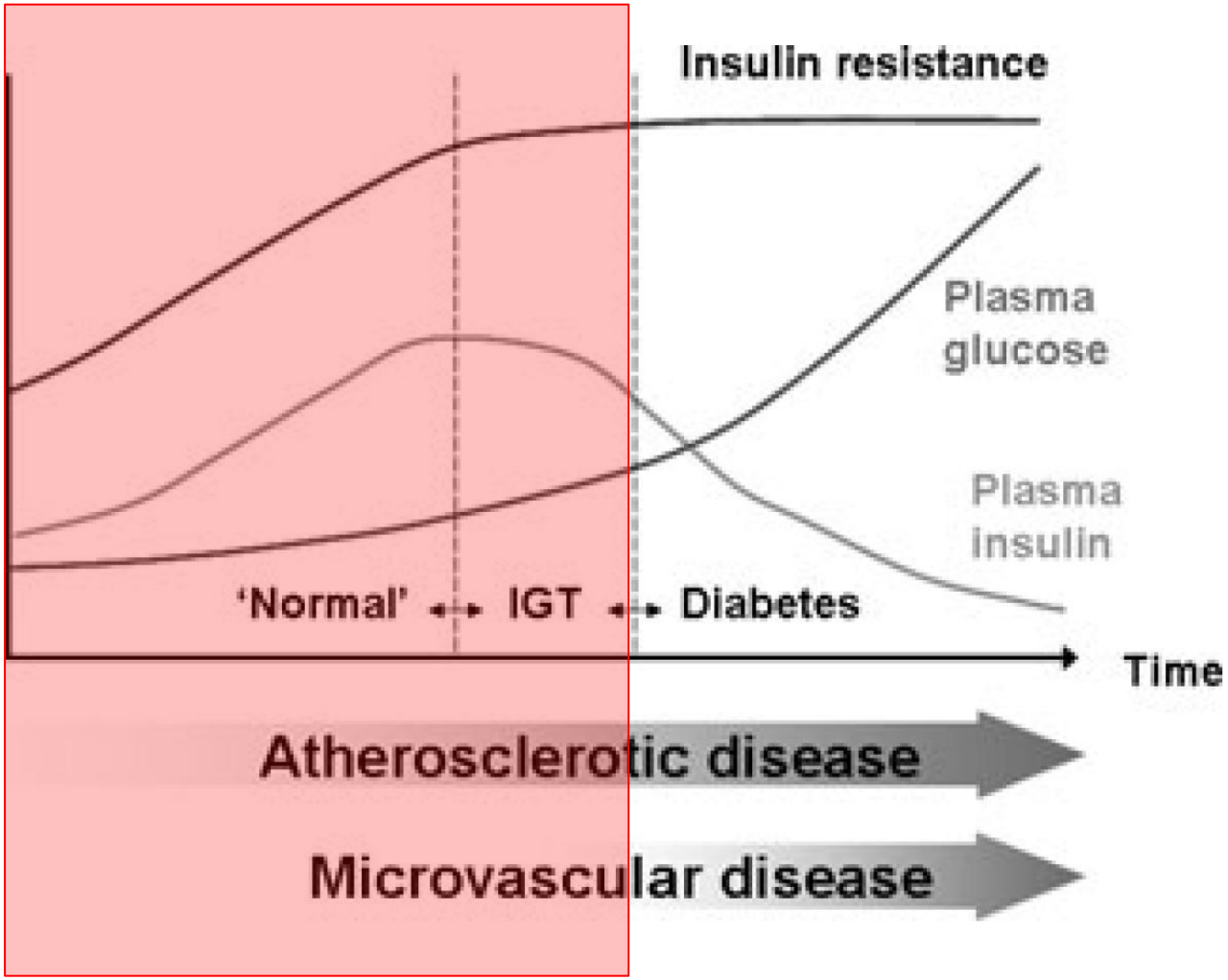
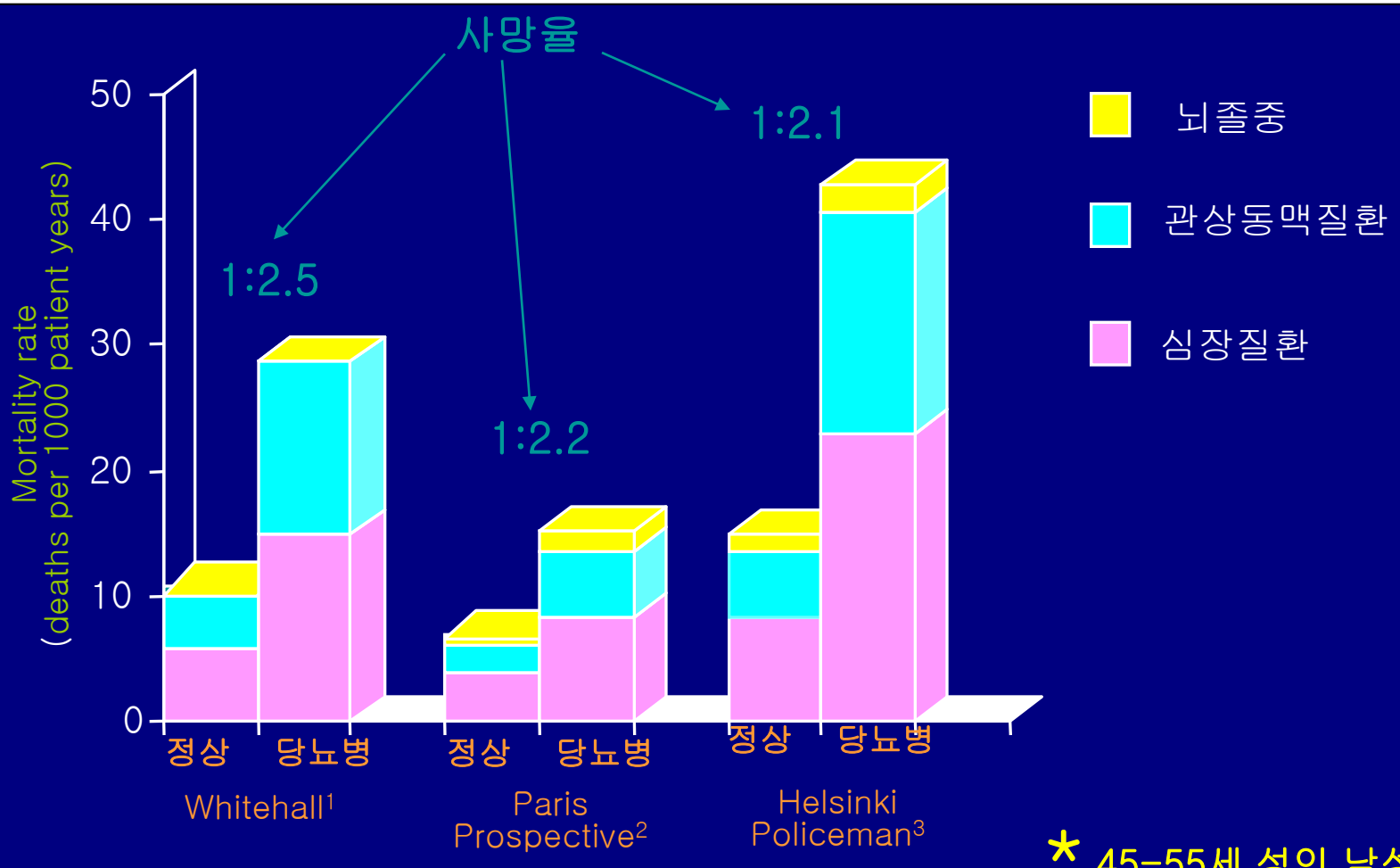
Increasing CV risk associated with the progression of glycemic status



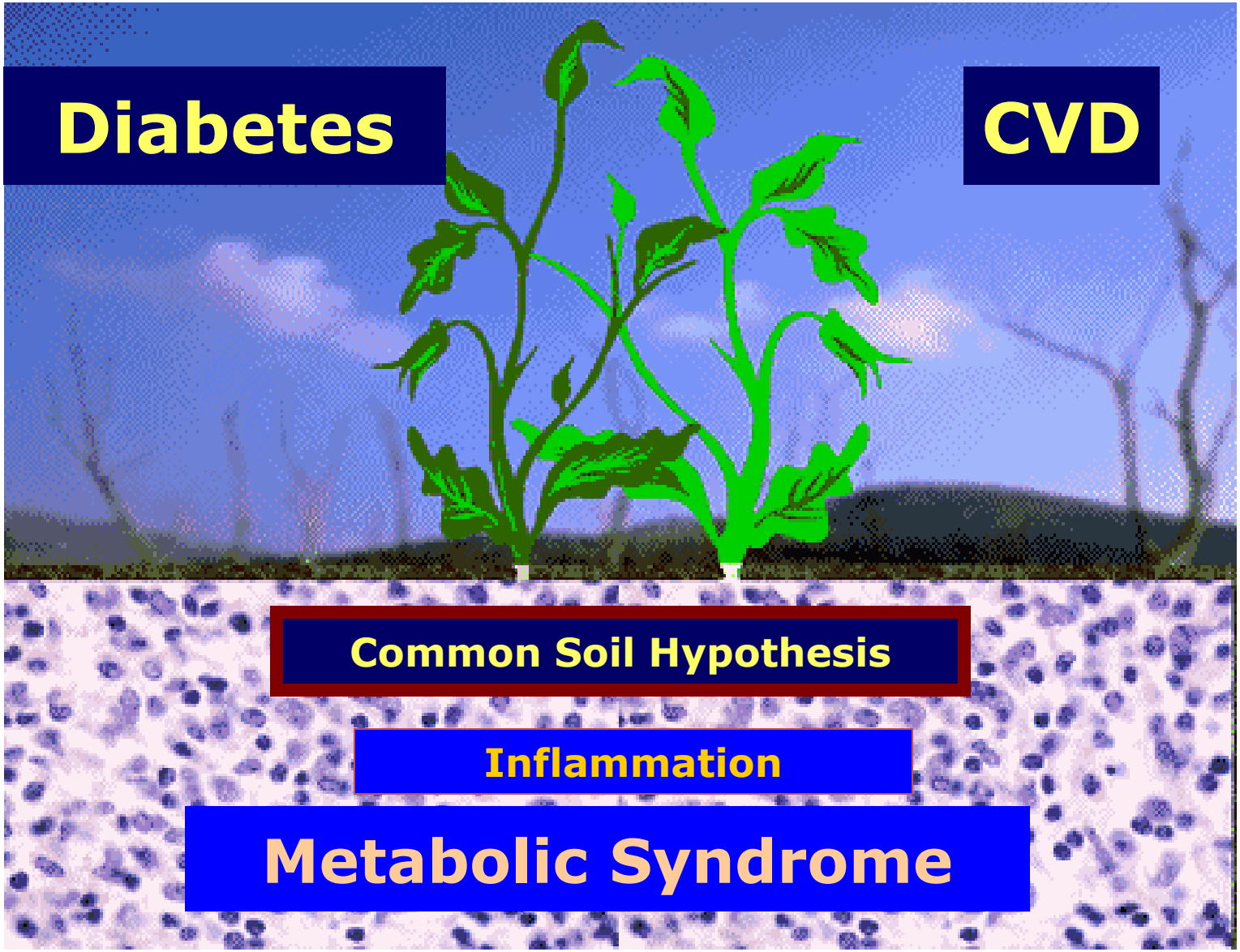
Cubbon R et al. Int J Clin Pract 63:287-299, 2007

제2형 당뇨병은 사망률을 증가시킨다



* 45-55세 성인 남성 대상

1. Reid DD et al. Lancet 1974;1:469-473 2. Ducimetière P et al. Diabetologia 1980;19:205-210
3. Pyörälä K. Diabetes Care 1979;2:131-141


Diabetes
CVD
Common Soil Hypothesis
Inflammation
Metabolic Syndrome

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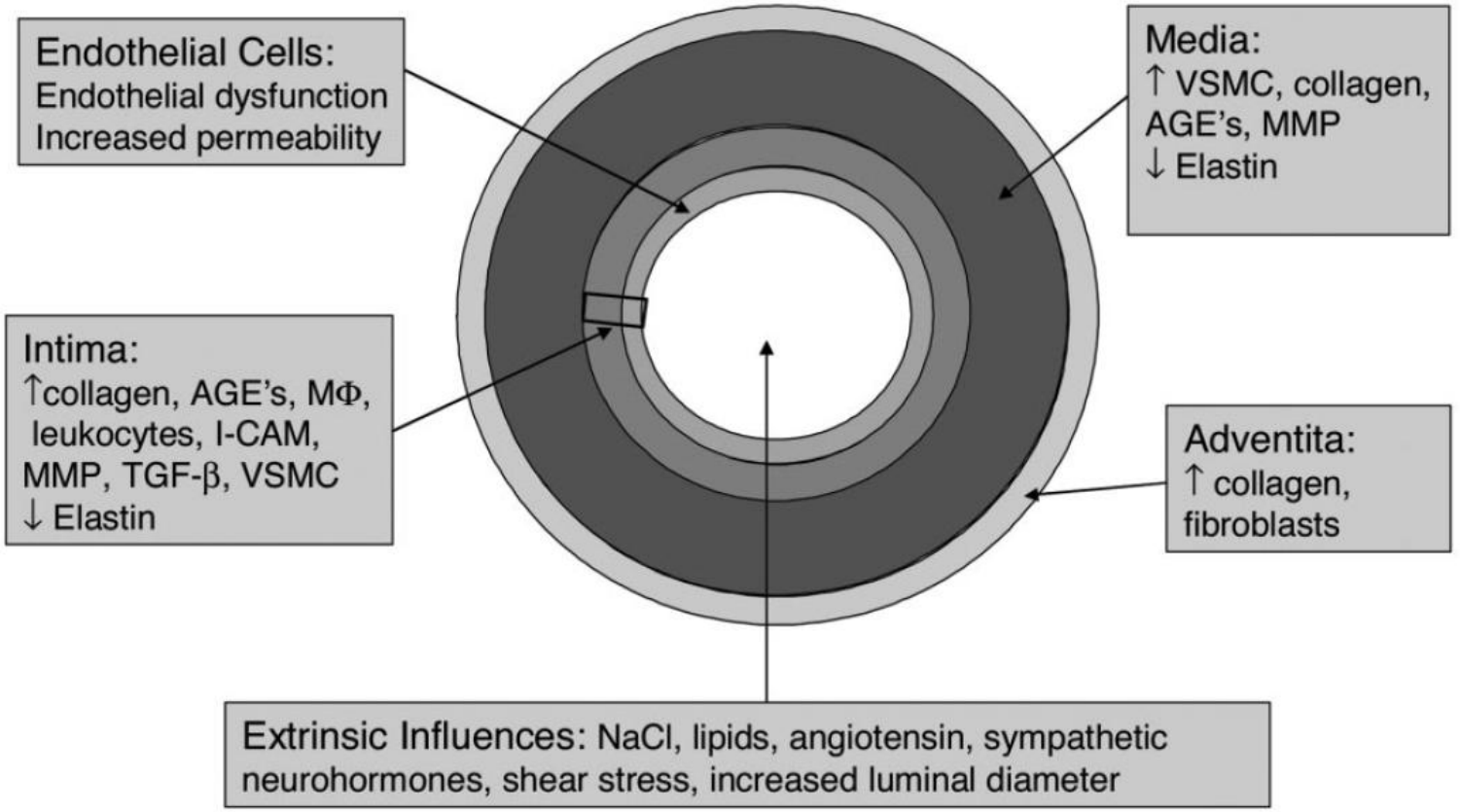
Multiple causes and locations of arterial stiffness



Zieman SJ et al. ATVB 25:932-943, 2005

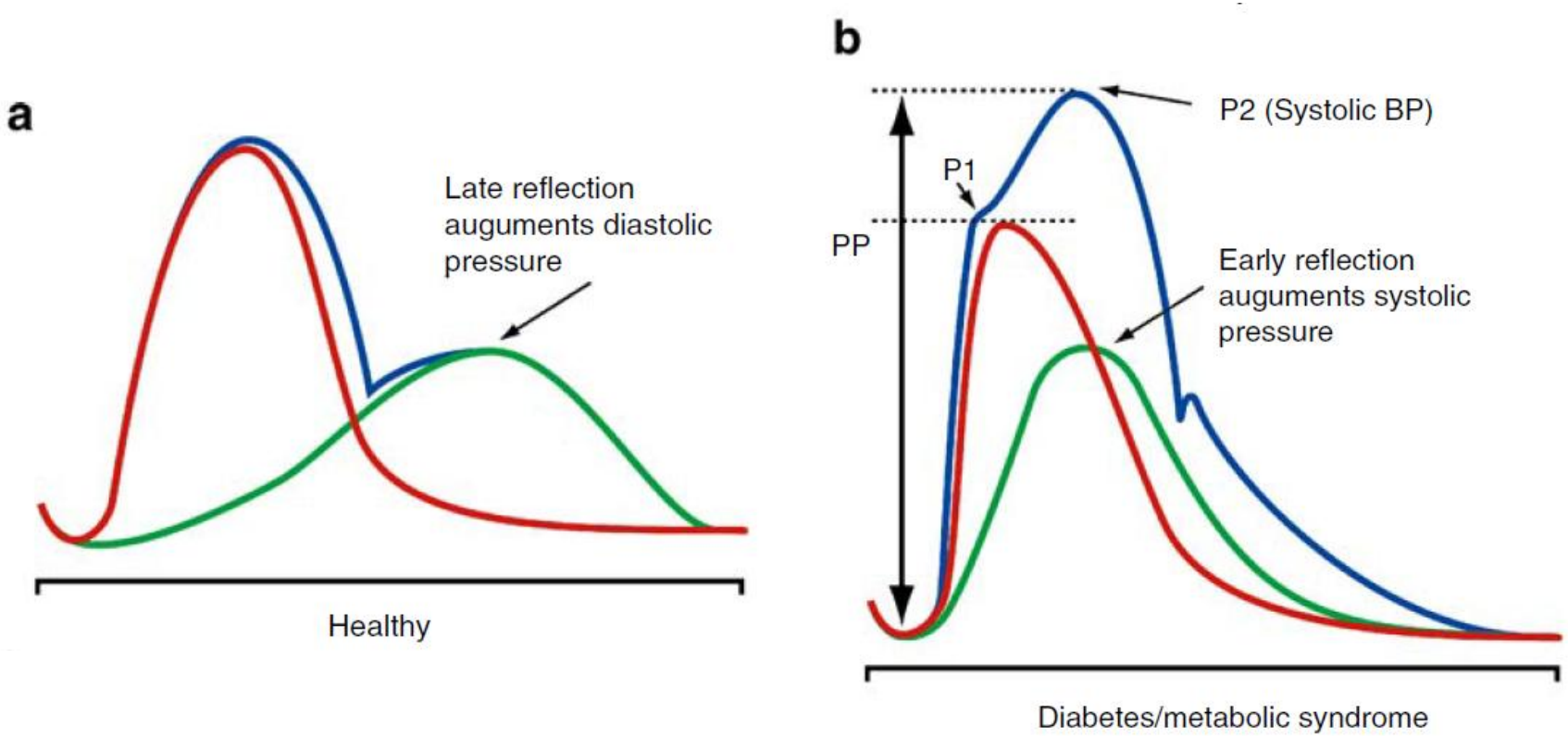
Indices of arterial stiffness

Definitions of the most commonly used indices of arterial stiffness

Method of measurement	Estimate	Definition	Calculation details (units)	Site of measurements	Comments
Arterial wall ultrasonography (echo-tracking) (see Fig. 3)	Compliance coefficient (CC)	Absolute change in lumen area for given increase in pressure	$\Delta A/\Delta P$ ($mm^2\ kPa^{-1}$)	Locally, most often at the carotid (an elastic artery) or the brachial, radial and femoral (muscular) arteries; (all peripheral sites)	These estimates are determined directly from simultaneous changes in (local) pulse pressure (ΔP) and arterial diameter (ΔD) or area (ΔA). This method has the advantage of allowing the concomitant assessment of arterial wall thickness (IMT), thereby enabling the calculation of the Young's elastic modulus (an estimate of the intrinsic elastic properties of the arterial wall material). The lower the DC or CC and the higher the YEM of an artery the higher its stiffness.
	Distensibility coefficient (DC)	Relative change in lumen area for a given change in pressure	$\Delta A/A \times \Delta P$ (kPa^{-1})		
	Young's (or incremental) elastic modulus (YEM or E_{inc})	The pressure step per squared centimetre required for (a theoretical) 100% stretch from resting length, determined by the arterial diameter (D) divided byDC mulitiplied by the thickness of the intima–media complex (IMT).	$D/DC \times IMT$ (kPa)		
Pressure sensors such as mechanotransducers or applanation tonometers (with ECG triggering)	Pulse wave velocity	The speed of the pressure wave travelling along an arterial segment, determined by the length (L) of the arterial segment under study divided by the time it takes for a pressure wave to travel from arterial location A to arterial location B within this segment (Δt)	$L/\Delta t$ (m/s)	Regionally over a given arterial segment, e.g.: carotid–femoral (central), or carotid-radial or femoral–dorsalis pedis (both peripheral)	The 'gold standard' for arterial stiffness. Greater values indicate greater stiffness.
Pulse wave analyses ([radial] applanation tonometry) (see Fig. 2)	Augmentation index (AIx)	The supplementary increase in blood pressure during systole due to the reflection of the forward travelling pressure waves from the peripheral circulation	$([P2–P1]/PP) \times 100$ (%)	At the radial or carotid artery from which the central aortic pressure and waveform are derived with the use (or not) of a transfer function	AIx is thus estimated from the difference between second (P2) and first (P1) systolic peaks of the arterial pulse wave expressed as a % of pulse pressure (PP). AIx is an estimate of stiffness and wave reflection and therefore provides indirect information on arterial stiffness.

Stehouwer CDA et al. Diabetologia 51:527-539, 2008

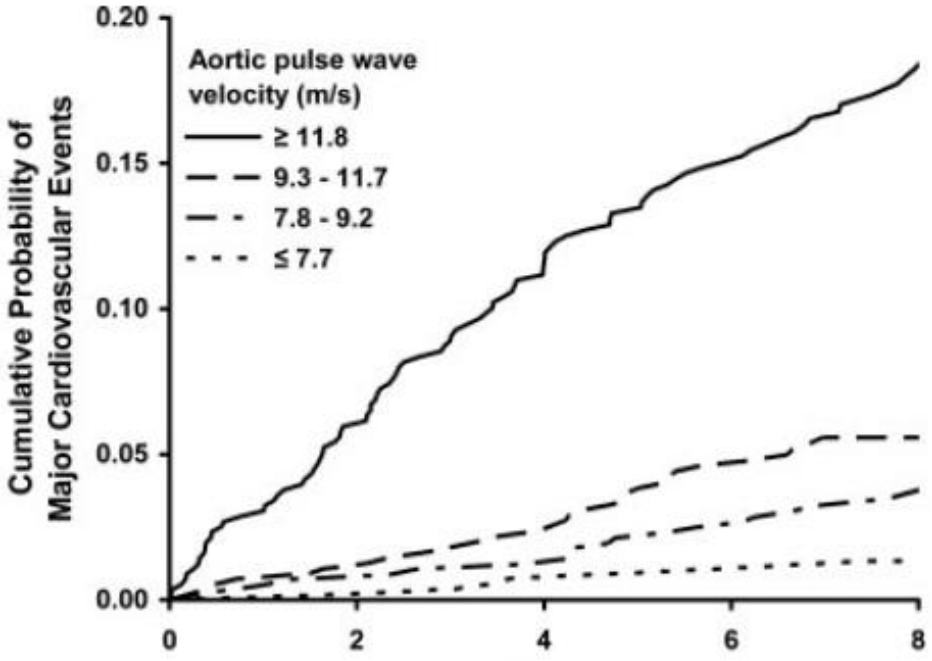
Measurement of arterial stiffness



Stehouwer CDA et al.
Diabetologia 51:527-539, 2008

Arterial stiffness and cardiovascular events – The Framingham Heart Study -

Median follow-up of 7.8 years in 2232 participants



Number at risk: Aortic pulse wave velocity (m/s)					
≥ 11.8	560	513	462	424	161
9.3 - 11.7	555	542	529	502	246
7.8 - 9.2	573	561	551	537	278
≤ 7.7	544	541	535	531	275

Mitchell GF et al. Circulation 121:505-511, 2010

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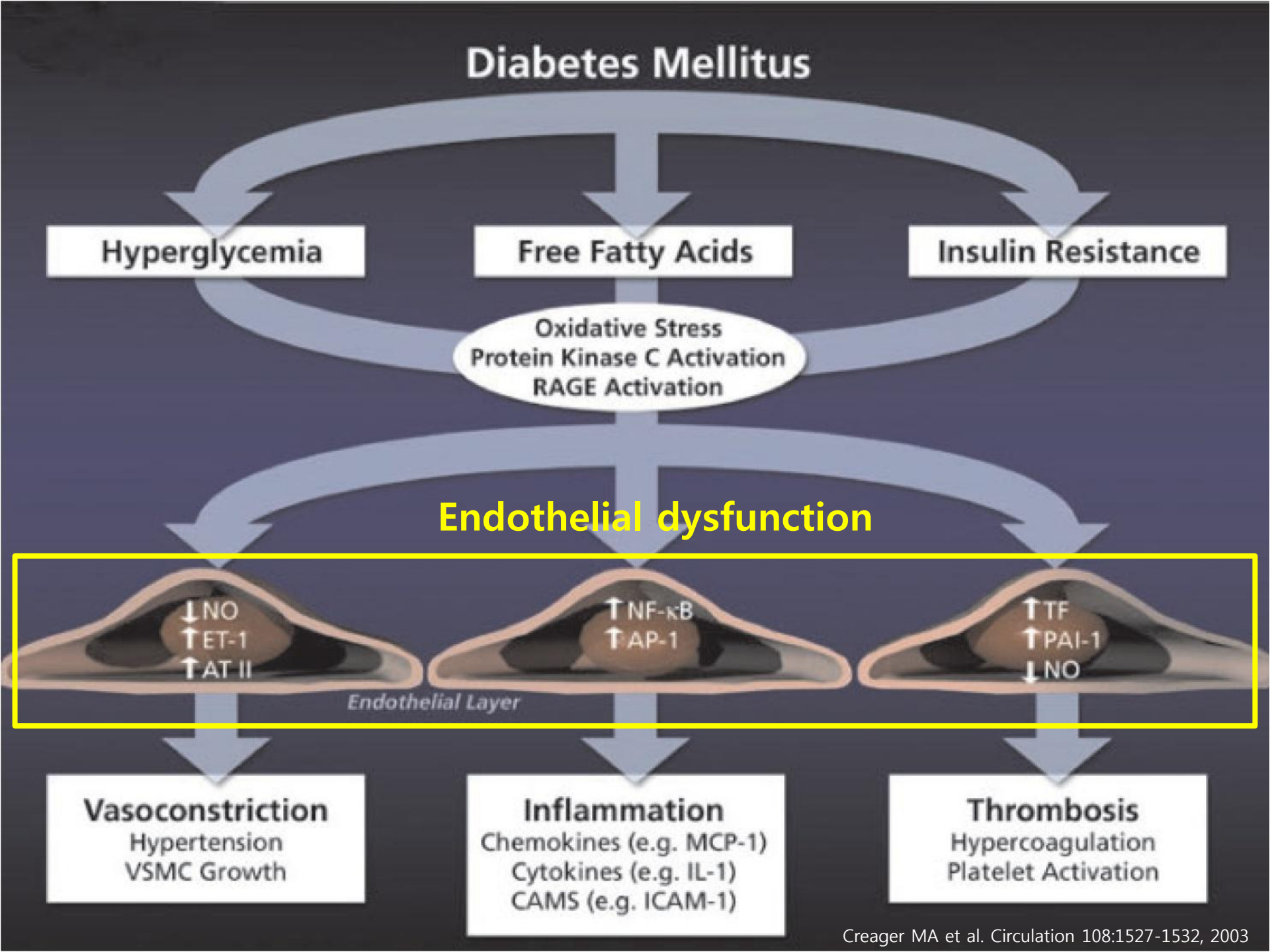
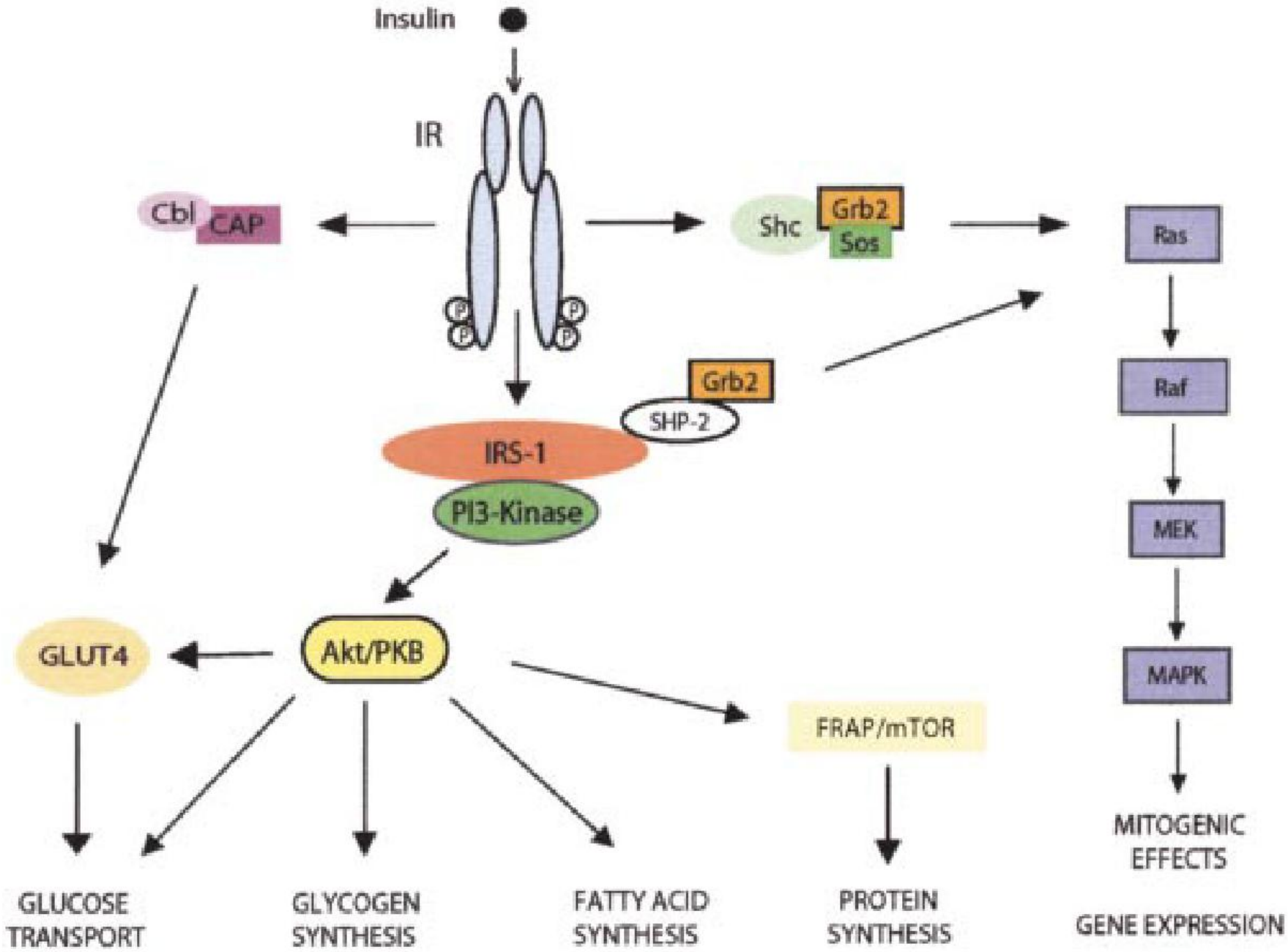
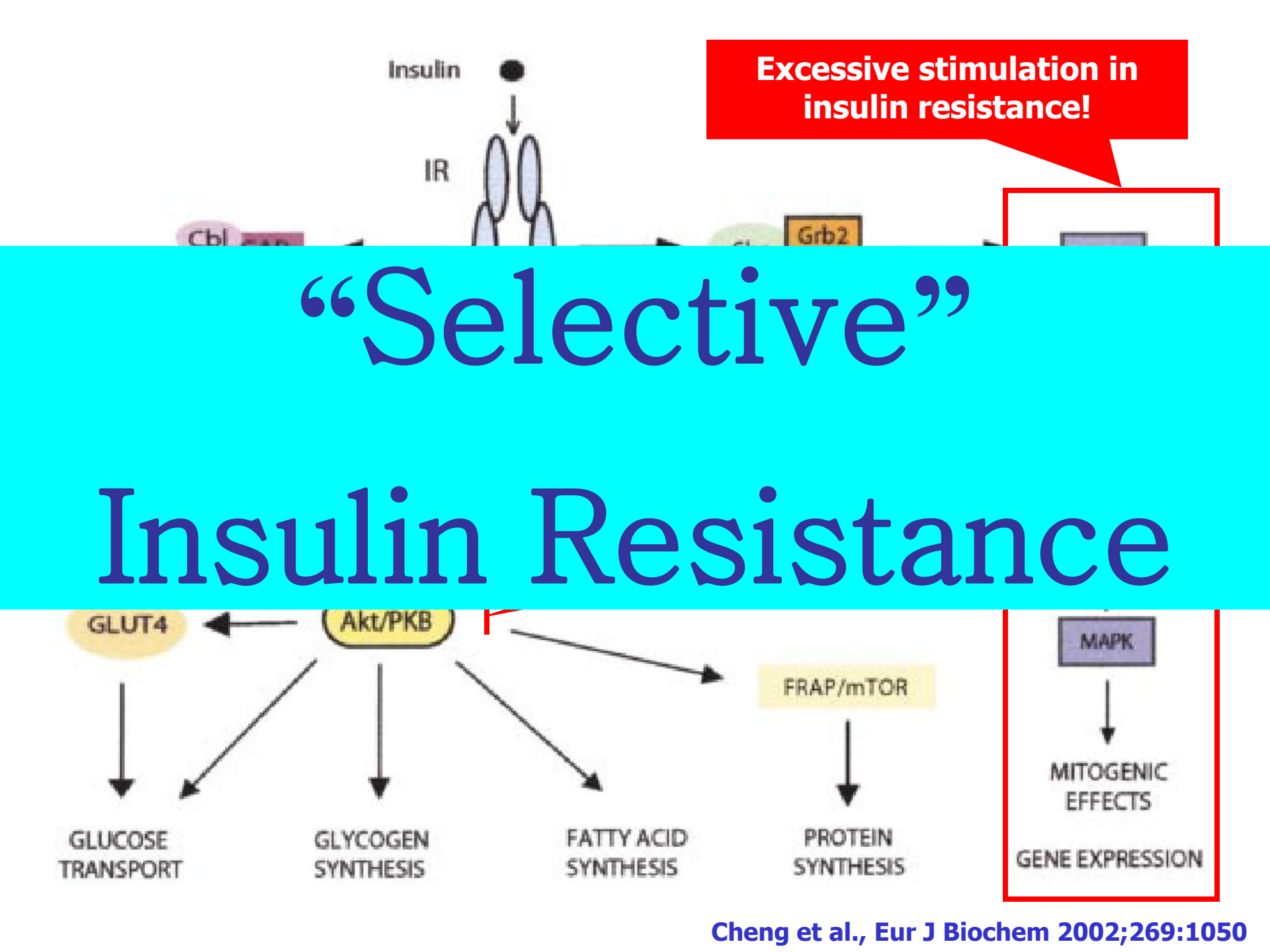


Creager MA et al. Circulation 108:1527-1532, 2003



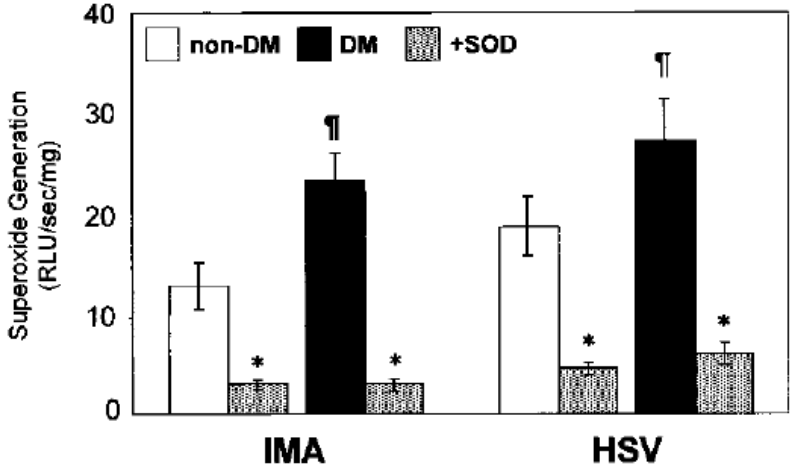
Cheng et al., Eur J Biochem 2002;269:1050

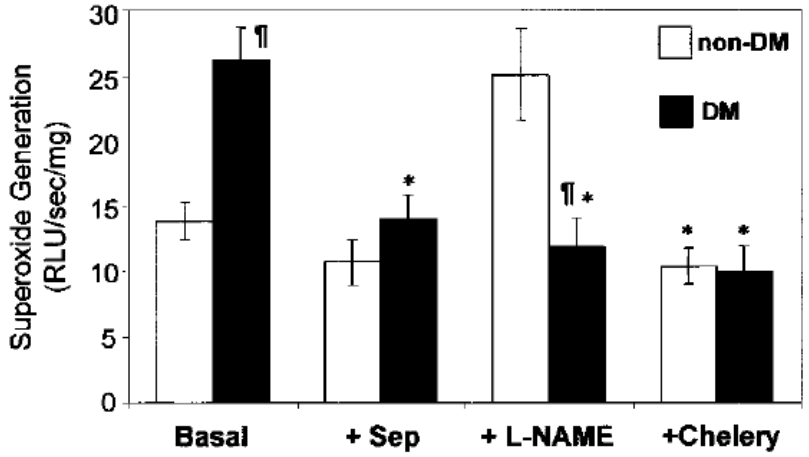


Cheng et al., Eur J Biochem 2002;269:1050

Increased vascular superoxide production in human DM

Saphenous vein and internal mammary arteries from 45 DM and 45 non-DM control undergoing coronary artery bypass surgery

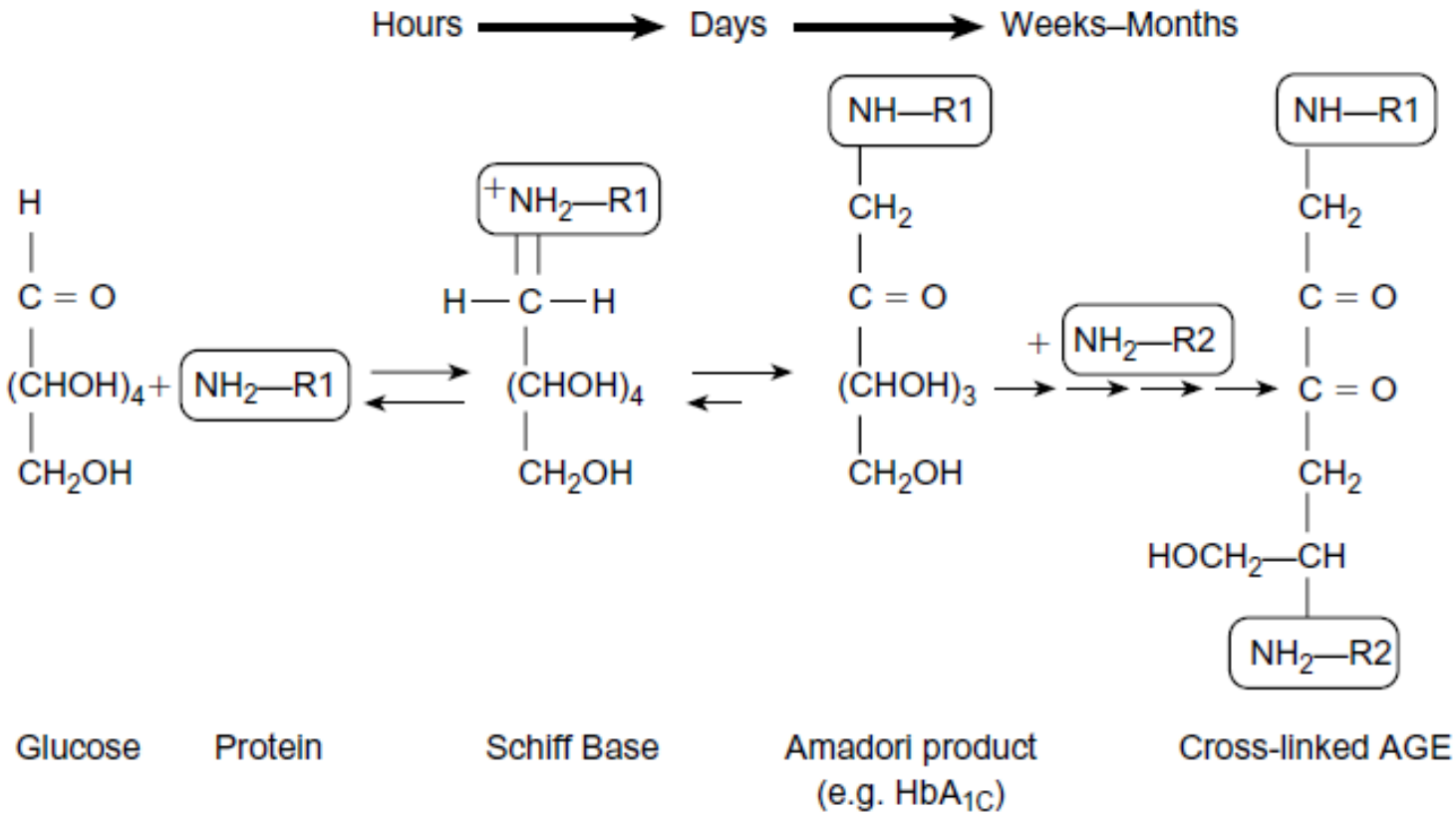




당뇨병 환자의 혈관에서는 superoxide production이 증가되어 있으며, 이는 NOS와 PKC signaling의 이상이 원인임을 알 수 있다.

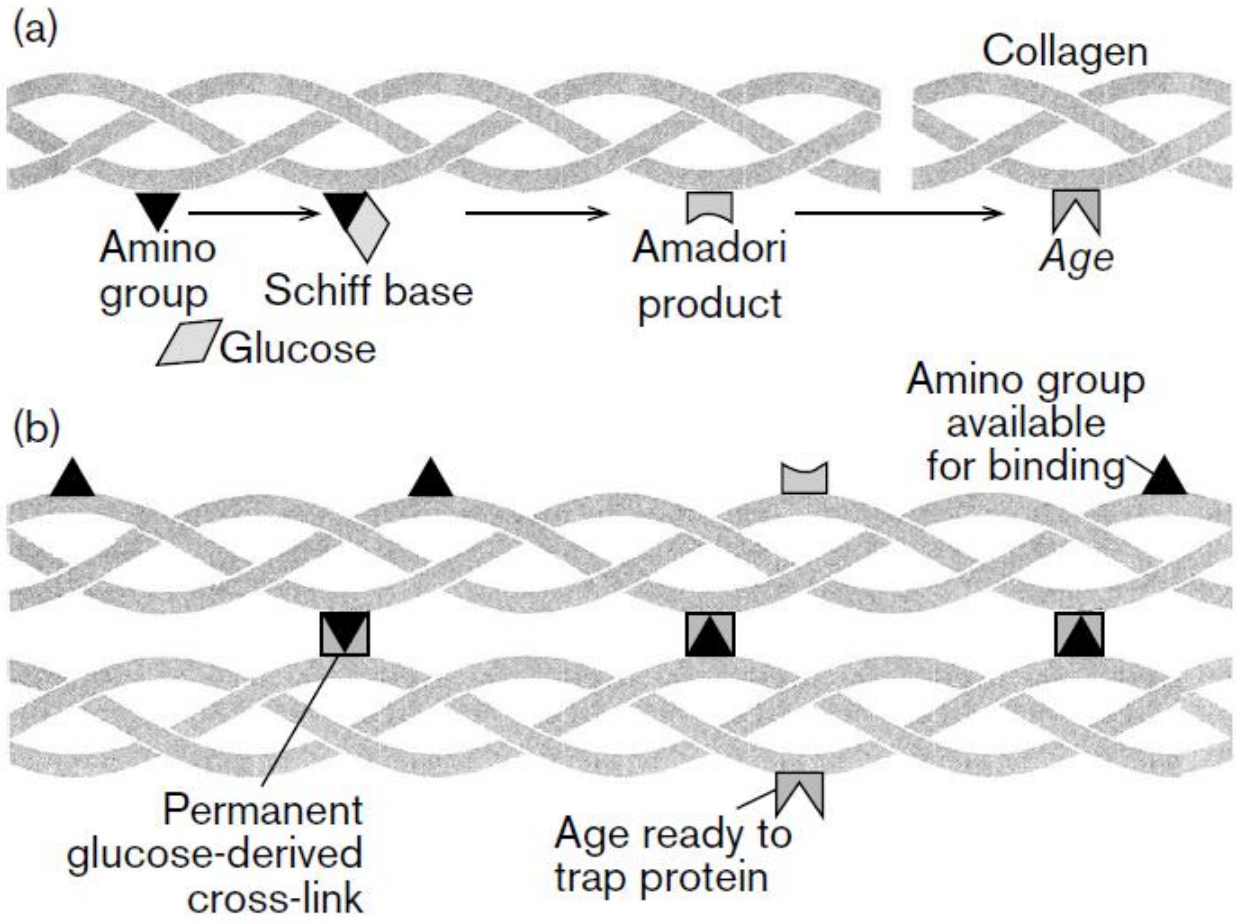
Guzik TJ et al. Circulation 105:1656-1662, 2002

Formation of advanced glycation end products (AGE)



Aronson D. J Hypertens 21:3-12, 2003

Formation of collagen cross-links by AGE



Aronson D. J Hypertens 21:3-12, 2003

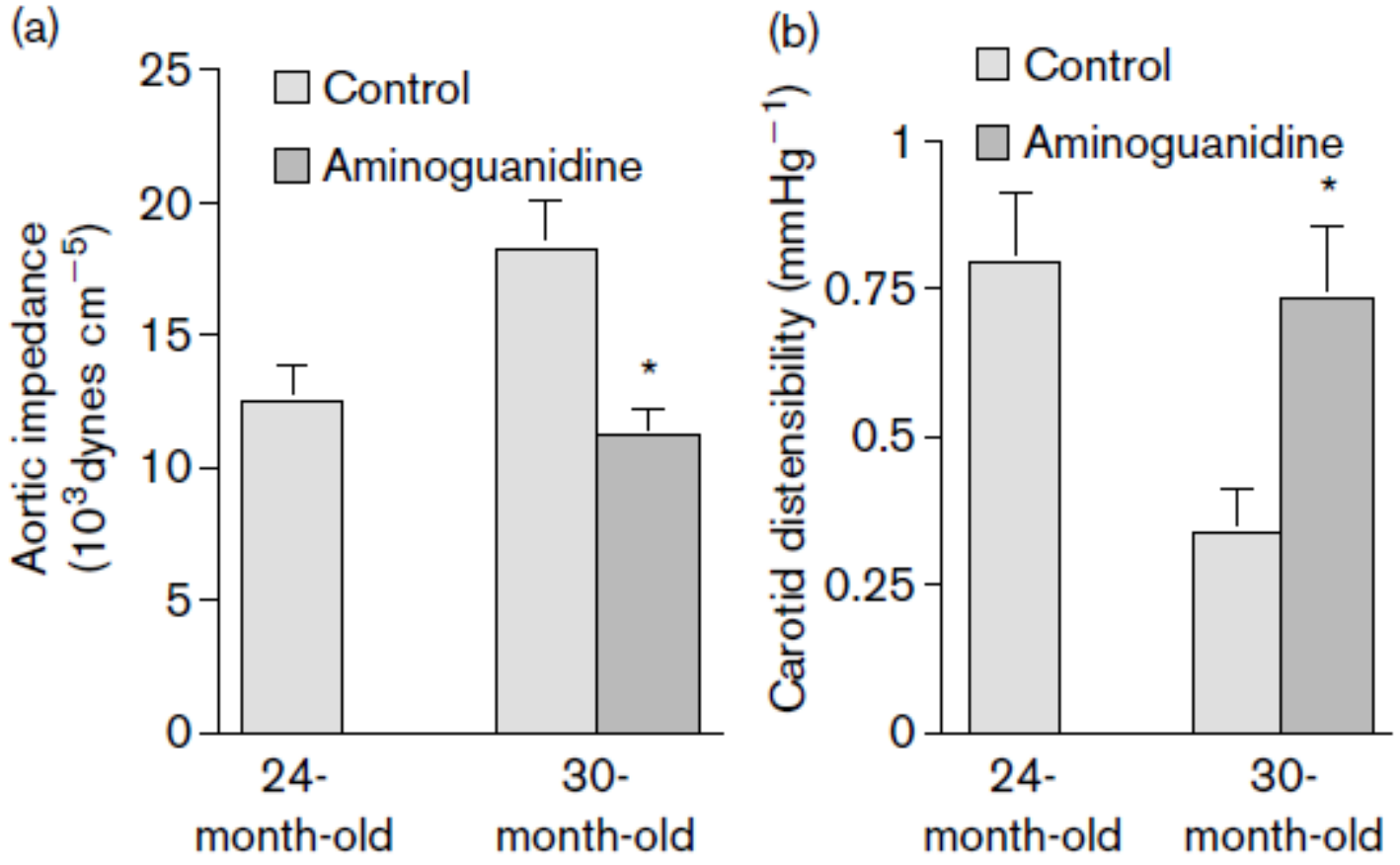
The association of arterial stiffness with AGE in type 1 diabetes

TABLE 3. Cross-Sectional Associations of Pulse Pressure, Systolic Pressure and Diastolic Pressure With Pentosidine, CML, and CEL

	Pulse Pressure, mm Hg			Systolic Pressure, mm Hg			Diastolic Pressure, mm Hg		
Advanced Glycation Products	β	SE	*P* Value	β	SE	*P* Value	β	SE	*P* Value
Pentosidine, nmol/mmol creatinine									
Crude	5.37	1.32	<0.001	4.77	1.61	0.001	−0.60	0.92	0.52
Model 1	0.77	1.11	0.48	0.52	0.74	0.48	−0.26	0.37	0.48
CML, μM/M lysine									
Crude	0.16	0.04	<0.001	0.19	0.05	<0.001	0.03	0.03	0.26
Model 1	0.09	0.03	0.003	0.06	0.02	0.003	−0.03	0.01	0.003
CEL, μM/M lysine									
Individuals with complications									
Crude	0.48	0.08	<0.001	0.59	0.10	<0.001	0.11	0.06	0.056
Model 1	0.24	0.07	0.001	0.16	0.05	0.001	−0.08	0.02	0.001
Individuals without complications									
Crude	0.01	0.07	0.87	0.07	0.09	0.44	0.06	0.07	0.42
Model 1	−0.03	0.06	0.62	−0.02	0.04	0.62	0.01	0.02	0.62
Interaction analyses adjusted for model 1									
Intercept	−15.19	5.54	0.006	−10.13	3.70	0.01	5.06	1.85	0.01
CEL, per μM/M lysine	−0.05	0.08	0.571	−0.03	0.06	0.57	0.02	0.03	0.57
Age, per year	0.37	0.07	<0.001	0.25	0.05	<0.001	−0.12	0.03	<0.001
Sex, male 1, female 2	1.68	1.13	0.138	1.12	0.75	0.14	−0.56	0.38	0.14
Mean arterial pressure, per mm Hg	0.41	0.05	<0.001	1.27	0.03	<0.001	0.87	0.02	<0.001
Duration of diabetes, per year	0.43	0.09	<0.001	0.29	0.06	<0.001	−0.15	0.03	<0.001
Presence of complications, no 0, yes 1	−7.51	3.46	0.030	−5.01	2.31	0.03	2.50	1.15	0.03
CEL×presence of complications	0.32	0.11	0.002	0.21	0.07	0.002	−0.11	0.04	0.002

Schram MT et al. Hypertension 46:232-237,2005

Effect of aminoguanidine on carotid artery compliance impedance



Corman B et al. PNAS 95:1301-1306, 1998

Mechanism of arterial stiffness in diabetes mellitus

Advanced glycation end product

Activation of renin-angiotensin system

Low-grade inflammation

Endothelial dysfunction

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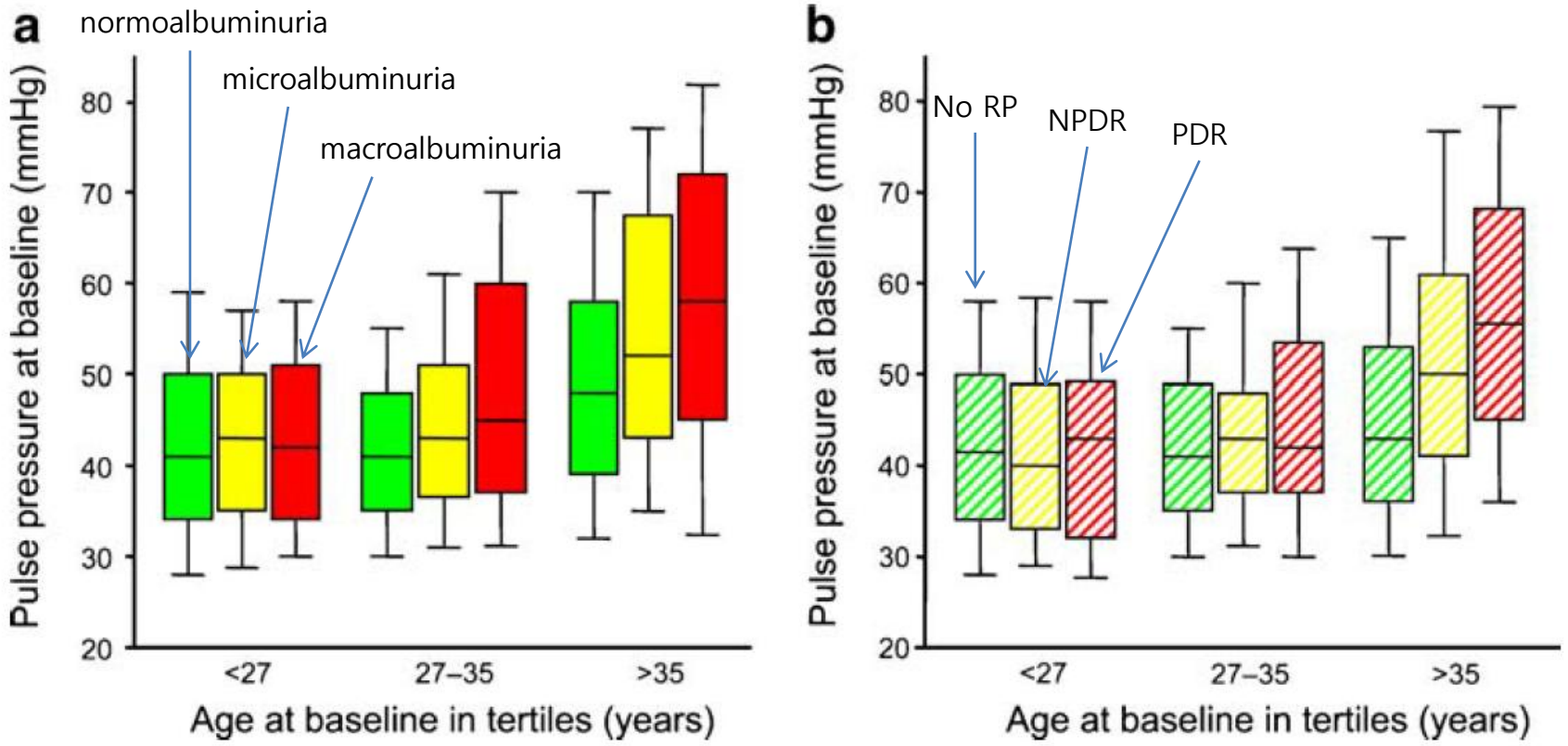
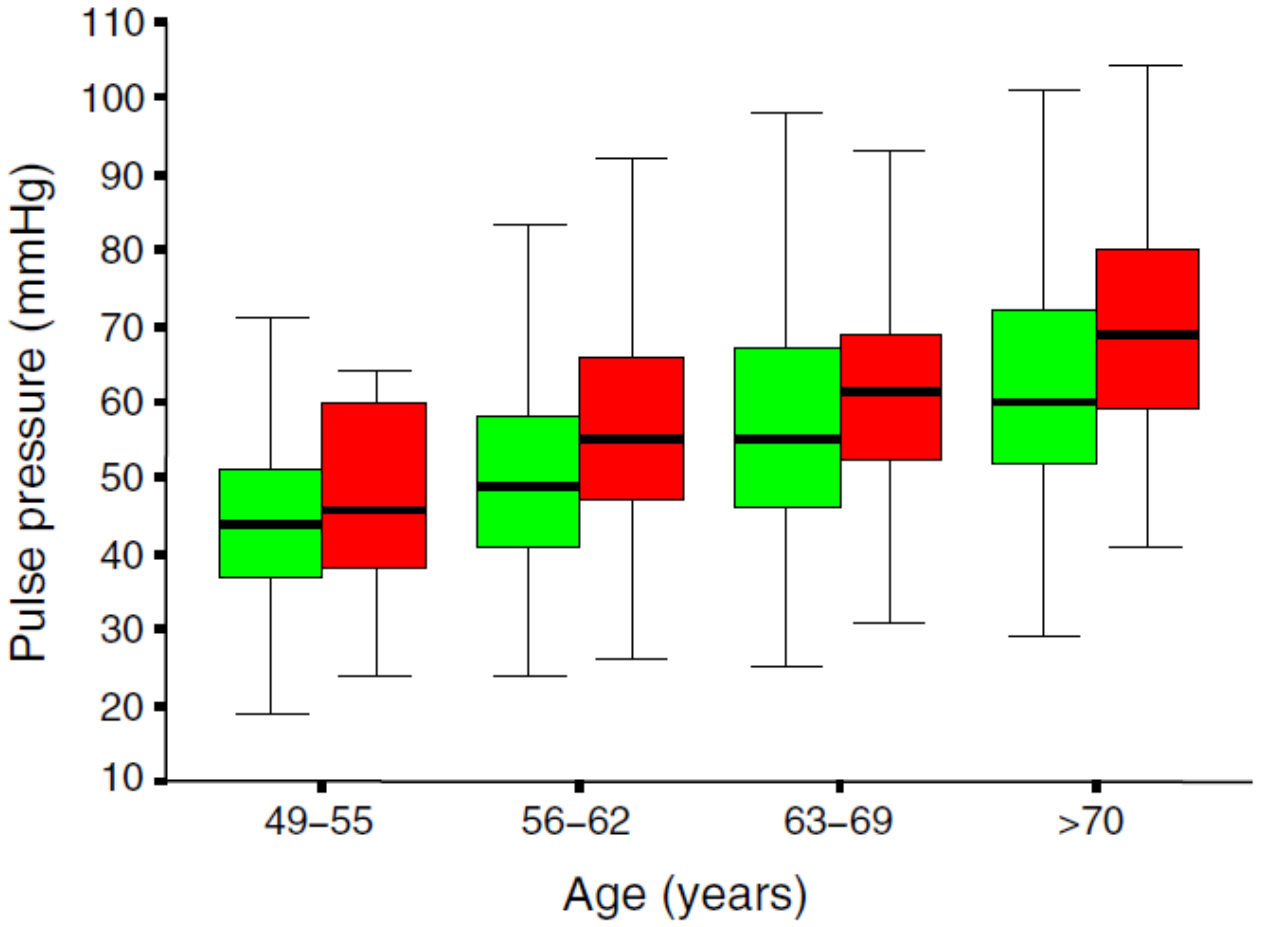
The association of pulse pressure with age among type 1 patients



The association was stronger in the presence of micro- or macroalbuminuria or retinopathy than their absence

Schram MT et al. J hypertens 21:2035-2044, 2003

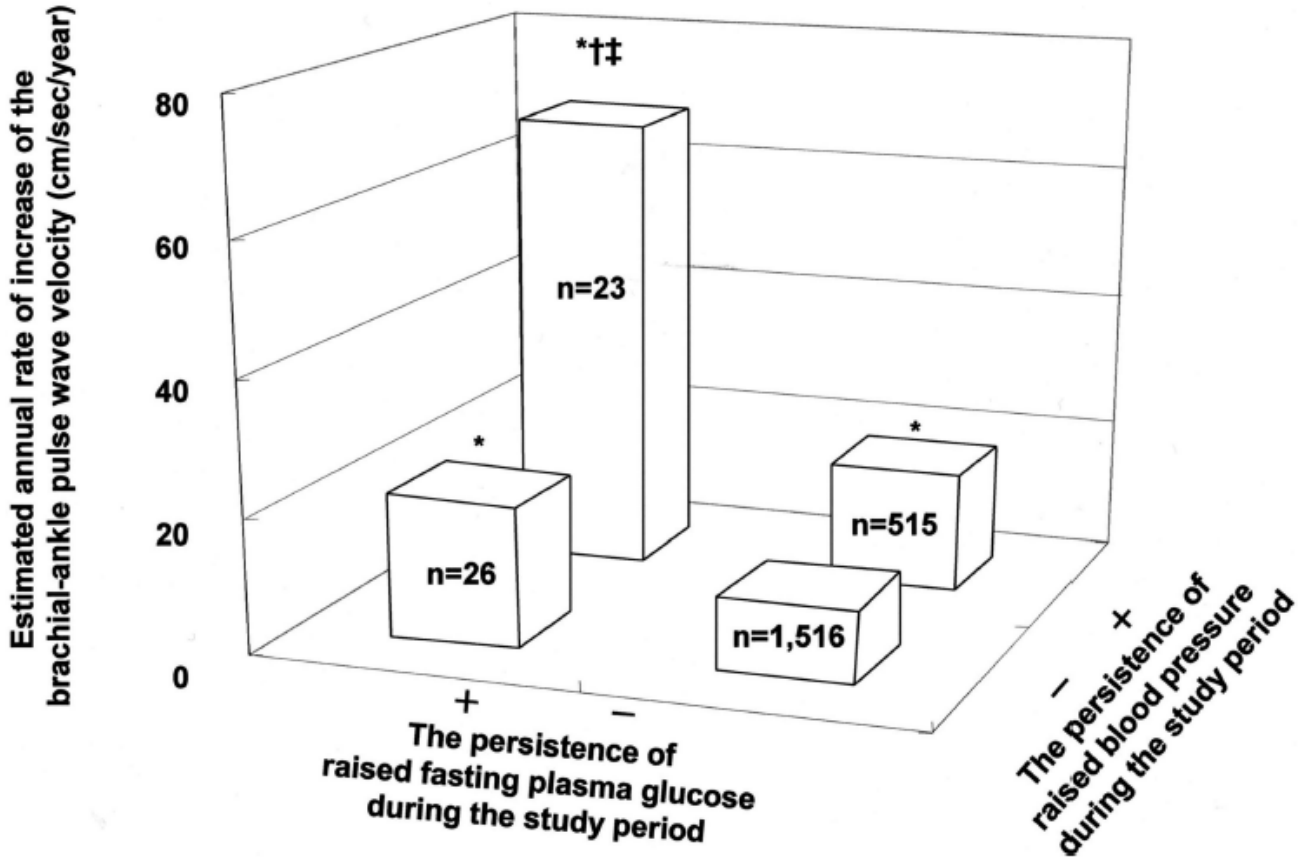
Increases in pulse pressure with aging is steeper in type 2 diabetes compared with non-DM



Schram MT et al. J Hypertens 20:1743-1751, 2002

Synergistic acceleration of arterial stiffening in the presence of raised BP and hyperglycemia

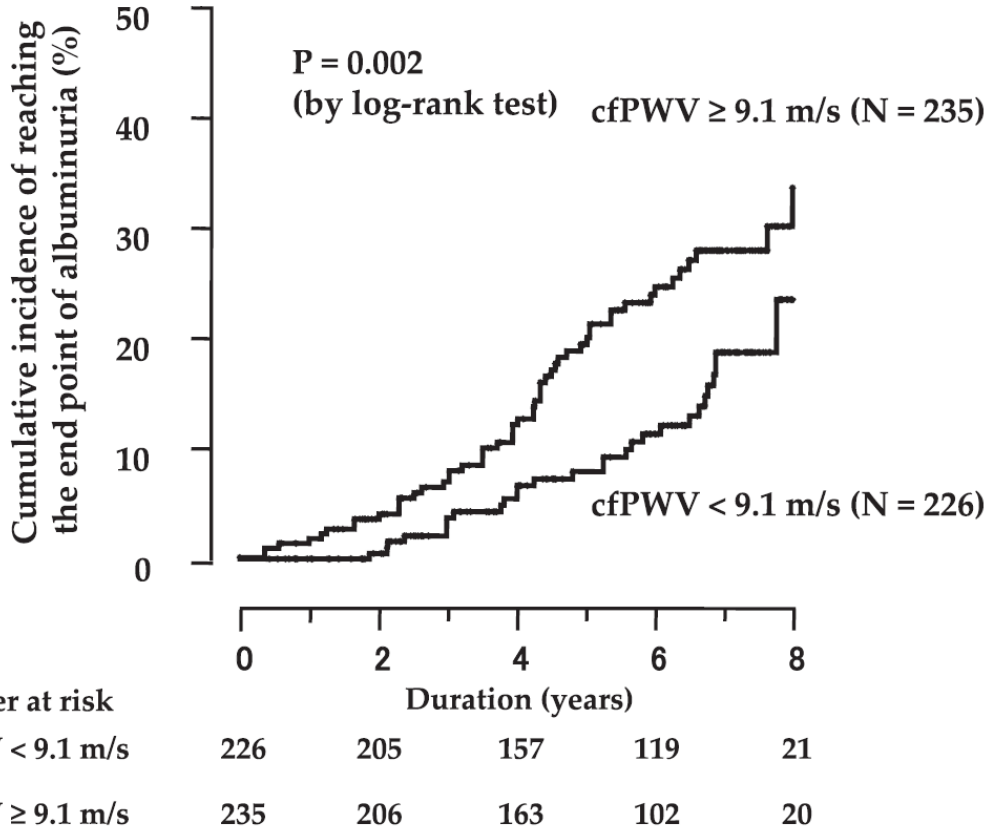
In 2080 Japanese men, baPWV was measured at the beginning of the study and at the end of the 3-year study period



Tomiyama H et al.
Hypertension 47:180-188, 2006

Arterial stiffness is associated with incident albuminuria and decreased GFR in T2DM

- In 46 Japanese T2DM patients (mean age 59 yrs), median F/U of 5.9yrs
- End point: transition from normo- to microalbuminuria
  transition from micro- to macroalbuminuria



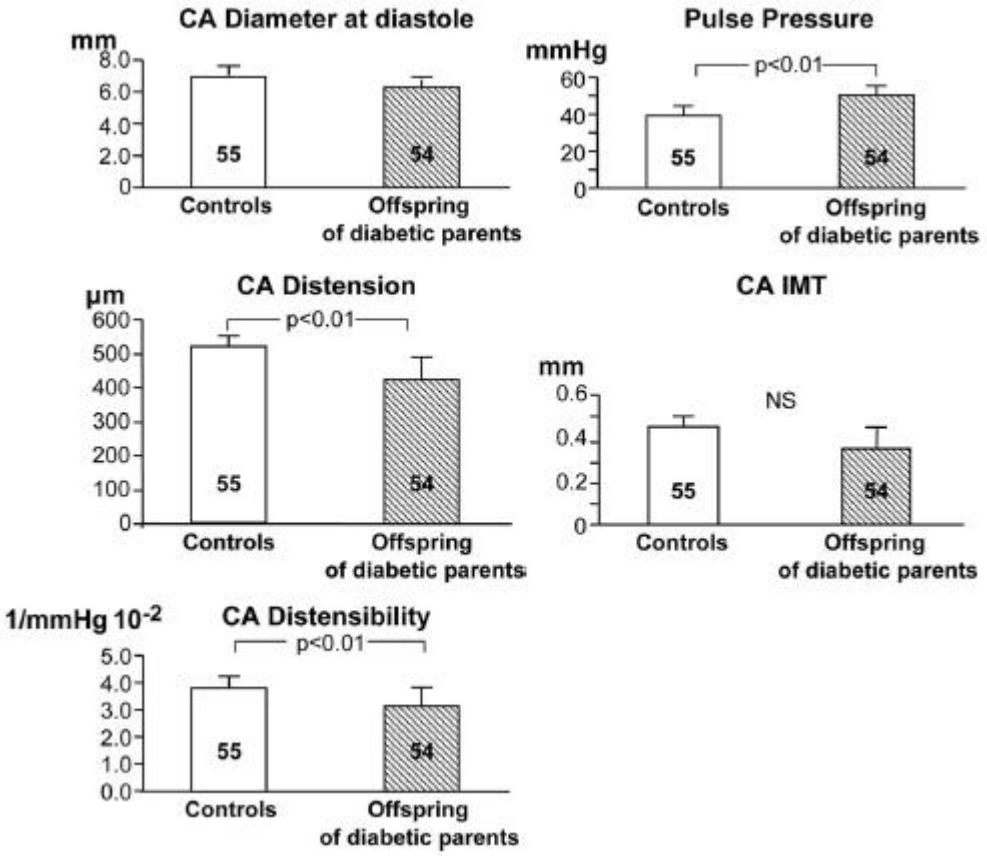
Number at risk					
PWV < 9.1 m/s	226	205	157	119	21
PWV ≥ 9.1 m/s	235	206	163	102	20

A significant association between annual change in eGFR and cf-PWV

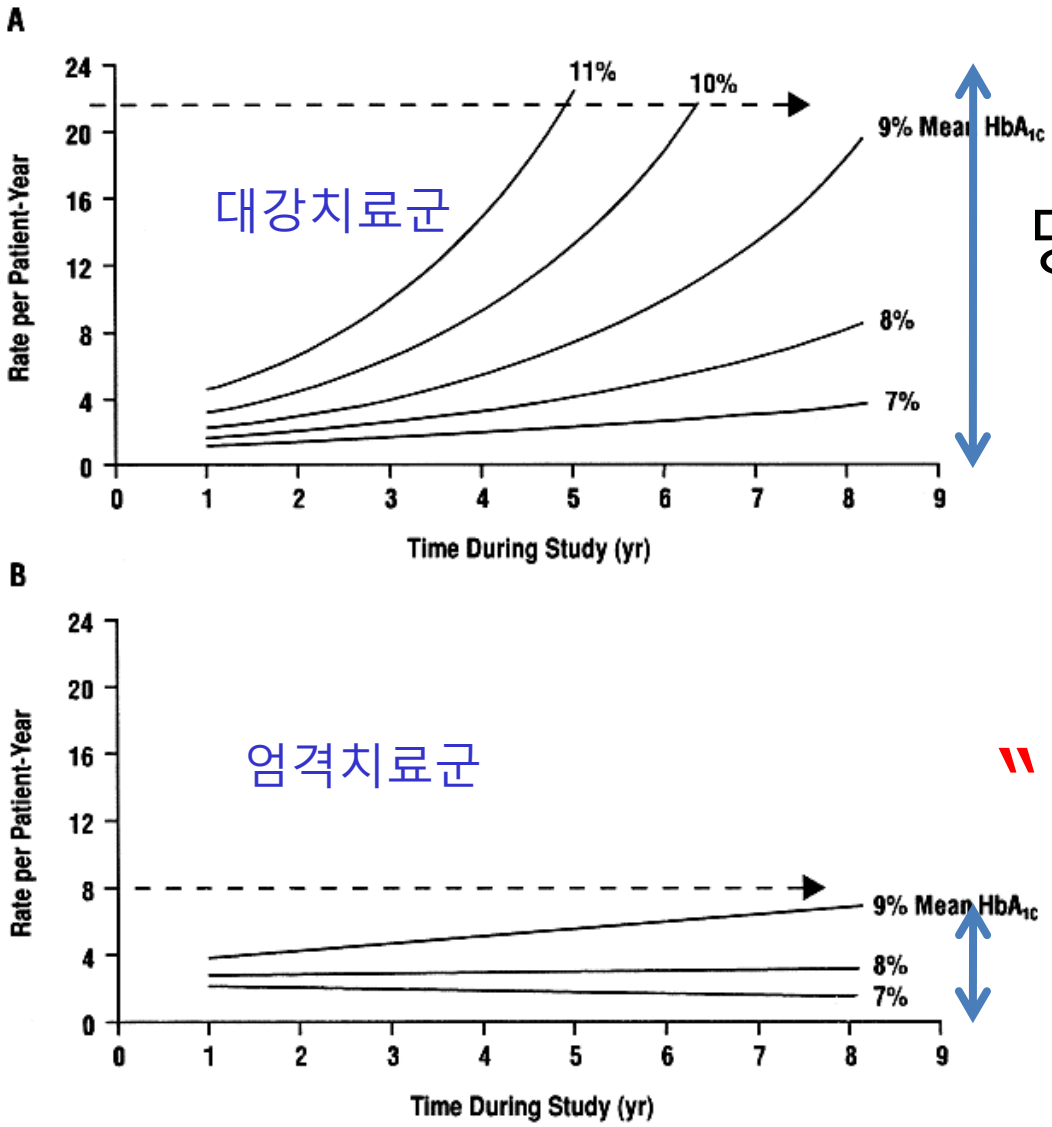
Bouchi R et al. Diabetes Care 34:2570-2575, 2011

Increased arterial stiffness in normoglycemic normotensive offspring of type 2 diabetes parents

In 54 normoglycemic, normotensive, healthy offspring of type 2 diabetes parents and 55 matched control



Giannattasio C et al. Hypertension 51:182-187, 2008



당화혈색소의 증가는 결국 같지만, 어떤 과정으로 그 당화혈색소에 도달했는가가 중요하다

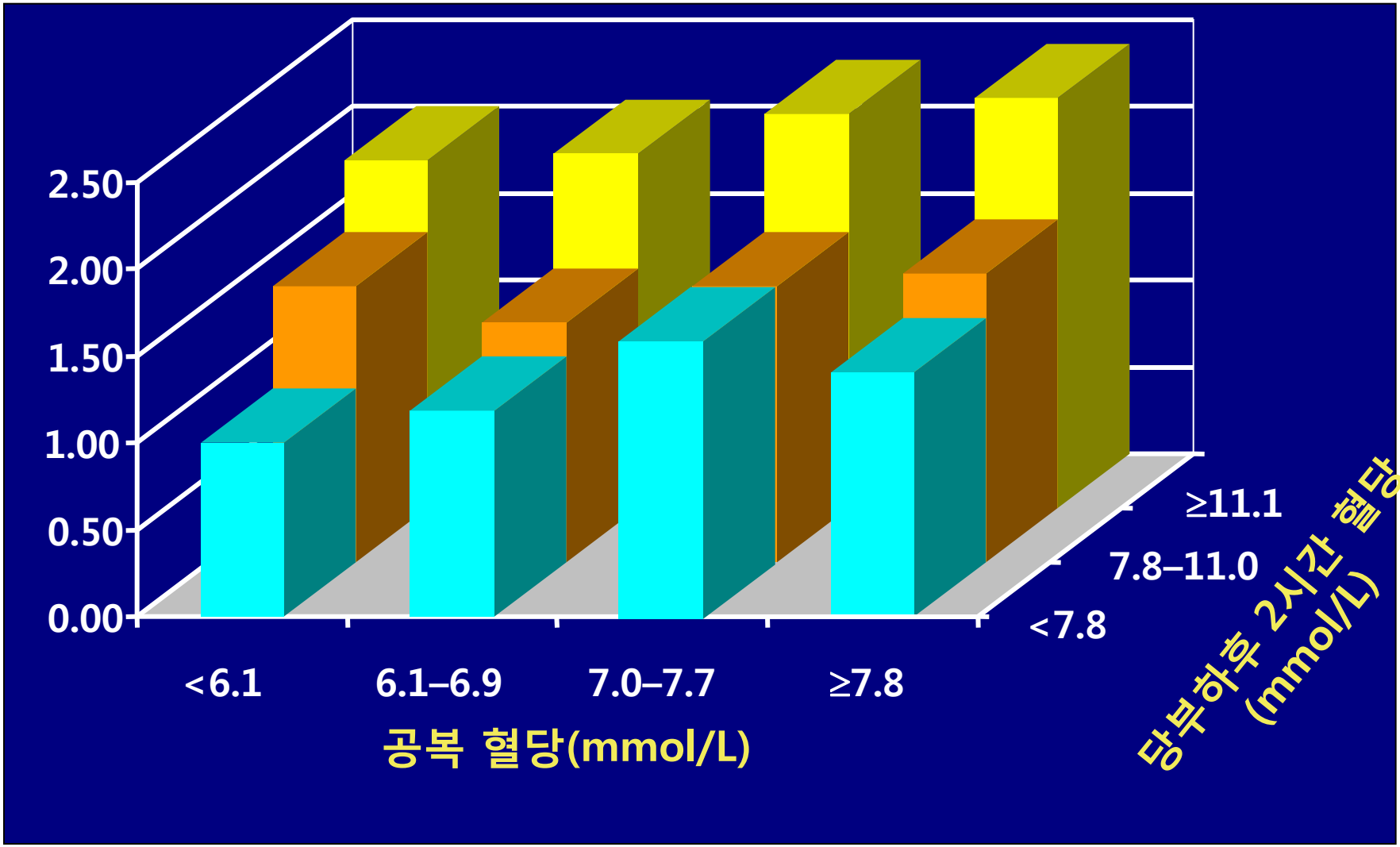
"당화혈색소의 질"

혈당의 증감의 폭이 클 경우, 혈관에 대한 스트레스는 더 크다..

Hirsch, Am J Med 118:S1 21, 2005

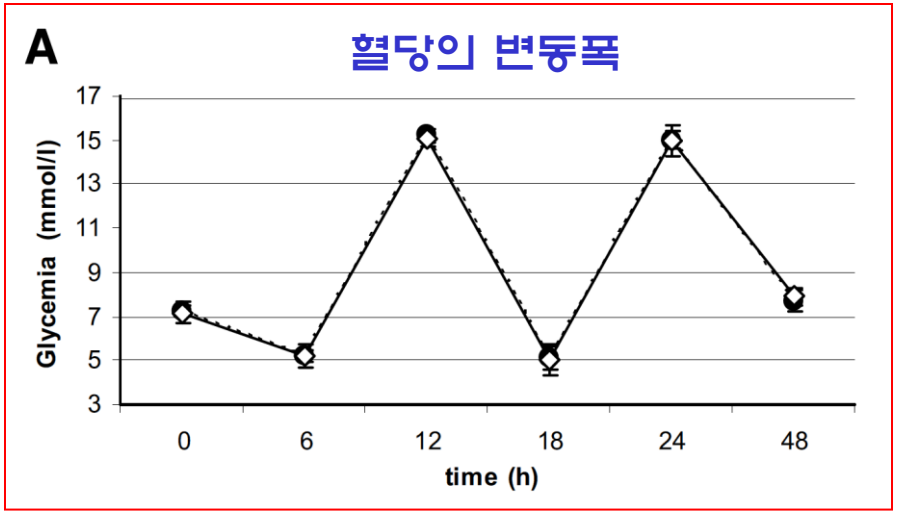
DECODE 연구

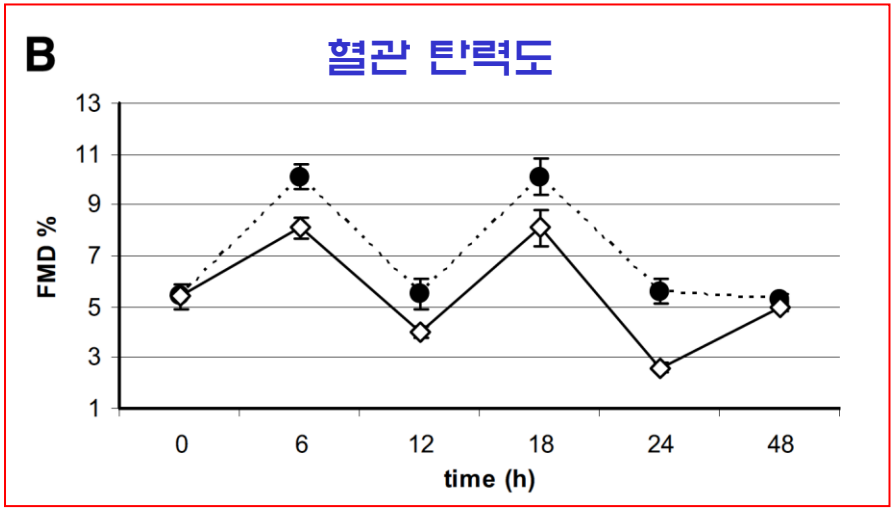
공복고혈당과 식후 고혈당이 심혈관질환에 미치는 영향



DECODE Study Group. Lancet 354:617-21, 1999

혈당의 변동폭과 혈관탄력도와의 관계





혈당이 증가함에 따라서 혈관 탄력도가 급속히 줄어든다

The association of baPWV with 30-minute post-challenge glucose in non-diabetic Korean adults

In 663 subjects with fasting hyperglycemia, 75g OGTT and baPWV were performed

Table 3. Bivariate correlations analyses between the parameters with mean baPWV

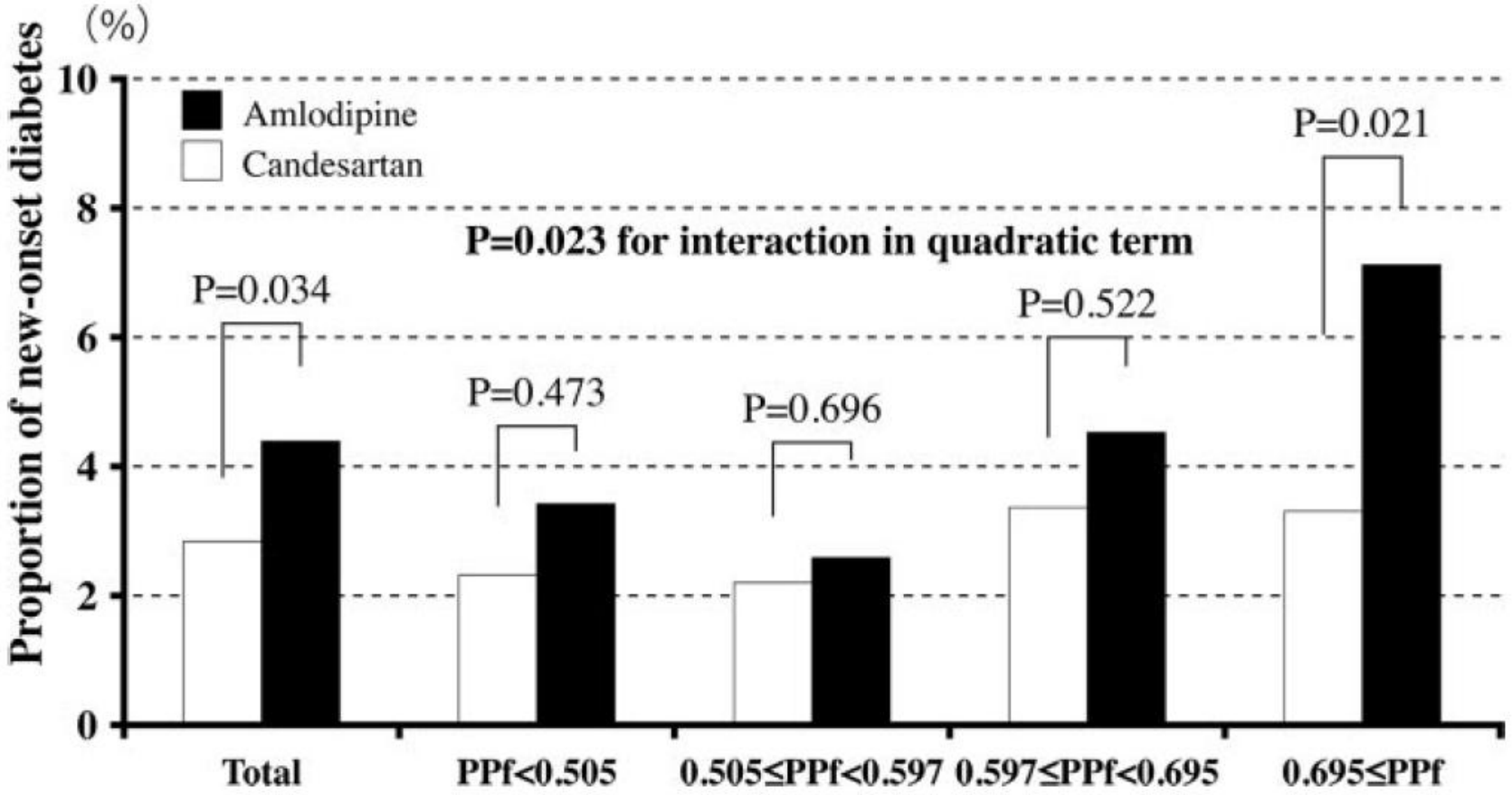
	Correlation coefficient	*P* value
Age, yr	0.465	< 0.01
Height, cm	-0.150	< 0.01
Weight, kg	-0.102	< 0.01
Waist circumference, cm	0.041	0.294
Body mass index, kg/m^2	0.004	0.918
SBP, mm Hg	0.381	< 0.01
DBP, mm Hg	0.268	< 0.01
Total cholesterol, mg/dL	0.145	< 0.01
Triglyceride, mg/dL	0.027	0.484
HDL-C, mg/dL	0.054	0.162
LDL-C, mg/dL	0.126	< 0.01
75 g OGTT 0-min glucose, mg/dL	0.073	0.063
75 g OGTT 30-min glucose, mg/dL	0.174	< 0.01
75 g OGTT 120-min glucose, mg/dL	0.164	< 0.01
HbA1c, %	0.141	< 0.01
HOMR-IR	0.039	0.318

Table 4. Backward multiple regression analysis with mean baPWV as the dependent variables

	beta	*P* value
Age	0.438	< 0.01
Male gender	-0.054	0.118
Body mass index	-0.047	0.164
75 g OGTT 0-min glucose	0.011	0.796
75 g OGTT 30-min glucose	0.099	0.002
75 g OGTT 120-min glucose	0.060	0.138
Total cholesterol	0.038	0.262
Triglyceride	0.084	0.010
SBP	0.337	< 0.01
HOMA-IR	0.032	0.347
R^2	0.346	

Choi ES, Rhee EJ et al.
Korean Diabetes J 34:287-293, 2010

Is pulse pressure a predictor of new-onset DM in high-risk hypertensive patients?
A subanalysis of CASE-J trial



Yasuno S et al. Diabetes Care 33:1122-127, 2010

Association of central aortic pressure indices with development of diabetes mellitus in essential hypertension

- In 178 nondiabetic subjects with hypertension at baseline, mean follow-up period of 31 months
- Central aortic pressure measured with applanation tonometry

Table 3 | Association between independent predictors and new diabetes mellitus using multivariate analysis

Factors	Model 1; HR (95% CI)	Model 2; HR (95% CI)
Central systolic blood pressure	1.24 (1.10–1.41)***	1.36 (1.19–1.55)***
Central diastolic blood pressure	1.17 (0.91–1.51)	1.25 (0.94–1.67)
Augmentation index corrected at heart rate 75 beats/min	1.58 (1.11–1.58)*	1.71 (1.16–2.52)**

Chen JY et al. Am J Hypertens 23:1069-1073, 2010

Arterial stiffness in diabetes

당뇨병 환자에서 arterial stiffness는 증가되어있으며 aging에 따른 증가가 더 심하게 나타난다

당뇨병 환자에서 혈압이 조절이 않 될 경우 arterial stiffness가 더 증가한다

식후 고혈당이 심혈관 질환의 위험도가 더 높다

합병증이 있을수록 arterial stiffness가 더 심해진다

Arterial stiffness가 당뇨병 유발의 위험인자일 수 있다

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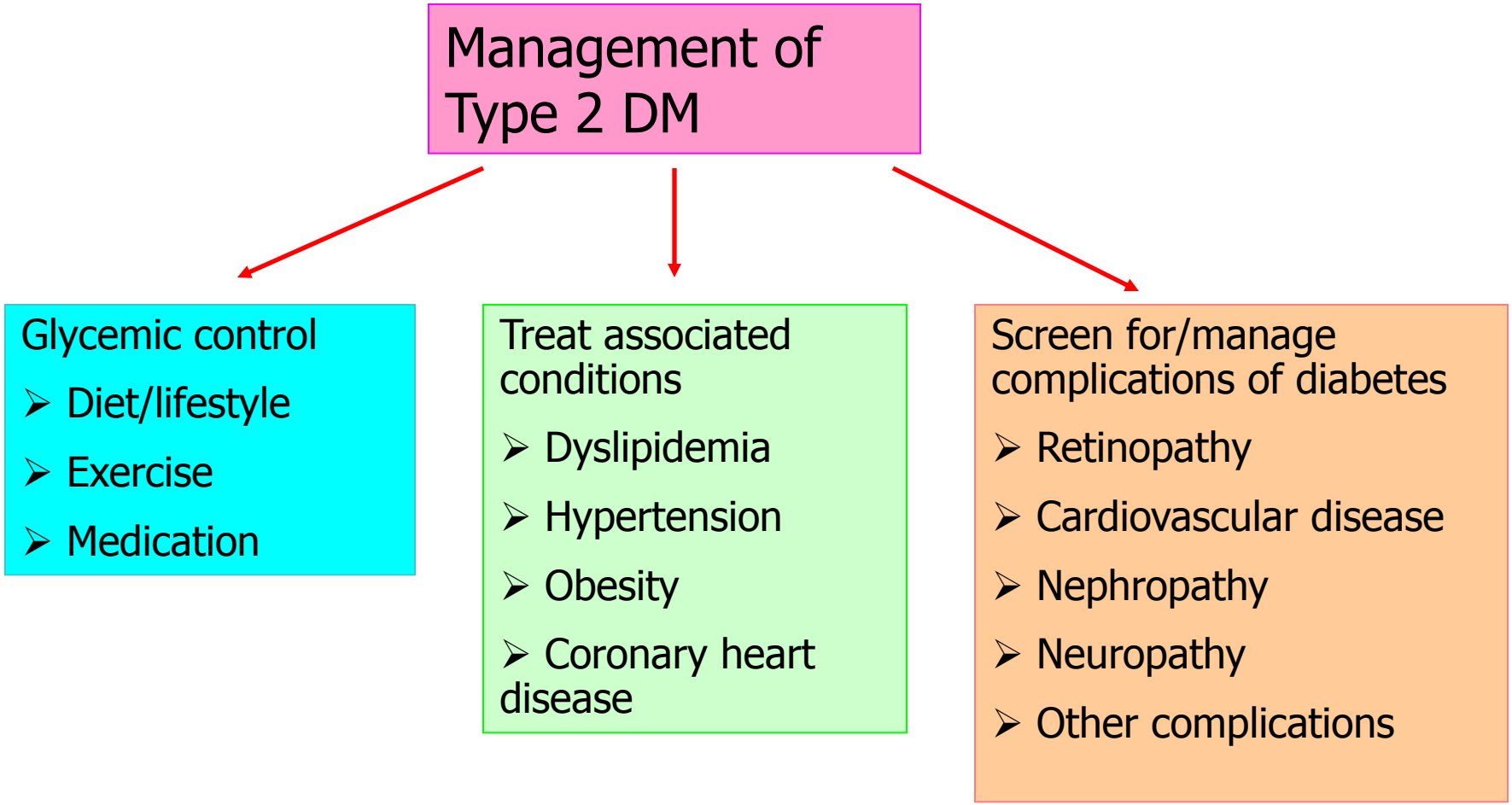
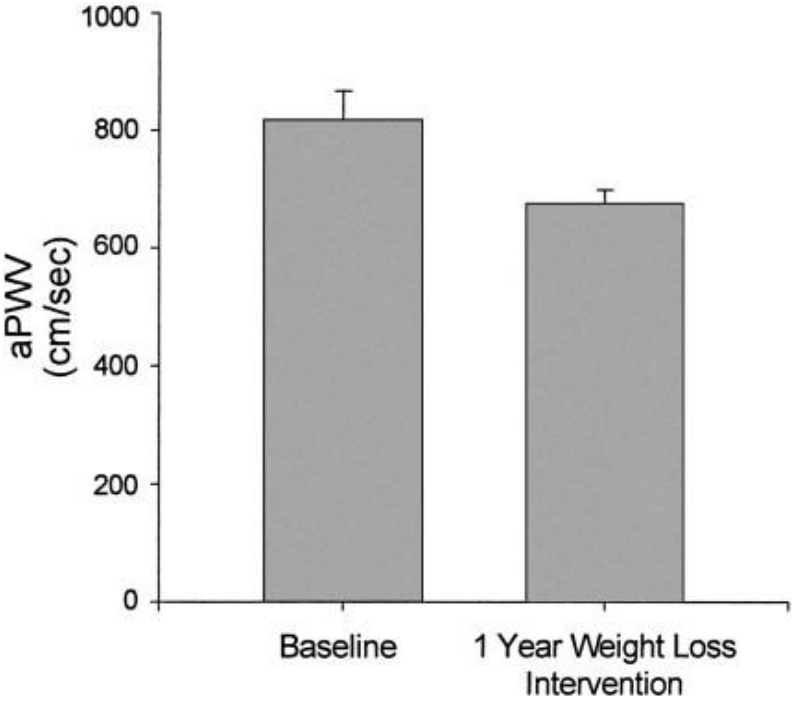
- 치료 방법

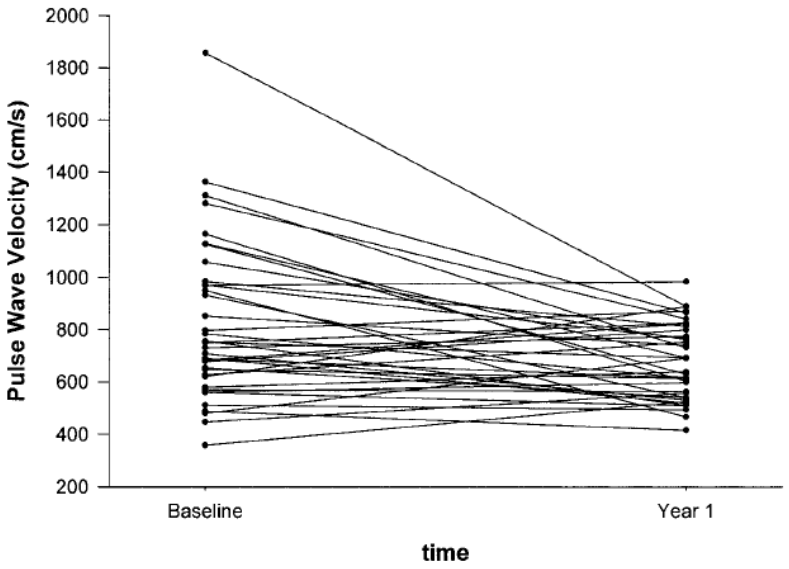
Essential elements in comprehensive diabetes care of type 2 DM



Effect of weight loss and nutritional intervention on arterial stiffness in type 2 diabetes

Arterial stiffness was assessed by measuring aortic PWV at baseline and at completion of a 1-year weight loss intervention with weight loss intervention + orlistat or placebo



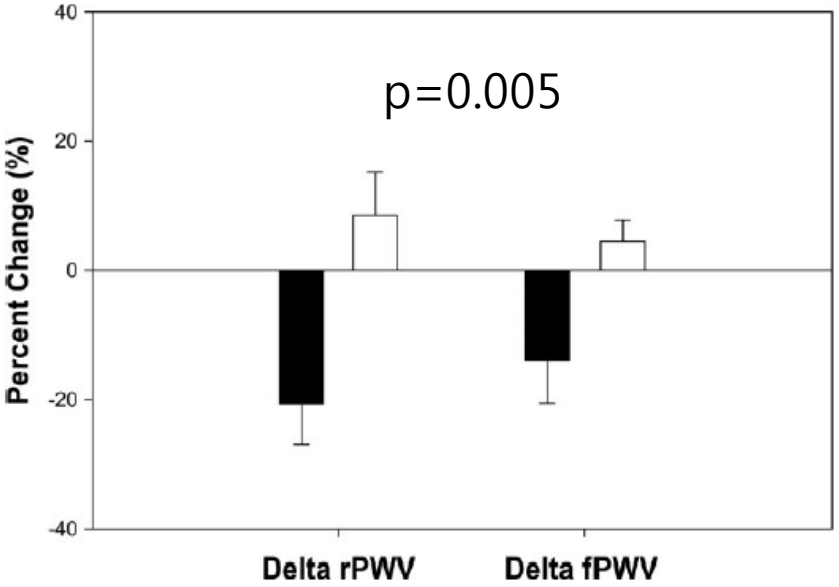


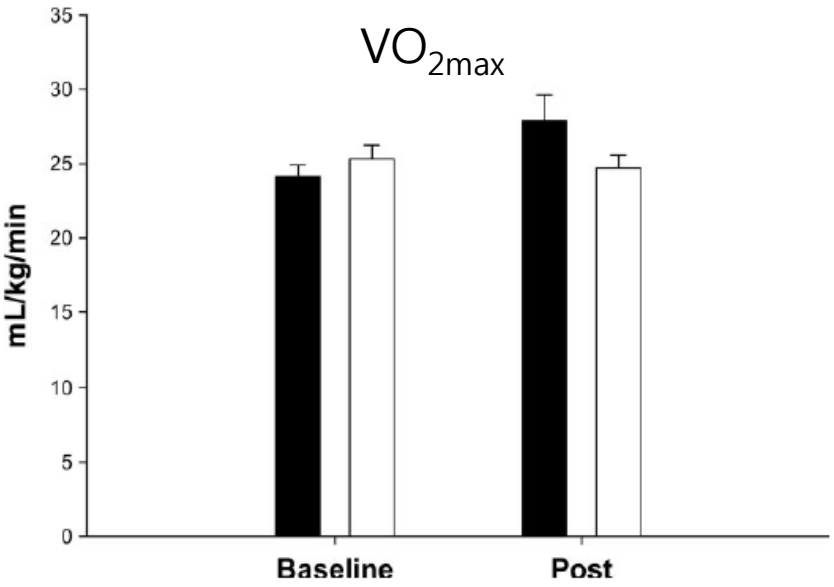
•Mean weight loss in 1 years was 7.8% from baseline Individuals in highest baseline values manifested the largest improvements

Barinas-Mitchell E et al. Diabetes Care 29:2218-2222, 2006

Short-term aerobic exercise reduces arterial stiffness in older adults with type 2 diabetes, hypertension, and hypercholesterolemia

- In 36 older adults (mean age 71 yrs) with T2DM, HTN, hyperChol
- Aerobic and nonaerobic exercise group, 3 months



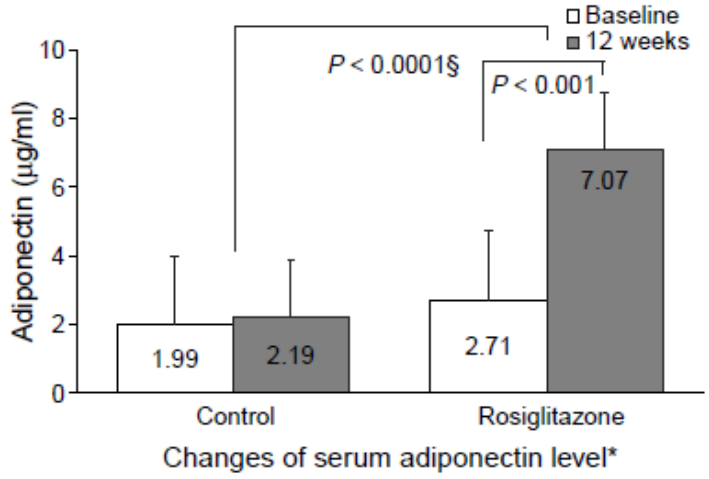


■ aerobic
□ nonaerobic

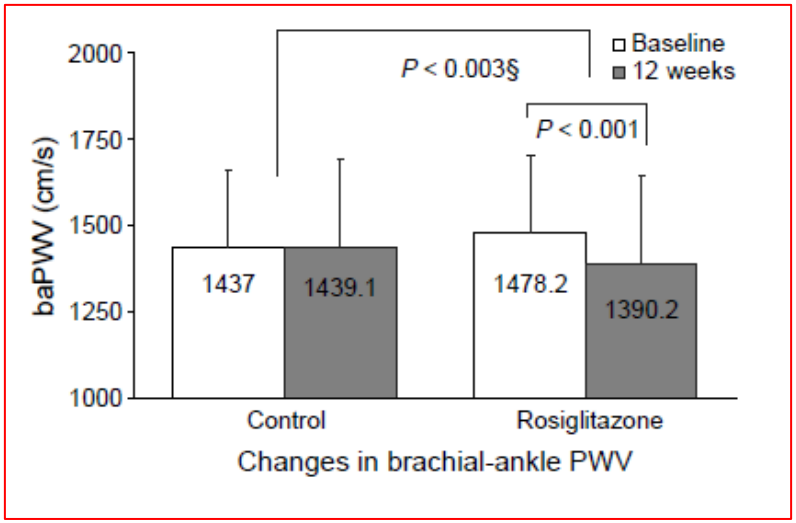
Madden KM et al. Diabetes Care 32:1531-1535, 2009

Effect of rosiglitazone on arterial stiffness in subjects with prediabetes and non-diabetic MS subjects

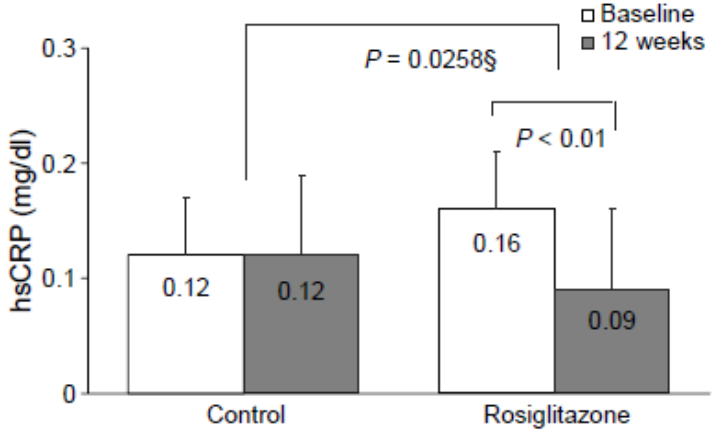
99 subjects with prediabetes or nondiabetic MS subjects were treated with rosiglitazone or placebe for 12 weeks



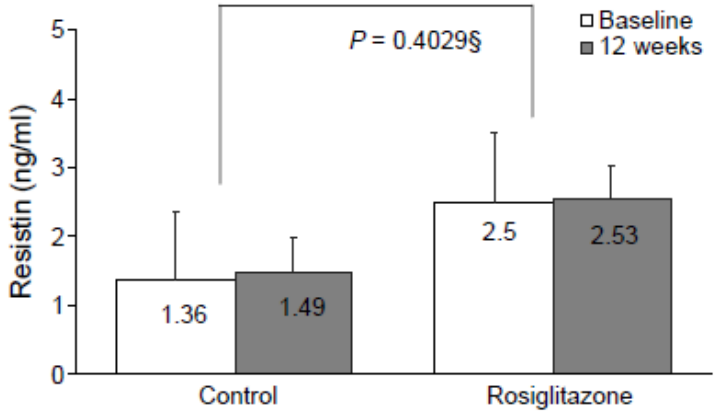
Changes of serum adiponectin level*



Changes in brachial-ankle PWV



Changes of serum high sensitive CRP*



Changes of serum resistin*

Kim SG et al. EJE 154:433–440, 2006

Effect of ARB on arterial stiffness in T2DM pt with HTN

Table 2. Changes in central hemodynamic parameters and PWV from baseline to week 12

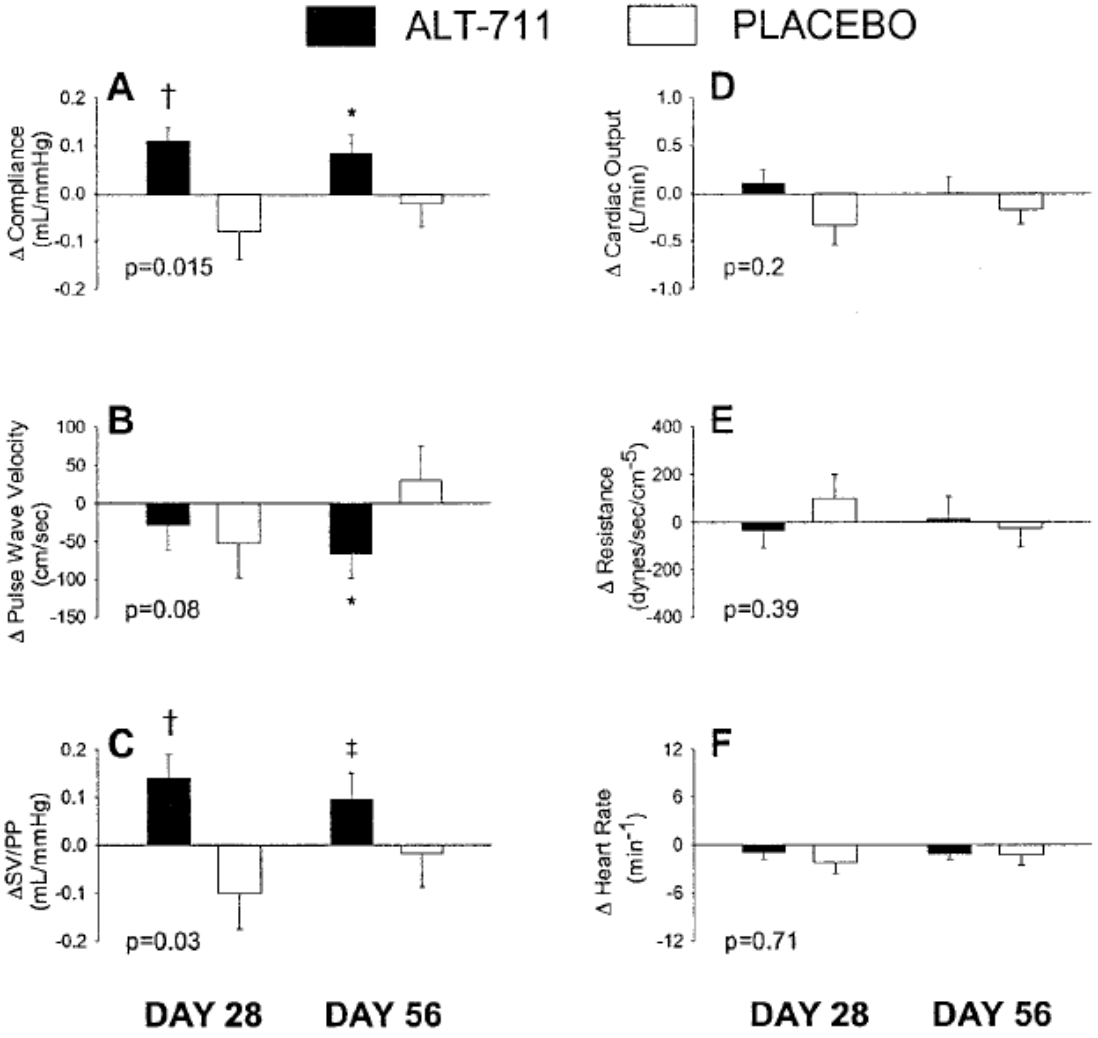
Sphygmocor parameter	Baseline value	Week 12 value	*P* value
Heart rate, bpm	71.3±11.4	69.7±10.8	0.054
Aortic augmentation index, %	29.5±7.4	27.8±7.9	<0.05
Aortic pulse pressure, mm Hg	44.4±8.5	38.9±10.2	<0.001
Subendocardial viability ratio	144.5±26.3	147.9±28.1	0.060
Ejection duration, msec	372.0±74.0	368.0±41.0	0.092
PWV, m/sec (n=47)	10.9±1.1	10.0±1.2	<0.05

A significant decrease in BP after 2 weeks of treatment

Kim JH et al. Diabetes Metab J 35:346-242, 2011

Improved arterial compliance by AGE crosslink breaker

- In 93 nondiabetic subjects with increased arterial stiffness in 9 US centers
- ALT-711, an oral nonenzymatic AGE breaker or placebo for 56 days



Kass DA et al. Circulation 104:1464-1470, 2001

당뇨병에서 Arterial stiffness의 치료

체중 감소, 운동

PPAR-γ agonist

RAAS의 차단

AGE crosslink breaker

결론

당뇨병 환자에서 arterial stiffness 증가

Survival, CVD risk와 연관성

내피세포 기능 이상, AGE, RAAS system의 활성화, ROS 증가가 기전

치료: 생활습관 교정, PPARγ agonist, RAAS blockade, AGE crosslink breakers


감사합니다