Clinical Impact of *Whole Blood Viscosity* on CVD Occurrence

GNUH
창원경상대학교병원

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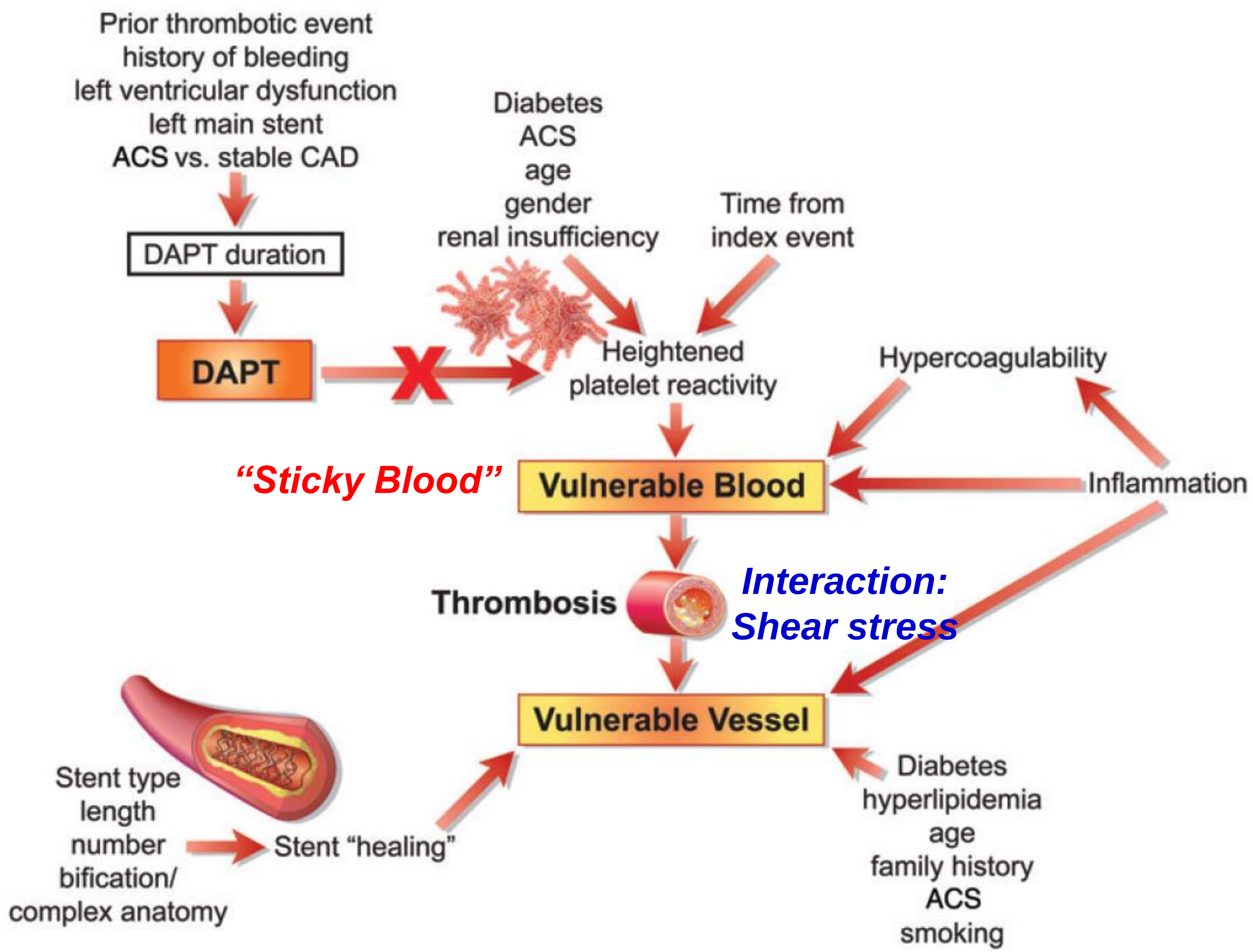
Changwon Hospital, Korea.

Mechanism of Atherothrombosis:
"Vulnerable Vessel" ← Shear stress →"Sticky Blood"



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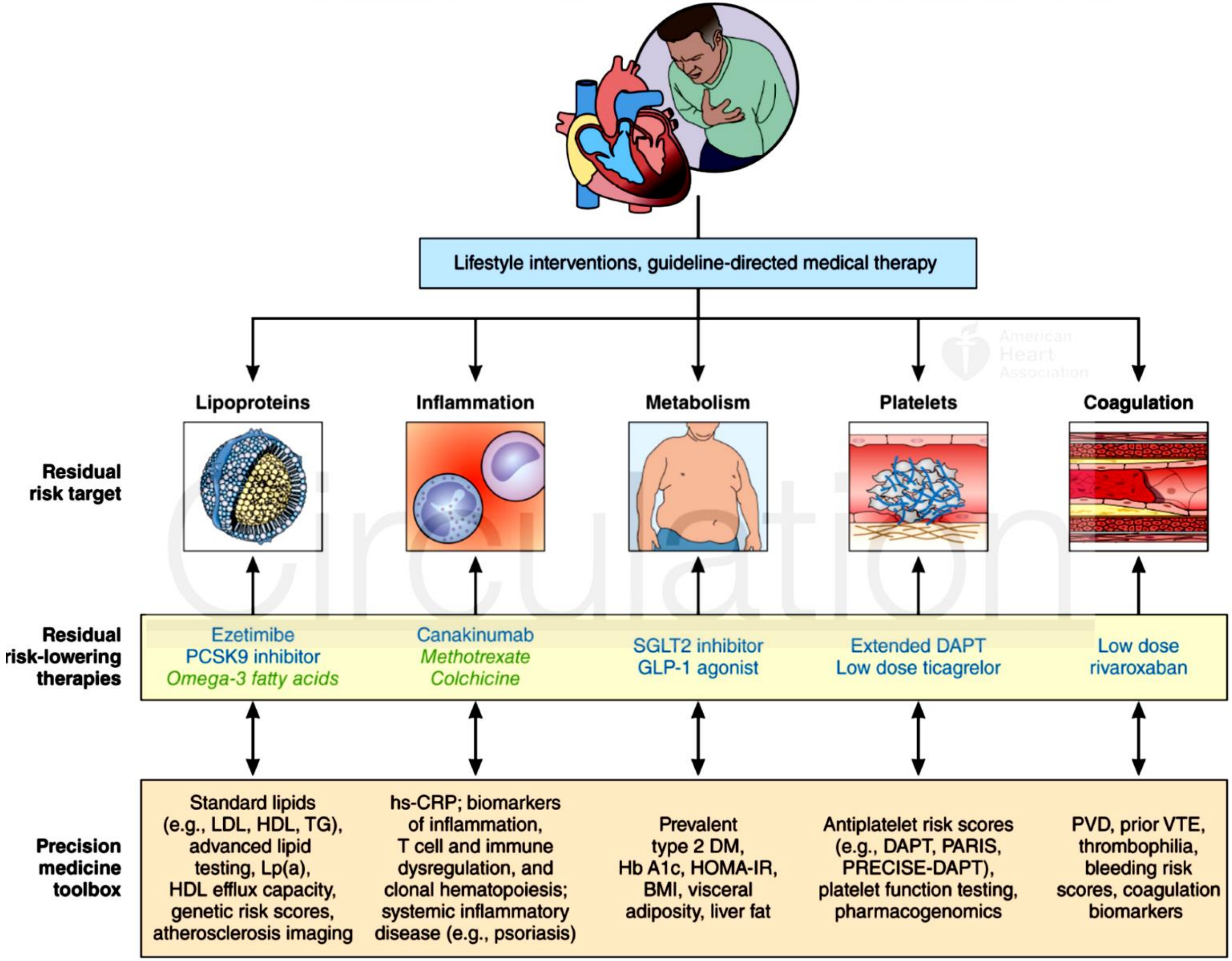
Gurbel P, et al. *Eur Heart J* 2014;35:951-4.

A Proposed Conceptual Framework for Addressing Residual ASCVD Risk



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Patel KV, et al. Circulation 2018;137:2551-3.

The Pathogenesis of CV Disease is Complex

- **Risk factors aiding in the development of ASCVD have been long promoted, such as genetics, dyslipidemia, hypertension, smoking, lack of adequate exercise, and metabolic syndrome.**
- **The pathogenesis of chronic CV diseases is still not fully understood.**
- **States of chronic, lower elevations of viscosity are clinically less obvious, and left unappreciated, can ultimately shorten one's lifespan by contributing to CV disease.**

"Blood" is thicker than "Water"

Sloop G, et al. Ther Adv Cardiovasc Dis 2015;9:19–25.

Viscosity in Prediction of CVD & Mortality

- **Scottish Heart Health Extended Cohort study (n = 3,386; 30–74 yo; 17-year FU)**

Age- & sex- (squares) and multivariable- (circles) adjusted HRs: Tertile groups of plasma viscosity

Table 3. Reclassification of 10-year predicted risk and changes in risk discrimination for cardiovascular disease and total mortality after addition of plasma viscosity to a model including ASSIGN risk score variables[a]

	Cardiovascular disease	Total mortality
Change in c-statistic[b]	0.002 (0.000–0.005)	0.006 (0.001–0.008)
Net reclassification improvement, categorical±		
Overall	0.0156 (−0.0196 to 0.0560)	0.0024 (−0.0324 to 0.0581)
With event	0.0174 (−0.0201 to 0.0508)	−0.0033 (−0.0347 to 0.0520)
Without event	−0.0018 (−0.0079 to 0.0140)	0.0057 (−0.0081 to 0.0134)
Integrated discrimination improvement	0.0022 (0.0005–0.0038)	0.0051 (0.0022–0.0081)
Relative integrated discrimination improvement (%)	2.40 (0.67–4.39)	4.14 (1.97–6.46)

Data are presented as point estimates (95% confidence intervals).

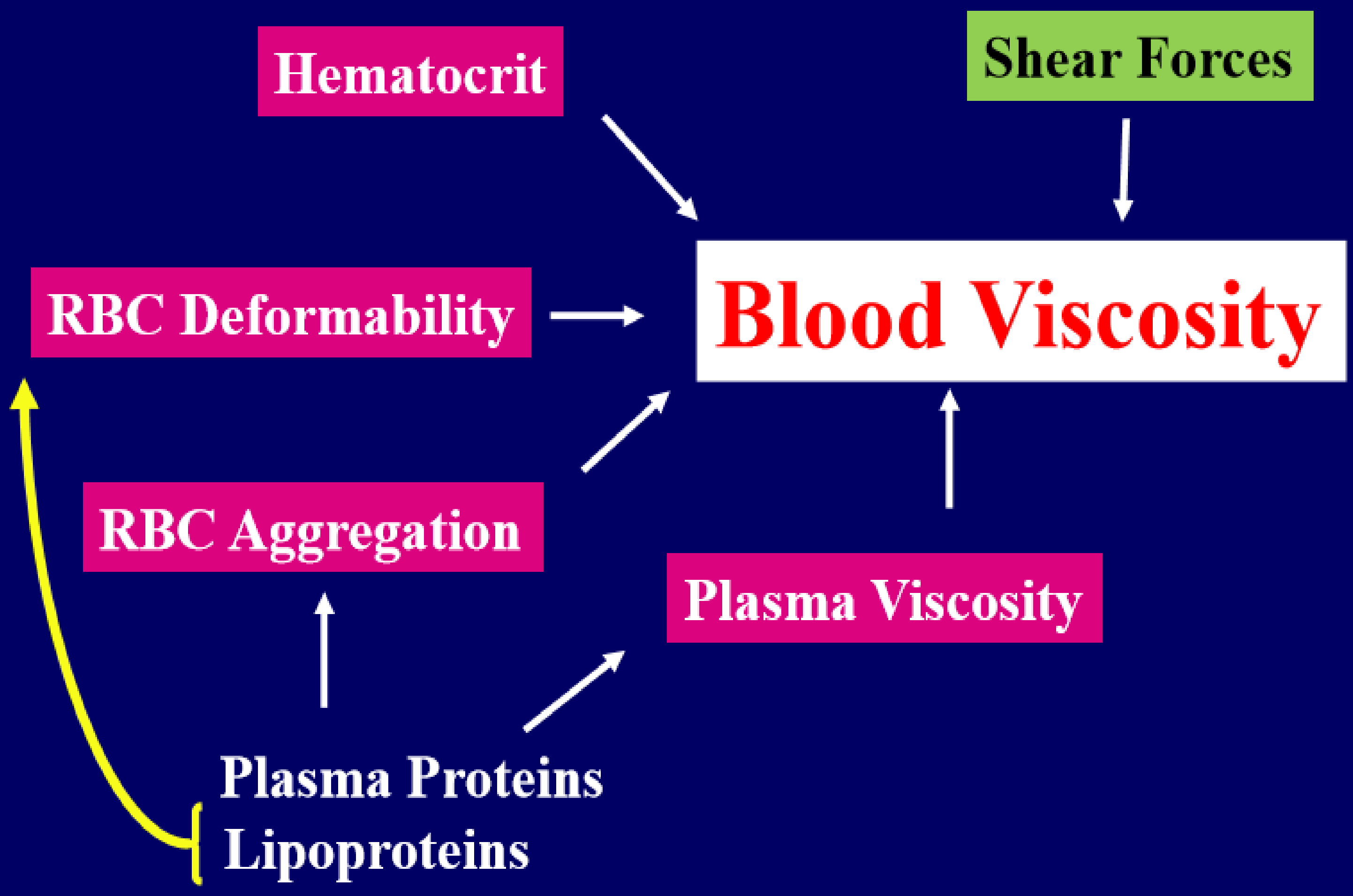
±Risk categories were <10, 10–20 and ≥20%.

[a]ASSIGN risk score variables are age and sex, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, diabetes mellitus, number of cigarettes smoked per day, family history of cardiovascular diseases and the Scottish Index of Multiple Deprivation.

Peters SA, et al. Eur J Prev Cardiol 2016.

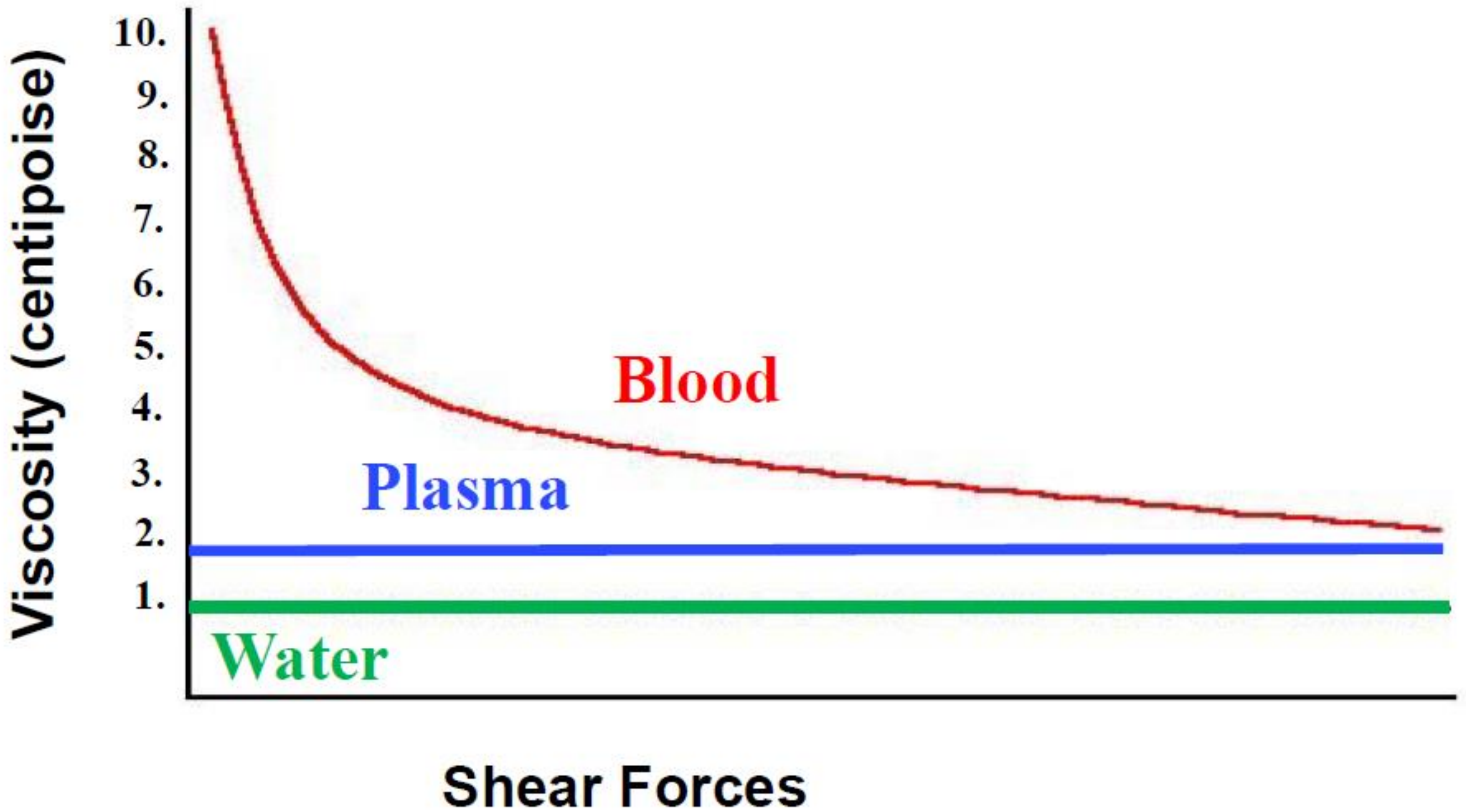
Mediators of Blood Viscosity

- **Viscosity: a resistance to flow in a blood vessel**
  → stickiness/heaviness + thrombogenecity



Viscosity of Newtonian & Non-Newtonian Fluids

- **Blood: Non-Newtonian Fluid**



- **Viscosity of blood decreases as shear rate increases due to both deformability and disaggregation of RBCs.**

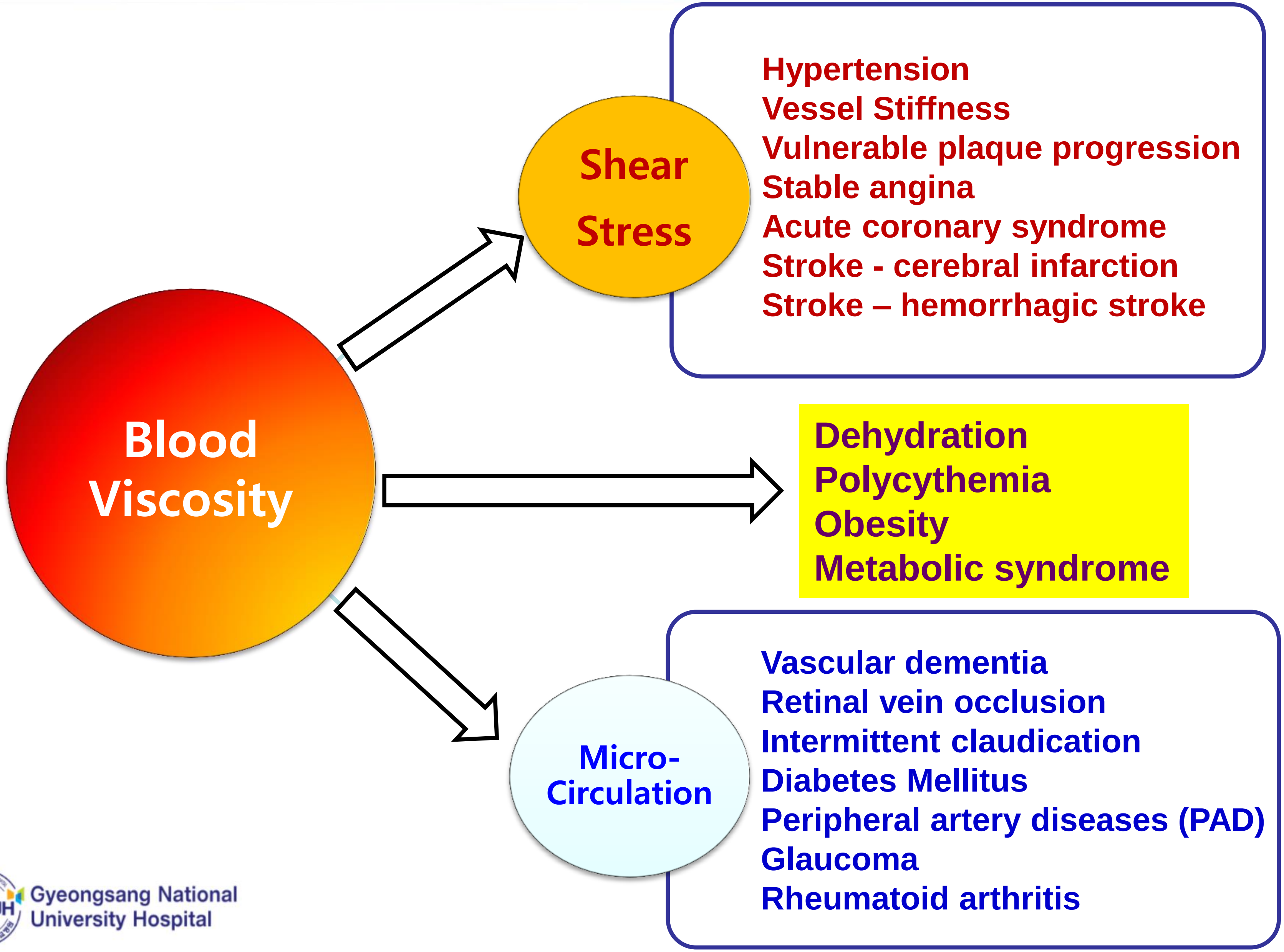
Sloop G, et al. Ther Adv Cardiovasc Dis 2015;9:19–25.

Association Btw Classic CVD RFs and Viscosity

	Fibrinogen	Plasma Viscosity	RBC deformability	RBC Aggregation
Htn	+	+	+	+
Lipids	+	+	+	+
Tob	+	+	+	+
DM	+	+	+	+
Obesity	+	+	+	+
Stress	+	+	+	+

Ernst E, et al. Thromb Haemost 1993;19.

CV Disease Occurrence Related with Viscosity



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Influence of Viscosity on Blood Pressure

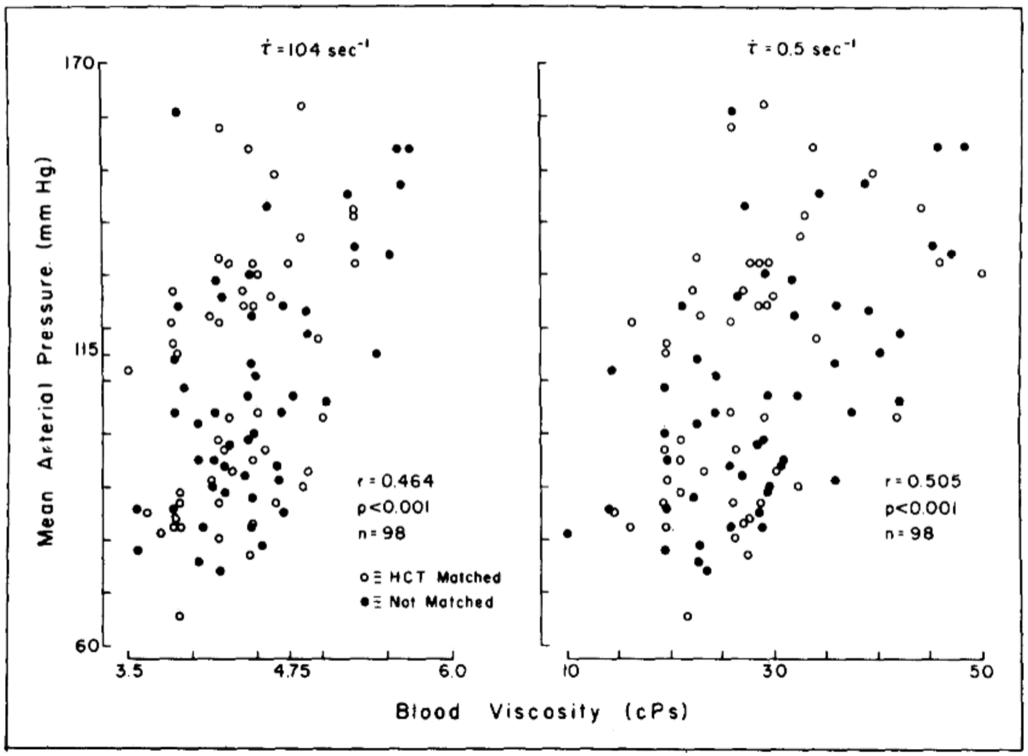
- **Determinants of blood pressure**
  - Cardiac output
  - Systemic vascular resistance

- **Determinants of systemic vascular resistance**
  – Vascular tone
  – Blood viscosity

- **Chronic hyperviscosity increases the mechanical load on the elastic elements of the vasculature, leading to**
  - acceleration of mechanical fatigue
  - reduced vascular compliance
  - decreased arterial compliance
  - accelerated arterial stiffness

Sloop G, et al. Ther Adv Cardiovasc Dis 2015;9:19–25.

Control of Blood Pressure



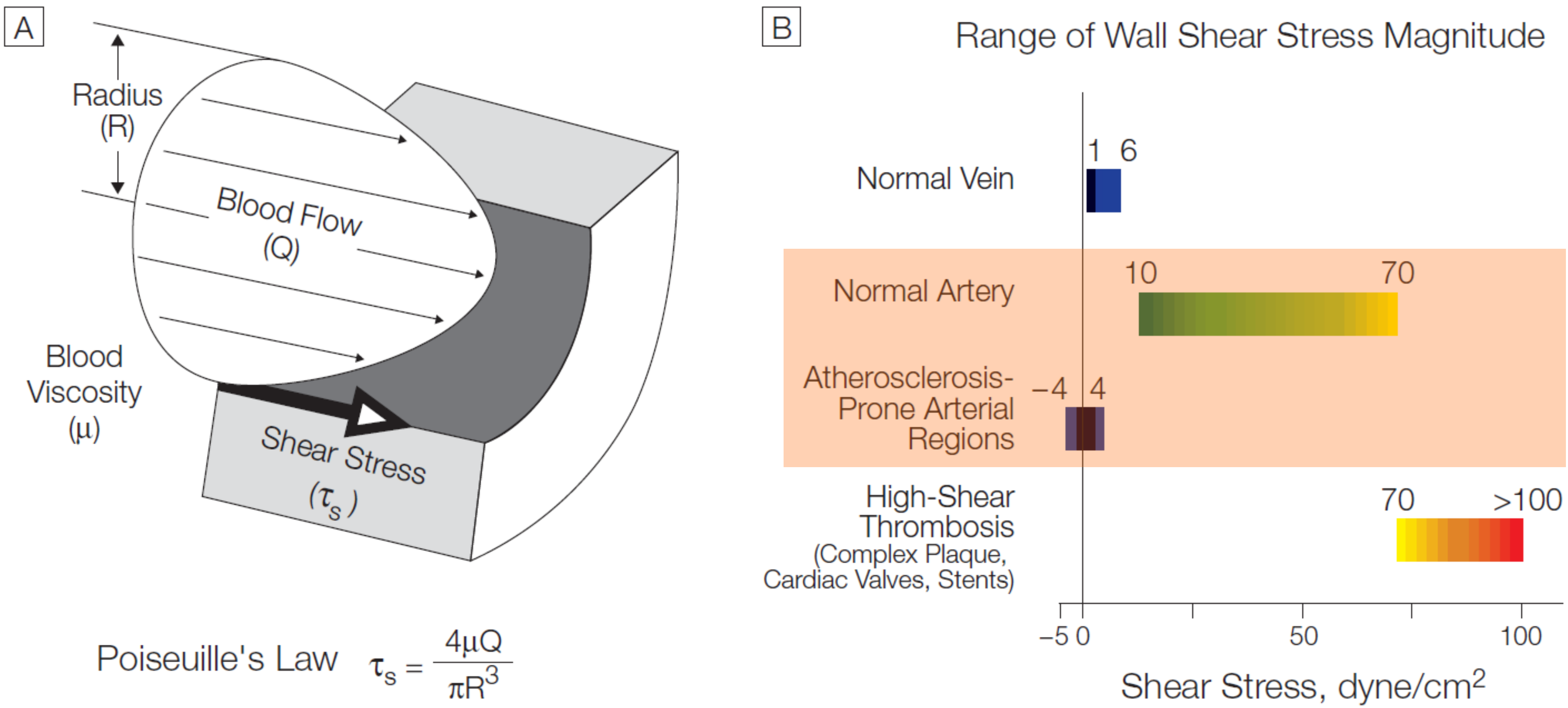
Close relationship between blood viscosity & arterial BP

- **Strategy of BP Control**
  - Salt restriction: limited
  - Antihypertensive agent
  - Reduction of blood viscosity: ex) phlebotomy

Letcher RL, et al. Am J Med. 1981;70(6):1195-1202.

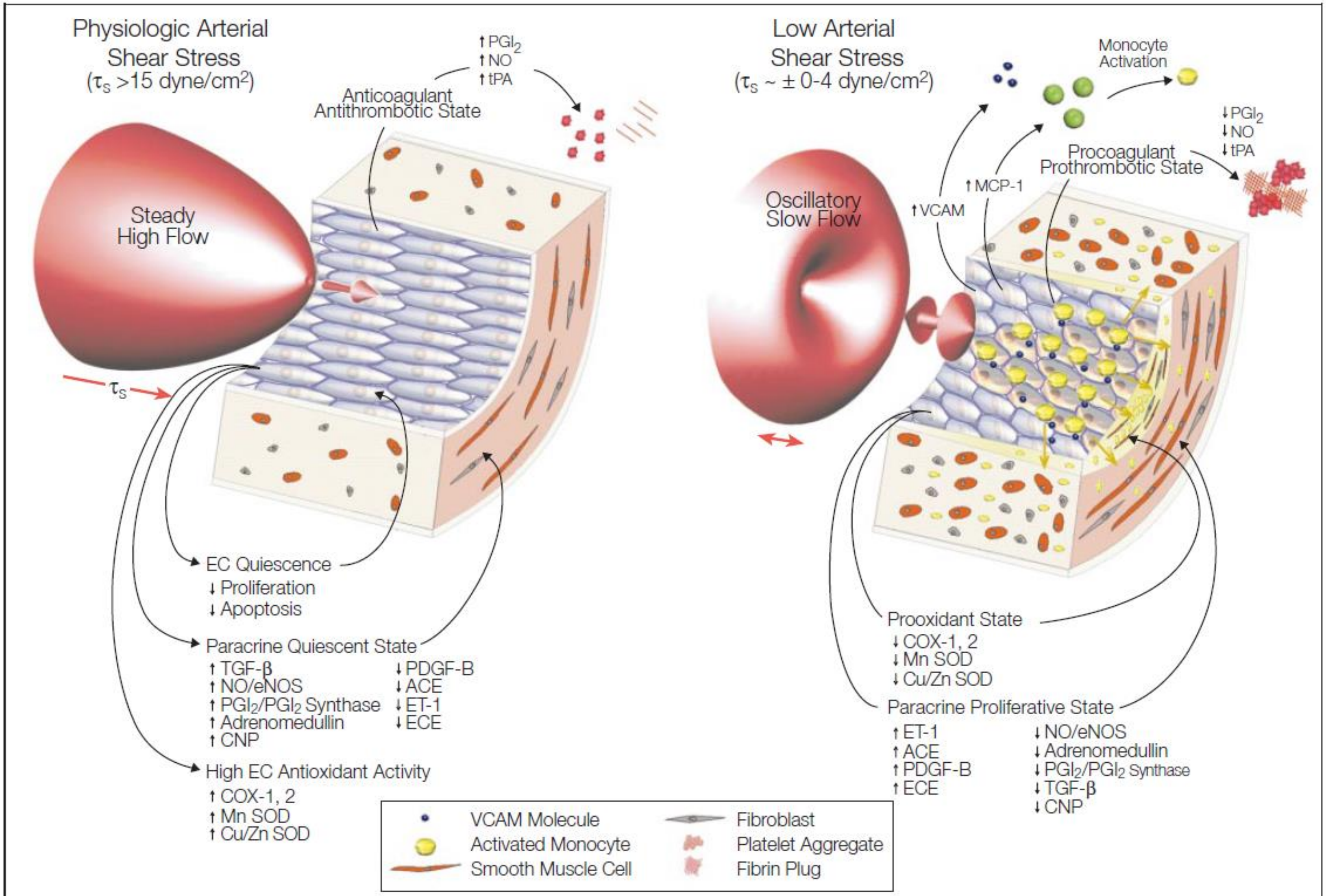
Concept of Atherogenesis: Wall Shear Stress in Vessel

- **Wall shear stress = Viscosity x Wall shear rate**



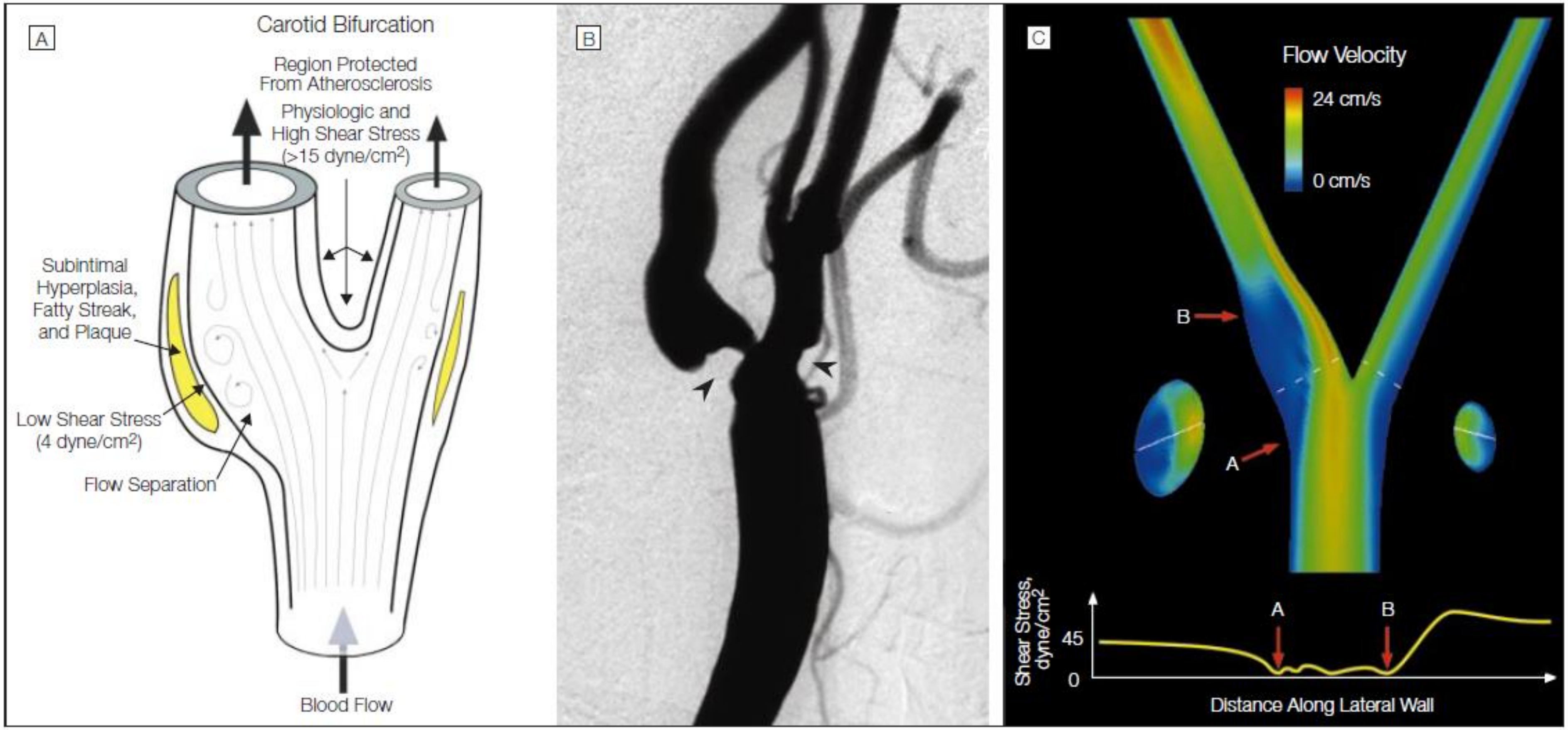
Malek AM, et al. JAMA 1999;282:2035.

Model of Atherogenesis



Malek AM, et al. JAMA 1999;282:2035.

Localization of Atherosclerotic Lesions in Bifurcation



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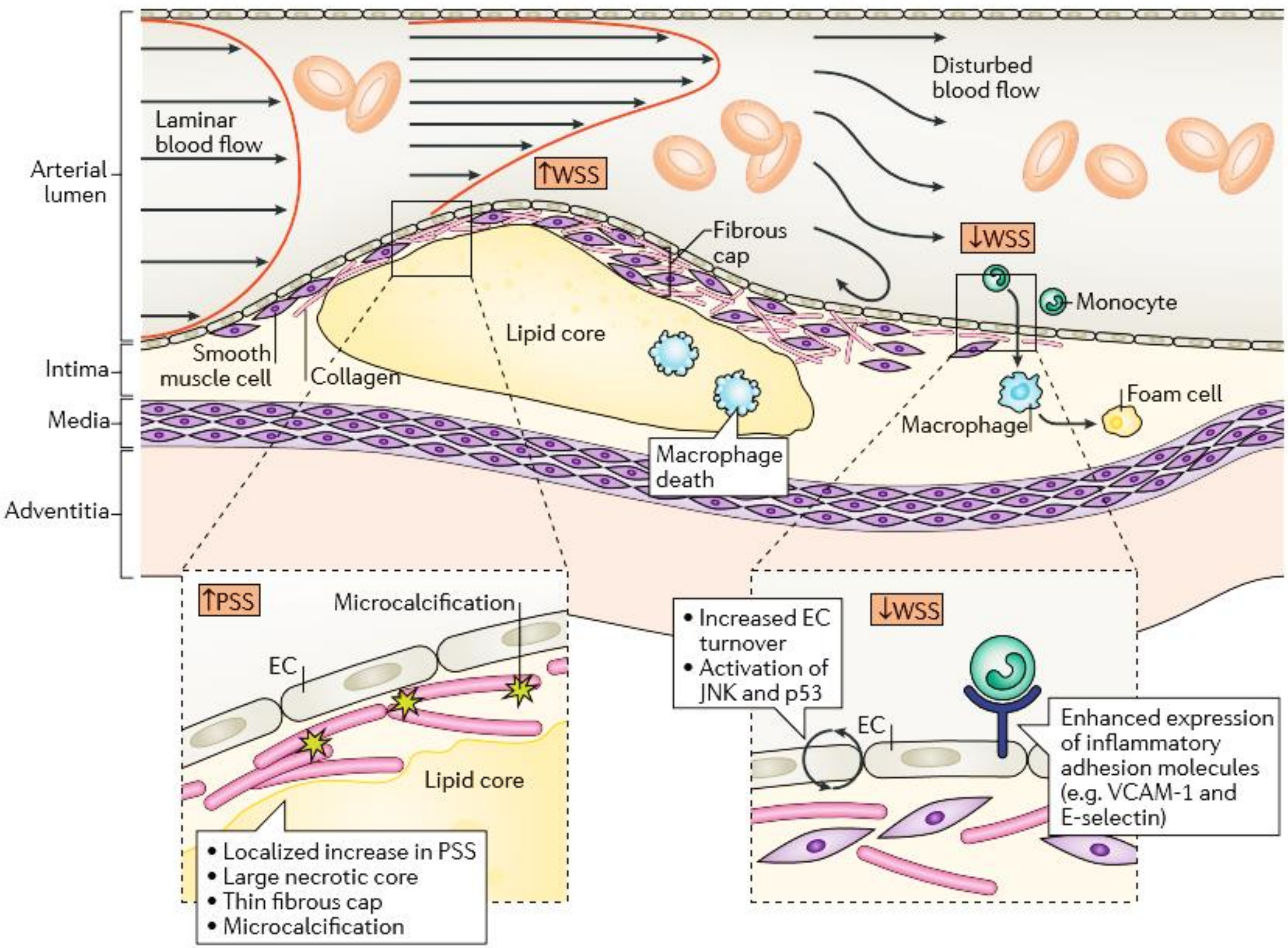
Malek AM, et al. JAMA 1999;282:2035.

Biomechanical Forces in Atherosclerosis



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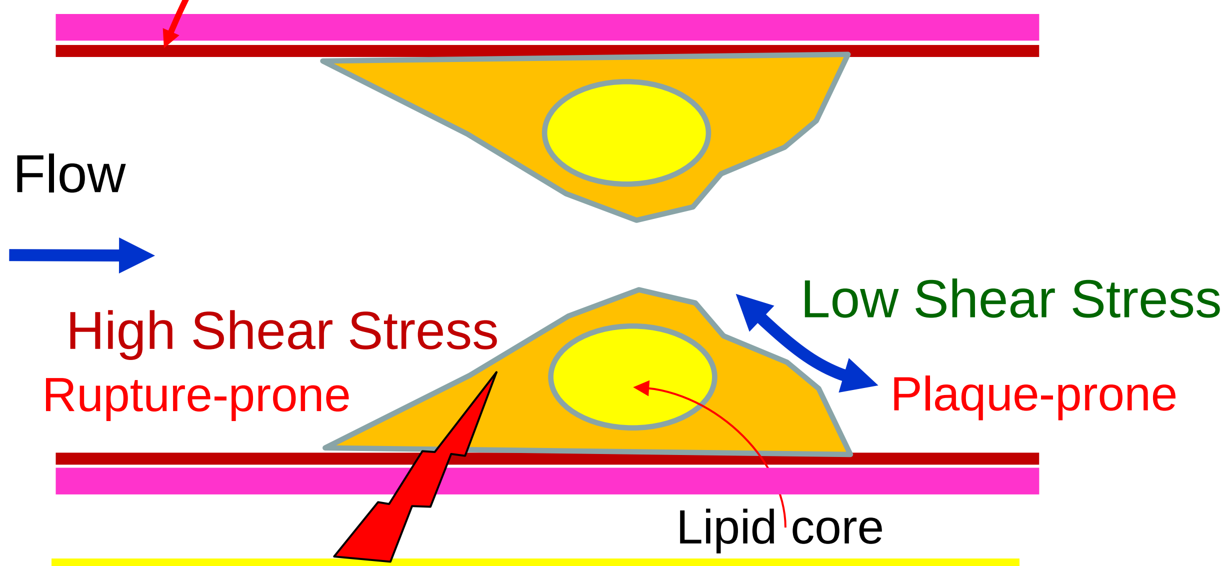
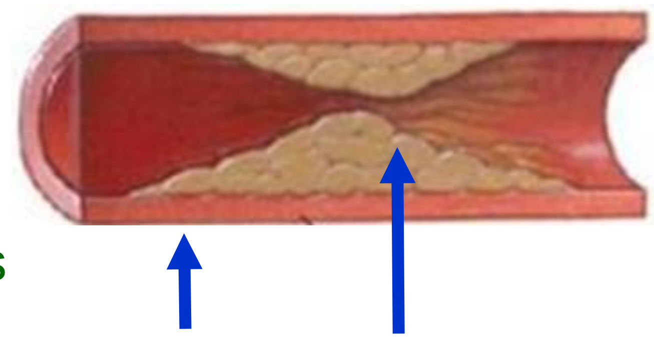
Brown AJ, et al. Nat Rev Cardiol. 2016;13(4):210-20..

Influence of WSS on Plaque Progress

Uni-directional Shear Stress = **15** dyne/cm^2





$$A_v = {}_A V$$

Rupture

Wall shear stress >300 dyne/cm^2

- **How to reduce plaque rupture in established atheroma?**
  - Plaque stabilization: ex) statin
  - ↓ shear rate: BP control, avoid strenuous activity
  - ↓ blood viscosity: ???

Brown AJ, et al. Nat Rev Cardiol. 2016;13(4):210-20..

Identification of High-risk Plaque to Cause ACS

TABLE 3 Comparison of C-Index Among Models With Various Combinations of Hemodynamic Parameters

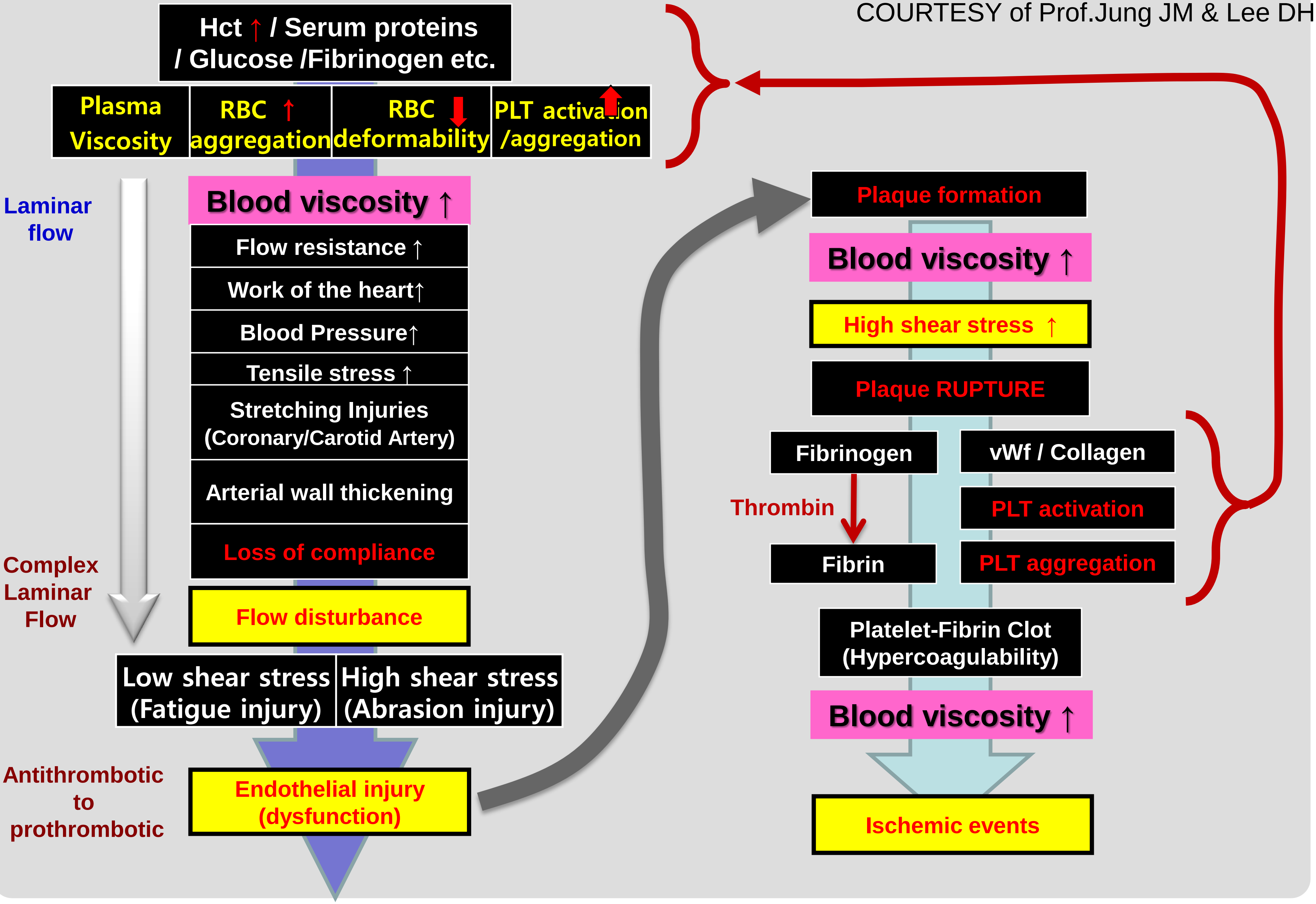
Prediction Models	C-index	p Value*	NRI	p Value*	IDI	p Value*
Model 2 (%DS + Lesion length + APC)	0.747					
Model 2 + FFR_{CT}	0.775	0.570	0.105	0.455	0.087	0.210
Model 2 + APS	0.765	0.197	0.279	0.047	0.099	0.037
Model 2 + WSS	0.772	0.027	0.377	0.007	0.266	<0.001
Model 2 + ΔFFR_{CT}	0.787	0.031	0.552	<0.001	0.260	<0.001
Model 2 + FFR_{CT} + APS	0.781	0.445	0.180	0.210	0.176	0.043
Model 2 + FFR_{CT} + WSS	0.778	0.085	0.113	0.426	0.246	0.002
Model 2 + FFR_{CT} + ΔFFR_{CT}	0.790	0.053	0.336	0.018	0.240	0.006
Model 2 + APS + WSS	0.778	0.038	0.453	0.001	0.360	<0.001
Model 2 + APS + ΔFFR_{CT}	0.791	0.005	0.429	0.003	0.312	<0.001
Model 2 + WSS + ΔFFR_{CT}	0.786	0.006	0.435	0.002	0.333	<0.001
Model 2 + FFR_{CT} + WSS + ΔFFR_{CT}	0.789	0.021	0.344	0.016	0.304	<0.001
Model 2 + FFR_{CT} + WSS + APS	0.783	0.079	0.244	0.090	0.335	<0.001
Model 2 + FFR_{CT} + ΔFFR_{CT} + APS	0.793	0.041	0.274	0.057	0.289	0.002
Model 2 + WSS + ΔFFR_{CT} + APS	0.786	0.013	0.409	0.004	0.400	<0.001
Model 2 + FFR_{CT} + WSS + ΔFFR_{CT} + APS	0.789	0.014	0.287	0.047	0.368	<0.001

- **Missing value of CFD analysis: blood viscosity (~ WSS)**

Lee JM, et al. JACC Cardiovasc Imaging. 2018 Mar 14.

Proposed Mechanism of Viscosity on IHD Occurrence

COURTESY of Prof.Jung JM & Lee DH.



GNUH Experience: WBV Measurement

KFDA - Class 1 A22240.01(1)

Scanning 모세관점도계의 원리를 이용한 임상용 전자동혈액점도검사기 상용화

KFDA Class I: 2009 GMP (ISO 13485) 인증

US FDA 2010 March 인증

보건복지부 신의료기술 고시2014. 2. 6

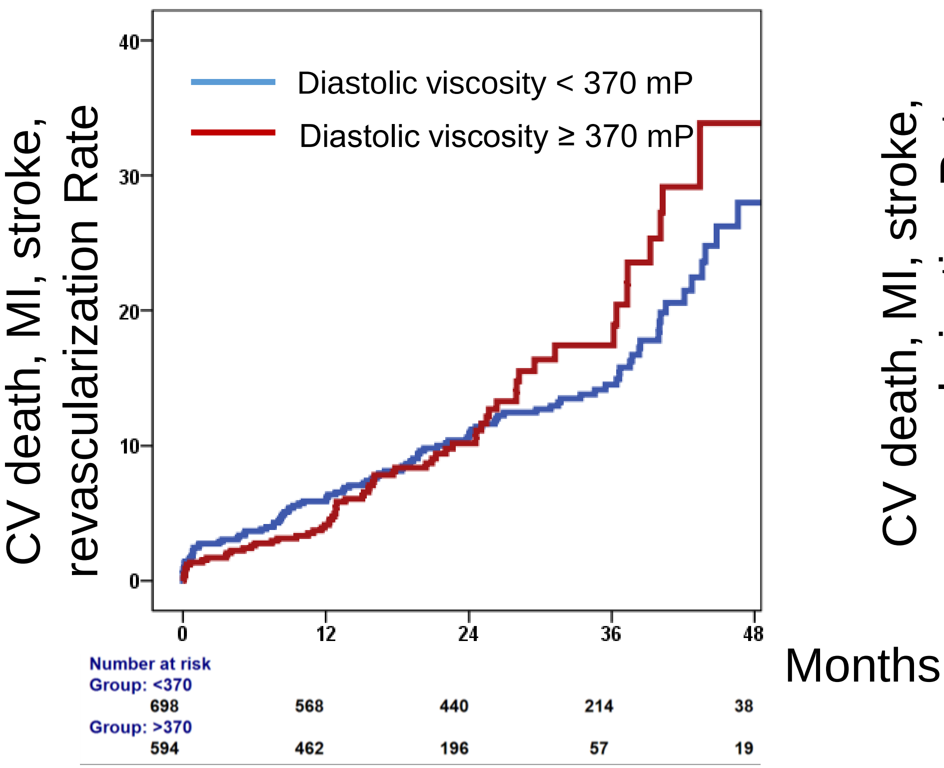
(351. 혈액점도검사 [스캐닝 모세관법])

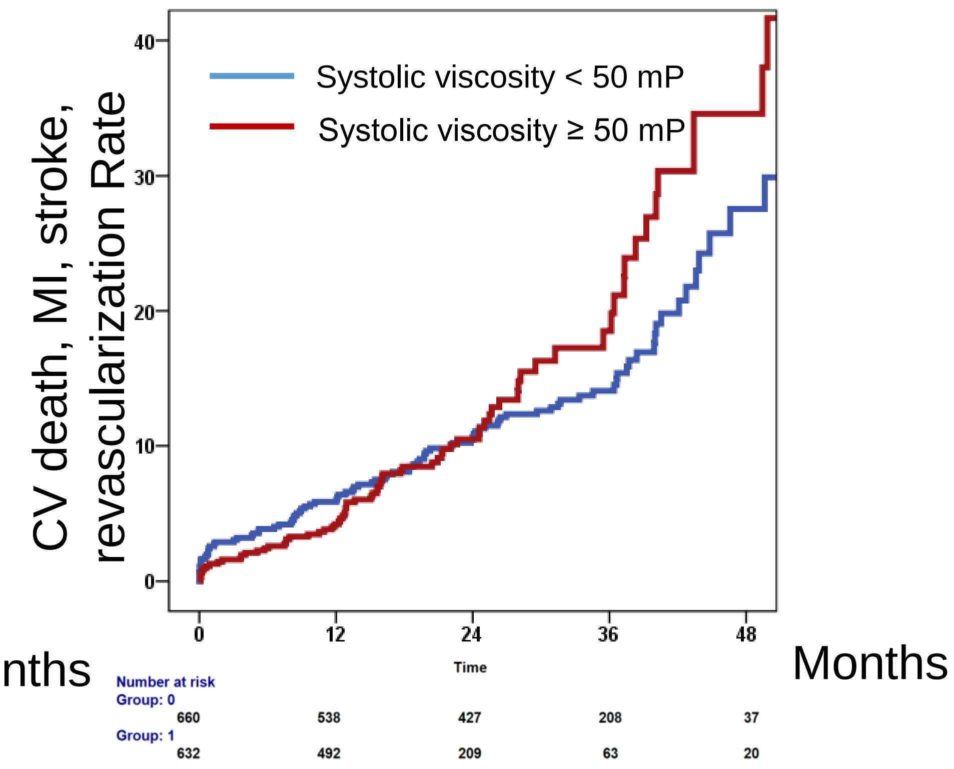
3 ml whole blood
in EDTA vacutainer

Viscosity measurement < 5 min

Impact of WBV on Occurrence of MACE

- **GNUH registry: PCI-treated CAD Pts (n = 1,292)**





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Park HW, Jeong YH, et al. Unpublished.

Impact of WBV on Occurrence of MACE

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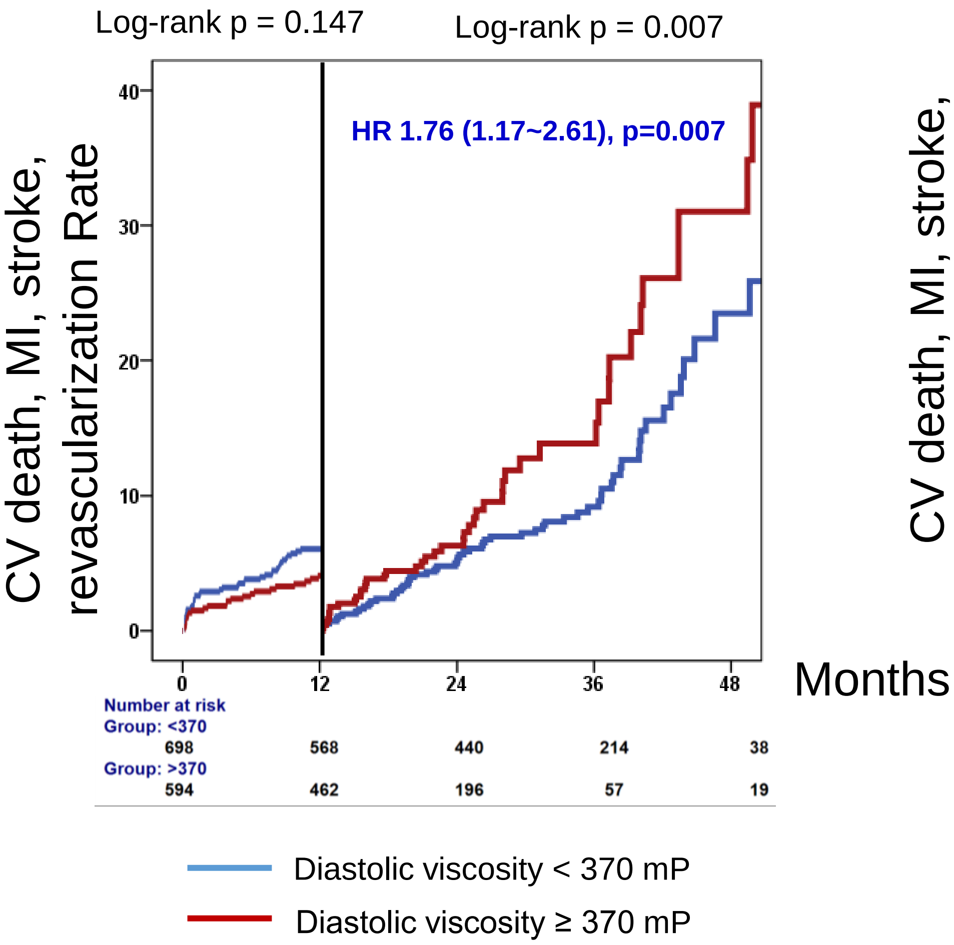

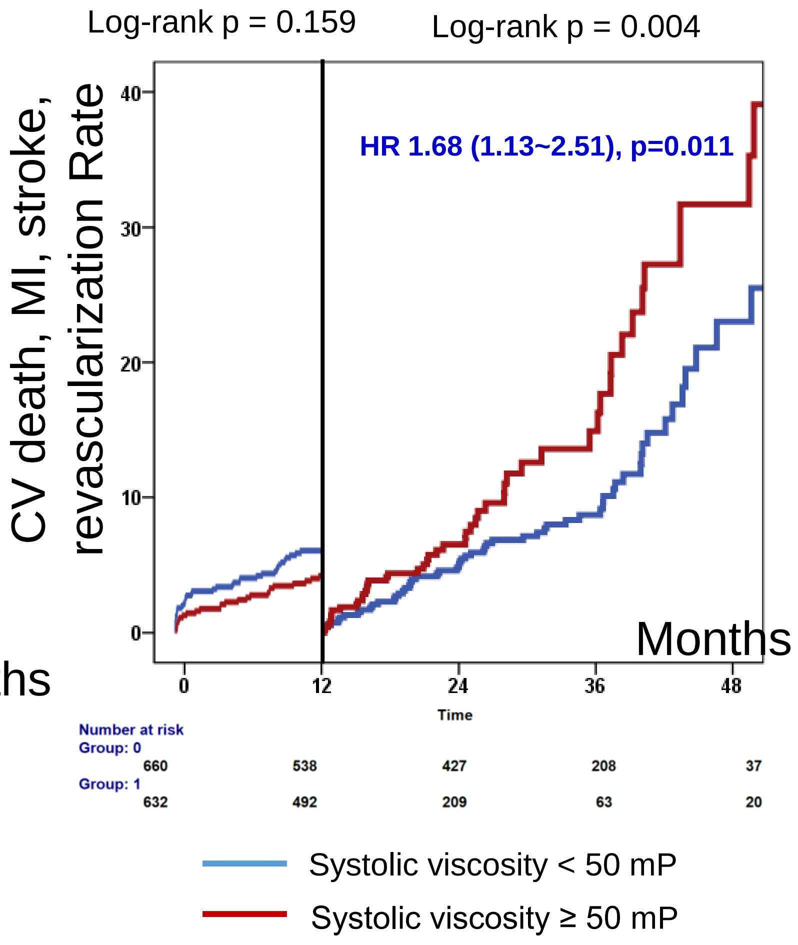

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Park HW, Jeong YH, et al. Unpublished.

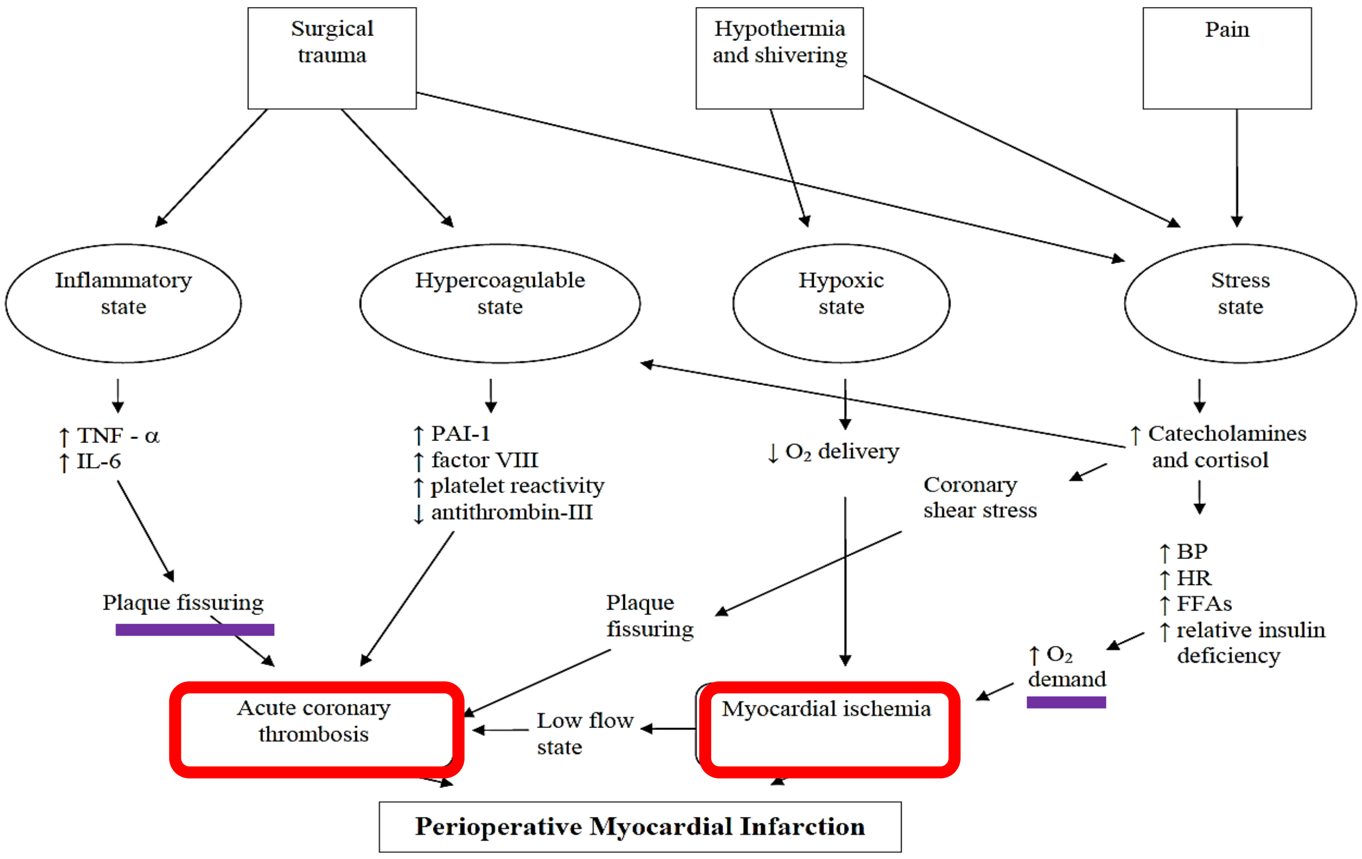
Impact of Whole Blood Viscosity on Occurrence of Cardiovascular Events After Non-cardiac Surgery
: A Post Hoc Analysis from the PANDA Trial

Jong-Hwa Ahn[1], Min Gyu Kang[2], Jeong Yoon Jang[1], Jin-Sin Koh[2], Yongwhi Park[1], Seok-Jae Hwang[2], Choong Hwan Kwak[1], Jin-Yong Hwang[2], Jeong Rang Park[2], Young-Hoon Jeong[1]

[1]Cardiovascular Center, Gyeongsang National University Changwon Hospital, Changwon, South Korea;
[2]Division of Cardiology, Departments of Internal Medicine, Gyeongsang National University Hospital, Jinju, South Korea

Peri-operative Time is in High-risk CV Event

- Perioperative cardiac complication
  - ***cardiac death, myocardial infarction***, pulmonary edema
  - major morbidity and mortality, undergoing non-cardiac surgery



Ahn JW, Jeong YH, et al. Unpublished.

Risk Stratification for Post-operative CV Events

1. Clinical risk score

Revised cardiac risk index (RCRI)

- High-risk surgery
- Ischemic heart disease
- Congestive heart failure
- Cerebrovascular disease
- Insulin therapy with DM
- Renal dysfunction

2. Functional testing

Stress modalities

Exercise or Pharmacologic

- Exercise ECG testing
- Stress radionuclide MPI
- Stress echocardiography
- Stress cardiac CT or MRI

3. Anatomical testing

Noninvasive coronary imaging

Coronary Angiography

- Computed tomography (CTA)

Ahn JW, Jeong YH, et al. Unpublished.

Study Design of PANDA

- Between July 2014 and April 2016, prospective observational study
- Enrollment from Gyeongsang National University Hospital

Patients with clinical risk factors*
before non-cardiac surgery (n=215)

CTA

≥50% maximal stenosis
CACS

DSE

Inducible ischemia
Nonviable infarction

Perioperative Cardiac Events at 30 days
1) Cardiac death,
2) Non-fatal myocardial infarction (MI),
3) Myocardial injury after noncardiac surgery (MINS)
4) Pulmonary edema,
5) Fatal arrhythmias

*Clinical risk factors (one or more RCRI)
1) Ischemic heart disease
2) Heart failure
3) Cerebrovascular disease
4) DM with insulin treatment
5) CKD (Scr > 2.0 mg/dL)
6) Undergoing high risk surgery

Exclusion
1) Postponed surgeries after prophylactic PCI (n=2)
2) Canceled surgeries (n=7)

Unique identifier: ***NCT02250963***

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Ahn JW, Jeong YH, et al. Unpublished.

WBV Substudy from PANDA

- Between July 2014 and April 2016, prospective observational study
- Enrollment from Gyeongsang National University Hospital

Patients with clinical risk factors before noncardiac surgery (n=215)

↓

Whole-blood viscosity (n =75)

High shear rate (300 s^{-1} : Systolic WBV)
Low shear rate (1 s^{-1} : Diastolic WBV)

↓

Perioperative Cardiac Events

1) CVD,
2) Non-fatal MI
3) MINS
4) Pulmonary edema
5) Fatal arrhythmias
6) Stroke
7) Systemic embolism

Evaluation of postoperative events

: ***Postop 3 times F/U (6 -12 h, 1d, and 3d)*** of CK-MB, troponin-I, ECG, and chest PA

Ahn JW, Jeong YH, et al. Unpublished.

Patients' Characteristics & Post-op Events

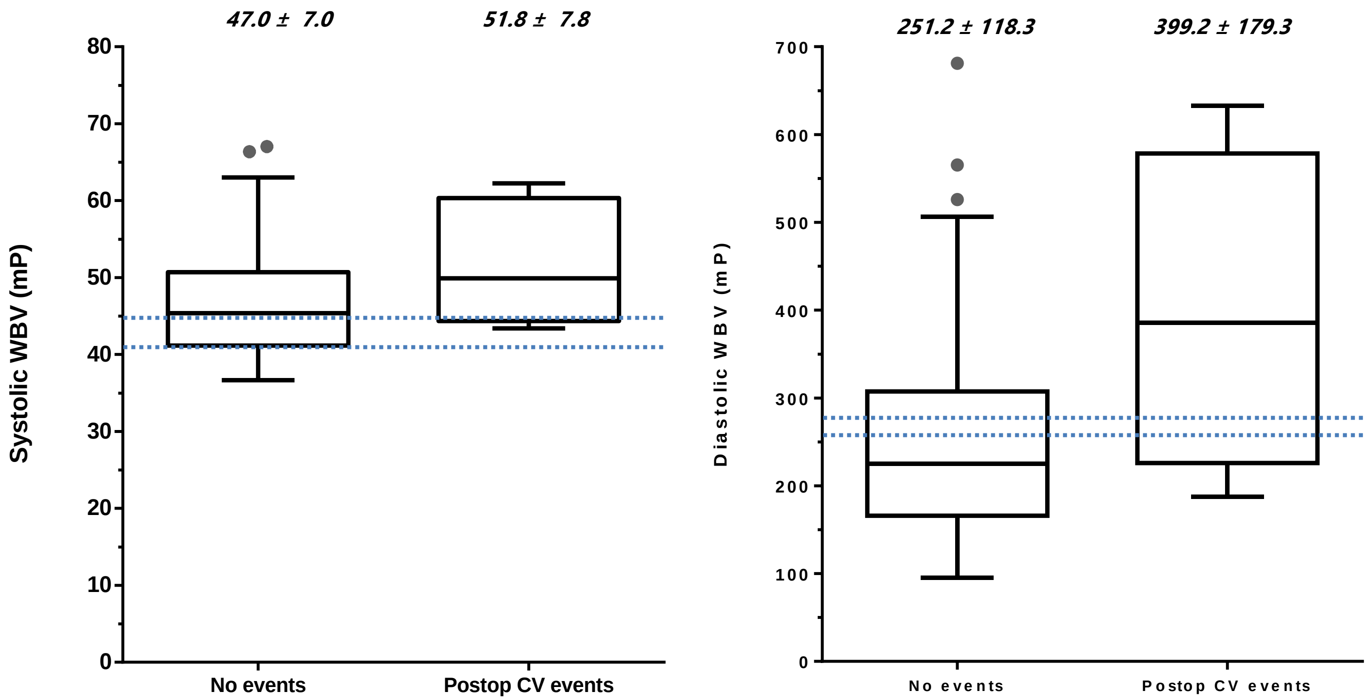
	Total (n = 75)
Male gender, n (%)	44 (58.7%)
Age, year	68.5 ± 8.6
Body mass index, kg/㎡	23.4 ± 3.4
Current smoking habits, n (%)	20 (26.7%)
Diabetes, n (%)	32 (42.7%)
Hypertension, n (%)	50 (66.7%)
Chronic kidney disease, n (%)	8 (10.7%)
Heart failure, n (%)	6 (8.0%)
Ischemic heart disease, n (%)	20 (26.7%)
Previous PCI, n (%)	6 (8.0%)
Hx of cerebrovascular accident, n (%)	24 (32.0%)
Revised cardiac risk index score	
I	48 (64.0%)
II	20 (26.7%)
III or IV	7 (9.3%)
Type of surgery	
High risk : vascular surgery	15 (20.0%)
Intermediate risk	60 (80.0%)

	Patients (n)
Postoperative cardiac events	8 (10.7%)
Cardiovascular death	1
Non-fatal myocardial infarction	4
Myocardial injury after noncardiac surgery	1
Pulmonary edema with heart failure	3
Ischemic stroke	1
Systemic embolism	1

Ahn JW, Jeong YH, et al. Unpublished.

Patients' Characteristics & Post-op Events

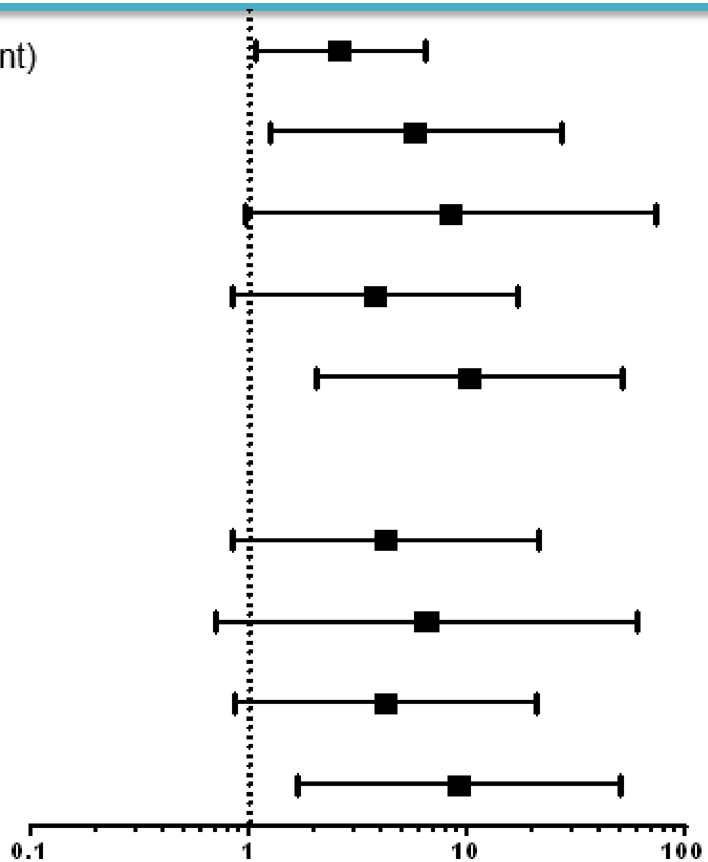
	Total patients (n=75)	No Events (n=67)	Events (n=8)	p
Viscosity, mP				
Systolic	47.5 ± 7.2	47.0 ± 7.0	51.8 ± 7.8	*0.078*
Diastolic	266.9 ± 132.8	251.2 ± 118.3	399.2 ± 179.3	*0.002*



Ahn JW, Jeong YH, et al. Unpublished.

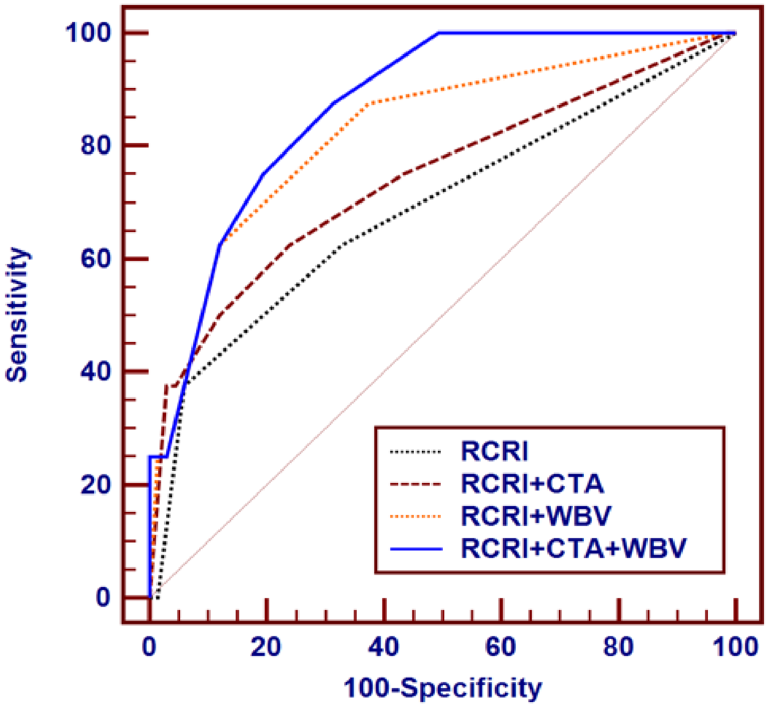
Hazard ratio of postop CV events

	Predictors	Hazard ratio	95% CI	*p*
Unadjusted	***RCRI score*** (per 1 point)	2.60	1.07 – 6.36	***0.036***
	CTA: *≥50% stenosis*	**5.78**	1.24 – 27.01	***0.026***
	CTA: *CACS ≥203*	8.40	0.95 – 74.19	*0.056*
	WBV: *systolic ≥52*	3.79	0.84 – 17.07	*0.083*
	WBV: *diastolic ≥425*	**10.17**	2.01 – 51.36	***0.005***
Adjusted for RCRI	**CTA:** *≥50% stenosis*	4.23	0.84 – 21.26	*0.080*
	CTA: *CACS ≥203*	6.48	0.70 – 59.80	*0.099*
	WBV: *systolic ≥52*	4.22	0.85 – 20.90	*0.077*
	WBV: *diastolic ≥425*	**9.14**	1.66 – 50.29	***0.011***



Ahn JW, Jeong YH, et al. Unpublished.

Discrimination Adding by WBV(Diastolic) & CTA (DS ≥ 50%)



	AUC	SE	95% CI	*P*
WBV+CTA+RCRI score	0.870	0.055	0.773 – 0.937	*0.091*/0.245/0.439§*
WBV+RCRI score	0.812	0.093	0.647 – 0.851	*0.171*/0.549†*
CTA+RCRI score	0.743	0.108	0.629 – 0.837	*0.440**
RCRI score	0.688	0.108	0.571 – 0.790	*Reference group*

*Comparison with the ROC curves of RCRI (Reference group)
†Comparison with the ROC curves of CTA + RCRI
§Comparison with the ROC curves of WBV + RCRI

Compared with RCRI alone (C-statistic: 0.688),
combination of "DBV ≥ 425 mP" + CTA + RCRI showed
the better discriminative power (C-statistic: 0.870) (p = 0.091)

***RCRI:** revised cardiac risk index*
***CTA:** maximal diameter stenosis on CTA*
***WBV:** diastolic blood viscosity ≥ 425 mP*

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Ahn JW, Jeong YH, et al. Unpublished.

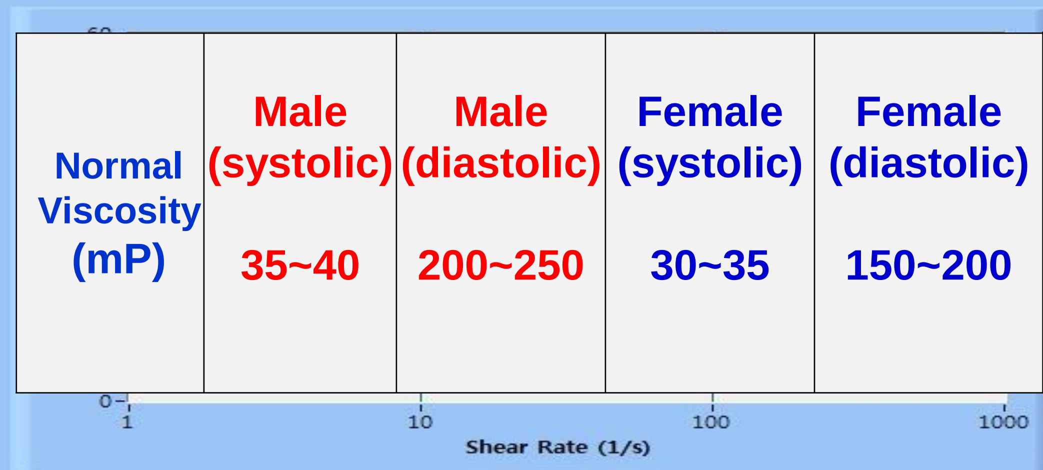
Whole Blood Viscometer Measurement

SHEAR-VISCOSITY

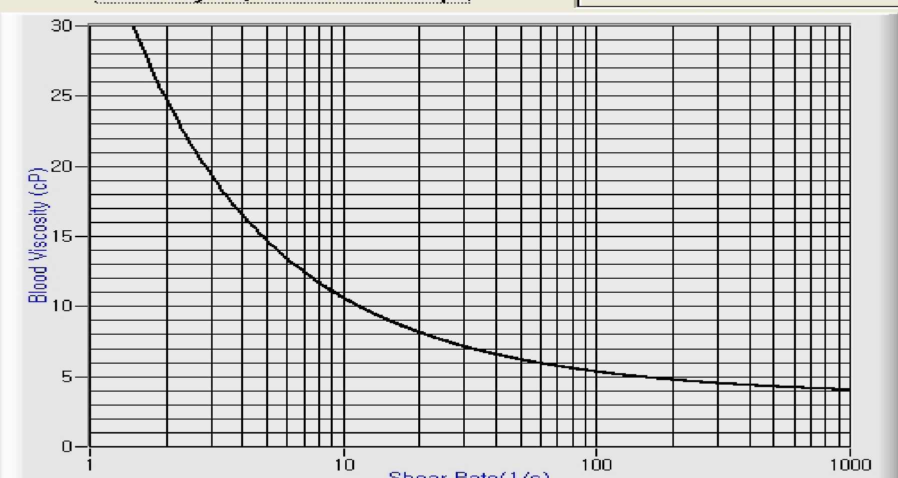
Shear Rate (1/s)	Blood Viscosity (mP)	Comments
1000	36.0	
300	36.9	Systolic Viscosity
150	37.7	
100	38.4	
50	39.8	
10	59.1	
5	76.6	
1	175.9	Diastolic Viscosity

혈액 점도 측정 결과		
	수축기혈액점도 Systolic Blood Viscosity	36.9 mP
	이완기혈액점도 Diastolic Blood Viscosity	175.9 mP

Normal Viscosity (mP)	Male (systolic)	Male (diastolic)	Female (systolic)	Female (diastolic)
	35~40	200~250	30~35	150~200



Raw Data | Viscosity vs. Shear Rate Graph | Alarm List | Comparison Graph



LEGEND

Shear vs Viscosity

SHEAR-VISCOSITY SUMMARY

SHEAR RATE (1/s)	Blood Viscosity (cP)	Blood Viscosity (mP)	
1000	4.06	40.6	
300	4.52	45.2	Systolic Viscosity
150	4.97	49.7	
100	5.34	53.4	
50	6.21	62.1	
10	10.63	106.3	
5	14.71	147.1	
2	24.77	247.7	
1	39.24	392.4	Diastolic Viscosity

TEST FILE INFORMATION

Date/Time Test	2011-01-10 11:59:00 AM
Disposable Tube I.D.	31631

Bio-Visco Inc. | KFDA 제 2966호 의료기기 제조업허가, 제 광주제신 09-27호 의료기기 제조품목신고(A22240.01(1)) | 0_01102011_31631 | www.bio-visco.com | 2011-01-10 | 오후 12:09

Next Step: How to control blood viscosity?

COURTESY of Prof.Jung JM & Lee DH.

	Male		Female			
	SBV[mP] @ 300 s^{-1}	DBV[mP] @ 1 s^{-1}	SBV[mP] @ 300 s^{-1}	DBV[mP] @ 1 s^{-1}	고려할 사항 (Possible Factors)	가능한 처방 (Proposed Prescription)
고점도 (4단계) (Hyper-Level 4)	Over 55	Over 400	Over 50	Over 350	--	Therapeutic phlebotomy or apheresis, saline therapy
고점도 (3단계) (Hyper-Level 3)	50~55	350~400	45~50	300~350	--	Statin or antiplatelet therapies, saline therapy
고점도 (2단계) (Hyper-Level 2)	45~50	300~350	40~45	250~300	Check LDL, TG, Glucose	Supplementation (Omega-3, Vitamine B3, Ginko biloba, other), saline therapy
고점도 (1단계) (Hyper-Level 1)	40~45	250~300	35~40	200~250	Check Hct for mild erythrocytosis	Hydration, diet, exercise, saline therapy
정상 점도 (Normal)	35~40	200~250	30~35	150~200	--	--
저점도 (1단계) (Hypo-Level 1)	30~35	150~200	25~30	100~150	Check Hct/Hgb for anemia	Dietary changes or medications for anemia correction
저점도 (2단계) (Hypo-Level 2)	Below 30	Below 150	Below 25	Below 100	Check medications	Dosage changes or stop administering medication(s)

Perspectives

1. Current target risk factors for residual ASCVD:

Limited value to explain whole spectrum of ASCVD

2. Concept of blood viscosity:

- Stickiness/heaviness + hypercoagulability

- Wall shear stress to explain plaque progression + rupture

3. How to solve chronic hyperviscosity syndrome?:

- Criteria of therapeutic range according to the cohorts

- ? Additional strategy to control viscosity in addition to the current medical treatment