

Is it Time for Vascular Centric Indicators in Management of Diabetes Mellitus?

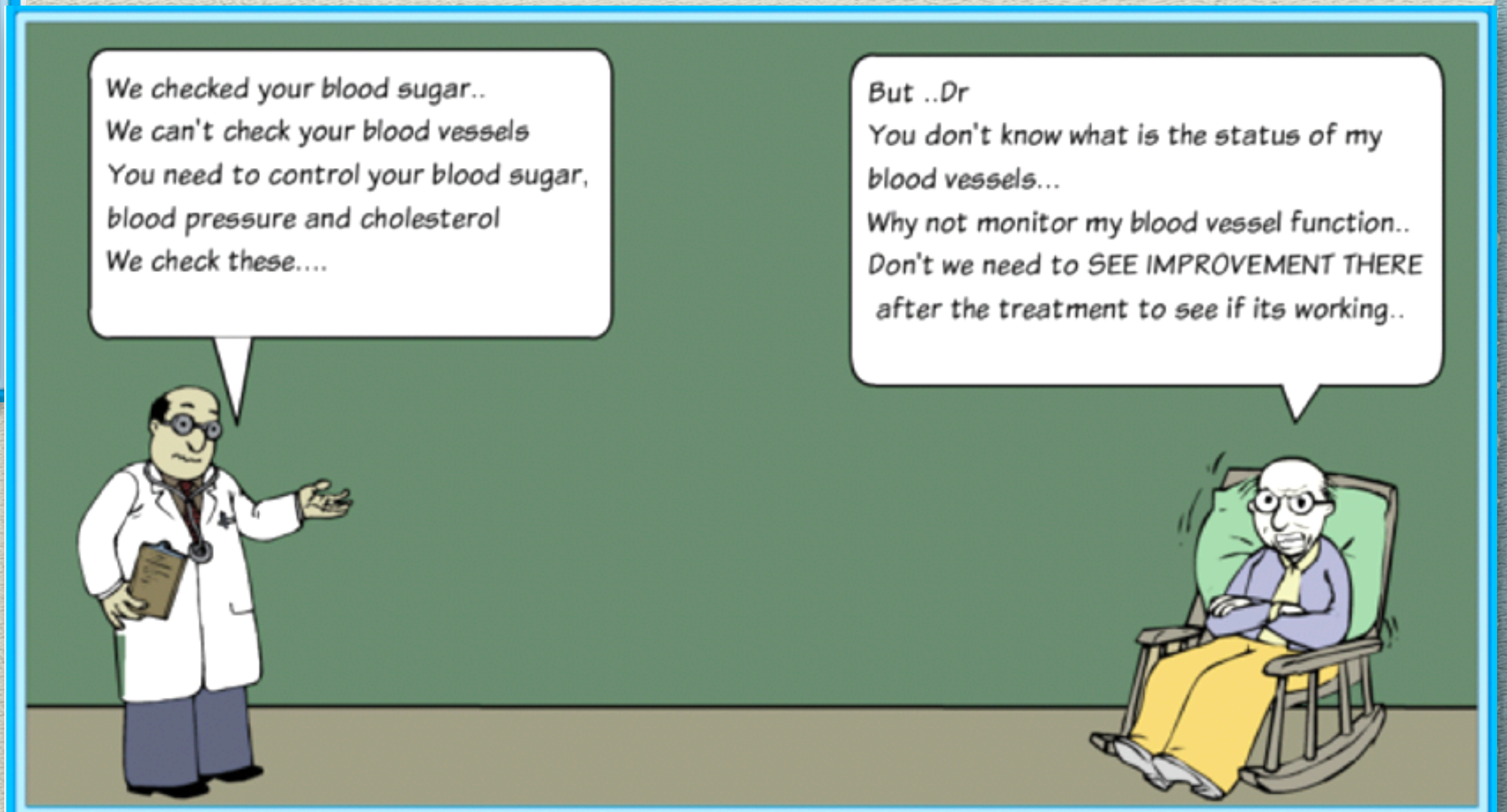
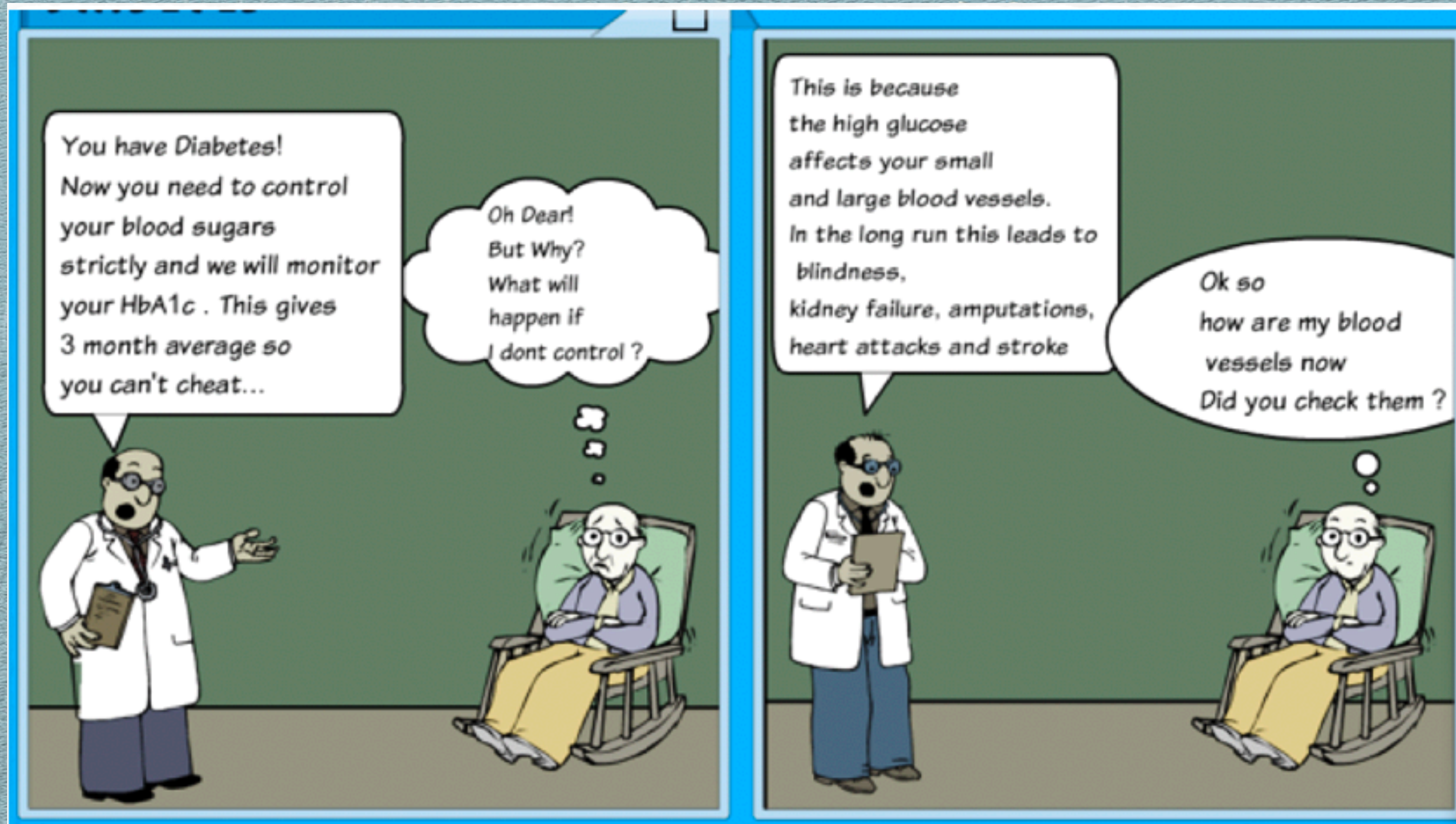
Dr. Rinkoo Dalan

MBBS, FRCP(Edin), FAMS(Endocrinology)

Senior Consultant, Endocrinology, Tan Tock Seng Hospital

Assistant Professor, Lee Kong Chian School of Medicine

The Patient Perspective



Inspiration for theme : 1st study: CRP in healthy and T2DM 2005-2010

High-sensitivity C-reactive protein concentrations among patients with and without diabetes in a multiethnic population of Singapore: CREDENCE Study

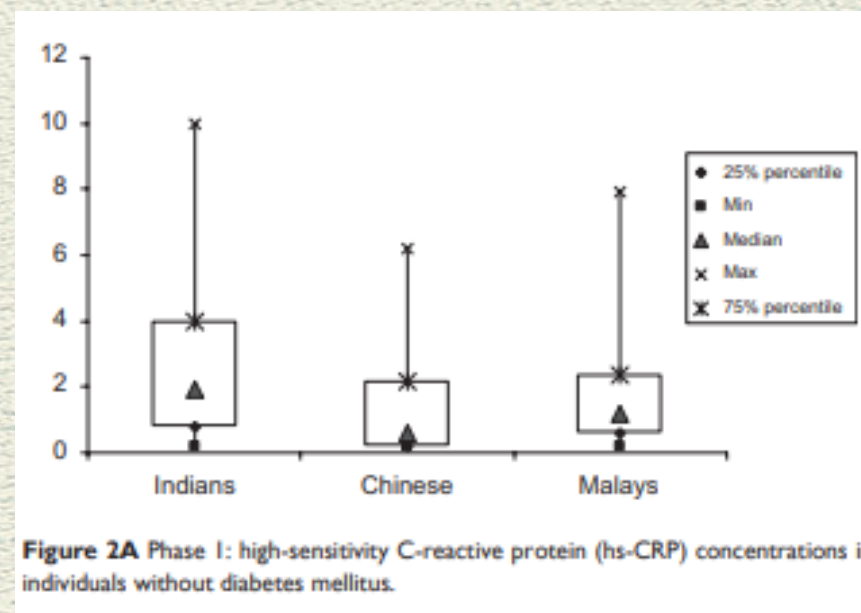


Figure 2A Phase 1: high-sensitivity C-reactive protein (hs-CRP) concentrations in individuals without diabetes mellitus.

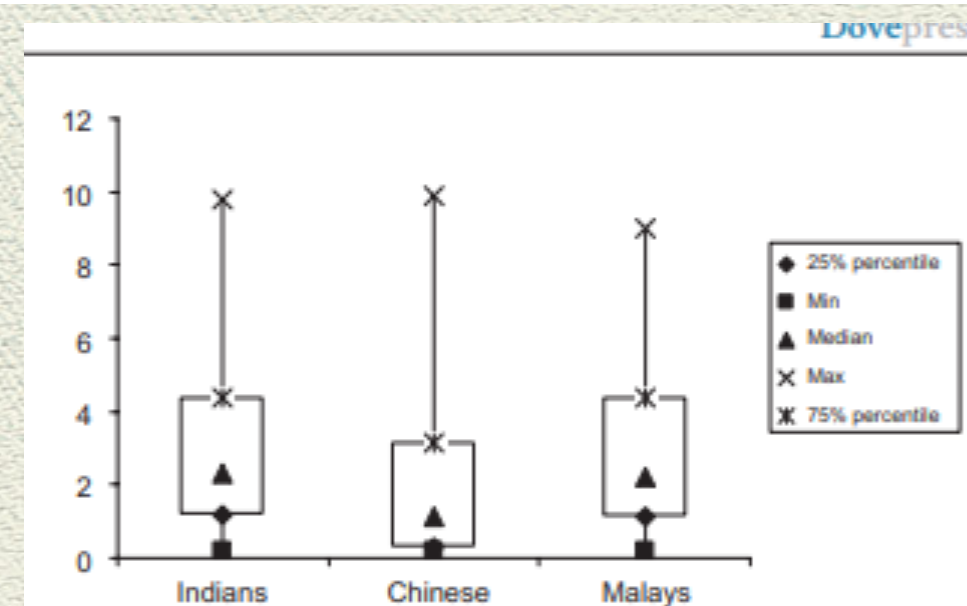


Figure 2B Phase 2: high-sensitivity C-reactive protein (hs-CRP) concentrations in individuals with diabetes mellitus.

Explored the C-reactive protein levels in three ethnic groups in healthy and type 2 DM –with the premise the DM would be a equaliser.....
However—the differences persisted in DM subjects....

Contents lists available at ScienceDirect

ELSEVIER

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Letter to the Editor

Predictors of cardiovascular complication in patients with diabetes mellitus: A 5-year follow-up study in a multiethnic population of Singapore: CREDENCE II study

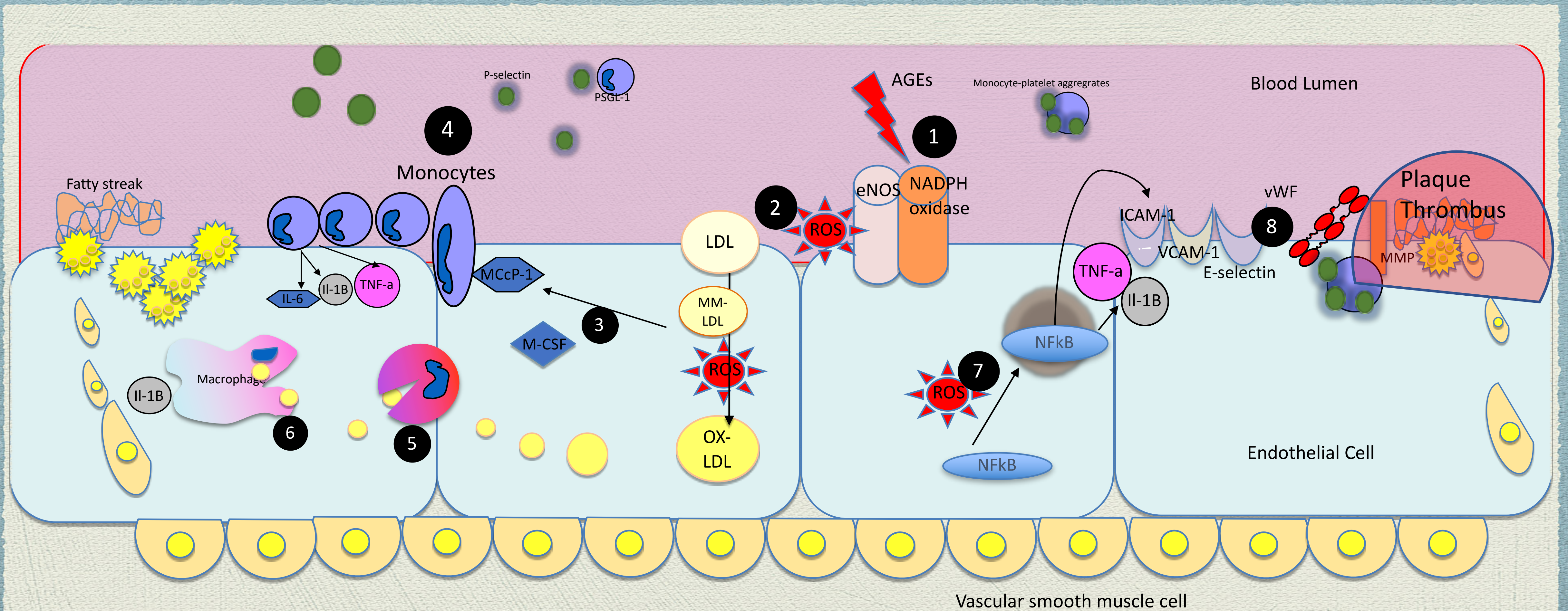
Rinkoo Dalan^{a,b,c,*}, Michelle Jong^{a,d}, Robin Choo^e, Daniel E.K. Chew^a, Melvin Khee Shing Leow^{b,f,g,h}

^a Department of Endocrinology, Tan Tock Seng Hospital, Singapore
^b DUKE-NUS Graduate Medical School, Singapore
^c Yong Loo Lin School of Medicine, National University of Singapore, Singapore
^d Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore
^e Singapore Institute for Clinical Sciences, A*STAR, Singapore
^f Tan Tock Seng Hospital, Singapore
^g Brenner Centre for Molecular Medicine, Singapore
^h National University of Singapore, Singapore

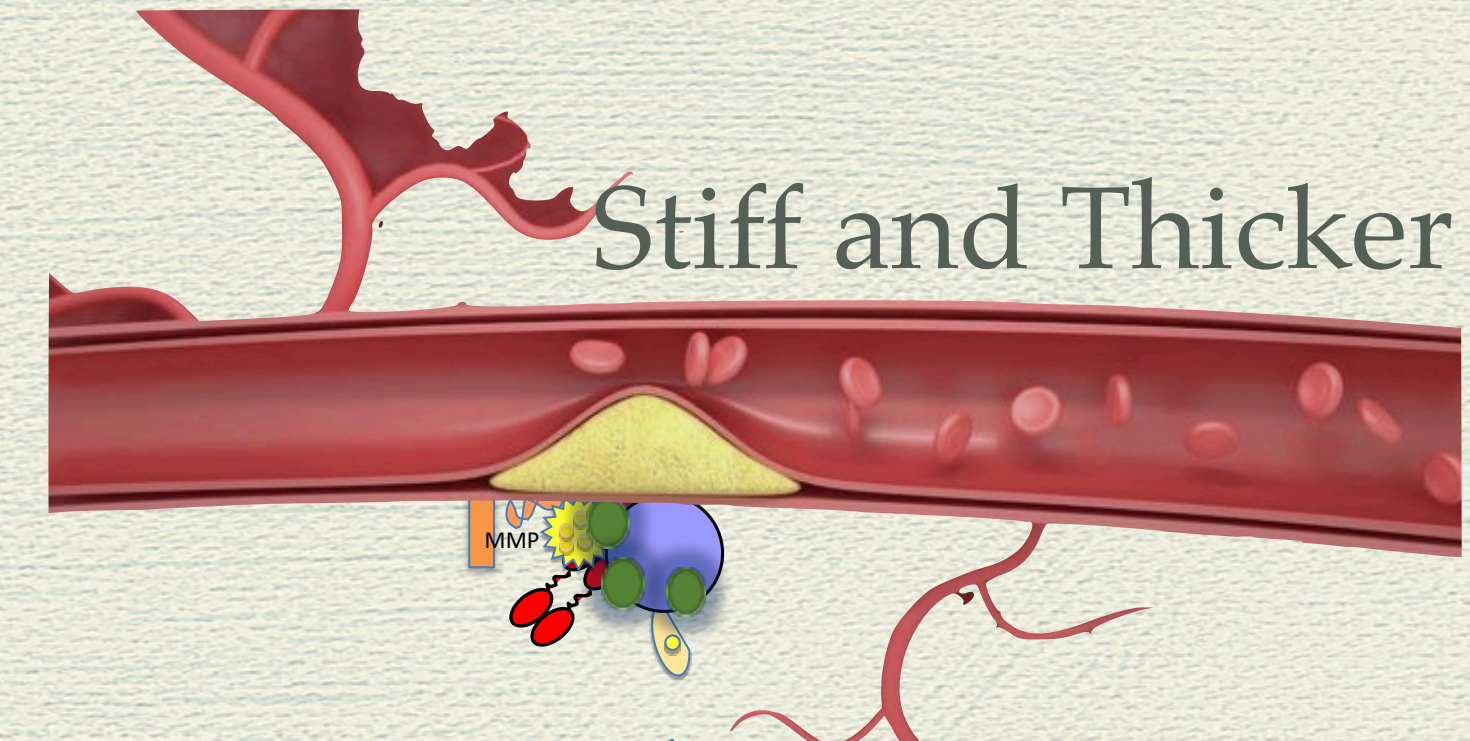
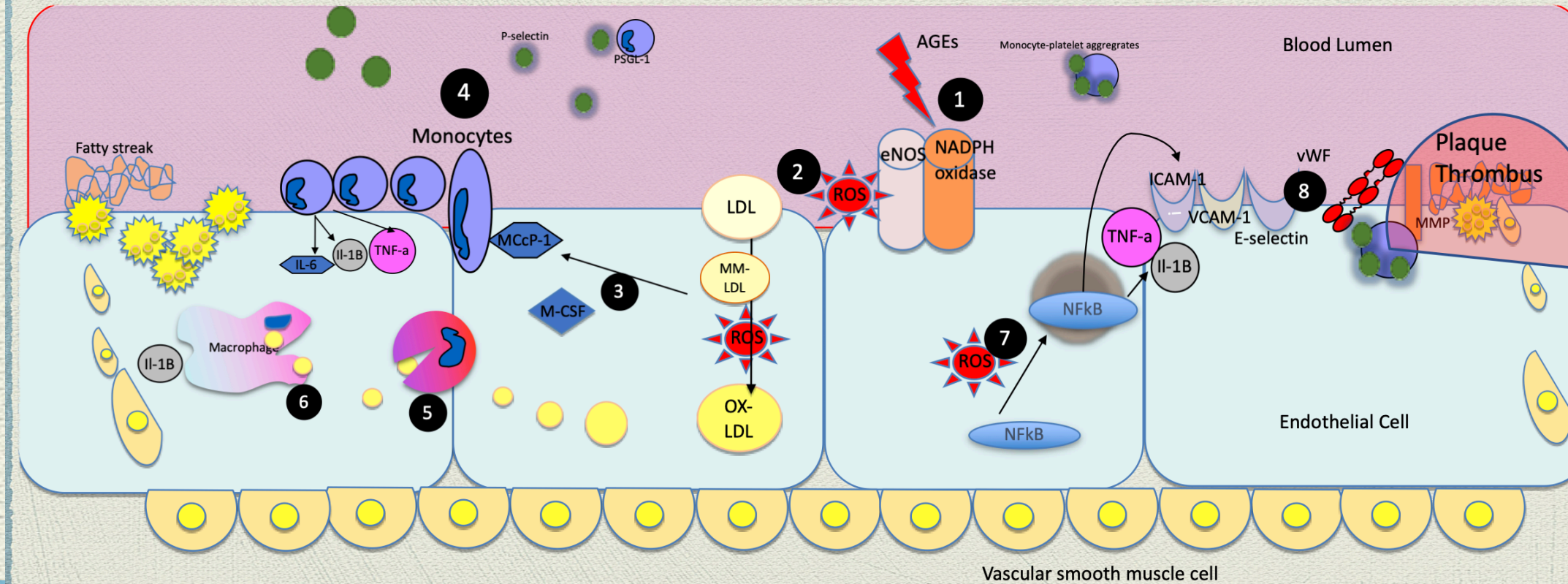
CrossMark

HbA1c remains the most important traditional modifiable factors in the control of subsequent CV complications. Low diastolic BP also correlated with all cause mortality and higher incidence of IHD in Indian patients. Although in CREDENCE [2], Indians had higher hs-CRP and were subsequently seen to have a higher risk of IHD when compared to Chinese, a statistically significant association was not seen between hs-CRP and CV events. The results of this study need to be verified in larger population wide studies with DM and in randomized controlled trials with diastolic BP >70 mm Hg and <70 mm Hg.

The Endothelium is activated in Diabetes



Summary of Biomarkers



Advanced Glycation End-Products

Formed by non-enzymatic glycation of proteins and lipids

*Dicarbonyls (Methylglyoxal) is a precursor

Receptors
*Soluble RAGE
*esRAGE

Measured by kits

AGE Reader

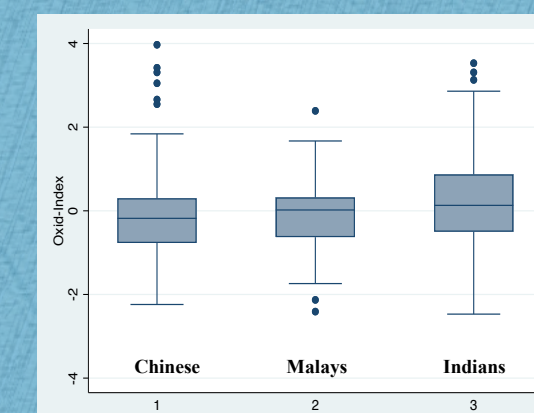


Oxidative Stress

Ox-LDL Assay
dROMs: derivatives of ROS metabolites
TAC: Total anti-oxidant capacity
Oxidative Index=dROMs-TAC



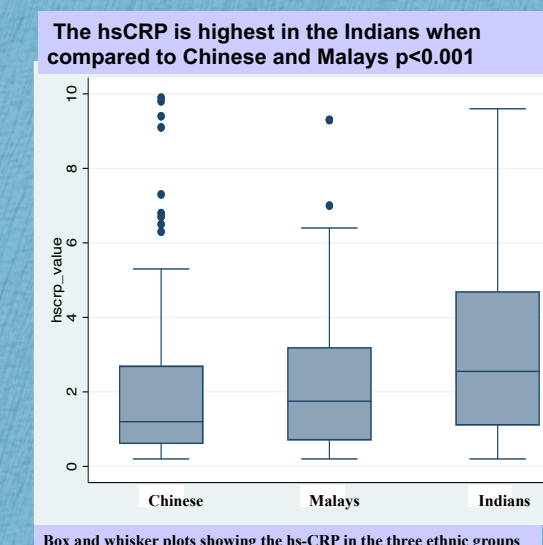
OXY Adsorbent Test
Diacron, Italy



Inflammation

Neutrophil
Monocyte-Platelet
Aggregates

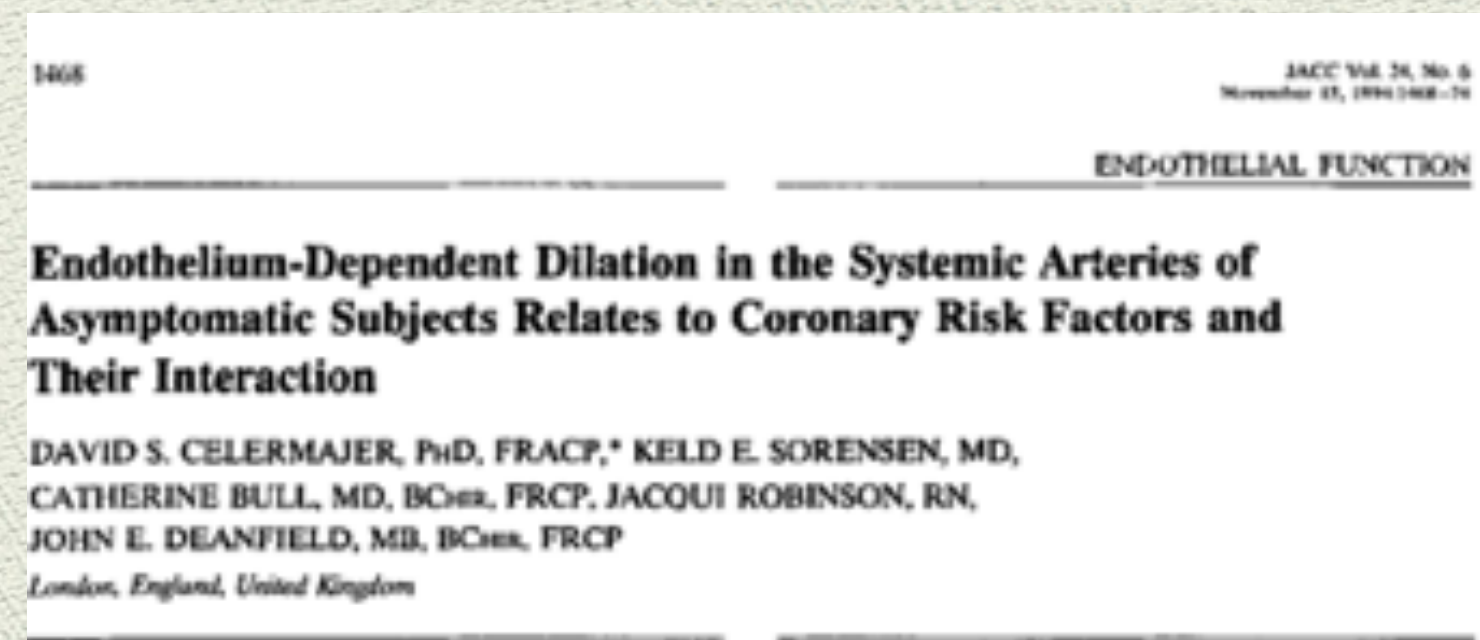
hs-CRP
Interleukins



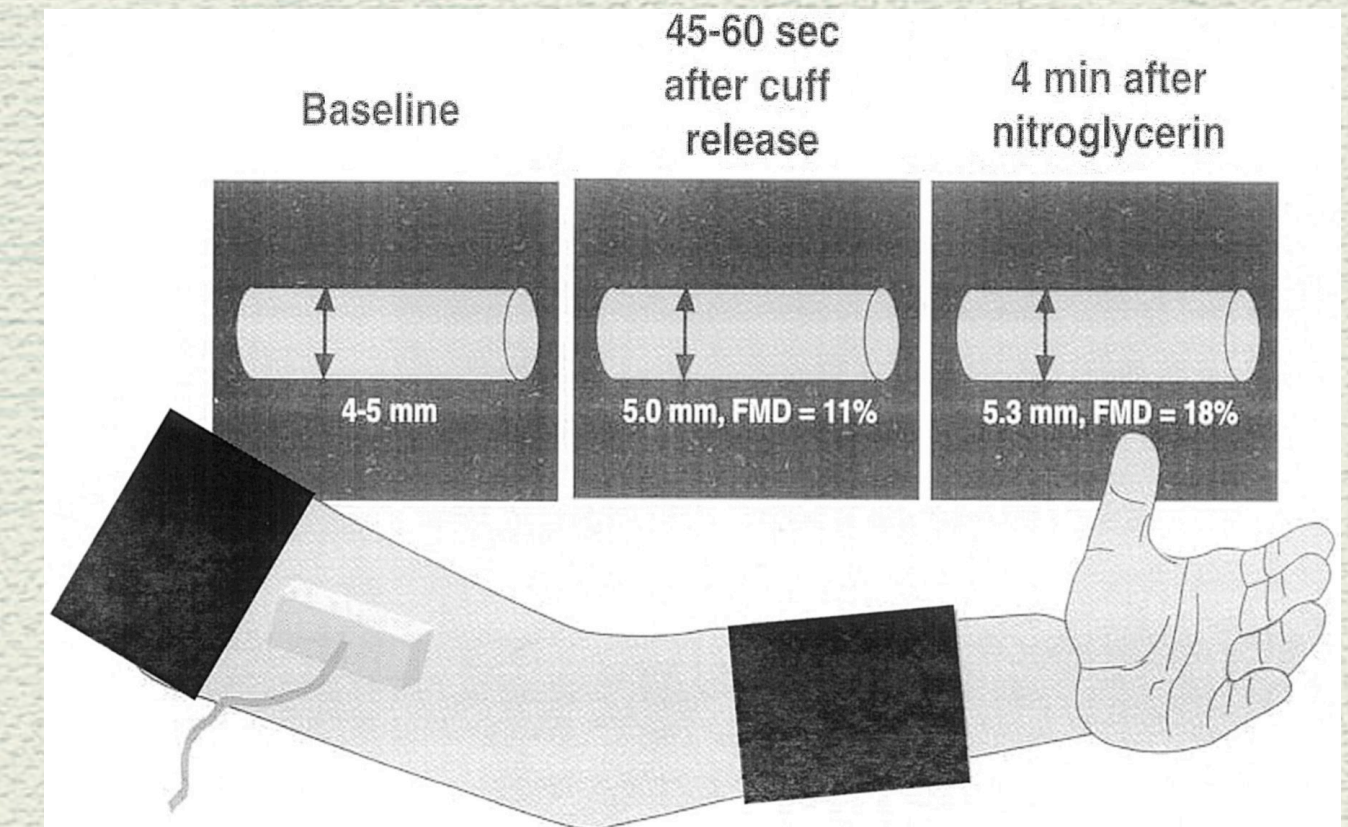
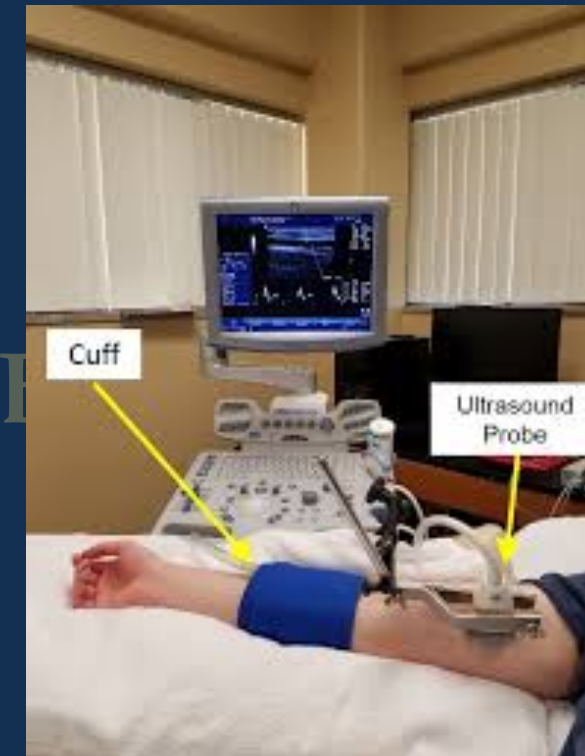
Vascular Reactivity
Vascular Stiffness
Vascular Thickness

Retinal AV index
RHI-EndoPAT
Sphygmocor
Carotid Artery
Ultrasound
Radial Artery-MDI

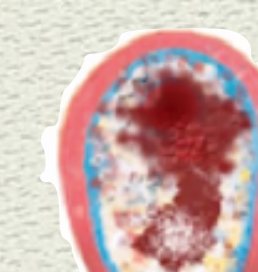
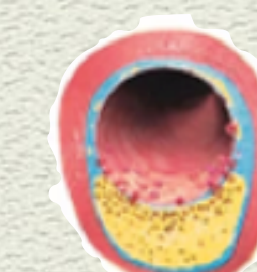
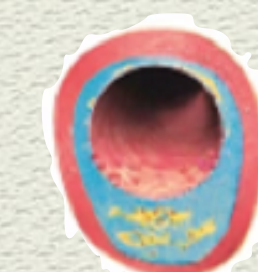
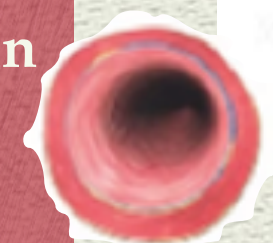
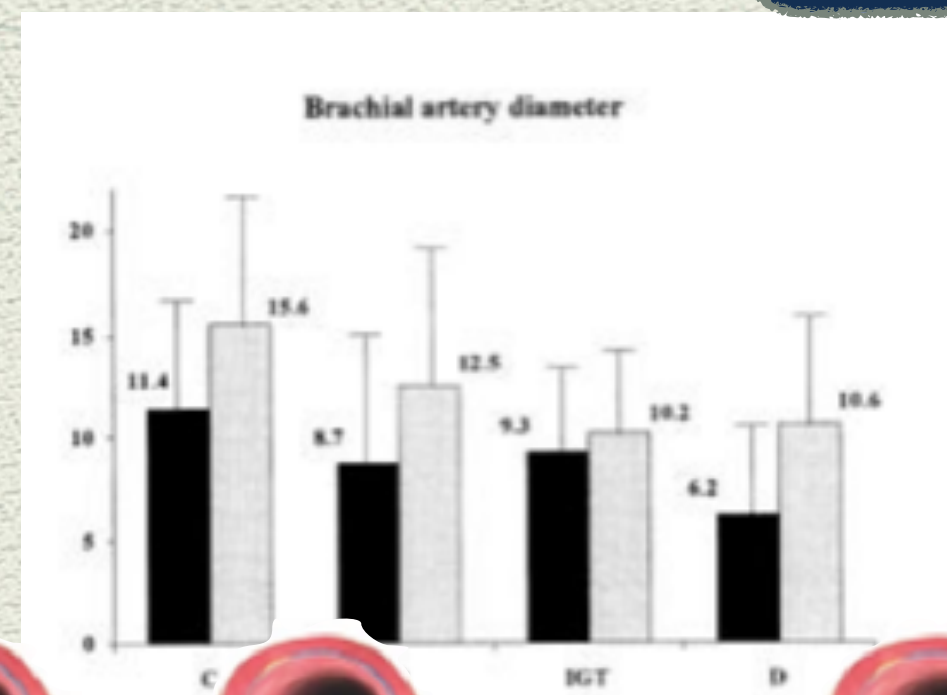
The Arteries become Stiff and Thicker



Brachial Artery FMD



“Loss of endothelium-dependent dilation in the systemic arteries occurs in the preclinical phase of vascular disease and is associated with interaction of the same risk factors known to predispose to atherosclerosis and its complications in later life”



Undetectable Structural Disorder

Undetectable Structural Disorder

Detectable Structural Disorder

Healthy

High Risk

Pre-diabetes

Diabetes

Diabetes with complications

Physiological Methods



Carotid Artery
Intima-Media
Thickness
And stiffness

Common
Carotid
Artery
4.3-7.7 mm

Arterioles
100-300 μm

Aorta
1-3 cm

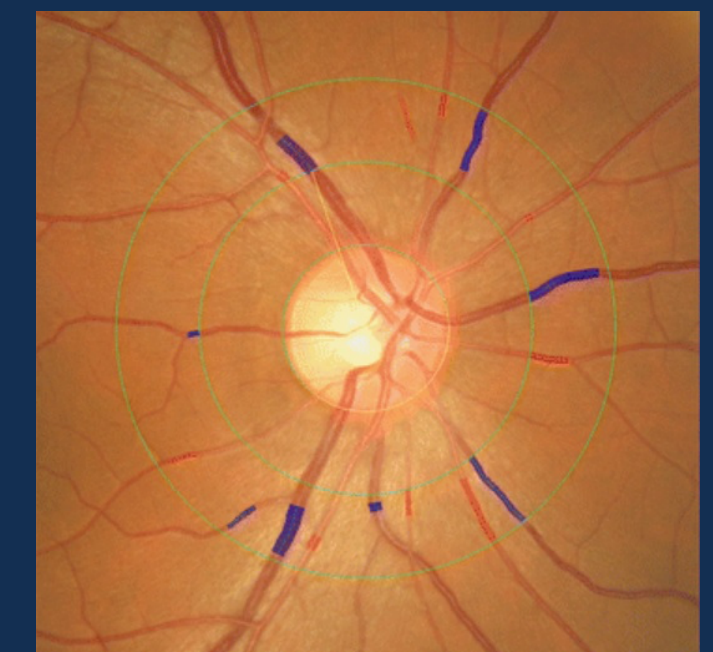
Capillaries
5-10 μm

ENDO-PAT
Reactive Hyperaemia
Index



Aortic Artery
Stiffness and
Blood pressure
Sphygmocor

Retinal
AV
Index



Vitamin D and endothelium

Contents lists available at ScienceDirect

IJC Metabolic & Endocrine

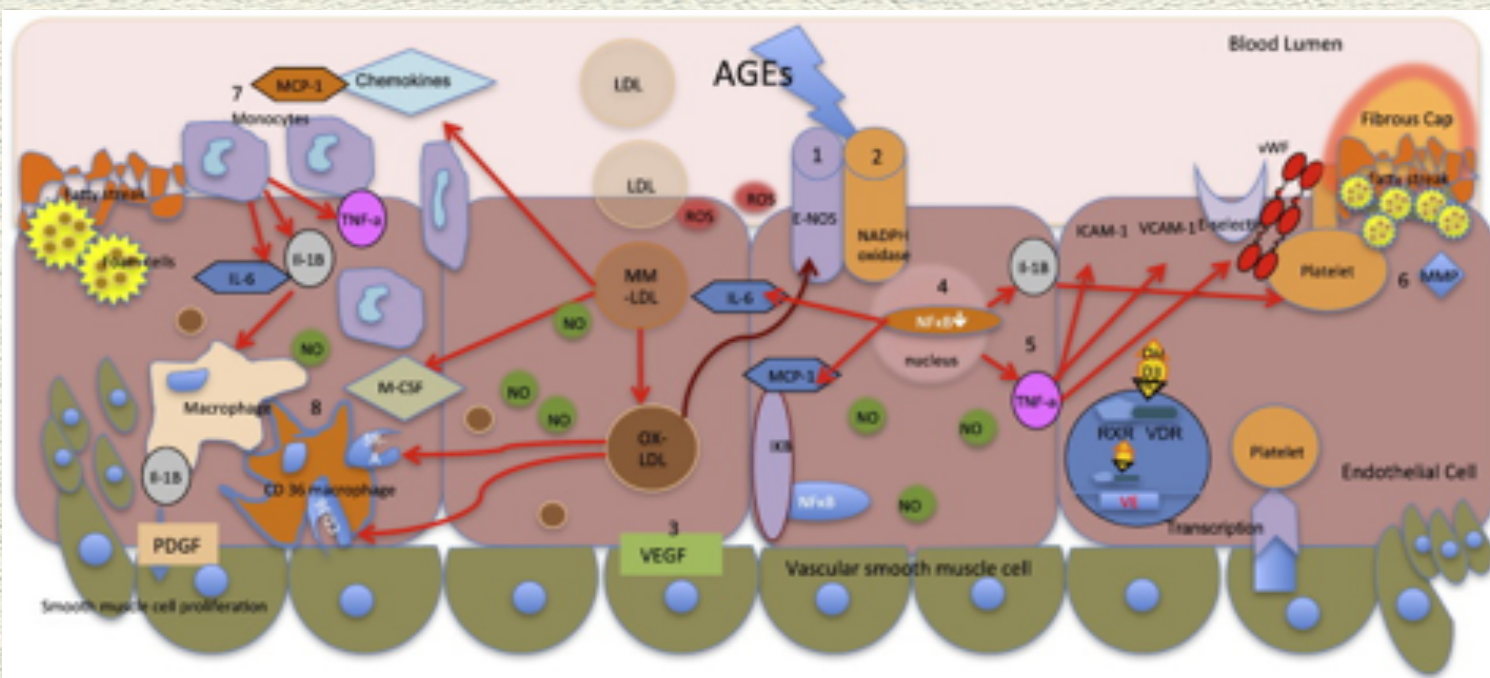
ELSEVIER journal homepage: <http://www.journals.elsevier.com/ijc-metabolic-and-endocrine>

Vitamin D and the endothelium: basic, translational and clinical research updates

Rinkoo Dalan^{a,b,c,*}, Huiling Liew^a, Wai Kit Alvin Tan^a, Daniel E.K. Chew^a, Melvin Khee-Shing Leow^{a,b,c,d,e}

^a Department of Endocrinology, Tan Tock Seng Hospital, Singapore
^b Duke-NUS Graduate Medical School, Singapore
^c Yong Loo Lin School of Medicine, NUS, Singapore
^d Brenner Centre for Molecular Medicine, Singapore
^e National University of Singapore, Singapore

CrossMark



Vitamin D is responsible for all steps in prevention of endothelial activation and arterial stiffness

Epidemiologicallythere was enough data to suggest a link in a cross sectional manner

Original Article

A randomised controlled trial evaluating the impact of targeted vitamin D supplementation on endothelial function in type 2 diabetes mellitus: The DIMENSION trial

Rinkoo Dalan^{1,2,3,6}, Huiling Liew¹, Pryseley Nkouibert Assam^{4,5}, Edwin SY Chan^{4,5}, Fahad Javaid Siddiqui^{4,5}, Alvin WK Tan¹, Daniel EK Chew¹, Bernhard O Boehm^{1,6,7} and Melvin KS Leow^{1,8-11}

Diabetes & Vascular Disease Research
2016, Vol. 13(3) 192–200
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DOI: 10.1177/1479164115621667
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Although a improvement was seen it only reached borderline significance
..P=0.07..

The trend was similar in other global studies...

Institution: National University of Singapore
Hello, Guest!

MY ALERTS SIGN IN JOIN SIGN OUT

f t

JAHA

Journal of the American Heart Association

HOME ABOUT THIS JOURNAL ALL ISSUES SUBJECTS BROWSE FEATURES RESOURCES AHA JOURNALS

SYSTEMATIC REVIEW AND META-ANALYSIS

Effect of Vitamin D Supplementation on Markers of Vascular Function: A Systematic Review and Individual Participant Meta-Analysis

Louise A. Beveridge, Faisal Khan, Allan D. Struthers, Jane Armitage, Ilaria Barchetta, Iain Bressendorff, Maria Gisella Cavallo, Robert Clarke, Rinkoo Dalan, Gavin Dreyer, Adam D. Gepner, Nita G. Forouhi, Ryan A. Harris, Graham A. Hitman, Thomas Larsen, Rajesh Khadgawat, Peter Marckmann, Frank H. Mose, Stefan Pilz, Alexandra Scholze, Marina Shargorodsky, Seth I. Sokol, Hans Stricker, Carmine Zoccali, Miles D. Witham

Physiological Methods

SCIENTIFIC REPORTS

OPEN **Proof-of-Concept Study for an Enhanced Surrogate Marker of Endothelial Function in Diabetes**

Received: 23 October 2017

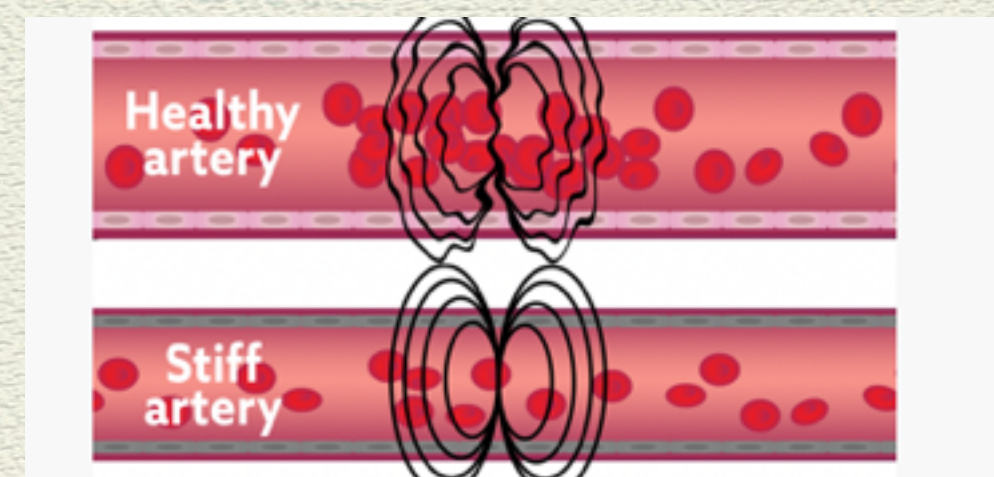
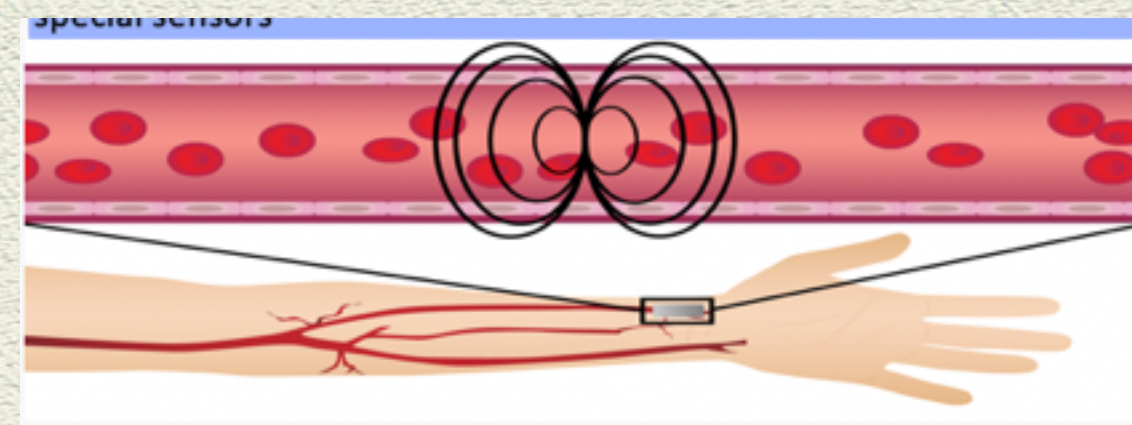
R. Dalan^{1,2,3}, S. Goh⁴, Sun Bin¹, A. Seneviratna¹ & C. T. Phua⁴

Radial Artery
1.2-2.6 mm

Researchers at Nanyang Poly and TTSH
way to test health of blood vessels



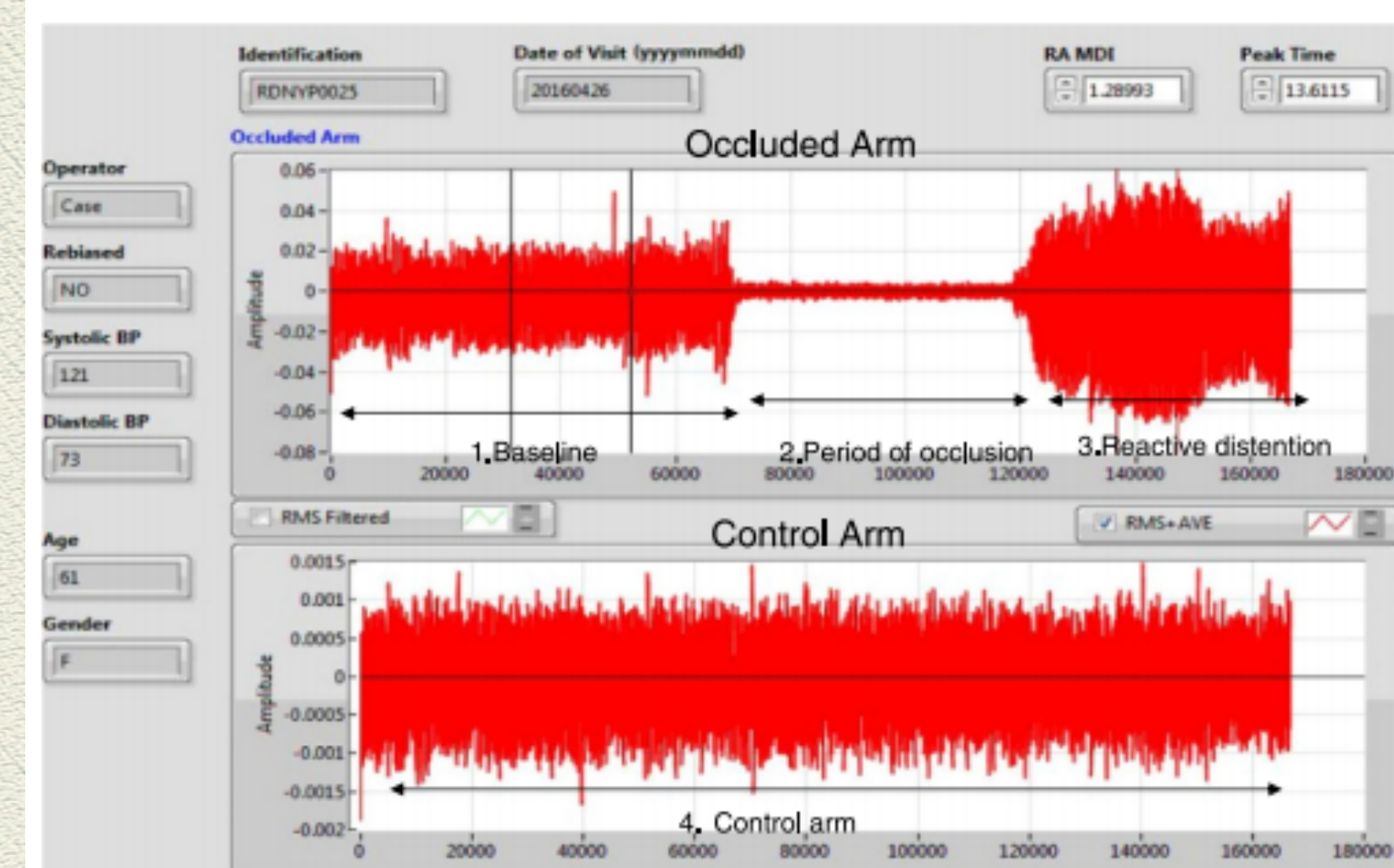
Nanyang Polytechnic's Dr Phua Chee Teck and Tan Tock Seng Hospital's Dr Rakesh Dalan showing how their device works. PHOTO: NANYANG POLYTECHNIC



PATENT PENDING



Figure 2. The process of obtaining the measurement.

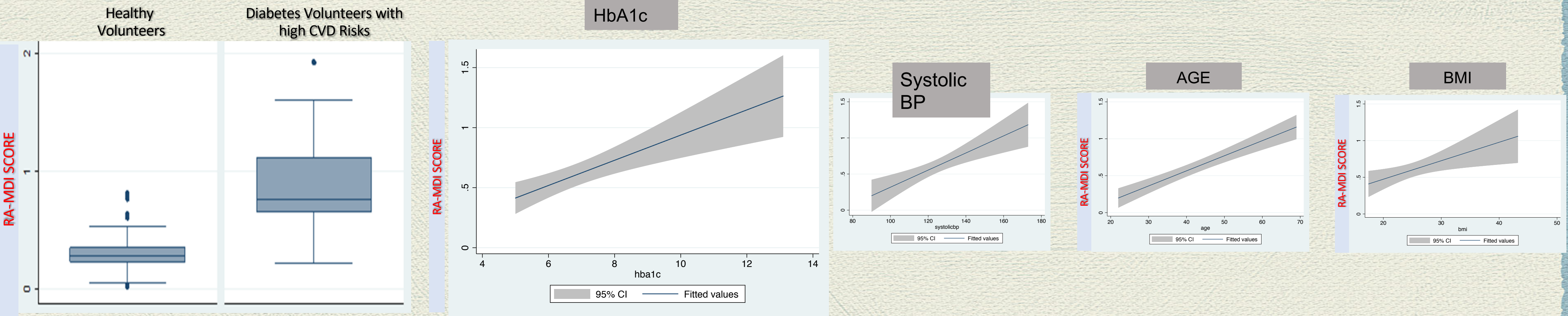


1. Baseline: The baseline readings are taken for 5–10 minutes. 2. The blood pressure (BP) cuff is inflated to >200 mmHg or 50 mmHg more than the systolic BP in the non-dominant arm for 5 minutes. The period of occlusion is shown. 3. The BP cuff is then released with reactive vasodilation. The period of reactive distension is shown. 4. The readings on the control arm (dominant hand) is recorded as well throughout the duration of the measurements.

Figure 4. The final analysis page on the reader.

This study is sponsored by National Health Innovation Centre (NHIC) I2D, I2P and I2I

Correlations with Diabetes and cardiovascular risk factors



Correlations with Framingham Risk Scores

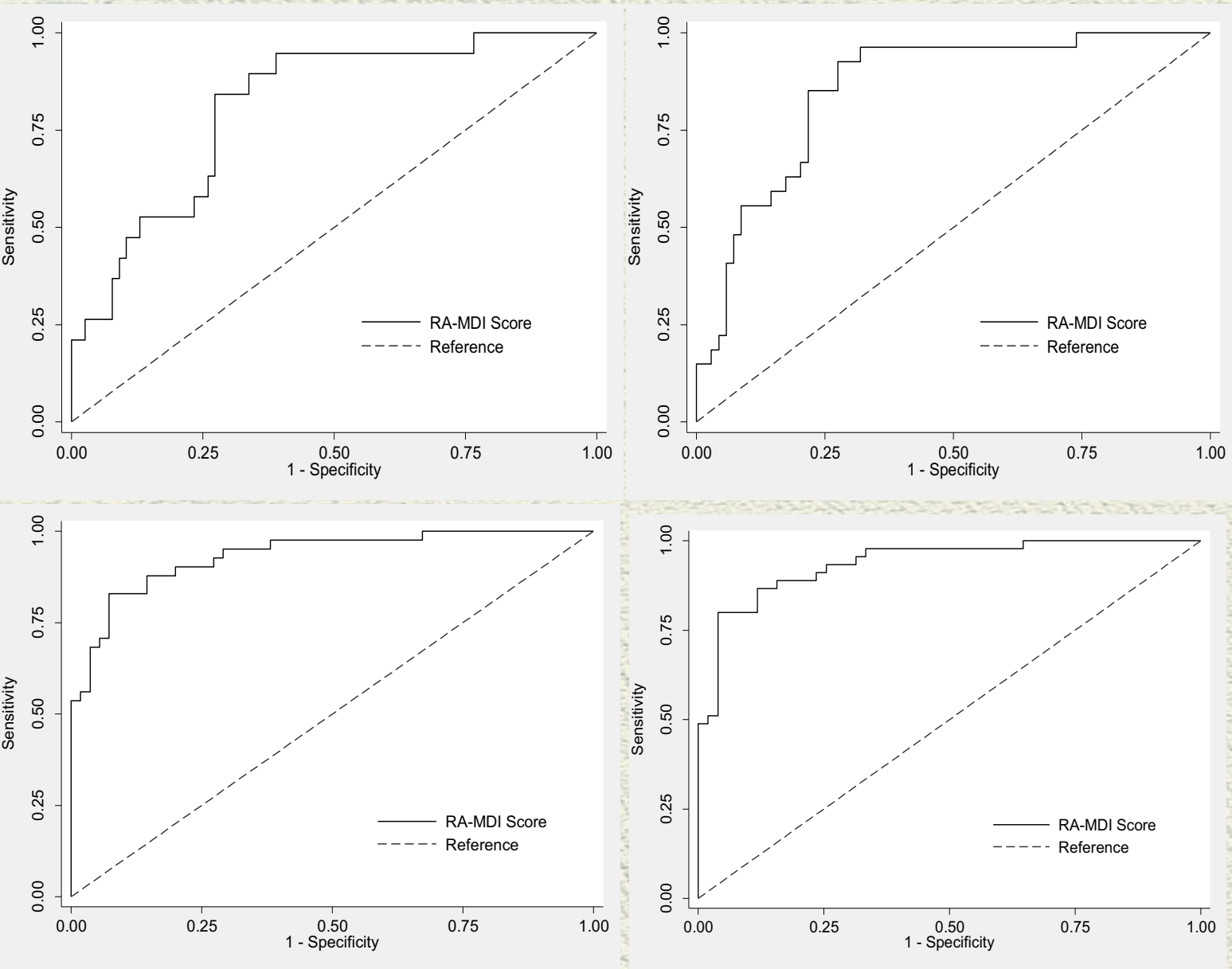


Fig.	Risk Scoring System	High	Low	Area under curve	95% confidence interval
A	FHS10 (Lipids)	≥20%	<20%	0.811	0.710–0.912
B	FHS10 (BMI)	≥20%	<20%	0.856	0.777–0.935
C	FHS30 (Lipids)-Full CVD	≥40%	<40%	0.934	0.885–0.982
D	FHS30 (BMI)-Full CVD	≥40%	<40%	0.937	0.891–0.984

Haptoglobin , Genotypes and Endothelium



Integrative Biology

PAPER



[View Article Online](#)
[View Journal](#)

Biological factors in plasma from diabetes mellitus patients enhance hyperglycaemia and pulsatile shear stress-induced endothelial cell apoptosis†

X. F. Liu,^a J. Q. Yu,^b R. Dalan,^{cde} A. Q. Liu^a and K. Q. Luo^{*a}

Cite this: DOI: 10.1039/c3ib40265g

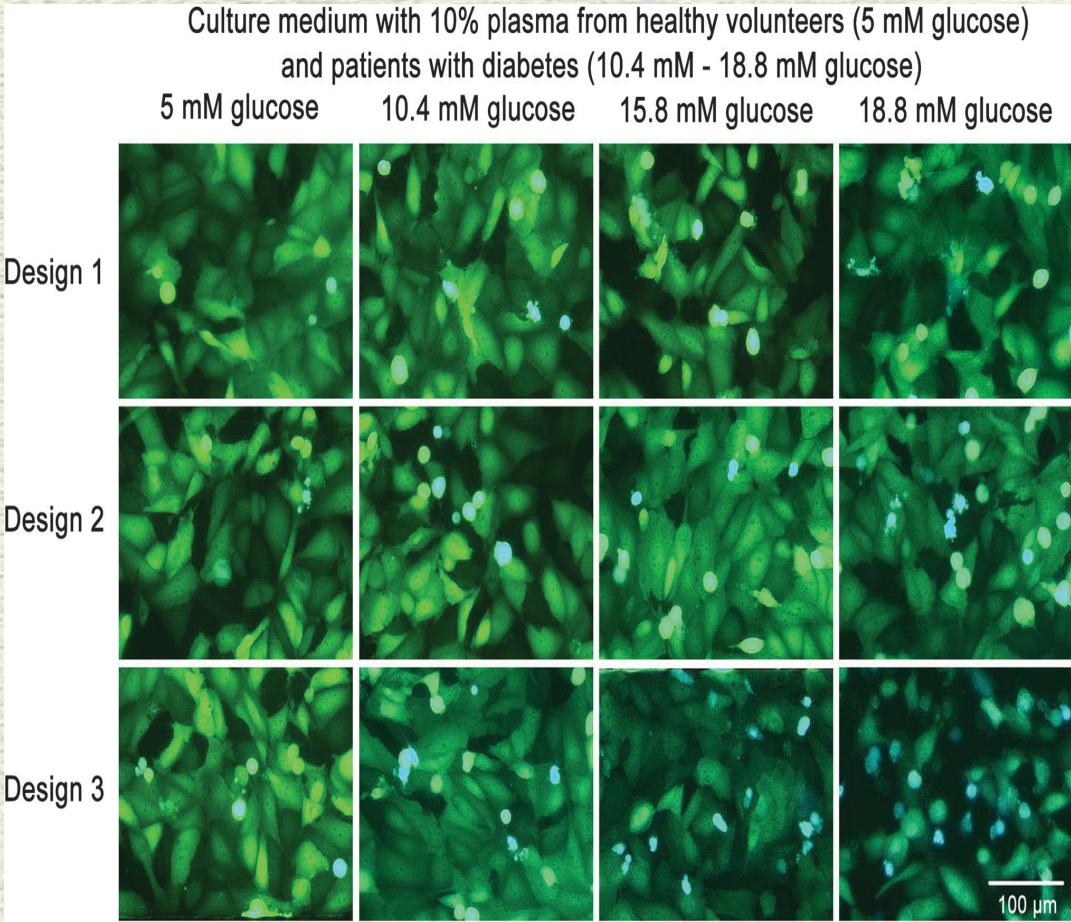



Fig. 4 Merged images of HUVEC-C3 cells with FRET effects in different microchannel designs using medium with 10% plasma from healthy volunteers or DM patients at defined glucose concentrations.

Further proteomics :
Haptoglobin was protective
against EC apoptosis

or updates

Review

European Journal of Preventive Cardiology




ESC
European Society of Cardiology

The protean role of haptoglobin and haptoglobin genotypes on vascular complications in diabetes mellitus

Rinkoo Dalan^{1,2,3} and Goh Liuh Ling¹

Abstract

Introduction and background: Haptoglobin (Hp) is considered to be an antioxidant and protective against cardiovascular complications. Polymorphisms in the Hp gene interact with diabetes mellitus to affect the risk of vascular complications.

European Journal of Preventive Cardiology
0(00) 1–18
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DOI: [10.1177/2047487318776829](https://doi.org/10.1177/2047487318776829)
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Haptoglobin , Genotypes and Endothelium

Brief Report

The haptoglobin 2-2 genotype is associated with inflammation and carotid artery intima-media thickness

Rinkoo Dalan^{1,2}, Huiling Liew¹, Liuh Ling Goh³, Xiao Gao³, Daniel EK Chew¹, Bernhard O Boehm^{1,2} and Melvin Khee Shing Leow^{1,2,4}

Diabetes & Vascular Disease Research
2016, Vol. 13(5) 373–376
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DOI: 10.1177/1479164116645247
dvr.sagepub.com


NMRC Transition Award 2014-2017

Relationship of haptoglobin phenotype to vascular changes and response to Vitamin E supplementation in patients with Diabetes Mellitus type 2: The EVAS trial. Amount \$825,000 + 20% indirect cost

Endothelial cell apoptosis correlates with low haptoglobin concentrations in diabetes

Rinkoo Dalan^{1,2,3}, Xiaofeng Liu^{4,5}, Liuh Ling Goh¹, Sun Bing¹ and Kathy Qian Luo⁶

Diabetes & Vascular Disease Research
2017, Vol. 14(6) 534–539
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DOI: 10.1177/1479164117719827
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We conducted a stratified RCT to see if vitamin E (an antioxidant) has a preferential effect on Vascular Function In patients with Diabetes and haptoglobin 2-2 genotype

This study is sponsored by National Medical Research centre Transition Award

In Vitro Methods

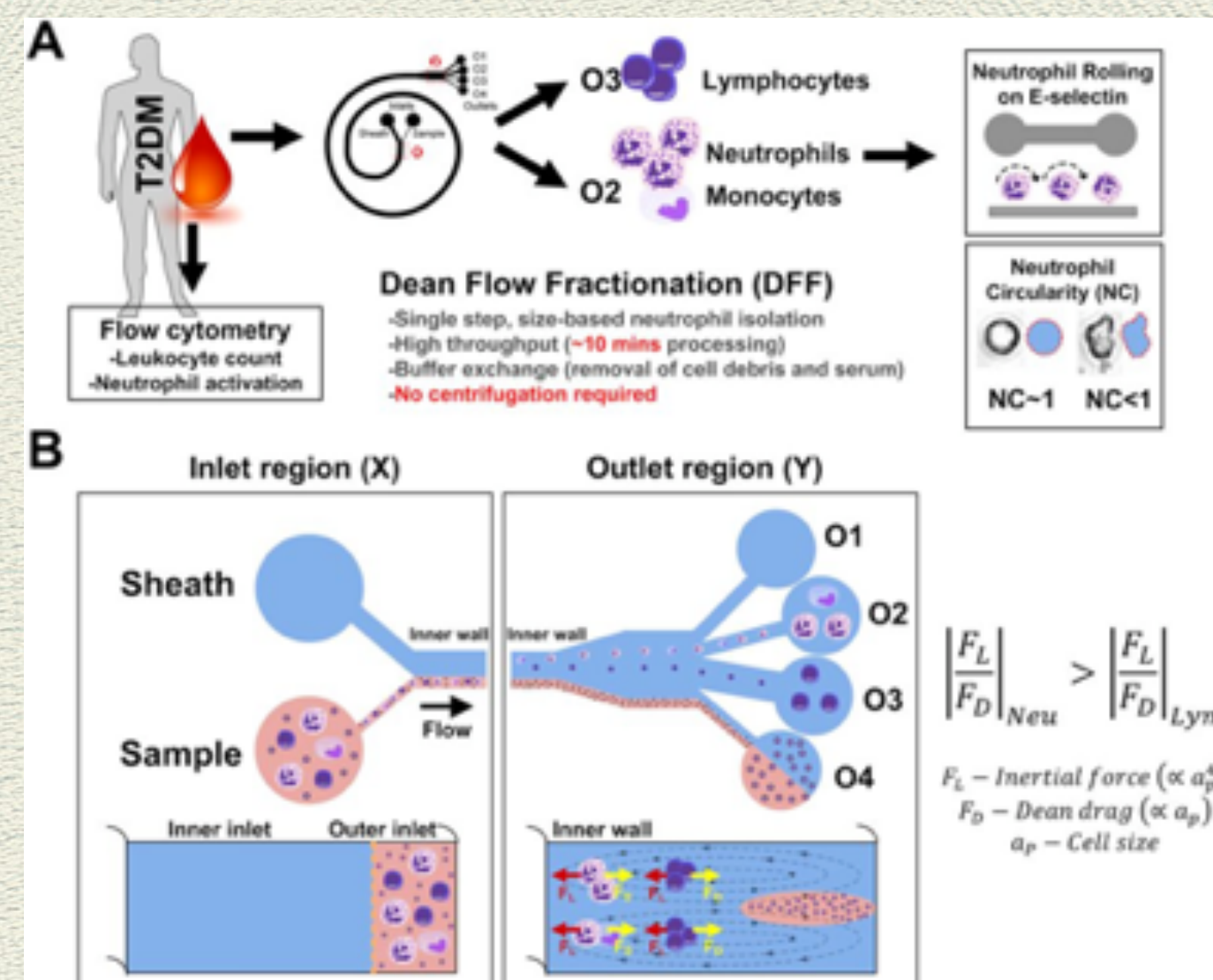
SCIENTIFIC REPORTS

OPEN

Rapid and label-free microfluidic neutrophil purification and phenotyping in diabetes mellitus

Han Wei Hou¹, Chayakorn Petchakup², Hui Min Tay³, Zhi Yang Tam³, Rinkoo Dalan^{1,3}, Daniel Ek Kwang Chew^{1,3}, King Ho Holden Li³ & Bernhard O. Boehm^{1,3,4}

Received: 05 March 2018
Accepted: 16 June 2018
Published: 06 July 2018



Multiplexed Label-Free Fractionation of Peripheral Blood Mononuclear Cells for Identification of Monocyte-Platelet Aggregates

Hui Min Tay[†], Wei Hseun Yeap[‡], Rinkoo Dalan[§], Siew Cheng Wong^{*†,1}, and Han Wei Hou^{*†,1}

[†] School of Mechanical and Aerospace Engineering, Nanyang Technological University, 50 Nanyang Avenue, 639798, Singapore

[‡] Singapore Immunology Network, Agency for Science, Technology and Research, 8a Biomedical Grove, 138648, Singapore

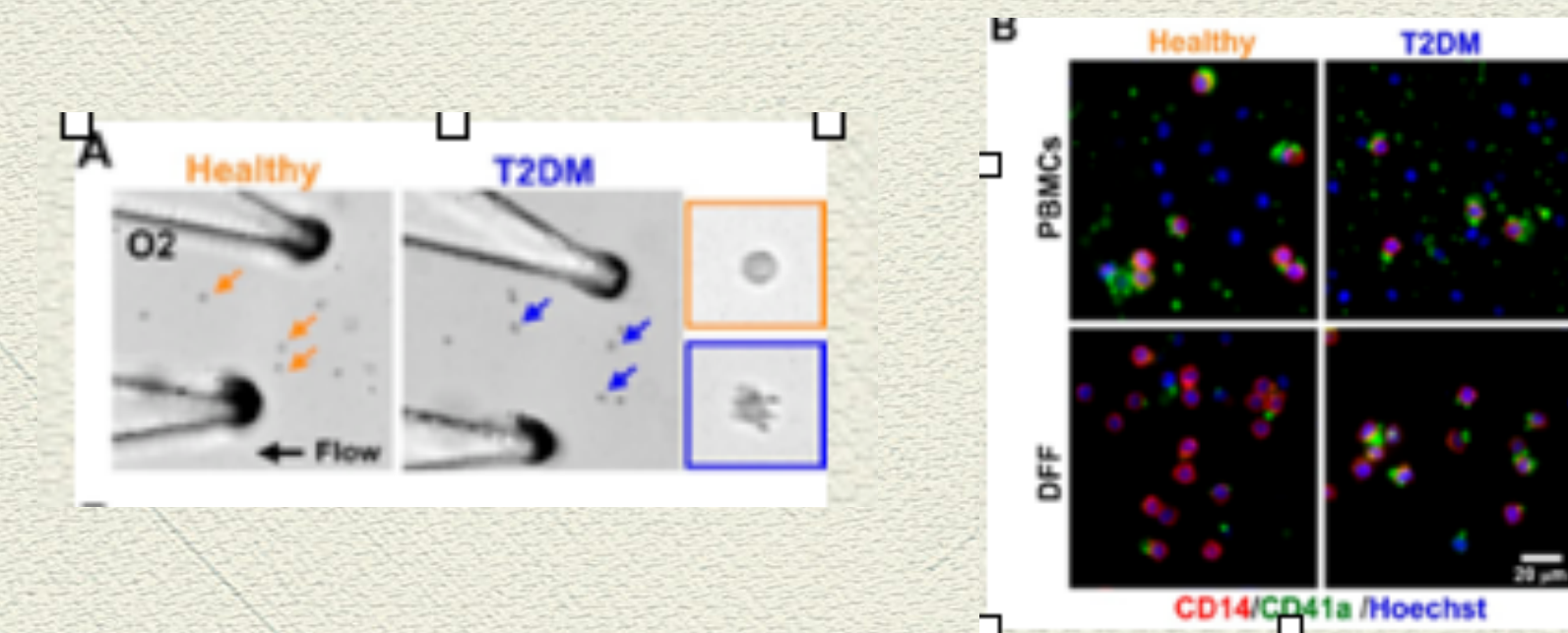
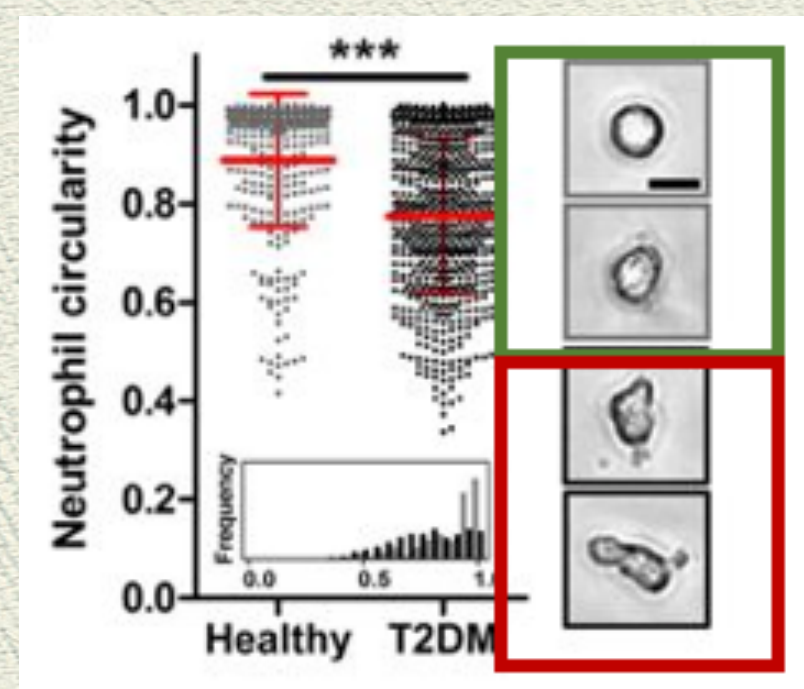
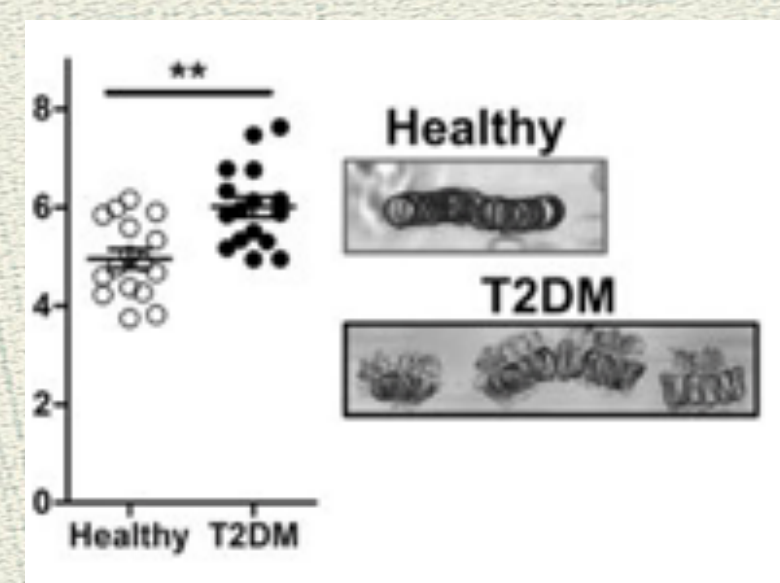
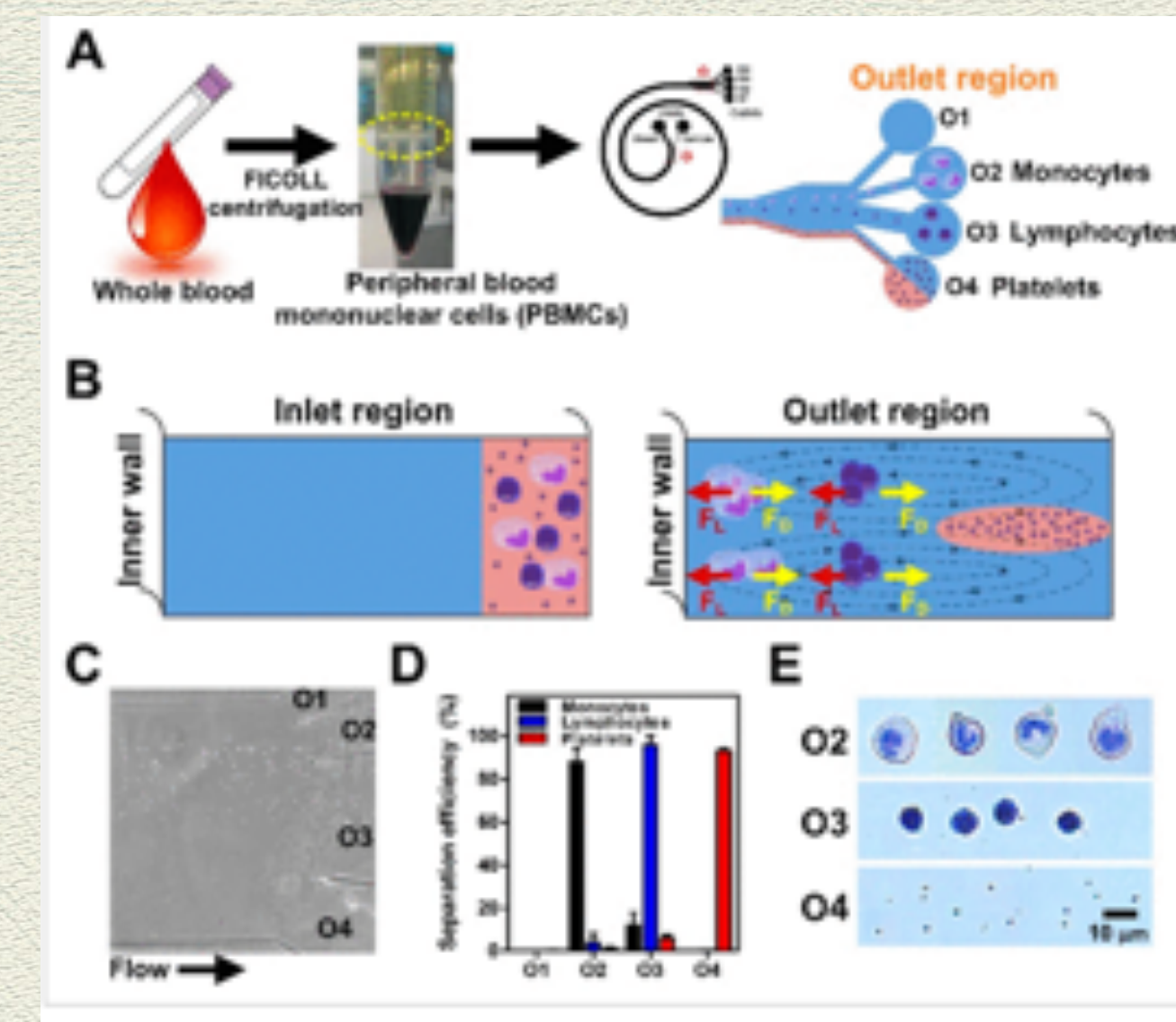
[§] Endocrine and Diabetes, Tan Tock Seng Hospital, 11 Jalan Tan Tock Seng, 308433, Singapore

^{*} School of Biological Sciences, Nanyang Technological University, 60 Nanyang Drive, 637551, Singapore

¹ Lee Kong Chian School of Medicine, Nanyang Technological University, Clinical Sciences Building, 11 Mandalay Road, 308232, Singapore

Anal. Chem., 2018, 90 (24), pp 14535–14542

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This study is sponsored by National Medical Research centre NIG grant to Ass Prof Hou HW

SGLT2-inhibitors and Cardiovascular Outcomes

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators

MACCE

Cardiovascular Mortality
Heart Failure

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes

S.D. Wiviott, I. Raz, M.P. Bonaca, O. Mosenzon, E.T. Kato, A. Cahn, M.G. Silverman, T.A. Zelniker, J.F. Kuder, S.A. Murphy, D.L. Bhatt, L.A. Leiter, D.K. McGuire, J.P.H. Wilding, C.T. Ruff, I.A.M. Gause-Nilsson, M. Fredriksson, P.A. Johansson, A.-M. Langkilde, and M.S. Sabatine, for the DECLARE-TIMI 58 Investigators*

REVIEW ARTICLE

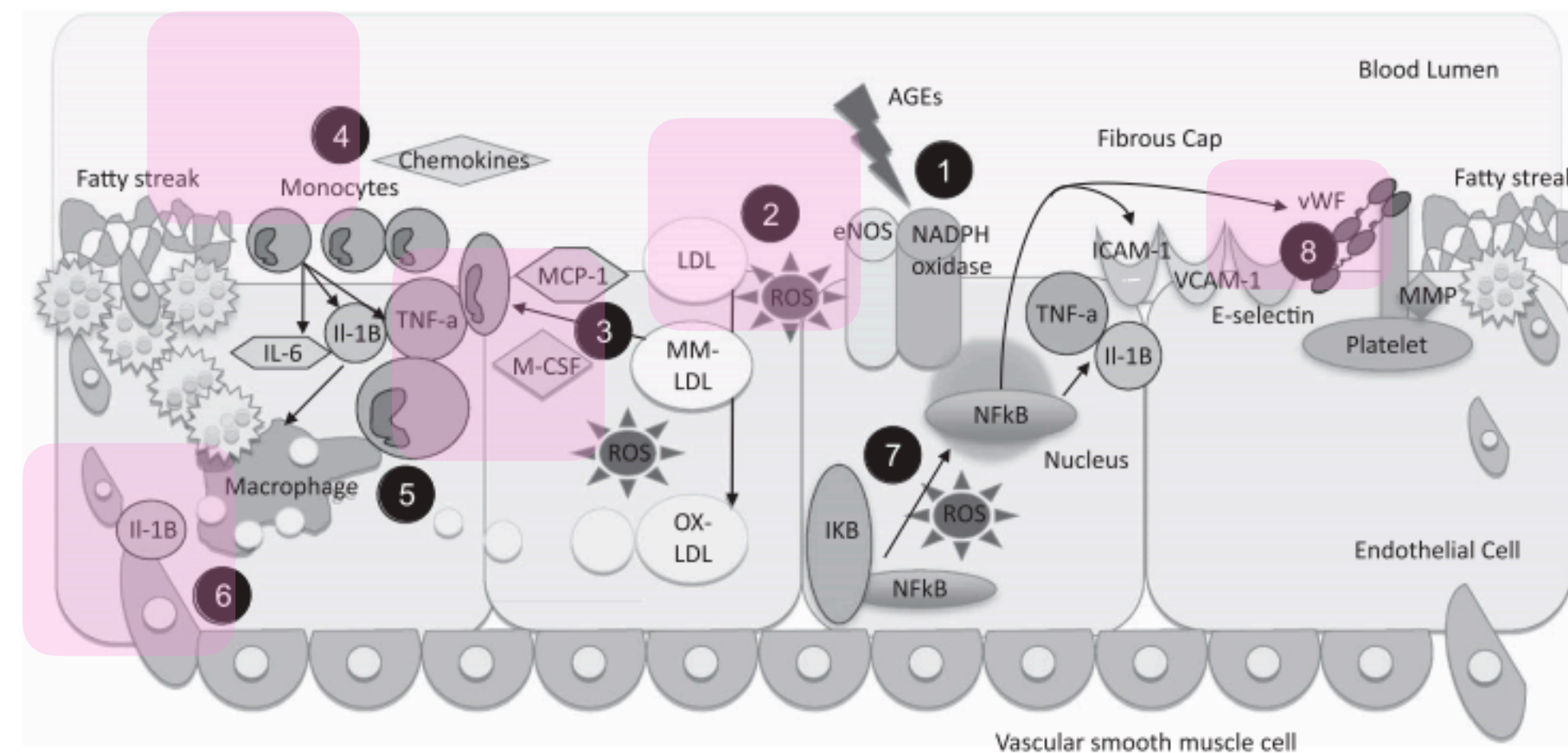
Sodium–Glucose Cotransporter-2 Inhibition in Type 2 Diabetes Mellitus

A Review of Large-Scale Cardiovascular Outcome Studies and Possible Mechanisms of Benefit

Rinkoo Dalan, MBBS, FRCP(Edin), FAMS(Endocrinology)

Cardiology in Review • Volume 26, Number 6, November/December 2018

SGLT2 Inhibitors in Diabetes Mellitus



Effects of Dapagliflozin and Metformin on Vascular Function in Newly-Diagnosed Treatment-Naïve Type 2 Diabetes – A Randomized Controlled Trial

The DMVascular Study

Design

12-week, randomised, controlled, open label trial

150 newly-diagnosed T2DM patients will be randomised to either of three allocation:

- i. Metformin 500mg (Glucophage XR) up to twice daily
- ii. Dapagliflozin 10mg (Forxiga) once daily
- iii. Dapagliflozin 5mg/Metformin 500mg Combo (Xigduo) once daily

Sponsored by National Medical Research Council Clinician Scientist Award

Thank You



Department of Endocrinology:

Center Grant and Molecular Diagnostic Lab

Clinical Research and Innovation Office

NHG Research and Development Office

Collaborators :

Nanyang Technological University
Lee Kong Chian School of Medicine

