Improving the Lives of Patients with Heart Attacks

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The 'Big Four' Diseases in Singapore

Diseases on the rise due to ageing population

Estimated numbers by 2030

1 in 7 adults aged 18 to 69 years to have **DIABETES**	1 in 220 residents to have a **HEART ATTACK**	1 in 180 residents to be diagnosed with a **CANCER**	1 in 230 residents to have a **STROKE**
UP 33% (since 2010)	**UP** 59% (since 2013)	**UP** 70% (since 2013)	**UP** 110% (since 2013)
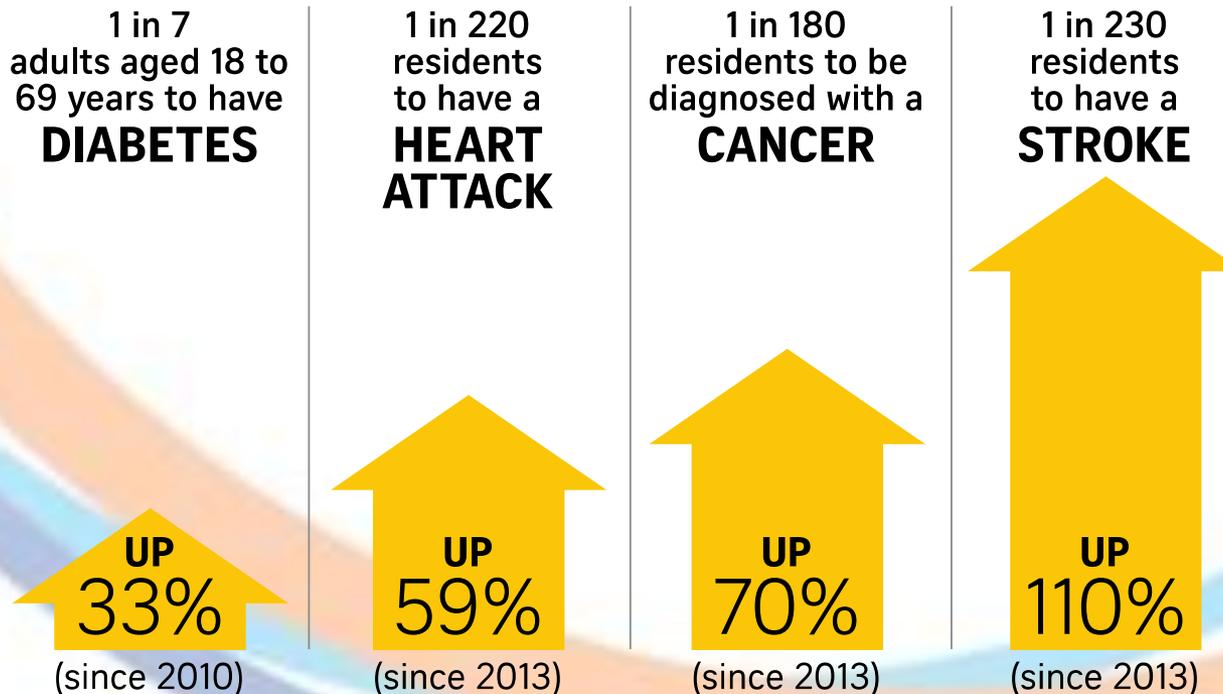
Source: MINISTRY OF HEALTH   SUNDAY TIMES GRAPHICS

Acute Myocardial Infarction: Common and Deadly Manifestation of IHD

If the plaque becomes unstable and ruptures, the clotting process, called thrombosis, starts inside the artery.

Acute Myocardial Infarction (AMI)

If the clot completely blocks the coronary artery, all muscle tissue below the blockage can die.

Dead cardiac muscle tissue (myocardial infarction)
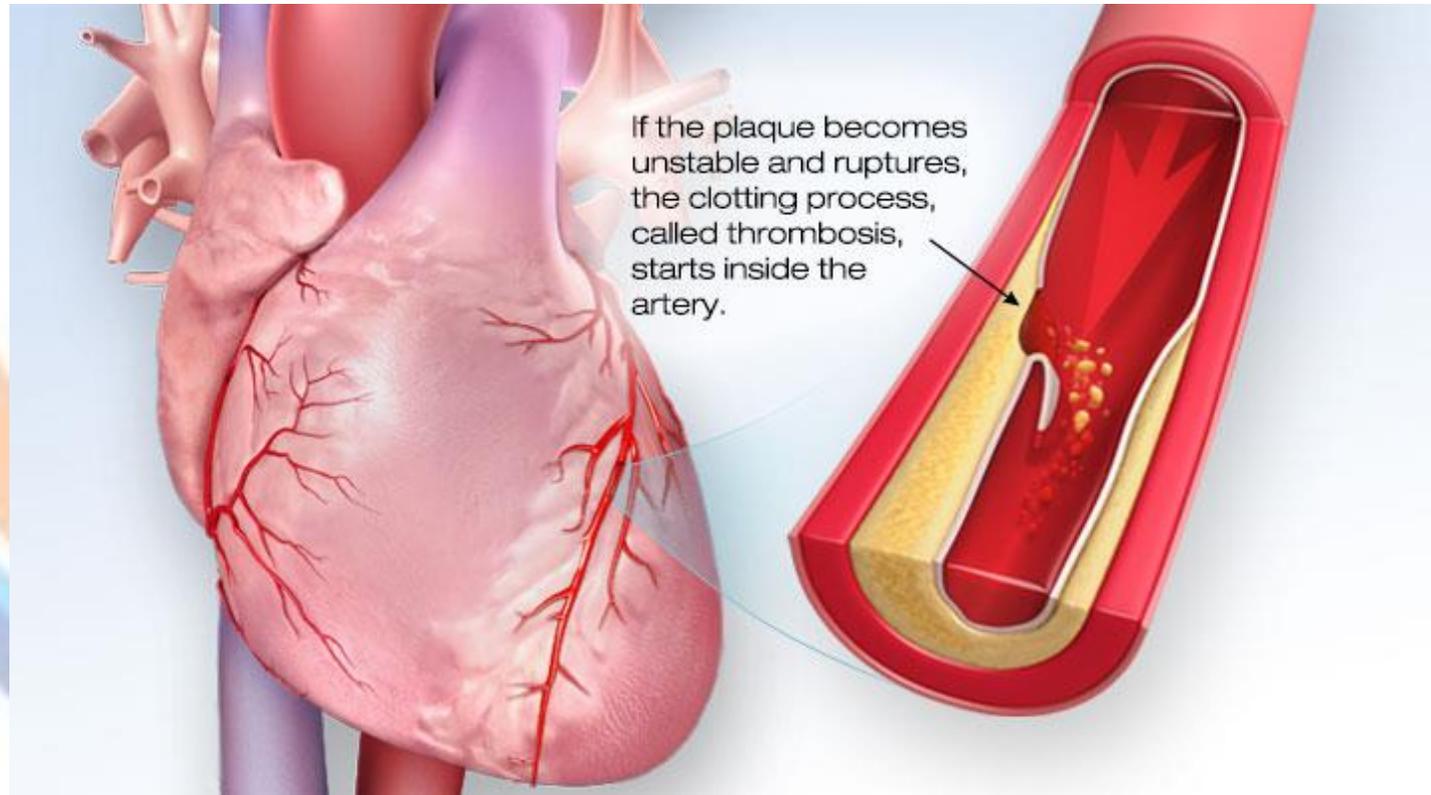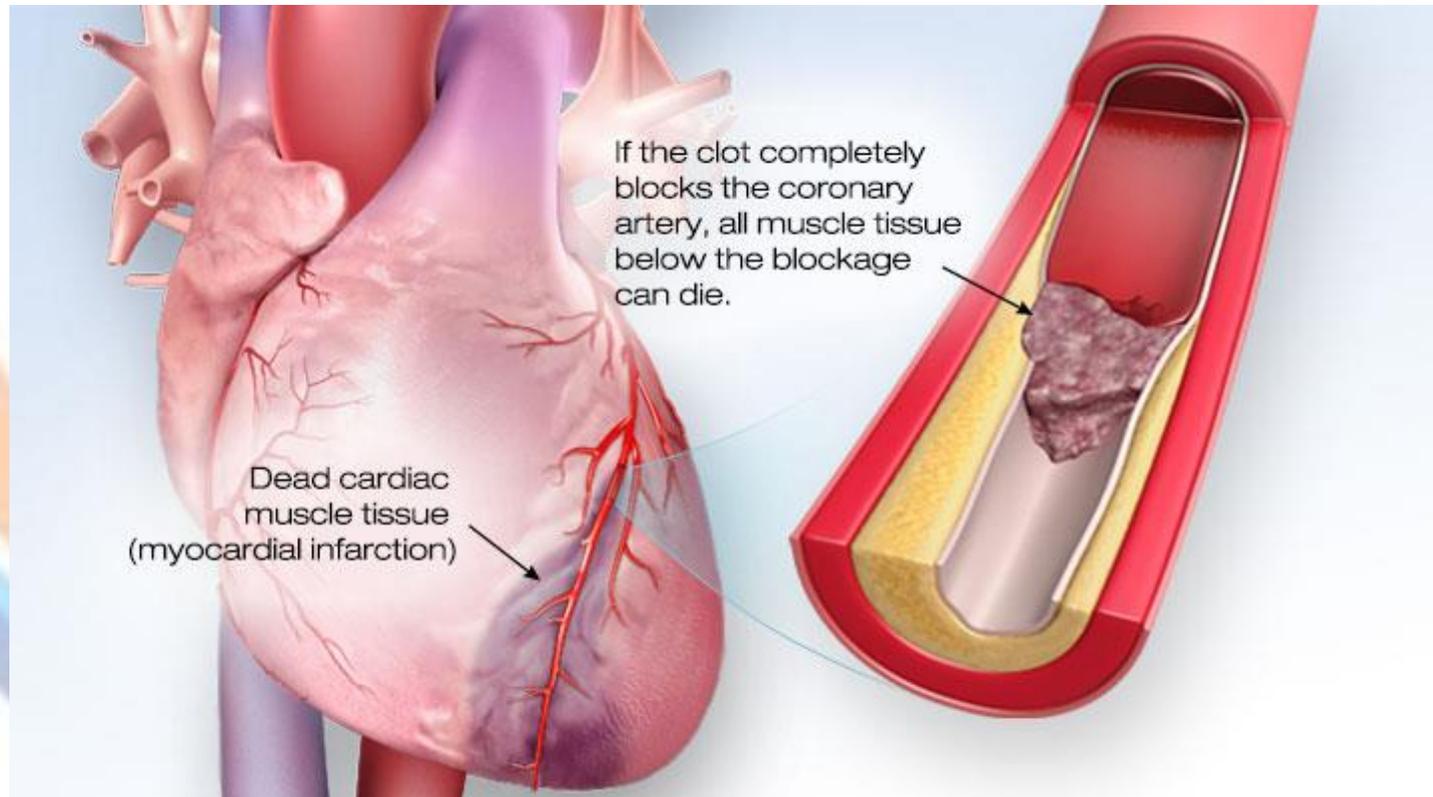
Improving the Lives of Patients with Heart Attacks

- Safer inhospital treatments
- Better risk prediction
- Improved systems of care

Coagulation cascade and anticoagulants
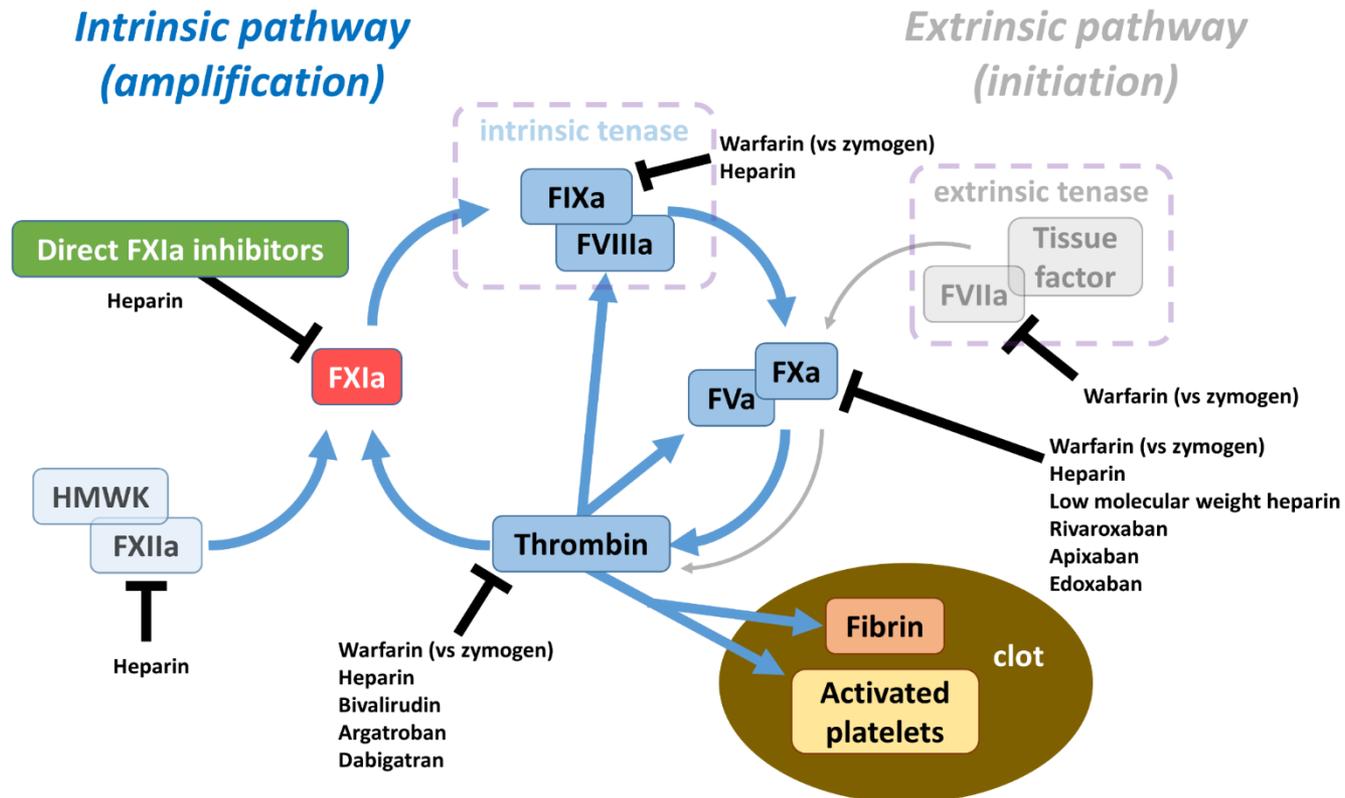
Bleeding is Associated with Higher Mortality

26,451 patients enrolled in 4 randomized trials of Acute Coronary Syndrome
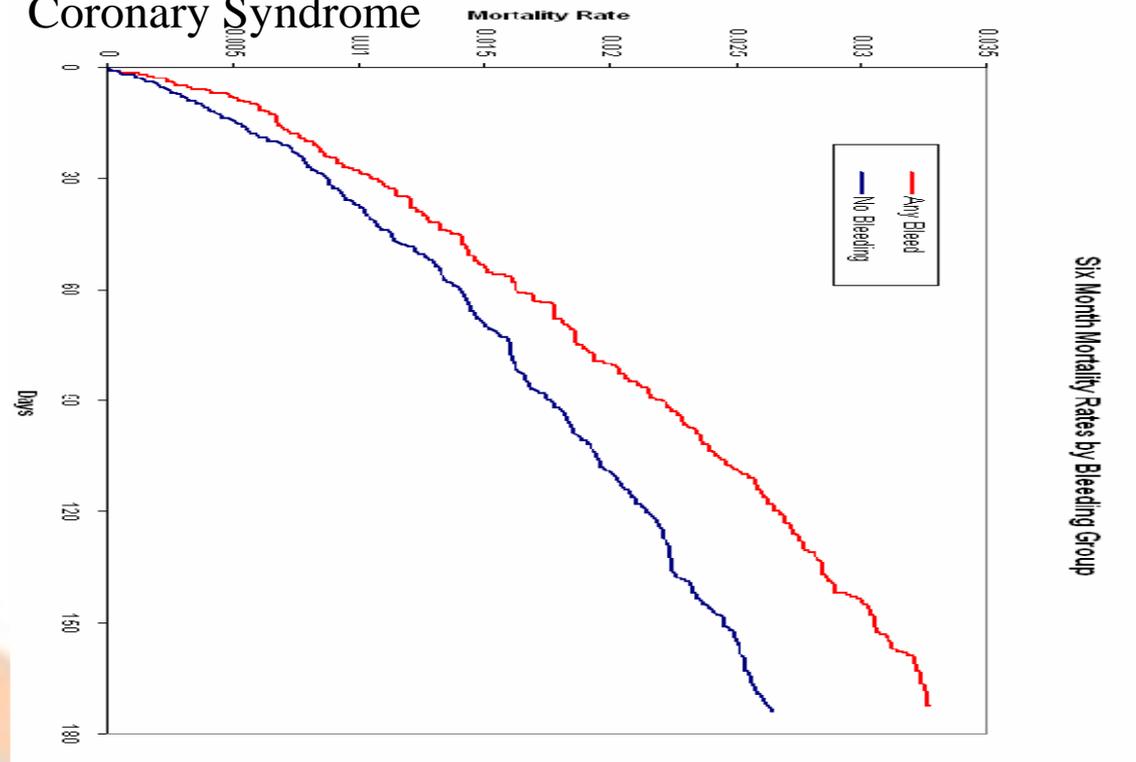
Chan, MY Am Heart J 2011

Factor IXa and drug-antidote interactions
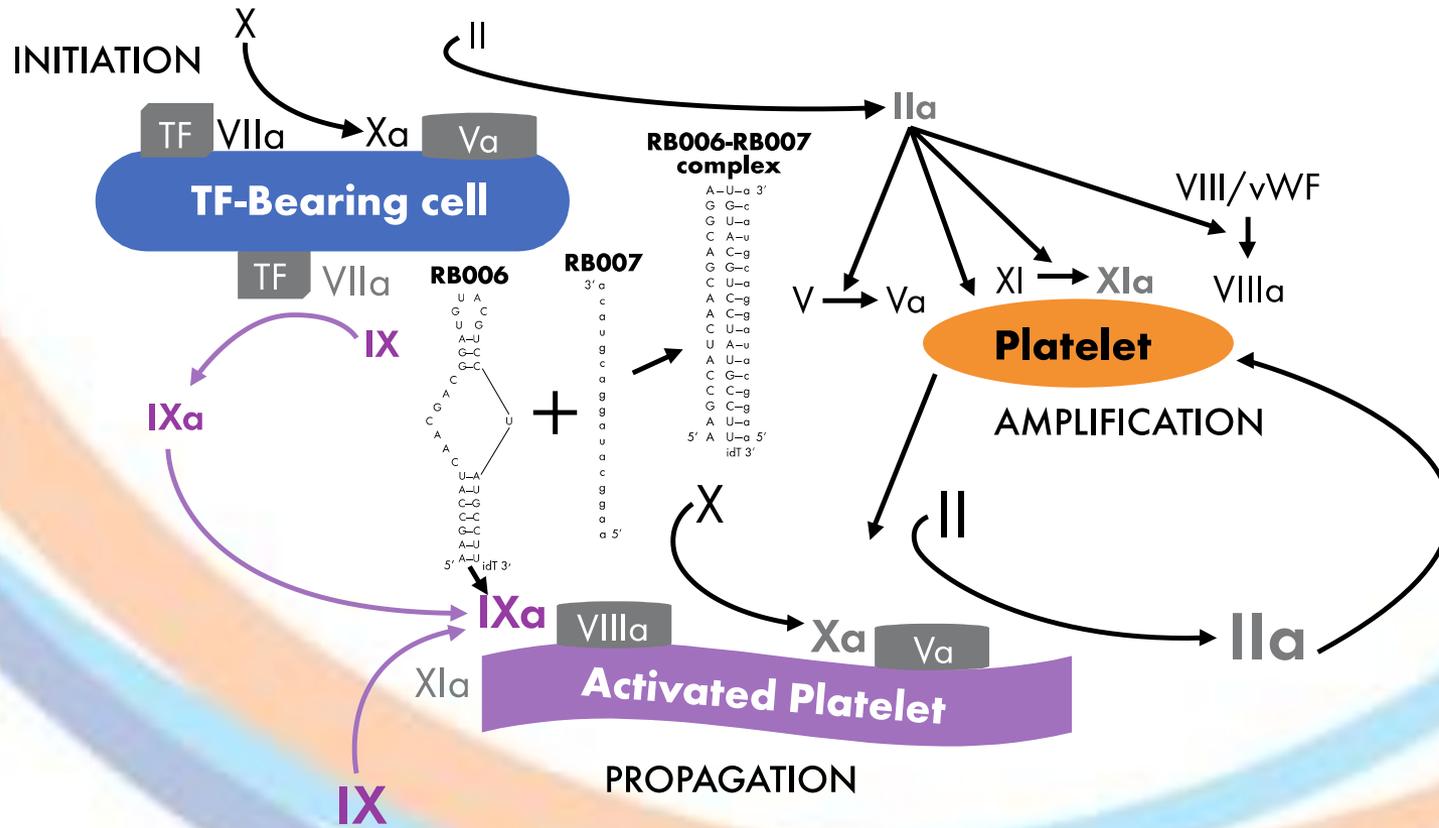
Phase 1b Randomized Study of Antidote-Controlled Modulation of Factor IXa Activity in Patients With Stable Coronary Artery Disease
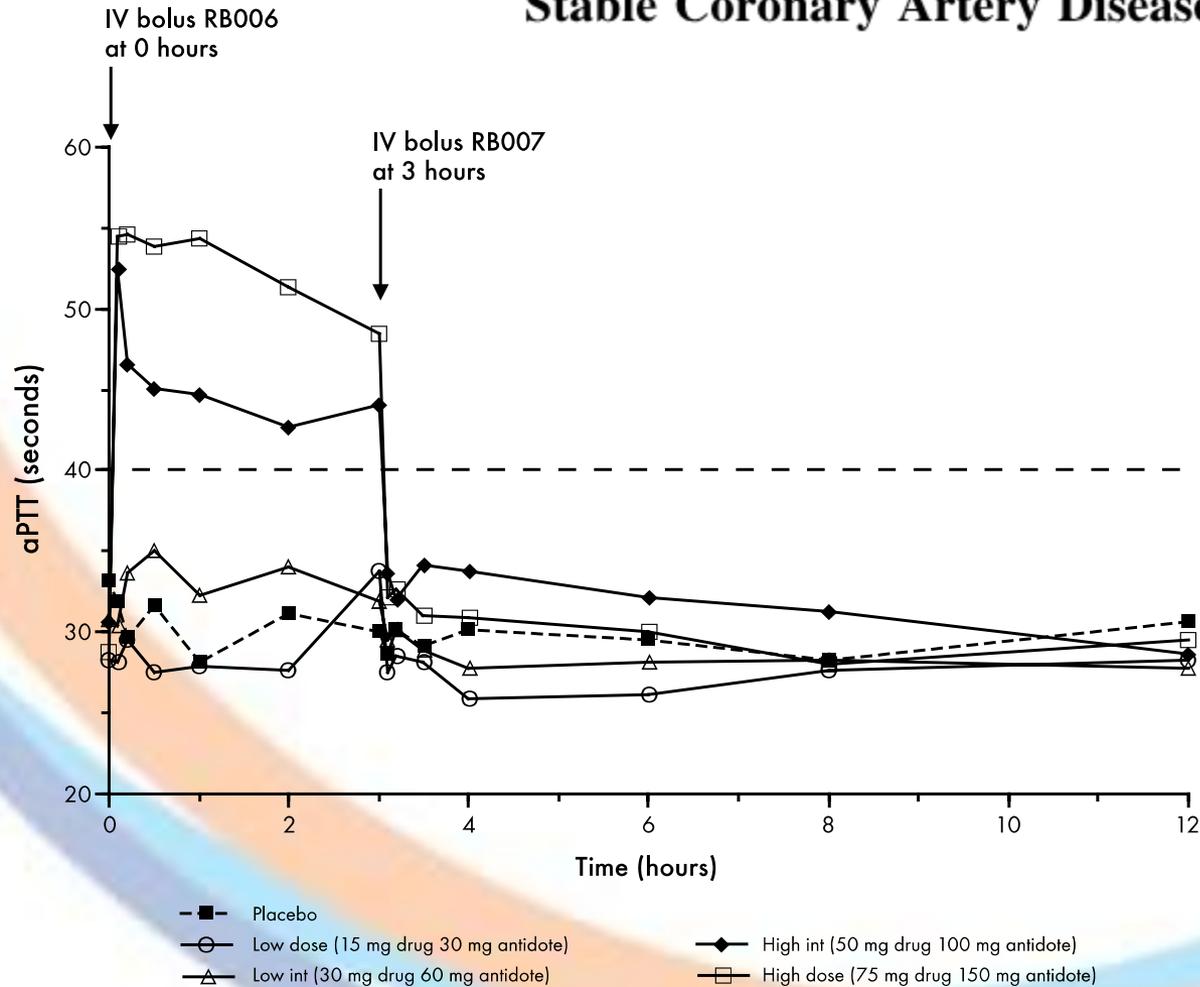
Figure 6. APTT recovery after administration of antidote (RB007). Horizontal dashed line denotes upper limit of normal. Placebo group includes all patients receiving placebo drug and placebo antidote (n=8). The 4 dose groups here included only patients receiving active drug followed by active antidote (n=27). $P<0.001$ across all dose groups for repeated measurements from 0 to 3 hours.

Chan, MY: Circulation. 2008;117:2865-2874.

FXIa as antithrombotic target with minimal bleeding risk

- **FXIa inhibition** has a favourable overall antithrombotic-haemostasis balance, resulting in minimal bleeding risk

- Genetic deficiency of FXI:

  – Rare spontaneous bleeding (Asakai et al. N Engl J Med 1991, 325:153-8)

  – protects from

  - ischaemic stroke (Salomon et al. Blood 2008, 111:4113-7)

  - venous thrombosis (Salomon et al. Thromb Haemost 2011, 105:269-73)

- Elevated FXI level

  – risk factor for stroke (Yang et al. Am J Clin Pathol 2006, 126:411-5)

  – myocardial infarction (Doggen et al. Blood 2006, 108:4045-51)

  – venous thrombosis (Meijers et al. N Engl J Med 2000, 342:696-701; Cushman et al. Blood 2009, 114:2878-83)

Our FXIa inhibitors: ability to engineer affinity & specificity
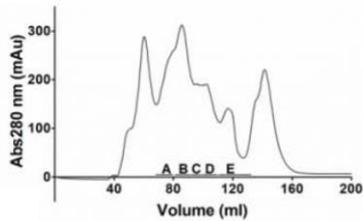
Purification from *B. fasciatus* venom
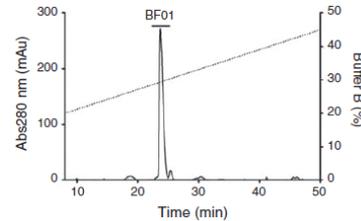
Purified to homogeneity, named **fasxiator**
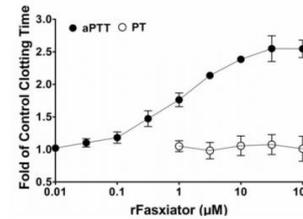
Only affects **intrinsic pathway** of blood coagulation
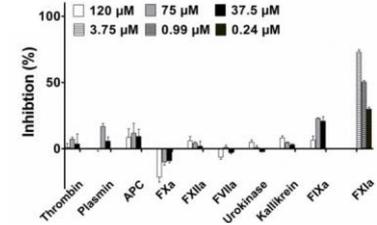
Most selective for FXIa
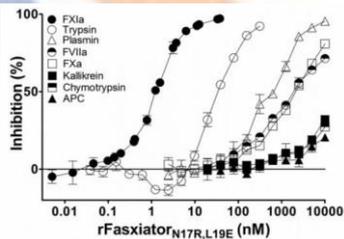
Further designs lead to a mutant with $K_i = 0.86$ nM and at least **170-fold more specific for FXIa** compared to other plasma serine proteases
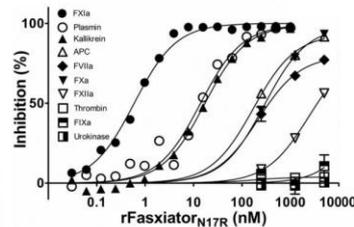
Potency improved **> 1000-fold** but specificity suffers
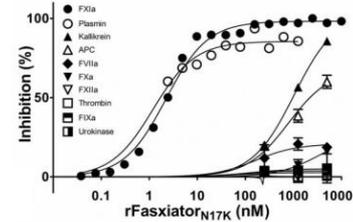
Engineered inhibitor with higher **potency**
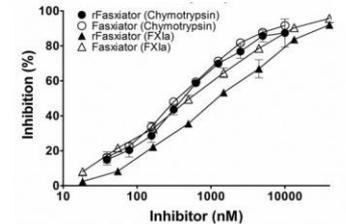
Recombinantly expressed inhibitor has identical activities

Our FXIa inhibitors: rich sources of molecules
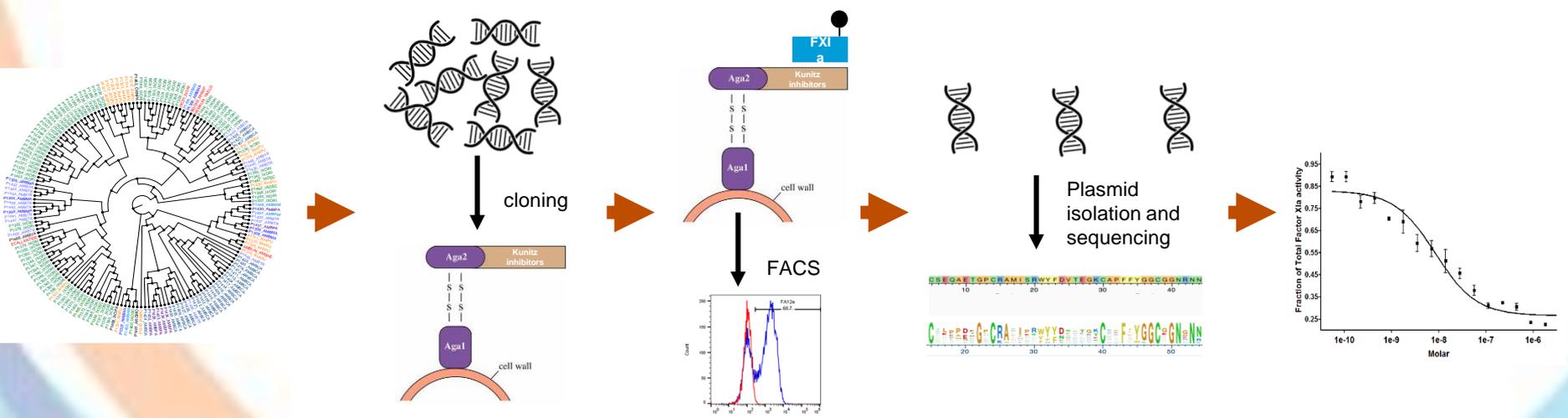
Kunitz-type protein sequences from multiple transcriptomes of ticks are filtered for their potential as FXIa inhibitors

Cloning of DNA sequences as a pool in yeast display vectors

cloning

Fluorescent-sorting of yeast cells that bind FXIa

FACS

Plasmid isolation and sequencing

Recover plasmids from selected colonies to identify sequences encoding FXIa-binding Kunitz-type protein

Recombinantly expressed identified sequences to confirm inhibition

166 unique sequences

8 FXIa-binding sequences identified

2 variants are produced, tested with confirmed activities

Pharmacodynamics: efficacy and safety

Doppler flow probe

Carotid artery thrombosis model (efficacy model)

Drug administered by I.V. bolus/infusion through femoral vein cannula

Right carotid artery

Ferric chloride-soaked filter paper

Blood flow (ml/min)

Time-to-occlusion (TTO)

Time after injury (min)

Tail incision model (safety model)

Rat tail

....

Filter paper

Bleeding time
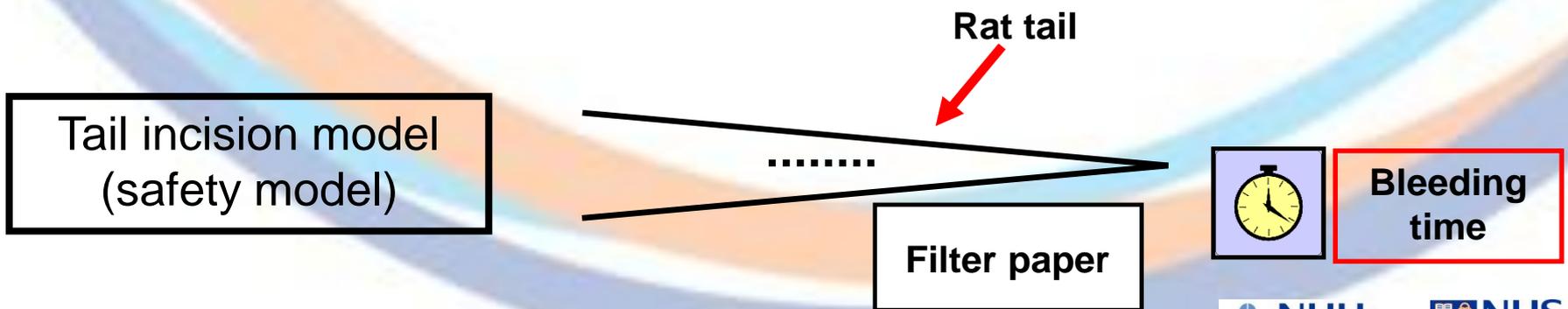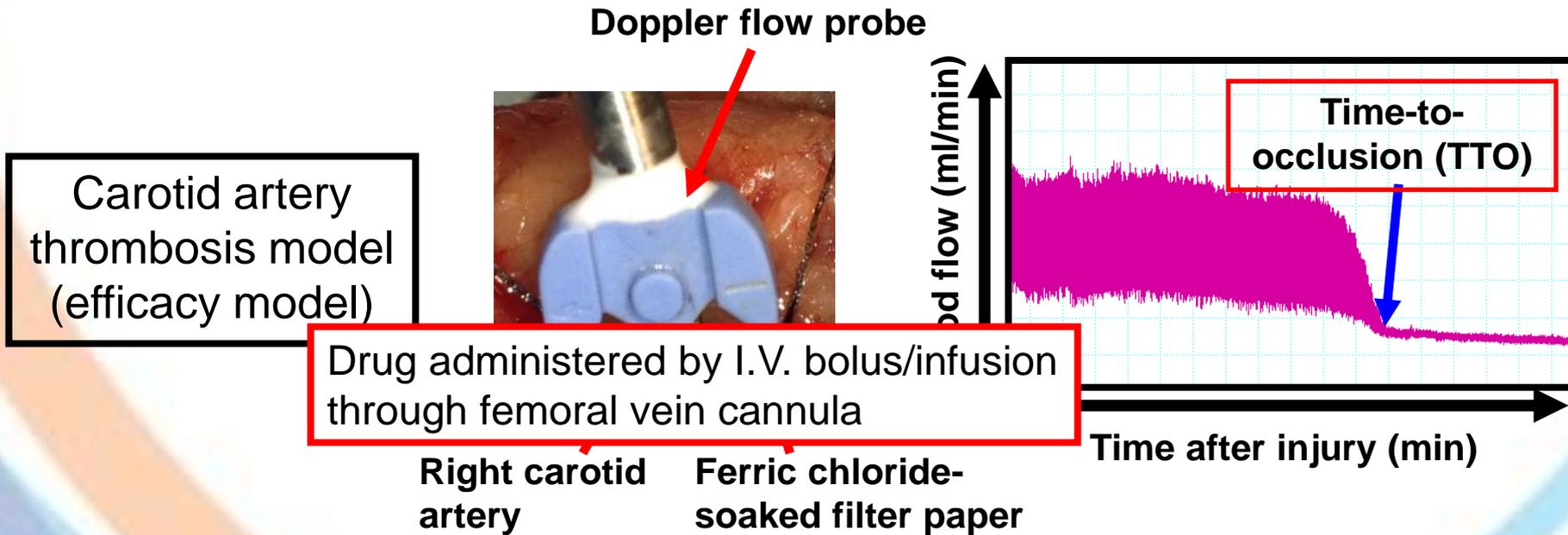
FXIa inhibitor has superior efficacy compared to heparin without risk of excessive bleeding (rat)

Efficacy model: Rat carotid artery thrombosis (TTO)

Safety model: Rat tail bleeding (TBT)

rFasxiatorN17R,L19E

Unfractionated heparin

At the same antithrombotic level, fasxiator mutant has much lower bleeding risk than heparin
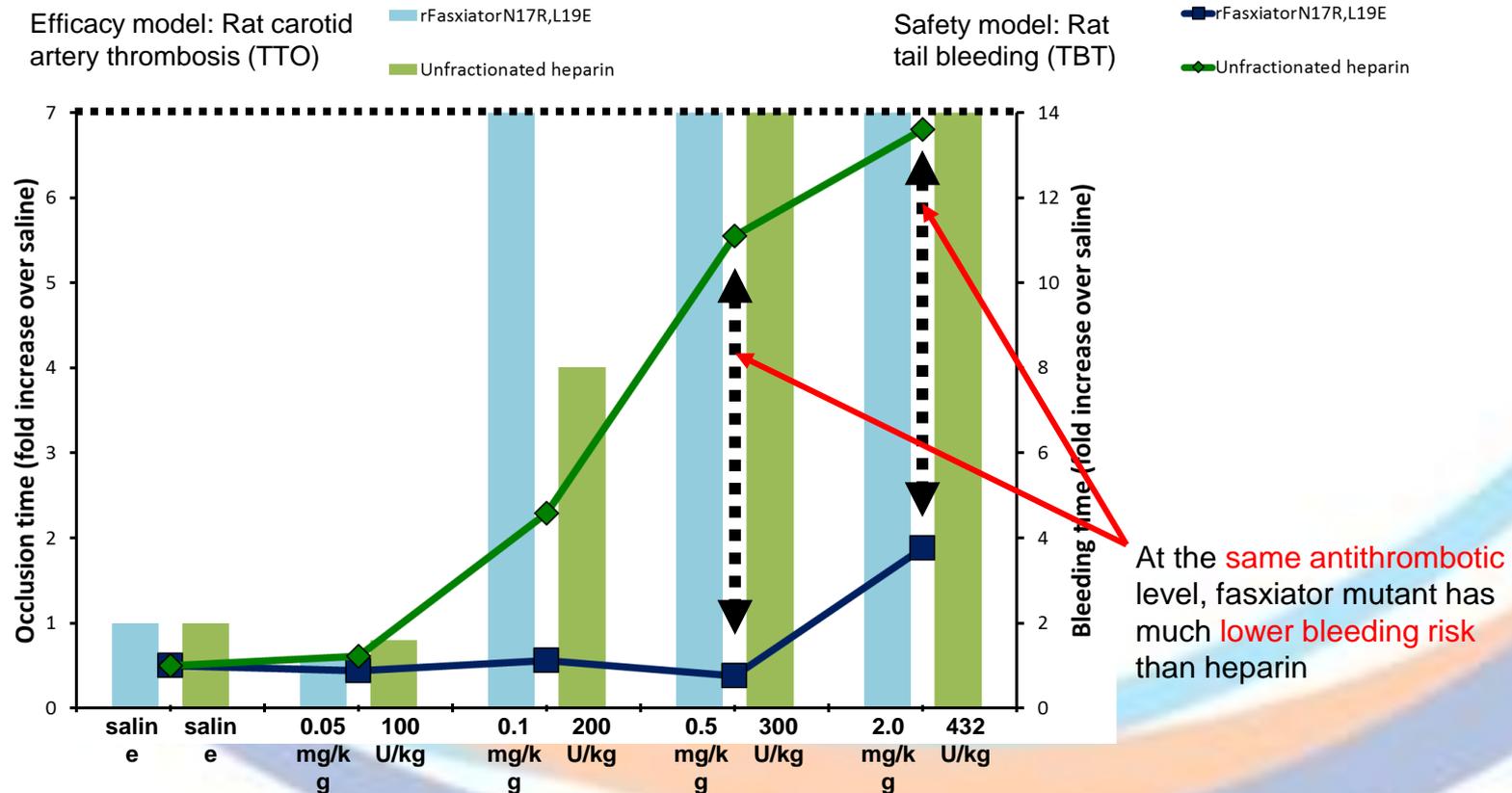
Porcine stent thrombosis model
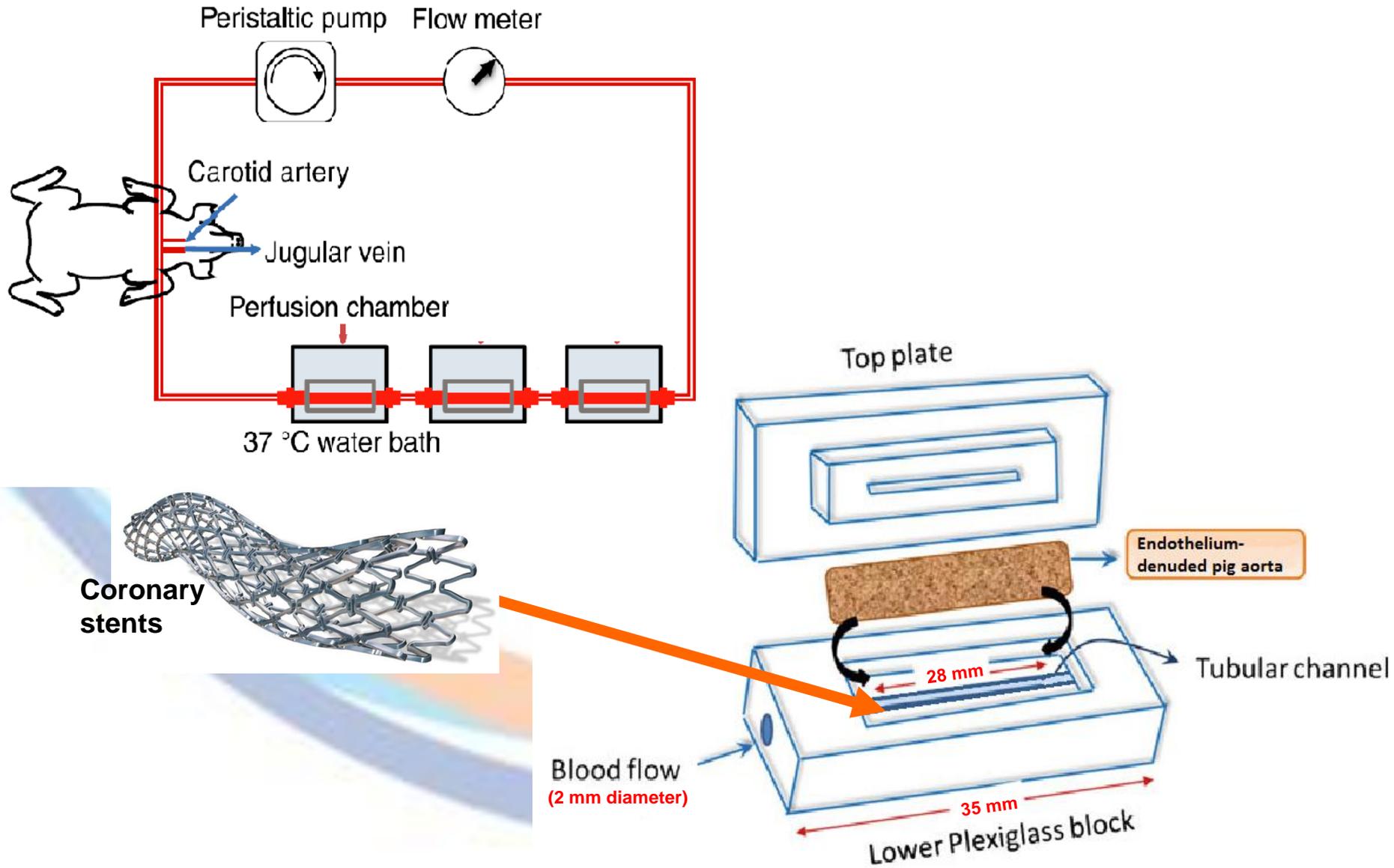
Porcine Ex Vivo Stent Thrombosis
Better efficacy & safety in combination with DAPT

DAPT | 0.1 mg/kg Variegin (+ DAPT) | 100 U/kg UFH (+ DAPT) | 0.75 mg/kg + 1.75 mg/kg/h Hirulog (+ DAPT) | 0.025 mg/kg Ultravariegin (+ DAPT)

Similar or better efficacy

8-10–times increased bleeding
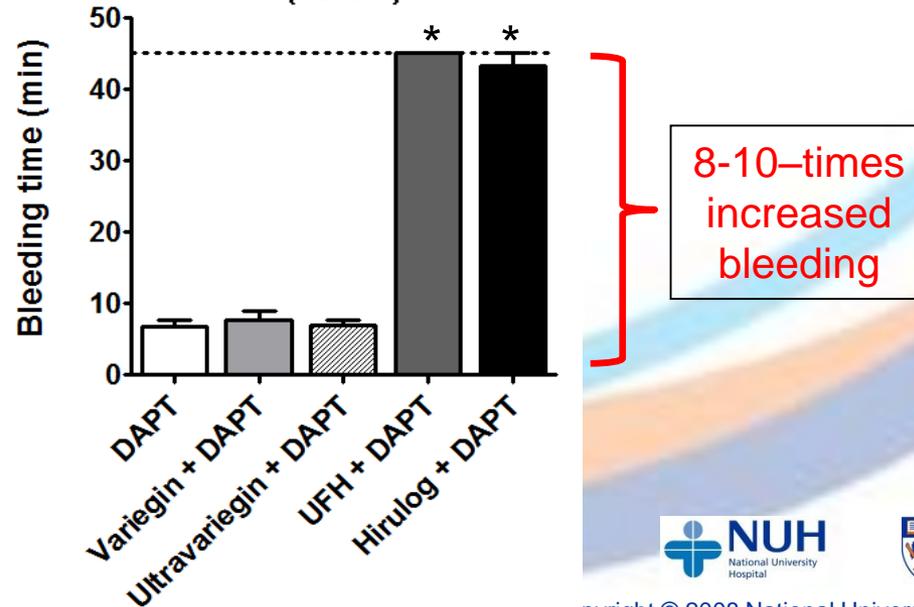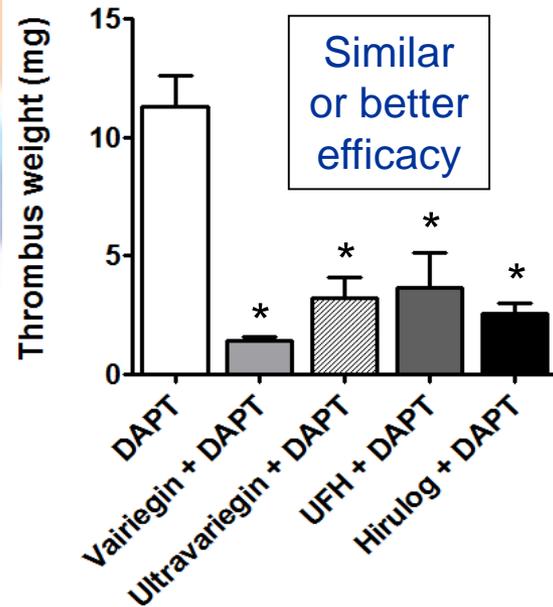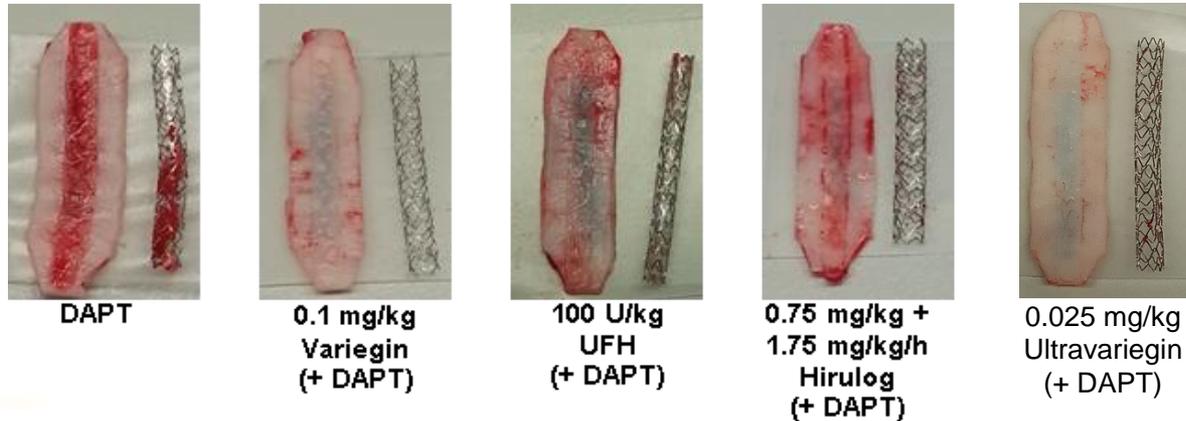
Singapore Myocardial Infarction Registry (SMIR) National Registry of Diseases Office (NRDO)

NUHS National University Health System

Data sources
ICD 9th Code 410 is used to identify AMI cases in the data sources.

Mediclaims

Hospital In-patient Discharge Summary

Enzyme lists Trop T/I, CPK, CKMB

MHA Death Registry

Un-matched Lists

Matched

Scan eMR to confirm diagnosis of AMI

MASTER LIST

Data extraction from Medical Case-notes @ MRO

Data entered into laptop

Centralized data repository

GRACE: Underestimation of Mortality Risk
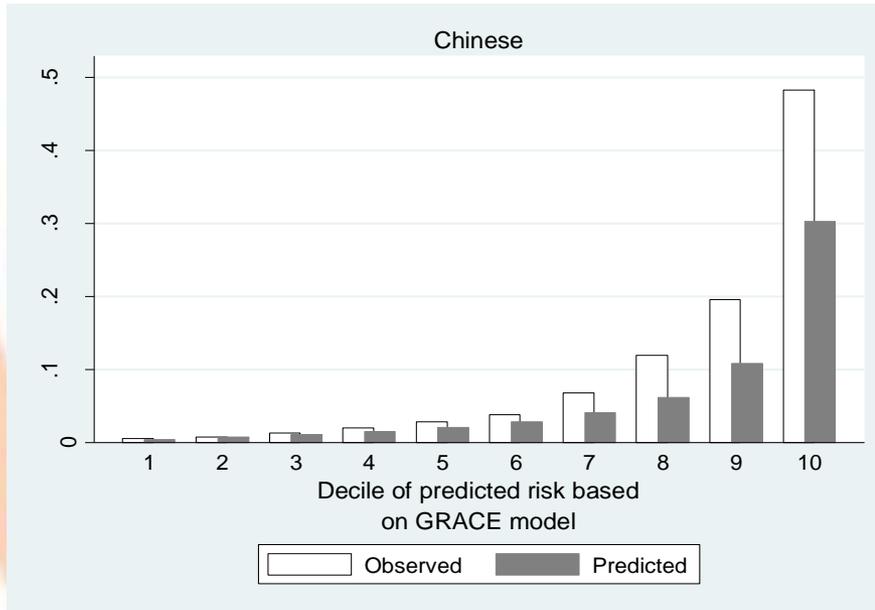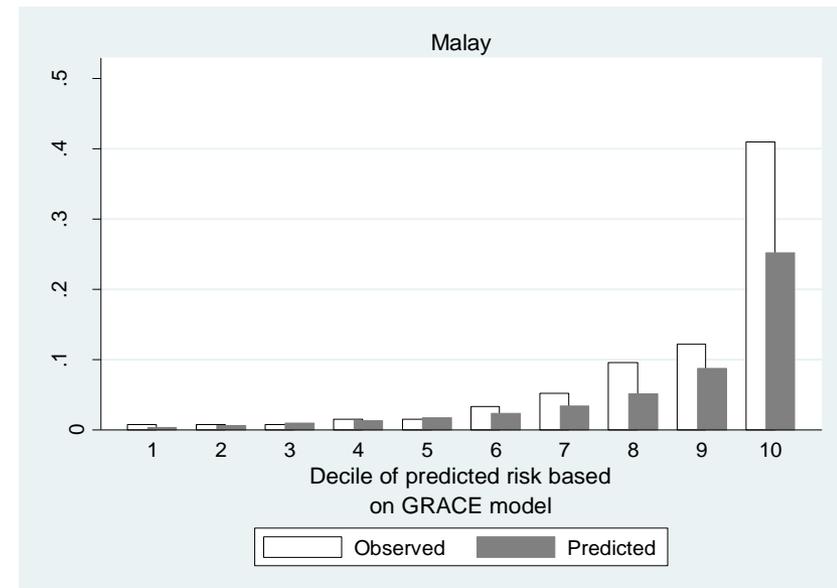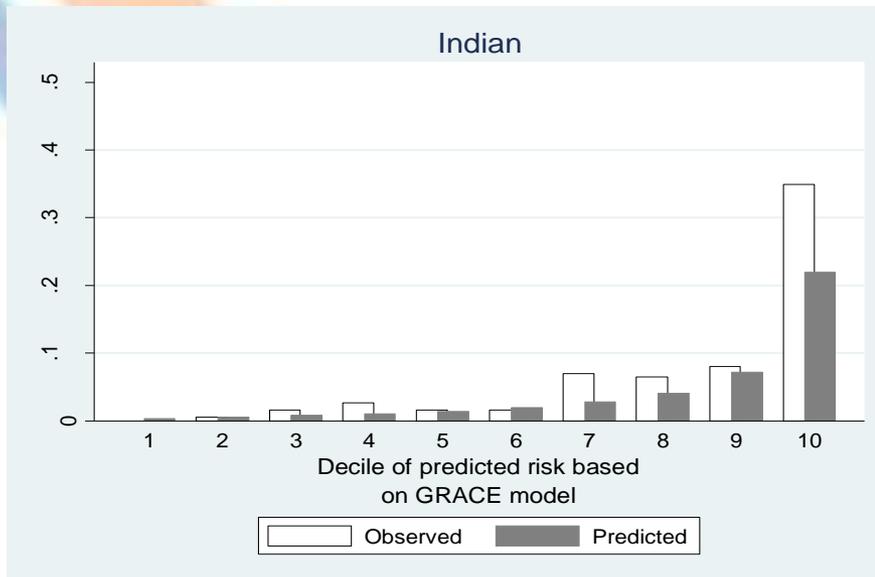
AMI Case-Fatality in Asians:
Grace model - Predicted vs. Observed

Recalibration of the GRACE Score

- retaining original regression coefficients
- Substitute the original score constants with constants derived using mean-centered values of risk factors from the Singapore cohort

$$P = \frac{\exp(f[x,M])}{1+\exp(f[x,M])}$$

Recalibrated GRACE Score

A — Chinese

B — Malay

C — Indian
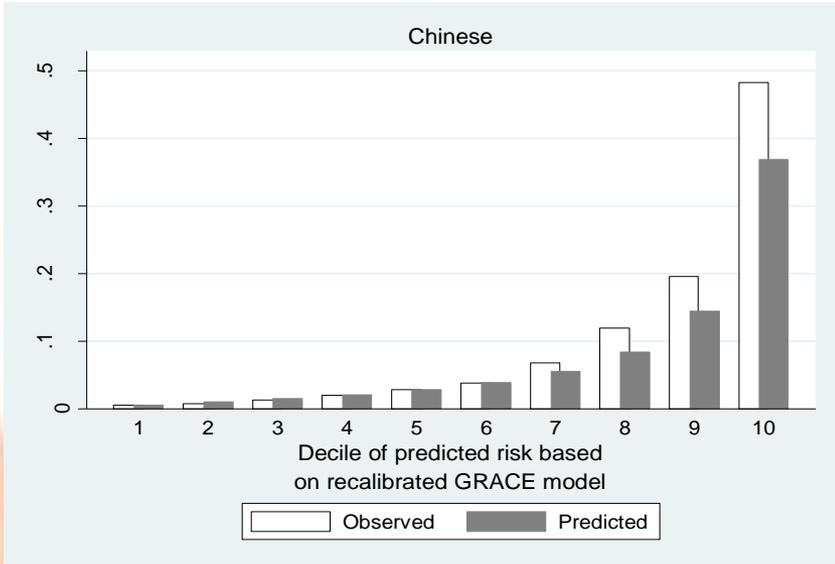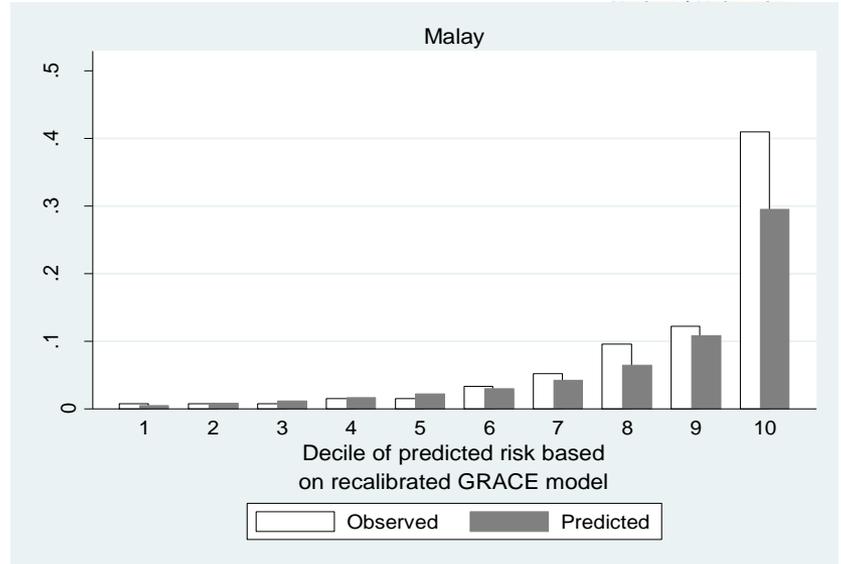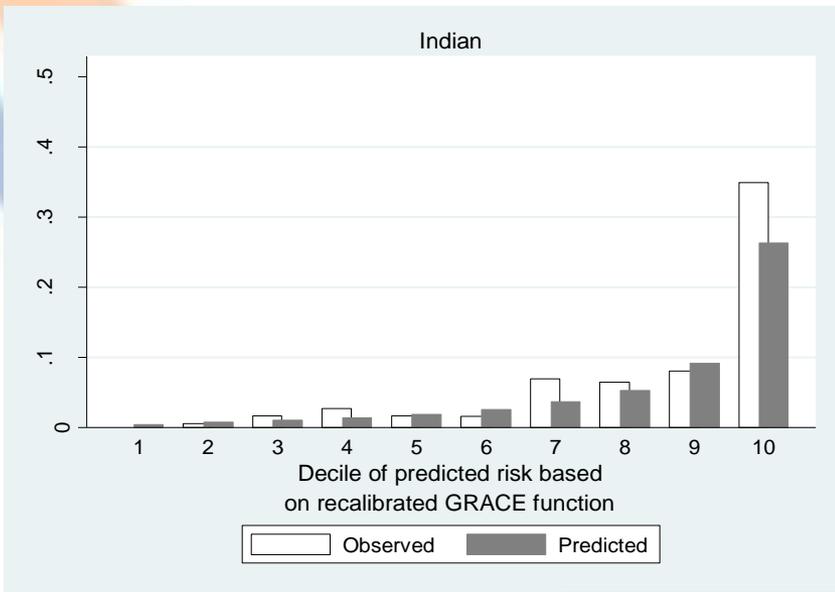
Recalibrated Grace Model: Predicted vs. Observed

Novel Prognostic Biomarkers

- Clinical data and blood at baseline (**single timepoint**) with follow up for MACCE

Carvalho, L, JACC BTS 2018 (in press)
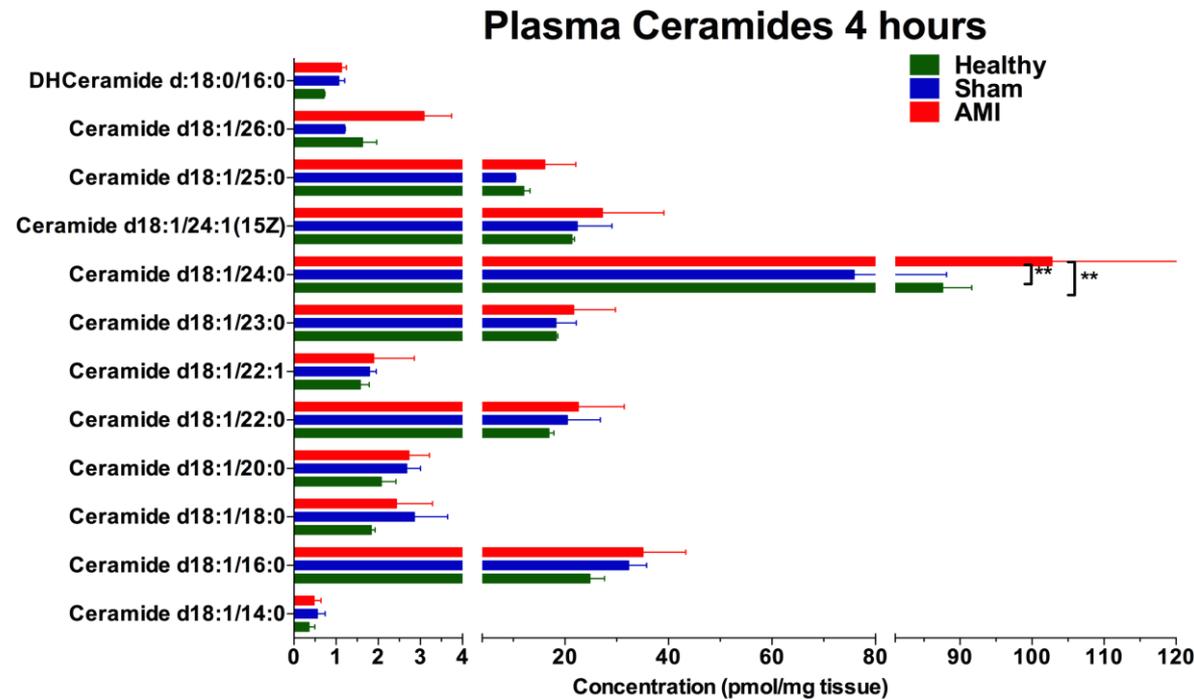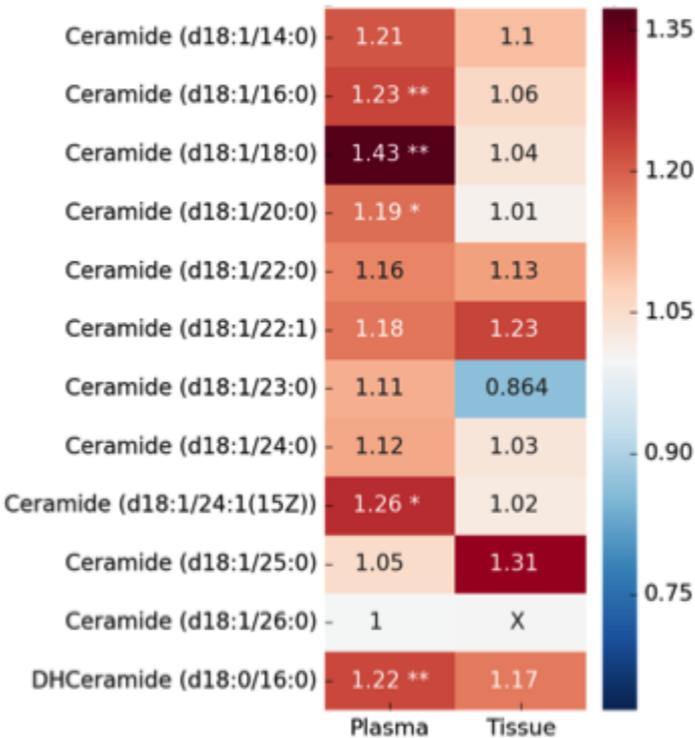
12-Ceramide Prognostic Signature classifies AMI patients into low and high risk of MACCE

Singapore

New Zealand
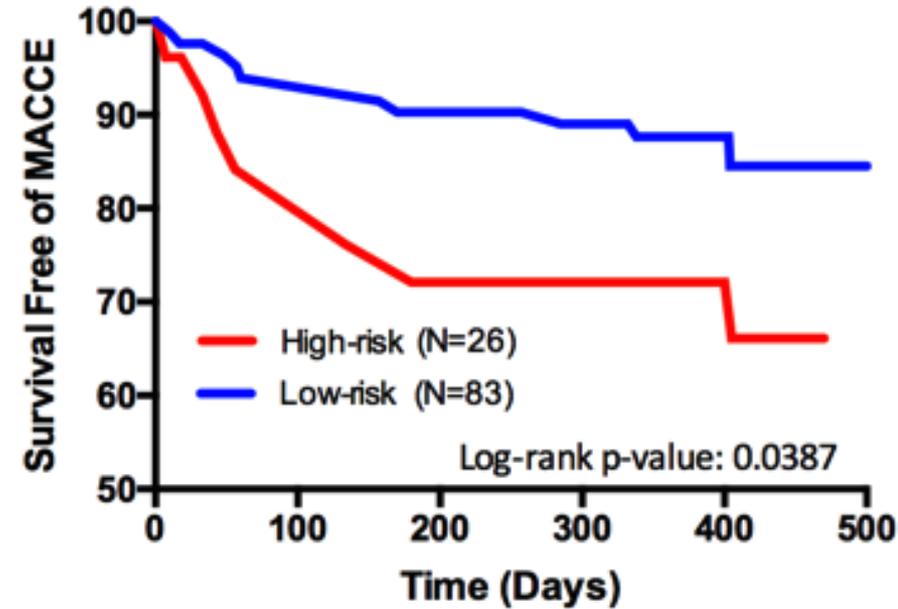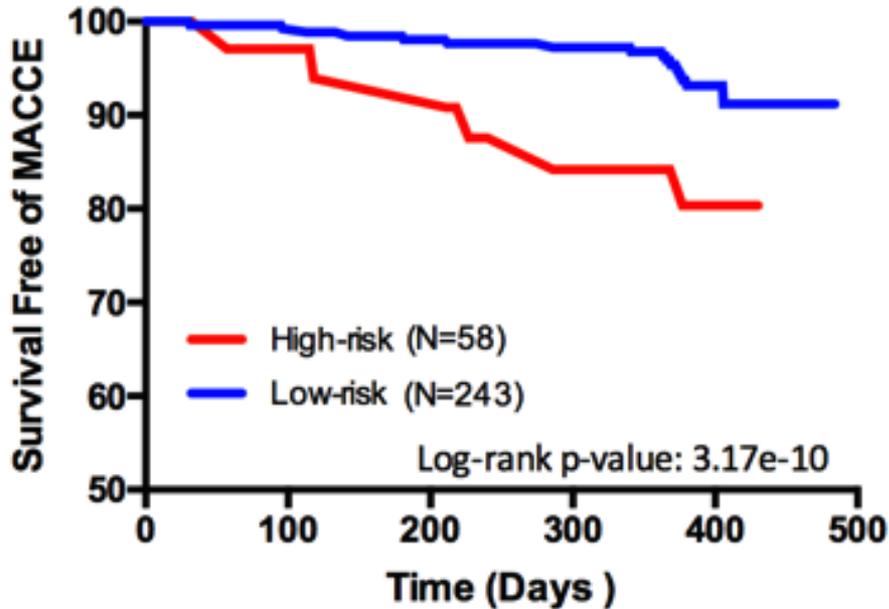
Carvalho, L, JACC BTS 2018 (in press)

18F Na-F Imaging of Vulnerable Plaque and Myocardial Scar
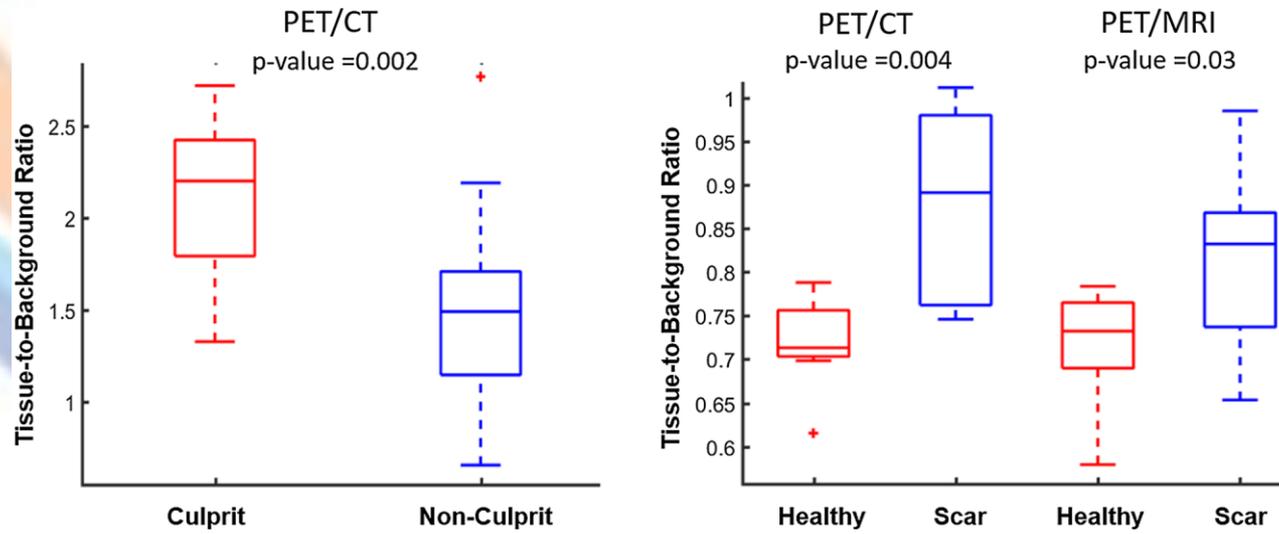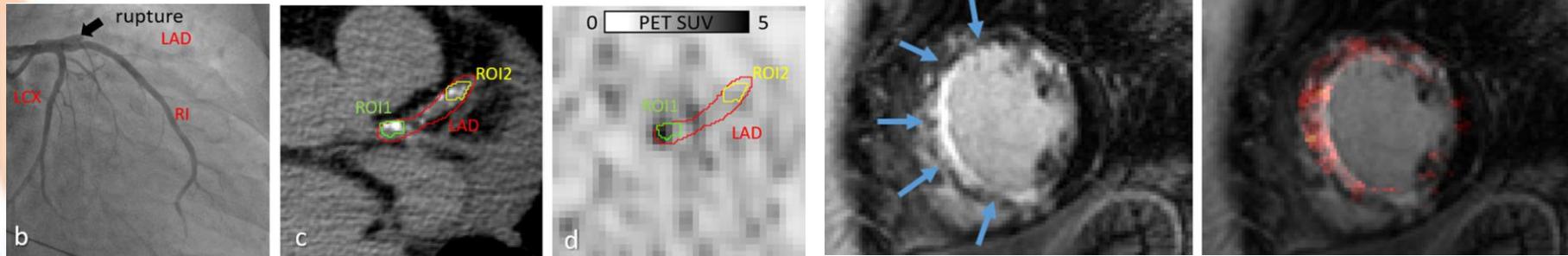
Marchesseau, S: J Nuclear Cardiology 2017

IMMACULATE Registry Longitudinal Multinational Cohort

- Clinical data, blood and imaging at baseline, 30D, 6M, 1Y and 2Y (**multiple timepoints**)

Post-MI Remodeling REGISTRY

1200 STEMI and NSTEMI patient with anterior or large inferior MI undergone primary PCI from 5 hospitals

⇩

3D Echocardiography, Sleep study and 24ml Blood sample for biomarker discovery (within 48-72 hours of symptom onset)

⇩

Study Visit (Coinciding with Clinic visits) at 4-6 weeks, 6 months, 1 year and 2 years Event follow up, Quality of Life, Clinical review and 24ml Blood collected at 30 days, 6 months, 1 year and 2 years, 3D Echocardiography and Sleep study at 6 months

⇩

Clinical event follow up for all patients up to 2 years

Heart With Muscle Damage and a Blocked Artery
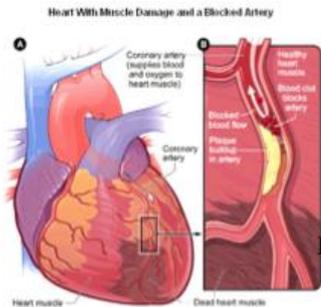
Myocardial cell death following acute coronary artery obstruction

⇩

Disproportionate thinning/weakening of the heart

⇩

Inability to withstand the pressure/volume load

⇩

Dilatation and remodeling of ventricles
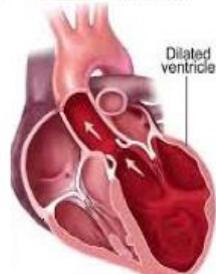
Uptitration of Medication needed in AMI

NUHS National University Health System

Telemedicine Blood pressure and pulse rate surveillance with drug titration protocol for Post-MI patients

- PI initiates post MI drugs to be titrated.
- Order is keyed into CPSS.
- Ensure patient has adequate dose drug for titration protocol.
- Recommendation is to prescribe daily target (maximum) dose of ACE-I/ARB and β–blocker at discharge for 4 weeks (till 30 day appointment with cardiologist).
- Clinical research coordinator (CRC) gives clear instructions to participant on drug titration protocol and symptoms and signs to be aware of.
- CRC issues Telemetrix+ BP/HR device to patient.

There will run-in period of <10 days from discharge to first CMR during which participant will be started on twice daily BP and HR self-check (Mon-Sun) after discharge. Adherence to BP/HR measurements will be assessed during this period.

Once 1st CMR acquired, proceed with drug titration protocol.
- Weekly titration X 8 weeks
- Alternate between ACE-I/ARB and BB titration
- Measure BP and HR again in 2 hours if drugs are uptitrated
- Maintain SBP≥110 mm Hg
- Maintain HR≥55 bpm
- Timeline: Reach target dose within 6 weeks(±2 weeks)
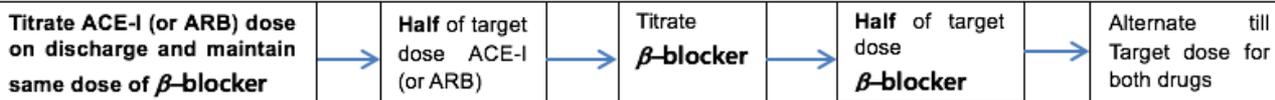
SBP>110 mm Hg and HR ≥55 bpm AND no symptoms of hypotension or bradycardia

NO
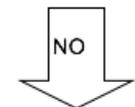
Down titrate and maintain highest tolerated dose at which target BP and/or HR is maintained
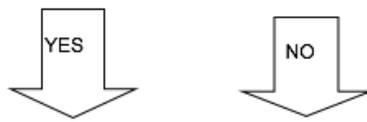
Titrate ACE-I (or ARB) dose on discharge and maintain same dose of β–blocker → Half of target dose ACE-I (or ARB) → Titrate β–blocker → Half of target dose β–blocker → Alternate till Target dose for both drugs

ACE I	Starting dose	1st Titration	2nd Titration	3rd Titration (if SBP >140 mm Hg)	Target dose	Max dose
Ramipril	2.5 mg OM	5 mg OM	10 mg OM	-	10 mg OM	10 mg OM
Perindopril	2 mg OM	4 mg OM	8 mg OM	16 mg OM	8 mg OD	16 mg OM
Lisinopril	2.5mg OM	5 mg OM	10 mg OM	20 mg OM	10 mg OD	40 mg OM
Enalapril	2.5 mg BD	5 mg BD	10 mg BD	20 mg BD	10 mg BD	20 mg BD

If intolerant of ACE I because of cough

ARB	Starting dose	1st Titration	2nd Titration	3rd Titration	Target dose	Max dose
Losartan	25mg OD	50 mg OM	100 mg OM	-	100 mg OM	100mg OM
Valsartan	40 mg BD	80 mg BD	160 mg BD	-	160 mg BD	160 mg BD

Target dose achieved?

YES → Maintain Target Dose

NO → Maintain highest tolerated dose at which target BP and/or HR is

β–blocker	Starting dose	1st Titration	2nd Titration	3rd Titration	Target Dose	Max dose
Bisoprolol	1.25 mg OM	2.5 mgOM	5 mg OM	10 mg OM	10 mg OM	20 mg OM
Carvedilol	3.125mg BD	6.25 mg BD	12.5 mg BD	25 mg BD	25 mg BD	50 mg BD

Nurse-led Physician Supported Telemedicine Service

Remote intensive management is nurse-led physician supported (NLPS) telemedicine intervention. Early up-titration of ACE-I/ARB and BB with web-based blood pressure monitoring and medication adherence coaching.

IMMACULATE trial
AMI-specific telemedicine service successfully implemented across a 3 healthcare clusters (NUHS, NHG and Singhealth)

NT-proBNP changes after NSTE-ACS

Chan, MY: Clinical Chemistry 63:1214–1226 (2017)

NUHS National University Health System

(Control group) 50%

STEMI/NSTEMI with NT-proBNP ≥300 pg/ml
(Randomization 1:1)

(Intervention group) 50%

Standard Care N = 150

Telehealth Mx N = 150

CMR (5-10 days) post MI

Face-to-face Cardiologist review @1, 6 and 12 mths*

1. **Telehealth <u>weekly</u> drug uptitration (2 months),**
2. **Telehealth review <u>bi-weekly</u> (next 4 months)**

CMR (6M)

*Substudies:

6-mth readmission (ALTRA)

Platelet reactivity, Meds adherence (TICA)

MR-PET (Cardiac efficiency)

QOL and cost effectiveness

Thank you to colleagues

- **Singapore Myocardial Infarct Registry**
  - Zheng Huili and Foo Ling Li
- **Ministry of Health**
  - Kelvin-Bryan Tan
- **National University Heart Centre and Cardiovascular Research Institute, Singapore**
  - A. Mark Richards, Devinder Singh, Chan Siew Pang and Eugene Tan
- **National Heart Centre**
  - Terrance Chua, Fei Gao, Chin Chee Tang, Derek Hausenloy and Jack Tan
- **Tan Tock Seng Hospital**
  - Ho Hee Hwa and Prabath Joseph