# Aortic Stenosis
# Biological Mechanisms and Imaging Diagnosis

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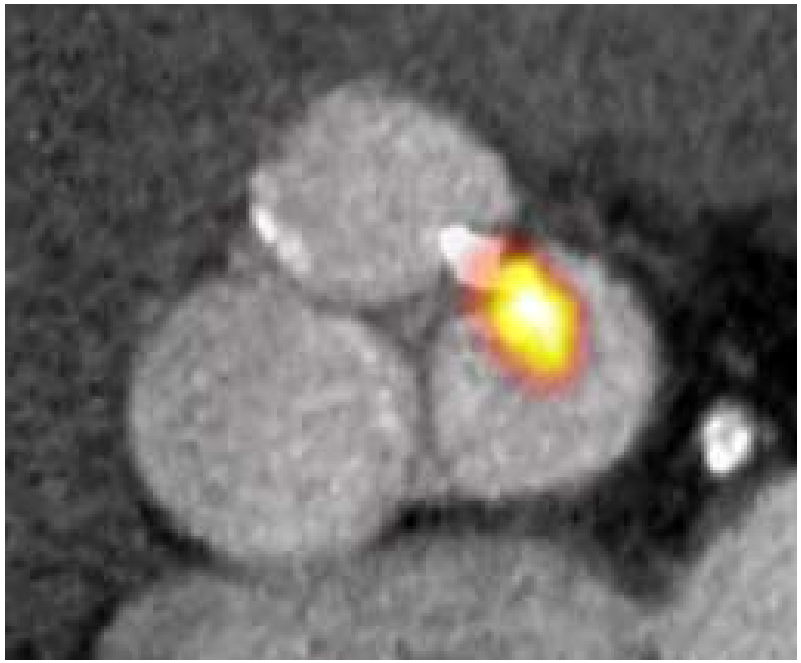
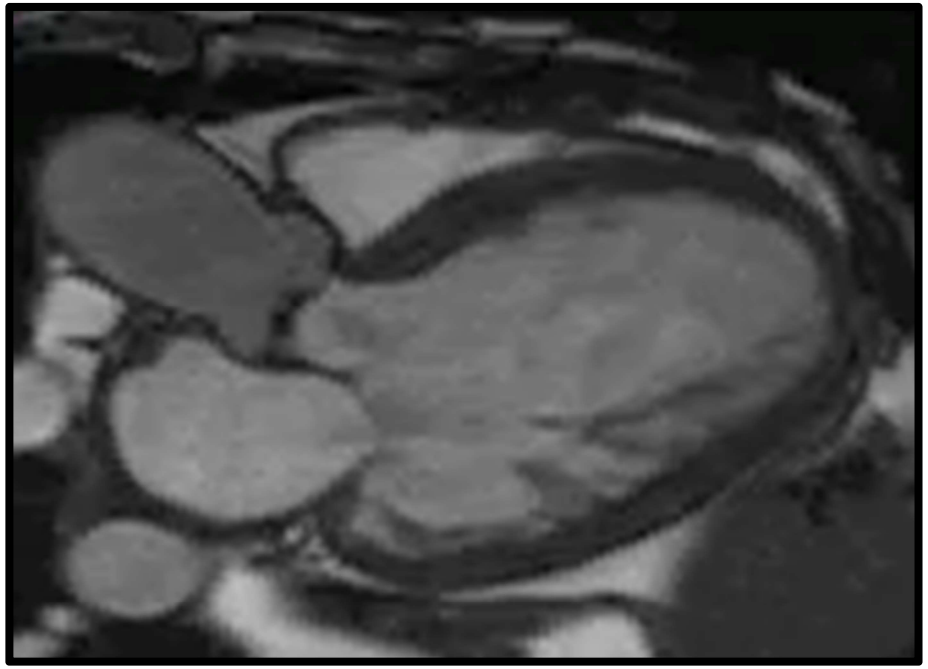
Edinburgh Heart Centre
@MarcDweck @EvoLVed_Trial

# Aortic Stenosis

*A Disease of the Valve and the Myocardium*

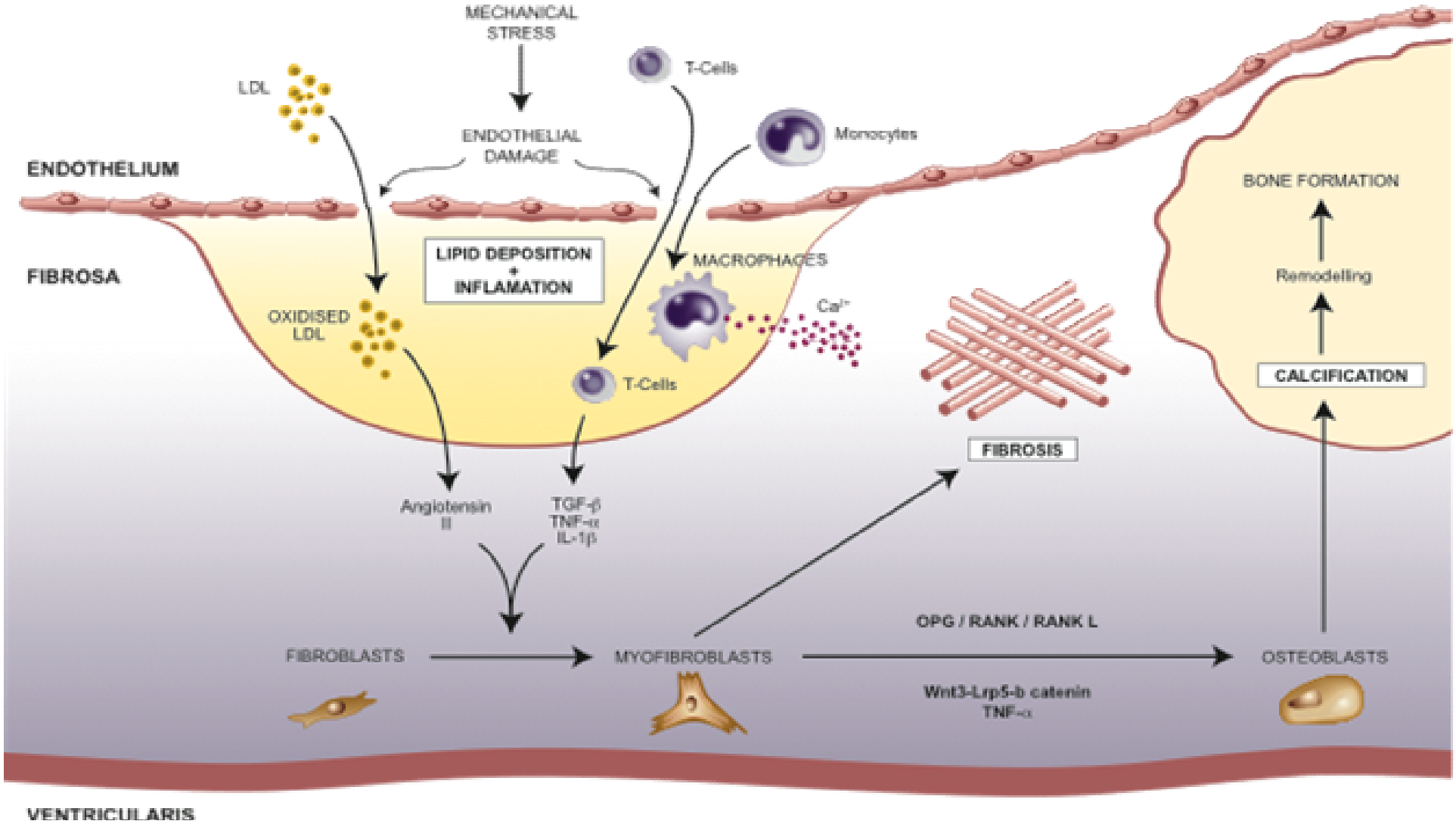




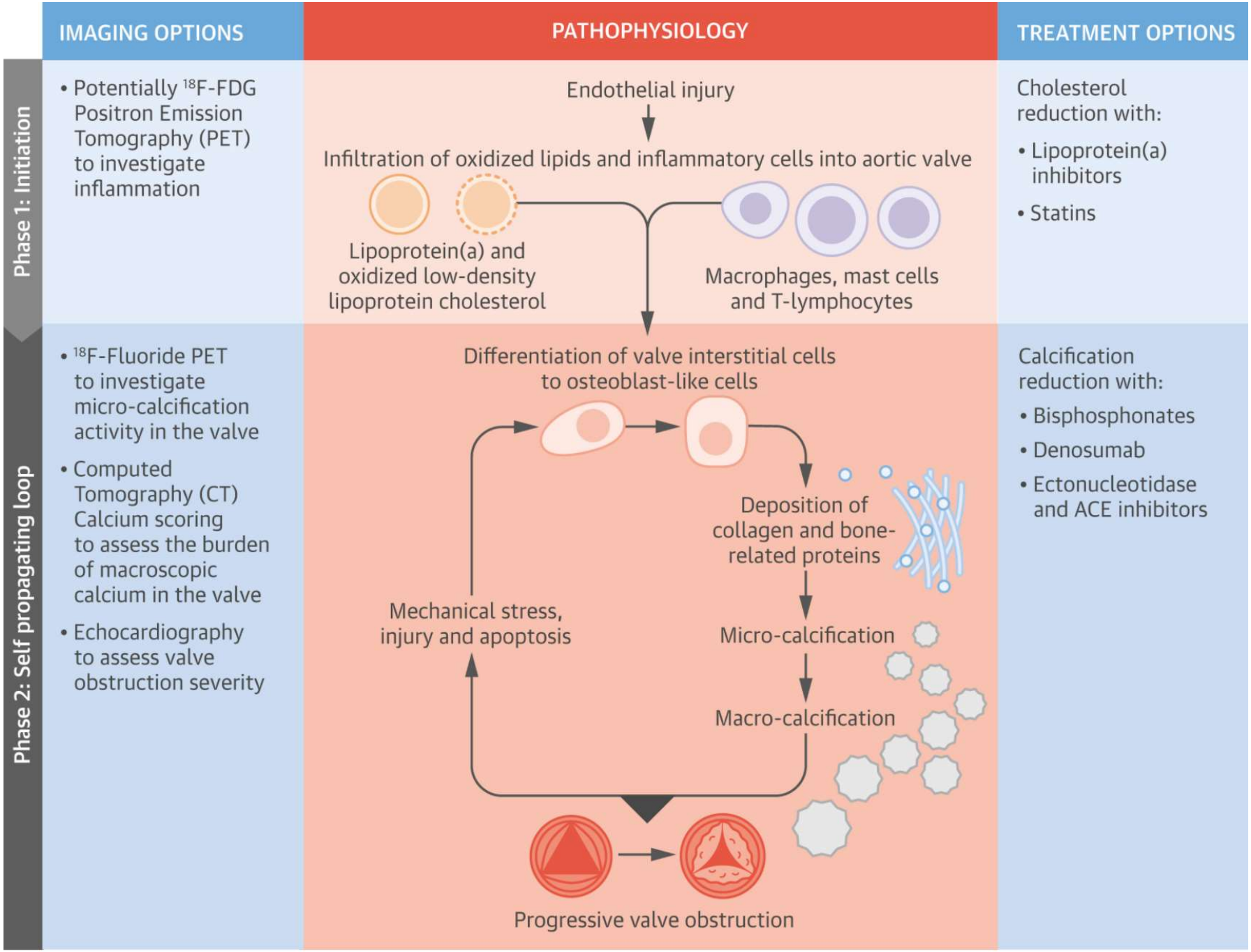
Echo remains the first line and gold standard imaging modality to assess both processes.

# The Valve

# Pathophysiology of Aortic Valve Narrowing




*Dweck MR, et al. Aortic stenosis: a disease of the valve and the myocardium. J Am Coll Cardiol. 2012;60:1854-63*

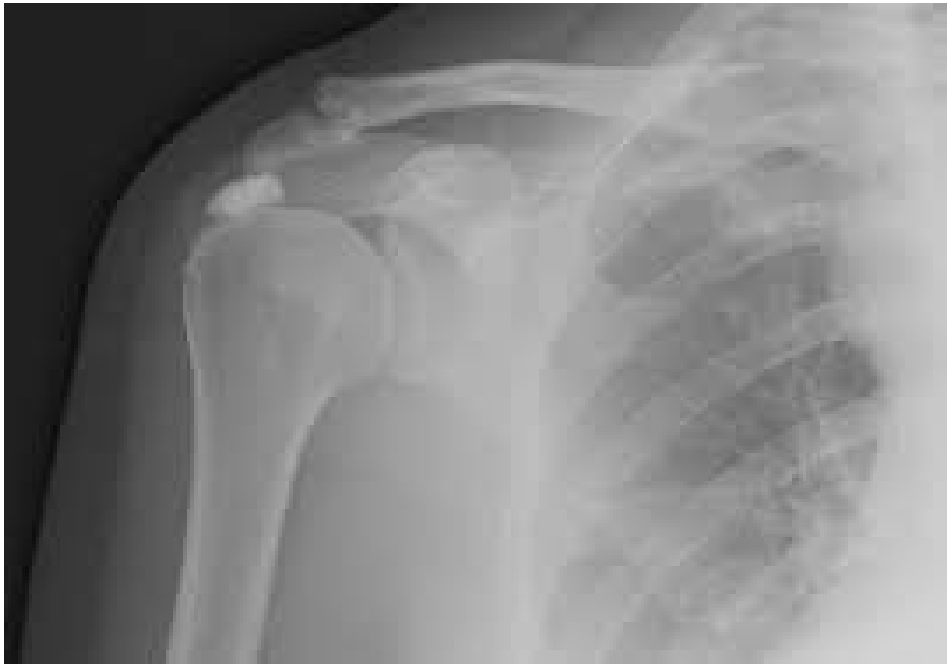


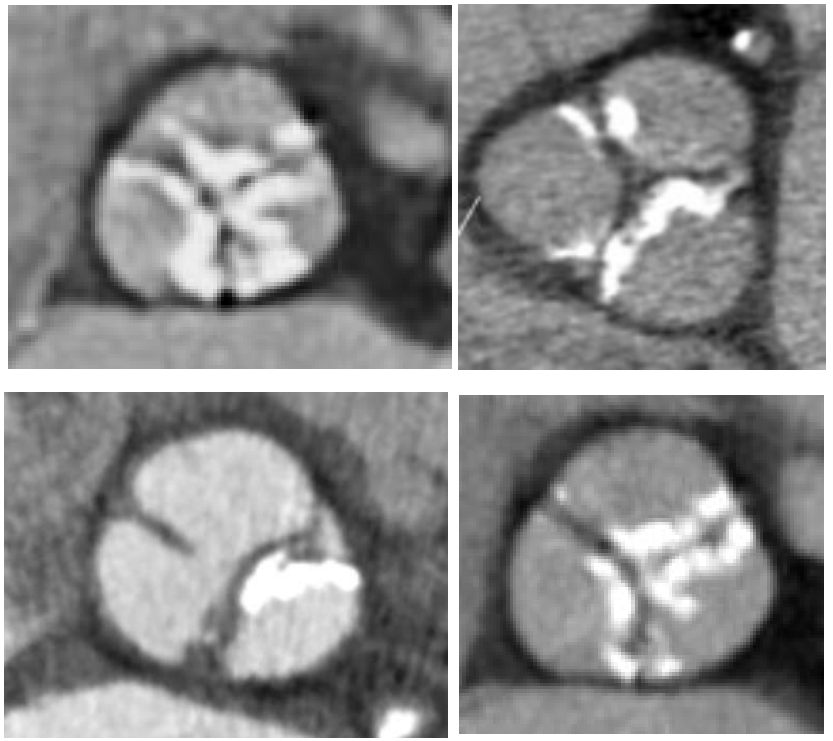

Pawade, T.A. et al. J Am Coll Cardiol. 2015; 66(5):561–77.

# The Valve

## Initiation Phase

# Mechanical Stress & Injury

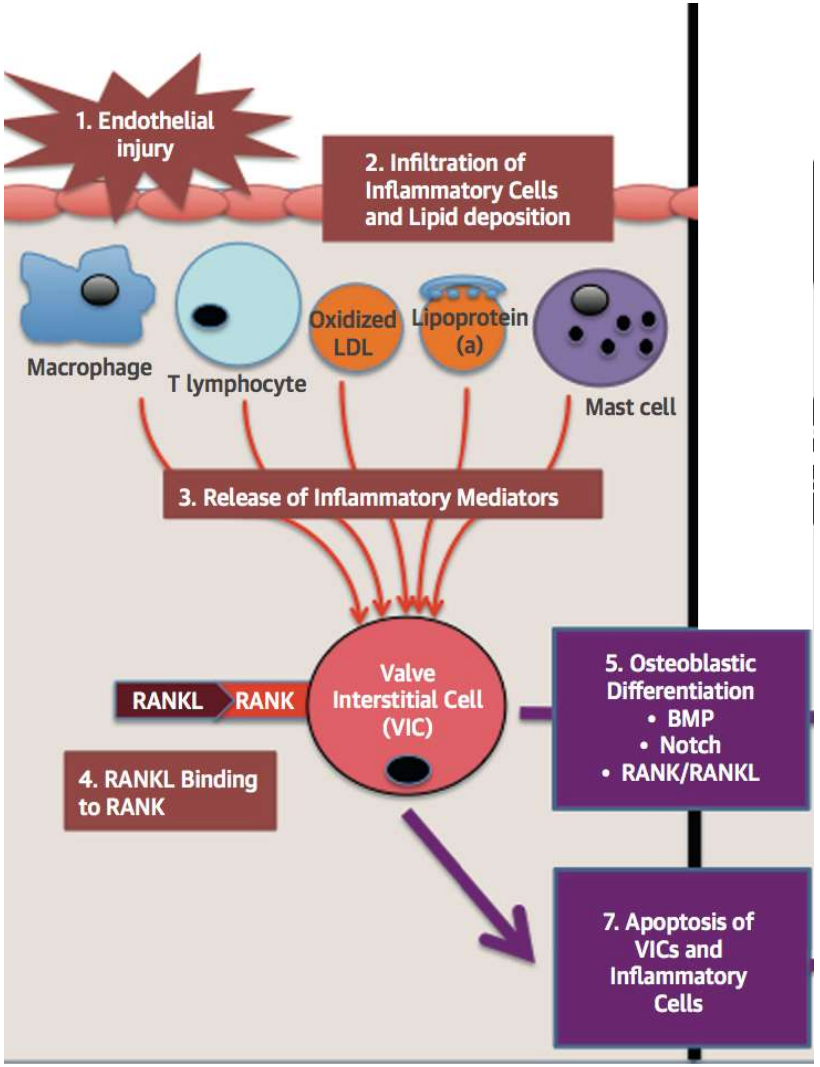




# Initiation Phase
# Similarities with Atherosclerosis

- Endothelial damage, lipid infiltration and inflammation

- Risk factors associated with incidence of AS
  - Smoking
  - Age
  - Hypertension
  - Hyperlipidaemia
  - Lp(a)



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# A Randomized Trial of Intensive Lipid-Lowering Therapy in Calcific Aortic Stenosis

S. Joanna Cowell, B.M., David E. Newby, M.D., Robin J. Prescott, Ph.D., Peter Bloomfield, M.D., John Reid, M.B., Ch.B., David B. Northridge, M.D., and Nicholas A. Boon, M.D., for the Scottish Aortic Stenosis and Lipid Lowering Trial, Impact on Regression (SALTIRE) Investigators

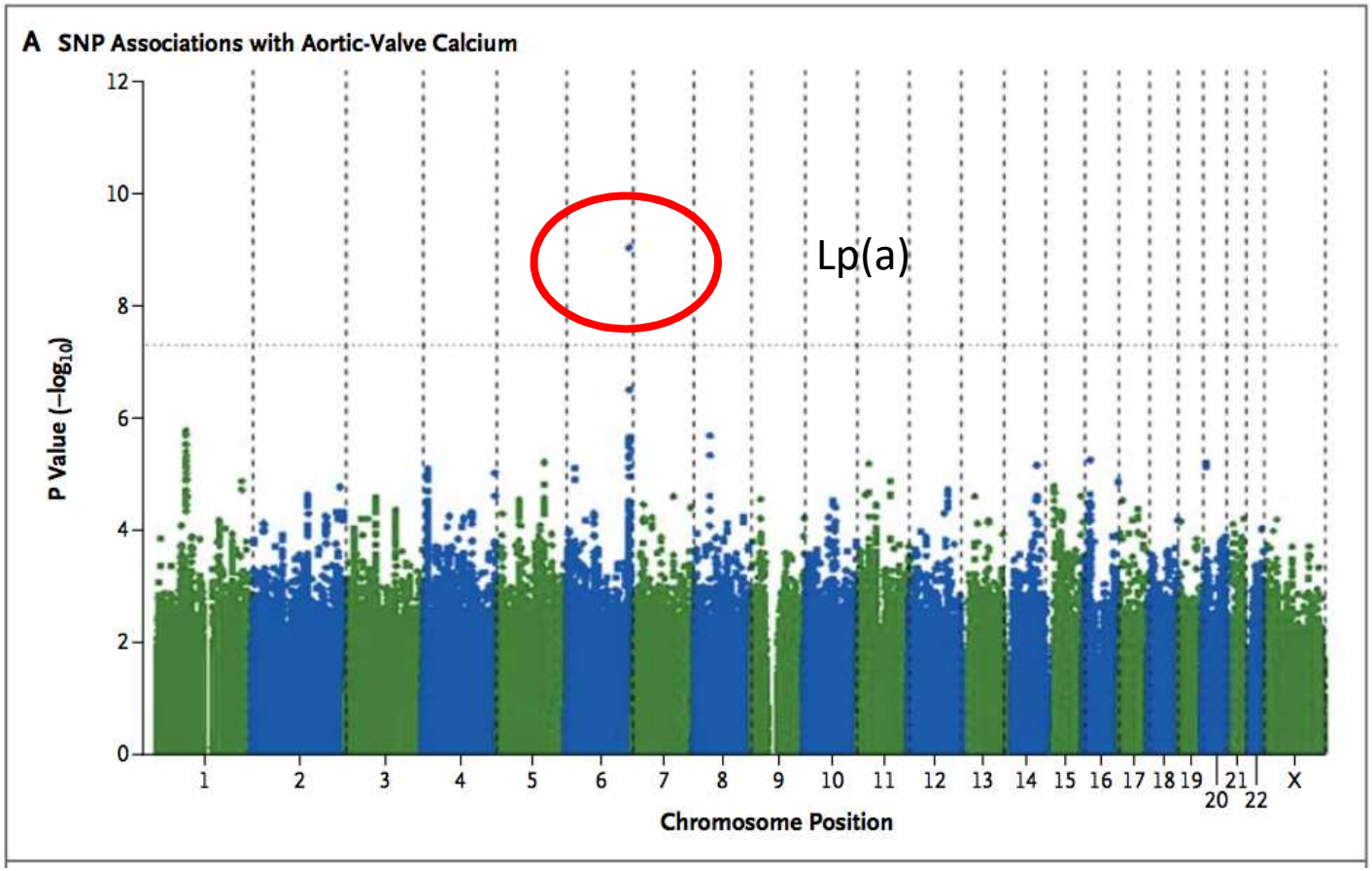
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Intensive Lipid Lowering with Simvastatin and Ezetimibe in Aortic Stenosis

Anne B. Rossebø, M.D., Terje R. Pedersen, M.D., Ph.D., Kurt Boman, M.D., Ph.D., Philippe Brudi, M.D., John B. Chambers, M.D., Kenneth Egstrup, M.D., Ph.D., Eva Gerdts, M.D., Ph.D., Christa Gohlke-Bärwolf, M.D., Ingar Holme, Ph.D., Y. Antero Kesäniemi, M.D., Ph.D., William Malbecq, Ph.D., Christoph A. Nienaber, M.D., Ph.D., Simon Ray, M.D., Terje Skjærpe, M.D., Ph.D., Kristian Wachtell, M.D., Ph.D., and Ronnie Willenheimer, M.D., Ph.D., for the SEAS Investigators*

# Genetic Associations with Valvular Calcification



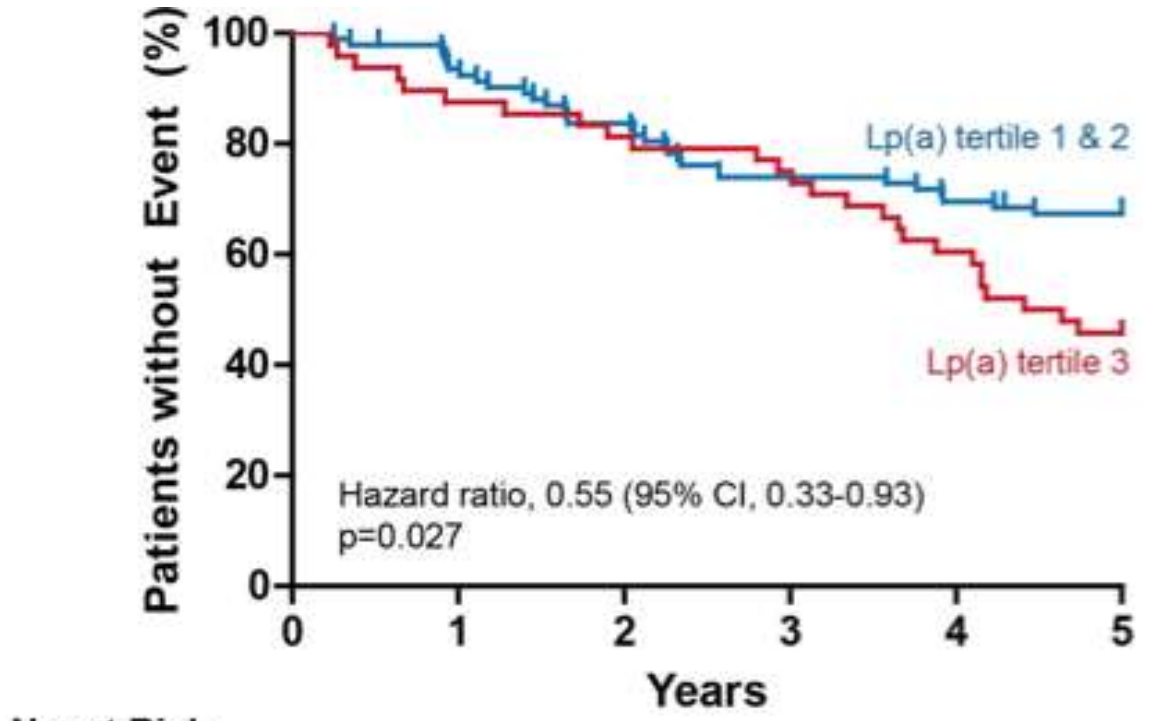

- Genome wide association in 6942 patients with aortic valve calcification
- Only one SNP in the lipoprotein(a) (*LPA*) locus (rs10455872) reached genome-wide significance

Thanassoulis NEJM 2013

# High Lp(a) Identifies Patients with Adverse Clinical Events

Edinburgh Heart Centre

Aortic valve replacement or cardiovascular death during follow-up




| No. at Risk | | | | | | |
|---|---|---|---|---|---|---|
| Tertile 1 & 2 | 93 | 87 | 78 | 70 | 65 | 61 |
| Tertile 3 | 48 | 43 | 40 | 37 | 30 | 22 |

Kang et al.
Unpublished

# Antisense therapy targeting apolipoprotein(a): a randomised, double-blind, placebo-controlled phase 1 study

*Sotirios Tsimikas, Nicholas J Viney, Steven G Hughes, Walter Singleton, Mark J Graham, Brenda F Baker, Jennifer L Burkey, Qingqing Yang, Santica M Marcovina, Richard S Geary, Rosanne M Crooke, Joseph L Witztum*

**Interpretation** ISIS-APO(a)$_{Rx}$ results in potent, dose-dependent, selective reductions of plasma Lp(a). The safety and tolerability support continued clinical development of ISIS-APO(a)$_{Rx}$ as a potential therapeutic drug to reduce the risk of cardiovascular disease and calcific aortic valve stenosis in patients with elevated Lp(a) concentration.

Tsimikas Lancet 2015

# The Valve

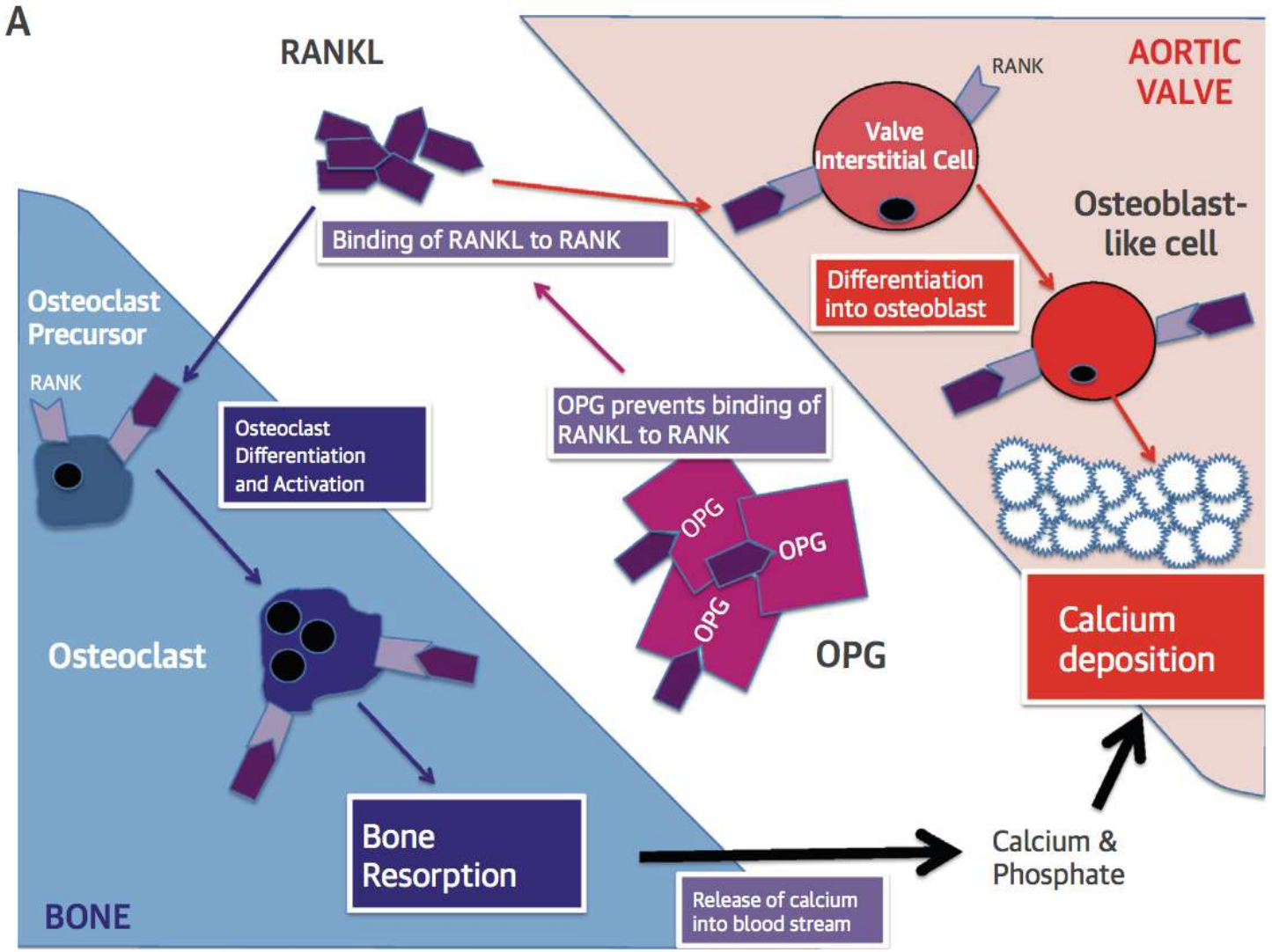
## Propagation Phase

# Predictors of Progression

- Atherosclerotic risk factors do not predict disease progression

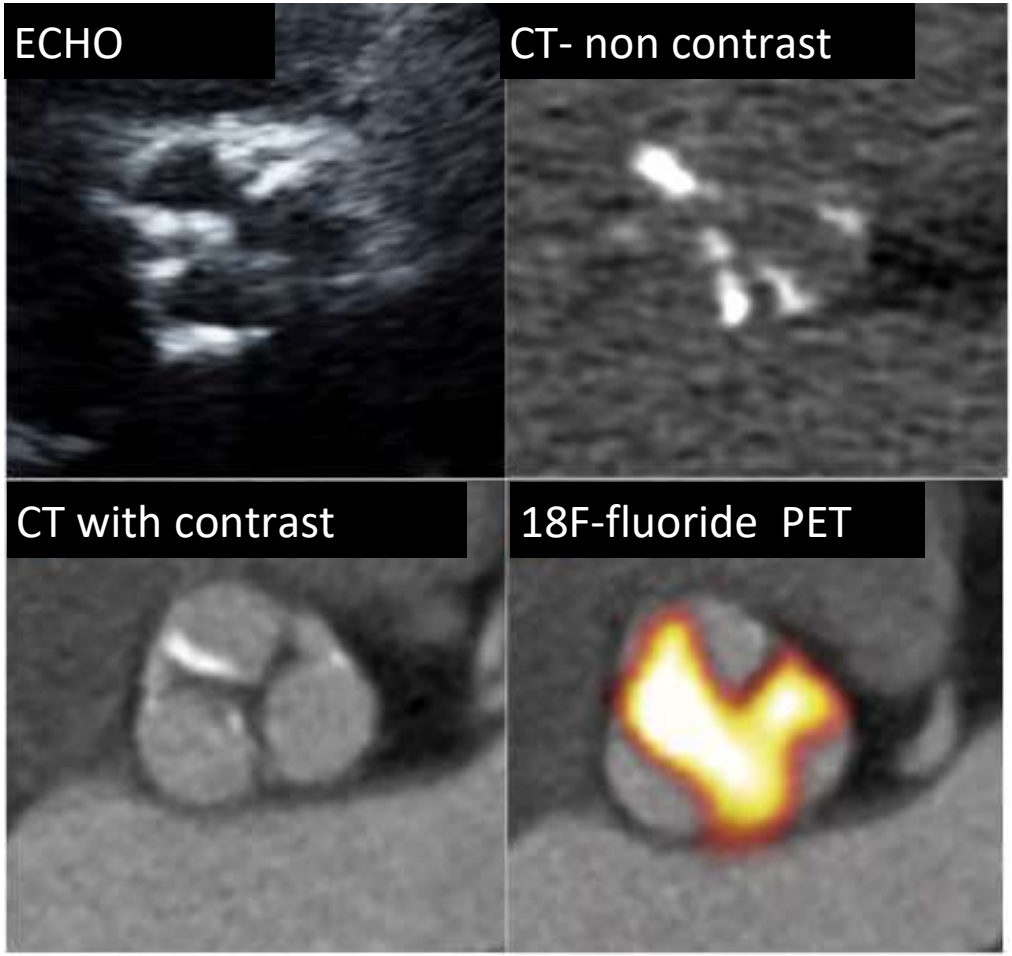
- Instead this appears more closely related to factors related to calcification
  - Imaging markers
  - Disorders of calcium metabolism (including osteoporosis)

# Link Between Osteoporosis and Aortic Stenosis



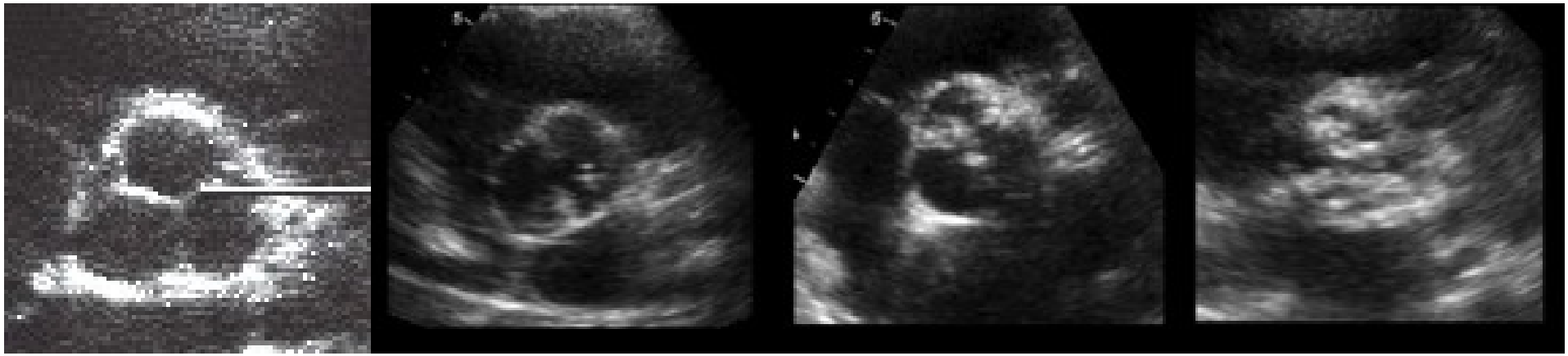

Pawade, Dweck JACC 2015

# Imaging Modalities Targeting Calcification




*Pawade T, Newby DE, Dweck MR. JACC. 2015*

# Calcification on Echo



| 1 = NORMAL | 2 = MILD | 3 = MODERATE | 4 = SEVERE |
|---|---|---|---|
| No calcium | Isolated small spots | Multiple bigger spots | Extensive all cusps |

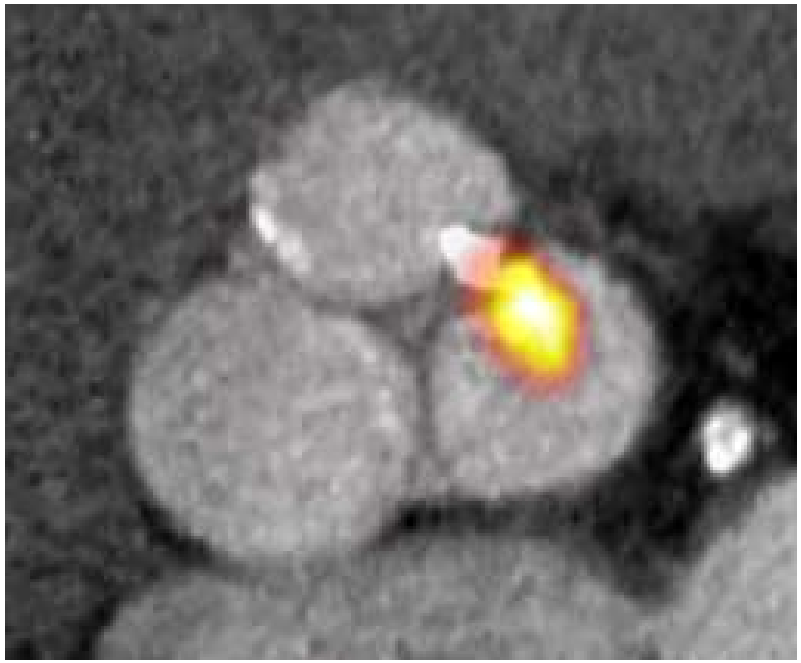
- Predicts faster rate of progression

Rosenhek Eur Heart J 2004

- Independent predictor of AVR / Death

Rosenhek NEJM 2000

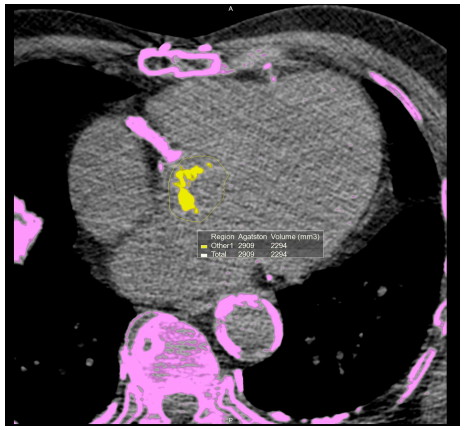
# 18F-Fluoride PET



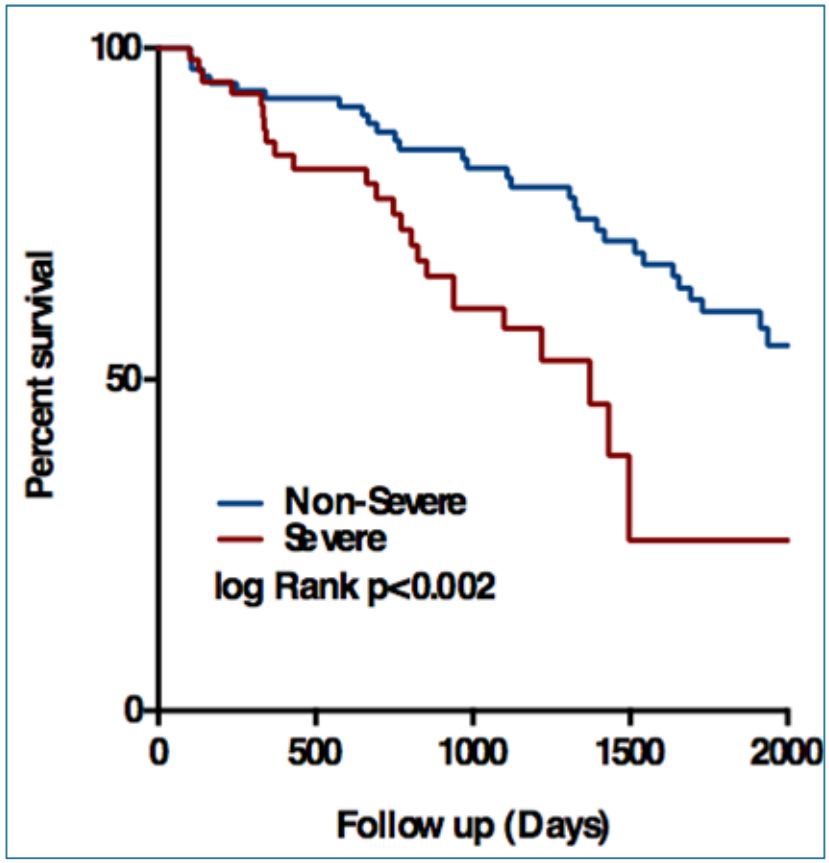
- Good prediction of disease progression
  - CT calcium score r=0.80 (0.69-0.87) p<0.001
  - Mean gradient r=0.32 (0.13-0.50), p=0.001
- Independent predictor of death & AVR
  - independent of age or sex HR 1.46 [1.24-1.71], p<0.001

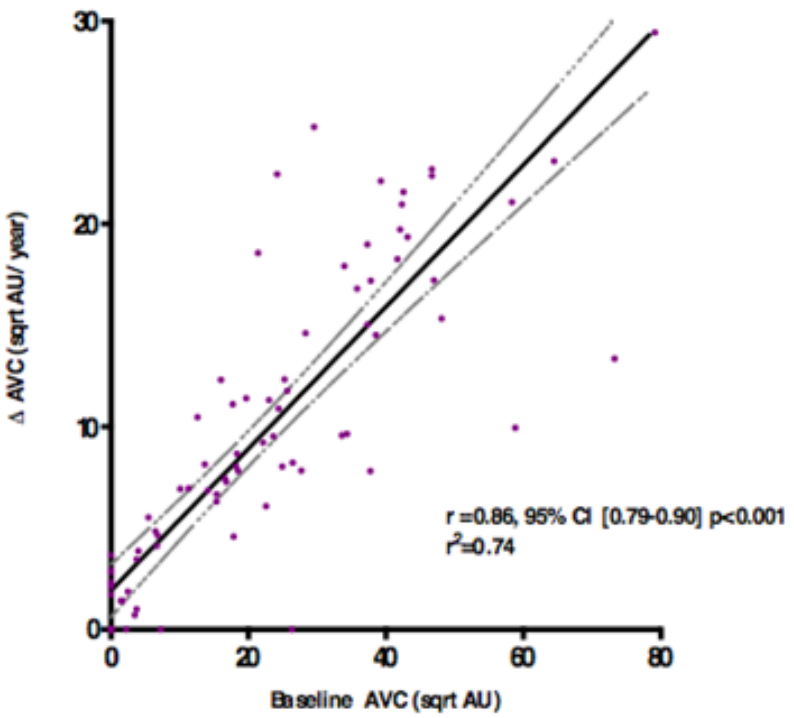
Jenkins & Vesey JACC 2015

# CT Calcium Scoring



Men 2065 AU
Women 1274 AU

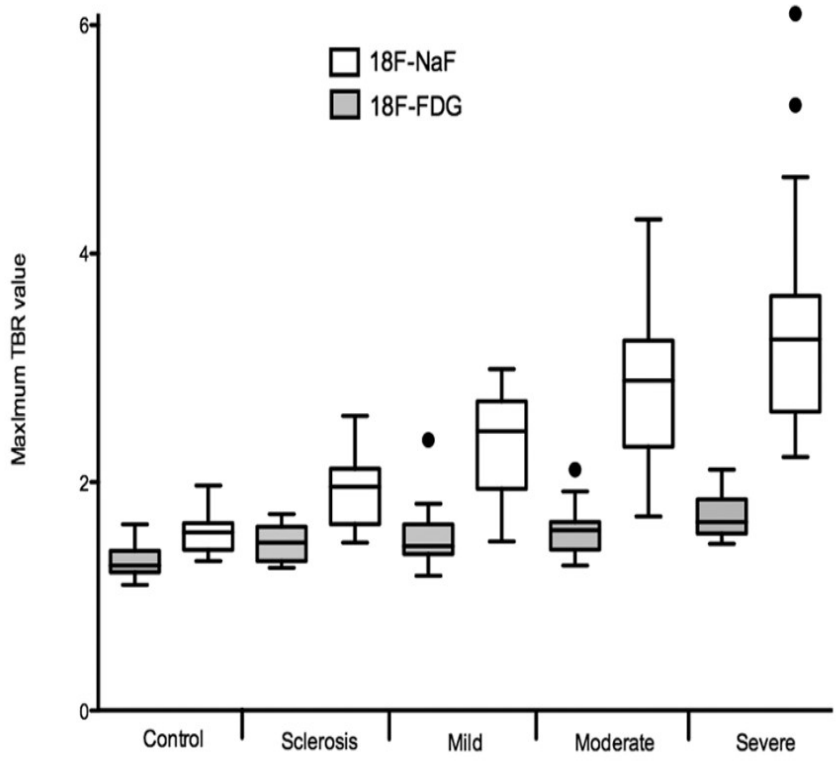


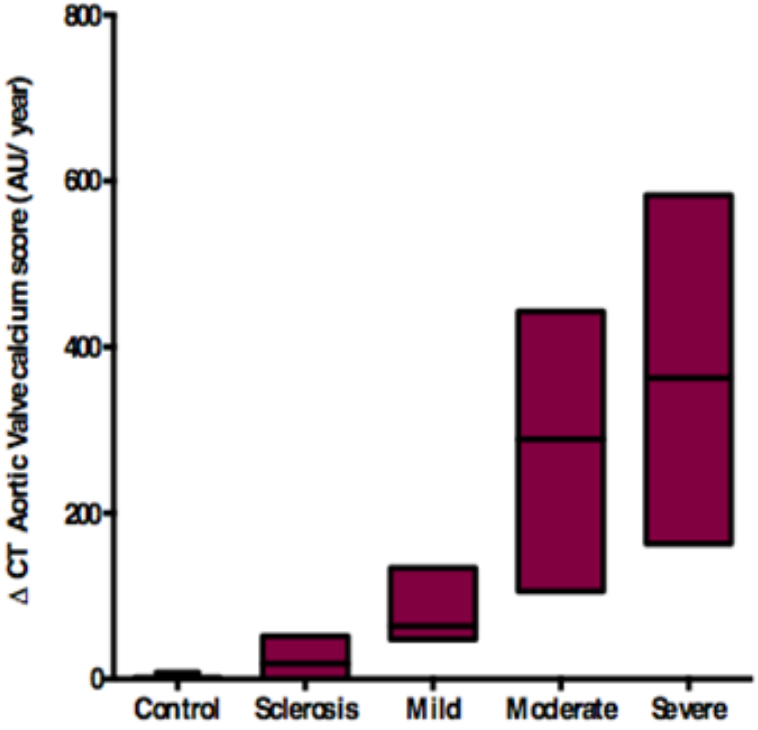

Clavel JACC 2013 Clavel JACC 2014 Pawade Circ Imaging 2018

# Disease Activity and Progression Increase with Disease Severity

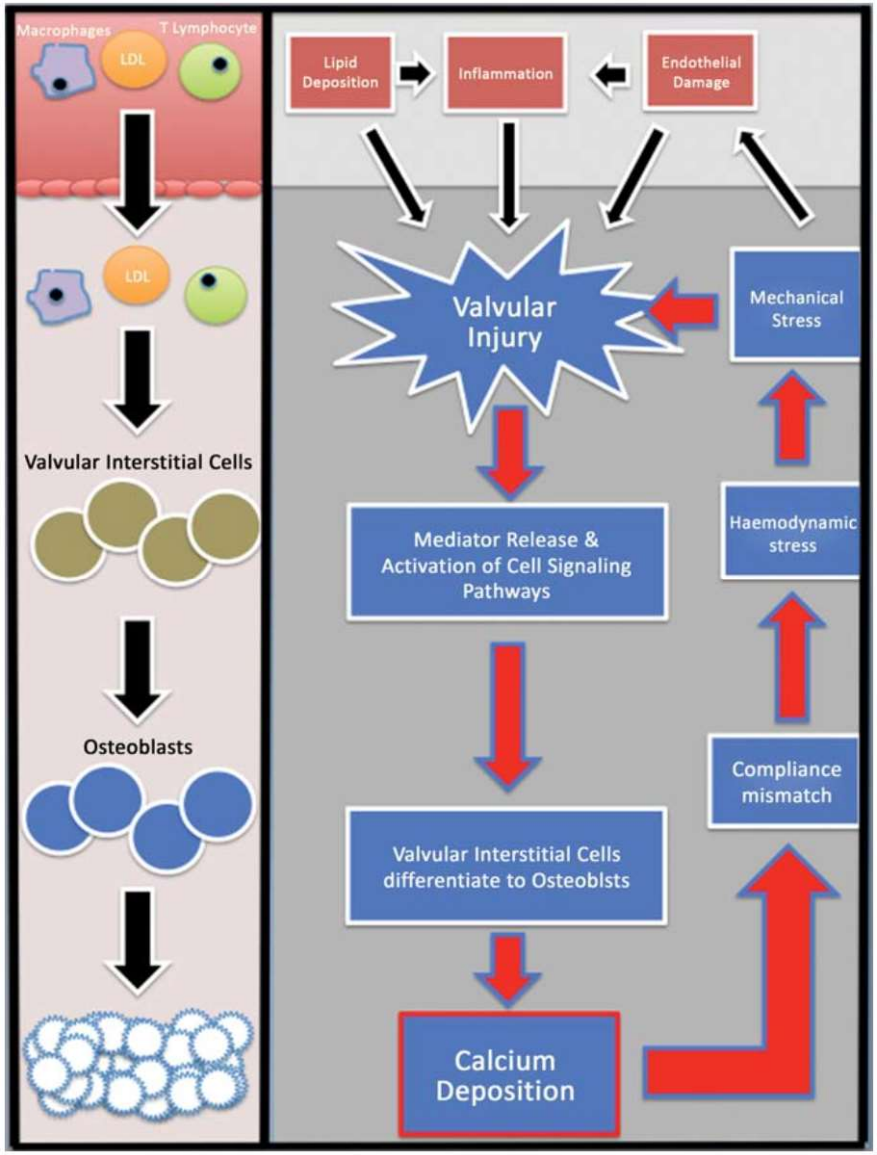
Disease Activity




Disease Progression



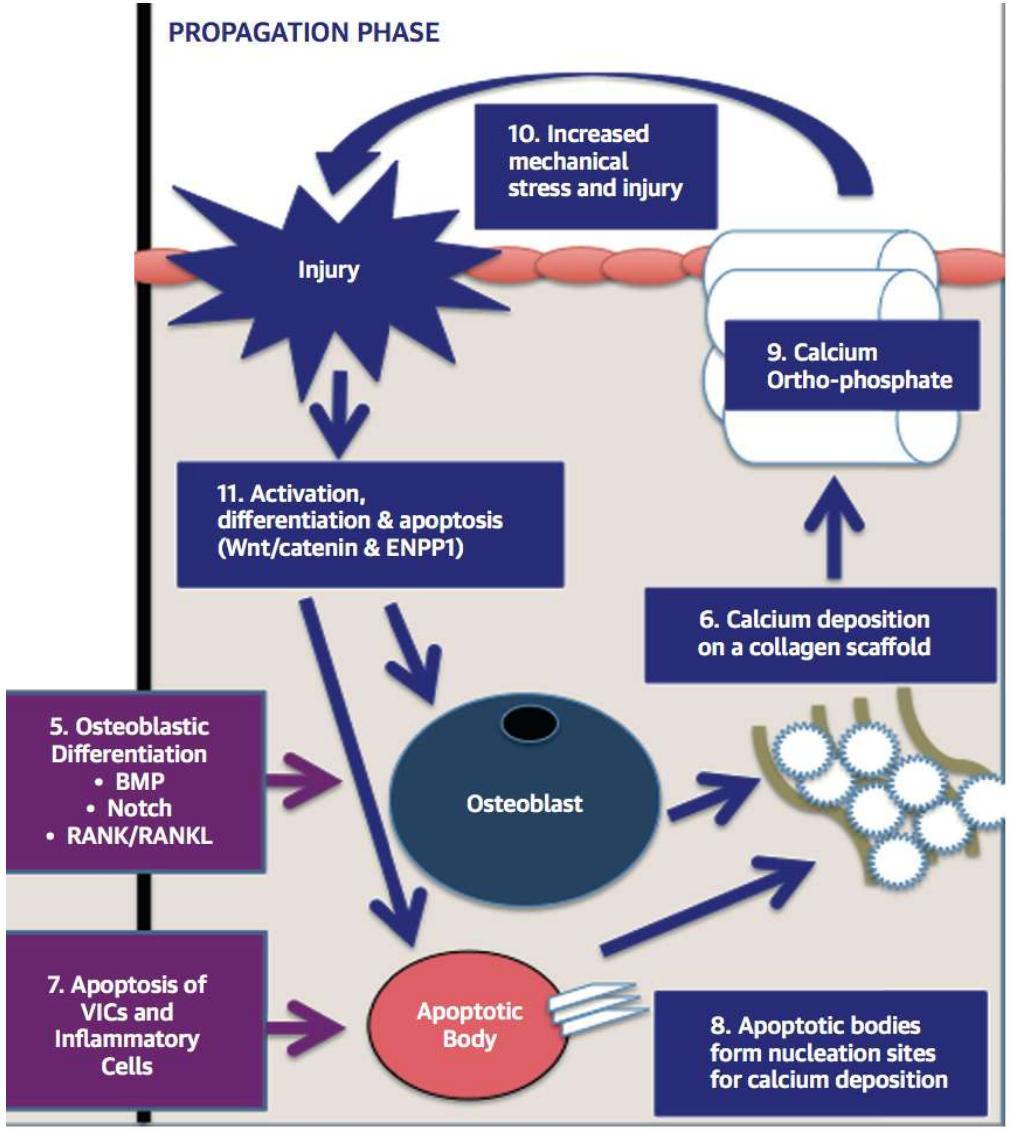
# Propagation Phase




Vicious cycle of calcification, mechanical stress, mechanical injury and further calcification

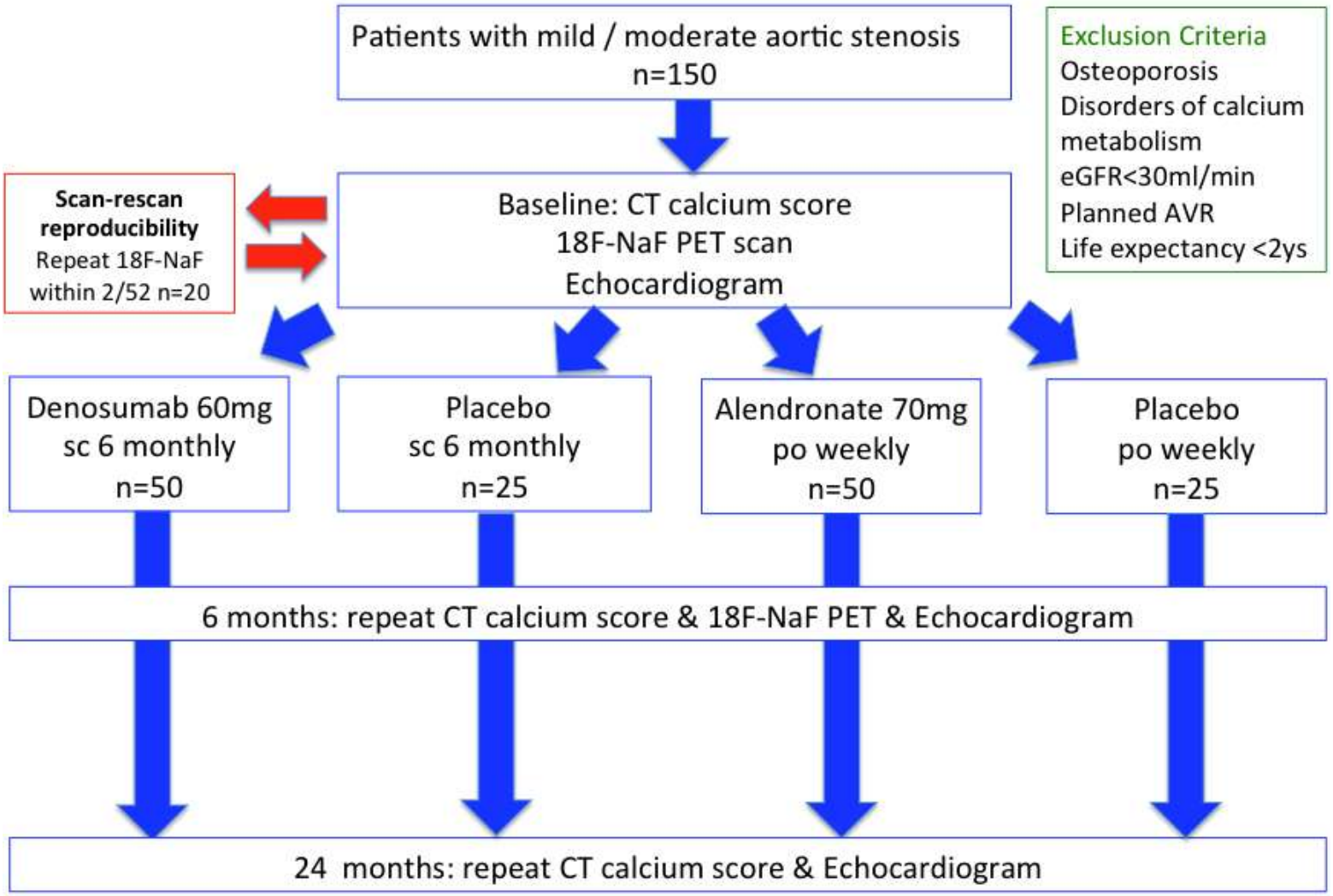
Pawade Heart 2015

# Mediators of Calcification



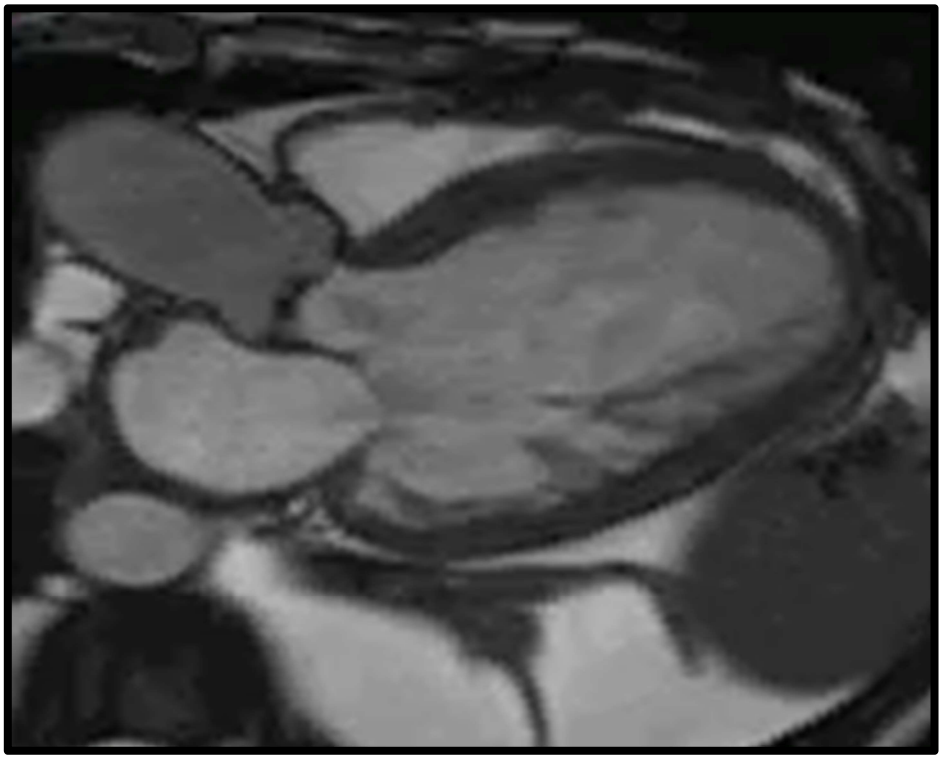

Pawade, Dweck JACC 2015

# SALTIRE 2

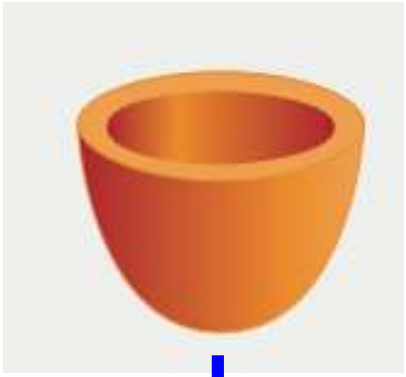

Patients with mild / moderate aortic stenosis
n=150
Exclusion Criteria
Osteoporosis
Disorders of calcium metabolism
eGFR<30ml/min
Planned AVR
Life expectancy <2ys
Scan-rescan reproducibility
Repeat 18F-NaF within 2/52 n=20
Baseline: CT calcium score
18F-NaF PET scan
Echocardiogram
Denosumab 60mg sc 6 monthly n=50
Placebo sc 6 monthly n=25
Alendronate 70mg po weekly n=50
Placebo po weekly n=25
6 months: repeat CT calcium score & 18F-NaF PET & Echocardiogram
24 months: repeat CT calcium score & Echocardiogram

# The Myocardium

# The Myocardium

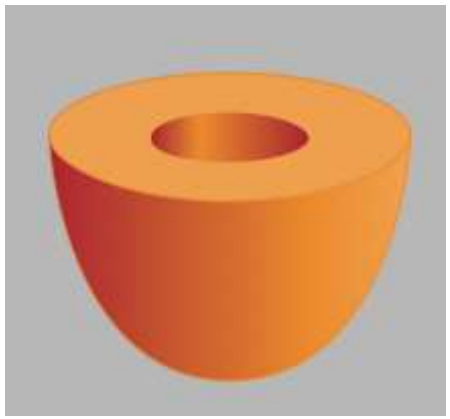


**Normal**



Increased afterload

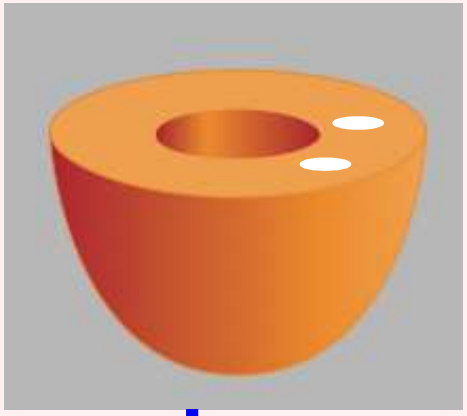
**LVH**



**Myocyte Cell Death**

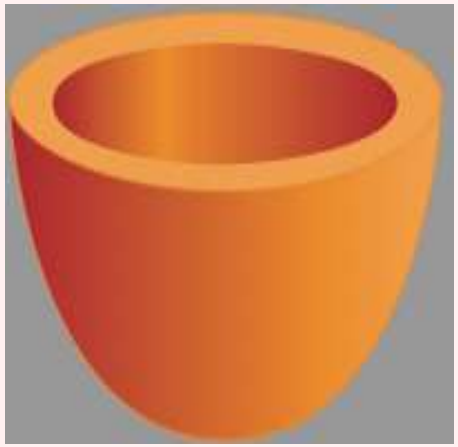
Myocardial ischemia
Angiotensin II
TGF-B

**DECOMPENSATION**



**Fibrosis**

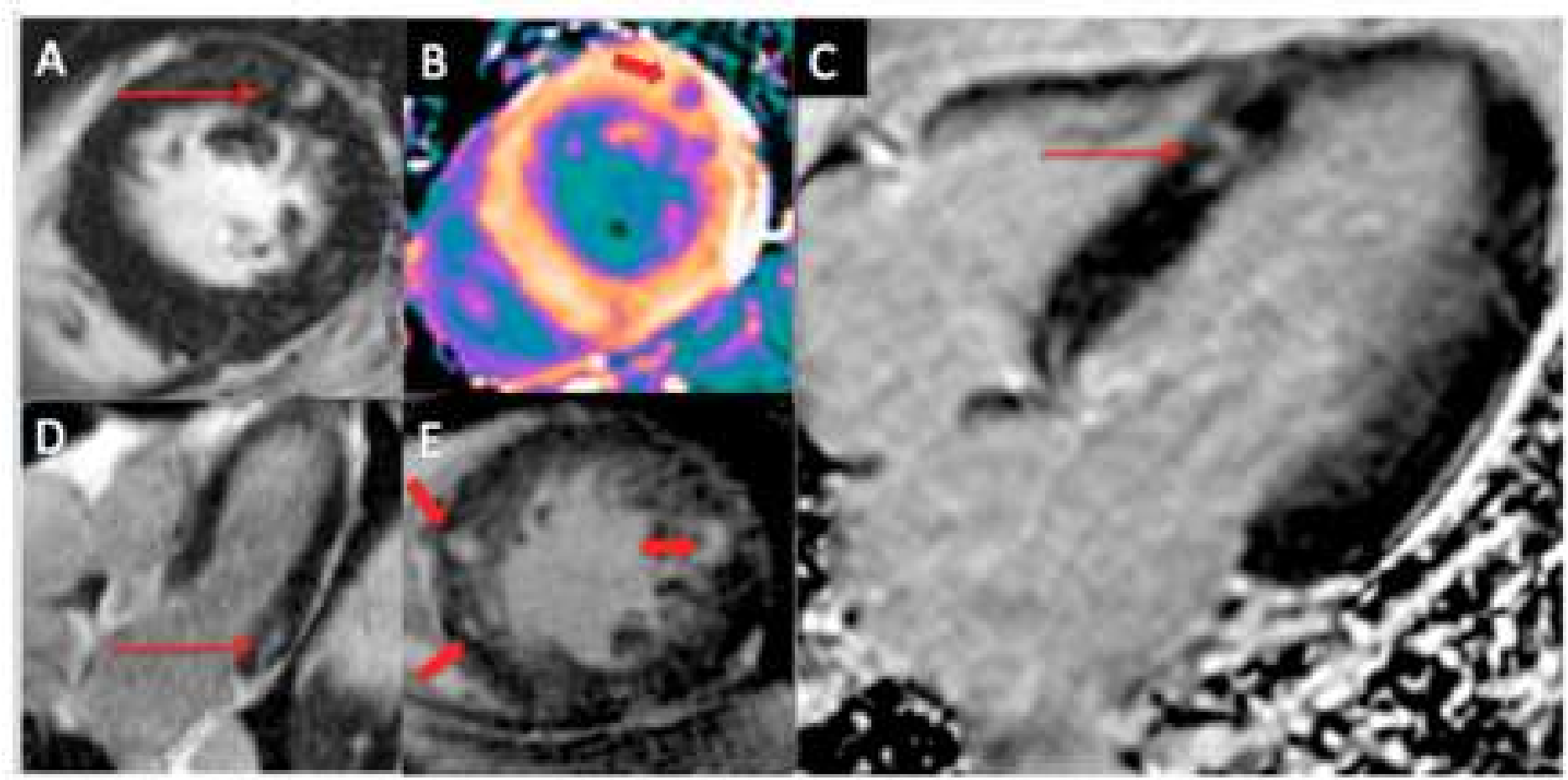
SYMPTOMS → **AVR**



**Heart Failure**

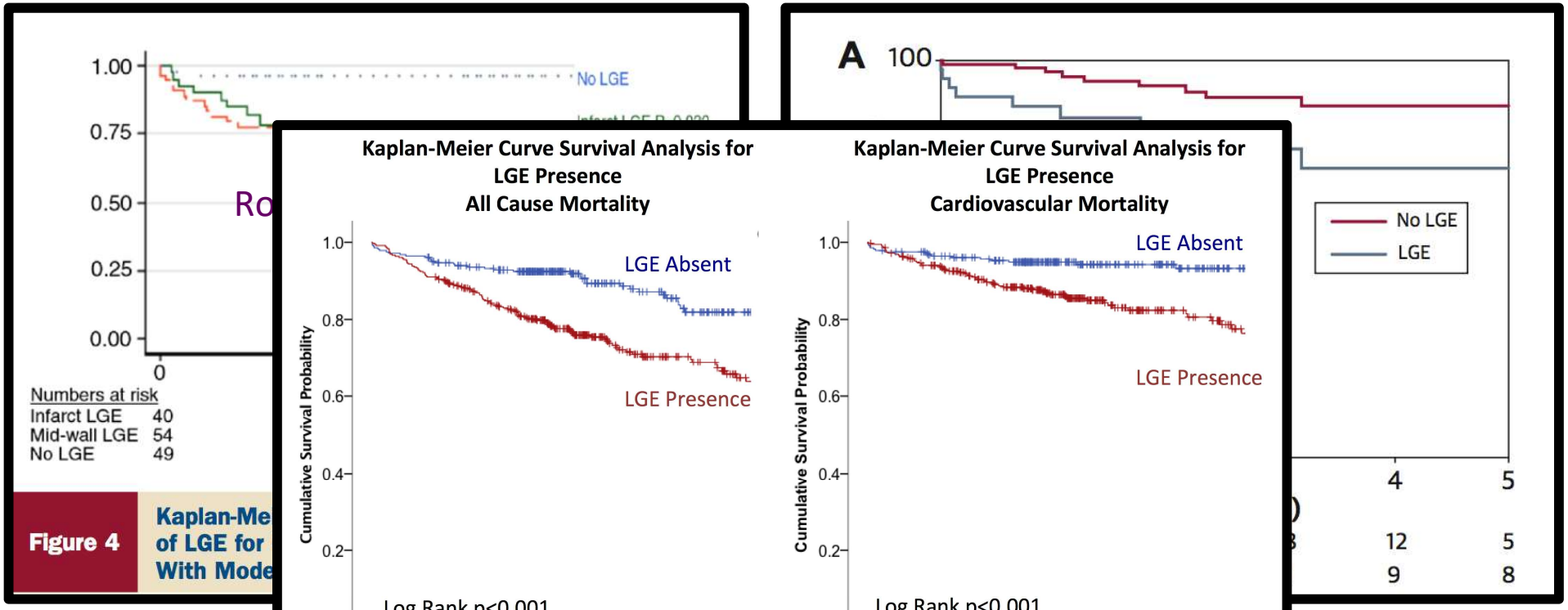
Adapted Dweck MR Aortic stenosis: a disease of the valve and the myocardium. *J Am Coll Cardiol. 2012;60:1854-63* .

# *MRI Detects*
# *Mid-Wall Myocardial Fibrosis*




Baronne-Rochette JACC 2014 Dweck JACC 2012 Chin Circulation 2016

# Mid Wall Fibrosis & Adverse Prognosis

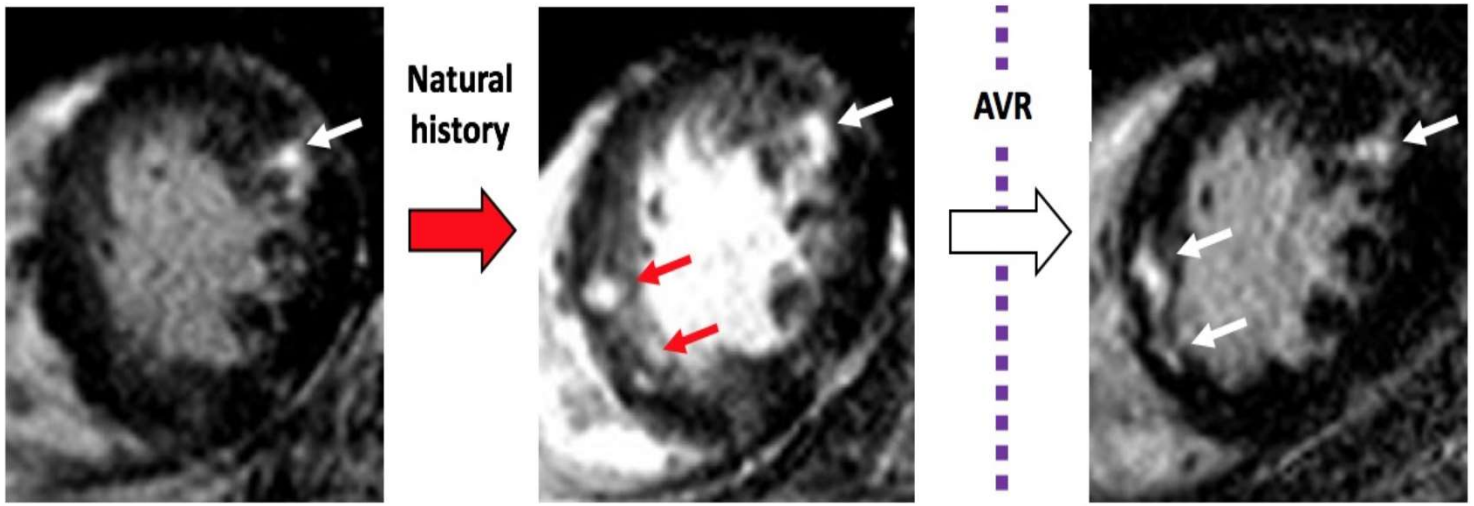



Dweck JACC 2011

hette JACC 2014

Triebel & Musa AS700

# Progresses with time and irreversible post-AVR




Everett Circulation CVS Imaging in press


@EvoLVed_Trial

Patients with Aortic Stenosis
AV Vmax >4.0 m/sec

**Screening for Decompensation**
hs-Troponin / ECG

No

**REGISTRY**
Watchful Waiting
Repeat ECG and troponin in 1 year

Yes

**CMR**

No Fibrosis

Mid-wall Fibrosis

RANDOMISATION (n=400)

EARLY SURGERY / TAVI (n=200)

STANDARD OF CARE (n=200)

3 Years Follow up
All cause mortality / Unplanned AS related hospital admission

Sir Jules Thorn Award Biomedical Research 2015 15/JTA.

# Conclusions

Valve stenosis

- Initiation phase similar to atherosclerosis
- Propagation phase dominated by calcification
- SALTIRE 2 trial

Hypertrophic response of the left ventricle

- Initially adaptive
- Ultimately decompensates and patients transition to heart failure and adverse events
- EVOLVED trial

# Acknowledgements


Twitter: @MarcDweck @evolved_trial

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University of Cambridge
Dr James Rudd
Dr Anthony Davenport

Mount Sinai Hospital, NY
Prof Zahi Fayad
Prof Valentin Fuster
Prof Jagat Narula

Universite Laval, Quebec
Dr Marie-Annick Clavel

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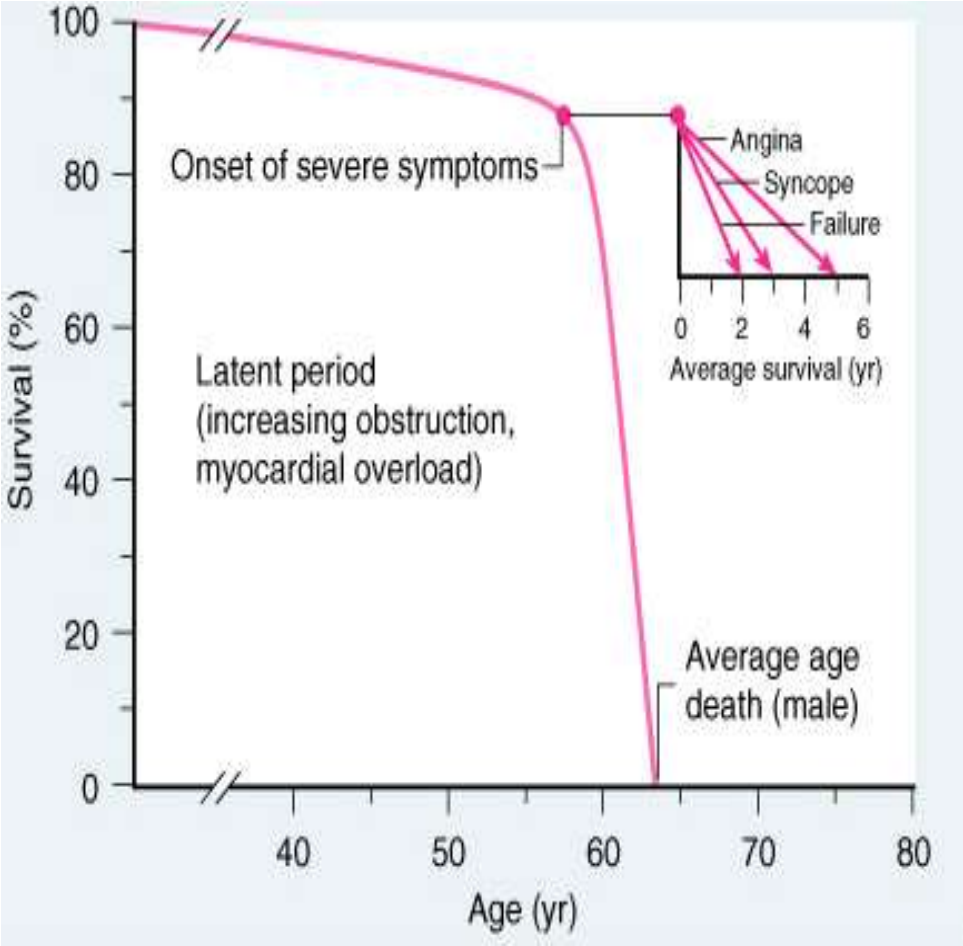
- British Heart Foundation Project Grant (PG/12/8/29371)
- British Heart Foundation Centre of Research Excellence Award.
- British Heart Foundation Clinical Lectureship
- Sir Jules Thorn Award 2016

Cedars Sinai Hospital
Prof Dan Berman
Prof Piotr Slomka
Dr Damini Dey

*Queen's Anniversary Prize 2016*

# Symptoms & Aortic Stenosis



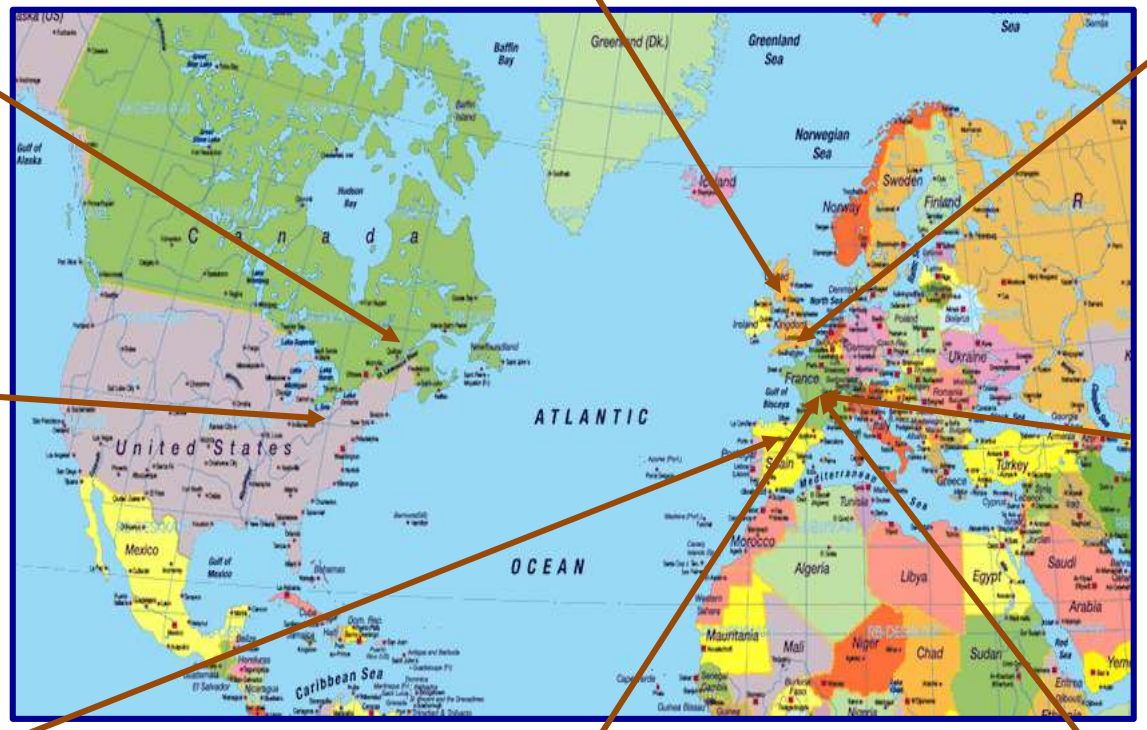



*Ross J Jr, Braunwald E: Aortic stenosis. Circulation 38[Suppl*

**QUEBEC, CANADA**
Cohort: Research
Scanner: Siemens
Analysis: Teracon

**EDINBURGH: UK**
Cohort: Research
Scanner: Siemens
Analysis: Vitrea

**LONDON, UK**
Cohort: Clinical
Scanner: Philips
Analysis: Aquarius




**PITTSBURGH, USA**
Cohort: Clinical
Scanner: GE Discovery
Analysis: Vitrea

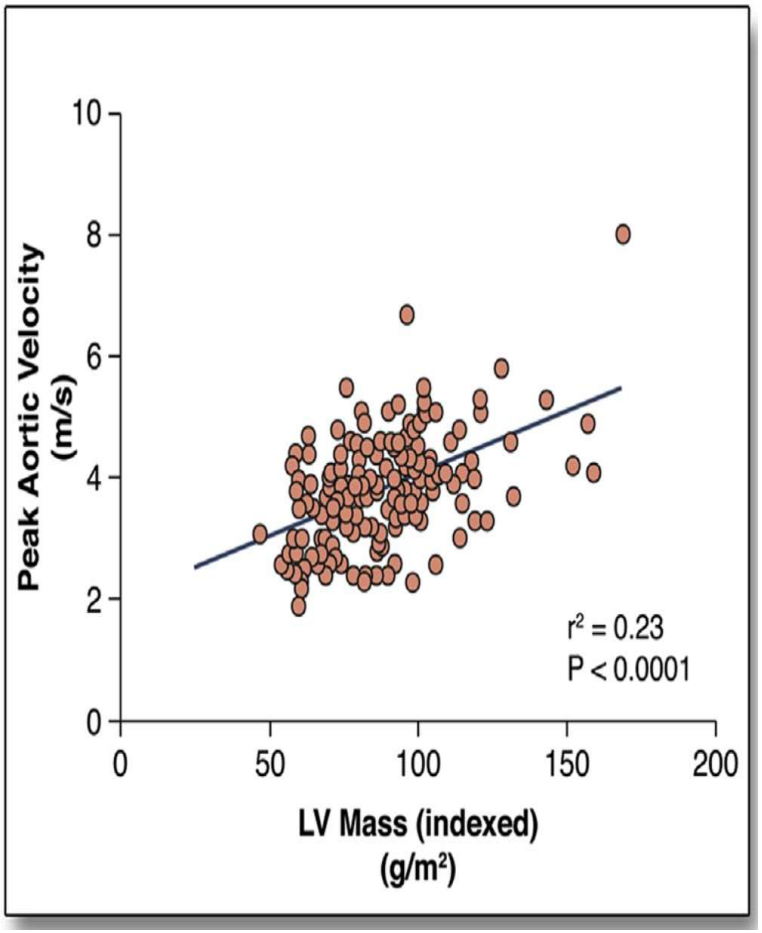
**AMIENS, FRANCE**
Cohort: Clinical
Scanner: GE Discovery
Analysis: Smartscore

**BARCELONA, SPAIN**
Cohort: Research
Scanner: Siemens
Analysis: Teracon

**PARIS, FRANCE**
Cohort: Research
Scanner: Phillips
Analysis: Aquarius

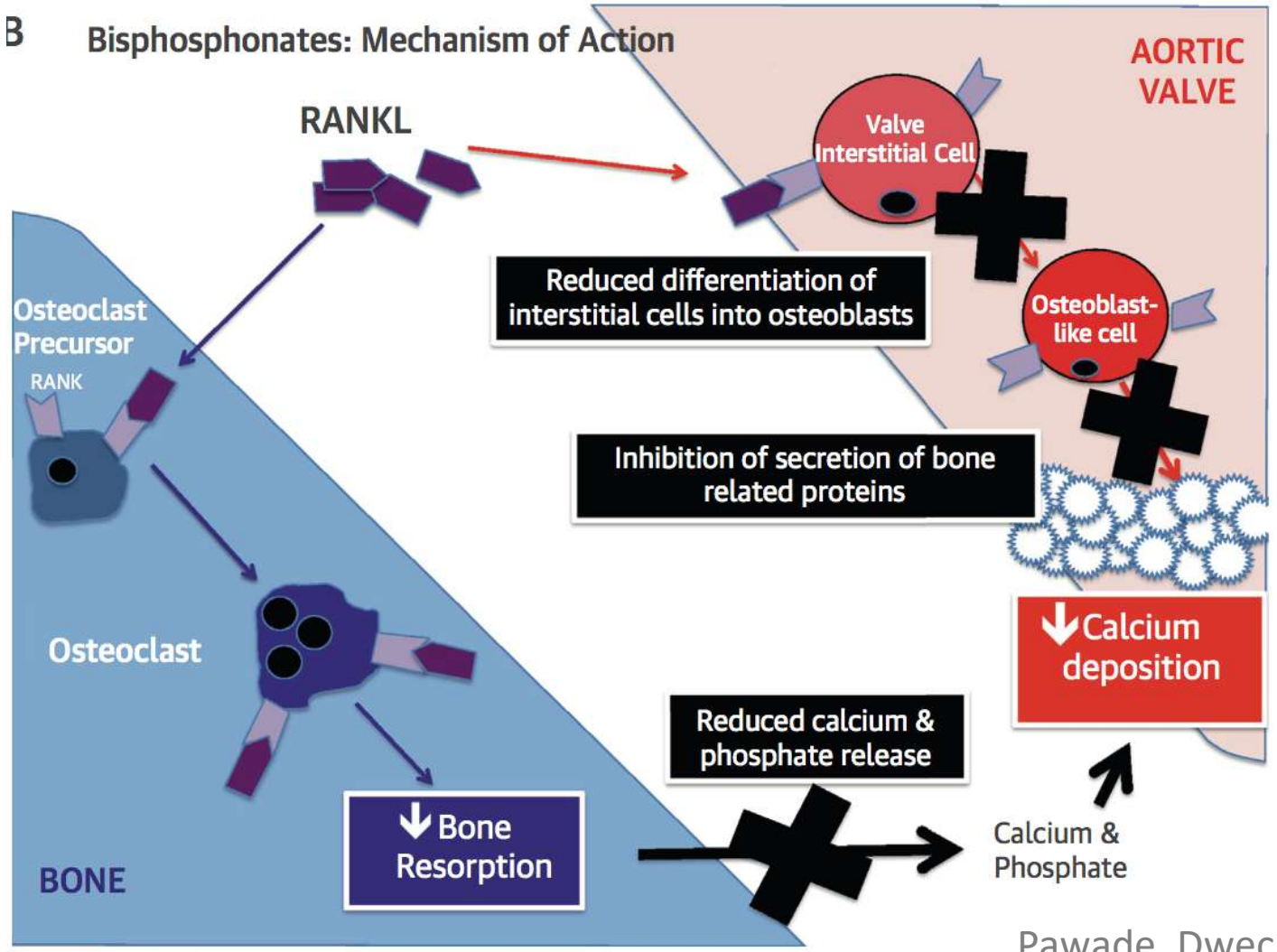
**ST-DENIS, FRANCE**
Cohort: Clinical
Scanner: GE Revolution
Analysis: Smartcore

# Severity of Valve Narrowing Modest Predictor of Hypertrophic Response



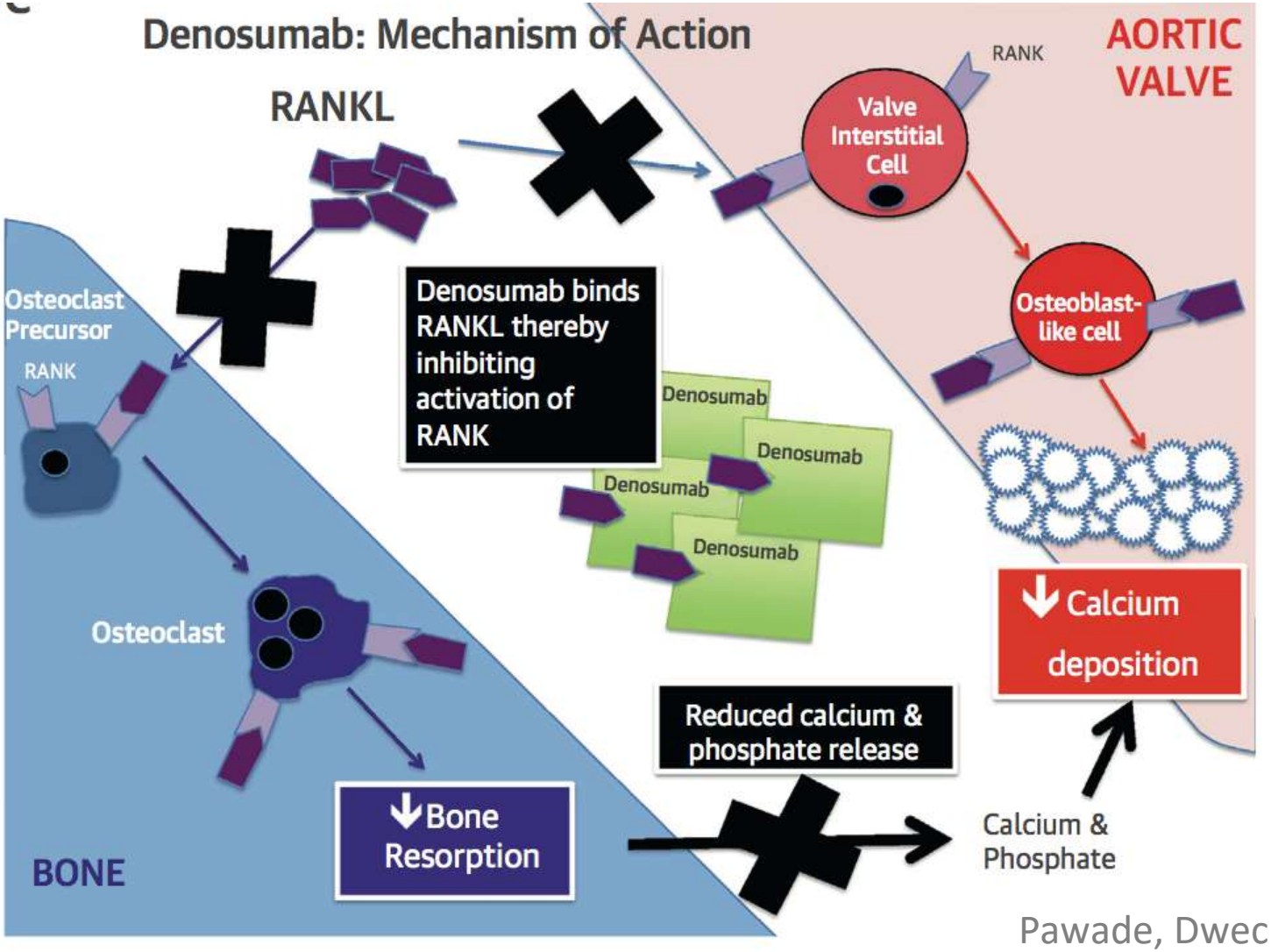

Chin JACC CVI 2017

# echanism of Action of Bisphosphonates



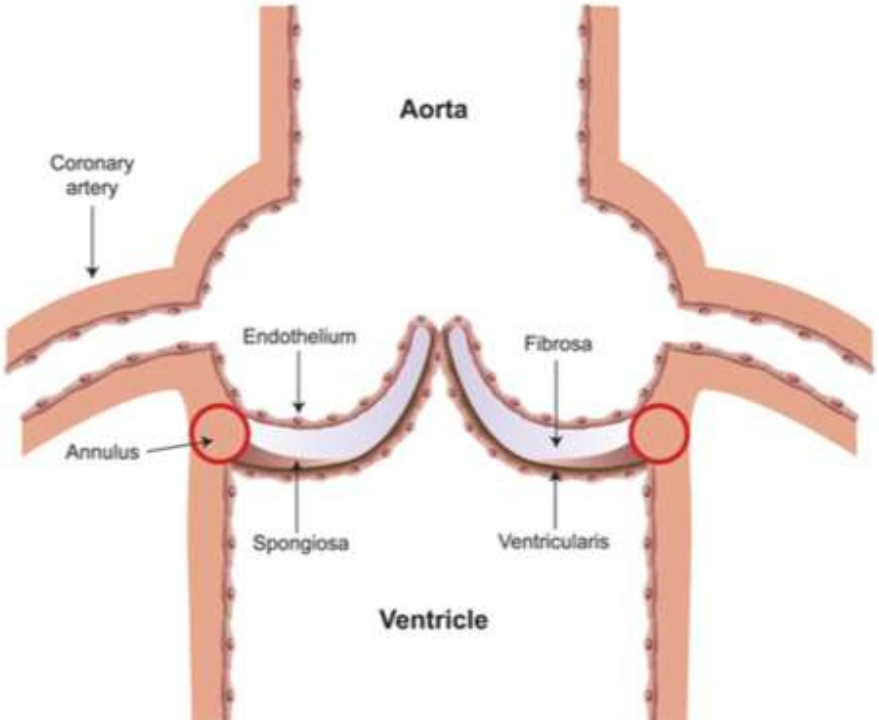

Pawade, Dweck JACC 2015

# Mechanism of Action
# Denosumab

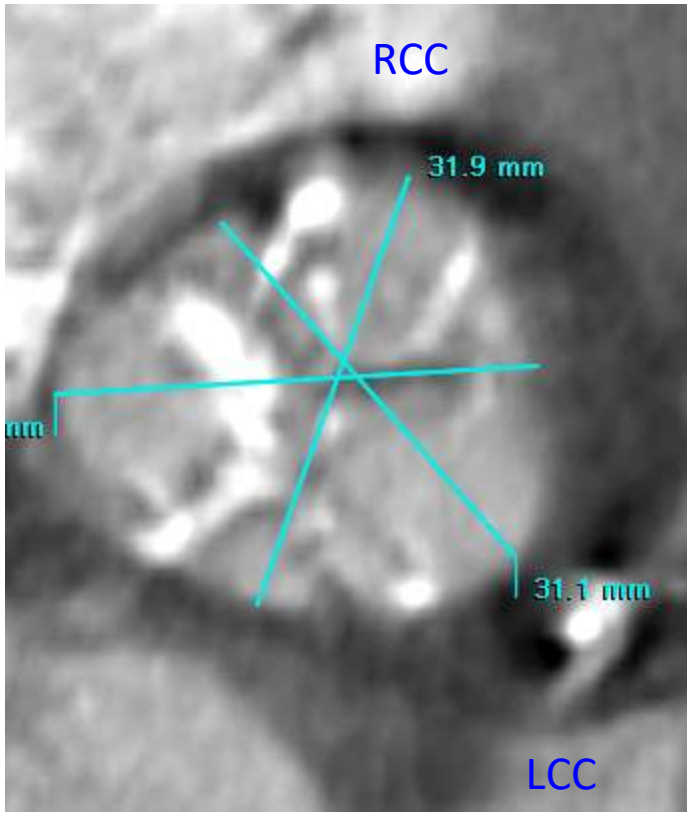



Pawade, Dweck JACC 2015

# Protective Shear Stress




NCC




- Non-coronary cusp often diseased more than LCC and RCC