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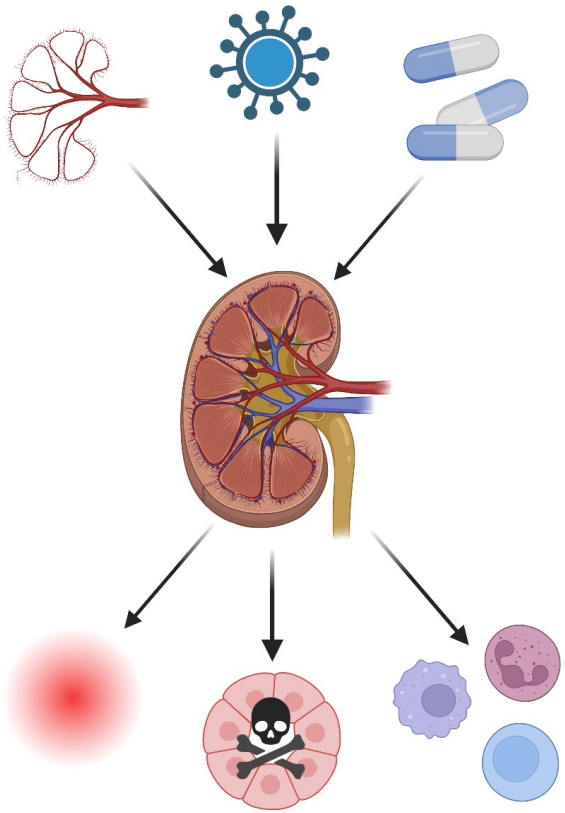
Manganese-enhanced MRI to define cardiovascular disease risk after acute kidney injury

Dr Lucy Kershaw and Prof Bean Dhaun
Lucy.Kershaw@ed.ac.uk

Acute kidney injury (AKI)



- AKI is a global health problem; affects up to 20% of hospital inpatients
- Costs 1% of the annual NHS budget in the UK (£1 billion)
- Multi-factorial: ischaemia-reperfusion injury, sepsis, drug toxicity
- Results in: inflammation, glomerular & tubular injury, microcirculatory dysfunction
- Treatment is supportive

AKI & cardiovascular disease (CVD)

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

Julie R. Ingelfinger, M.D., *Editor*

Cardiovascular Consequences of Acute Kidney Injury

Matthieu Legrand, M.D., Ph.D., and Patrick Rossignol, M.D., Ph.D.

Legrand *et al*, *NEJM,* 2020

AKI & cardiovascular disease (CVD)

- AKI is independently associated with increased risk of death from cardiovascular events
- Increased risk of admission due to heart failure
- Increased risk of myocardial infarction
- Increased risk of stroke
- Risks remain despite resolution of AKI

AKI & chronic kidney disease (CKD)

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

Julie R. Ingelfinger, M.D., *Editor*

Acute Kidney Injury and Chronic Kidney Disease as Interconnected Syndromes

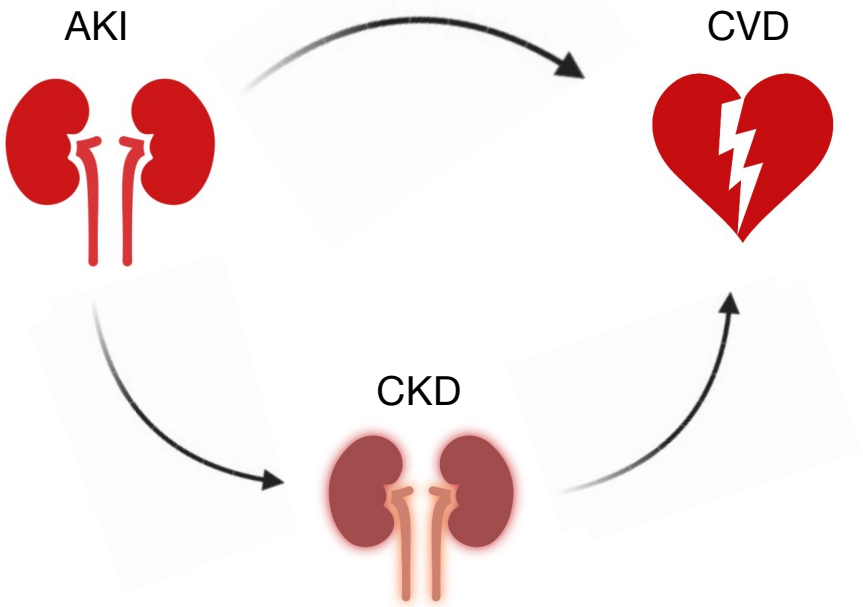
Lakhmir S. Chawla, M.D., Paul W. Eggers, Ph.D.,
Robert A. Star, M.D., and Paul L. Kimmel, M.D.

Chawla *et al*, *NEJM,* 2014

AKI & chronic kidney disease (CKD)

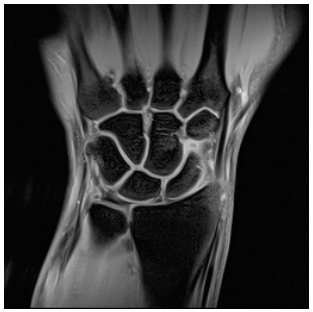
- AKI survivors: ~30% left with CKD
- Remaining 70%: 28-fold increased risk of developing CKD & cardiovascular disease
- Currently, no treatments that prevent progression of AKI to CKD (or CVD)

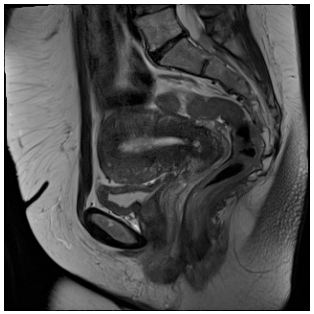
AKI to CVD and CKD progression

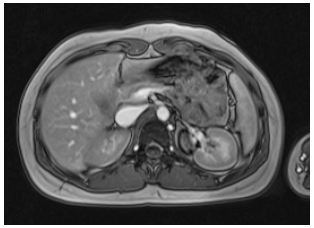


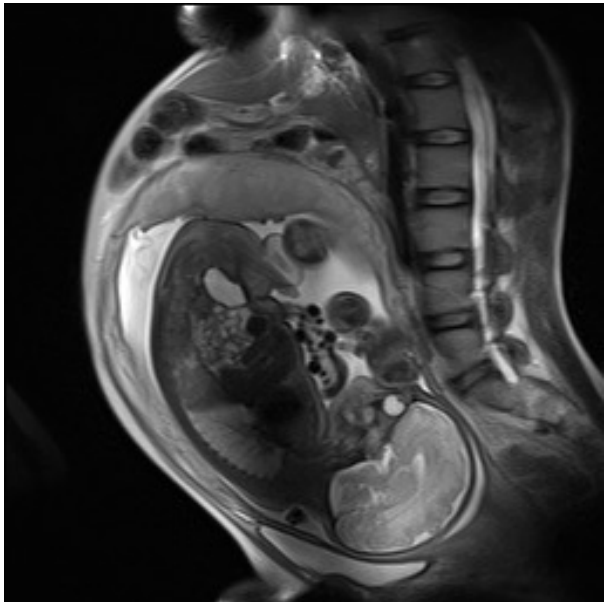
Currently, there are no reliable biomarkers that identify those patients with AKI who will go on to develop cardiovascular disease or CKD

MEMRI









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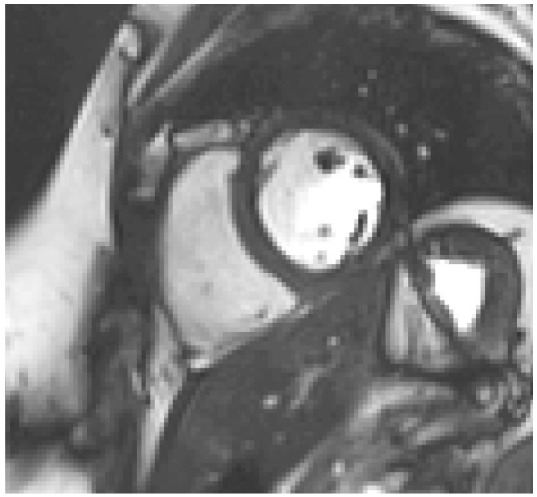

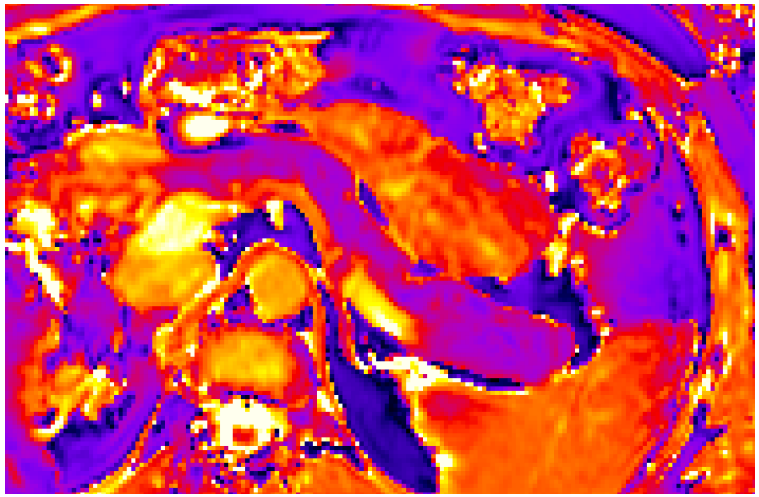

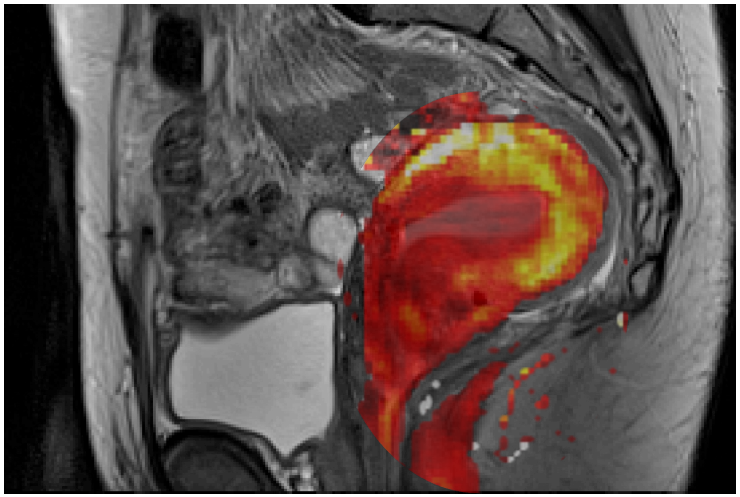

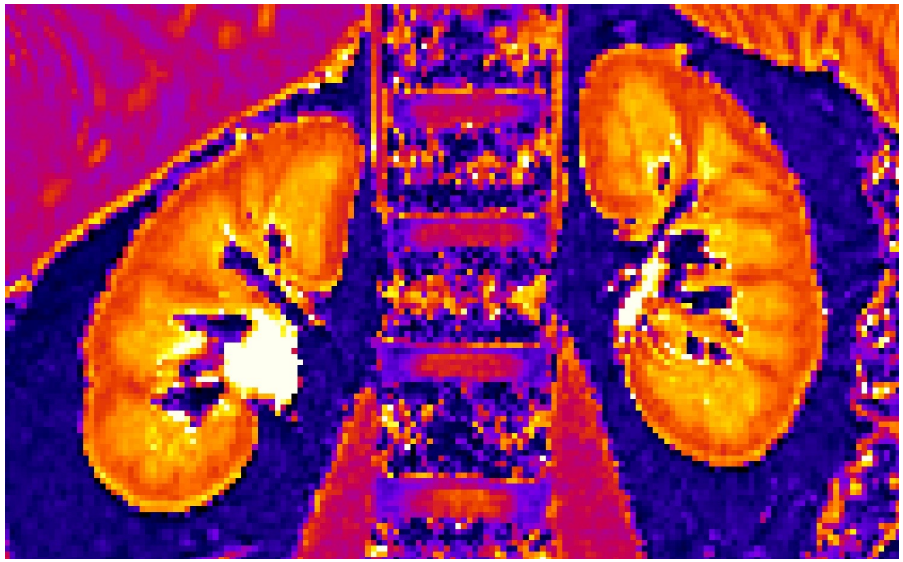

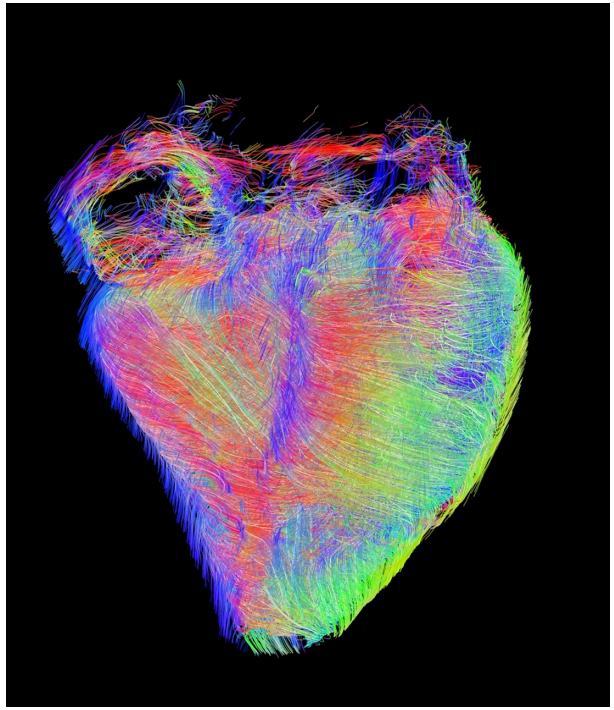

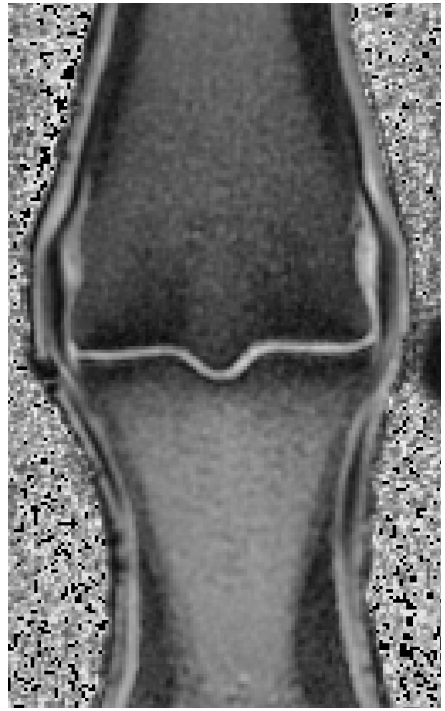

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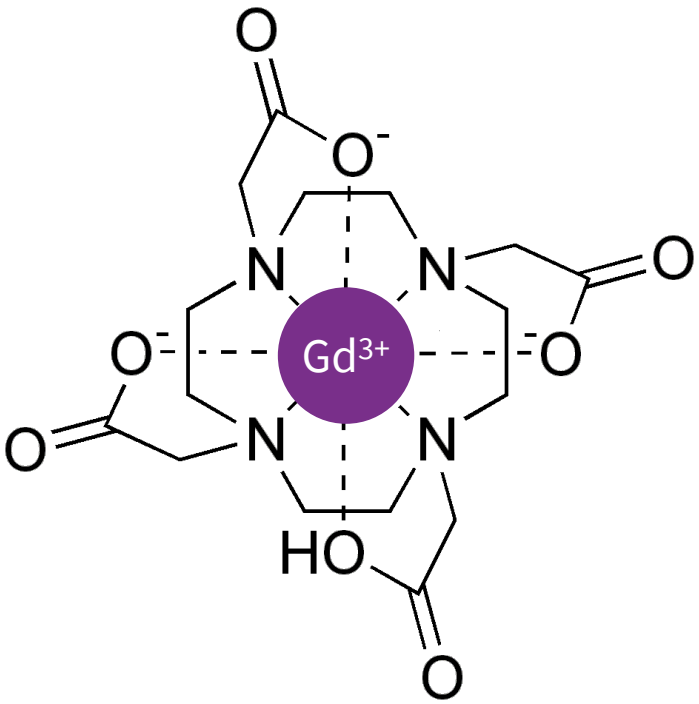
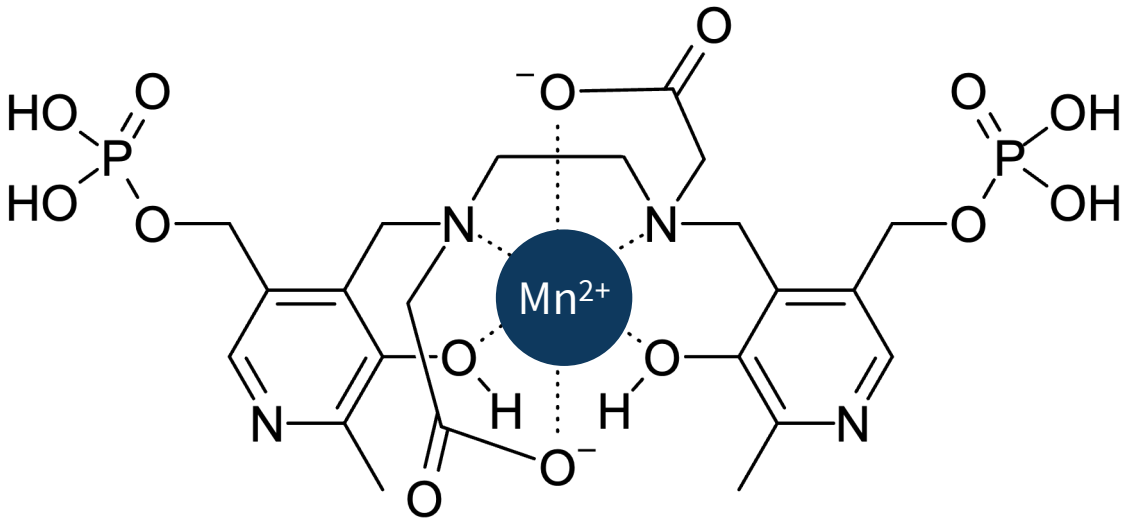
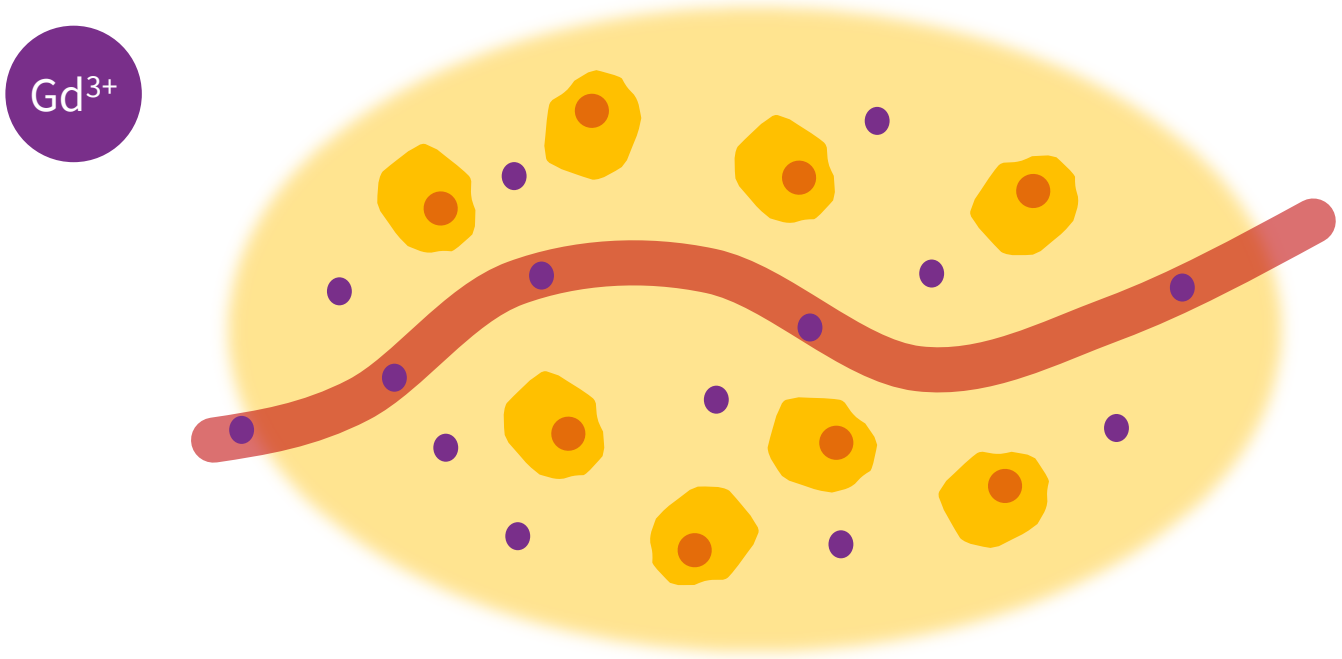
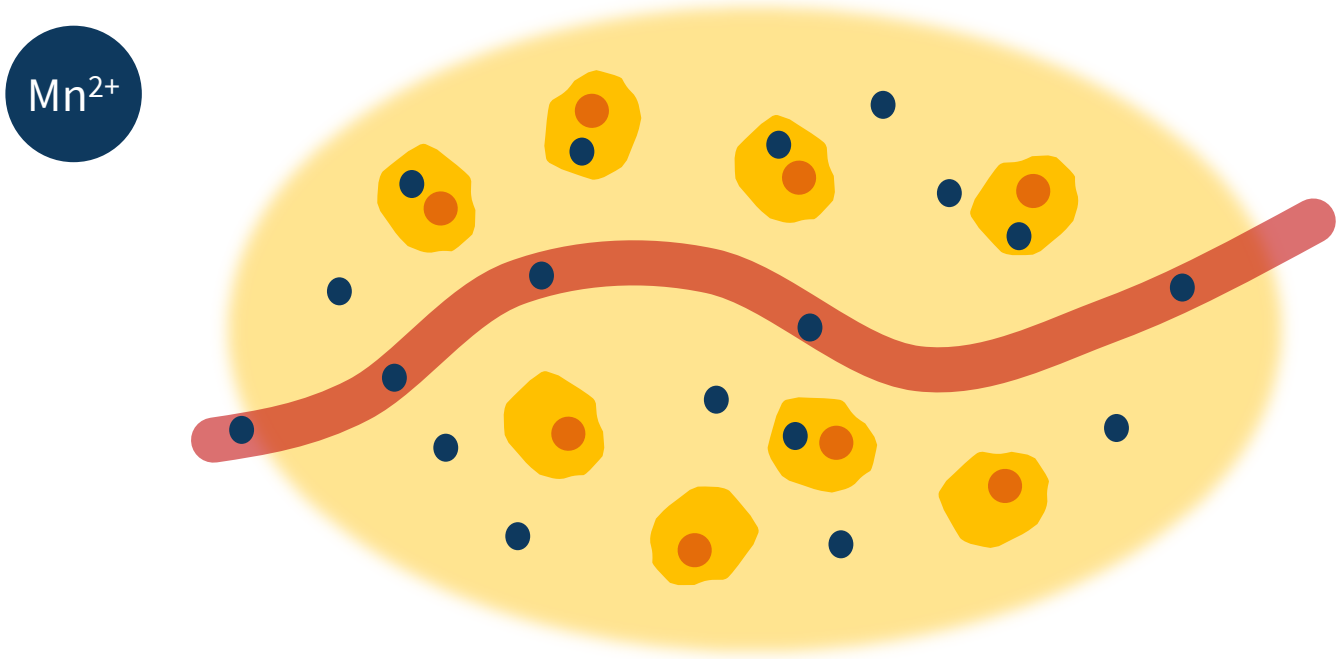
Contrast agents

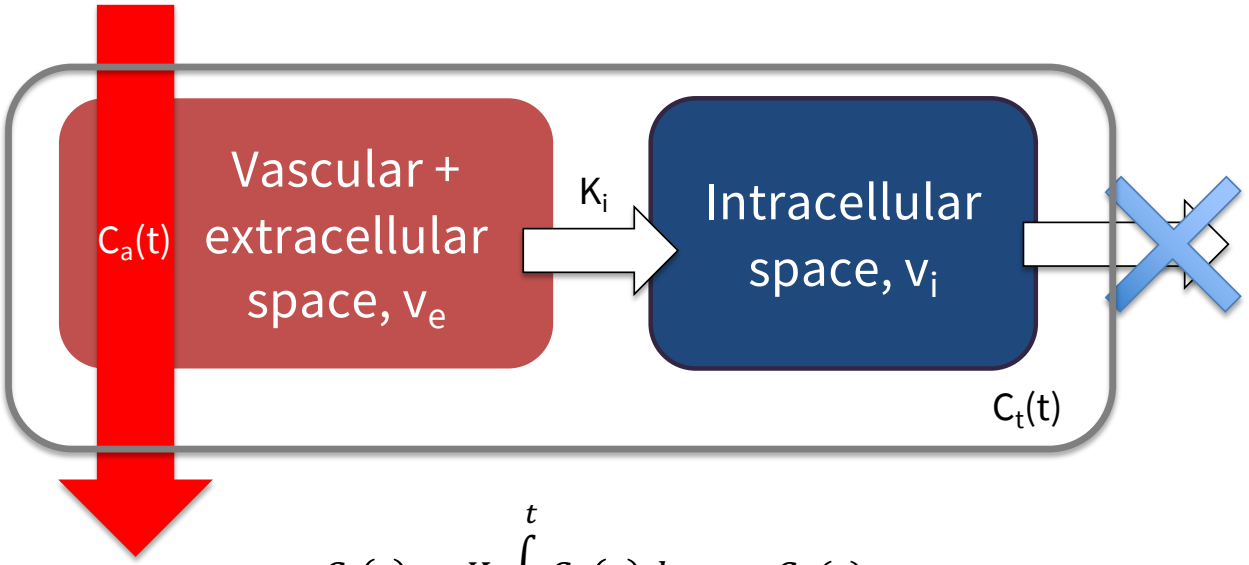




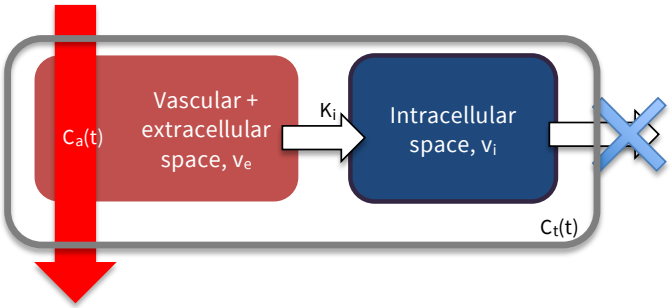
$$\Delta R_1 = r_1[CA]$$


Gd^{3+}


Mn^{2+}

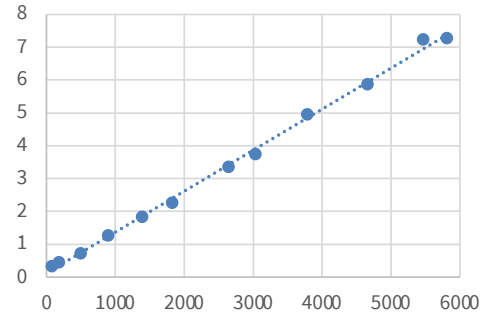


$$C_t(t) = K_i \int_0^t C_a(\tau)d\tau + v_e C_a(t)$$



$$C_t(t) = K_i \int_0^t C_a(\tau)d\tau + v_e C_a(t)$$

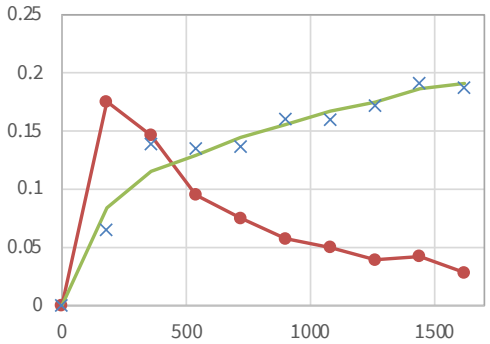
$\frac{C_t(t)}{C_a(t)}$



Slope = K_i

$\frac{\int}{C_a(t)}$

ΔR_1



Fit for K_i and v_e

t

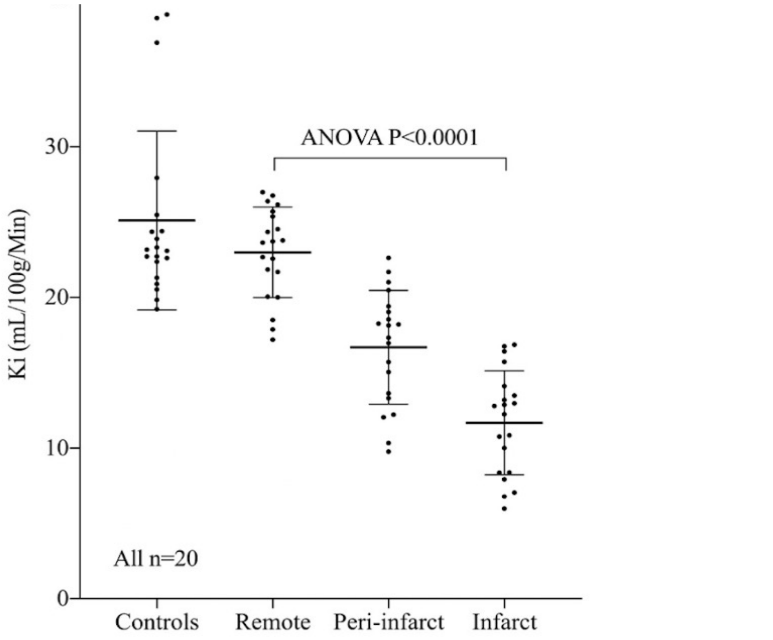
Why does this help us?

$$Mn^{2+} == Ca^{2+}$$

openheart

Assessment of stunned and viable myocardium using manganese-enhanced MRI

Nick B Spath ,[1] Trisha Singh ,[1] Giorgos Papanastasiou,[1] Andrew Baker,[1] Rob J Janiczek,[2] Gerry P McCann ,[3] Marc R Dweck ,[1] Lucy Kershaw,[1] David E Newby,[1] Scott Semple[1]



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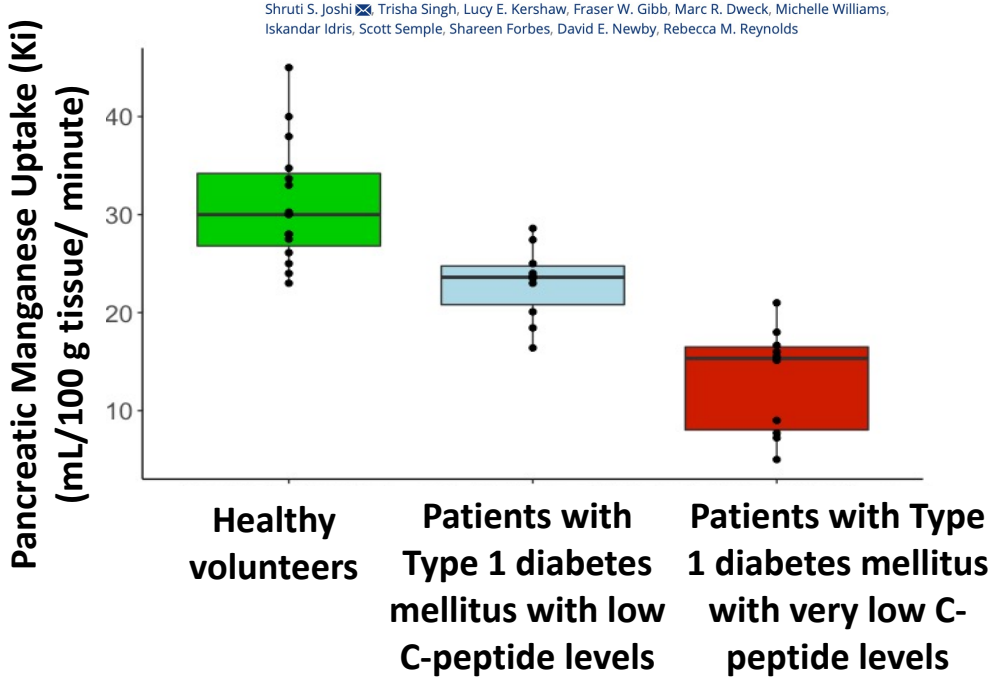
Non-invasive imaging of functional pancreatic islet beta-cell mass in people with type 1 diabetes mellitus

Shruti S. Joshi, Trisha Singh, Lucy E. Kershaw, Fraser W. Gibb, Marc R. Dweck, Michelle Williams, Iskandar Idris, Scott Semple, Shareen Forbes, David E. Newby, Rebecca M. Reynolds



British Heart Foundation

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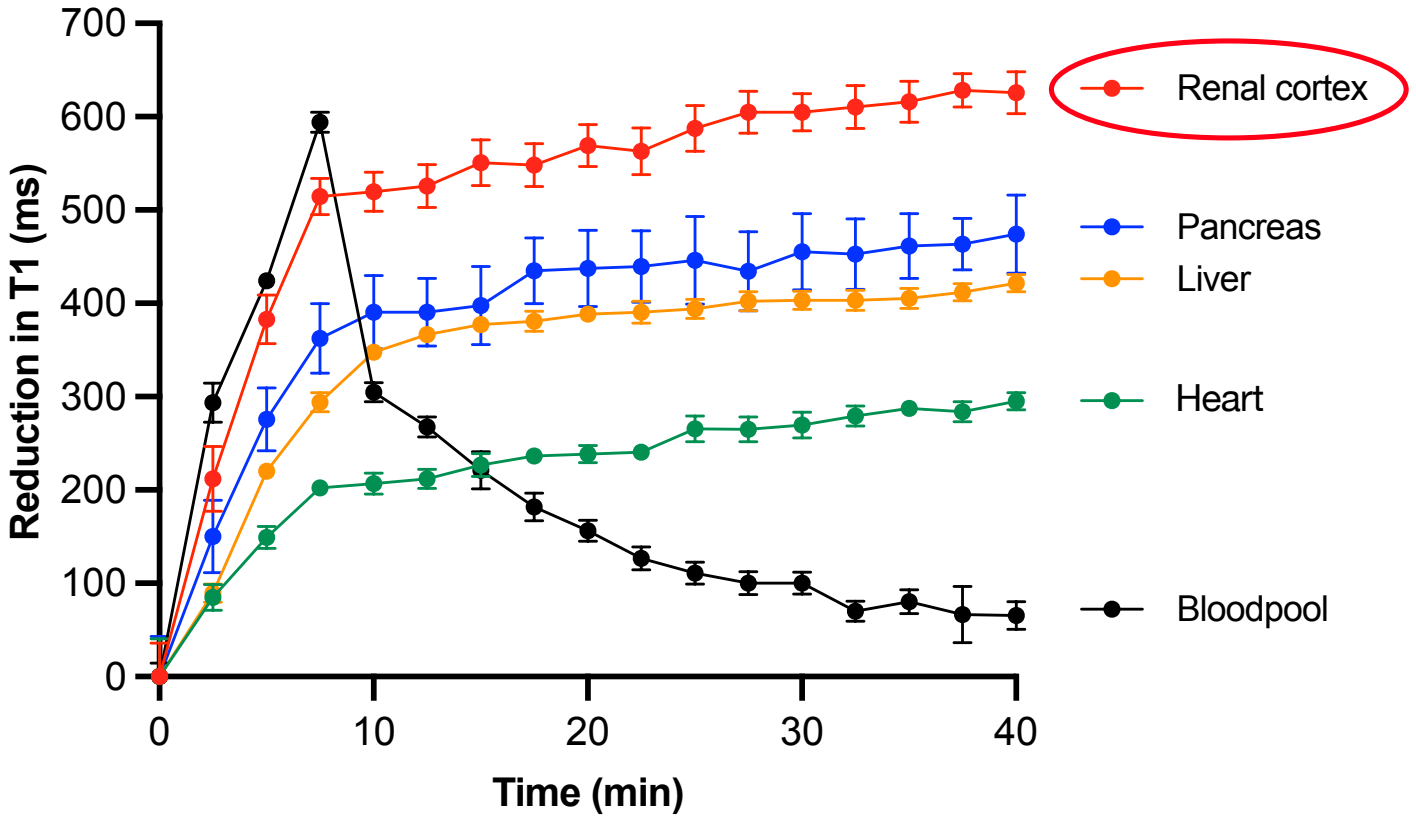
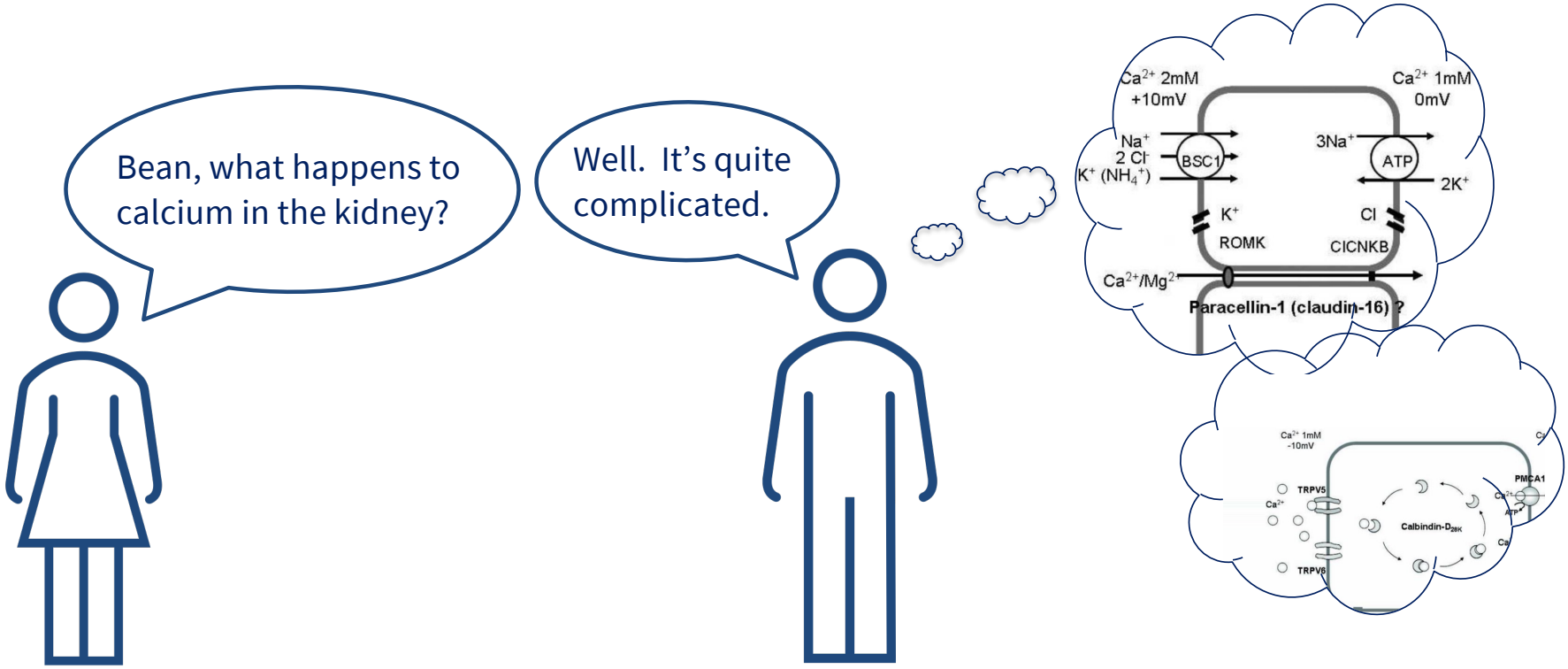
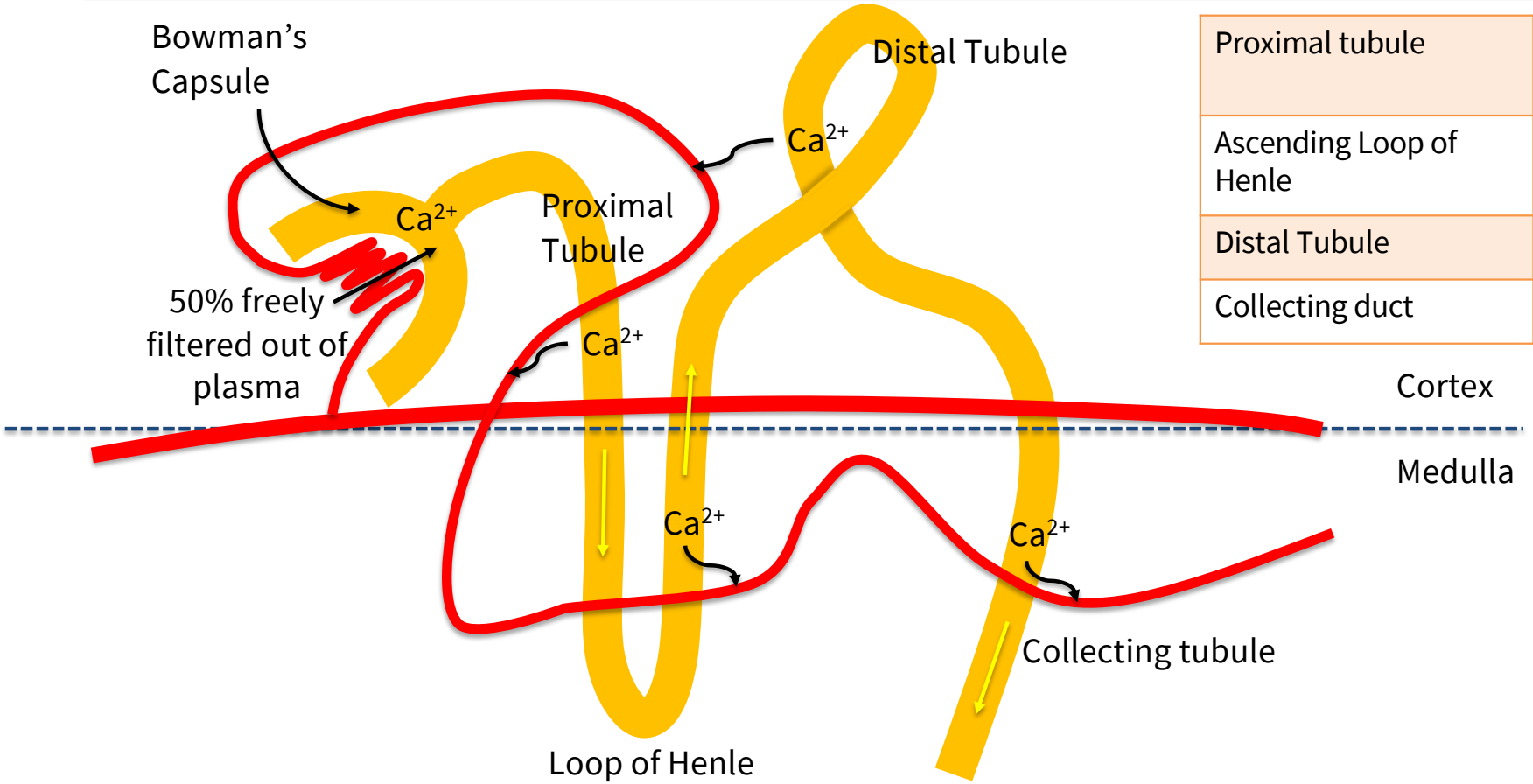



Bean, what happens to calcium in the kidney?
Well. It's quite complicated.
Ca2+ 2mM
+10mV
Ca2+ 1mM
0mV
Na+
2 Cl-
K+ (NH4+)
BSC1
3Na+
ATP
2K+
K+
ROMK
Cl
CICNKB
Ca2+/Mg2+
Paracellin-1 (claudin-16) ?
Ca2+ 1mM
-10mV
TRPV5
Ca2+
TRPV6
Calbindin-D28K
PMCA1
Ca2+
ATP



Proximal tubule	60-70%	Passive (+active)
Ascending Loop of Henle	20%	Passive (+active)
Distal Tubule	5-10%	Active
Collecting duct	5%	Passive

Imaging

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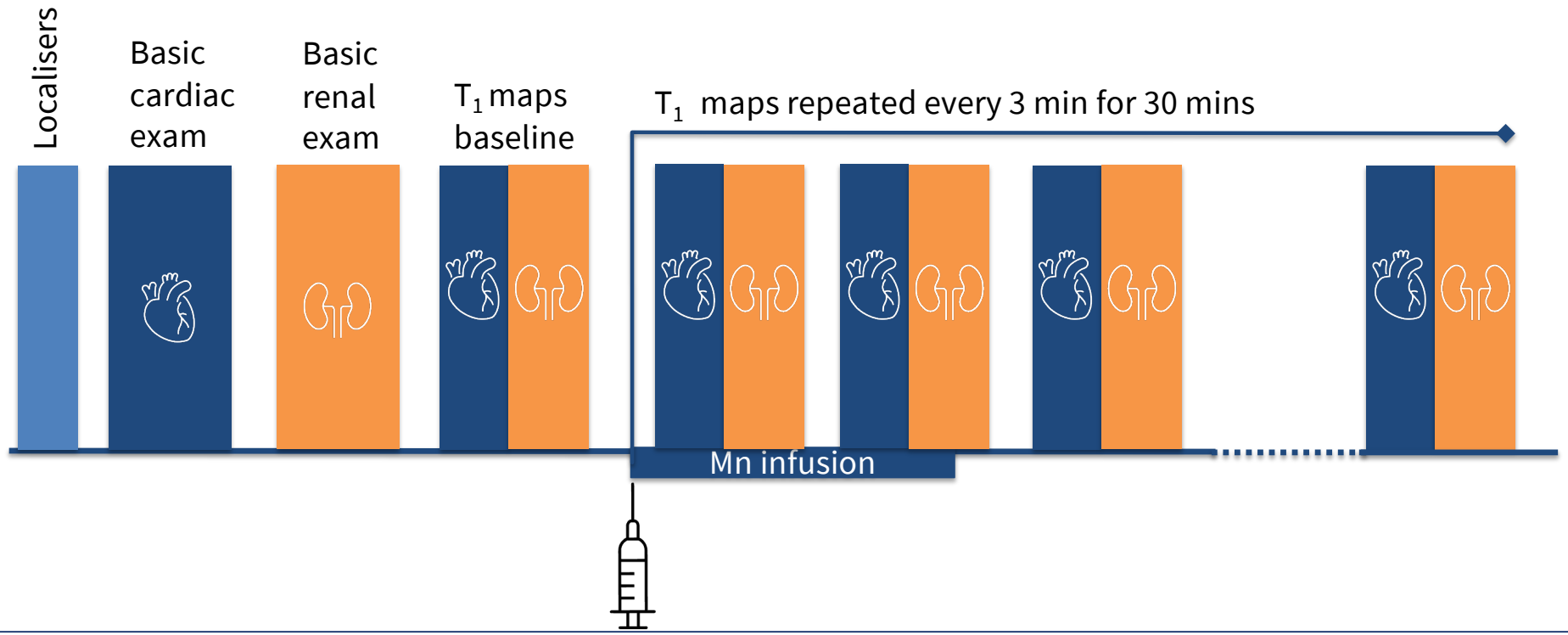
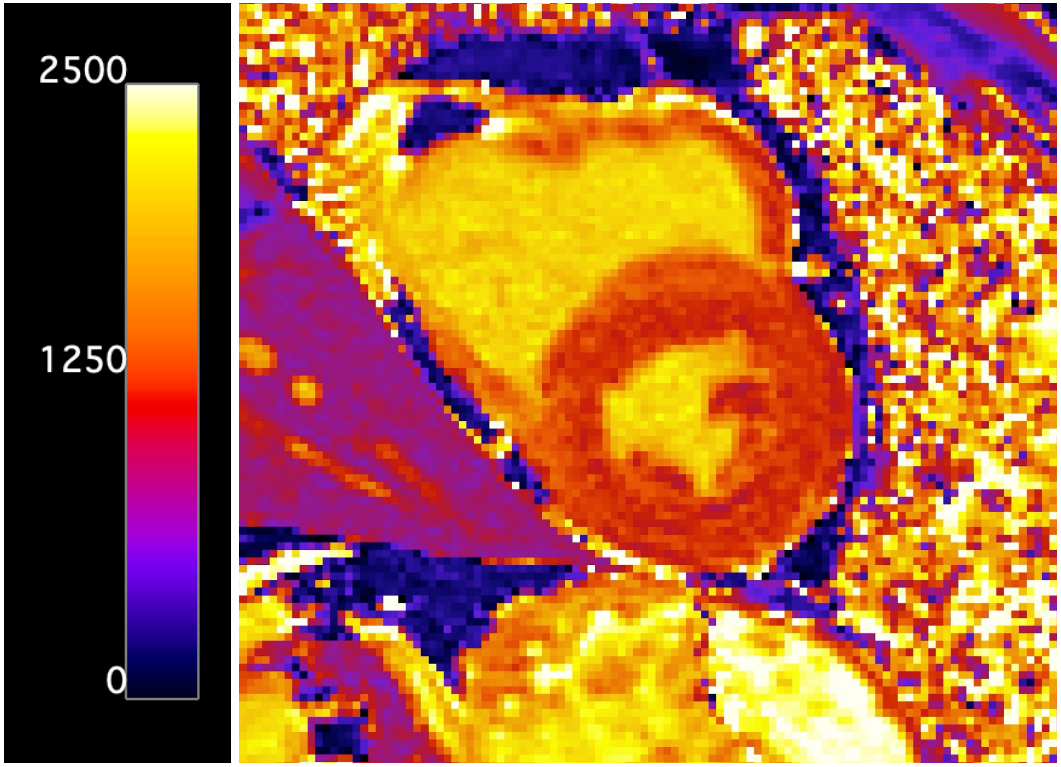
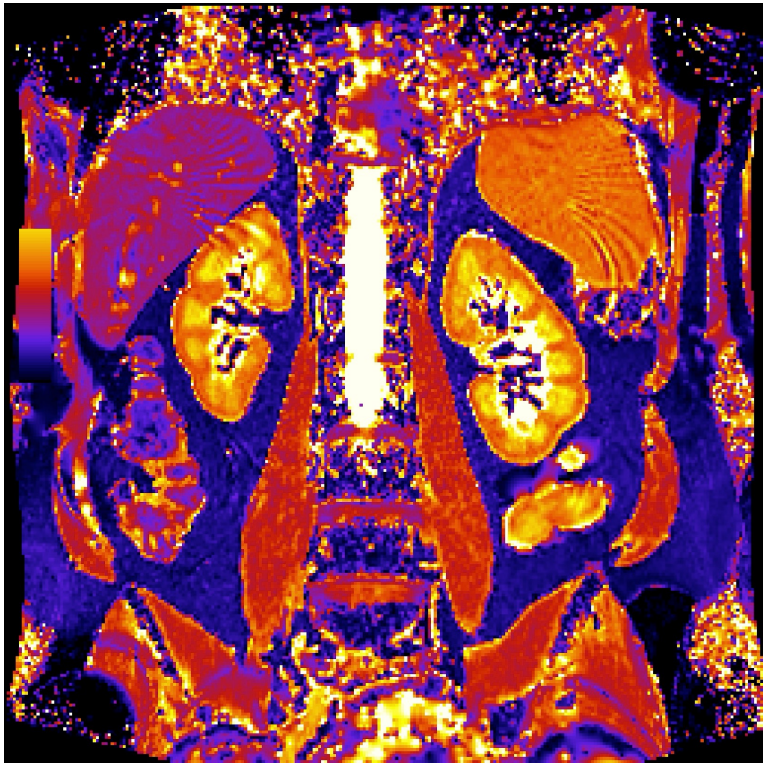

Localisers
Basic cardiac exam
Basic renal exam
T1 maps baseline
T1 maps repeated every 3 min for 30 mins
Mn infusion


2500
1250
0




50
0

Acquisition

- Faster
- Fewer breath holds
- Better resolution

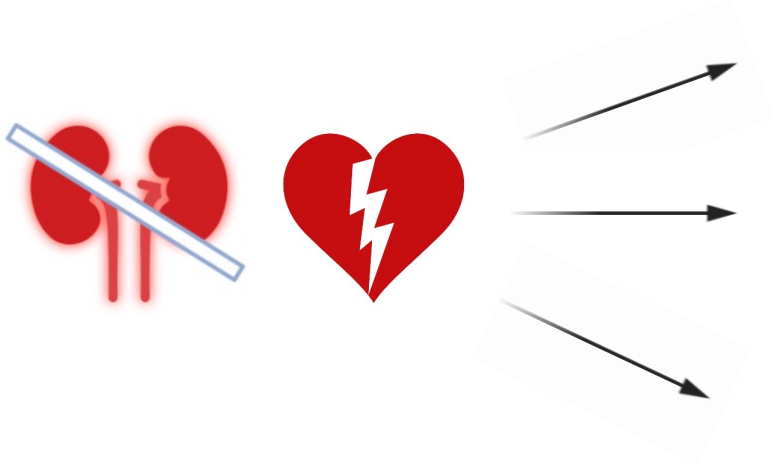
Analysis

- More complex models
- Better registration
- Automated region drawing

MEMRI-Kidney

MEMRI-Kidney

1. Cellular calcium handling is altered in the hearts & kidneys of patients presenting with AKI;
2. Cardiac and renal cellular calcium handling improves with AKI resolution;
3. Cardiac and renal cellular calcium remains abnormal in those with ongoing injury who are at increased risk of CVD and CKD



Resolution of AKI, normal Mn uptake, no development of CVD or CKD at 6 months

CKD based on conventional markers, abnormal Mn uptake

Resolution of AKI on conventional markers, abnormal Mn uptake → these are the patients at risk of CVD and CKD

Study design

Study 1

AKI
n=20

Age & sex-matched
subjects
n=20

MRI at
presentation

- 24h blood pressure
- arterial stiffness
- endothelial function

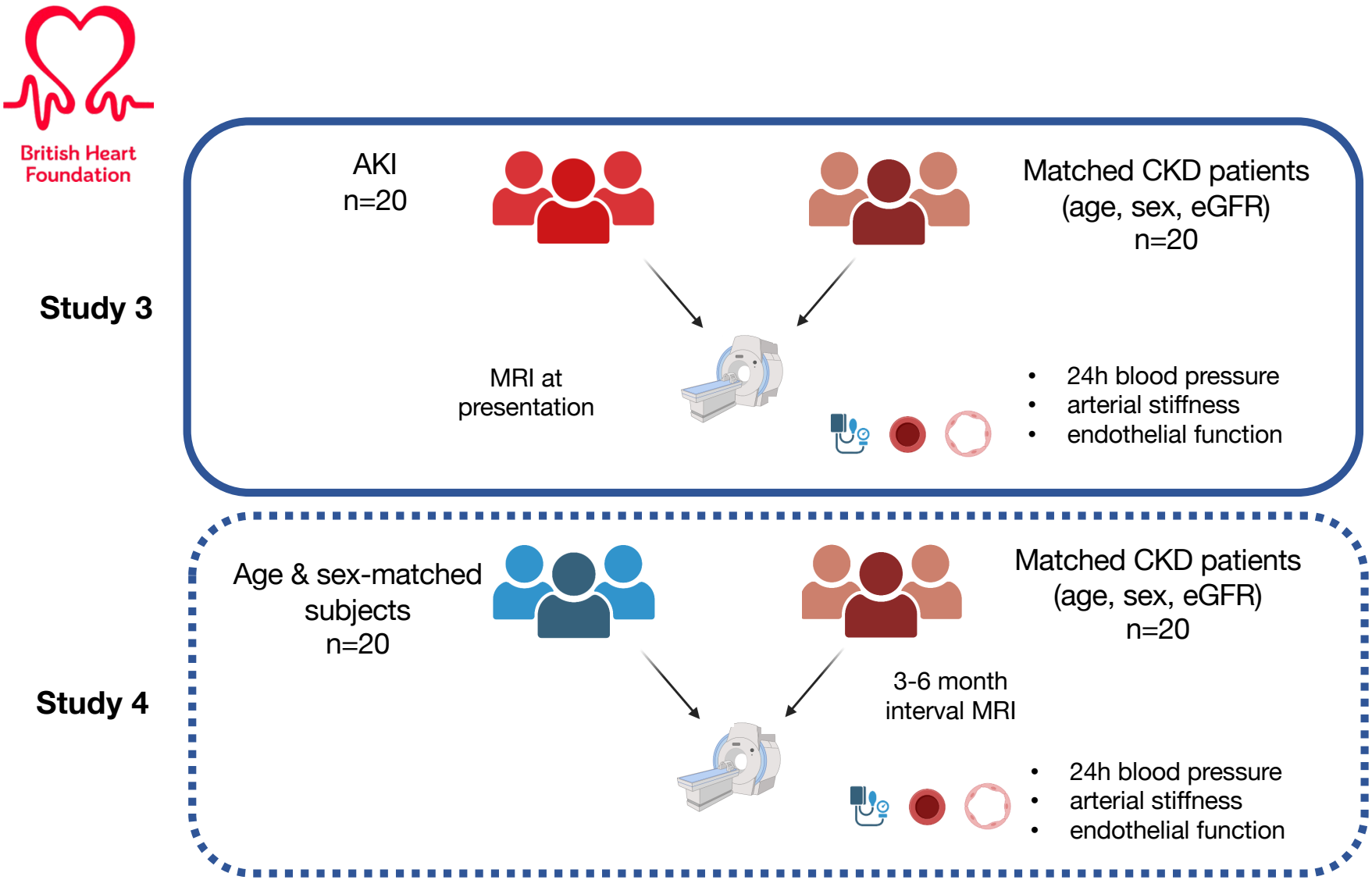
Study 2

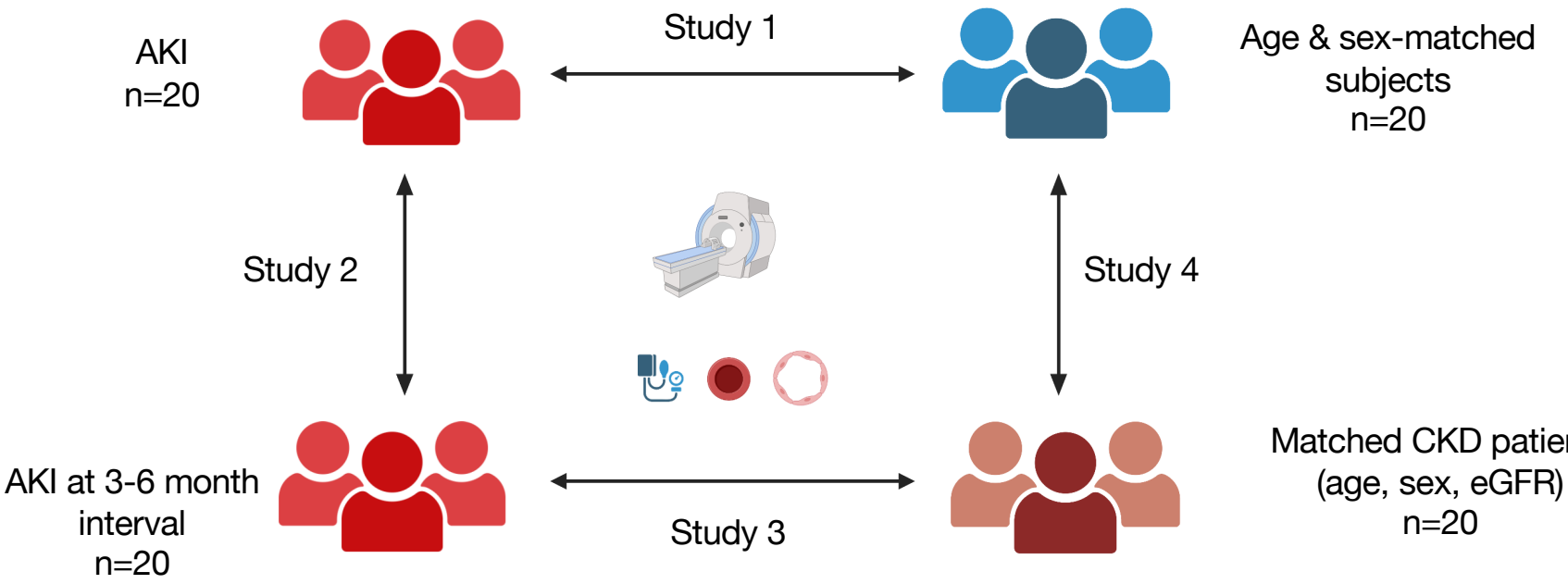
AKI
n=20

AKI
n=20

3-6 month
interval MRI

- 24h blood pressure
- arterial stiffness
- endothelial function


British Heart Foundation
THE UNIVERSITY OF EDINBURGH
Study 3
AKI
n=20
Matched CKD patients
(age, sex, eGFR)
n=20
MRI at
presentation
24h blood pressure
arterial stiffness
endothelial function
Study 4
Age & sex-matched
subjects
n=20
Matched CKD patients
(age, sex, eGFR)
n=20
3-6 month
interval MRI
24h blood pressure
arterial stiffness
endothelial function


AKI
n=20
Study 1
Age & sex-matched
subjects
n=20
Study 2
Study 4
AKI at 3-6 month
interval
n=20
Study 3
Matched CKD patients
(age, sex, eGFR)
n=20

Thank you

Dr Hannah Preston
Prof David Newby
Prof Scott Semple

QMRI Research Radiographers