3rd International Conference on Functional Renal Imaging 2019

MRI in (Clinical) Drug Development Pathways

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and

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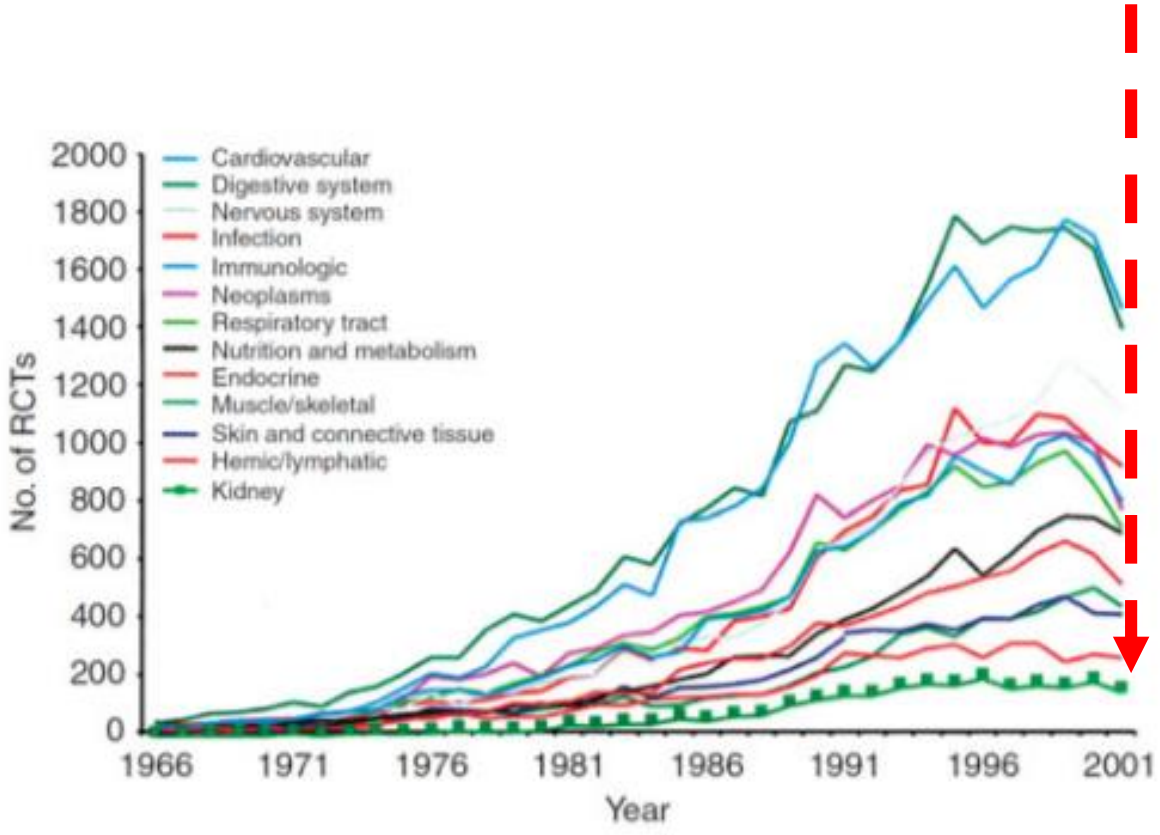
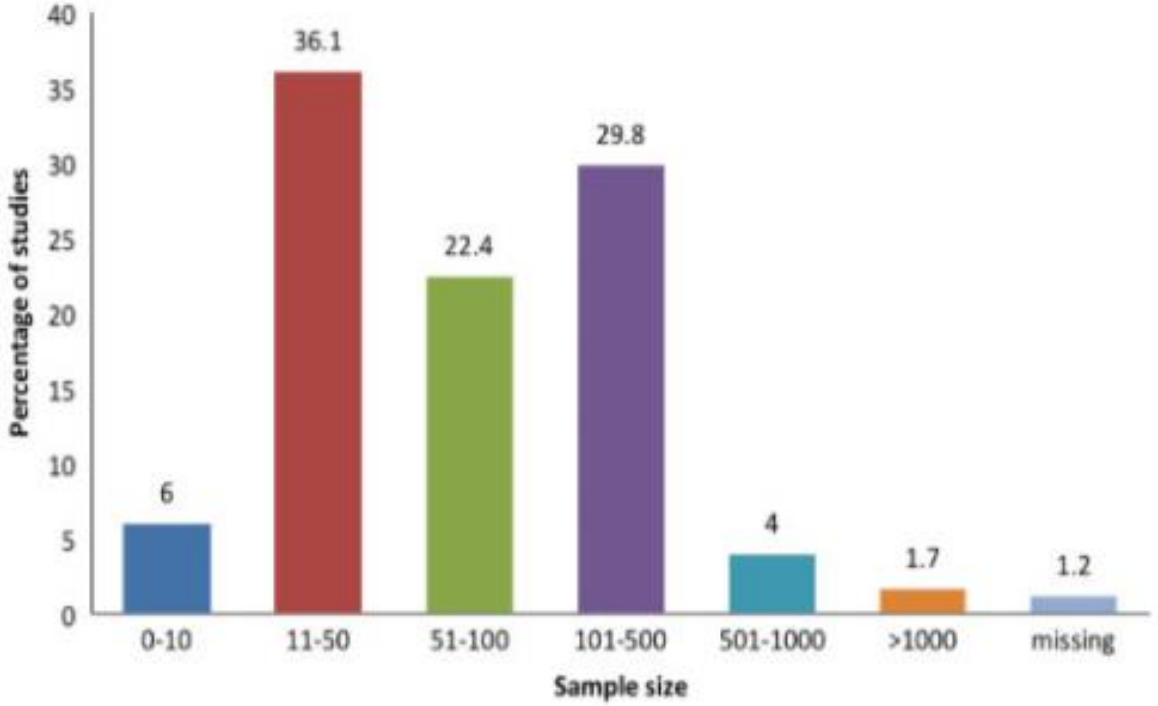
A relative dearth of clinical trials in nephrology: why?



Note relatively small sample sizes – includes all study types



Current Phase 3 trial end-points for treatment interventions in CKD:

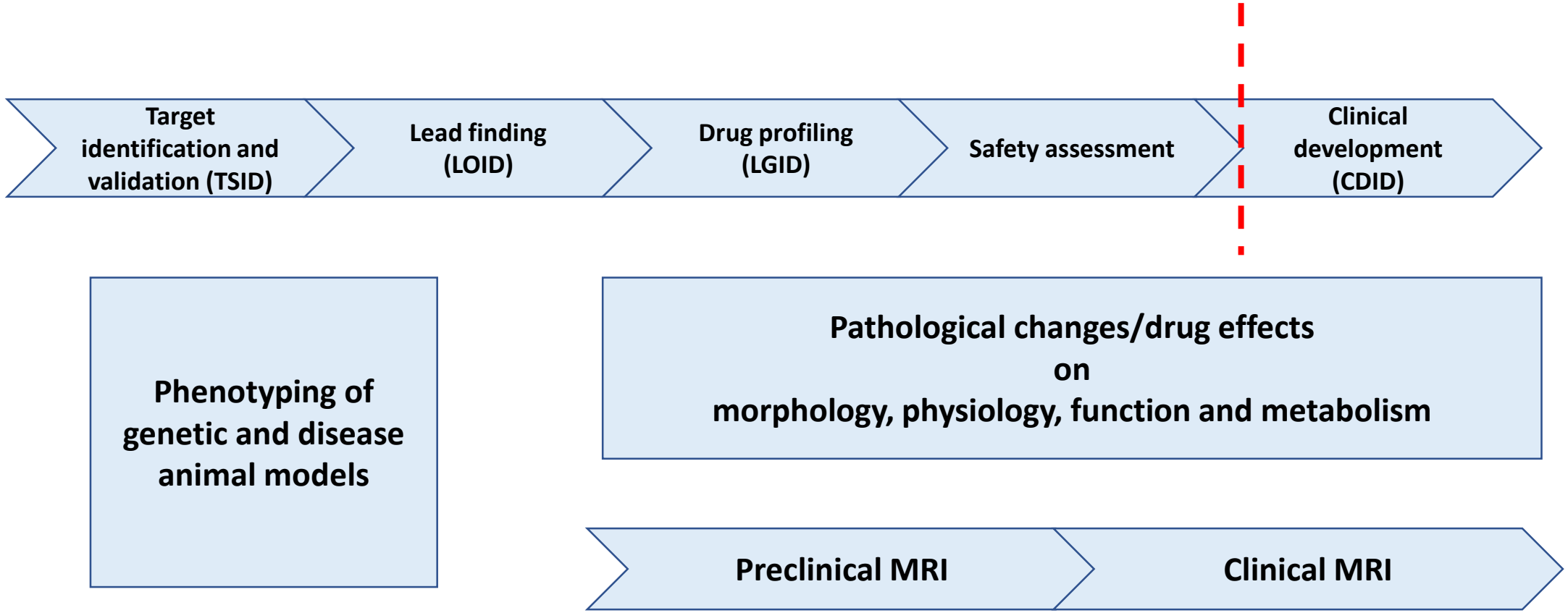
- death
- dialysis/transplantation (renal replacement)

(May take >5 years)

- doubling of serum creatinine (57% decline in eGFR – 40% decline now accepted – delay in reaching)
- (albuminuria, eGFR slope, and albuminuria + eGFR slope are under consideration)

(Kovesdy, *NDT* 2019)

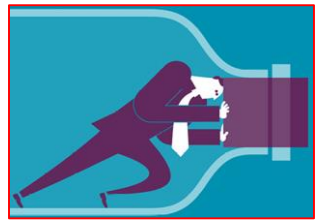
Generic flow of a drug development project from **target identification** to **registration** (at the end of clinical development) – use of MRI



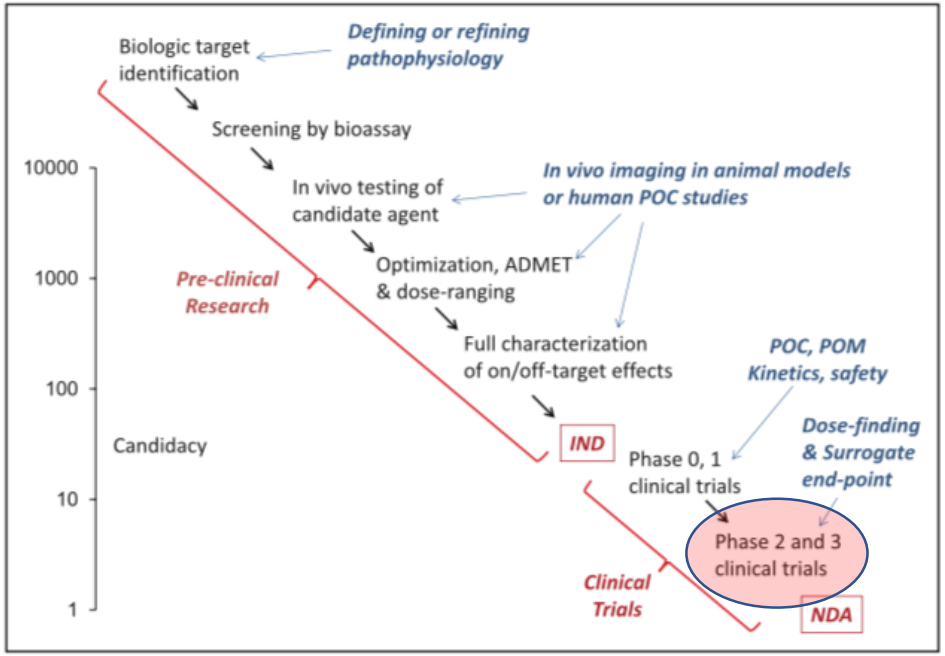
(Taken from Allegrini, *Eur Pharm Rev* 2012)

Cost and attrition

Progression from Phase 2 to 3 is often the challenge and 'bottleneck'



High attrition rate



(Linder & Link, *Circ Cardiovasc Imaging* 2018)

Lessons from AstraZeneca's drug pipeline (2005-10)

Right target

- Strong link between target and disease
- Differentiated efficacy
- Available and predictive biomarkers

'5 Rs'

Right tissue

- Adequate bioavailability and tissue exposure
- Definition of PD biomarkers
- Clear understanding of preclinical and clinical PK/PD
- Understanding of drug–drug interactions

Right safety

- Differentiated and clear safety margins
- Understanding of secondary pharmacology risk
- Understanding of reactive metabolites, genotoxicity, drug–drug interactions
- Understanding of target liability

Right patients

- Identification of the most responsive patient population
- Definition of risk–benefit for given population

Right commercial potential

- Differentiated value proposition versus future standard of care
- Focus on market access, payer and provider
- Personalized health-care strategy, including diagnostic and biomarkers

Need for:

Non-invasive disease classifiers
(diagnostic biomarkers)
Means to stratify patients
Reliable surrogate end-points
(prognostic biomarkers)
Efficacy biomarkers
(treatment response biomarkers)

- Genetic suppor
- Efficacy biomar

☐ Closed ☐ Active or successful

(Cook et al, *Nat Drug Dis* 2014)

Non-proteinuric CKD

or

What do we do if we cannot use and monitor albuminuria?

Why do we use albuminuria/proteinuria?

- It is a feature of glomerular disease pathology and is characteristic of many patients with DKD
- It is easily measured in urine (usually as UACR or UPCR)
- It has been shown to be linked to CKD (DKD) progression (cause and/or effect?)
- It is assumed that its reduction is a marker of a treatment benefit
- It is assumed to link animal models with human disease (mainly DKD)
- While not (yet) a regulatory approved end-point in clinical trials*, it is used in Phase 2 to build confidence for Phase 3

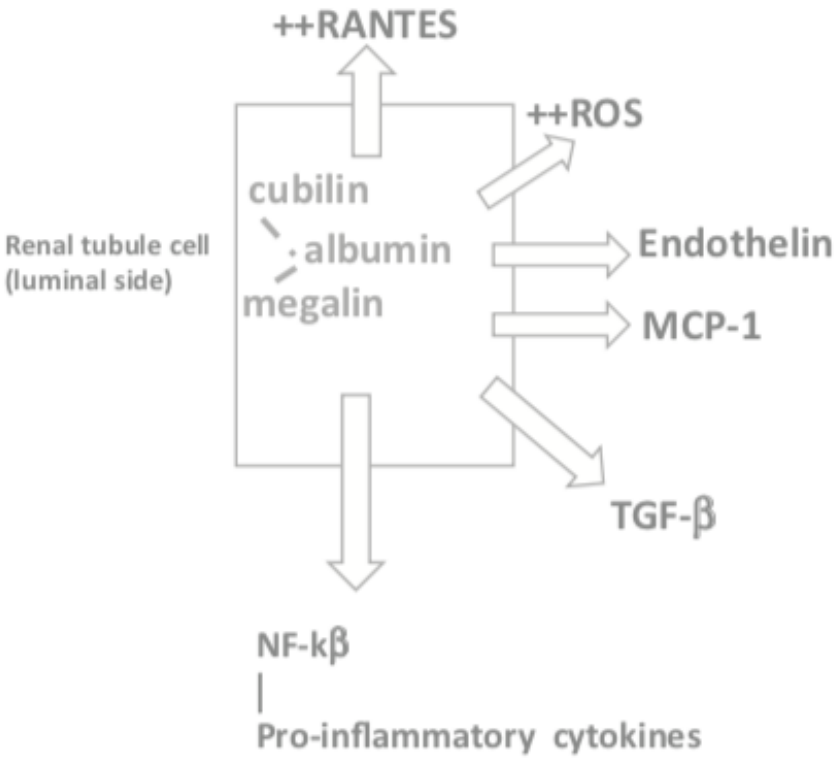
However:

- Glomerular disease with albuminuria/proteinuria accounts for only around 20% of CKD patients reaching ESRD
- 60% of CKD is non-proteinuric
- 20-30% of DKD is non-albuminuric
- In general, those with DKD and albuminuria progress faster toward ESRD than those without
- Both groups more likely to reach ESRD than to die of a CV-related event

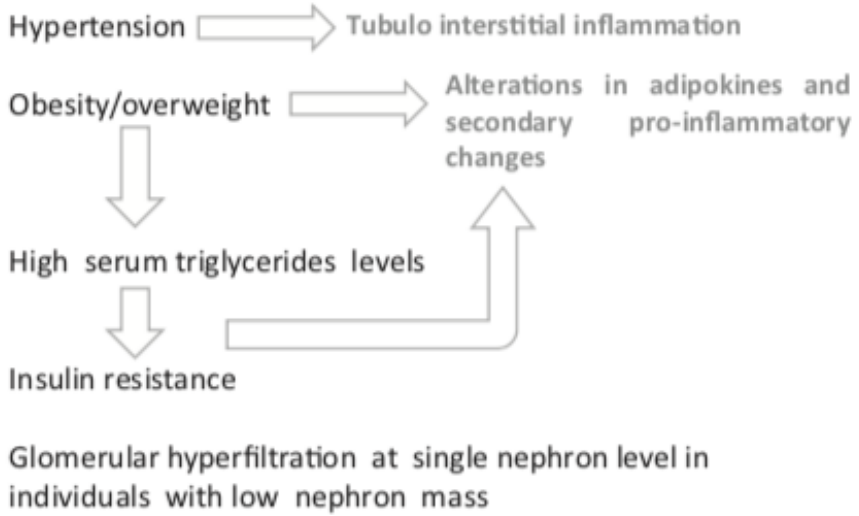
*Proteinuria reduction is accepted as a treatment end-point in FSGS, membranous and IgA

Proteinuric and non-proteinuric CKD: hypothesized disease mechanisms

Nephrotoxic mechanism(s) of proteinuria

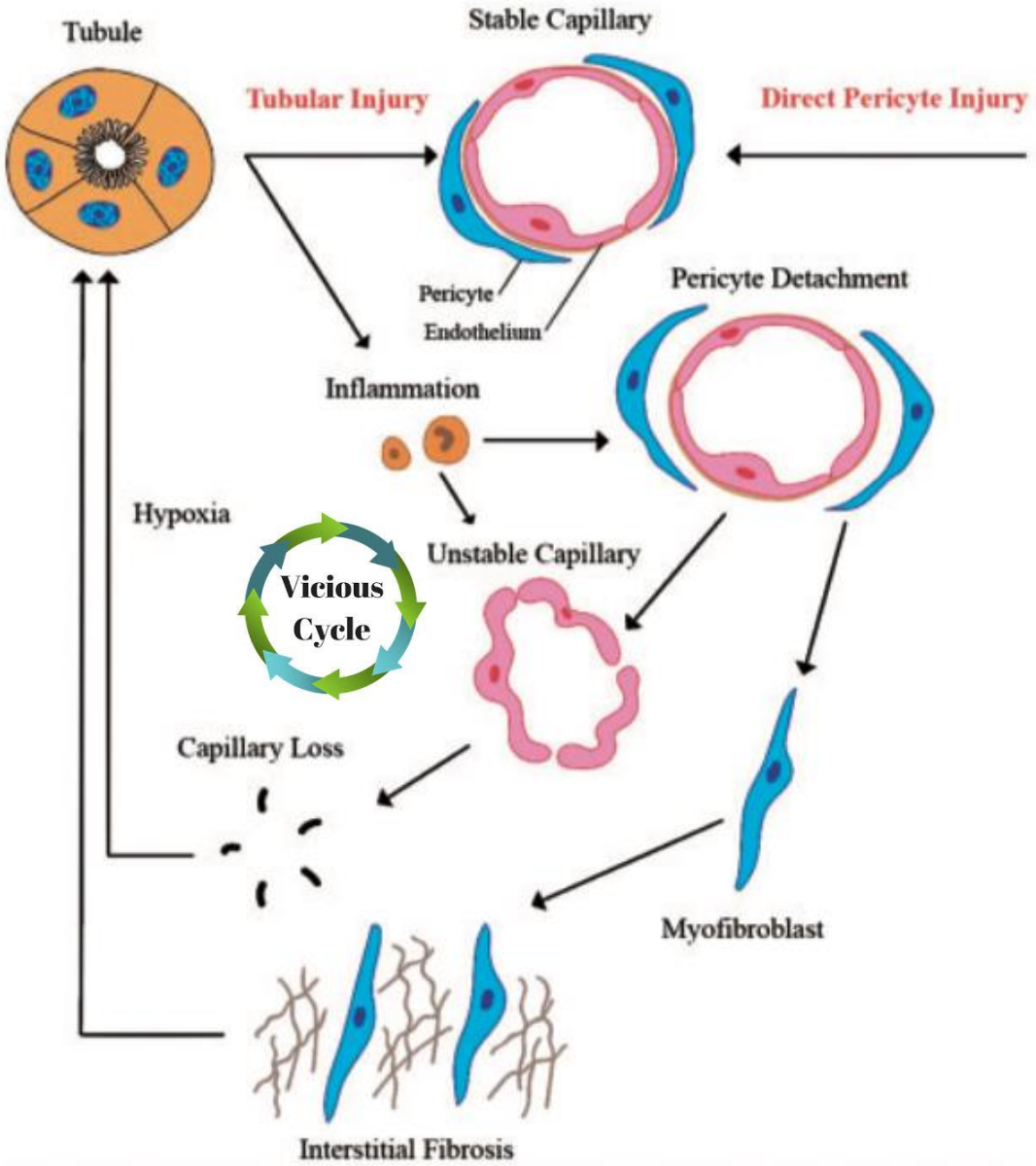


Risk factors and mechanisms in non-proteinuric renal diseases



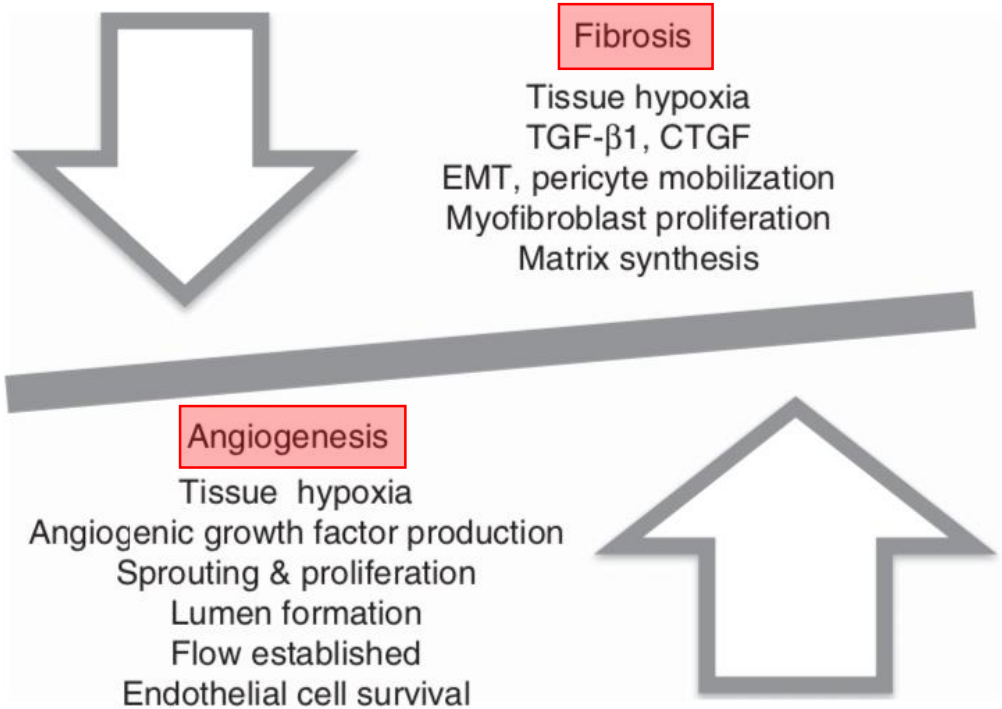
(Bolignano & Zoccali, *NDT* 2017)

Detecting renal vasculopathy – a key driver in CKD



(Afsar et al, *CJK* 2018)

Vicious cycle of *vascular* (peritubular) *rarefaction* and its relationship to *fibrosis*



(Ballermann & Obeidat, *KI* 2014)

MRI's potential in CKD drug development

Clinical assessment of renal function currently relies on:

- serum creatinine
- albuminuria/proteinuria
- renal ultrasound (structure and size)
- renal biopsy*

Problems:

- limited reproducibility – need for large cohorts
- limited sensitivity to changes in disease progression
- limited prognostic value
- limited application to patient stratification
- limited justification for renal biopsy and its risks

Potential value of MRI:

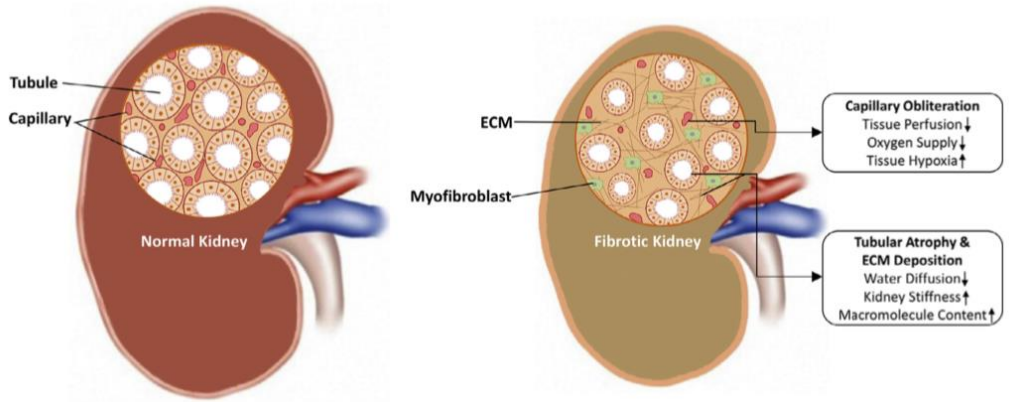
- single integrated method for structure and function
- high precision and likely (serial) reproducibility
- potential for adaptation to drug mechanism of action
- early detection and monitoring of disease progression
- potential for 'stress testing' (cf. CFR in cardiology)

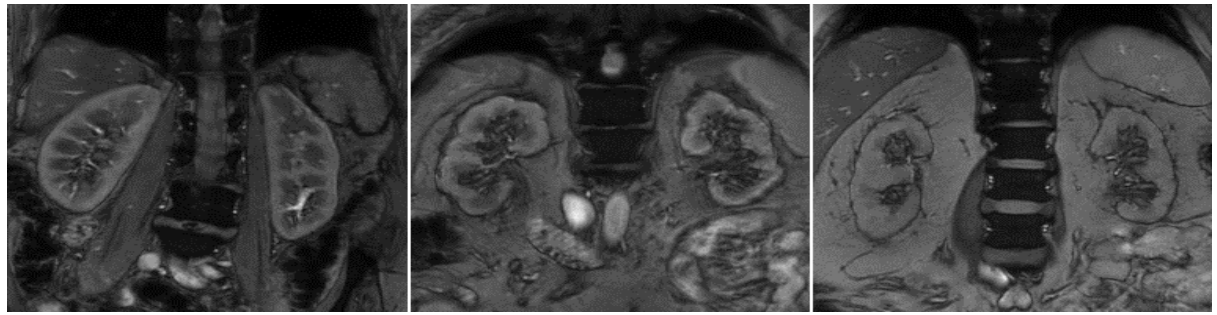
MRI Sequence	Principle	Advantages	Disadvantage	Application
Conventional DWI	Quantifies displacement of water molecules to evaluate tissue microstructure	Choice of b-values is easy Shorter scan time	Motion-related artifacts Information of micro-perfusion and water molecules diffusion cannot be separated	Monitor allograft function Evaluate interstitial fibrosis and tubular atrophy
IVIM DWI	Separately estimates tissue micro-perfusion and water molecules diffusion to assess tissue microstructure	Evaluates micro-perfusion and water diffusion separately	Motion-related artifacts Choice of b-values is not standardized	Monitor allograft function Evaluate interstitial fibrosis and tubular atrophy
DTI	Investigates directionality of water molecular motion due to anisotropy of tissue	Accounts for directionality of water diffusion, such as along renal tubules	Chemical shifts and susceptibility image artifacts FA is non-specific for pathophysiological change	Monitor allograft function Evaluate interstitial fibrosis and tubular atrophy
DKI	Calculates non-gaussian behavior of water diffusion to more accurately reflect tissue microstructural complexity	Accounts for non-gaussian motion of water molecular	Low SNR	Evaluate interstitial fibrosis and tubular atrophy
BOLD	Quantifies tissue oxygenation based on paramagnetic properties of blood deoxyhemoglobin	Evaluates tissue oxygen bioavailability	R2* cannot distinguish causes of oxygenation changes	Monitor allograft function
ASL	Quantifies perfusion by selectively labeling inflowing blood	Evaluates tissue perfusion without exogenous contrast materials	Low SNR Perfusion is affected by other factors such as orientation of imaging slice, and renal cortical T1 values	Monitor allograft perfusion
MRE	Quantifies viscoelastic properties of tissues based on their response to external mechanical vibration	Quantifies tissue fibrosis	Kidney stiffness measurement is multifactorial, and is affect by renal perfusion	Quantify renal fibrosis
MTI	Evaluates macromolecule (i.e., collagen) based on interactions of protons from free water and macromolecules	Quantifies tissue fibrosis	MTR is affected by structural and functional alterations besides fibrosis Low SNR	Quantify renal fibrosis

ASL = arterial spin labeling, BOLD = blood oxygen-level-dependent, DKI = diffusion kurtosis imaging, DTI = diffusion tensor imaging, DWI = diffusion-weighted imaging, FA = fractional anisotropy, IVIM = intravoxel incoherent motion, MRE = magnetic resonance elastography, MTI = magnetization transfer imaging, MTR = magnetization transfer ratio, SNR = signal-to-noise ratio

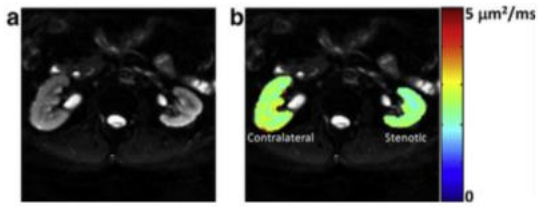
(Yu et al, *KJR* 2018)

MRI and renal fibrosis

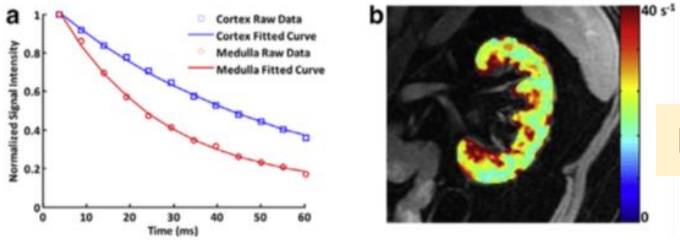




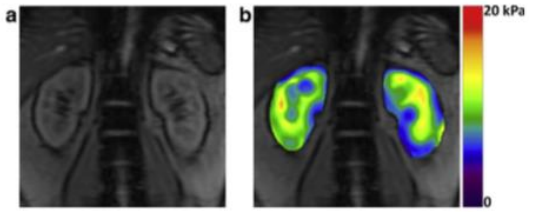
Normal (eGFR>90 ml/min) CKD3 (eGFR<60 ml/min) CKD4 (eGFR<30 ml/min)



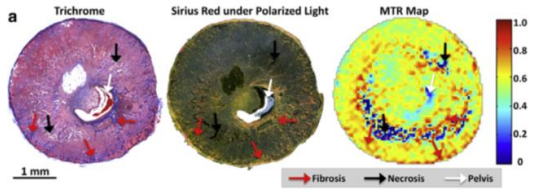
Diffusion MRI



BOLD MRI



MR elastography



Magnetization transfer imaging

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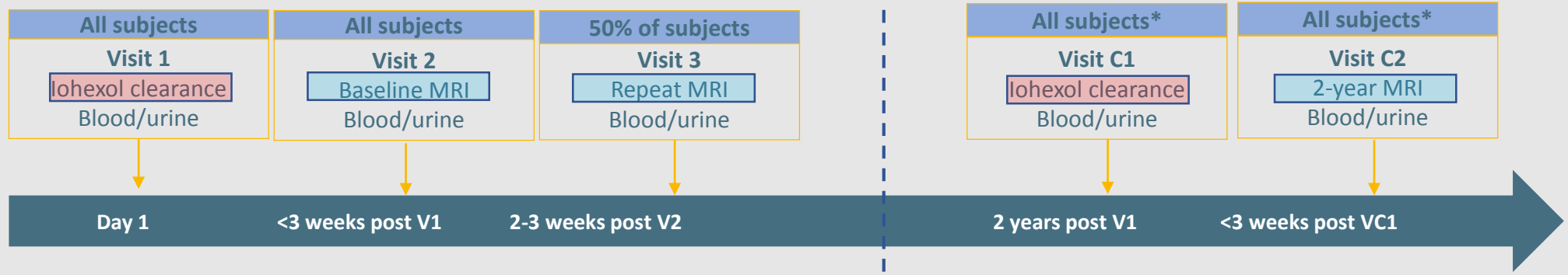
(Jiang et al, *Trans Res* 2019)

Study AM-01 CKD (over 2 years): evaluating a broad range of renal imaging variables, including sensitivity and repeatability

Study design



T1, Diffusion (ADC)

Macrostructure

Kidney volume, cortical volume
medullary volume

Renal perfusion
(ASL)

Subjects:
38 DKD patients (CKD2-4)
20 healthy controls
(age- and sex-matched)

(With thanks to Paul Hockings)

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MRI measurements, CKD stage and correlation with mGFR

	MRI measurement	Units	Healthy Controls	CKD3	CKD4	mGFR correlation (r)	p-value of correlation	coefficient of variation
Hemodynamics	Mean arterial flow	ml/s	9.43 (1.76)	6.39 (1.46)	4.30 (1.28)	0.85	<0.0001	0.07
	RARI	No units	0.68 (0.06)	0.81 (0.06)	0.84 (0.06)	0.76	<0.0001	0.02
	End diastolic velocity	cm/s	17.0 (3.9)	11.3 (3.2)	6.7 (2.5)	0.79	<0.0001	0.12
	Peak systolic velocity	cm/s	54.3 (8.3)	59.8 (14.2)	43.1 (11.1)	0.32	0.02	0.09
	Global perfusion	ml/100g/min	458 (54)	339 (54)	267 (86)	0.78	<0.0001	0.08
Macrostructure	Kidney volume (BSA corrected)	ml	109.0 (12.8)	98.1 (25.6)	86.3 (19.0)	0.42	0.001	0.04
Oxygenation	R2* cortex	s^{-1}	17.3 (1.4)	17.2 (1.6)	17. 0 (1.2)	0.07	0.59	0.04
	R2* medulla	s^{-1}	26.0 (2.3)	24.5 (3.7)	22.8 (3.6)	0.35	0.01	0.05
Microstructure	R1 cortex	s^{-1}	1.17 (0.10)	1.02 (0.07)	0.95 (0.12)	0.70	<0.0001	0.05
	R1 medulla	s^{-1}	0.77 (0.05)	0.78 (0.04)	0.76 (0.07)	0.08	0.53	0.04
	ADC cortex	$mm^2s^{-1} \times 10^{-3}$	2.52 (0.19)	2.37 (0.17)	2.27 (0.22)	0.48	0.0002	0.06
	ADC medulla	$mm^2s^{-1} \times 10^{-3}$	2.33 (0.18)	2.21 (0.24)	2.17 (0.24)	0.29	0.03	0.05

(With thanks to Paul Hockings)

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MRI measurements shows correlation with albuminuria

	MRI measurement	Units	Correlation to UACR	p value of correlation
Hemodynamics	Mean arterial flow	ml/s	-0.73	<0.0001
	RARI	No unit	0.67	<0.0001
	End diastolic velocity	cm/s	-0.73	<0.0001
	Peak systolic velocity	cm/s	-0.29	0.03
	Global perfusion	ml/100g/min	-0.68	<0.0001
Macrostructure	Kidney volume	ml	-0.44	0.0005
Oxygenation	R2* cortex	s^{-1}	-0.06	0.67
	R2* medulla	s^{-1}	-0.32	0.02
Microstructure	R1 cortex	s^{-1}	-0.72	<0.0001
	R1 medulla	s^{-1}	-0.25	0.06
	ADC cortex	$mm^2s^{-1} \times 10^{-3}$	-0.38	0.003
	ADC medulla	$mm^2s^{-1} \times 10^{-3}$	-0.32	0.02

(With thanks to Paul Hockings)

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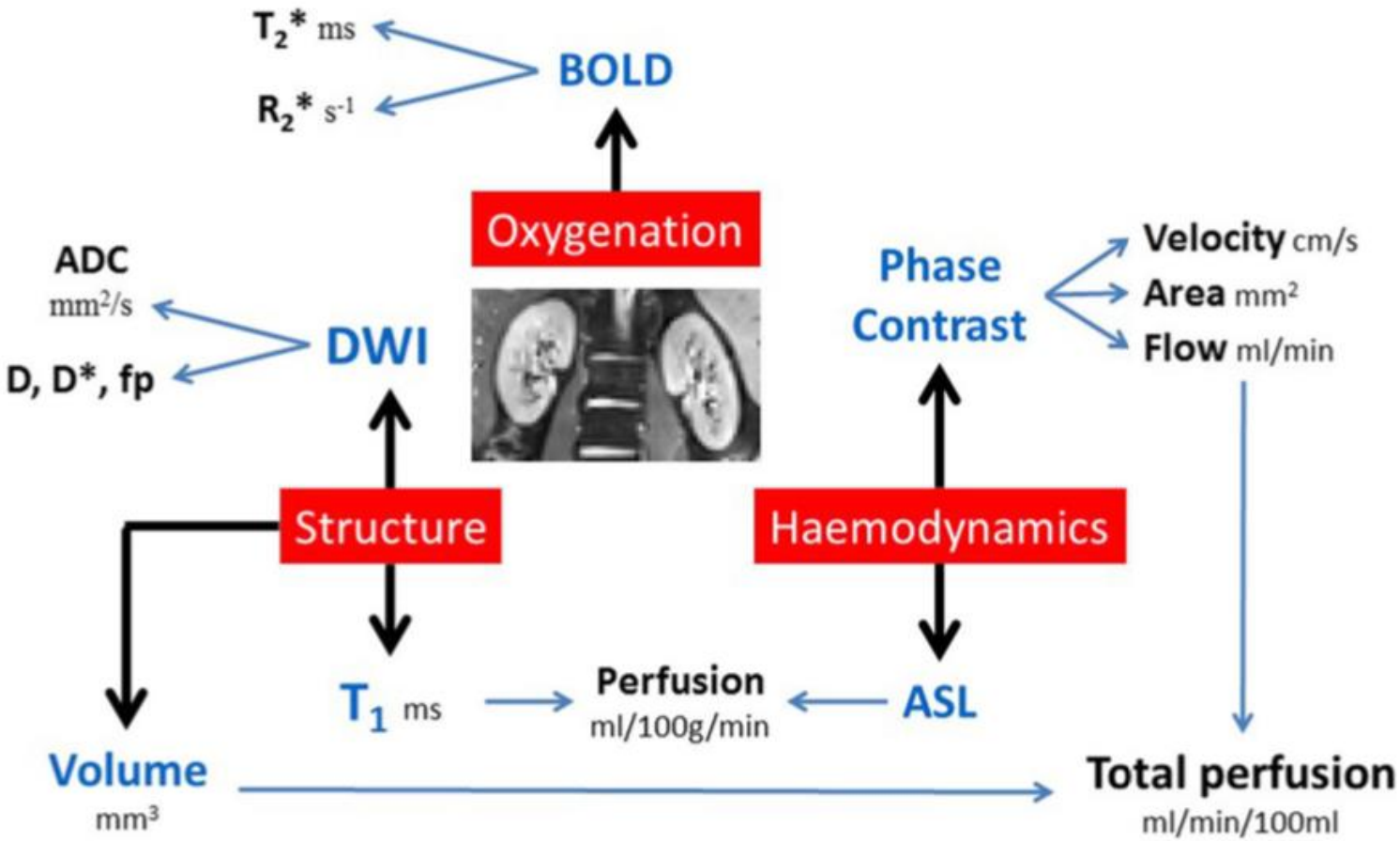
The Future: multiparametric MRI imaging



A need for the equivalent of CVD clinical trial MACE* – a composite end-point of clinical events (or measures) that can show benefit

*Major Adverse Cardiac Events

(Cox et al, *Front Physiol* 2017)

CKD and prospective observational studies

- CKD has few targeted therapies and currently only late disease outcome measures
  - *death, dialysis or transplantation*
- Need for *better validated* kidney disease targets
- Need for *better validated* kidney disease measures of progression and outcome
- Opportunity to re-classify kidney disease

HEROIC
tHe East and noRth lOndon diabetes Cohort Study

Prospective 4-yr London-based study of 500 DKD (Diabetic Kidney Disease - type 1 and 2) patients aiming to:

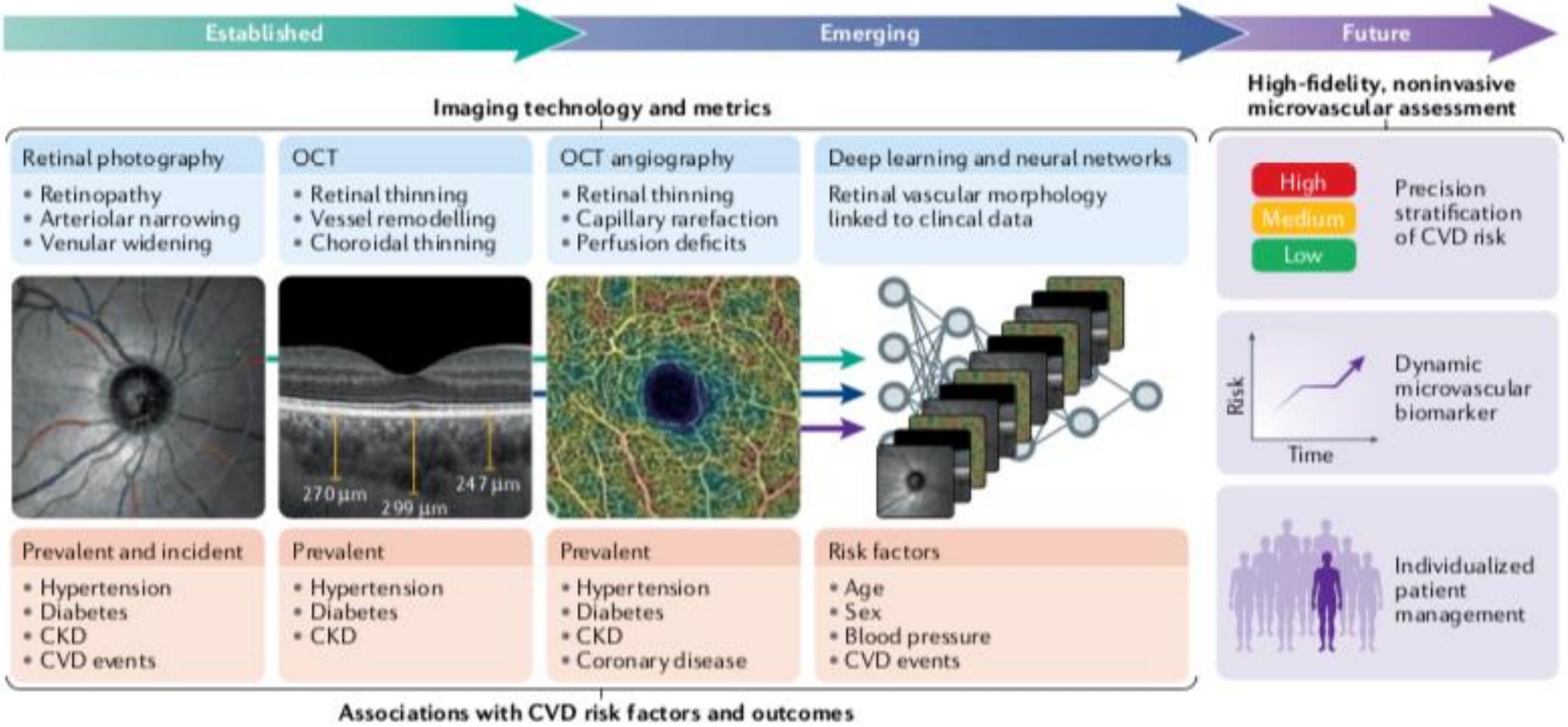
- Recruit patients with **biopsy-confirmed DKD** risk stratified by **proteinuria** and **eGFR slope**
- Apply **'phenomics'** (blood, urine and tissue) to identify **genetic** and other risk factors for **progression** and **complications**, including **Heart Failure**
- Serially record **cardiorenal MRI** imaging at 0, 1 and 3 years and non-invasive **retinal angiography** (OCT)
- **Patient segment, target identify, and target validate**
- (Full recruitment expected by early 2021)

NURTURE
National Unified Renal Translational Research Enterprise

Prospective long-term UK-based study of 3000 'all-cause' CKD patients aiming to:

- Elucidate risk factors for **progression** and **outcomes**
- Identify **stratification** biomarkers (blood, urine and tissue)
- Link to NHS GP/hospital **EMRs** and **UK Renal Registry**
- Exploit genetically rich **steroid resistant nephrotic syndrome** (SRNS) patient subset (ca. 1100)
- **Patient segment, target identify, and target validate**
- (Full recruitment expected by late 2019)

Precision profiling (stratification): use of retinal imaging

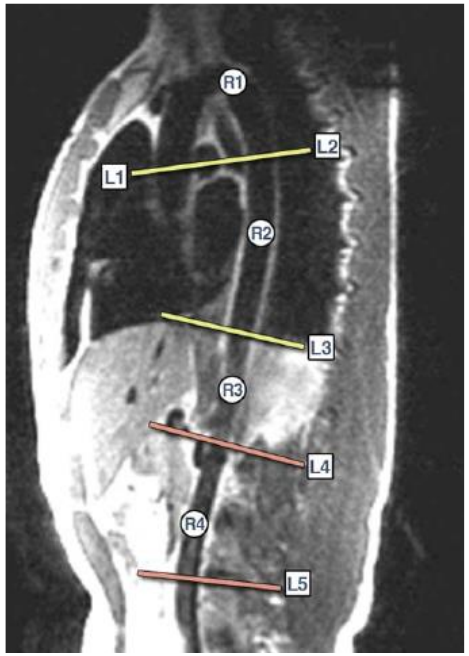


CVD is a significant co-morbidity with eGFR <60 ml/min ('Stage 3')

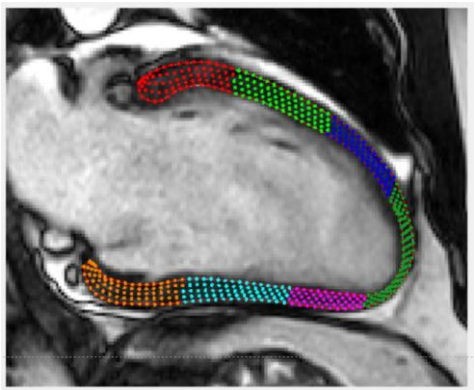
(Farah et al, *Nat Rev Cardiol* 2019)

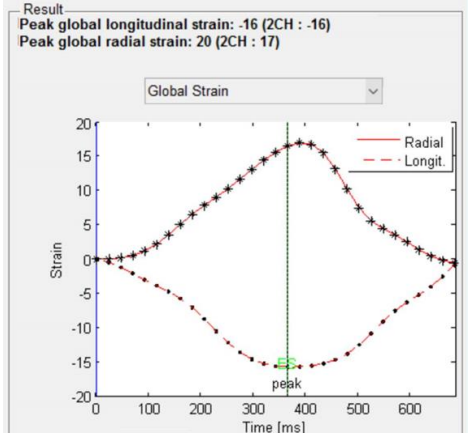
Potential for a ’game change’ in CKD clinical trial design: cardio-renal (multi-morbidity) integration?

Aortic stiffness
(Pulse wave velocity)

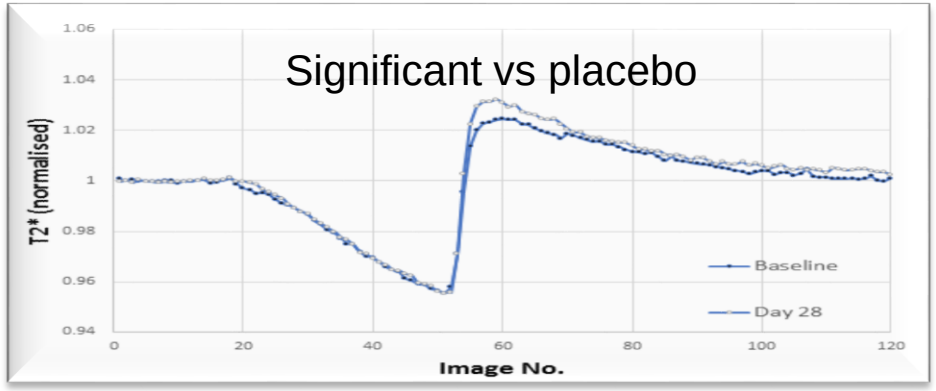


Diastolic dysfunction
(EDV, Strain)





Microvascular function
Oxygenation: reactive hyperemia



(With thanks to Paul Hockings)

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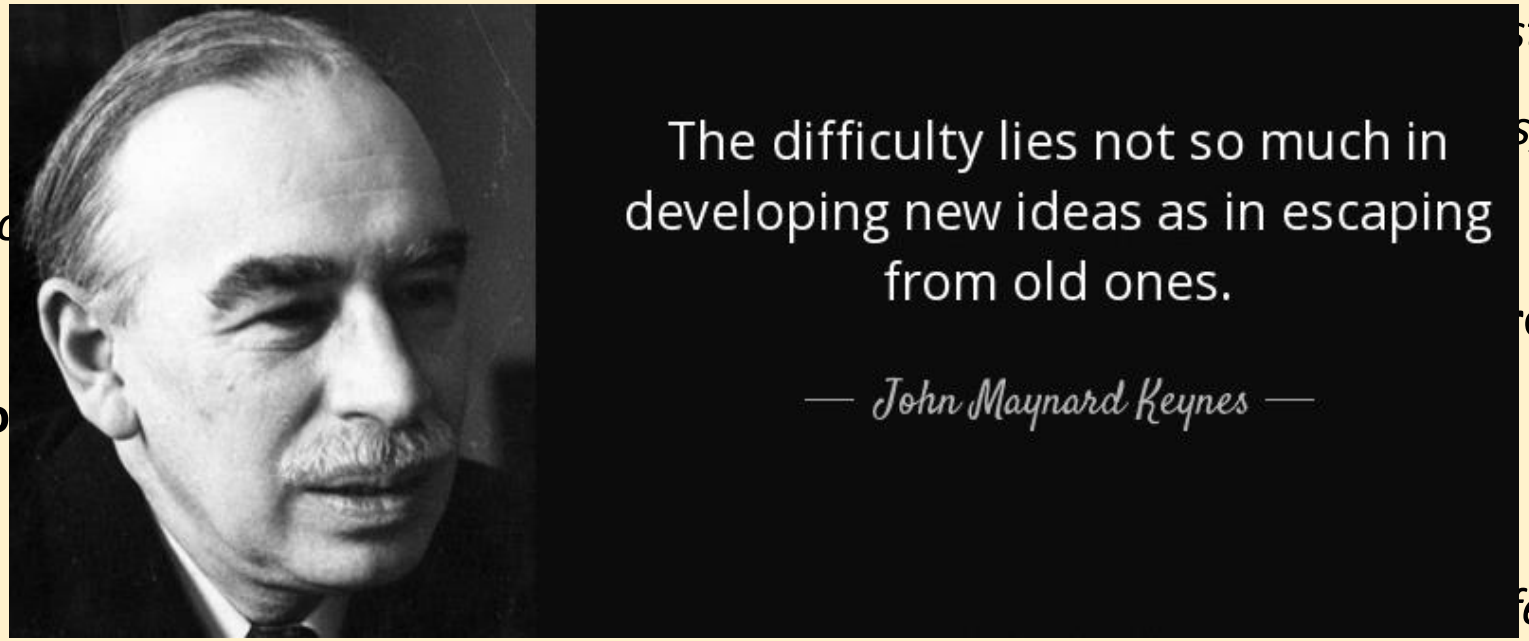
Some (of my) questions for inclusion of MRI in future CKD intervention clinical trials

Apart from needing standardized protocols across machines and agreed observer-independent analytical methods:

- **Which MRI** *staging)***?**
- **Which MRI** *s,*
  inflammatic
- **Which MRI** **renal function**
  and likely o
- **Which MRI**
- **Which MRI** *fety)***?**
- **(Cost, convenience, time taken, and opportunity for re-analysis?)**



Phase 2 → **Phase 3**

Over to you!