EPIDEMIOLOGICAL INSIGHTS

(OR, WHY DOES CKD CAUSE HEART FAILURE?)

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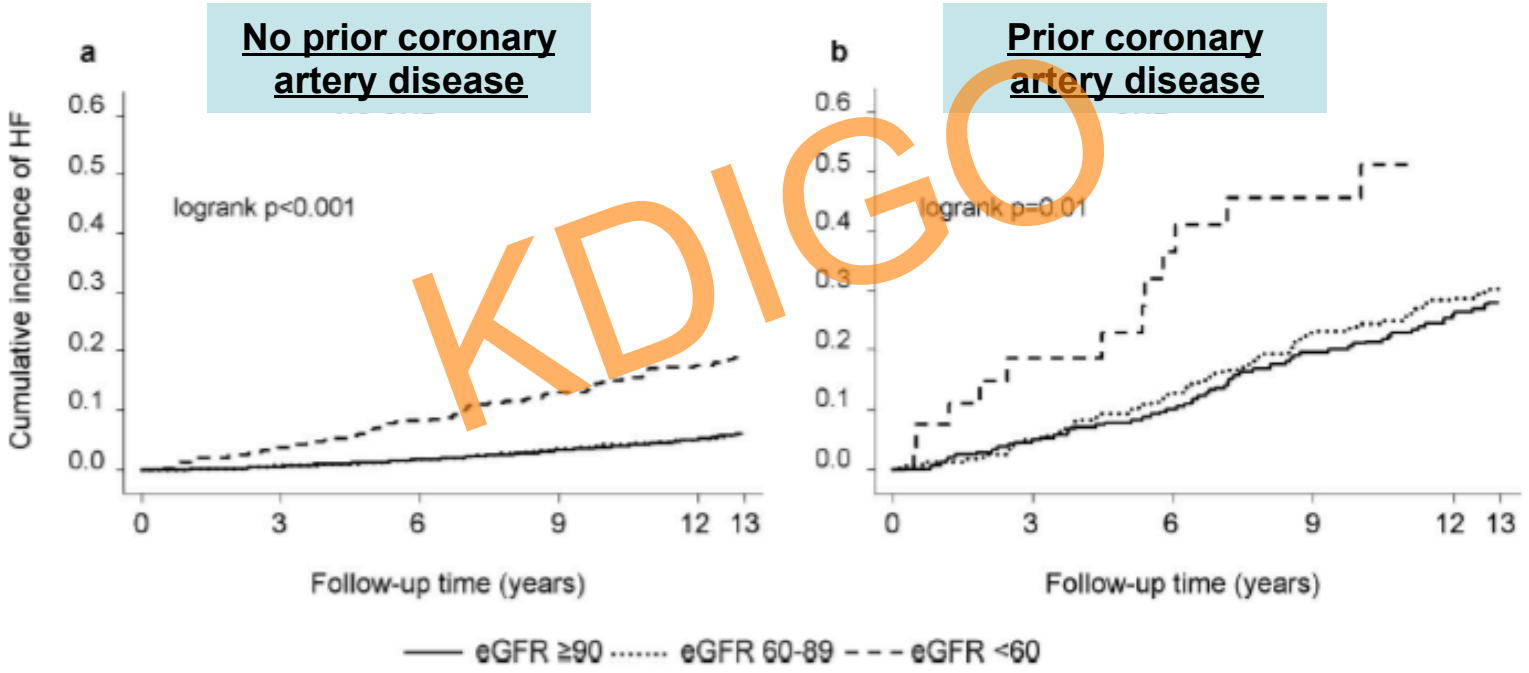
Disclosure of interests

Unrestricted grant provided by Novartis to the University of Oxford (study sponsor) to conduct the UK-HARP-3 trial of sacubitril/valsartan vs irbesartan in patients with CKD (Co-PI)

Presentation overview

- Epidemiological evidence that CKD is associated with an increased risk of heart failure (and vice versa)
- Potential problems in interpreting the evidence for risk factors for heart failure in CKD
- Suggested framework for conceptualising risk factors for heart failure in the context of CKD
- Contribution from intrinsic risk factors (defined as those that arise as a direct consequence of CKD)
- Contribution from extrinsic risk factors (defined as causal risk factors that are not a direct result of CKD)
- Implications for prevention of heart failure in CKD

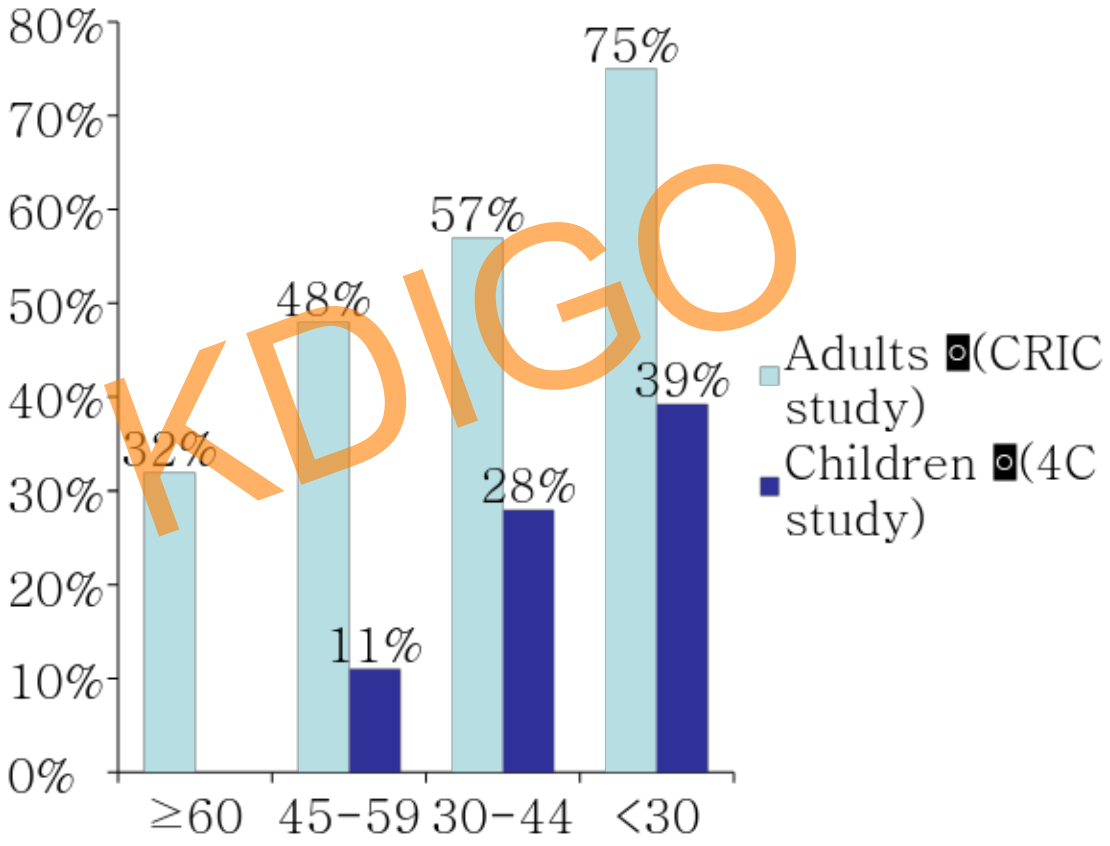
Cumulative incidence of heart failure by eGFR in 14,800 ARIC study participants[1]



[1]Kottgen *et al.* JASN 2007; 18:1307-15

Echocardiographic findings from 700 children[1] and 3500 adults[2] with CKD

Prevalence of LV hypertrophy

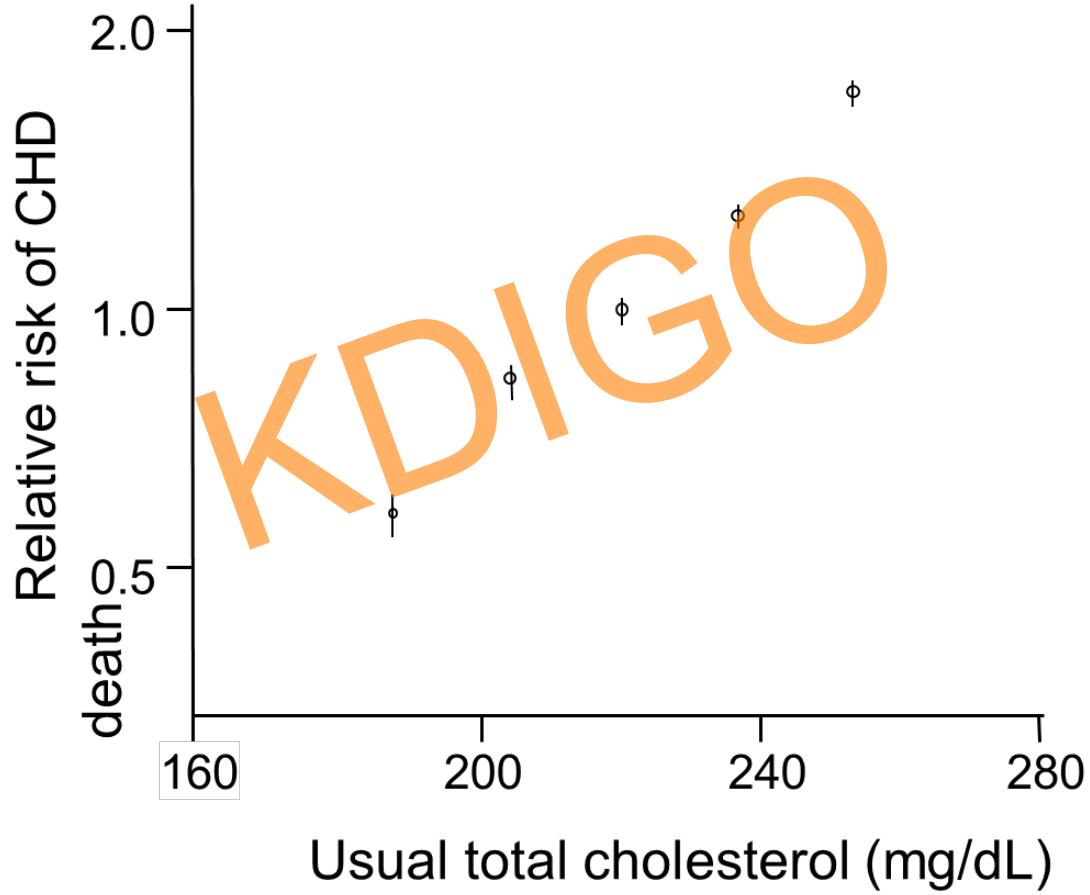


[1]Schaefer *et al.* CJASN 2017; 12:19-28
[2]Park *et al.* JASN 2012; 23:1725-34

Problems in interpreting observational studies among patients with CKD

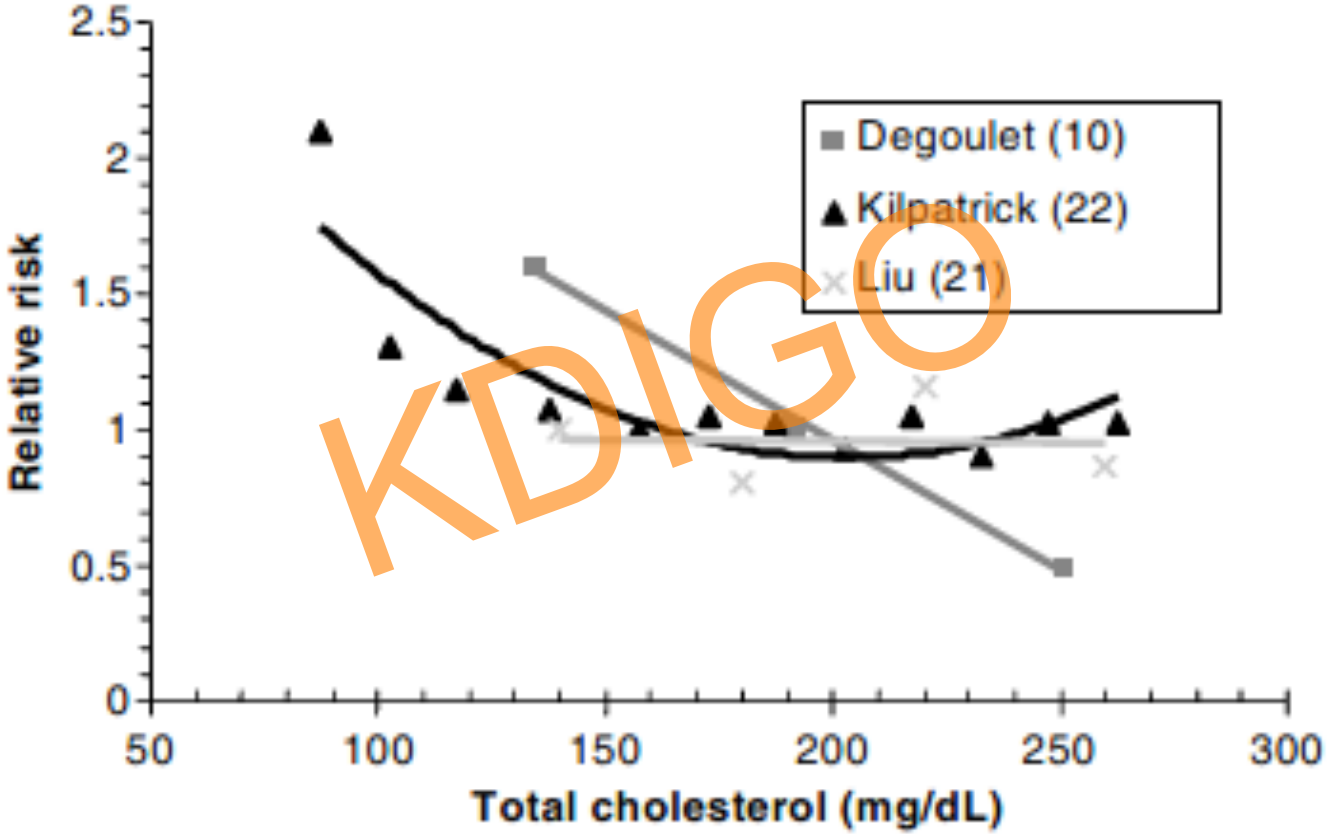
- Kidney disease may distort associations between exposures and CV outcomes
  - Example: LDL cholesterol and CHD
- CVD is highly prevalent, but (a) may be subclinical, and (b) atherosclerotic and structural heart disease co-exist, complicating interpretation
  - Example: BP and vascular events
- Conclusion: assessment of causation by risk factors for heart failure in CKD should be informed by:
  - evidence in those without CKD (in whom reverse causality is less problematic)
  - separate consideration of atherosclerotic and non-atherosclerotic disease
  - Studies in which confounding can be minimised eg, RCTs and Mendelian Randomization studies

Association between cholesterol and risk of CHD in 350,000 healthy men[1]



Stamler et al. *JAMA* 1986; 256: 2823-8

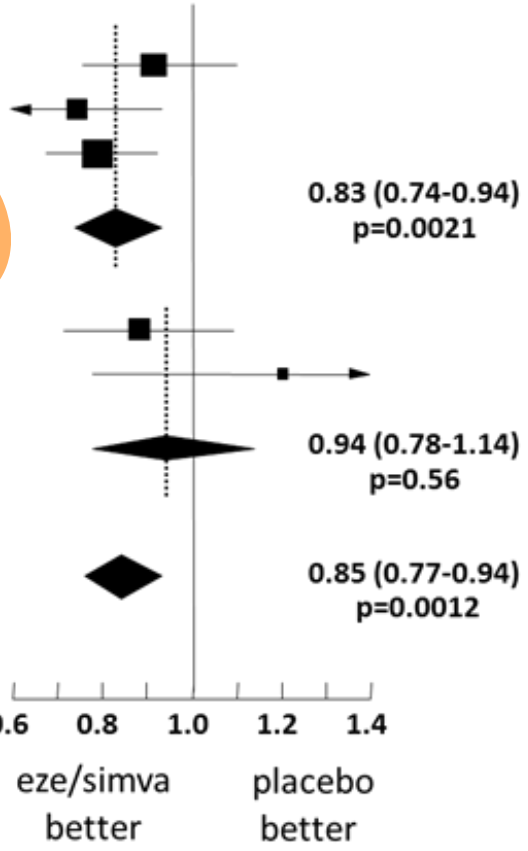
Inverse association between cholesterol and RR for CV mortality in dialysis patients[1]



[1]Baigent et al. Seminars in Dialysis 2007; 20:498-503

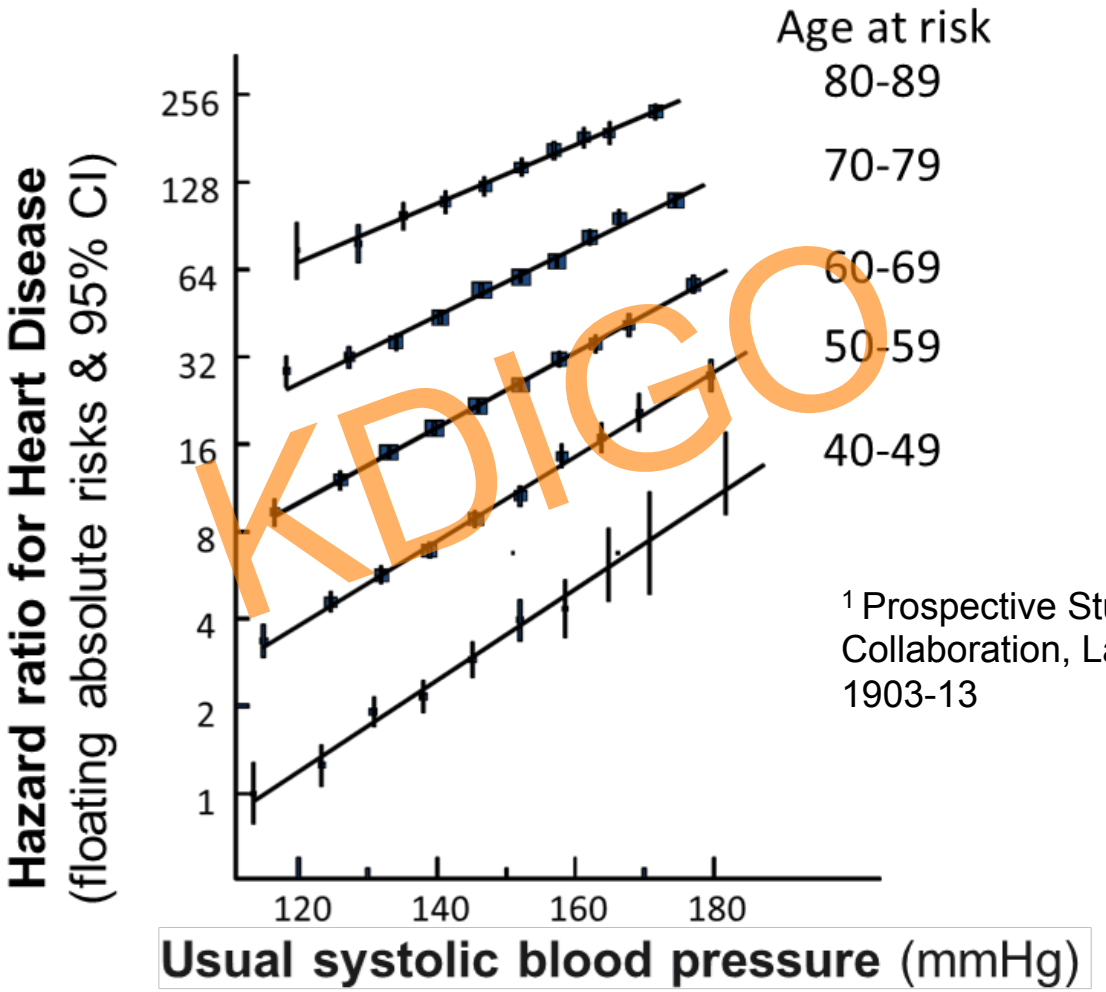
SHARP: reducing LDL cholesterol prevents major vascular events in CKD[1]

Event	eze/simva (n=4650)		placebo (n=4620)		Risk ratio & 95% CI
Major coronary event	213	(4.6%)	230	(5.0%)	
Non-hemorrhagic stroke	131	(2.8%)	174	(3.8%)	
Any revascularization procedure	284	(6.1%)	352	(7.6%)	
Major Atherosclerotic Event	**526**	**(11.3%)**	**619**	**(13.4%)**	**0.83 (0.74-0.94) p=0.0021**
Other cardiac death	162	(3.5%)	182	(3.9%)	
Hemorrhagic stroke	45	(1.0%)	37	(0.8%)	
Other Major Vascular Events	**207**	**(4.5%)**	**218**	**(4.7%)**	**0.94 (0.78-1.14) p=0.56**
Major Vascular Event	**701**	**(15.1%)**	**814**	**(17.6%)**	**0.85 (0.77-0.94) p=0.0012**



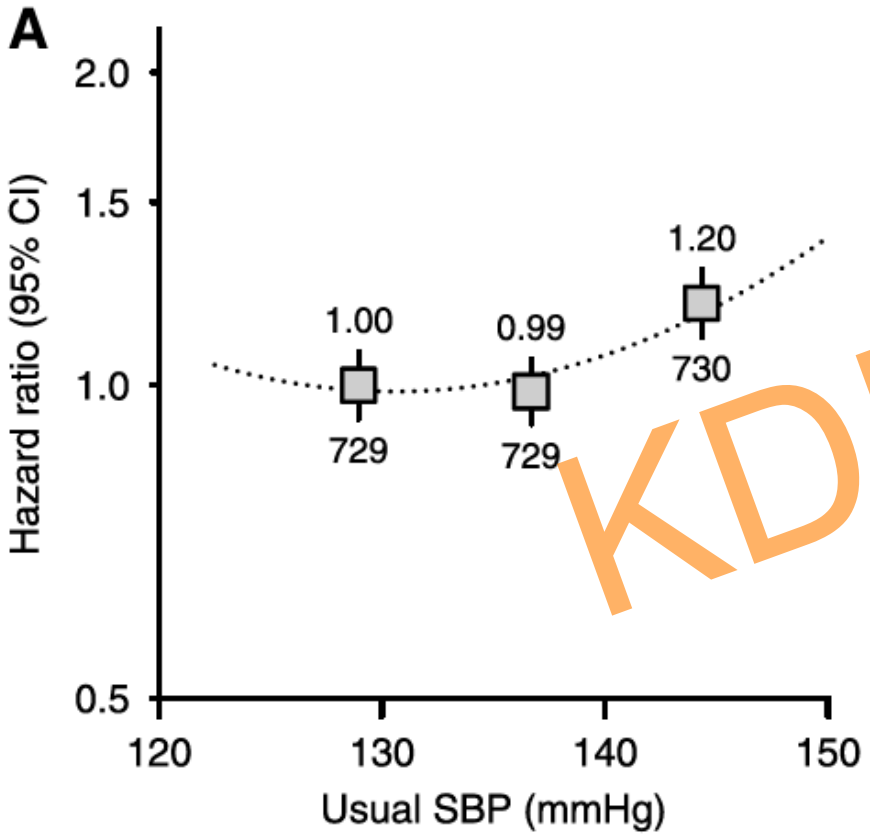
[1] Baigent C et al, for SHARP investigators. Lancet 2011; 377: 2181-92

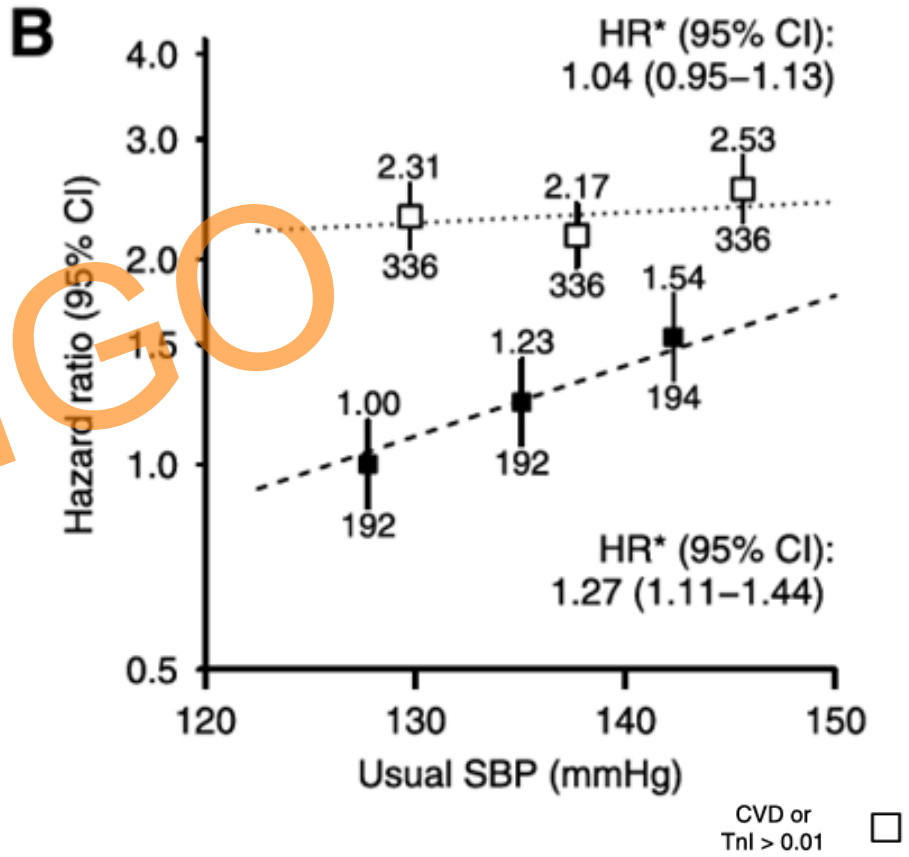
Meta-analysis of 1 m healthy adults in 61 prospective studies: association of SBP with CHD[1]



[1] Prospective Studies Collaboration, Lancet 2002; 360: 1903-13

SHARP trial: association between systolic BP and MAJOR VASCULAR EVENTS (A) overall and (B) subdivided by evidence of prior CVD[1]





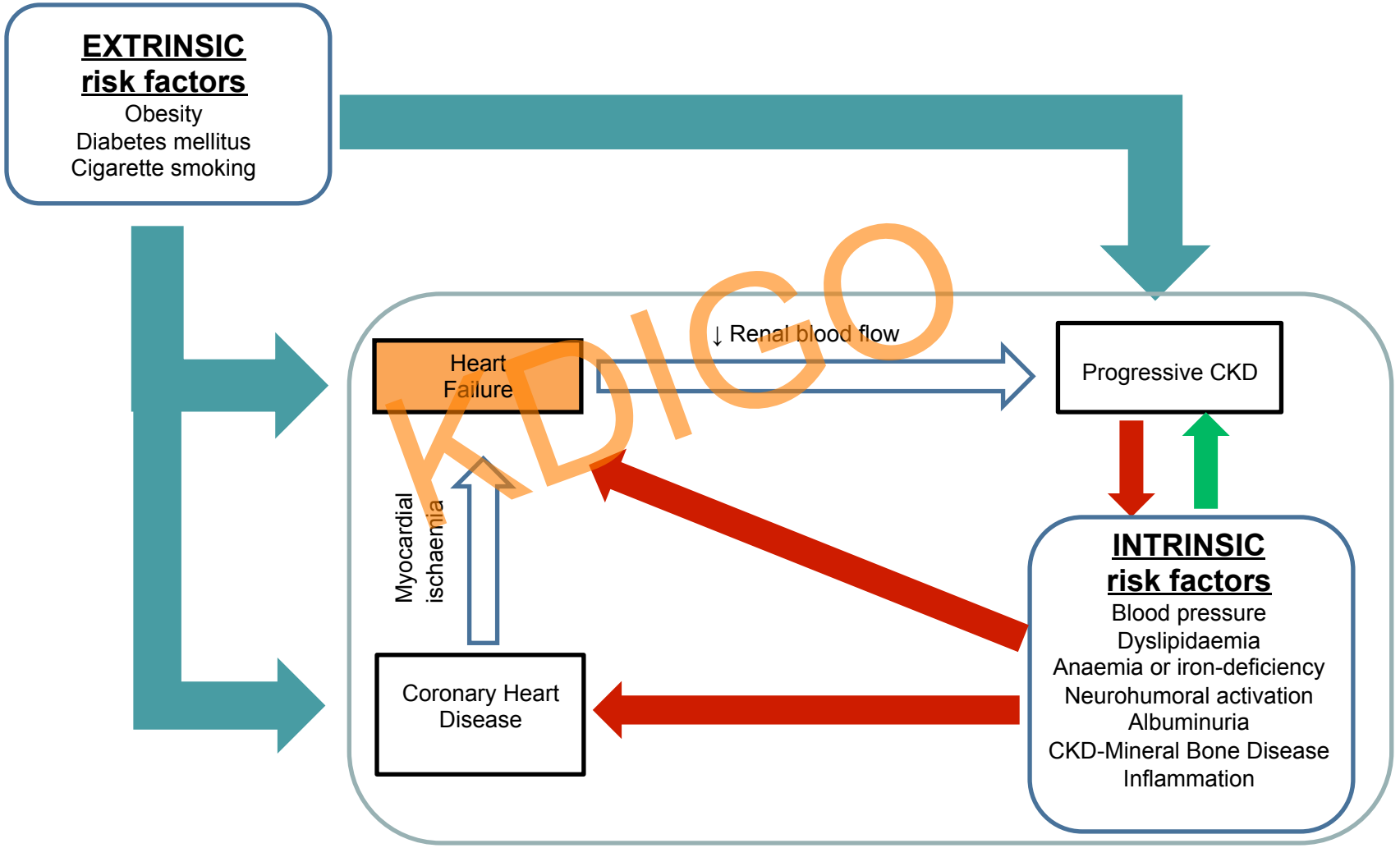
[1] Herrington *et al.* Hypertension 2017; 69 (in press)

Definitions

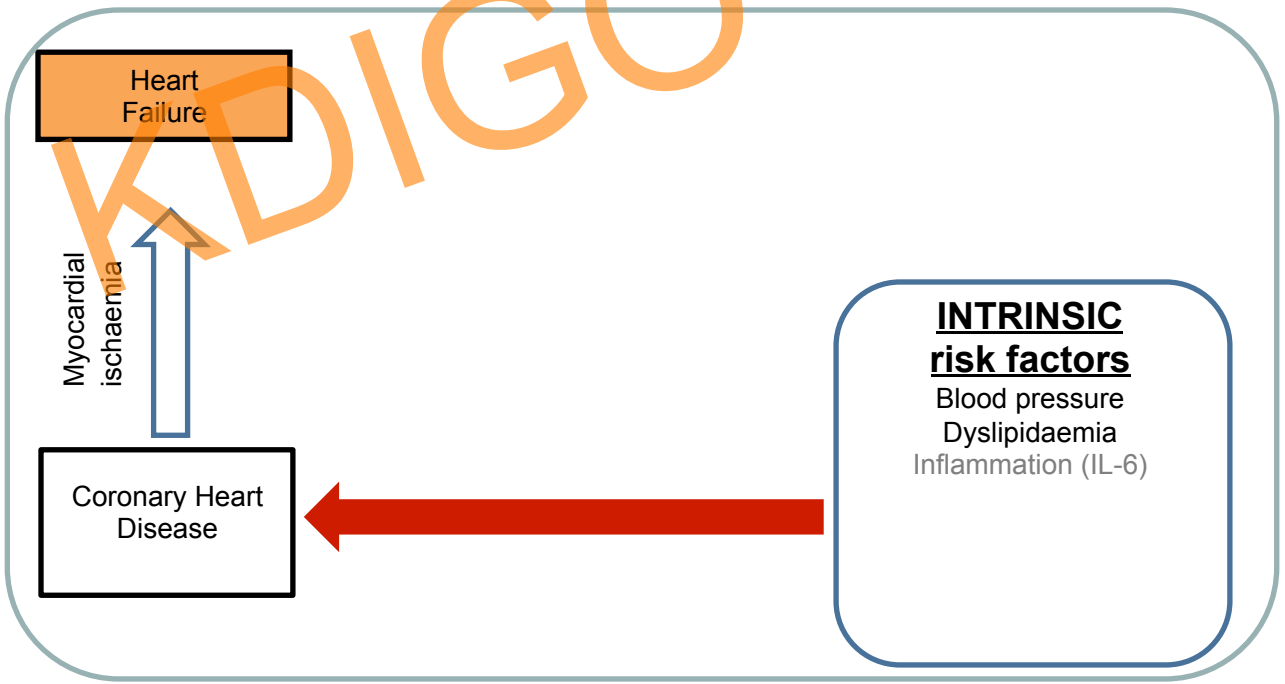
- **Intrinsic risk factors**: exposures that arise as a direct consequence of CKD

- **Extrinsic risk factors**: known causes of heart failure that are NOT a direct consequence of CKD

Suggested framework for the causation of heart failure in patients with CKD



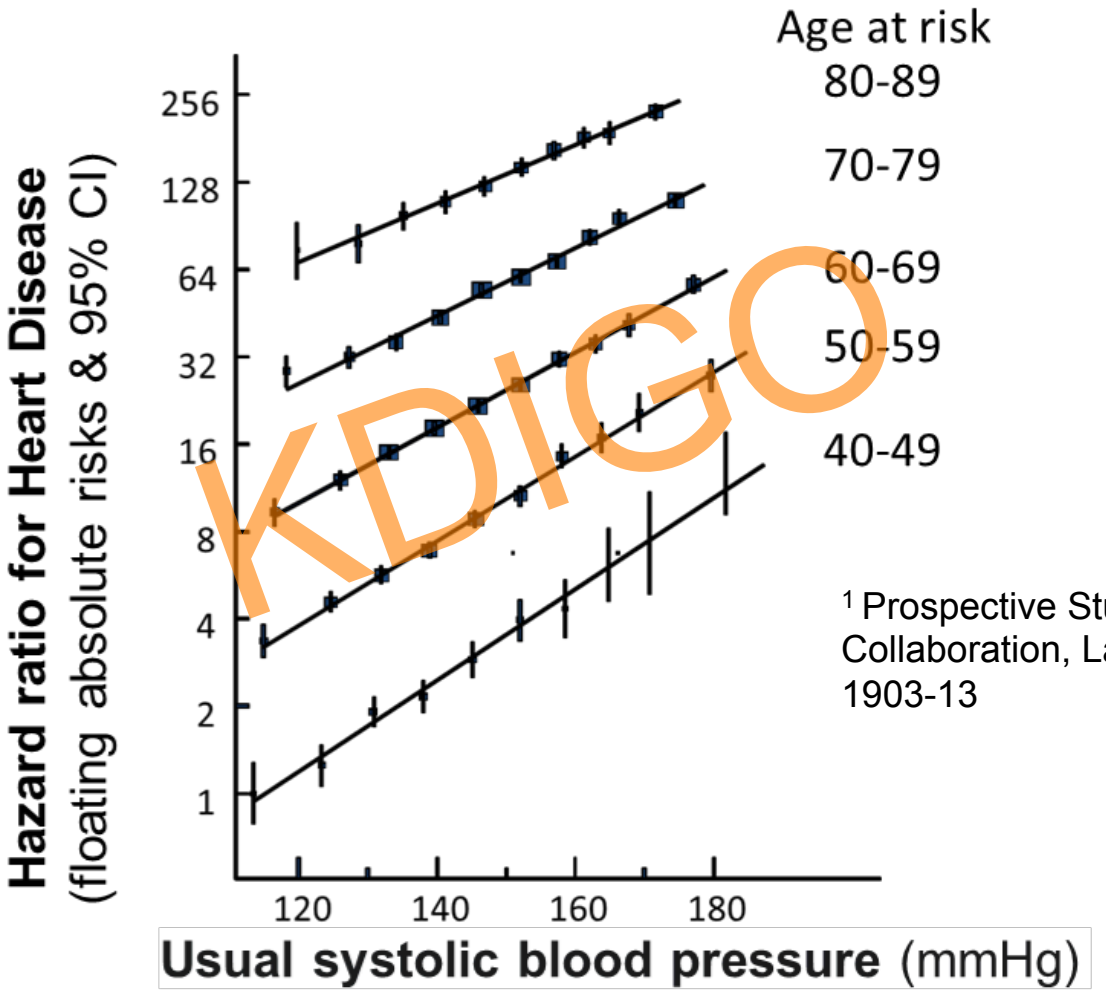
INTRINSIC RISK FACTORS: Heart failure mediated through myocardial ischaemia



INTRINSIC RISK FACTORS and the risk of coronary heart disease (CHD)

- Blood pressure
- Dyslipidaemia
  - LDL cholesterol
  - Triglycerides
  - Lp(a)
- Inflammation

Meta-analysis of 1 m healthy adults in 61 prospective studies: association of SBP with CHD[1]



[1] Prospective Studies Collaboration, Lancet 2002; 360: 1903-13

Genetic risk scores and selected CV outcomes[1]

Phenotype	Consortium	Total N or Cases/ controls	SBP		DBP	
			Effect/ mmHg	P	Effect/ 1mmHg	P
Heart						
CHD	CARDIoGRAM plus4D	63,746/130,681	1.042	$\mathbf{10^{-44}}$	1.069	$\mathbf{10^{-38}}$
Heart failure	CHARGE	2,526/18,400	1.021	0.03	1.035	0.02
LV wall thickness (cm)	CHARGE	11,311	0.004	$\mathbf{10^{-8}}$	0.007	$\mathbf{10^{-8}}$

[1] Ehret et al. Nature Genetics 2016; 48: 1171-84

Genetic risk scores for lipids and CHD

Allele score	CHD (incident/prevalent) Odds ratio (95% CI)	CHD (incident/prevalent) P-value	CHD (incident only) Odds ratio (95% CI)	CHD (incident only) P-value
HDL cholesterol				
Unrestricted (48 SNPs)	0.53 (0.40-0.70)	8.8×10^{-6}	0.68 (0.47-0.97)	0.032
Restricted (19 SNPs)	0.91 (0.42-1.98)	0.817	1.33 (0.49-3.59)	0.579
Log Triglycerides				
Unrestricted (67 SNPs)	1.62 (1.24-2.11)	3.7×10^{-4}	1.59 (1.15-2.20)	5.1×10^{-3}
Restricted (27 SNPs)	1.61 (1.00-2.59)	0.05	1.63 (0.91-2.91)	0.098
LDL cholesterol				
Unrestricted (42 SNPs)	1.78 (1.58-2.01)	2.0×10^{-21}	1.43 (1.24-1.66)	9.7×10^{-7}
Restricted (19 SNPs)	1.92 (1.68-2.19)	4.6×10^{-22}	1.49 (1.26-1.75)	1.6×10^{-6}

[1] Holmes M et al. Eur Heart J 2015; 36: 539-550

Characteristic serum lipid distribution at different stages of CKD[1]

	LDL-C	sdLDL	TRG	HDL-C	Lp(a)
Predialysis CKD (Stages 3-4)	↔ OR ↓	↑	↑	↓	↑*
Nephrotic syndrome (Stages 3-4)	↑	↑	↔ OR ↑ ↓	OR ↔ OR ↑	↑
Hemodialysis (Stage 5)	↔ OR ↓	↑	↑	↓	↑
Peritoneal dialysis (Stage 5)	↑	↑	↑	↓	↑
Renal transplantation (Stage 5)	↑	↑	↑	↑	↓*

* Mainly in individuals with high-molecular-weight apolipoprotein(a) phenotypes.

Tsimihodimos V et al. *Am J Nephrol*. 2008;28(6):958 973.

Mendelian Randomization: potential role for Lp(a)[1]

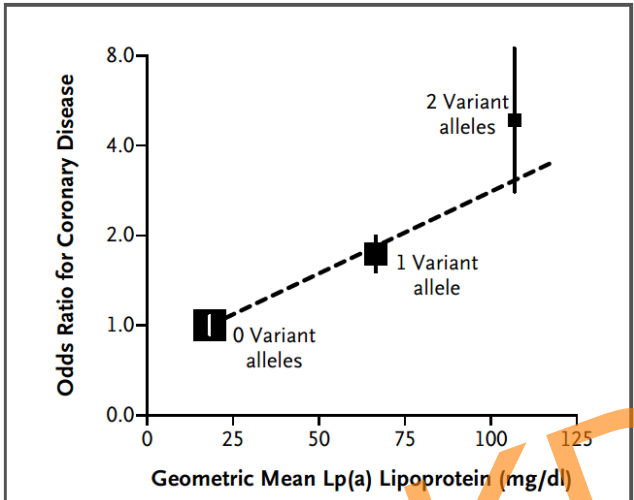


Figure 3. Association of the *LPA* Genotype Score with the Lp(a) Lipoprotein Level and the Risk of Coronary Disease in the PROCARDIS Cohort.

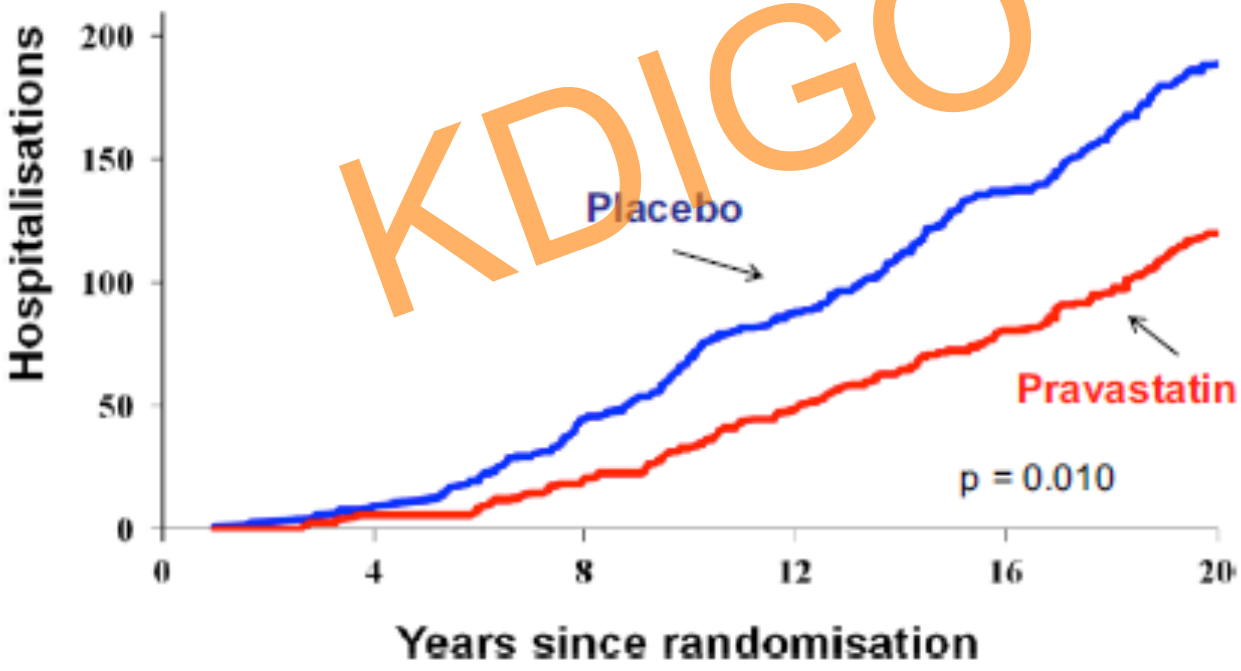
The odds ratios (squares, with the size inversely proportional to the sampling variation) are for the association of the *LPA* genotype score (no variant alleles, one variant allele, or two variant alleles) with the risk of coronary disease, as measured with the use of "floating absolute risks" which summarize the sampling variation for the three genotype scores without the selection of an arbitrary baseline genotype score. The vertical lines indicate 95% confidence intervals.

- MR studies show that Lp(a) is a cause of CHD[1]
- BUT, risk of increased Lp(a) in general population is for low-molecular weight isoforms of Lp(a), whilst in CKD it is high-molecular weight isoforms that are increased

[1] Clarke et al, for the PROCARDIS investigators. NEJM 2009; 361: 2518-28

Long term follow up of the WOSCOPS trial: lowering LDL cholesterol prevents heart failure

20 year follow-up of WOSCOPS – pravastatin 40mg versus placebo reduced hospitalisation for heart failure by **35%**



207 admissions in 123 subjects

133 admissions in 91 subjects

Ford *et al.* Circulation 2016; 133:1073-80

Markers of inflammation: IL6R is implicated in the causation of CHD

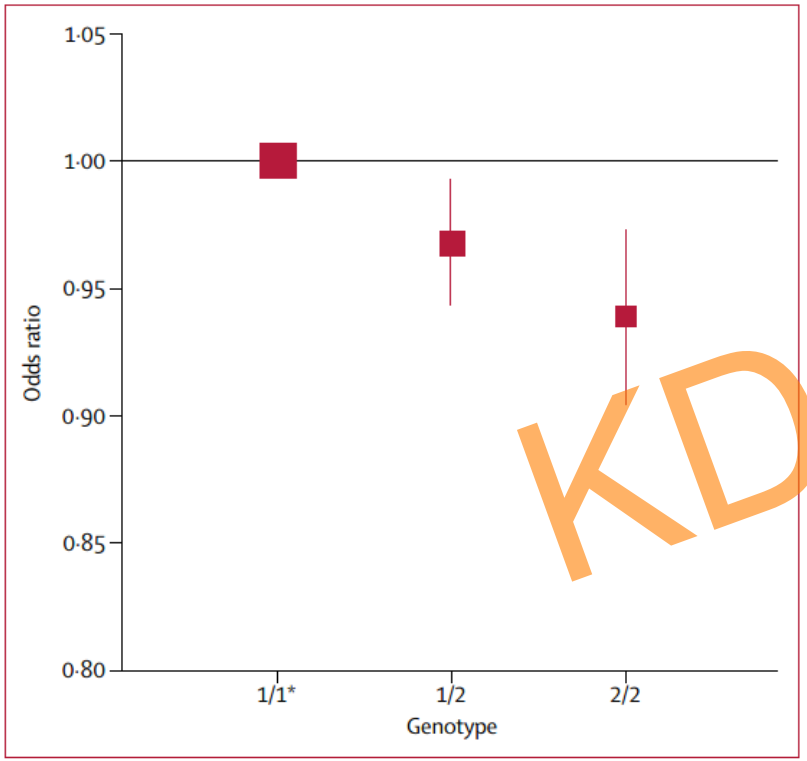
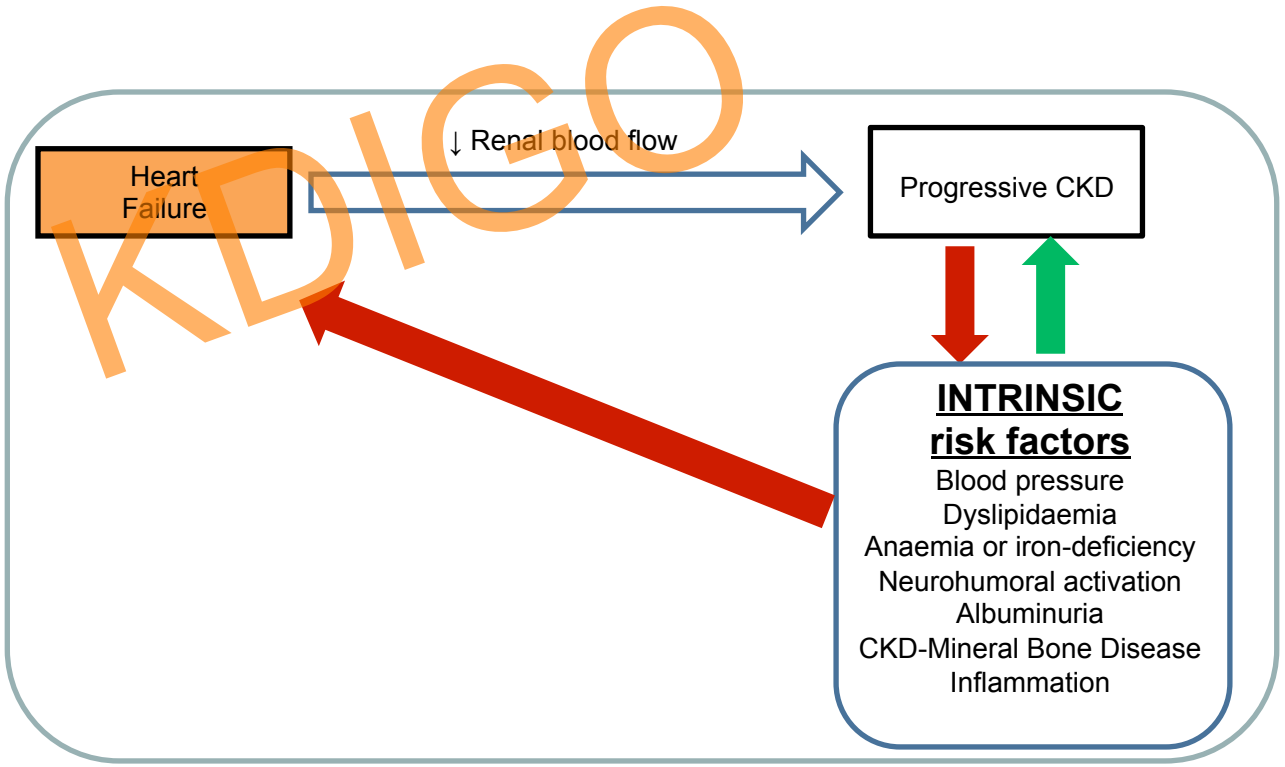


***Figure 2: IL6R* genotypes and risk of coronary heart disease**
Data are shown for 51 441 cases and 136 226 controls. The odds ratio per minor allele was 0·966 (95% CI 0·950–0·982, $p=4{\cdot}5\times10^{-5}$). Details of the genotypes studied are provided in appendix p 12. Error bars show 95% CI. *Reference group (represented by a square with in arbitrary fixed size).

Among markers of inflammation (CRP, fibrinogen, IL-6, soluble IL6R), genetic risk score experiment shows that the IL6R pathway is involved in causation of CHD[1]

[1] IL6R Genetics Consortium Emerging Risk Factors Collaboration. Lancet 2012; 379: 1205-13

Suggested framework for the causation of heart failure in patients with CKD

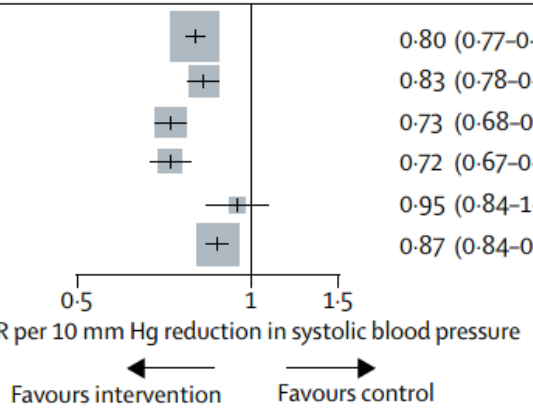


Evidence that raised blood pressure is a cause of heart failure[1,2]

(a) Observational study (CALIBER)[1]

(a) Meta-analysis of randomized trials[2]

	Studies	Intervention		Control		RR (95% CI) per 10 mm Hg reduction in systolic blood pressure
		Events	Participants	Events	Participants	
Major cardiovascular events	55	13209	137319	14068	128259	0·80 (0·77–0·83)
Coronary heart disease	56	4862	136986	5301	128548	0·83 (0·78–0·88)
Stroke	54	4635	136682	5378	128641	0·73 (0·68–0·77)
Heart failure	43	3284	115411	3760	107440	0·72 (0·67–0·78)
Renal failure	16	890	39888	834	39043	0·95 (0·84–1·07)
All-cause mortality	57	9775	138298	9998	129700	0·87 (0·84–0·91)



[1]Rapsomaniki et al. Lancet 2014; 383: 1899-911
[2]Ettehad et al., Lancet 2016; 387: 957-67

Genetic risk scores and selected CV outcomes[1]

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			Effect/ mmHg	P	Effect/ 1mmHg	P
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[1] Ehret et al. Nature Genetics 2016; 48: 1171-84

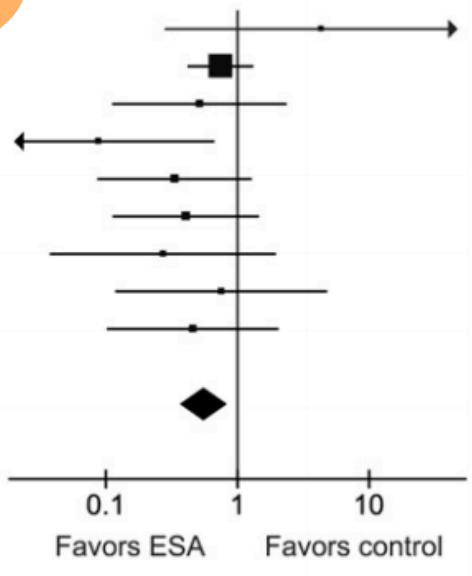
Evidence that anaemia is a cause of heart failure[1]

Meta-analysis of ESA trials show reduced hospitalization for heart failure

A: Heart Failure Hospitalizations

	ESA Events	ESA Total	Control Events	Control Total	Weight	Peto Odds Ratio [95% CI]
Cleland 2005	3	18	0	6	2.2%	4.31 [0.28, 66.37]
Ghali 2008	25	162	31	157	50.5%	0.74 [0.42, 1.32]
Kourea 2008	3	21	5	20	7.2%	0.51 [0.11, 2.36]
Mancini 2003	1	15	4	8	4.1%	0.09 [0.01, 0.67]
Palazzuoli 2006	4	20	8	18	9.2%	0.33 [0.09, 1.28]
Palazzuoli 2007	4	26	8	25	10.2%	0.40 [0.11, 1.46]
Parissis 2008	2	21	3	11	4.3%	0.27 [0.04, 1.96]
Ponikowski 2007	2	19	3	22	4.9%	0.75 [0.12, 4.80]
van Veldhuisen 2007	4	110	4	55	7.4%	0.46 [0.10, 2.05]
Total: ESA (48/412) versus control (66/322)						**0.56 [0.37, 0.84]**

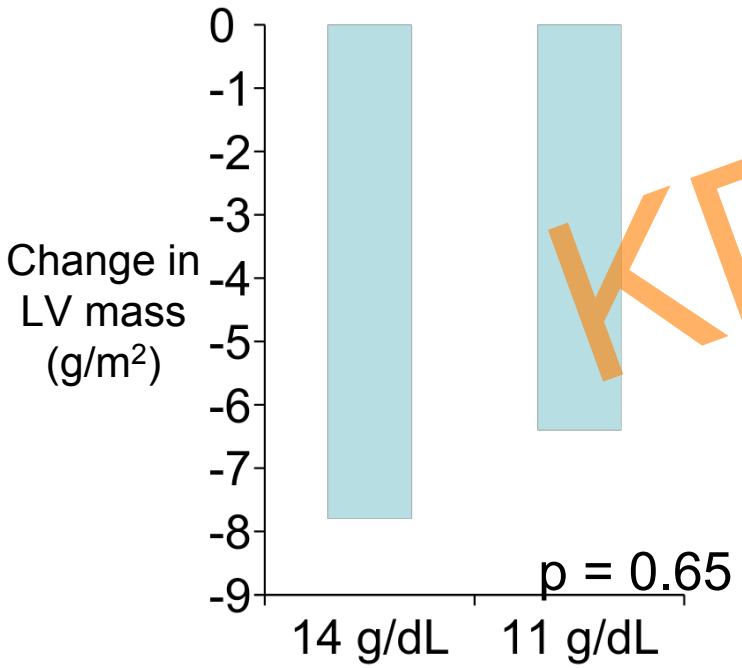
Heterogeneity: Chi² = 7.78, df = 8 (*P* = .46); I² = 0%
Test for overall effect: Z = 2.80 (*P* = .005)



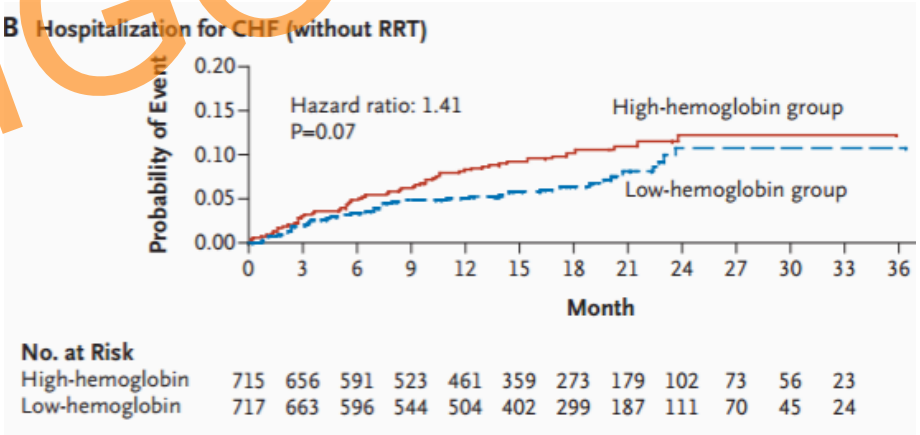
[1]Kotecha at al. Am Heart J 2011; 161: 822-831e2

Lack of evidence that increasing haemoglobin reduce LV mass[1] or risk of heart failure hospitalisation[2] in CKD

CREATE: No effect of higher Hb target on LV mass



CHOIR: stopped early for harm in higher Hb target group (13.5 g/dL vs 11.5 g/dL)

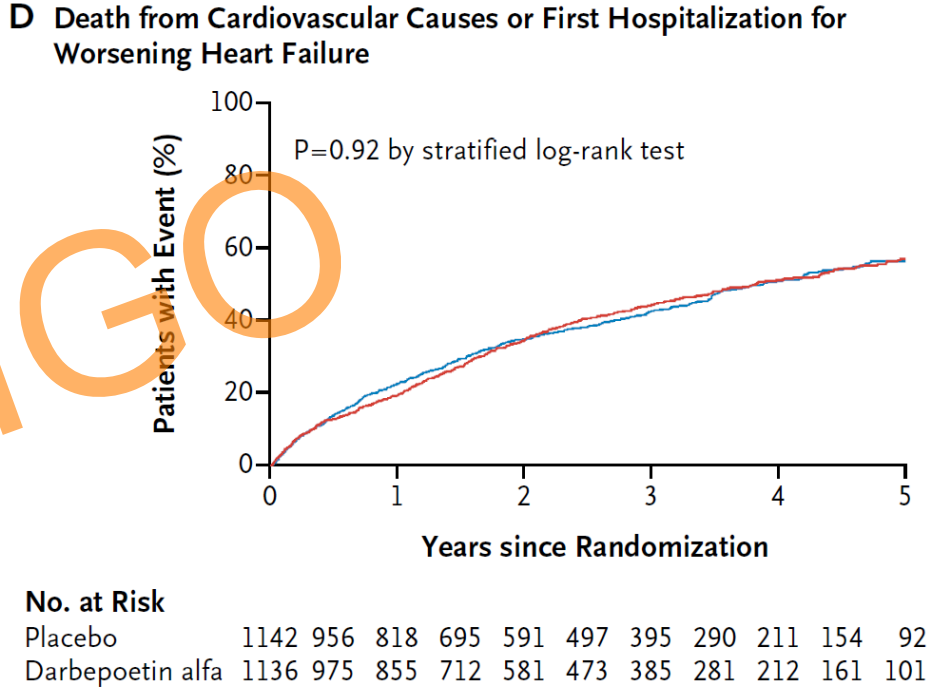


[1]CREATE investigators NEJM 2006; 355: 2071-84

[2]CHOIR investigators NEJM 2006; 355: 2085-98

RED-HF: No effect of darbepoietin alfa on heart failure hospitalisation[1]

- RED-HF trial
- 2278 patients with systolic heart failure (HFrEF)
- Darbepoietin alfa vs placebo
- Median Hb 13.0 vs 11.5 g/dL
- Mean f.u. 28 months



[1]Swedberg K et al. for the RED-HF group. NEJM 2013; 368: 1210-9

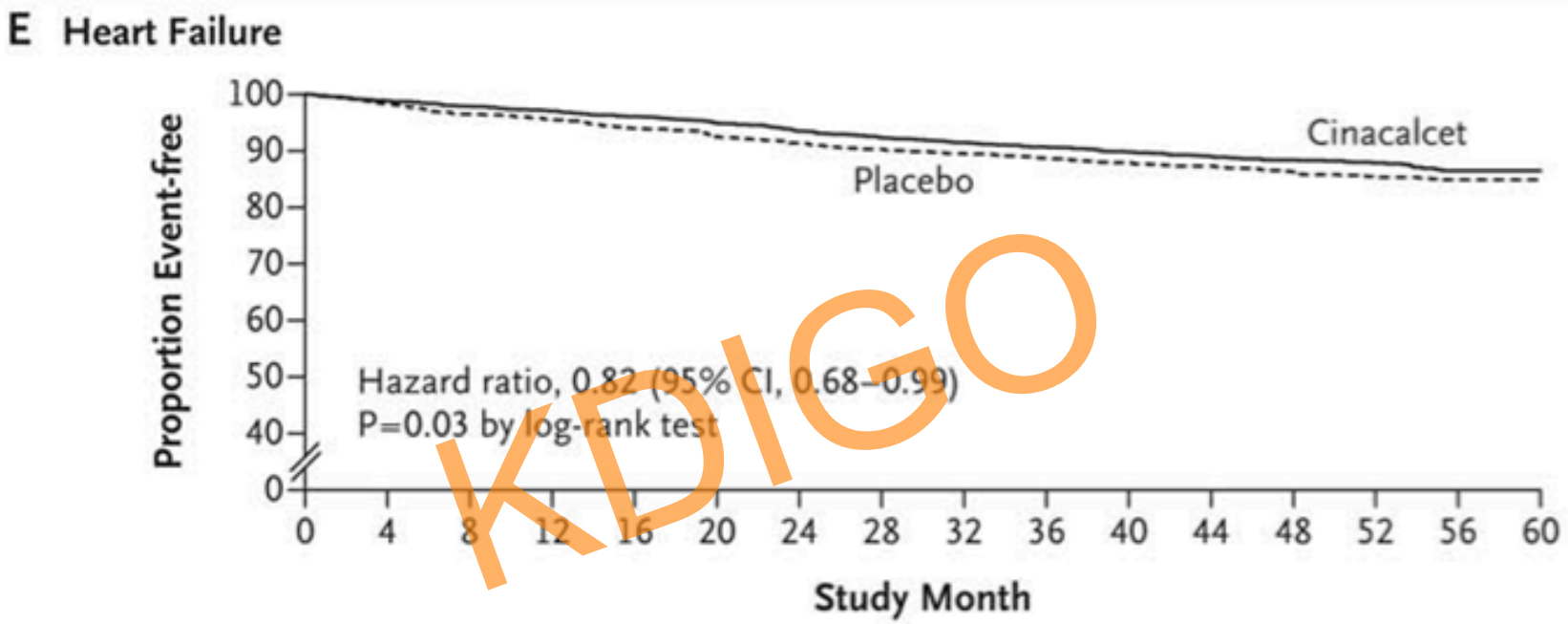
Associations between neurohumoral activation (sympathetic tone) and (a) CHD or (b) heart failure

- Heart rate (HR) independent risk factor for CV outcomes
- Inhibition of the I_f channel with ivabradine reduces HR (but not contractility)
- SHIFT trial (6558 patients with systolic HF), ivabradine reduced risk of heart failure hospitalisation (16% vs 21%; P<0.0001- right panel)[1]
- SIGNIFY trial (19,102 patients with stable CHD), ivabradine had no effect on risk of MI (4.1% vs 3.9%; P=0.43)

SHIFT trial: Hospitalisation for worsening heart failure

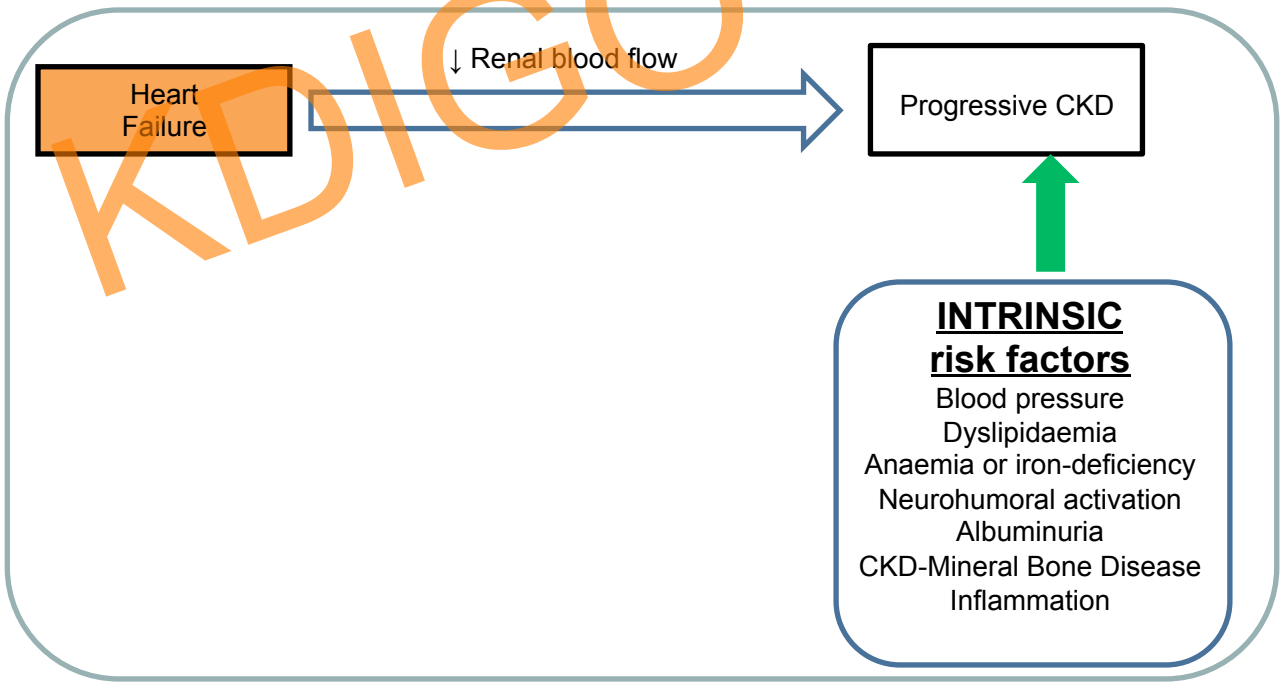
[1]Swedberg K et al. for SHIFT investigators. Lancet 2010; 376:875-85
[2]Fox K et al for the SIGNIFY investigators. NEJM 2014; 371: 1091-99

EVOLVE: effect of cinacalcet on risk of heart failure[1]



[1] The EVOLVE Trial Investigators* NEJM 2012; 367:2482-2494

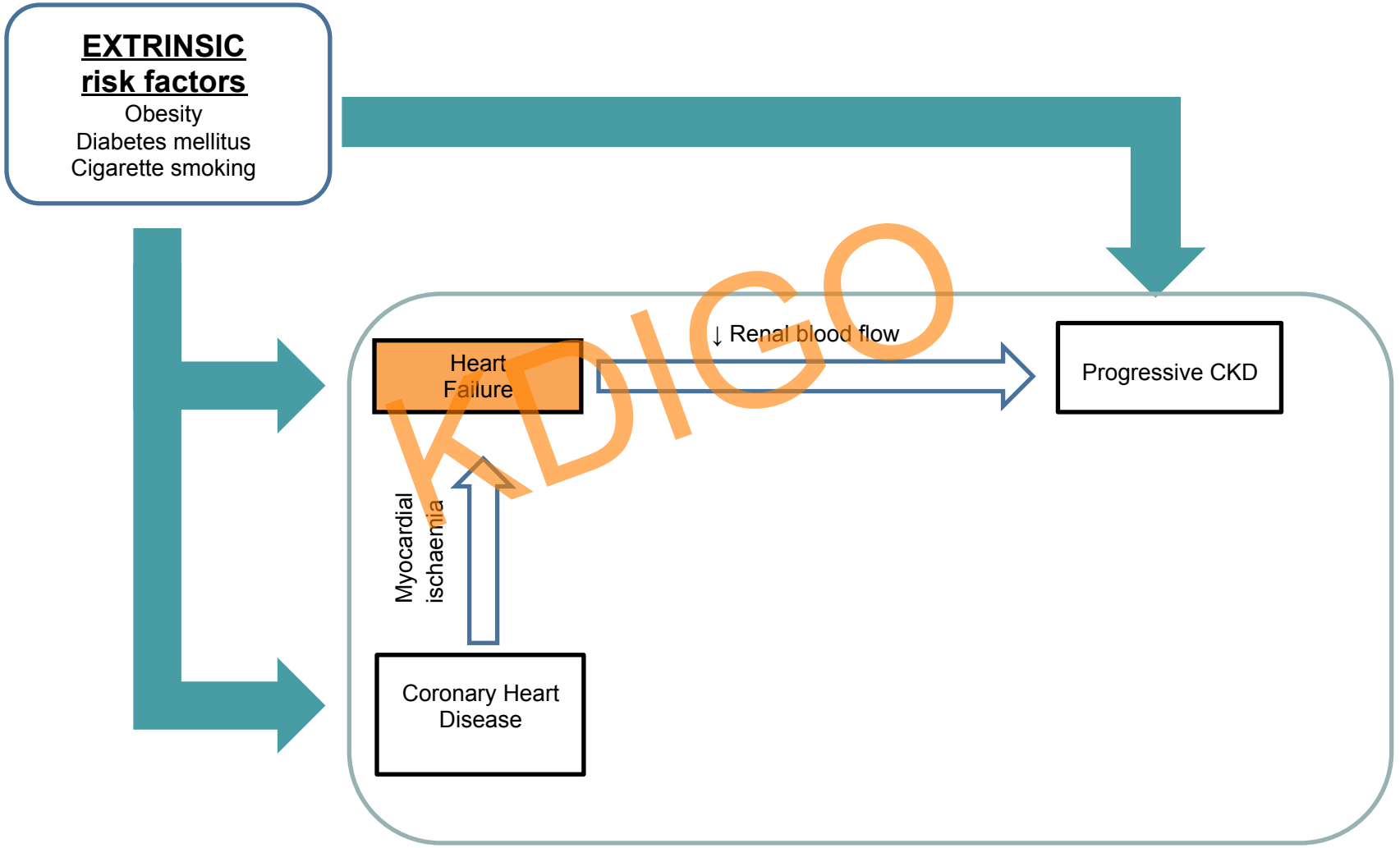
Suggested framework for the causation of heart failure in patients with CKD



INTRINSIC RISK FACTORS and risk of CKD progression (ie, loss of glomerular filtration)

- Blood pressure: ↑BP associated with ↑progression, BUT genetic risk scores (GRS) suggest causal association for ↑ uACR (not ↓ eGFR)
- Increased glomerular pressure/hyperfiltration: EMPA-REG demonstrated that empagliflozin↓progression, as have trials in which ↓uACR (+ ↓ BP) reduce progression
- Dyslipidaemia: No evidence that ↑LDL cholesterol ↑progression
- Neurohumoral activation: RAAS inhibition slows progression. Animal and human studies with moxonidine suggest ↑SNS activity a cause of glomerulosclerosis, but renal denervation trials inconclusive at best.
- Mineral bone disease: observational studies show that ↑ FGF23 independently predicts ↑ progression, but proof of causation lacking
- Inflammation: ↑CRP, IL6 associate with ↑progression, but proof of causation lacking

Suggested framework for the causation of heart failure in patients with CKD



EXTRINSIC RISK FACTORS and risk of (a) CHD (b) heart failure & (c) CKD progression

	CHD	Heart failure	CKD progression
Diabetes mellitus	RR = 2.0 (1.8-2.2)[1]	RR = 1.9 (1.5-2.3)[2] RR = 1.6 (1.4-1.7)[3]	Renal death RR = 3.0 (2.4-3.8)[4]
Higher body mass index	RR per 5 kg/m^2 = 1.4 (1.3-1.4)[5]	RR per 5 kg/m^2 = 1.9 (1.6-2.2)[5]	ESRD: RR* = 6.1 (5.0-7.5)[6] CKD stages 4-5: RR = 1.9 (1.9-2.0)[7]
Cigarette smoking	RR = 1.5 (1.3-1.8) for atherosclerotic events in CKD patients[8]	RR = 1.6 (1.4-1.8)[2]	RR ↑ in some observational studies[7]; no effect on progression (serial eGFRs) in SHARP[8]

* BMI 30-35 vs 18.5-25 kg/m^2

[1] ERFC Lancet 2010; 375: 2215-2222; [2] He et al. Arch Intern Med 2001; 161: 996-1002; [3] Shah AD et al. Lancet Diab Endo 2015; 3: 105-13; [4] Emerging Risk Factors Collaboration NEJM 2011; 364: 829-41; [5] Whitlock et al. Lancet 2009; 9669: 1083-1096; [6] Hsu et al. Ann Intern Med, AJKD 2006; 144(1): 21-8; [7] Herrington et al. PlosONE 2017; 12(3): e0173515; [8] Staplin et al. AJKD 2016; 68: 371-80

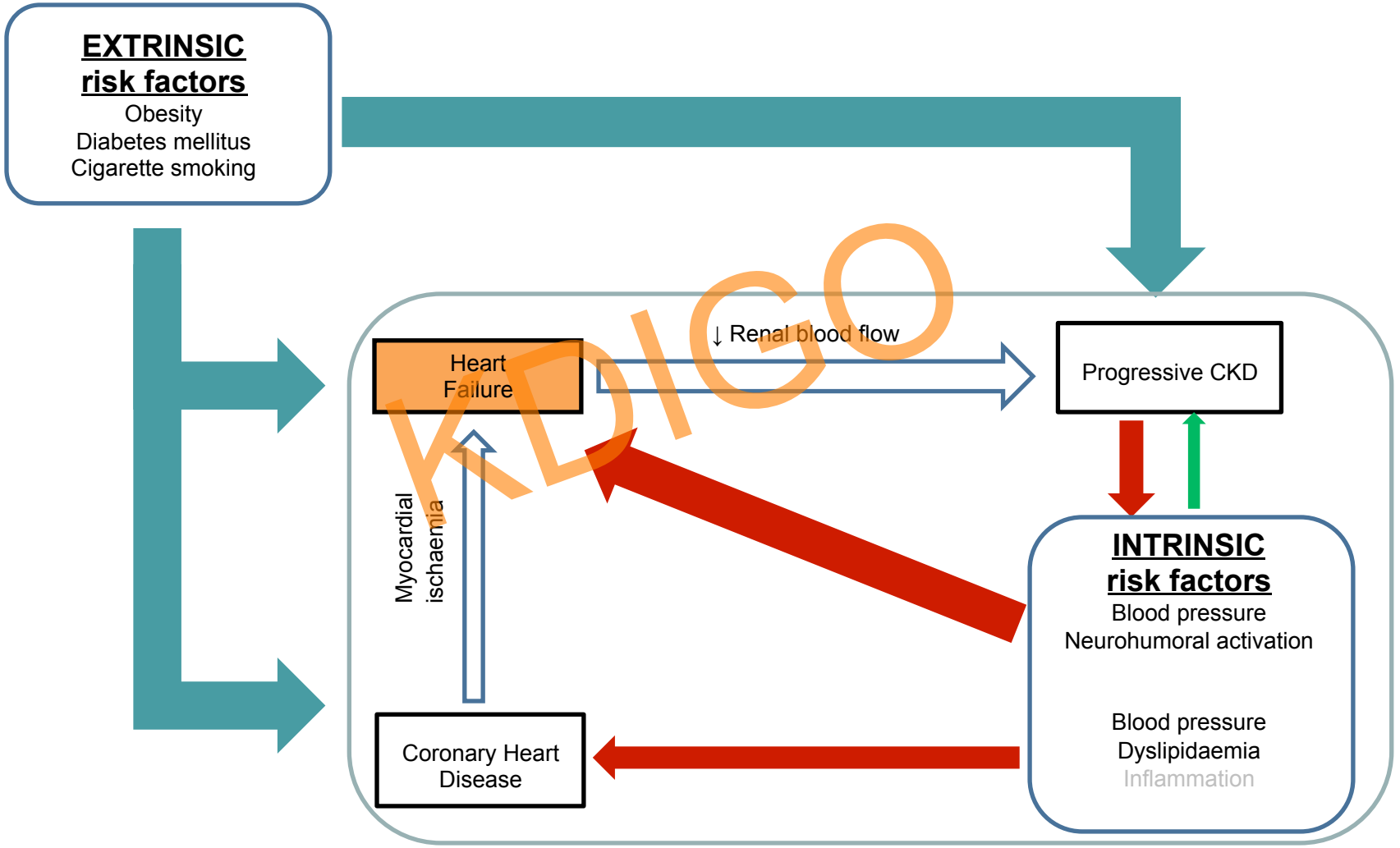
SUMMARY: aetiological relevance of INTRINSIC RISK FACTORS

	CHD	Heart failure	CKD progression
Blood pressure	+++	+++	+/-
Dyslipidaemia	+	+	-
Anaemia/ iron-deficiency	+/-	+/-	-
Neurohumoral activation	+/-	++	++
Albuminuria	+/-	+/-	+/-
Mineral Bone Disease	+/-	+/-	+/-
Inflammation	+	+/-	+/-

SUMMARY: aetiological relevance of EXTRINSIC RISK FACTORS (by definition, causal)

	CHD	Heart failure	CKD progression
Diabetes	+++	+++	+++
Higher body mass index	++	++	++
Cigarette smoking	+++	+++	+/-

Suggested framework for the causation of heart failure in patients with CKD



Conclusions: priorities for prevention of heart failure in CKD, based on current knowledge

- Treatments for extrinsic risk factors likely to be effective:
  - Quitting cigarette smoking
  - Improved diabetic control
  - Avoidance of overnutrition
- Treatments for intrinsic risk factors (based on current evidence) – treat now or conduct RCTs:
  - Intensive blood pressure reduction
  - Reduce neurohormonal activation (eg, RAAS blockade, MRAs)
  - Reduce sympathetic activity (eg, beta-blockers)
- Modification of other intrinsic risk factors more speculative and requires new RCT or convincing genetic risk score evidence

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