Caveolin-1 polymorphism association with arterial stiffness in non-dialysis CKD

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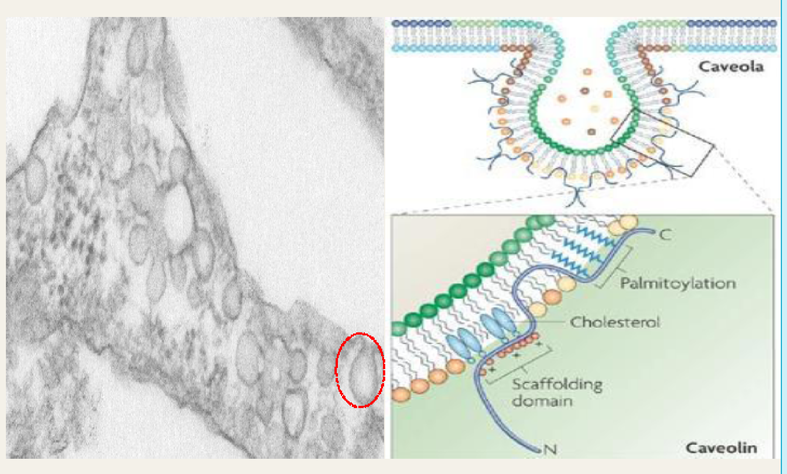
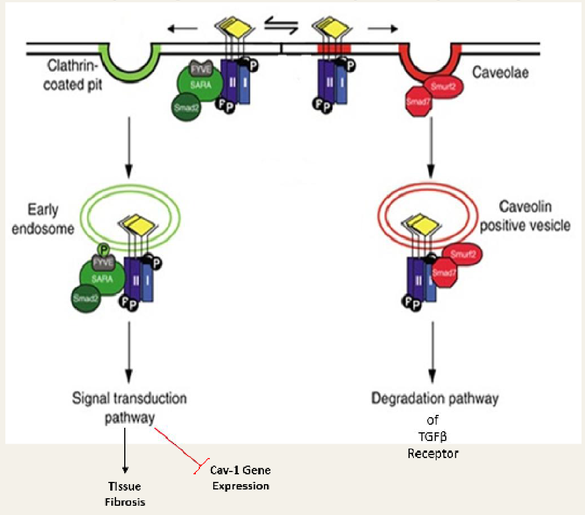
Introduction

- Arteriosclerosis is an independent predictor of increased cardiovascular mortality in CKD; characterised by medial artery fibrosis and arterial stiffness as measured by aortic pulse wave velocity (aPWV)
- Caveolin-1 acts as a intracellular signalling 'chaperone' in human fibrotic and vascular diseases
- Caveolin-1 rs4730751 CC genotype protective in time to renal allograft failure and in ANCA vasculitis, death from vascular disease
- We sought to assess the association between caveolin-1 single nucleotide polymorphism (*CAV1* SNP) and arterial stiffness in two independent cohorts of early and more advanced stage CKD



Example of reduced TGFβ induced fibrosis via endocytosis of its receptor by the caveolae lipid raft pathway



Methods

- 'Earlier' staged CKD cohort from the Chronic Renal Impairment in Birmingham (CRIB) RCTs 2005-2011
- Inclusion criteria: genetic testing consent, aPWV measurement at baseline, age 18-30, eGFR 30-89, bp <140/90 for at least 6 months
- Exclusion criteria: diabetes mellitus, peripheral vascular disease, symptomatic CV disease (previous MI, known heart failure, valvular heart disease), atrial fibrillation
- 'More advanced' CKD cohort from the Renal Impairment in Secondary Care (RIISC) study. Prospective ongoing observational cohort with patients with CKD stage 4 or 5, or CKD stage 3 with either accelerated progression and/or proteinuria. Same exclusion criteria as CRIB
- White patients selected only to limit population stratification
- Blood collected via PAXgene tubes. *CAV1* rs4730751 genotyping using Taqman technology

Baseline Characteristics of the cohorts

	CRIB			RIISC			
Characteristic	**CC genotype**	**Non-CC genotype**	**p* value**	**CC genotype**	**Non-CC genotype**	**p** value**	**P*** value**
Number of patients (%)	74 (51)	70 (49)		92 (63)	55 (37)		0.054
Age (years)	54 (45-63)	61 (49-67)	**0.020**	58 (49-69)	57 (39-70)	0.368	0.470
Male (%)	41 (55)	38 (54)	0.893	49 (53)	36 (66)	0.147	0.610
Body surface area (m^2)	1.9 (1.8-2.1)	1.9 (1.8-2.0)	0.534	1.9 (1.7-2.1)	2.0 (1.8-2.1)	0.424	0.818
Body mass index (Kg/m^2)	27.9 (24.1-29.9)	27.6 (24.6-32.0)	0.615	27.9 (24.1-32.7)	28.2 (24.1-31.6)	0.687	0.354
Mean arterial pressure (mmHg)	93 (85-102)	92 (85-98)	0.372	104 (97-114)	102 (97-112)	0.487	**<0.001**
Systolic blood pressure (mmHg)	124 (115-135)	129 (119-143)	0.225	124 (114-136)	122 (113-137)	0.994	0.422
Diastolic Blood Pressure (mmHg)	73 (68-80)	73 (66-82)	0.954	79 (71-86)	78 (74-84)	0.485	**<0.001**
Estimated glomerular filtration rate ($mls/min/1.73m^2$)	53 (40-59)	50 (42-57)	0.908	27 (20-37)	28 (21-38)	0.153	**<0.001**
Albumin:creatinine (mg/mmol)[1]	5.1 (1-50)	12 (1-37)	0.738	28 (7-111)	18 (7-111)	0.702	**<0.001**
High sensitive C-reactive protein (mg/l)[1]	1.4 (0.7-4.8)	2.1 (0.7-6.4)	0.369	2.3 (0.8-4.9)	2.1 (1.4-4.4)	0.431	0.263
Fasting glucose (mmol/l)	4.9 (4.4-5.2)	4.9 (4.4-5.3)	0.995	4.9 (4.6-5.4)	4.9 (4.4-5.2)	0.678	0.323
Total cholesterol (mmol/l)	4.8 (4.4-5.5)	4.6 (4.0-5.1)	**0.024**	4.9 (4.0-6.0)	4.8 (4.2-5.6)	0.604	0.071
Serum phosphate (mmol/l)	1.1 (0.9-1.2)	1.1 (1.0-1.2)	0.744	1.2 (1.0-1.3)	1.1 (0.9-1.2)	0.122	0.367
Aortic pulse wave velocity (m/s)	8.1 (7.0-9.4)	8.6 (7.5-10.8)	**0.003**	8.7 (7.9-9.8)	9.4 (8.0-10.8)	**0.021**	0.065
Current Smoker (%)	9 (12)	11 (16)	0.538	19 (21)	8 (15)	0.355	0.299
Previous Smoker (%)	28 (38)	26 (37)	0.931	35 (38)	24 (44)	0.503	0.645
Diagnoses							
Glomerular diseases (%)	44 (59)	28 (40)	**0.020**	25 (27)	14 (25)	0.819	**<0.001**
Systemic Diseases (%)	11 (12)	13 (19)	0.551	11 (12)	8 (15)	0.651	0.291
Tubulointerstitial diseases (%)	5 (7)	7 (10)	0.482	13 (14)	8 (15)	0.945	0.109
Familial nephropathies (%)	10 (14)	8 (11)	0.705	17 (18)	5 (9)	0.123	0.541
Miscellaneous (%)	6 (8)	14 (20)	**0.039**	26 (28)	20 (36)	0.305	**<0.001**
Medication frequency							
Angiotensin conversion enzyme inhibitors (%)	52 (70)	39 (56)	0.070	35 (38)	14 (26)	0.117	**<0.001**
Angiotensin II receptor blockers (%)	17 (23)	22 (31)	0.254	27 (29)	19 (35)	0.511	0.430
β blockers (%)	10 (14)	16 (23)	0.145	28 (30)	12 (22)	0.256	0.062
Calcium channel blockers (%)	16 (22)	19 (27)	0.440	42 (46)	21 (38)	0.376	**0.001**
Alpha blockers (%)	9 (12)	7 (10)	0.680	15 (16)	14 (26)	0.177	**0.042**
Diuretics (%)	24 (32)	19 (27)	0.488	28 (30)	19 (35)	0.605	0.697
Statins (%)	31 (44)	32 (43)	0.900	45 (49)	24 (44)	0.535	0.585

Key:
CRIB (Chronic Renal Impairment in Birmingham studies)
RIISC (Renal Impairment In Secondary Care study)
p* (p value comparing CC and non CC genotype in CRIB)
p** (p value comparing CC and non-CC genotype in RIISC)
p*** (p value comparing across all patients in CRIB versus RIISC cohorts)
p value by Student's t-test for continuous variables and χ^2 for categorical variables unless:
[1]variables p value tested by Mann-Whitney U.

Multivariate analysis of aPWV adjusted for age, gender, eGFR and mean arterial pressure (MAP) in CRIB & RIISC cohorts

Variable	Coefficient (95% Confidence Interval)	P value
Chronic Renal Impairment in Birmingham Randomised Control Trials		
Age	0.094 (0.068, 0.119)	<0.001
Gender (Female)	0.452 (-0.161, 1.065)	0.147
eGFR ($mls/min/1.73m^2$)	-0.014 (-0.036, 0.008)	0.204
MAP (mmHg)	-0.005 (-0.030, 0.021)	0.720
Genotype (CC)	-0.621 (-1.218, -0.024)	**0.042**
Renal Impairment In Secondary Care		
Age	0.087 (0.067, 0.106)	<0.001
Gender (Female)	0.116 (-0.423, 0.654)	0.672
eGFR ($mls/min/1.73m^2$)	0.015 (-0.004, 0.034)	0.123
MAP (mmHg)	0.040 (0.019, 0.061)	<0.001
Genotype (CC)	-0.984 (-1.523, -0.445)	**<0.001**

Summary of multivariate analyses models of aortic pulse wave velocity and CC versus non-CC genotype of caveolin-1 polymorphism with R squared values in CRIB & RIISC cohorts

Variables Included	Coefficient (95% Confidence Interval)	p value	R squared	Adjusted R squared
Chronic Renal Impairment in Birmingham RCTs				
Age, sex, MAP, eGFR	-0.621 (-1.218, -0.024)	0.042	0.349	0.325
Age, sex, MAP, eGFR, phosphate	-0.636 (-1.239, -0.034)	0.039	0.361	0.332
Age, sex, MAP, eGFR, phosphate, cholesterol	-0.770 (-1.378, -0.162)	0.013	0.398	0.366
Age, sex, MAP, eGFR, phosphate, cholesterol, HsCRP	-0.728 (-1.342, -0.113)	0.021	0.403	0.366
Age, sex, MAP, eGFR, phosphate, cholesterol, HsCRP, ACR	-0.790 (-1.425, -0.155)	0.015	0.415	0.373
Age, sex, MAP, eGFR, phosphate, cholesterol, HsCRP, ACR, BMI	-0.780 (-1.412, -0.149)	0.016	0.427	0.380
Renal Impairment In Secondary Care				
Age, sex, MAP, eGFR	-0.984 (-1.496, -0.445)	<0.001	0.453	0.433
Age, sex, MAP, eGFR, phosphate	-0.979 (-1.526, -0.432)	0.001	0.455	0.430
Age, sex, MAP, eGFR, phosphate, cholesterol	-0.939 (-1.496, -0.381)	0.001	0.456	0.426
Age, sex, MAP, eGFR, phosphate, cholesterol, HsCRP	-0.857 (-1.454, -0.260)	0.005	0.478	0.440
Age, sex, MAP, eGFR, phosphate, cholesterol, HsCRP, ACR	-0.732 (-1.328, -0.137)	0.016	0.477	0.432
Age, sex, MAP, eGFR, phosphate, cholesterol, HsCRP, ACR, BMI	-0.695 (-1.288, -0.102)	0.022	0.490	0.441

Conclusions

- CAV1 rs4730751 CC genotype is associated with lower arterial stiffness in patients with 'early' and 'late' stage non-dialysis CKD
- Exclusion criteria may limit generalisability
- CAV1 effect may be due to TGFβ signalling or effects on nitric oxide on vascular endothelium as it binds to eNOS. Aortic smooth muscle cells deficient in CAV1 have been shown to be pro-arteriosclerotic
- *CAV1* SNP rs4730751 may offer insight into explaining some of the burden of accelerated cardiovascular disease seen in CKD that is not accounted for by traditional and non-traditional risk factors
- The gene variant may also be a potential 'biomarker' in isolation or in combination with other gene variants and known risk factors
- Further mechanistic studies are warranted to evaluate the association of this gene variant and whether manipulation of CAV1 represents a therapeutic target

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52 ERA 28--SP
D) Genetic diseases and molecular genetics.
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DOI: 10.3252/pso.eu.52era.2015
ePosters supported by F. Hoffmann- La Roche Ltd.