Predictive Value of Measures of Vascular Calcification for Risk of Death in Incident Dialysis Patients

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BACKGROUND

Vascular calcifications (VC) are a useful marker of cardiovascular disease and several methods are available for the assessment of their presence and extension. However, which of these measures best predicts long-term survival and whether a measure of vascular calcification adds to the predictive value of traditional Framingham risk stratification, has not been determined through a concurrent comparison of these measures in a single prospective cohort.

METHODS

We utilized data from 184 patients incident to dialysis recruited in the INDEPENDENT study (ClinicalTrials.gov: NCT00710788) with data on coronary artery calcification (CAC) and abdominal aorta vascular calcification (AOC)

For the present study we examined the association of (1) CAC evaluated via Agatston score (2), CAC evaluated via volume score (3), and AOC evaluated via X-ray (Kauppila score) and the risk of all-cause mortality.

Follow-up: until any lethal event or completion of 36 months.

The predictive and additional value of each of measure of vascular calcification (VC) is tested using regression models, ROC methods

RESULTS

Table 1. Demographic and clinical characteristics of the study cohort

Variable	Total (n=184) Mean (SD)[n]	Alive (n=115) Mean (SD)[n]	Expired (n=69) Mean (SD)[n]	P-Value
Age (years)	**62.63 (15.8)[184]**	**58.55 (15.17)[115]**	**69.42 (14.53)[69]**	**< 0.0001**
Male (%)	51.09% [94]	49.57% [57]	53.62% [37]	0.703
Body Weight (Kg)	68.34 (13.19)[184]	69.29 (13.58)[115]	66.76 (12.47)[69]	0.198
Diabetes (%)	21.74% [40]	19.13% [22]	26.09% [18]	0.356
Systolic Blood Pressure (mmHg)	**135.42 (18.7)[184]**	**132.77 (18.78)[115]**	**139.84 (17.85)[69]**	**0.012**
Diastolic Blood Pressure (mmHg)	75.9 (9.78)[184]	75.91 (9.24)[115]	75.87 (10.69)[69]	0.978
Framingham score (unit)	**11.85 (3.56)[184]**	**11.14 (3.7)[115]**	**13.04 (2.97)[69]**	**<0.001**
QTd (msec)	30.09 (14.21)[184]	30.66 (13.49)[115]	29.13 (15.39)[69]	0.495
Coronary Artery Calcification				
Agatston score	**569.1 (1098.44)[184]**	**226.94 (579.82)[115]**	**1139.36 (1468.17)[69]**	**< 0.0001**
Volume score	**229.2 (334.14)[184]**	**112.39 (223.5)[115]**	**423.87 (393.96)[69]**	**< 0.0001**
Abdominal Aorta VC (Kauppila score)	**13.27 (9.24)[184]**	**10.07 (8.85)[115]**	**18.59 (7.22)[69]**	**< 0.0001**
Pulse Wave Velocity (m/sec)	**9.52 (3.77)[184]**	**9.21 (3.71)[115]**	**10.04 (3.85)[69]**	**0.156**
Albumin (g/dl)	3.78 (0.42)[184]	3.79 (0.38)[115]	3.77 (0.48)[69]	0.794
Creatinine (g/dl)	7.92 (2.59)[184]	8.05 (2.45)[115]	7.69 (2.82)[69]	0.376
Hemoglobin (g/dl)	11.04 (1.63)[184]	11.11 (1.76)[115]	10.92 (1.39)[69]	0.428
Sodium (mE/l)	**139.27 (3.51)[184]**	**139 (3.79)[115]**	**139.72 (2.98)[69]**	**0.152**
Potassium (mEq/l)	5.15 (0.75)[184]	5.09 (0.74)[115]	5.25 (0.77)[69]	0.175
Calcium (mg/dl)	**8.81 (0.9)[184]**	**8.91 (0.99)[115]**	**8.64 (0.71)[69]**	**0.036**
Phosphate (mg/dl)	**4.59 (1.31)[184]**	**4.44 (1.2)[115]**	**4.84 (1.45)[69]**	**0.055**
Parathyroid Hormone (pg/ml)	**259.78 (227.67)[184]**	**236.62 (180.38)[115]**	**298.38 (287.29)[69]**	**0.111**
C-reactive protein (mg/l)	5.05 (3.37)[184]	4.99 (3.64)[115]	5.14 (2.89)[69]	0.762

Table 2 predictors of all-cause of death forcing in the model CAC measured via volume (a) or Agatston score (b)

Variable	HR	lower .95	upper .95	Pr(>|z|)
Kauppila score per 1 unit increase	0.9781	0.9192	1.041	0.4855
log(volume score) per 1 log increase	**1.8082**	**1.3486**	**2.424**	**<0.001**
Pulse Wave velocity (m/sec)	**1.0898**	**0.9979**	**1.19**	**5.56E-02**
Age (years	1.0181	0.9841	1.053	0.2996
Framingham score, per 1 unit increase	0.9825	0.8297	1.164	0.838
Diabetes, yes vs no	**2.8998**	**1.2826**	**6.556**	**0.011**
ASCVD, yes vs no	0.5691	0.2558	1.266	0.1671
Systolic blood pressure (mmHg)	1.0098	0.995	1.025	0.1953
Serum phosphate (mg/dl)	1.052	0.8625	1.283	0.617
Serum Calcium (mg/dl)	0.8909	0.6347	1.251	0.5044
Serum sodium (mEq/l)	1.0363	0.9486	1.132	0.4295
iPTH (pg/ml)	1.0004	0.9994	1.001	0.4272
use of ARBs, yes vs no	1.1667	0.4845	2.809	0.731
Use of beta-blockers, yes vs no	0.8832	0.4863	1.604	0.6835
Use of vitamin D, yes vs no	0.7688	0.4323	1.367	0.3708
Use of calcium based phosphate binder, yes vs no	1.9395	0.5371	7.004	0.3119
Use of Calcium channel blockers	**1.7561**	**0.9514**	**3.241**	**0.072**
Use of cinacalcet, yes vs no	1.0687	0.6232	1.832	0.8092

Variable	HR	lower .95	upper .95	Pr(>|z|)
Kauppila score per 1 unit increase	0.9634	0.9016	1.029	0.26968
log(Agatston score) per 1 log increase	**1.7213**	**1.343**	**2.206**	**0.000018**
Pulse Wave velocity (m/sec)	**1.0947**	**1.0026**	**1.195**	**0.04359**
Age (years	1.0164	0.9815	1.052	0.36148
Framingham score, per 1 unit increase	0.9792	0.8241	1.164	0.81153
Diabetes, yes vs no	**2.9713**	**1.3526**	**6.527**	**0.00669**
ASCVD, yes vs no	**0.4728**	**0.2036**	**1.098**	**0.08141**
Systolic blood pressure (mmHg)	1.0091	0.9944	1.024	0.22409
Serum phosphate (mg/dl)	1.0561	0.8681	1.285	0.58515
Serum Calcium (mg/dl)	0.8855	0.6258	1.253	0.49225
Serum sodium (mEq/l)	1.0319	0.9453	1.126	0.48241
iPTH (pg/ml)	1.0002	0.9992	1.001	0.76081
use of ARBs, yes vs no	1.2997	0.5457	3.096	0.55388
Use of beta-blockers, yes vs no	0.8438	0.4697	1.516	0.57001
Use of vitamin D, yes vs no	0.6468	0.3593	1.164	0.14621
Use of calcium based phosphate binder, yes vs no	1.9412	0.5423	6.949	0.308
Use of Calcium channel blockers	**1.773**	**0.958**	**3.281**	**0.06826**
Use of cinacalcet, yes vs no	0.9841	0.5759	1.682	0.95339

For each VC assessment separately, the most parsimonious model to predict all-cause mortality was selected starting from a model adjusted for VC measure (CAC or KS), Pulse Wave Velocity, age, Framingham score, diabetes, ASCVD, systolic blood pressure, serum levels of phosphate, calcium, PTH, use of ARBs, beta-blockers, vitamin D, calcium containing phosphate binder, calcium channel blockers and cinacalcet. The predictive value of the model with and without the measurement of VC was calculated. Addition of the information derived by vascular calcification detection improved outcome prediction independently of the recording site (abdominal aorta v.s. coronary artery) and method used (Agatston vs volume score). Despite a significant improvement in outcome prediction with the addition of VC, the overall model performance was at the most modest, indicating the great complexity of CKD patients undergoing dialysis and the limitation of risk prediction in this population.

Most parsimonoous model (stepwise selection)

Variable	HR	lower .95	upper .95	Pr(>|z|)
CAC-Agatstone score	1.6279	1.4176	1.869	5.07E-12
Pulse wave velocity (m/sec)	1.1023	1.011	1.202	0.0273
Diabete (y vs n)	3.597	1.7437	7.42	0.00053
ASCVD (y vs n)	0.5582	0.2718	1.146	0.11226
Systolic blood pressure (mmHg)	1.011	0.9974	1.025	0.11198
Use of calcium containing phosphate binder (y vs n)	2.9523	0.9032	9.65	0.07321
Use of calcium channel blockers (y vs n)	1.9427	1.1263	3.351	0.01696

Model fit statistics (AIC-adding CAC)	624.31 (final model with CAC)
loglink (without CAC)	305.16
logling (with CAC)	333.41
Comparison with vs without CAC	Chisq 43.697 (p<0.001)
Overall performance (R-square)	
without CAC	0.119 (max possible= 0.977)
with CAC	0.352 (max possible= 0.977)

logistic regression			
Best cutoff to discriminate expired vs alive patients at univariate analyses	257.5 (specif 80.9%-sensit 73.9%)		
Metrics of discrimination- C-statiscs (95%CI)			
without CAC	0.742 (0.669 - 0.8157)		
with CAC	0.901 (0.854 -0.947)		
Difference in C statistics (SD)	0.158 (0.026); p-value for comparison p<0.001		
Model fit statistics (AIC)			
without CAC	225.53		
with CAC	160.18		
Comparison between models (ANOVA)	LR (Chisq) 67.3; d.f. 1 (p<0.001)		
Metrics of Calibration (adding CAC)	Chi-square	Df	p-value
Hosmer-Lemeshow goodnes of fit	21.116	8	0.006
Patient reclassification (adding CAC)	Coeff	95%CI	p-value
IDI (95%CI)	0.311	(0.241 - 0.381)	p<0.001
NRI categorical (95%CI)	0.301	(0.173 - 0.430)	p<0.001
NRI continuous (95%CI)	1.275	(0.976 - 1.573)	p<0.001

CAC measured via the Agatston score

Fully adjusted model: adjusted for : Vascular calcification, Pulse Wave Velocity, age, Framingham score, diabetes, ASCVD, systolic blood pressure, serum levels of phosphate, cacium, PTH, use of ARBs, beta-blockers, vitamin D, calcium containing phosphate binder, calcium channel blockers, cinacalcet

Most parsimonoous model (stepwise selection)

Variable	HR	lower .95	upper .95	Pr(>|z|)
CAC-Volume score	1.7301	1.4469	2.069	1.86E-09
Pulse wave velocity (m/sec)	1.0968	1.0082	1.193	0.03158
Age (years)	1.0167	0.9967	1.037	0.10152
Diabete (y vs n)	3.1042	1.4553	6.622	0.00338
ASCVD (y vs n)	0.5692	0.282	1.149	0.11584
Systolic blood pressure (mmHg)	1.0103	0.9966	1.024	0.13968
Use of calcium containing phosphate binder (y vs n)	2.6029	0.8045	8.421	0.11029
Use of calcium channel blockers (y vs n)	1.6822	0.9516	2.974	0.07356

Model fit statistics (AIC-adding CAC)	627.21 (final model with CAC)
loglink (without CAC)	305.6
logling (with CAC)	327.45
Comparison with vs without CAC	Chisq 43.697 (p<0.001)
Overall performance (R-square)	
Without CAC	0.175 (max possible= 0.977)
With CAC	0.349 (max possible= 0.977)

logistic regression			
Best cutoff to discriminate expired vs alive patients at univariate analyses	66.5 (specif 70.4%-sensit 81.2%)		
Metrics of discrimination- C-statiscs (95%CI)			
without CAC	0.776 (0.707 - 0.845)		
with CAC	0.896 (0.848 -0.943)		
Difference in C statistics (SD)	0.120 (0.021); p-value for comparison <0.001		
Model fit statistics (AIC)			
without CAC	214.03		
with CAC	162.83		
Comparsin between models (ANOVA)	LR (Chisq) 53.1; d.f. 1 (p<0.001)		
Metrics of Calibration (adding CAC)	Chi-square	Df	p-value
Hosmer-Lemeshow goodnes of fit	11.897	8	0.155
Patient reclassification (adding CAC)	Coeff	95%CI	p-value
IDI (95%CI)	0.241	(0.177 - 0.305)	p<0.001
NRI categorical (95%CI)	0.301	(0.173 - 0.429)	p<0.001
NRI continuous (95%CI)	1.072	(0.774 - 1.370)	p<0.001

CAC measured via the Volume score

Fully adjusted model: adjusted for : Vascular calcification, Pulse Wave Velocity, age, Framingham score, diabetes, ASCVD, systolic blood pressure, serum levels of phosphate, cacium, PTH, use of ARBs, beta-blockers, vitamin D, calcium containing phosphate binder, calcium channel blockers, cinacalcet

Most parsimonoous model (stepwise selection)

Variable	HR	lower .95	upper .95	Pr(>|z|)
Kauppila score (1U increase)	1.095	1.0577	1.133	2.50E-07
Pulse wave velocity (m/sec)	1.061	0.9961	1.13	0.0658
Age (years)	1.019	1.0002	1.038	0.0473
Systolic blood pressure (mmHg)	1.013	0.9987	1.027	0.0747
Use of calcium channel blockers (y vs n)	1.476	0.8923	2.44	0.1295

Model fit statistics (AIC-adding Kauppila) 624.31 (final model with CAC)	
loglink (without Kauppila)	332.34
logling (with kauppila)	316.34
Comparison with vs without Kauppila	Chisq 31.89 (p<0.001)
Overall performance (R-square)	
without Kauppila	0.130 (max possible= 0.977)
with kauppila	0.269 (max possible= 0.977)

logistic regression			
Best cutoff to discriminate expired vs alive patients at univariate analyses	14.5 (specif 67.0%-sensit 78.3%)		
Metrics of discrimination- C-statiscs (95%CI)			
without CAC	0.730 (0.655 - 0.806)		
with CAC	0.841 (0.782 -0.900)		
Difference in C statistics (SD)	0.110 (0.017); p-value for comparison <0.001		
Model fit statistics (AIC)			
without CAC	222.78		
with CAC	186.81		
Comparison between models (ANOVA)	LR (Chisq) 37.9; d.f. 1 (p<0.001)		
Metrics of Calibration (adding CAC)	Chi-square	Df	p-value
Hosmer-Lemeshow goodnes of fit	8.032	8	0.43
Patient reclassification (adding CAC)	Coeff	95%CI	p-value
IDI (95%CI)	0.177	(0.123 - 0.232)	p<0.001
NRI categorical (95%CI)	0.246	(0.130 - 0.361)	p<0.001
NRI continuous (95%CI)	0.921	(0.623 - 1.220)	p<0.001

Abdominal Aorta calcification

Fully adjusted model: adjusted for : Vascular calcification, Pulse Wave Velocity, age, Framingham score, diabetes, ASCVD, systolic blood pressure, serum levels of phosphate, cacium, PTH, use of ARBs, beta-blockers, vitamin D, calcium containing phosphate binder, calcium channel blockers, cinacalcet

CONCLUSIONS

Limitations

- Observational study (unmeasured potential bias)
- Vascular calcification (VC) were measured only once at baseline
- Abdominal aorta vascular calcification screening was left to the attending physician and not protocollized
- Dataset composed patient incident to dialysis only

Strengths

- A relatively large study sample allowed us to control for many potential confounders
- High accuracy of vascular calcification detetction
- Carefully adjudicated outcome data

These analyses support to the hypothesis that vascular calcification detection improves event prediction in patients incident to dialysis. Overall, it appears that CAC is a better predictor of outcome than abdominal aorta VC although the difference is small. Of interest, in each model VC is more important than the Framingham risk score in predicting all-cause mortality.

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