

## BACKGROUND

- Resistance to Erythropoietin Stimulating Agents (ESAs) has been associated with increased mortality.
- Importantly, ESA doses may considerably vary over time. Longitudinal changes in hemoglobin concentration in dialysis patients have been reported, potentially leading to dose adjustments in ESA use.
- This, in turn, points to the need to evaluate longitudinal assessments of ESA requirements in the association with specific clinical events.
- This prompted us to investigate the association of time-varying ESA responsiveness with sudden death and other cardiovascular outcomes in dialysis patients using a time-dependent approach.

## METHODS

- The German Diabetes and Dialysis (4D) study included 1255 diabetic dialysis patients, of whom 1012 were receiving ESA treatment.
- In those patients, the Erythropoietin Resistance Index (ERI) was assessed every 6 months during a median follow-up of 4 years.
- The association between the ERI and CV endpoints was analyzed by time-dependent Cox regression analyses with repeated ERI measures.

## RESULTS

### Demographic characteristics:

- Data from 1012 male patients were available
- Mean age was 66 (8) years

Table 1: Baseline patient characteristics, study population n=1012

Characteristic	
Age years	66 (8)
Gender % men	54
Systolic BP mmHg	145 (22)
Diastolic BP mmHg	76 (11)
BMI kg/m <sup>2</sup>	27.5 (4.8)
Duration of diabetes years	18.1 (8.8)
Time on dialysis months	8.2 (6.9)
Arterio-venous fistula %	82
History of	
CAD %	28.5
CHF %	35.4
PVD %	44.6
Smoker or ex-smoker %	40.4
ACE-inhibitor use %	48
Laboratory parameters	
LDL cholesterol mg/dl	126 (30)
Hemoglobin g/dl	10.9 (1.3)
Ferritin ug/l	487 (426)
Transferrin ug/l	1.9 (0.3)
Iron saturation %	22.2 (11.3)
Albumin g/dl	3.8 (0.3)
Parathyroid hormone pg/ml	102 (119)
C-reactive protein mg/l	5.8 (2.3-12.4)
Calcium mmol/l	2.3 (0.2)
Phosphate mg/dl	6.1 (1.6)
HbA1c %	6.7 (1.3)
25(OH)D3 nmol/l	39.0 (28-55)

Values are presented as mean ± SD or median with interquartile range as appropriate or percentages. Abbreviations: CAD = coronary artery disease; CHF = congestive heart failure, PVD = peripheral vascular disease, BMI = The body-mass index is the weight in kilograms divided by the square of the height in meters, LDL = low-density lipoprotein, HbA1c = glycosylated hemoglobin,

## CONCLUSIONS

- In diabetic dialysis patients we observed that time-varying erythropoietin resistance is associated with sudden death, infectious complications and all-cause mortality.

Outcome	Hazard Ratio per 5 units ERI (95% CI)	p-value
<b>Sudden Death</b>		
Crude	1.20 (1.08-1.33)	<0.001
Adjusted <sup>1</sup>	1.18 (1.06-1.31)	<b>0.0019</b>
Adjusted <sup>2</sup>	1.18 (1.06-1.31)	0.0020
Adjusted <sup>3</sup>	1.19 (1.07-1.33)	0.0019
<b>Mortality</b>		
Crude	1.25 (1.19-1.31)	<0.001
Adjusted <sup>1</sup>	1.24 (1.18-1.30)	<0.001
Adjusted <sup>2</sup>	1.24 (1.18-1.30)	<0.001
Adjusted <sup>3</sup>	1.25 (1.18-1.32)	<0.001
<b>Infectious Death</b>		
Crude	1.27 (1.15-1.40)	<0.001
Adjusted <sup>1</sup>	1.27 (1.15-1.41)	<0.001
Adjusted <sup>2</sup>	1.27 (1.15-1.41)	<0.001
Adjusted <sup>3</sup>	1.27 (1.13-1.42)	<0.001
<b>Heart F. Death</b>		
Crude	1.21 (0.99-1.49)	0.06
Adjusted <sup>1</sup>	1.25 (1.02-1.54)	<b>0.03</b>
Adjusted <sup>2</sup>	1.25 (1.01-1.54)	0.04
Adjusted <sup>3</sup>	1.29 (1.04-1.60)	0.02
<b>MI</b>		
Crude	1.04 (0.92-1.16)	0.56
Adjusted <sup>1</sup>	1.04 (0.92-1.17)	0.56
Adjusted <sup>2</sup>	1.03 (0.92-1.16)	0.59
Adjusted <sup>3</sup>	1.01 (0.99-1.04)	0.37
<b>Stroke</b>		
Crude	1.16 (1.01-1.33)	0.04
Adjusted <sup>1</sup>	1.11 (0.97-1.28)	0.13
Adjusted <sup>2</sup>	1.12 (0.97-1.28)	0.13
Adjusted <sup>3</sup>	1.16 (1.01-1.34)	0.04

**During follow up, a total of 495 patients died, thereof 136 patients of sudden death and 102 of Infectious death**

Per 5 units increase of the ERI, the adjusted and time-dependent risk for sudden death was increased by 19 %. Similarly, mortality increased by 24 % and infectious death increased by 27 %.