Dual compared to single Renin-Angiotensin system inhibition and risk of renal replacement therapy or death in pre-dialysis patients: PREPARE-2 study

Pauline W.M. Voskamp[1], Friedo W. Dekker[1], Merel van Diepen[1], Ellen K. Hoogeveen[1] for the PREPARE-2 study group, [1] Dept of Clinical Epidemiology, Leiden University Medical Center, Leiden, the Netherlands

Background

- Chronic kidney disease (CKD) is a leading cause of death due to premature cardiovascular disease. Hypertension is a major cause of accelerated loss of kidney function. Therefore, slowing down or prevention of kidney function decline, by optimal treatment of hypertension is important.
- Current guidelines on hypertension in pre-dialysis patients with CKD 4-5, recommend the use of renin–angiotensin system (RAS) inhibitors, such as angiotensin converting enzyme blockers (ACEi) or angiotensin II receptor blockers (ARB). Combined ACEi and ARB use is discouraged, based on expert opinion.
- Since ACEi or ARBs alone do not block the entire RAS and work via different pathways, it has been hypothesized that dual RAS blockade can improve reno protective effects.

Objective

To explore in incident pre-dialysis patients with CKD stage 4-5, among baseline non, single and dual RAS blockade medication users the association with risk of RRT or death, and differences in the annual rate of kidney function decline.

Methods

PREdialysis PAtient REcord-2 (PREPARE-2) study
Observational prospective follow-up study in 502 incident CKD stages 4-5 patients referred to outpatient clinics from 25 Dutch hospitals between 2004-2011. Medication use at baseline Was known in 495 patients. We used multiple imputation for missing data.

Exposure:	ACEi use, ARB use, dual RAS blockade use
Outcomes:	Time until start of dialysis, renal replacement therapy (RRT), RRT & death, eGFR (CKD-EPI) decline
Confounders:	Age, sex, race, current smoker, diabetes mellitus, and pkd
Statistical methods:	Cox proportional hazards regression analysis, Linear Mixed Model

Conclusion

- Dual and single RAS blockade in pre-dialysis patients were not associated with an increased risk for RRT or death.
- Dual and single RAS blockade were not associated with an accelerated kidney function decline compared to no RAS blockade.
- In single RAS blockade users, ACEi use was associated with a decreased risk for RRT.

Results

Table 1. Incidence rates (95% CIs) of dialysis, RRT and RRT & death combined, according to ACEi and/or ARB drug use at baseline (n=495).

	No ACEi or ARB (n=122)	ACEi only (n=161)	ARB only (n=135)	ACEi and ARB (=77)
Person years (py)	185.4	285.8	219.6	145.4
Dialysis/100 py (95% CI)	36 (25 to 50)	29 (19 to 42)	38 (27 to 52)	31 (21 to 44)
RRT/100 py (95% CI)	41 (29 to 56)	34 (24 to 48)	43 (31 to 58)	34 (24 to 48)
Combined RRT/death /100 py (95%CI)	46 (34 to 61)	39 (28 to 53)	49 (36 to 65)	38 (27 to 52)

Table 3. Crude and adjusted hazard ratios (95% CI) for start of dialysis, RRT and the combined endpoint according to ACEi and/or ARB drug use at baseline (n=495).

	Start of dialysis	RRT	RRT or death
No ACEi or ARB	Reference	Reference	Reference
ACEi, crude	0.77 (0.56 to 1.07)	0.78 (0.58 to 1.05)	0.79 (0.60 to 1.05)
ACEi, adjusted	0.73 (0.52 to 1.02)	0.70 (0.52 to 0.96)	0.74 (0.55 to 1.00)
ARB, crude	0.99 (0.72 to 1.37)	0.98 (0.72 to 1.32)	1.00 (0.75 to 1.33)
ARB, adjusted	0.92 (0.66 to 1.29)	0.90 (0.66 to 1.23)	0.94 (0.70 to 1.26)
ACEi and ARB, crude	0.86 (0.59 to 1.25)	0.80 (0.56 to 1.14)	0.81 (0.57 to 1.13)
ACEi and ARB, adjusted	0.77 (0.51 to 1.16)	0.70 (0.47 to 1.04)	0.74 (0.51 to 1.06)

Table 2. Baseline characteristics according to ACEi or ARB drug use at baseline (n=495).

	No ACEi or ARB	ACEi only	ARB only	ACEi and ARB
Men	75 (62)	119 (74)	80 (60)	62 (81)
Age	72 (60-79)	67 (56-76)	68 (55-74)	63 (49-74)
Caucasian ethnicity	120 (98)	152 (94)	121 (90)	64 (83)
PKD: Renal vascular disease	42 (34)	49 (30)	49 (36)	11 (14)
PKD: Diabetes	7 (6)	24 (15)	18 (13)	21 (27)
PKD: Glomerulonephritis	9 (7)	24 (15)	12 (9)	21 (27)
Diabetes Mellitus, yes	17 (14)	42 (26)	36 (27)	29 (38)
Cardio Vascular Disease, yes	49 (40)	69 (43)	54 (40)	30 (39)
Hypertension, yes	99 (81)	142 (88)	123 (91)	74 (96)
Systolic blood pressure	140 (20)	140 (22)	144 (24)	148 (22)
Diastolic blood pressure	78 (10)	77 (13)	78 (12)	79 (11)
eGFR (ml/min/1.73 m²)	13.1 (10.2-17.2)	14.8 (11.7-19.3)	14.5 (11.1-18.0)	16.5 (11.7-19.7)
Proteinuria (g/24h)	1.0 (0.4-1.9)	1.0 (0.3-2.1)	0.9 (0.3-2.0)	1.7 (0.6-3.6)

Data are presented as: number (%), mean (SD) for blood pressure, median (IQR) for the other continuous variables. PKD; primary kidney disease.

Table 4. Annual rate of decline of kidney function according to ACEi and/or ARB drug use at baseline (n=495).

Mean decline in eGFR(ml/min/1.73 m²)/y	-1.48 (95%CI -1.87 to -1.08)	
Change in decline in eGFR(ml/min/1.73m²)/y	Crude (95%CI)	Adjusted (95%CI)
No ACEi or ARB	Reference	Reference
ACEi	-0.71 (-1.86 to 0.44)	-1.11 (-2.24 to 0.02)
ARB	-0.53 (-1.73 to 0.66)	-0.80 (-1.96 to 0.37)
ACEi and ARB	-0.19 (-1.55 to 1.18)	-0.20 (-1.56 to 1.16)

References

Go AS, et al. The New England journal of medicine. 2004;351(13):1296-305. James PA, et al. Jama. 2014;311(5):507-20. Kidney Disease: Improving Global Outcomes (KDIGO) Blood Pressure Work Group. Kidney inter, Suppl2012. p. 77. Teo K, et al. American heart journal. 2004;148(1):52-61.

Corresponding author: p.w.m.voskamp@lumc.nl

Nefrovisie
Richtlijnen · Registratie · Visitatie

NIERSTICHTING