Is Dual Blockade in DKD Dead?

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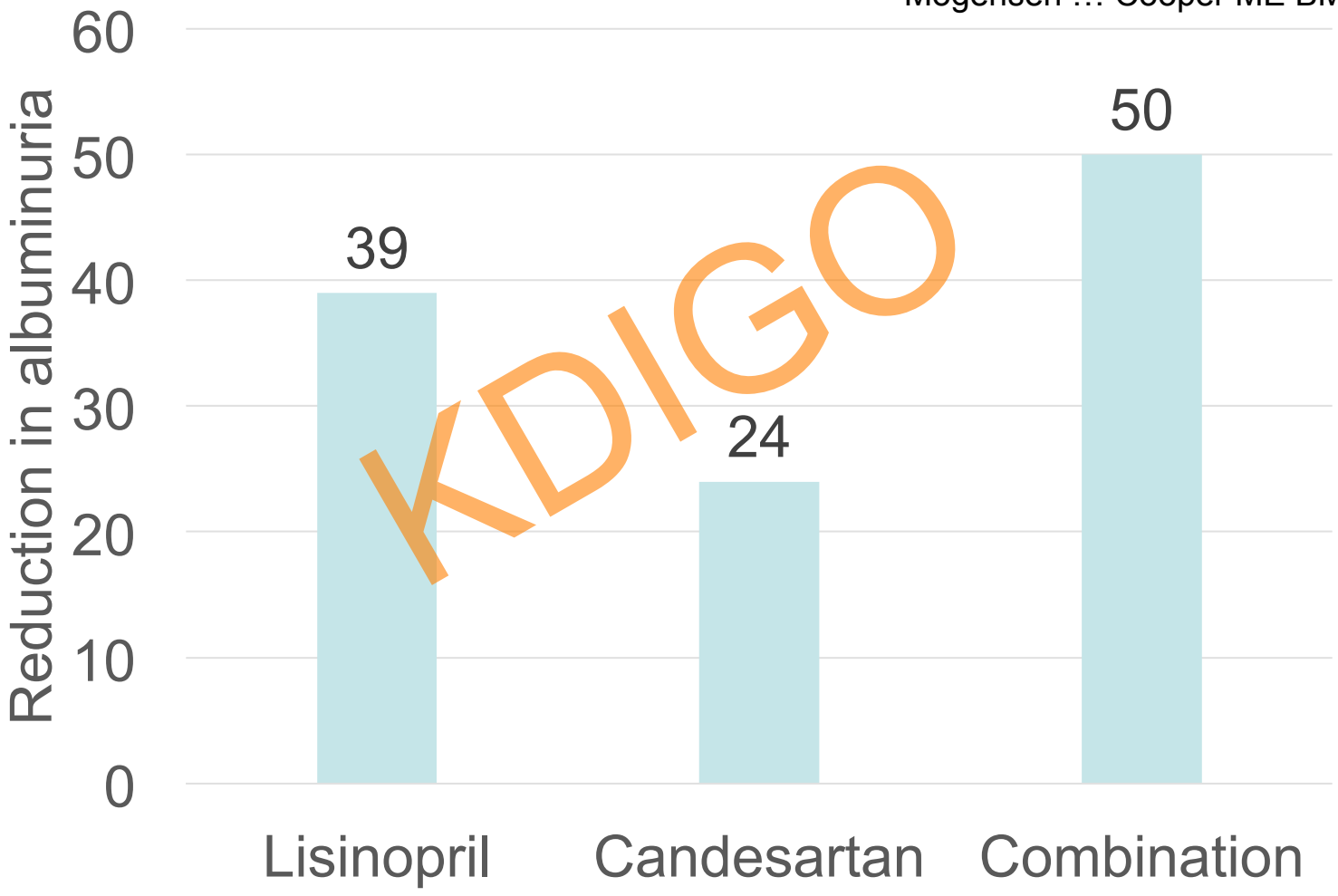
Disclosure of Interests

MC has received honoraria for educational symposia and expert panels provided on behalf of:

Astra-Zeneca, Abbott, Reata, Abbvie, Sanofi Aventis, BMS, Boehringer Ingelheim, Lilly, MSD, Servier, Janssen-Cilag, Novartis, Novo Nordisk

THE CALM (BEFORE THE STORM)

Mogensen … Cooper ME BMJ 2000



THE EVIDENCE

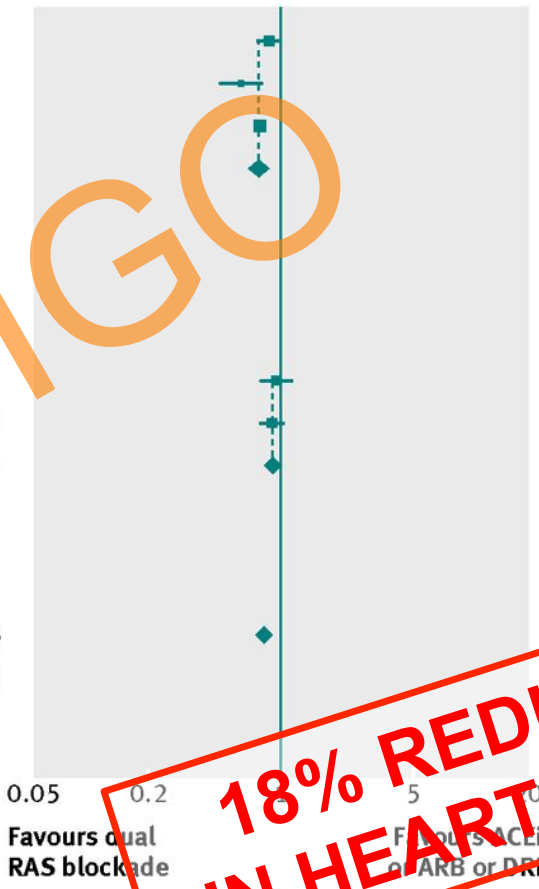
"Although dual blockade of the RAS may have seemingly beneficial effects on certain surrogates (*e.g. BP albuminuria*)...

it failed to reduce mortality and was associated with an excessive risk of adverse events... **The risk to benefit ratio argues against the use of dual therapy."**

Makani H et al. BMJ 2013;346:bmj.f360

LESS HOSPITALISATION FOR CHF

Trial	Events/total: Dual RAS blockade	Events/total: ACEi or ARB or DRI	Risk ratio, M-H, random (95% CI)	Weight (%)	Risk ratio, M-H, random (95% CI)
Cohort with heart failure					
CHARM Added 2003[18]	309/1276	356/1272		21.6	0.87 (0.76 to 0.99)
Cice 2010[19]	56/165	92/167		11.5	0.62 (0.48 to 0.79)
Val HeFT 2001[31]	923/2511	1189/2499		28.5	0.77 (0.72 to 0.83)
Subtotal	1288/3952	1637/3938		61.6	0.77 (0.68 to 0.88)
Test for heterogeneity: τ^2=0.01, χ^2=5.85, df=2, P=0.05, I^2=66%					
Test for overall effect: z=3.85, P<0.001					
Cohort without heart failure					
ALTITUDE 2012[46]	205/4274	219/4287		16.3	0.94 (0.78 to 1.13)
ONTARGET 2008[25]	332/8502	748/17 118		22.1	0.89 (0.79 to 1.01)
Subtotal	537/12 776	967/21 405		38.4	0.91 (0.82 to 1.01)
Test for heterogeneity: τ^2=0.00, χ^2=0.19, df=1, P=0.67, I^2=0%					
Test for overall effect: z=1.81, P=0.07					
Total (95% CI)	1825/16 728	2604/25 343		100.0	0.82 (0.7[illegible] to 0.92)
Test for heterogeneity: τ^2=0.01, χ^2=12.60, df=4, P=0.01, I^2=68%					
Test for overall effect: z=3.58, P<0.001					
Test for subgroup differences: χ^2=3.57, df=1, P=0.06, I^2=72%					



18% REDUCTION IN HEART FAILURE

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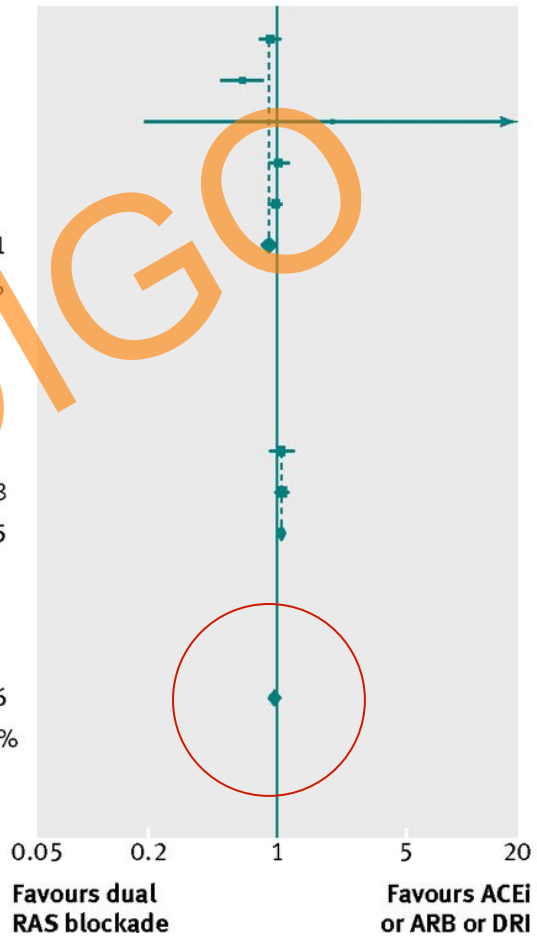
NO EFEFCT ON MORTALITY

Trial	Events/total: Dual RAS blockade	Events/total: ACEi or ARB or DRI	Weight (%)	Risk ratio, M-H, random (95% CI)
Cohort with heart failure				
CHARM Added 2003[18]	377/1276	412/1272	17.0	0.91 (0.81 to 1.02)
Cice 2010[19]	58/165	91/167	7.8	0.65 (0.50 to 0.83)
Kum 2008[22]	2/25	1/25	0.1	2.00 (0.19 to 20.67)
Val HeFT 2001[31]	495/2511	484/2499	17.3	1.02 (0.91 to 1.14)
VALIANT 2003[33]	941/4885	1937/9818	21.4	0.98 (0.91 to 1.05)
Subtotal	1873/8862	2925/13 781	63.7	0.92 (0.82 to 1.03)
Test for heterogeneity: τ^2=0.01, χ^2=12.17, df=4, P=0.02, I^2=67%				
Test for overall effect: z=1.45, P=0.15				
Cohort without heart failure				
ALTITUDE 2012[46]	376/4274	358/4287	15.0	1.05 (0.92 to 1.21)
ONTARGET 2008[25]	1065/8502	2003/17 118	21.4	1.07 (1.00 to 1.15)
Subtotal	1441/12 776	2361/21 405	36.3	1.07 (1.00 to 1.14)
Test for heterogeneity: τ^2=0.00, χ^2=0.04, df=1, P=0.84, I^2=0%				
Test for overall effect: z=2.05, P=0.04				
Total (95% CI)	3314/21 638	5286/35 186	100.0	0.97 (0.89 to 1.06)
Test for heterogeneity: τ^2=0.01, χ^2=19.50, df=6, P=0.003, I^2=69%				
Test for overall effect: z=0.67, P=0.50				
Test for subgroup differences: χ^2=5.06, df=1, P=0.02, I^2=80.3%				



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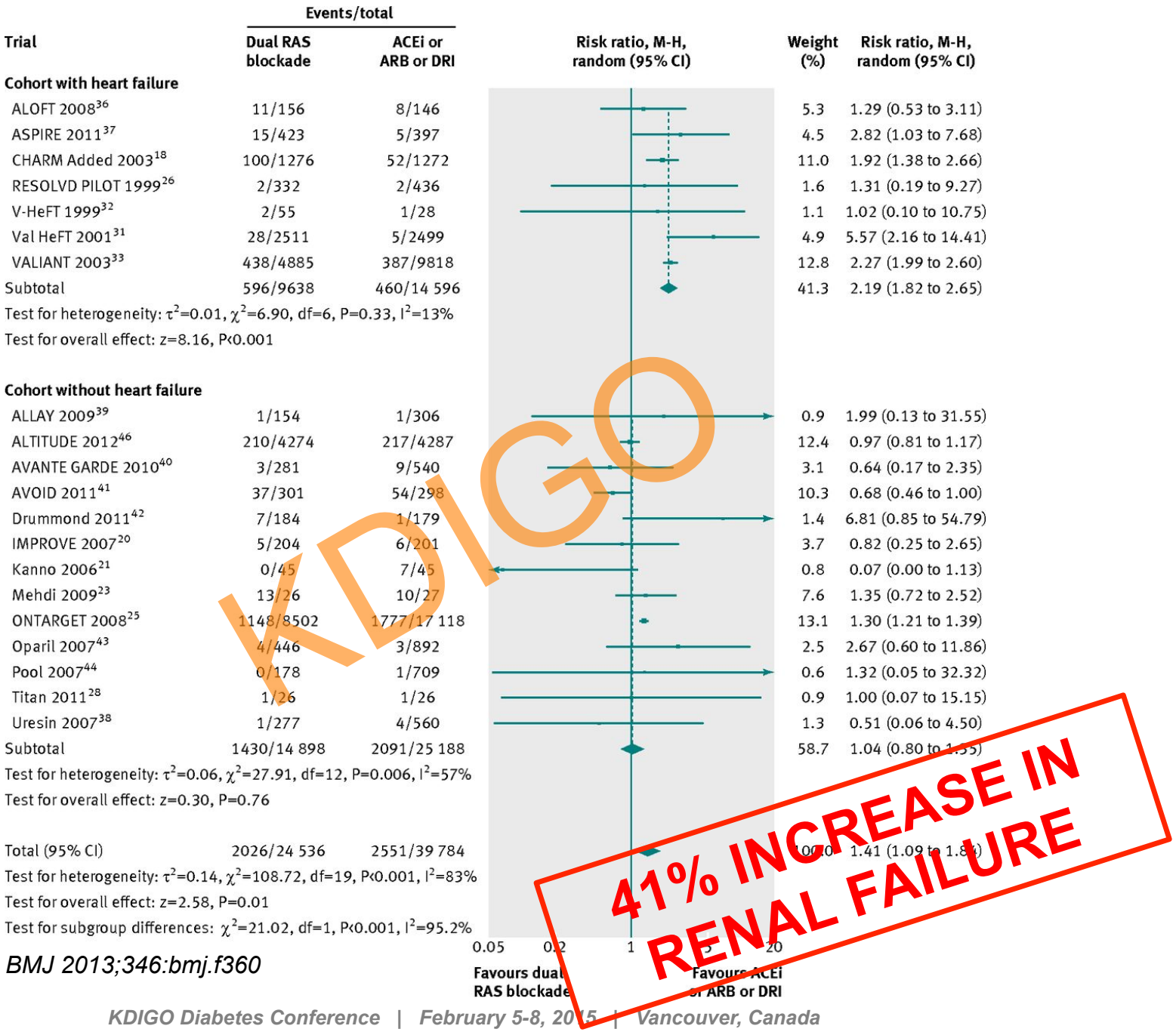

Trial	Events/total: Dual RAS blockade	Events/total: ACEi or ARB or DRI	Risk ratio, M-H, random (95% CI)	Weight (%)	Risk ratio, M-H, random (95% CI)
Cohort with heart failure					
ALOFT 2008[36]	11/156	8/146		5.3	1.29 (0.53 to 3.11)
ASPIRE 2011[37]	15/423	5/397		4.5	2.82 (1.03 to 7.68)
CHARM Added 2003[18]	100/1276	52/1272		11.0	1.92 (1.38 to 2.66)
RESOLVD PILOT 1999[26]	2/332	2/436		1.6	1.31 (0.19 to 9.27)
V-HeFT 1999[32]	2/55	1/28		1.1	1.02 (0.10 to 10.75)
Val HeFT 2001[31]	28/2511	5/2499		4.9	5.57 (2.16 to 14.41)
VALIANT 2003[33]	438/4885	387/9818		12.8	2.27 (1.99 to 2.60)
Subtotal	596/9638	460/14 596		41.3	2.19 (1.82 to 2.65)
Test for heterogeneity: τ^2=0.01, χ^2=6.90, df=6, P=0.33, I^2=13%					
Test for overall effect: z=8.16, P<0.001					
Cohort without heart failure					
ALLAY 2009[39]	1/154	1/306		0.9	1.99 (0.13 to 31.55)
ALTITUDE 2012[46]	210/4274	217/4287		12.4	0.97 (0.81 to 1.17)
AVANTE GARDE 2010[40]	3/281	9/540		3.1	0.64 (0.17 to 2.35)
AVOID 2011[41]	37/301	54/298		10.3	0.68 (0.46 to 1.00)
Drummond 2011[42]	7/184	1/179		1.4	6.81 (0.85 to 54.79)
IMPROVE 2007[20]	5/204	6/201		3.7	0.82 (0.25 to 2.65)
Kanno 2006[21]	0/45	7/45		0.8	0.07 (0.00 to 1.13)
Mehdi 2009[23]	13/26	10/27		7.6	1.35 (0.72 to 2.52)
ONTARGET 2008[25]	1148/8502	1777/17 118		13.1	1.30 (1.21 to 1.39)
Oparil 2007[43]	4/446	3/892		2.5	2.67 (0.60 to 11.86)
Pool 2007[44]	0/178	1/709		0.6	1.32 (0.05 to 32.32)
Titan 2011[28]	1/26	1/26		0.9	1.00 (0.07 to 15.15)
Uresin 2007[38]	1/277	4/560		1.3	0.51 (0.06 to 4.50)
Subtotal	1430/14 898	2091/25 188		58.7	1.04 (0.80 to 1.35)
Test for heterogeneity: τ^2=0.06, χ^2=27.91, df=12, P=0.006, I^2=57%					
Test for overall effect: z=0.30, P=0.76					
Total (95% CI)	2026/24 536	2551/39 784		100.0	1.41 (1.09 to 1.84)
Test for heterogeneity: τ^2=0.14, χ^2=108.72, df=19, P<0.001, I^2=83%					
Test for overall effect: z=2.58, P=0.01					
Test for subgroup differences: χ^2=21.02, df=1, P<0.001, I^2=95.2%					

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41% INCREASE IN RENAL FAILURE

OTHER SIDE EFEFCTS

- ☒ Increase hyperkalemia (↑**55%**)
- ☒ Increase hypotension (↑**66%**)
- ☒ Increase drug withdrawal due to AE (↑**27%**)

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But what about specifically **patients with DKD**? (who have higher risk of these complications but also heart failure, albuminuria and hypertension)

VA-NEPHRON-D

Fried LF et al. N Engl J Med 2013;369:1892-1903.

Table 2. Efficacy End Points and Mortality.*

End Point	Losartan plus Placebo (N=724)	Losartan plus Lisinopril (N=724)	Hazard Ratio with Losartan plus Lisinopril (95% CI)	P Value
	no. of patients (%)			
Primary end point†	152 (21.0)	132 (18.2)	0.88 (0.70–1.12)	0.30
Secondary end point‡	101 (14.0)	77 (10.6)	0.78 (0.58–1.05)	0.10
ESRD	43 (5.9)	27 (3.7)	0.66 (0.41–1.07)	0.07
Death	60 (8.3)	63 (8.7)	1.04 (0.73–1.49)	0.75
Myocardial infarction, heart failure, or stroke	136 (18.8)	134 (18.5)	0.97 (0.76–1.23)	0.79
Myocardial infarction	40 (5.5)	52 (7.2)	1.30 (0.87–1.97)	0.20
Congestive heart failure	106 (14.6)	89 (12.3)	0.82 (0.62–1.09)	0.17
Stroke	18 (2.5)	18 (2.5)	0.98 (0.52–1.85)	0.95

* CI denotes confidence interval, and ESRD end-stage renal disease.

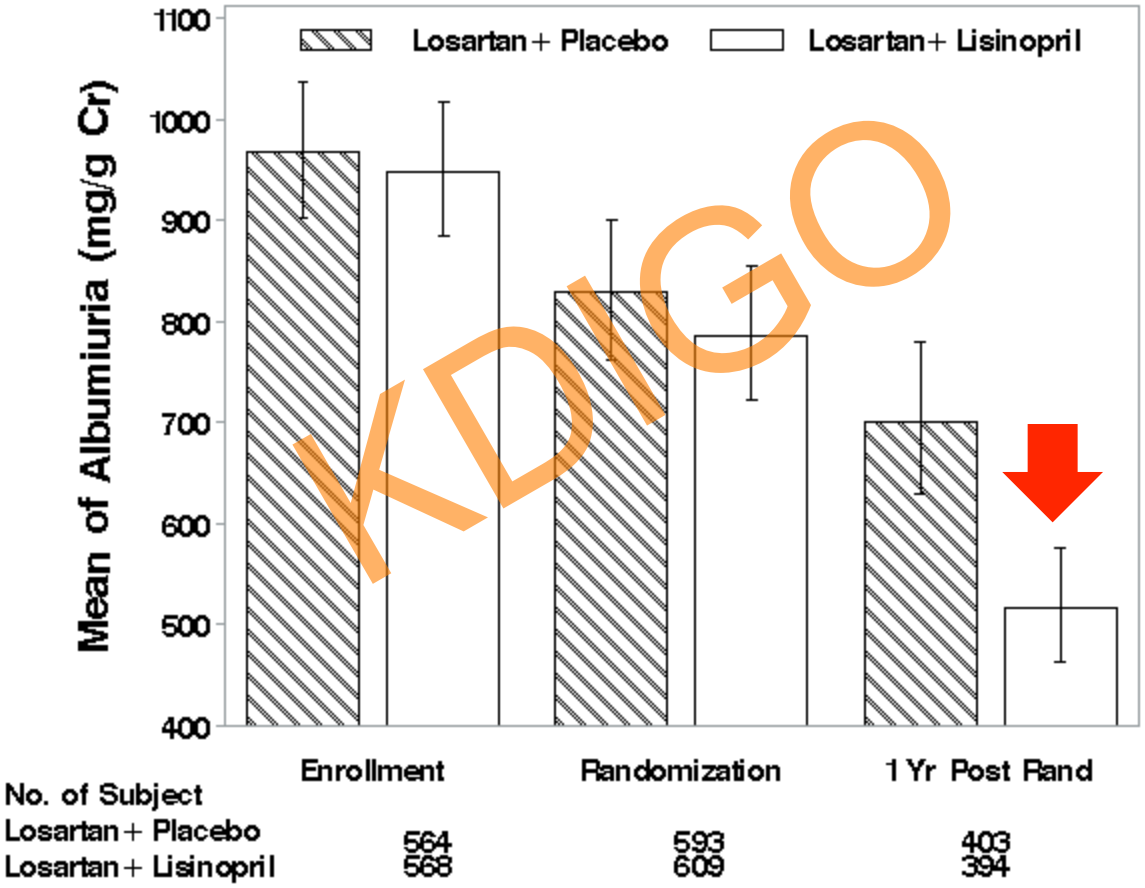
† The primary end point was the first occurrence of a change in the estimated GFR (a decline of ≥30 ml per minute per 1.73 m^2 if the initial estimated GFR was ≥60 or a decline of ≥50% if the initial estimated GFR was <60 ml per minute per 1.73 m^2), ESRD, or death.

‡ The secondary end point was the first occurrence of a change in the estimated GFR (as defined above) or ESRD.

VA-NEPHRON-D

Fried LF et al. N Engl J Med 2013;369:1892-1903.

As in ONTARGET and ALTITUDE, combination therapy decreased albuminuria



VA-NEPHRON-D.

Fried LF et al. N Engl J Med 2013;369:1892-1903.

The study was stopped early (median FU of 2.2 y) owing to safety concerns along with low conditional power (<5% for the observed trend) to detect a treatment effect on the primary end point.

↑ **Hyperkalemia**
HR 2.8 (95% CI, 1.8 to 4.3; P<0.001).

↑**Acute kidney injury**
HR 1.7 (95% CI, 1.3 to 2.2; P<0.001).

GUIDELINES

The use of a combination of ACE-Is and ARBs as a dual blockade of the RAS cannot be recommended at present *K/DOQI*

"No significant benefits of combination use were seen in people who did not have heart failure and there was an increased risk of hyperkalaemia, hypotension, and impaired renal function" *European safety review*

MHRA advised that people with diabetic nephropathy should not be given an ARB with an ACE inhibitor because they are already prone to developing hyperkalaemia. *NICE*

IS CLOSE MONITORING ENOUGH?

Closely monitor blood pressure, renal function and electrolytes in patients ..
On agents that affect the RAS

vs

Since we have no outcome data showing benefit for dual RAS blockade, this is not simply a question of closely monitoring?”


R.I.P
DUAL RAS
BLOCKADE