The Treatment Effect of RAS Blockade on Proteinuria in IgA Nephropathy Patients as a Surrogate for Renal Events and Decline in eGFR: An Analysis of Randomized Controlled Trials

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Disclosures

- Jonathan Barrett-Consultancy/Advisory Board: Alnylam, Astellas, BioCryst, Calliditas, Chinook, Dimerix, Novartis, Omeros, Travere Therapeutics, Vera Therapeutics, Visterra; Steering Committee: Internal IgA Nephropathy Network; Editorial Board: Kidney International, CJASN, Clinical Science, Glomerular Diseases.
- Alex Mercer has received consultancy fees and speaker's honoraria from Travere Therapeutics Inc as a part of JAMCO Pharma Consulting with ownership interests.
- Leah Conley is an employee of Travere Therapeutics Inc and may have an equity or other financial interest in Travere Therapeutics Inc.
- Kevin Carroll provides statistical consultancy services to Travere Therapeutics and other biotech companies. He does not hold stock in Travere Therapeutics or any other biotech/pharma company. He is not an employee, board member or non-executive board member of any pharma/biotech company or any clinical research service provider

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Background

- Renin-Angiotensin System Blockade (RASB) is the cornerstone of standard-of-care in IgA nephropathy (IgAN).
- Randomized controlled trials (RCTs) have shown the treatment benefit of RASB therapy on proteinuria and risk of renal failure.
- Trial level analyses of RCTs across a variety of mechanisms of actions are part of a growing body of evidence supporting proteinuria change as a surrogate for risk of renal failure (Inker et al, 2016[1]; Thompson et al, 2019[2]) and decline in eGFR (Inker et al, 2021[3]) in IgAN.

Objective

To describe relationships between the treatment effect of RASB on:

1. **Proteinuria vs risk of renal events**
2. **Proteinuria vs decline in eGFR**

1. Inker L, et al. Early change in Urine Protein as a Surrogate End Point in Studies of IgA Nephropathy: An Individual-Patient Meta-analysis 2. Thompson A, et al. Proteinuria Reduction as a Surrogate End Point in Trials of IgA Nephropathy. *Clin J Am Soc Nephrol.* 2019;14(3):469-481. 3. Inker L, et al. Association of Treatment Effects on Early Change in Urine Protein and Treatment Effects on GFR Slope in IgA Nephropathy: An Individual Participant Meta-analysis. *Am J Kidney Dis.* 2021 Mar 26;S0272-6386(21)00502-3. doi: 10.1053/j.ajkd.2021.03.007.

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Methods

Systematic Literature Review

April 2019 and January 2020

- Of the 893 references identified in the original systematic search (PubMed, Cochrane, Embase), 9 RCTs, including 10 potential comparisons, met the inclusion criteria

Inclusion Criteria

- RCT in patients with biopsy-proven IgAN
- Investigating RASB as an intervention
- Sample size >25
- Proteinuria at baseline and at >3 months
- At least 1 renal event (defined as ≥50% decline in eGFR, CKD Stage 5, dialysis or transplantation) OR eGFR at baseline and ≥12 months follow-up

Statistical Methods

- Trial Level (TL) meta-regression analysis (Burzykoski & Buyse (2006) and Joffe & Greene (2008))
- Simple Weighted Linear Regression (SWR) analysis*
- Proteinuria change from baseline was calculated from the value closest to 6 months
- Annualized change in eGFR was calculated per year of follow-up**

Eligible RCTs

Analyzed Treatment Group Comparisons & Sample size (n)											
	Intervention	Enalapril (23)	Losartan & Temocapril (13)	Valsartan (54)	Enalapril and/or Losartan (37)	Losartan (18)	Losartan 200mg (63)	Enalapril 20 mg (61)	Losartan and Mizoribine (34)	Candesartan (40)	Losartan and Lisinopril (31)
	Comparator	No treatment (21)	Temocapril (14)	Placebo (55)	No treatment (38)	Antiplatelet therapy (18)	Losartan 100 mg (43)	Enalapril 10 mg (40)	Mizoribine (35)	No treatment (37)	Lisinopril (31)
Source		Praga et al, 2003	Horita et al, 2006	Li et at, 2006	Woo et al, 2007	Shimizu et al, 2008	Woo et al, 2009a	Woo et al, 2009b	Xie et al, 2011	Kohaguru et al, 2018	Shima et al, 2019

*Given the assumptions made in this analysis; to compensate for potential underestimation of error associated with the regression line, a 99.9% CB was applied in the SWR analysis.
**If annualized change in eGFR was reported, these data were used.

Results

Treatment effects and follow-up duration for proteinuria and eGFR

Source	Proteinuria				eGFR / CrCl				
	Change from baseline (%)		Treatment effect (log scale)	Follow-up duration (months)	Change from baseline		Treatment effect (mL/min)	Follow-up duration (months)	Annualized Treatment effect (mL/min)
	Intervention	Comparator			Intervention	Comparator			
Praga et al, 2003 [1]	-40%	6%	-0.57	12	-7.0	-35.0	28.0	76	4.4
Horita et al, 2006 [2]	-71%	-50%	-0.55	12	-6.1	-9.4	3.3	12	3.3
Li et at, 2006 [3]	-28%	13%	-0.45	5.5	-13.5	-9.1	-4.5	24	1.4
Woo et al, 2007 [4]	-48%	-17%	-0.46	62	-3.9	-30.3	26.4	62	5.1
Shimizu et al, 2008 [5]	-44%	-14%	-0.44	12	-0.2	0.7	-0.9	12	-0.9
Woo et al, 2009a [6]	-28%	-5%	-0.28	12	-21.0	-4.4	16.6	75	2.8
Woo et al, 2009b [6]	-28%	-17%	-0.14	12	-20.7	-18.6	-2.1	75	-0.3
Xie et al, 2011 [7]	-48%	-48%	0.00	6	-0.6	0.0	-0.6	12	-0.6
Kohaguru et al, 2018 [8]*	NA	NA	-0.33	6	NA	NA	3.5	24	3.5
Shima et al, 2019 [9]	-60%	-57%	-0.10	24	3.6	4.2	-0.6	24	-0.3

Treatment effects and follow-up duration for renal event analyses

Source:	Renal events			
	Number of Events (%)		Hazard Ratio	Renal event definition
	Intervention	Comparator		
Praga et al, 2003 [1]	3 (13%)	12 (57%)	0.23	Doubling of serum creatinine (57% decline in eGFR)
Li et at, 2006 [3]	1 (2%)	4 (7%)	0.25	Doubling of serum creatinine or ESRD requiring RRT
Woo et al, 2007 [4]	7 (19%)	21 (55%)	0.34	End Stage Renal Failure
Woo et al, 2009a [6]	7 (11%)	9 (21%)	0.53	CKD Stage 5
Woo et al, 2009b [6]	19 (31%)	9 (23%)	1.38	CKD Stage 5

*data extracted from figure in publication

1. Praga M, Gutierrez E, Gonzalez E, Morales E, Hernandez E. Treatment of IgA nephropathy with ACE inhibitors: a randomized and controlled trial. *J Am Soc Nephrol.* 2003;14(6):1578-1583. 2. Li PK, Leung CB, Chow KM, et al. Hong Kong study using valsartan in IgA nephropathy (HKVIN): a double-blind, randomized, placebo-controlled study. *Am J Kidney Dis.* 2006;47(5):751-760. 3. Horita Y, Taura K, Taguchi T, Furusu A, Kohno S. Aldosterone breakthrough during therapy with angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers in proteinuric patients with immunoglobulin A nephropathy. *Nephrology.* 2006;11:462-466 4. Woo KT, Lau Y-K, Zhao Y, et al. Disease progression, response to ACEI/ATRA therapy and influence of ACE gene in IgA nephritis. *Cellular & Molecular Immunology*. 2007;4(3):227-232 5. Shimizu A, Takei T, Uchida K, Tsuchiya K, Nitta K. Low-dose losartan therapy reduces proteinuria in normotensive patients with immunoglobulin A nephropathy. *Hypertens. Res.* 2008;31(9):1711-1717
6. Woo KT, Chan C-M, Tan H-K, et al. Beneficial effects of high dose losartan in IgA nephritis. *Clinical Nephrology*. 2009;71(6):617-624 7. Xie Y, Huang S, Wang L, et al. Efficacy and safety of mizoribine combined with losartan in the treatment of IgA nephropathy: A mulitcenter, randomized, controlled study. *Am. J. Med. Sc.* 2011;341(5):367-372 8. Kohagura K, Arima H, Miyasato, H, et al. Add-on effect of angiotensin receptor blockade (candesartan) on clinical remission in active IgA nephropathy patients treated with steroid pulse therapy and tonsillectomy: a randomized, parallel-group comparison trial. *Kidney Blood Press. Res.* 2018;43:780-792 9. Shima Y, Nakanishi K, Sako, M, et al. Lisinopril versus lisinopril and losartan for mild childhood IgA nephropathy: a randomized controlled trial (JSKDC01 study). *Pediatric Nephrology* 2019;34:837-846

Results

RASB treatment effect on proteinuria vs renal events

- **Trial Level analysis**
  - A statistical association was found with treatment effects on proteinuria versus renal event.
  - As individual subject level data were not available, the correlation between errors on treatment effects for proteinuria and treatment effects for renal events were unknown, resulting in wide 80% confidence bands (CB) on the meta-regression line and wide 95% CI for the slope estimate.
- **Simple Linear Weighted Regression (SWR) analysis**
  - A statistical association predicting that a 30% treatment effect on proteinuria would be estimated to result in at least a 64% reduction in risk of renal events.
  - SWR approach not hampered by lack of subject level data.

Proteinuria vs Risk of Renal Events

	Slope (95% CI)	Intercept (95% CI)	R^2 (95% CI)
TL analysis	15.30 (0.57, 38.79)	6.15 (-0.22,15.86)	0.88 (0.22, 1.00)
SWR analysis	3.5 (2.4, 4.7)	0.99 (0.40, 1.58)	0.97

Figure 1A

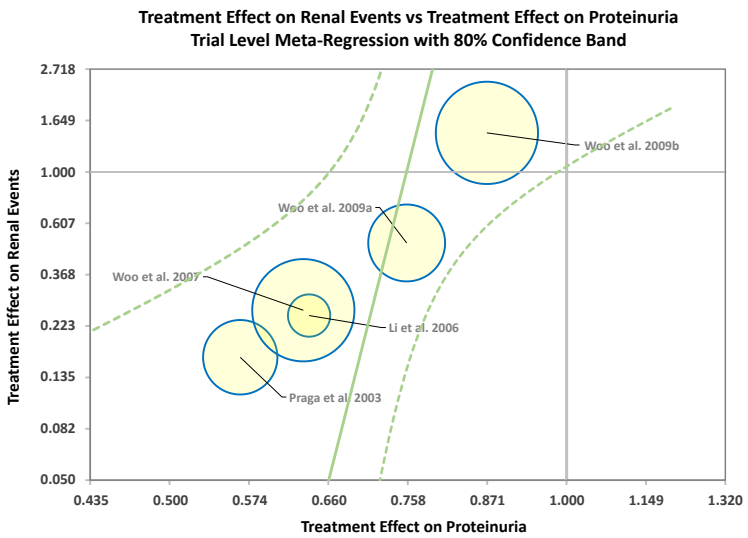


Figure 1B

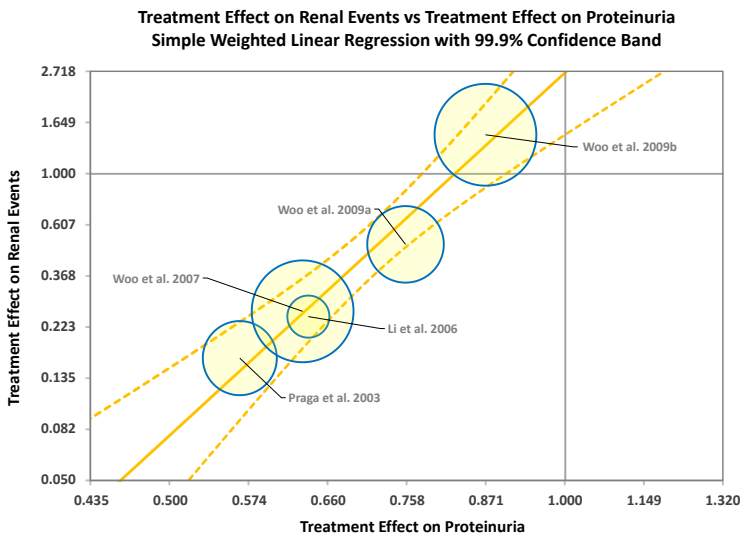
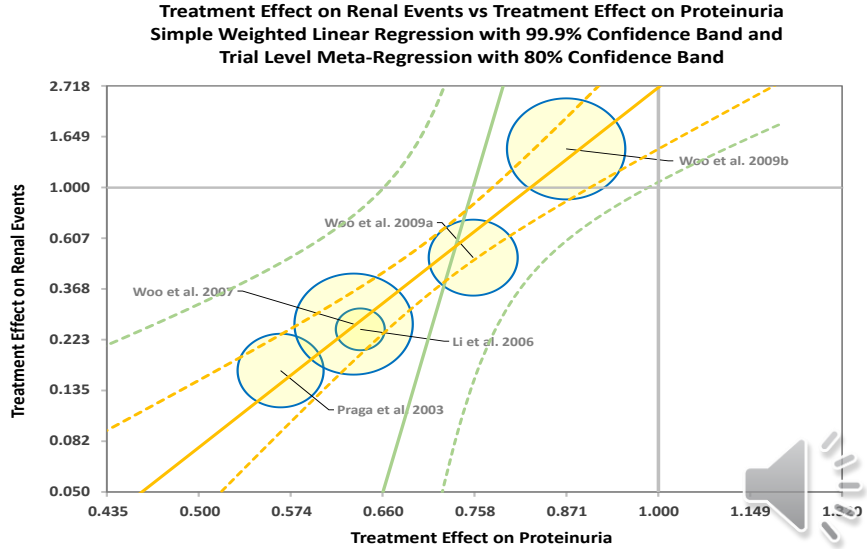


Figure 1C



Results

RASB treatment effect on proteinuria vs eGFR decline

- Comparable associations between TL and SWR analyses.
  - A 30% treatment effect on proteinuria would be estimated to result in a 2.6 mL/min (TL analysis) to 3.9 mL/min slower decline (SWR analysis) in annualized eGFR.

Proteinuria vs eGFR Decline

	Slope (95% CI)	Intercept (95% CI)	R^2 (95% CI)
Trial Level	-5.1 (-30.2, 35.0)	1.25 (-8.0,15.7)	0.89 (0.15, 1.00)
Simple Weighted Linear Regression	-7.6 (-11.5, -3.6)	-0.45 (-2.97, 2.07)	0.71

Figure 1D

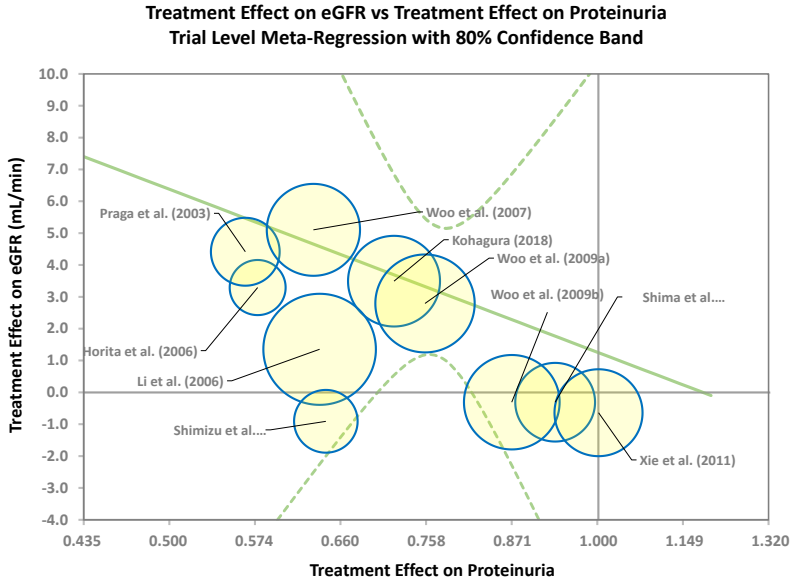
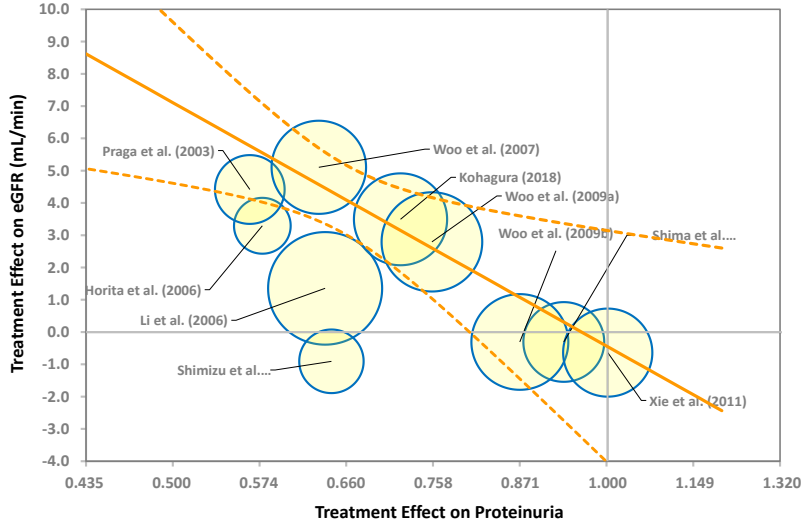


Figure 1E



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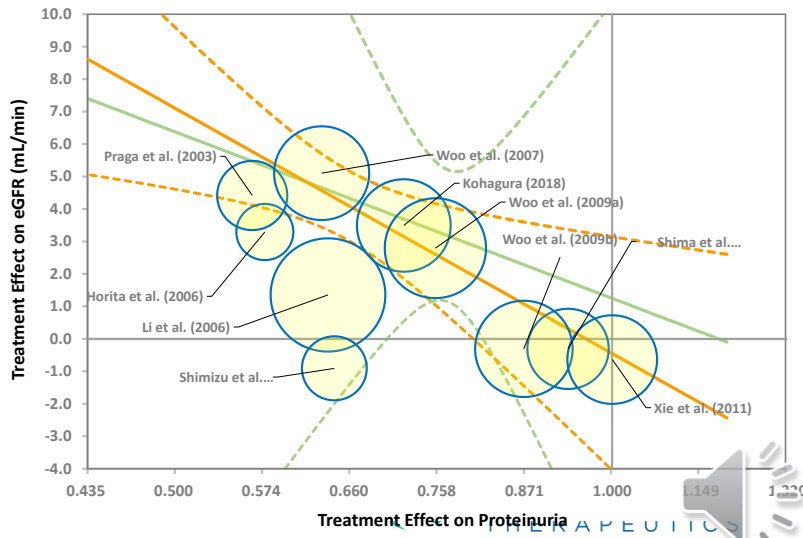

Limitations

- Low number of RCTs with small sample sizes with limited number of events and limited follow-up period in some cases.
- Lack of availability of individual patient level data.
- Wide confidence bands and credibility intervals for TL analyses lending uncertainly in the precision of associations.
- Potential underestimation of error associated with the regression line for SWR analysis.

Conclusions

- In patients with IgAN, associations were seen between treatment effects of RASB on proteinuria and on the clinically relevant endpoints of renal events and annualized change in eGFR.
- Consistent with TL analyses of RCTs across a variety of mechanisms of actions (Inker et al, 2016[1]; Thompson et al, 2019[2]; Inker et al, 2021[3]), these data, specific to RASB, contribute to the growing evidence base supporting the use of proteinuria as a valid surrogate endpoint in IgAN.

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1. Inker L, et al. Early change in Urine Protein as a Surrogate End Point in Studies of IgA Nephropathy: An Individual-Patient Meta-analysis 2. Thompson A, et al. Proteinuria Reduction as a Surrogate End Point in Trials of IgA Nephropathy. *Clin J Am Soc Nephrol.* 2019;14(3):469-481. 3. Inker L, et al. Association of Treatment Effects on Early Change in Urine Protein and Treatment Effects on GFR Slope in IgA Nephropathy: An Individual Participant Meta-analysis. *Am J Kidney Dis.* 2021 Mar 26;S0272-6386(21)00502-3. doi: 10.1053/j.ajkd.2021.03.007.

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