EARLY CHANGE IN PROTEINURIA AS A SURROGATE ENDPOINT IN STUDIES OF IGA NEPHROPATHY: AN UPDATED PATIENT-LEVEL META-ANALYSIS AND DISCUSSION OF APPROPRIATE METHODOLOGY

Authors: Nicolas Maillard[1,2], Khalil El Karoui[3,4], Alex Mercer[5], Barnaby Hunt[6], Kevin J Carroll[7]

Affiliations:

[1] Department of Nephrology, Dialysis, Transplantation, CHU de Saint-Etienne, Saint-Etienne, France

[2] INSERM U1111 CIRI Team GIMAP Université de Lyon, Lyon, France

[3] Department of Nephrology, Sorbonne University, APHP, CHU Hôpital Tenon, Paris, France.

[4] INSERM U955, Corakid, Paris, France

[5] JAMCO Pharma Consulting, Stockholm, Sweden

[6] Ossian Health Economics and Communications, Basel, Switzerland

[7] KJC Statistics Ireland, Dublin, Ireland

Corresponding author: Barnaby Hunt

Ossian Health Economics and Communications GmbH

Bäumleingasse 20, 4051 Basel, Switzerland

Telephone: +41 61 271 6214

E-mail: hunt@ossianconsulting.com

SUPPLEMENTARY APPENDIX

Figure S1 Literature search flow diagram

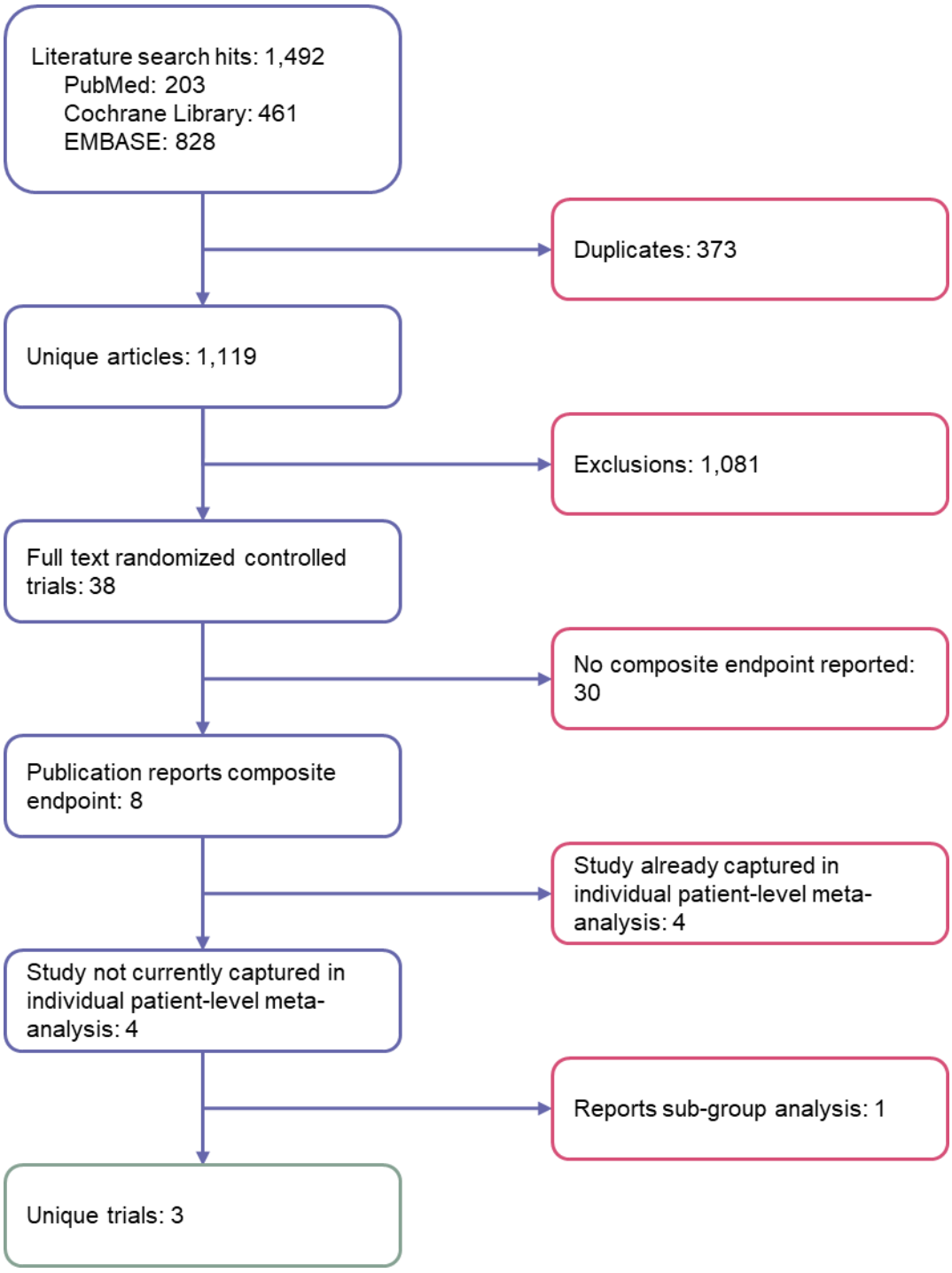

Table S1 PubMed search strategy

Line	Search aim	Search terms	Hits
#1	Immunoglobulin A nephropathy	"glomerulonephritis, IgA"[MeSH Terms] OR ("Immunoglobulin A"[MeSH Terms] AND "Glomerulonephritis"[MeSH Terms]) OR "IgAN"[Title/Abstract] OR "IgA nephropathy"[Title/Abstract] OR "Berger's disease"[Title/Abstract] OR "IgA deposits"[Title/Abstract]	11,824
#2	Randomized controlled trials	"randomized controlled trial"[Publication Type] OR "controlled clinical trial"[Publication Type] OR "clinical trial"[Publication Type] OR "randomized controlled trials as topic"[MeSH Terms] OR "clinical trials as topic"[MeSH Terms] OR "random allocation"[MeSH Terms] OR "double blind method"[MeSH Terms] OR "single blind method"[MeSH Terms] OR "randomized"[Title/Abstract] OR "randomised"[Title/Abstract] OR "randomly"[Title/Abstract] OR "trial"[Title/Abstract]	2,275,794
#3	Randomized controlled trials in people with immunoglobulin A nephropathy	#1 AND #2	819
#4	Limit to studies published from 2019 onwards	#3 AND ("2019/01/01"[Date - Publication] : "2024/08/16"[Date - Publication])	203

Table S2 EMBASE search strategy

Line	Search aim	Search terms	Hits
#1	Immunoglobulin A nephropathy	'immunoglobulin a nephropathy'/exp OR 'igan':ti,ab OR (('iga':ti,ab OR 'immunoglobulin a':ti,ab) AND ('nephropathy':ti,ab OR 'glomerulonephritis':ti,ab))	21,514
#2	Randomized controlled trials	'randomized controlled trial'/exp OR 'controlled clinical trial'/de OR 'randomization'/de OR 'double blind procedure'/de OR random*:ti,ab,tt OR (open NEXT/1 label):ti,ab,tt OR ((double OR single OR doubly OR singly) NEXT/1 (blind OR blinded OR blindly)):ti,ab,tt OR (controlled NEAR/8 (study OR design OR trial)):ti,ab,tt OR ((assign* OR match OR matched OR allocation) NEAR/6 (alternate OR group OR groups OR intervention OR interventions OR patient OR patients OR subject OR subjects OR participant OR participants)):ti,ab,tt OR (parallel NEXT/1 group*):ti,ab,tt OR (crossover:ti,ab,tt OR 'cross over':ti,ab,tt) OR (controlled NEAR/8 (study OR design OR trial)):ti,ab,tt OR trial:ti,tt	2,896,935
#3	Randomized controlled trials in people with immunoglobulin A nephropathy	#1 AND #2	1,602
#4	Limit to studies published from 2019 onwards	#3 AND (2019:py OR 2020:py OR 2021:py OR 2022:py OR 2023:py OR 2024:py OR 2025:py)	828

Table S3 The Cochrane Library search strategy

Line	Search aim	Search terms	Hits
#1	Immunoglobulin A nephropathy	MeSH descriptor: [Glomerulonephritis, IGA] explode all trees OR ("IgAN"):ti,ab,kw OR ("immunoglobulin A nephropathy"):ti,ab,kw	850
#2	Limit to studies published from 2019 onwards	Limit #1 to published between 1 January, 2019 and February 26, 2025	461

Table S4 Baseline characteristics of patients with IgA nephropathy enrolled in published clinical trials with no published patient-level data

	DAPA-CKD		MAIN		NefIgArd	
	Dapagliflozin	**Placebo**	**Mycophenolate mofetil plus supportive care**	**Supportive care**	**Budesonide**	**Placebo**
Characteristics						
Number of randomized patients	137	133	85	85	182	182
Age (years)*	52.2 (13.1)	50.1 (13.1)	35.0 (8.7)	38.2 (9.8)	43 (36 to 50)	42 (34 to 49)
Percentage female	32.1%	33.1%	50.6%	38.8%	35.7%	32.4%
Race						
White	39.4%	40.6%	No data reported	(study conducted in China)	75.8%	75.3%
Black	0.0%	0.8%			0.0%	0.0%
Asian	59.9%	57.9%			23.6%	22.0%
Other	0.7%	0.8%			0.5%	2.7%
eGFR (mL/minutes/1.73 m^2)*	44.3 (12.4)	43.2 (12.0)	50.9 (18.2)	49.3 (17.7)	56.14 (45.50 to 70.97)	55.11 (45.96 to 67.74)
SBP (mmHg)*	127.7 (16.2)	127.0 (1.39)	126.3 (18.3)	126.1 (18.8)	126 (121 to 132)	124 (117 to 130)
DBP (mmHg)*	78.7 (11.8)	79.5 (10.1)	82.6 (13.7)	80.9 (12.4)	79 (76 to 84)	79 (74 to 84)

	DAPA-CKD		MAIN		NefIgArd	
	Dapagliflozin	Placebo	Mycophenolate mofetil plus supportive care	Supportive care	Budesonide	Placebo
Proteinuria measurements						
Mean proteinuria (g/day)	NR	NR	2.1 (1.9)	1.7 (1.3)	2.71 (1.73)	2.71 (2.20)
Median proteinuria (g/day)	NR	NR	NR	NR	2.29 (1.61 to 3.14)	2.17 (1.53 to 3.39)
Mean UPCR (g/g)	NR	NR	NR	NR	1.48 (0.85)	1.48 (1.15)
Median urinary UPCR (g/g)	NR	NR	NR	NR	1.28 (0.90 to 1.76)	1.25 (0.88 to 1.74)
Mean total urine albumin (g/day)	NR	NR	NR	NR	2.12 (1.34)	2.11 (1.58)
Median total urine albumin (g/day)	NR	NR	NR	NR	1.77 (1.24 to 2.49)	1.70 (1.12 to 2.54)
Mean UACR (g/g)	NR	NR	NR	NR	1.15 (0.68)	1.15 (0.84)
Median UACR (g/g)	0.89 (0.58 to 1.47)	0.903 (0.50 to 1.63)	NR	NR	0.99 (0.68 to 1.40)	0.98 (0.66 to 1.42)

* Values are mean (standard deviation) for DAPA-CKD and MAIN, and median (interquartile range) for NefIgArd. DBP, diastolic blood pressure, eGFR, estimated glomerular filtration rate; NR, not reported; SBP, systolic blood pressure; UACR, urinary albumin-to-creatinine ratio; UPCR, urinary protein-to-creatinine ratio.

Change in eGFR results from PROTECT double-blind period

The primary analysis of eGFR-based endpoints included only on-treatment data (i.e., data were censored after treatment discontinuation) and imputed missing data, assuming they were missing at random. Per US Food and Drug Administration (FDA) request, the modified intention to treat (mITT) analysis evaluated data from all patients regardless of treatment discontinuation and imputed data for patients who initiated rescue immunosuppressive therapy, received dialysis or kidney transplant, or died, assuming that these data were not missing at random. Results of the mITT analysis were largely consistent with those of the primary analysis (Table S5), with between-group differences for eGFR endpoints that favored sparsentan versus irbesartan.

Table S5 Changes in eGFR in PROTECT

Endpoint	Primary on-treatment analysis[1] (as per protocol)	mITT analysis (FDA preferred)
eGFR total slope from day 1 to week 110, mL/min/1.73 m^2/year		
Sparsentan	−2.9 (−3.6 to −2.2)	−3.0 (−3.7 to −2.4)
Irbesartan	−3.9 (−4.6 to −3.1)	−4.2 (−4.9 to −3.5)
Difference	1.0 (−0.03 to 1.94)	1.2 (0.2 to 2.1)
P value	0.058	0.017*
eGFR chronic slope from weeks 6 to 110, mL/min/1.73 m^2/year		
Sparsentan	−2.7 (−3.4 to −2.1)	−2.9 (−3.6 to −2.2)
Irbesartan	−3.8 (−4.6 to −3.1)	−4.2 (−4.9 to −3.5)
Difference	1.1 (0.1 to 2.1)	1.3 (0.3 to 2.3)
P value	0.037	0.0087*
Absolute change in eGFR from baseline to week 110, mL/min/1.73 m^2		
Sparsentan	−5.8 (−7.4 to −4.2)	−6.1 (−7.7 to −4.4)
Irbesartan	−9.5 (−11.2 to −7.9)	−9.9 (−11.5 to −8.3)
Difference	3.7 (1.5 to 6.0)	3.8 (1.6 to 6.1)
P value	ND†	ND†

eGFR, estimated glomerular filtration rate; FDA, US Food and Drug Administration; mITT, modified intention to treat; ND, not determined. *Nominal P value based on post hoc analysis. †P value not calculated per hierarchical statistical testing plan. eGFR total slope, eGFR chronic slope and absolute change in eGFR were key secondary endpoints.

Summary of systematic literature review process

Literature searches across the PubMed, EMBASE and Cochrane Library databases identified a total of 1,492 articles (Figure S1). After removal of 373 duplicates, 1,119 unique articles were taken forward for screening by title and abstract. This identified 38 full-text publications describing randomized controlled trials performed in adults with IgA nephropathy published between 2019 and the present day for full-text review. Across these, eight publications reported both proteinuria data and a composite endpoint reflecting efficacy in terms of preventing progression of renal disease. Of these eight, three publications related to the STOP-IgAN and TESTING (two publications), studies that were already included in the previous patient-level analysis performed by Thompson *et al.* 2019. While these publications presented updated data, they are provided only in aggregate and thus could not be included in the current update. Hence, STOP-IgAN and TESTING are included in the current update based on the same data as included in Thompson *et al*. 2019. One further publication reported data from PROTECT. Patient-level data from PROTECT were available to the study authors and, thus, these data have already been included in the present update.

Summary of heterogeneity across the published randomized controlled trials not included in the individual patient-level meta-analysis

Across the three trials, reporting of the baseline characteristics (but not necessarily the characteristics themselves) varied, making comparisons between the studies difficult (Table S4). In DAPA-CKD and MAIN, mean and standard deviation values for age, eGFR, systolic blood pressure and diastolic blood pressure were reported, whereas medians and interquartile ranges were reported in NefIgArd. Additionally, proteinuria at baseline in NefIgArd was reported using a variety of measurements, summarized as both means and medians, whereas only median urinary albumin-to-creatinine ratio (UACR) was reported from DAPA-CKD and only mean proteinuria in terms of g/day was reported from MAIN. Where study characteristics can be compared, notable heterogeneity between the study populations was observed, with the average age in the DAPA-CKD population approximately 15 years higher than the average age in the MAIN population, eGFR notably lower in the DAPA-CKD

population than in the other two studies, and DAPA-CKD and NefIgArd enrolling a mix of ethnicities whereas MAIN was conducted exclusively in China.

The reporting of the proteinuria treatment effect also differed between the trials, both in terms of the measure used and the timing of the data collection. Mean percentage difference in UACR between dapagliflozin and placebo at month 4 and over the median follow-up of 2.1 years was reported from the DAPA-CKD trial. The MAIN study assessed change from baseline in mean urinary protein excretion over the 3-year trial period, expressed in g/day and as a percentage change in each trial arm. In the NefIgArd study, the proteinuria measures were ratios of time-averaged urinary protein-to-creatinine ratio and UACR between 12 and 24 months compared with baseline. All of these proteinuria measurement times fall outside of the 5 to 12 month window used in the present meta-analysis.

There was also heterogeneity in the reporting of composite endpoints in studies not included in the meta-analysis. In the DAPA-CKD trial, two composite endpoints were reported, with a primary endpoint of decline in eGFR ≥50%, kidney failure or death from a kidney disease-related or cardiovascular cause, and a secondary endpoint of decline in eGFR ≥50%, kidney failure or death from a kidney disease-related cause (i.e., the primary endpoint with cardiovascular death excluded). The primary endpoint used in the MAIN trial was similar, though not identical, to that used in the DAPA-CKD trial, expressed as composite of doubling of serum creatinine, kidney failure or death due to kidney or cardiovascular cause (doubling of serum creatinine is equivalent to a 57% reduction in eGFR). The composite endpoint reported in the NefIgArd trail was not aligned with the other two studies, with the publication reporting the percentage of patients with ≥30% reduction in eGFR or kidney failure (no mortality aspect was included in the endpoint, with two deaths occurring in the budesonide arm, though neither were considered to be treatment-related). Notably, none of these endpoints were aligned with the composite endpoint used in the present meta-analysis of doubling of serum creatinine level, kidney failure or death.

Within-study correlation of errors is unknown when only aggregate data are available

With aggregate data, it is not possible to make allowance for the observed correlation between endpoints within each study. In the 2022 publication by Lafayette *et al*., a range of possible

correlations are assumed and employed using copula-based analyses within which the association one is trying to estimate is itself implicitly assumed. Given that the within study correlation of errors is unknown, it is infeasible to execute a truly comprehensive set of assumptions as the number of possible correlation values across 13 trials is extremely large. To see this, if simplifying to just three possible levels of correlation, say, <0.33, 0.33–0.67 and >0.67, there would be approximately 1.6 million possible configurations of correlations across 13 studies, and this would rise to over 67 million if four levels of correlation were assumed. Further, it is in general problematic to make assumptions about the unknown within-subject correlation of endpoints X and Y when the ultimate goal of the analysis itself is to estimate the association between treatment effects on the same variables. While the approach to *post-hoc* sample virtual patient-level data based simply upon the mean and standard deviation of the reported aggregate data under some assumed copula is the best that can reasonably be attempted in the absence of patient-level data, unfortunately this approach cannot be expected to get reliably close to the true nature of the correlation of errors within a set of multiple trials and, thus, the underlying relationship that is the target of the analysis. Only with access to patient-level data measured over time can this be achieved.