

Original Paper

Efficacy and Safety of Agents in IgA Nephropathy: An Update Network Meta-Analysis

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Key Words

IgA nephropathy • Renin-angiotensin system • Steroid • Proteinuria

Abstract

Background/Aims: The present network meta-analysis of randomized controlled trials (RCTs) was to explore the efficacy and safety of different pharmacologic interventions in IgA nephropathy with proteinuria more than 0.75 g/d. **Methods:** We systematically searched the Cochrane Library, Embase, and PubMed database for studies compared the rate of clinical remission and/or serious adverse events in IgA nephropathy patients with proteinuria (> 0.75 g/d) up to August 1, 2018. We ranked the comparative effects of all drugs against placebo on the surface under the cumulative ranking area (SUCRA) probabilities. **Results:** There were 29 RCTs comprising 2517 participants included for the comparisons of 9 interventions. The rank of the most effective treatments for inducing clinical remission was renin-angiotensin system inhibitors (RASi) in combination with steroid, tonsillectomy combined with steroid pulse therapy, and azathioprine plus RASi with SUCRA of 82.9%, 80.5%, and 67.6%, respectively. RASi in combination with steroid (SUCRA 3.9%) was the most effective in prevention of end-stage renal disease or doubling serum creatinine, followed by RASi monotherapy (SUCRA 38.4%) and azathioprine combined with steroid (SUCRA 49.0%). As for the occurrence of serious adverse events, azathioprine combined with RASi (SUCRA 88.0%) and steroid plus RASi (SUCRA 74.6%) showed the first and second highest incidence of adverse events, respectively. **Conclusion:** RASi combined with steroid demonstrated the most effective therapeutic approach for IgA nephropathy patients in terms of reducing proteinuria and stabilizing renal function.

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Introduction

Immunoglobulin A (IgA) nephropathy was the most prevalent primary glomerulonephritis worldwide [1]. The deposition of IgA immune complexes in the mesangial area has been proposed as the critical factor in the onset of IgA nephropathy [2, 3]. Approximately 15 to 20 percent of patients with IgA nephropathy will develop end-stage renal disease (ESRD) within 10 years, furthermore 30 to 40 percent within 20 years [4]. Therefore, effective treatment measures are needed for reducing proteinuria and to prevent the decline in kidney function. Various treatments have been studied in IgA nephropathy patients, such as renin-angiotensin system inhibitors (RASi), steroid, mycophenolate mofetil, azathioprine, cyclosporine A, and tonsillectomy, etc [1]. Unfortunately, the optimal treatment remains controversial.

The Kidney Disease Improving Global Outcomes (KDIGO) guidelines 2012 suggested the use of systemic glucocorticoids in IgA nephropathy patients with proteinuria level > 1 g/d and estimated glomerular filtration rate (eGFR) > 50 ml/min per 1.73 m² despite supportive care [5]. However, a recent retrospective study [6] for those with proteinuria more than 3.0 g/d indicated that only 4% of individuals with RASi monotherapy reached a level < 1.0 g/d compared with 64% of those receiving steroid. More recently, the outcomes differed between The Therapeutic Evaluation of Steroids in IgA Nephropathy Global (TESTING) [7] and the Supportive versus Immunosuppressive Therapy for the Treatment of Progressive IgA Nephropathy (STOP-IgAN) [8] studies. Therefore, it is necessary to analyze the optimal therapeutic strategies for the IgA nephropathy patients with proteinuria more than 0.75 g/d.

To explore the efficacy and safety of different pharmacologic interventions in IgA nephropathy with proteinuria more than 0.75 g/d, we conducted the present network meta-analysis of randomized controlled trials (RCTs).

Materials and Methods

Data Sources and Search Strategy

We systematically searched the Cochrane Library, Embase, and PubMed database for articles up to August 1, 2018. No language restrictions were imposed during the searches. To identify studies involving relevant participants, we performed the search with keywords including the following terms: IgA nephropathy, immunoglobulin A nephropathy, and IgA nephritis. To identify studies involving therapies, we performed the search with keywords including the following terms: RASi, steroid, mycophenolate mofetil (MMF), azathioprine, cyclosporine A, and tonsillectomy. Electronic search strategies showed in the Supplementary Material S1 (for all supplementary material see www.karger.com/doi/10.1159/000496000). These 2 categories of keywords were combined using the Boolean operator “and”. In this network meta-analysis, the presentations were based on the Preferred Reporting Items for reporting systematic reviews and meta-analyses (PRISMA) of studies that evaluate interventions [9].

Selection Criteria

We collected all RCTs on comparison of therapeutic effects of different drugs in IgA nephropathy patients with proteinuria more than 0.75 g/d. Inclusion criteria of studies: (a) study population was biopsy-proven IgA nephropathy patients, (b) study design was RCTs, (c) the information of the interventions included placebo, RASi, steroid, MMF, tonsillectomy, azathioprine, and cyclosporine A, (d) the subjects with proteinuria or 24-hour urinary protein excretion more than 0.75 g/d and eGFR ≥ 20 ml/min per 1.73 m² or serum creatinine less than 3.5 mg/dl, and (e) articles provided exact data of clinical remission, serious adverse events and/or ESRD or doubling serum creatinine level between patients with treatment group and control group.

In this network meta-analysis, clinical remission was defined as the achievement of proteinuria less than 1.0 g/d or 50% greater of proteinuria reductions [5, 7]. The definition of ESRD was appeared one of these conditions: (a) serum creatinine level over 707 μ mol/L, and (b) need for maintenance dialysis or kidney transplantation [7]. Serious adverse events were defined according to the International Conference

on Harmonization Guideline for Clinical Safety Data Management [7]. The definition of serious adverse events was appeared one of the following conditions: all-cause mortality, serious infections, liver function damage, gastrointestinal hemorrhage, new diabetes, osteonecrosis or fracture, and cardiovascular events.

Criteria for exclusion were as follows: (a) studies such as systemic reviews, case reports, comments, conference abstracts, editorials, etc, (b) the subjects with mild or severe proteinuria, or pathology confirmed as crescent, and (c) articles that had no definitions on clinical remission or renal function.

Included trials reported comparisons of 9 interventions (placebo, RASi, steroid, MMF, steroid plus RASi, tonsillectomy combined with steroid pulse therapy [TSP], azathioprine plus RASi, azathioprine steroid, and cyclosporine A in combination with steroid). The supportive and immunosuppressive interventions were made up according to the type of drugs, monotherapy or combination, regardless of dose.

Data Extraction and Quality Assessment

We assessed risk of bias in contributing studies with standard criteria. Two authors (Y-PP and W-Q) selected studies and extracted data independently. Disagreements were resolved through discussions or referral to the third author (X-GS). Our search strategy and selection criteria were described in the panel. Reference lists of identified RCTs were manually scanned to identify related research references at the same time as indicated in Fig. 1. The RCTs studies quality assessment were completed by using Review Manager 5.3 (Cochrane Collaboration, Oxford, UK) risk of bias tool including the following 7 domains: (a) random sequence generation (selection bias), (b) allocation concealment (selection bias), (c) performance bias, (d) detection bias, (e) attrition bias, (f) reporting bias, and (g) other bias.

Data Synthesis and Analysis

The network meta-analysis was performed using Stata (version 14.0, Stata SE), WinBUGS (version 1.4.3, MRC Biostatistics Unit, Cambridge, UK), and R software (version 3.5.1, R foundation for statistical computing). The odds ratio (OR) with corresponding 95% confidence interval (CI) was utilized to compare different agents with respect to various clinical outcomes. We conducted conventional meta-analyses for treatments that were directly compared in RCTs by Bayesian random-effects model. Convergence was checked using the Brooks-Gelman-Rubin diagnostic and trace plots [10]. The stability of the results was obtained by sensitivity analyses with discarding each study sequentially. Ranking probabilities for all treatments were used the surface under the cumulative ranking area (SUCRA) [11]. Node-splitting approach was used to assess the inconsistency [12].

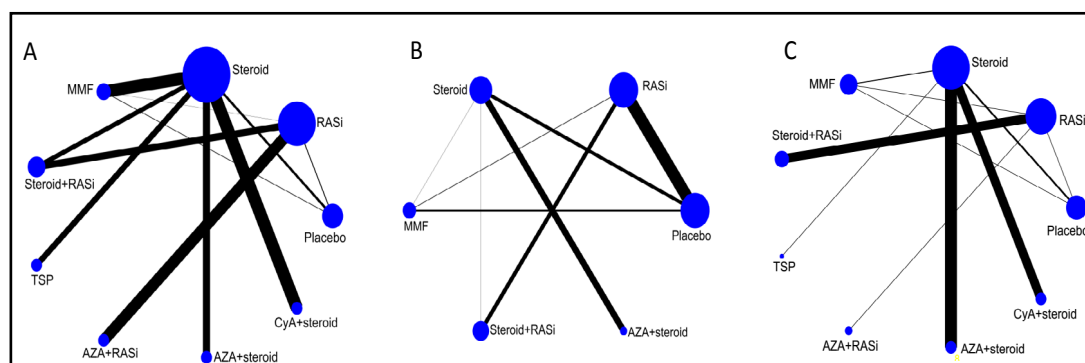


Fig. 1. Network plot of treatment comparisons for bayesian network meta-analysis. Lines represent trials comparing 2 classes of drug or drugs for (A) clinical remission, (B) ESRD and doubling of serum creatinine level, and (C) serious adverse events of IgA nephropathy. The size of the nodes (blue circles) corresponds to the sample size of interventions. Comparisons are linked with a line, of which the thickness corresponds to the number of trials that assessed the comparison. Abbreviations: MMF, mycophenolate mofetil; RAS, renin-angiotensin system; TSP, tonsillectomy combined with steroid pulse therapy.

Results

Characteristics of Included Studies

A total of 29 RCTs with 2517 participants were available for network meta-analysis, and the selection process details were showed in the Supplementary Material S2. Supplementary Material S3 summarized the essential baseline characteristic of these studies. The overall risk of bias was showed in Supplementary Material S4.

Network plot of treatment comparisons for bayesian network meta-analysis was showed in Fig. 1. The comparisons were connected by a straight line, of which the thickness corresponds to the number of trials that assessed the comparison. The size of the nodes (blue circles) corresponds to the sample size of interventions.

Efficacy Outcomes-Clinical Remission

Compared to placebo, the most effective treatments to induce remission were RASi monotherapy, steroid monotherapy, MMF monotherapy, RASi combined with steroid, TSP, azathioprine plus RASi, azathioprine in combination with steroid, and cyclosporine A plus steroid (OR of 6.1, 95% CI 2.5 - 16.0; 4.2, 95% CI 1.8 - 11.0; 5.6, 95% CI 2.1 - 18.0; 19.0, 95% CI 6.3 - 61.0; 20.0, 95% CI 5.7 - 77.0; 46.0, 95% CI 10.0 - 240.0; 5.7, 95% CI 1.6 - 23.0; and 10.0, 95% CI 3.0 - 38.0, respectively). RASi combined with steroid ranked the best treatment to induce clinical remission (Table 1).

RASi combined with steroid and TSP ranked the best and second (SUCRA of 82.9% and 80.5%, respectively, Fig. 2A), followed by RASi combined with azathioprine, Cyclosporine A plus steroid and azathioprine combined with steroid (SUCRA of 67.6%, 66.2%, and 44.2%, respectively). Placebo was ranked the least effective treatment.

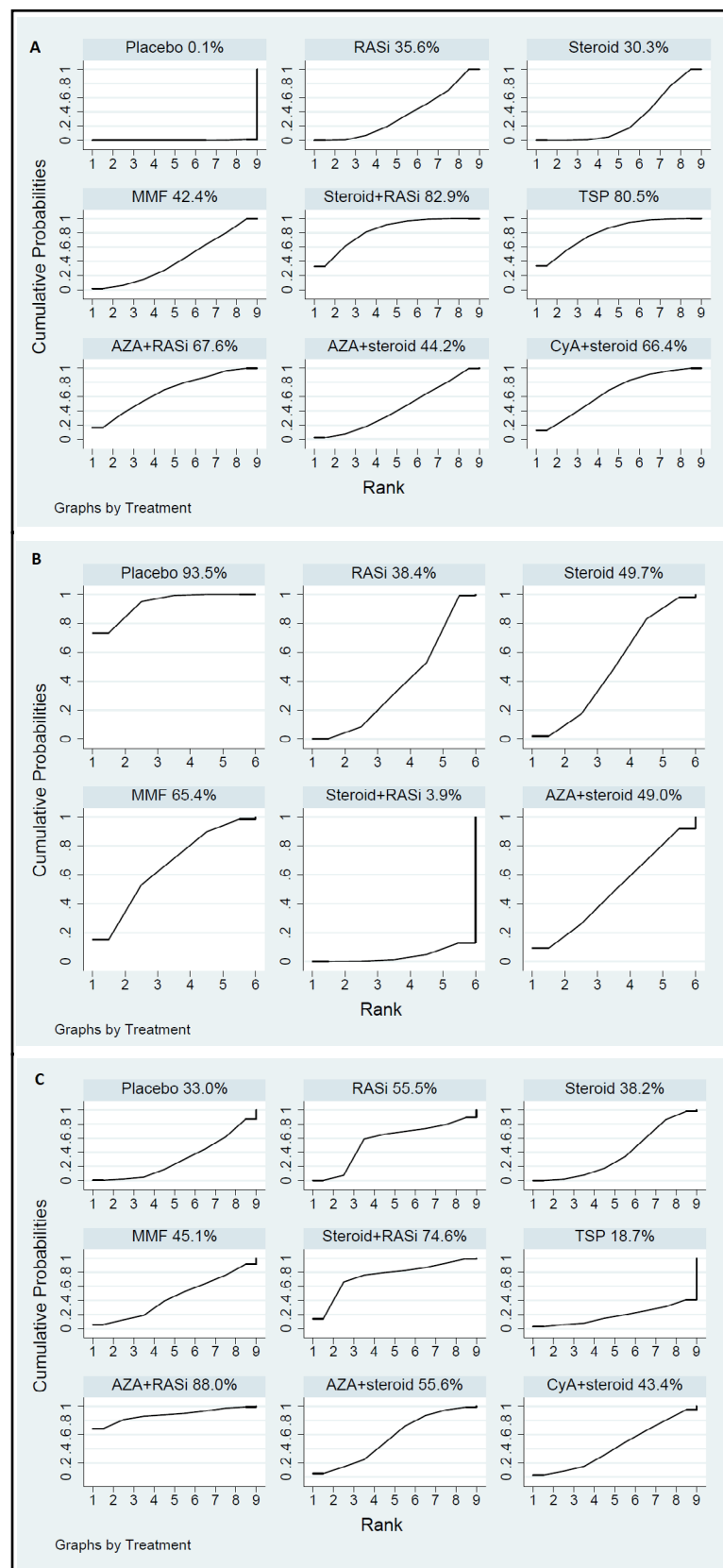
Safety Outcomes

ESRD or Doubling of Serum Creatinine. Compared to Placebo, RASi plus steroid and RASi displayed the lowest risks for ESRD or doubling of serum creatinine level (OR 0.04, 95% CI 0.01 - 0.17 and 0.01, 95% CI 0.04 - 0.43, respectively). There was no evidence that steroid monotherapy, MMF or azathioprine plus steroid showed different effects on ESRD or doubling serum creatinine compared to RASi or each other (Supplementary Material S5).

Table 1. Summary of results from network meta-analysis (on the lower triangle) and traditional pairwise meta-analysis (on the upper triangle) on clinical remission. On the lower triangle, the column-defining treatment is compared to the row-defining treatment, and odds ratios (OR) < 1 favor the column-defining treatment. On the upper triangle, the row-defining treatment is compared to the column-defining treatment, and OR < 1 favor the row-defining treatment. To obtain ORs for comparisons in the opposite direction, reciprocals should be taken. Significant results are in bold. Direct comparisons within 2 inconsistent loops are underlined. Abbreviations: RASi, renin-angiotensin system inhibitors; MMF, mycophenolate mofetil; TSP, tonsillectomy combined with steroid pulse therapy; AZA, azathioprine; CyA, cyclosporine A

OR 95%CI	Placebo	RASi	Steroid	MMF	RASi + steroid	TSP	AZA + RASi	AZA + steroid	CyA+ steroid
Placebo		7.8 (2.8, 25.0)	2.5 (0.9, 6.8)	16 (2.4, 130.0)					
RASi	6.1 (2.5, 16.0)			1.5 (0.1, 20.0)	3.4 (1.6, 7.4)				
Steroid	4.2 (1.8, 11.0)	0.7 (0.2, 2.2)		0.9 (0.3, 2.6)	2.0 (0.2, 26.0)				
MMF	5.6 (2.1, 18.0)	0.9 (0.3, 3.4)	1.3 (0.6, 3.5)						
RASi + steroid	19.0 (6.3, 61.0)	3.2 (1.5, 6.5)	4.6 (1.3, 16.0)	3.5 (0.8, 13.0)					
TSP	20.0 (5.7, 77.0)	3.3 (0.8, 15.0)	4.7 (1.9, 12.0)	3.5 (0.9, 13.0)	1.0 (0.2, 5.2)				
AZA + RASi	46.0 (10.0, 240)	7.4 (2.2, 27.0)	11.0 (2.0, 61.0)	8.2 (1.3, 47.0)	2.4 (0.6, 11)	2.3 (0.3, 16.0)			
AZA + steroid	5.7 (1.6, 23.0)	0.9 (0.2, 4.3)	1.4 (0.5, 3.6)	1.0 (0.3, 3.7)	0.3 (0.1, 1.5)	0.3 (0.1, 1.1)	0.1 (0.01, 0.9)		
CyA+ steroid	10.0 (3.0, 38.0)	1.7 (0.4, 7.2)	2.4 (1.0, 5.9)	1.8 (0.5, 6.3)	0.5 (0.1, 2.5)	0.5 (0.1, 1.8)	1.0 (0.07, 1.1)	1.8 (0.5, 6.7)	

Fig. 2. Rankings of SUCRA for efficacy of treatments to induce end points in IgA nephropathy. (A) clinical remission, (B) ESRD and doubling of serum creatinine level, and (C) serious adverse events of IgA nephropathy. The graphs display the distribution of probabilities of treatment ranking from best through worst for each outcome. Ranking indicates the probability that drug class is first “best,” second “best,” etc. For example, RAS inhibitors plus antiplatelets and steroid combined with tonsillectomy were among the best treatments for inducing disease remission, while Placebo provided the lowest probability of disease remission (worst). On the other hand, the ranking suggests that MMF posed the highest risk for incurring ESRD or creatinine doubling (worst), while RAS inhibitors plus steroid incurred the lowest probability of ESRD or creatinine doubling (best). Abbreviations: MMF, mycophenolate mofetil; RAS, renin-angiotensin system, TSP, tonsillectomy combined with steroid pulse therapy.



As for the prevention of ESRD or doubling of serum creatinine level, RASi plus steroid (SUCRA 2.5%) was the best treatment, followed by RASi monotherapy (SUCRA 37.4%), steroid monotherapy (SUCRA 50.5%). MMF was the least effective in preventing progression to ESRD (SUCRA 64.2%) (Fig. 2B).

Serious adverse events. For serious adverse events, RASi combined with azathioprine (SUCRA 88.0%) and RASi plus steroid (SUCRA 74.6%) were ranked highly, followed by azathioprine plus steroid (SUCRA 55.6%), RASi alone (SUCRA 55.5%). In addition, there were non-significant differences among all interventions in the occurrence of serious adverse events, as illustrated in Fig. 2C and Supplementary Material S5.

Sensitivity Analysis and Publication Bias

We performed a subgroup analysis in IgA patients with proteinuria > 1 g/d, and there was non-significant difference compared with the group with proteinuria > 0.75 g/d. Firstly, 50,000 instances of iterations were increased to acquire satisfactory convergence, as showed in diagnostics and trace plots (Supplementary Material S6). Secondly, there was minimal heterogeneity in the results of clinical remission, ESRD, and serious adverse events, as showed in Supplementary Material S7. Then, Pair-wise and network meta-analysis estimates were similar in magnitude and testing without revealing evidence of inconsistency between direct and indirect treatment effects, as depicted in Supplementary Material S8. Publication bias was tested by funnel plot (Supplementary Material S9).

Discussion

The present network meta-analysis provided a unified hierarchy of evidence for all proteinuria lowering agents in IgA nephropathy patients with proteinuria more than 0.75 g/d. This network meta-analysis indicated that RASi plus steroid, steroid combined with tonsillectomy, azathioprine plus RASi and Cyclosporine A combined with steroid were superior to RASi monotherapy for inducing clinical remission. Compared to Placebo, RASi in combination with steroid and RASi monotherapy indicated lower risks for ESRD or doubling of serum creatinine level. Therefore, RASi plus steroid was in association with the lowest risks for worse renal function and was the best treatment to maintain disease remission. For serious adverse events, all interventions available were not significant in pair-wise and network meta-analysis.

KDIGO guideline recommend long-term RASi treatment with proteinuria more than 1 g/d [5]. The current cumulative evidence showed that RASi had statistically significant effects in reducing proteinuria and protecting kidney function [13]. RASi was the fundamental for long-term treatment of progressive IgA nephropathy [14, 15]. The KDIGO guidelines also suggest that IgA nephropathy patients with persistent proteinuria more than 1.0 g/d despite 3 to 6 months of supportive care, and an eGFR \geq 50 ml/min per 1.73 m² accept glucocorticoids therapy [5]. The TESTING study [7] found that RASi combined with steroid was consistent with potential renal benefit but associated with an increased risk of serious adverse events. In the present study, however, the efficacy of RASi was less effective than RASi combined with steroid and TSP in inducing clinical remission.

The galactose-deficient IgA1 (GdIgA1) has a deficiency in the O-glycan located at the hinge region of IgA1 [3, 16]. GdIgA1 binds to its antibody to form a circulating immune complex that eventually deposits in the kidney and causes the renal function to deteriorate [3, 17]. Nakata and his colleague found that serum GdIgA1 levels decreased more than half after tonsillectomy, which indicated that the palatine tonsils are probably major sites of GdIgA1-producing cells [18]. A meta-analysis suggested that TSP is helpful in inducing clinical remission and inhibiting the development of ESRD in IgA nephropathy patients [19].

Some multicenter RCTs showed that MMF did not decrease proteinuria significantly in patients with IgA nephropathy who had persistent proteinuria after intensive supportive

care [20, 21], but had fewer serious adverse events [21]. One meta-analysis by Xu *et al.* [22] suggested the evidence that did not support the use of MMF in moderately advanced IgA nephropathy. Floege and his colleague [23] offered a possible interpretation for the different outcomes observed in the Chinese subjects compared with Belgium and America. The present network meta-analysis indicated that MMF was associated with a higher risk to ESRD and less effective in clinical remission than RASi alone.

Stangou *et al.* [24]. reported that treatment with steroid and azathioprine appeared to be an effective therapeutic approach for IgA nephropathy patients in terms of reducing proteinuria. Liu *et al.* [25]. suggested that both steroids monotherapy and combined treatment with Cyclosporine A remarkably reduced the levels of proteinuria and ameliorated renal function in the IgA nephropathy patients. However, infection was the most serious complication during the treatment [25]. Our network meta-analysis showed that RASi combined with azathioprine, Cyclosporine A plus steroid and azathioprine combined with steroid also had a highly efficacy in clinical remission, but not in ameliorating renal function.

Our study has potential limitations. Firstly, we did not control for dosage in our analyses. And the usage of steroid was not uniform, some with direct oral prednisone, and the others methylprednisolone pulse therapy. Secondly, the effect of pathological types on treatment was not considered. Thirdly, although the heterogeneity in the network analyses was low, it is likely that the low power to detect heterogeneity is due to limited data. Hence, there is needed to perform several larger, multicenter RCTs to acquire more robust results.

Conclusion

In conclusion, the current network meta-analysis suggested that RASi combined with steroid was the best therapeutic option in terms of reducing proteinuria and stabilizing renal function in IgA nephropathy patients with proteinuria > 0.75 g/d. Nonetheless, RASi plus steroid was associated with the highly risk of serious adverse events.

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Disclosure Statement

The authors declare that they have no competing interests.

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