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Renal outcome in patients with congenital anomalies of the kidney and urinary tract

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Congenital Anomalies of the Kidney and Urinary Tract (CAKUT) are a major cause of morbidity in children. We measured the risk of progression to end-stage renal disease in 312 patients with CAKUT preselected for the presence of anomalies in kidney number or size. A model of dialysis-free survival from birth was established as a function of the renal CAKUT categories of solitary kidney; unilateral and bilateral hypodysplasia; renal hypodysplasia associated with posterior urethral valves; and multicystic and horseshoe kidney. Cox regression analysis took into account the concomitant presence of vesicoureteral reflux, year of diagnosis, and time-varying values of serum creatinine, proteinuria, and hypertension. By 30 years of age, 58 patients had started dialysis, giving a yearly incidence of 0.023 over a combined 2474 patient risk years. The risk for dialysis was significantly higher for patients with a solitary kidney or with renal hypodysplasia associated with posterior urethral valves (hazard ratios of 2.43 and 5.1, respectively) compared to patients with unilateral or bilateral renal hypodysplasia, or multicystic or horseshoe kidney, and was independent of other prognostic factors. Our study shows that sub-clinical defects of the solitary kidney may be responsible for a poorer prognosis compared to more benign forms of CAKUT. Prospective studies are needed to validate these results.

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Congenital anomalies of the kidney and urinary tract are a major cause of morbidity and collectively represent a significant cause of Chronic Kidney Disease in children and young adults.[1–4] Moreover, reduced nephron mass can predispose to adult-onset diseases such as hypertension and chronic renal failure.[5] Data from birth defect registries[6–9] indicate a prevalence of these congenital anomalies varying from 3 to 6 per 1000 births, with relevant impact on life expectancy (http://www.marchofdimes.com). However, to the best of our knowledge, studies on renal survival of congenital abnormalities of the kidney and urinary tract have not been conducted. One reason can be traced to the intrinsic difficulty in carrying out a cohort study for conditions that are present at birth and in which the follow-up may need to be extended for decades. Another problem arises from the existence of different phenotypes, which can present incomplete penetrance, variable aggregation and clinical presentation, thus making uniform and extended data collections difficult and introducing selection bias. A broad but clinically useful diagnostic scheme consists in the classification of malformations depending on whether the kidney, the collecting system, or both are affected. The uncertainty in the clinical classification resulted in the aggregation of different entities under the single label acronym Congenital Anomalies of the Kidney and Urinary Tract (CAKUT): Congenital Anomalies of the Kidney and Urinary Tract.[10] There is not only clinical but also genetic support to the use of CAKUT, because it is well known that mutations in a single gene can have pleiotropic effects on the development of the urogenital tract. For example, mutations in the PAX2 gene are associated with the renal coloboma syndrome, a rare autosomal-dominant disorder in which different individuals in the same family can present various anomalies, including renal agenesis/hypodysplasia, vesicoureteral reflux (VUR) and/or secondary obstruction.[11] Another example is the gene for autosomal-dominant renal hypodysplasia (OMIM %610805) localized on chromosome 1p32–33, in which family members of index cases with hypodysplastic kidneys showed ureteric anomalies.[12]

Although the term CAKUT can be useful for a general classification, it may not be useful from an epidemiological perspective as different clinical, anatomical, and genetic entities may have different prognoses. In this paper, we report longitudinal data on a cohort of 312 children referred for different renal and urinary tract anomalies who were followed until the age of 30 years. The basic criteria for enrollment included the presence of CAKUT characterized by a defect of the number or size of at least one kidney, excluding cases with isolated ureteric anomalies such as vesicoureteral reflux and duplicated collecting systems.

RESULTS

Clinical characteristics of the study cohort are described in Table 1. Subjects were subdivided into 6 CAKUT categories as described in the methods section and were enrolled over 20 years (number of patients enrolled per year: 9.7 ± 2.2 before 1990 and 21.5 ± 8.1 after 1990). The main criteria for enrollment were the presence of a defect in size or number of at least one kidney and the exclusion of all syndromic associations and familial forms of disease. Isolated ureteric conditions such as vesicoureteral reflux and duplicated collecting systems without congenital anomalies of the kidney were excluded from this study. For most of the categories there was a clear prevalence of male patients by a factor of about three, with the only exceptions of multicystic kidney ($M/F = 0.9$) and of posterior urethral valves, observed only in male patients, as expected. Neonatal diagnosis was made in 56% of the patients with ample variability among CAKUT categories. As expected the majority of patients with multicystic dysplastic kidney and bilateral hypodysplasia were diagnosed at or before birth whereas only about 50% of patients belonging to the other categories were diagnosed at this time. Postnatal diagnosis was made in these patients because of other clinical signs, such as proteinuria and/or hypertension or, in a large fraction of individuals, by imaging studies conducted for other reasons, highlighting the fact that the unilateral defect can be present in asymptomatic individuals and therefore be underdiagnosed.

All patients with posterior urethral valves had at least one surgical treatment and almost 50% had neonatal urinary tract diversion. Fifty-three percent of the children with solitary kidney and VUR had a surgical treatment consisting of reimplantation (22%) or surgical cystoscopic correction (29%); all had been treated with prophylaxis for urinary tract infection for at least 1 year. Only three patients with multicystic kidneys had nephrectomy.

By 30 years of age (median follow-up 6 years, range 2–30), 58 patients started dialysis. During the study there were 2474 patient-years at risk, with an incidence rate of 0.023 per year (95% confidence interval from 0.018 to 0.030 per year). This yearly incidence rate remained approximately constant over time. Censored individuals with follow-up times shorter than the median were similar to those observed for longer time. The unadjusted risk for dialysis commencement associated with group E or F (incidence rate 0.005, 95% 0.001 to 0.022) was similar to B diagnosis (0.007, 95% CI 0.002 to 0.020). This crude risk estimate was greater in category A (0.023, 95% CI 0.015 to 0.035), C (0.029, 95% CI 0.012 to 0.071) and D (0.048, 95% CI 0.032 to 0.070). Controlling for time-varying values of serum creatinine, proteinuria, referral period, and concomitant presence of VUR, a significantly different clinical course was observed by CAKUT category (Figure 1). Dialysis survival probabilities were greater for categories F (no events) and E (two events), and for category B (four events) as compared with categories C (five events), A (21 events), and D (26 events). It is interesting that except for posterior urethral valves and bilateral hypodysplasia, renal deterioration may not be detectable until late adolescence. This observation highlights the importance of a smooth transition of care for patients from pediatric to adult nephrology services. Notably patients with bilateral hypodysplasia, (with high creatinine and proteinuria at diagnosis) did not progress to ESRD faster than patients with solitary kidney. One possible explanation is that patients with unilateral defects are usually considered to have a good prognosis and therefore they may not have been stringently monitored. If our results are true, patients with a solitary kidney should be considered as having a progressive disease. These patients would in fact require the same attention as those with bilateral hypodysplasia and posterior urethral valves to control all other possible co-morbidities, such as hypertension and proteinuria.

Table 1 | Patient characteristics by CAKUT category

	Gender		Neonatal diagnosis	Neonatal creatinine	Age at diagnosis post-natal	Creatinine at diagnosis	Proteinuria >1 g/day at diagnosis	Hypertension at diagnosis	ACEi within 1 year of diagnosis	Dialysis at follow-up
Category (n)	Female	Male	Count (%)	Mean mg per 100 ml (s.d.)	Mean years (s.d.)	Mean mg per 100 ml (s.d.)	Count (%)	Count (%)	Count(%)	Count (years ± s.d.)
SK (71)	19	52	29 (41)	0.68 (0.95)	15 (15.4)	0.68 (0.70)	5 (7)	2 (2.8)	0 (0)	21 (21 ± 13.6)
URHD (93)	27	66	45 (48)	0.48 (0.61)	2.3 (3.5)	0.43 (0.25)	6 (6.4)	0 (0)	24 (26)	4 (15 ± 2)
BRHD (19)	4	15	14 (74)	1.46 (1.29)	1.09 (0.59)	0.76 (0.27)	9 (47)	2 (10.5)	4 (21)	5 (8.4 ± 2.8)
PUV (68)	0	68	39 (57)	1.51 (2.13)	3.51 (2.9)	0.70 (0.91)	18 (26.4)	1 (1.4)	26 (38)	26 (12 ± 6)
MCDK (40)	21	19	36 (90)	0.46 (0.34)	4.76 (8.6)	0.42 (0.10)	0 (0)	1 (2.5)	0 (0)	2 (20 ± 11)
HSK (21)	8	13	11 (52)	0.28 (0.09)	5.4 (7.9)	0.31 (0.10)	3 (14.2)	0 (0)	5 (24)	0

ACEi: angiotensin-converting enzyme inhibitor; BRHD: bilateral renal hypodysplasia; HSK: horseshoe kidney; MCDK: multicystic dysplastic kidney; PUV: posterior urethral valves; SK: solitary kidney; URHD: unilateral renal hypodysplasia.

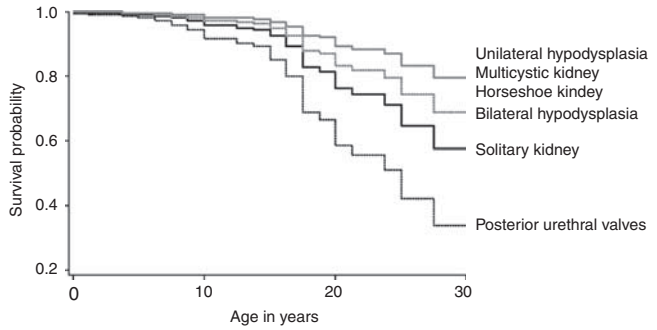

Figure 1 | Survival probabilities by CAKUT category, adjusted for the concomitant presence of vesicoureteral reflux, time-varying values of serum creatinine (mg per 100 ml) and proteinuria ($\geqslant$1 g/day vs less), and referral period (before 1990 vs 1990 and thereafter).

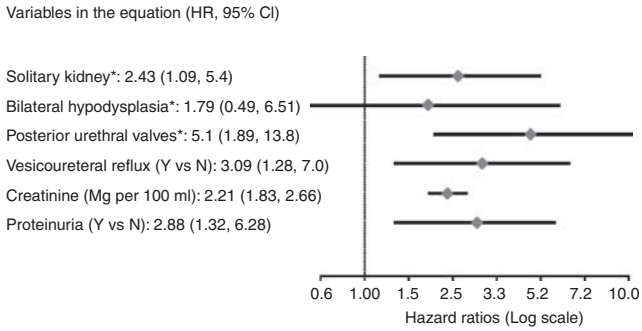

Figure 2 | Forest plot of the hazard ratios associated with the variables in the final Cox's model of renal survival (model stratified by referral period, before 1990 vs 1990 and thereafter). The reference level (*) for the effect estimates associated with the CAKUT categories (solitary kidney, bilateral hypodysplasia and posterior urethral valves) includes multicystic kidney, horseshoe kidney, and unilateral hypodysplasia.

Male gender predicted shorter renal survival in crude analysis but not in adjusted models. This confounding effect is probably due to the fact that urethral valves are restricted to male patients. As expected the hazard for event occurrence increased with higher values of serum creatinine (HR 2.27; 95% CI 1.88, 2.72; per mg per 100 ml) and was greater in the presence of proteinuria (6.42; 95% CI 3.94, 10.45; values $>$ vs $\leqslant$1 g/day). No other specific factor (age at diagnosis, surgical treatment, selected drugs) was found to influence the outcome.

Figure 2 shows the final Cox model stratified by referral period (before vs 1990 and thereafter). As compared to subjects with multicystic kidney, horseshoe kidney or unilateral hypodysplasia, those with bilateral hypodysplasia did not show a significantly greater risk for dialysis initiation by 30 years of age. Conversely, both solitary kidney (Hazard Ratio 2.43, 95% CI 1.09 to 5.4) and posterior urethral valves diagnoses (HR 5.1, 95% CI 1.9, 13.7) predicted worse outcomes independent of the other covariates in the model (vesicoureteral reflux and change in the levels of serum creatinine and proteinuria). Table 2 shows the hazard ratios for dialysis initiation by the age of 30 years by combination of CAKUT categories and the presence and absence of VUR.

Table 2 | Hazard ratios (HRs) and 95% confidence intervals (95% CI) by combination of CAKUT category and concomitant vesicoureteral reflux (model adjusted for time-varying levels of serum creatinine and proteinuria, and stratified by referral period; multiplicative model)

	Vesicoureteral reflux			
	VUR absent		VUR present	
CAKUT category[a]	HR	95% CI	HR	95% CI
Solitary kidney	2.42	1.08, 5.40	7.50	2.72, 20.68
Bilateral hypodysplasia	1.78	0.49, 6.52	5.52	1.04, 29.37
Posterior urethral valves	5.10	1.88, 13.1	15.8	2.8, 88.8

[a]Reference category: multicystic kidney, horseshoe kidney, unilateral hypodysplasia.
VUR: vesicoureteral reflux.

DISCUSSION

There are few studies on long-term outcome of patients with CAKUT because of the lack of a homogeneous classification and because of difficulties in separating the different subphenotypes. Moreover, results derived from the analysis of clinical parameters in different databases cannot readily be compared because of possible differences in enrollment criteria and heterogeneity of the applied technical approaches. For these reasons we still lack data on the long-term outcome of children presenting an anomaly of the number (single kidney) or size (hypodysplasia) of the kidneys with the exception of renal hypodysplasia associated with posterior urethral valves.[13–16] This study included a homogeneous population of children and young adults enrolled in a single national referral center, where the same physicians utilized the same standardized diagnostic and classification approaches. The main enrollment criterion for this study was the diagnosis of a primary congenital anomaly of renal morphology that was associated with a defect in the number or size of at least one kidney. This choice was dictated by the necessity to exclude patients with isolated VUR or other primary urinary tract anomalies, such as duplicated collecting systems, which may represent different clinical entities with relatively good prognosis. Moreover, the goal of this study is to assess the prognosis of patients with a primary defect in kidney parenchyma development associated or not to other urinary tract anomalies. The inclusion of patients carrying a defect of renal size may lead to misinterpretations of hypoplasia and dysplasia. Only kidney biopsy, considered unethical because of the relevant risk of bleeding in small kidneys or kidney function impairment in most serious cases, can help to make a distinction. Therefore, patients with renal hypoplasia and dysplasia were considered in the same category, under the hypodysplasia phenotype. This could constitute a limitation, as the two conditions may carry a different hazard of renal function decline and the estimated hazard associated with hypodysplasia may not reflect the true hazard of either of them. Scarring processes due to VUR and infections may contribute to kidney shrinking. Thus, VUR associated with primary renal hypodysplasia should be distinguished from secondary parenchymal scars.[17–19]

Dimercaptosuccinic acid (DMSA) scan is the technique of choice to distinguish between the two categories and has been used in our study to differentiate primary hypodysplasia and reduced kidney size secondary to reflux nephropathy. DMSA scan was generally normal at enrollment in patients with a solitary kidney whereas in the VUR it showed the presence of scars in some individuals. In these patients the presence of both solitary kidney and VUR resulted in an additive effect (but no interaction, see below) for progression to end-stage renal failure (Table 2).

This study reports clinical outcome data on a large cohort of patients with different anatomic categories belonging to the CAKUT complex. Patients were followed for a variable period of time until 30 years of age. These data are of unique value for addressing the long-term outcome. However, the observational design of the study raises the concern that some form of bias accounts for the findings. In fact, some factors potentially impacting outcome such as the presence of proteinuria, hypertension and the disparity of pharmacological treatment based on angiotensin-converting enzyme inhibitors (ACEi) in recent years were unequally distributed by CAKUT categories. This may mask confounding by other unmeasured factors or have introduced confounding *per se*. It is noteworthy that proteinuria greater than 1 g per day was more frequent in patients with bilateral than in those with unilateral hypodysplasia in spite of similar progression. Moreover, ACEi have been utilized in a quite different manner in the two categories with the worst outcome, such as in patients with solitary kidney and in patients with urethral valves. However, assuming that ACEi therapy is nephro-protective in CAKUT patients (which might not be true in children with hypodysplastic kidney[20]), the effect of confounding in this case would push the results of the present analysis toward the null hypothesis. Most importantly, excluding and including all these factors as covariates in our analytical model did not change the results. Another potential limitation may be the over-sampling of patients with worse prognosis as compared to those usually referred to peripheral centers, resulting in an ascertainment bias, which would not make our results promptly applicable to the general population. Finally, prognosis may have changed over time due to the introduction of routine prenatal ultrasonography and improvement of the diagnostic and therapeutic strategies. This additional source of bias was accounted for by stratifying the survival model by study period.

Our findings indicate an overall poor renal survival for CAKUT patients, only partially expected on the basis of the available literature. As expected, high serum creatinine, presence of proteinuria and VUR were associated with a higher risk of progression to renal disease in all CAKUT categories. Survival data by CAKUT subgroups showed a significantly poorer outcome for patients carrying bilateral renal hypodysplasia, solitary kidney, and posterior urethral valves, compared with the other categories. The high risk of renal replacement therapy in patients with posterior valves of urethra is not new and is in agreement with data from the literature.[13–16] The clinical outcome of patients with a single kidney was instead unexpected and raises the possibility of subclinical renal defects in the solitary kidney. These differences in the overall risk of developing ESRD were independent of the concomitant presence of VUR and other risk factors such as kidney function parameters and proteinuria. Subjects who left the study earlier were similar to those who remained under observation for longer times, both within and across disease categories. Although this does not exclude the possibility that the independent censoring assumptions be violated, it is unlikely that those with only certain disease categories and worse outcomes systematically failed to be referred back to the center.

According to the chosen model, the effect of CAKUT categories was not modified by the presence of VUR (no evidence of interaction). However, it is important to note that in multiplicative models (for example, the Cox's model) the effects are measured as ratios and the joint effect of two or more factors is the product (rather than the sum) of their effects (Table 2). Interaction parameters are ratios chosen to measure departures from a multiplicative model. Statistical assessment of this departure tests whether there is a departure from multiplicativity rather than the existence of a biological phenomenon.[21] Nevertheless, the relatively small sample size can make interaction estimates across six categories inaccurate.

Outcome data from patients with congenital solitary kidney are limited.[22–25] The literature abounds instead of follow-up data of surgical solitary kidneys generally associated with favorable outcome.[26] Data from the transplantation program in Sweden showed that the risk of ESRD at 12 years was less than 0.6% in kidney donors.[26] Long-term survivors from a Wilms' tumor diagnosed during childhood experienced a risk of ESRD of 1.19% over a period of time comparable with the one of this study (Oeffinger KC, personal observation).

In conclusion, this study represents a complete and adequately sized report on clinical outcome of patients with CAKUT phenotypes. The national referral, single center design allowed the standardization of enrollment criteria, diagnostic approaches, and therapeutic strategies. The detailed follow-up and statistical model used accounted for many measured potential confounders and covariates, thus making the overall results reliable and clinically useful for assessing the risk of progression to ESRD of different CAKUT categories. It is noteworthy that the unexpected high risk in patients with solitary kidney highlights potential subclinical defects of the solitary kidney, which may account for a poorer prognosis as compared with other forms of the CAKUT complex. Randomized prospective studies are needed to investigate the applicability of these results to the general population of patients with CAKUT.

MATERIALS AND METHODS

Patients

To be eligible for this study, patients had to have been followed at the Nephrology Department of the G Gaslini Children Hospital as in

and/or outpatients between 1980 and 2000 and had to have been diagnosed with any urinary tract malformation belonging to the CAKUT diagnostic group including a defect of the renal parenchyma documented by renal ultrasonography and DMSA scan. Isolated ureteric anomalies such as non-syndromic VUR and duplicated collecting systems represent different entities with higher prevalence in the general population and favorable outcome and were, therefore, excluded. Moreover, these cases were excluded because they were not representative of conditions with defective renal parenchyma. Familial cases and patients presenting one or more extra-renal features were excluded.

Therefore, the CAKUT categories analyzed in this study include any primary anomaly of the kidney number, size and/or morphology associated with additional malformations of the urinary tract.[27] Six major phenotypes were recognized for our study: (A) solitary kidney with or without defects of the urinary tract; (B) unilateral renal hypodysplasia with/without urinary tract defects; (C) bilateral renal hypodysplasia with/without urinary tract defects; (D) renal hypodysplasia associated with stenosis of urethral valves; (E) multicystic kidney; and (F) horseshoe kidney.

For this study, either renal hypoplasia or dysplasia was defined as hypodysplasia because of the impossibility to make a reliable distinction between these entities. The category solitary kidney comprises kidney agenesis and the 'empty renal fossa' on imaging studies (static renal scintigraphy and ultrasonography) that can result from the involution of a multicystic dysplastic kidney. Because only prenatal ultrasonography, not always available, can distinguish between these two conditions, the general term of solitary kidney has been adopted. Hypodysplasia was considered in the presence of a reduction of renal size by two s.d. from the mean size for the age, with clear exclusion of renal scarring by DMSA scan and in the presence of compensatory hypertrophy of the contralateral kidney.[28] The categories from A to D present renal hypodysplasia, justifying the inclusion in this study. Multicystic kidney fits into the CAKUT category because it combines lack of normal renal tissue such as glomeruli and collecting ducts with the presence of primitive tubules surrounding the stroma.[29,30] The following criteria identified multicystic kidneys: presence of a unilateral multiloculated abdominal mass with thin-walled cysts and with lack of tissue inside; presence of atresic ureter; the previous two conditions with associated hydronephrosis (hydronephrotic variant); no functional parenchyma at scintigraphy; no detectable renal artery by Doppler ultrasonography.

For each eligible patient data were collected on demographics, type of malformation, date of diagnosis and date of onset of ESRD that required replacement therapy, such as hemodialysis and/or peritoneal dialysis. Clinical criteria for starting replacement therapy included the presence of metabolic acidosis, hyperkalemia, increase of body weight over 10% in 1 week, oliguria, severe and intractable hypertension, severe nausea and failure to thrive. No patients were subjected to preemptive transplantation. Hypertensive state, serum creatinine and proteinuria within the first year of age and repeated during follow-up were collected, together with specific surgical and medical treatments.

Imaging studies

Static renal scintigraphy was recorded 3–4 h after injection of a weight-scaled dose of technetium-99 m DMSA to obtain views in the posterior and both posterior oblique projections for 300 kilocounts or more. Focal or diffuse areas of decreased uptake in the first scan, without evidence of cortical loss, indicated acute pyelonephritis. Renal scarring was defined as decreased uptake with distortion of the contours or as cortical thinning with loss of parenchymal volume. Two nuclear physicians, blinded to the test results, interpreted the scans independently and resolved discrepancies by discussion.

Statistical analyses

Univariate analyses. Data are expressed as mean ± s.d., median and inter-quartile range, or frequencies, as appropriate.

Survival functions. Cox's regression was used to model renal survival as a function of the CAKUT categories. As the conditions of interest are by definition congenital, survival was measured from birth and follow-up carried out until December 2006, the date of the last visit, the date of dialysis initiation for ESRD, or the thirtieth birthday, whichever occurred first. Differences in penetrance or severity of the disease at presentation were taken into account including both time-invariant clinical characteristics (gender, serum creatinine, hypertensive state and proteinuria within the first year of age), concomitant vesicoureteral reflux, and time-varying values of repeated lab measures (serum creatinine and proteinuria), diagnosis of hypertension during follow-up and antihypertensive therapies. All repeated measures for each patient were averaged to obtain one 5-year mean value and mitigate the effect of short-term variations. Hence, up to six varying values of serum creatinine (mg per 100 ml), proteinuria ($\leqslant$1 g/day or greater) and hypertension diagnosis (present vs absent) were available for each individual. Changes in the practice patterns and center experience were accounted for by considering the period of children referral in the analyses (that is, after 1990 vs before 1990). Centers of origin (regions or countries) were also considered to take into account possible differences in the follow-up care, genetic background or other potential unmeasured confounders.

Model building. The largest possible meaningful model considered included the CAKUT categories, time-invariant and time-varying covariates, and interpretable interaction terms, considering the overall model fit and hazard proportionality. A manual hierarchical elimination approach was followed, monitoring variations of the exposure regression coefficient to identify variables that were eligible to be dropped as non-confounders and non-modifiers. The contribution of the covariates to explain the dependent variable was assessed by means of a two-tailed Wald test, with P-values <0.05 considered as significant. Model specification, proportionality assumption and overall fit were checked by re-estimation, formal and graphical tests based on residuals, and testing the interaction with time of the variables in the model. Sensitivity analyses were conducted to check the robustness of the final model, considering influential observations and outliers, and censored follow-up times shorter than the median value. Analyses were performed using the STATA 9.2 SE software (Stata Corp, College Station, TX, USA).

DISCLOSURE

All the authors declared no competing interests.

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