

## The COOPERATE trial: a letter of concern

In the context of a meta-analysis,<sup>1</sup> we had reason to take an in-depth look at a study by Naoyuki Nakao and colleagues<sup>2</sup> published in *The Lancet* in 2003. We detected implausibilities of serious concern.

In this single-centre trial, the researchers investigated the role of angiotensin-converting enzyme (ACE) inhibitors versus angiotensin-II receptor blockers versus combination therapy on time to doubling of serum creatinine concentration or end-stage renal disease (combined primary endpoint) or on proteinuria (secondary endpoint) in 263 patients with chronic non-diabetic renal disease. To assure similarity between the groups, the investigators reported stratification on three variables—baseline renal function (glomerular filtration rate <45 or ≥45 mL/min per 1.73 m<sup>2</sup>), baseline proteinuria (<1 g per day, 1–3 g per day, or >3 g per day), and responsiveness to trandolapril in the prerandomisation period. Nakao and colleagues report that combination therapy versus both losartan and trandolapril monotherapy resulted in a significant reduction in the primary endpoint (hazard ratios 0.4, 95% CI 0.17–0.69; and 0.38, 0.18–0.63, respectively).

A closer look at their table 1 shows a highly unusual balance in the distribution of baseline characteristics across the three treatment groups (table). A  $\chi^2$  test for independence between randomisation and the respective covariate for categorical variables not known to be affected by stratification (sex, renal disease, ACE polymorphism) shows that the balance is much better than one would expect from random fluctuations. For example, the similarity in the distribution of the ACE polymorphisms between the three groups is closer than one would expect in 988 of 1000 repetitions (p=0.988) and with similar results

for the distribution of renal disease (p=0.972) and sex (p=0.997).

Throughout the paper, all 95% CIs for the hazard ratio are incompatible with the reported analysis technique; they are neither symmetric around the estimate on the log scale (as would be expected for a standard Cox regression analysis) nor on the reported scale. If these data are in fact correct and a non-standard method was used to calculate these CIs and corresponding p values, we would expect this information to be provided in the article.

Further concerns arise from table 3, which reports the effect of baseline proteinuria on the efficacy of combination therapy. Nakao and colleagues describe an “overall result of combination therapy”, but fail to report to which comparison this refers. Corrections to this table were reported,<sup>3</sup> but although the changes corrected numerical inconsistencies in the data, they created incompatibilities in the reported results. This (corrected) “overall” result (hazard ratio 0.34, 95% CI 0.19–2.68; p=0.31) suggests that the effect of combination therapy is not significant, whereas all other reported comparisons indicate that it is.

A further implausibility arises from the 18-week run-in phase in which the investigators chose the maximum dose of trandolapril (3 mg per day) for the study and detected differential

reactions to trandolapril (“good” and “low” responders). As a consequence, Nakao and colleagues introduced “reaction to trandolapril” as a stratification variable. However, this is not possible given the way that the trial was described. All 263 patients would have to complete the run-in phase before randomisation was launched (which would be more than 2 years after the first patient had been recruited). Or the stratification rule would have had to change during the trial. If either of these situations occurred, why were they not reported?

The number and seriousness of the inconsistencies found in the Nakao paper led us to wonder whether it is possible that this is only a case of extremely sloppy reporting or a hint towards more severe problems with the data. In fact we excluded the COOPERATE trial from our meta-analysis<sup>1</sup> on the basis of the implausibility of the data and internal inconsistencies and we mentioned the reason for excluding the study in our review.

We suggest that, on the basis of the information provided above, a further look into this trial is warranted.

JFEM has received honoraria from Boehringer-Ingelheim, Novartis, and Aventis, and grants from Aventis and Novartis. The other authors declare that they have no conflict of interest.

\*Regina Kunz, Marcel Wolbers,  
Tracy Glass, Johannes F E Mann  
rkunz@uhbs.ch

	Losartan (n=89)	Trandolapril (n=86)	Combination (n=88)	$\chi^2$ test
<b>Demographics</b>				
Sex (male)	48 (54%)	46 (53%)	47 (53%)	p=0.997
<b>Renal disease</b>				
Glomerular	58 (65%)	56 (65%)	57 (65%)	
Hypertension	15 (17%)	16 (19%)	15 (17%)	
Polycystic kidney disease	3 (3%)	5 (5%)	4 (5%)	
Unknown	13 (15%)	9 (10%)	12 (14%)	p=0.972
<b>ACE gene polymorphism</b>				
DD	9 (11%)	11 (13%)	10 (11%)	
ID	49 (49%)	41 (48%)	42 (48%)	
II	40 (40%)	34 (39%)	36 (41%)	p=0.9876

**Table: Categorical variables from Nakao and colleagues' table 1**

Submissions should be made via our electronic submission system at <http://ees.elsevier.com/thelancet/>

Basel Institute for Clinical Epidemiology and Clinic for Transplantation Immunology and Nephrology, University Hospital Basel, Hebelstrasse 10, 4123 Basel, Switzerland

- 1 Kunz R, Friedrich C, Wolbers M, Mann JF. Meta-analysis: effect of monotherapy and combination therapy with inhibitors of the renin angiotensin system on proteinuria in renal disease. *Ann Intern Med* 2008; **148**: 30–48.
- 2 Nakao N, Yoshimura A, Morita H, Takada M, Kayano T, Ideura T. Combination treatment of angiotensin-II receptor blocker and angiotensin-converting-enzyme inhibitor in non-diabetic renal disease (COOPERATE): a randomised controlled trial. *Lancet* 2003; **361**: 117–24.
- 3 Department of error. *Lancet* 2003; **361**: 1230.

## Health professionals don't feel secure in their own country

We support the recommendation of Edward Mills and colleagues (Feb 23, p 685)<sup>1</sup> that countries recruiting health professionals from sub-Saharan Africa should make financial “amends” to the region. However, we caution that such an action could become the means by which governments of rich countries appease their collective conscience, with little effect on the ongoing skills shortage in sub-Saharan African countries.

As such, Mills and colleagues' proposal does not adequately address the “push” factors that are driving emigration. Although poor salaries and heavy workloads clearly matter, a survey by the Southern African Migration Project<sup>2</sup> of more than 1700 South African health professionals found that general conditions in the country, including a lack of family security, personal safety, and children's futures, contributed to more dissatisfaction than did poor working conditions.

The lack of political accountability for the safety and security of citizens (whether health professionals or not) is what drives our most skilled professionals away. Isn't this neglect the true human rights violation,

rather than the active recruitment of health professionals as claimed by Mills and colleagues?

Most survey respondents believed that increasing regulation to stem the brain drain would have the opposite effect, undermining health professionals' rights at an individual level. Despite the massive imbalance in health-worker distribution, we need to remember that poor countries also gain from the global exchange of information and skills within the health sector. Interestingly, more than a third of survey respondents had spent periods working overseas but had chosen to return home. African governments should make that decision easier for them.

We declare that we have no conflict of interest.

\*Nandi Siegfried, David Pienaar  
nandi.siegfried@mrc.ac.za

South African Cochrane Centre, Medical Research Council, PO Box 19070, Tygerberg 7505, South Africa (NS); and University of Cape Town, Cape Town, South Africa (DP)

- 1 Mills EJ, Schabas WA, Volmink J, et al. Should active recruitment of health workers from sub-Saharan Africa be viewed as a crime? *Lancet* 2008; **371**: 685–88.
- 2 Pendleton W, Crush J, Lefko-Everett K. The haemorrhage of health professionals from South Africa: medical opinions. In: Crush J, ed. Migration policy series no 47. Cape Town: Southern African Migration Project, 2007.

## Train and trap to trap and trash

In your Feb 23 Editorial (p 623),<sup>1</sup> you propose, as the solution to the shortage of medical professionals in poor countries, to: “[Demand] that rich countries stop actively recruiting from poorer nations”. You go on to argue that: “Richer countries can no longer be allowed to exploit and plunder the future of resource-poor nations.”

Strong words and well meaning in their intent too, but this proposal is likely to be counterproductive. A ban on recruitment of skilled professionals by rich nations from poor countries will dissuade training

for emigration, and thus reduce the pool of medical professionals available for the globe as a whole. Any proposal to train and then “trap” skilled workers in poor nations will only discourage schooling, and therefore runs the risk of trashing the hopes and aspirations of many poor people to improve their wellbeing through emigration. Furthermore, the proposed scheme will rob rich nations of manpower that they desperately need given their rapidly ageing population. The train and trap proposal, therefore, will create losses for all—the potential trainee, and residents of the source and destination nations.

The proposal to ban recruitment to improve the wellbeing of poor nations could do the very opposite: it could discourage investment into the skills in demand and thus rob the investor, his or her nation, and the global community at large of latent potential for betterment of each of the above-mentioned.

I declare that I have no conflict of interest.

Satish Chand  
satish.chand@anu.edu.au

Australian National University, Canberra, ACT 0200, Australia

- 1 The Lancet. Finding solutions to the human resources for health crisis. *Lancet* 2008; **371**: 623.

## Chinese doctors' salaries

David McCoy and colleagues (Feb 23, p 675)<sup>1</sup> give a detailed description of the ubiquitous low salaries of health workers in sub-Saharan Africa. A similar situation also exists in China.

Doctors in China have long been a group of people whose low financial incomes and social positions are distinctively in contrast to their high training costs, academic degrees, the technical demands of their career, and professional risks.<sup>2</sup> The effect of the market-oriented health-care reform over the past 10 years in China has been negative for doctors. Incentives



Yang Tian