

echocardiogram (at 1 week) revealed the continued presence of thrombus. We therefore decided to withdraw the catheter, without initial resolution of the clot. However, 2 weeks later we found it had disappeared.

Persistent left superior vena cava is a relatively frequent anatomic variable of central venous drainage (1% in the general population). It is often found during central catheter placement or when using imaging techniques.<sup>1</sup> Catheter placement using this access is not contraindicated and pacemaker electrode deployment via this route has been described elsewhere.<sup>2</sup> However, both in central catheter placement and pacemaker electrode deployment, control X-ray projections must be studied to exclude anomalous trajectories. In selected cases, echocardiography is useful in clarifying catheter location with respect to cardiac structures.<sup>3</sup>

We have found no other cases of catheter thrombosis in the left superior vena cava in the literature. Hence, we consulted general guidelines on deep vein thrombosis to decide what action to take. Guidelines include catheter withdrawal, anticoagulation therapy or fibrinolysis<sup>4</sup> and, occasionally, thrombectomy by aspiration,<sup>5</sup> or surgical withdrawal of the clot.<sup>6</sup> Several studies discuss the hypothetical chance that fibrinolysis and catheter withdrawal might help dislodge fragments of thrombotic material, although results of series reported show catheter withdrawal can be performed safely.<sup>4</sup> In our patient, given good clinical tolerance and the large amount of thrombotic material, we initially decided against manipulating the catheter. However, faced with no initial improvement, we finally opted for withdrawal, which gave rise to no complications and enabled us to resolve the patient's condition.

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## Increased Mortality in Patients With Diabetes Associated With Olmesartan for the Prevention/Delay of Microalbuminuria Onset: a Matter of Concern?

*Aumento de mortalidad asociado a olmesartán en pacientes diabéticos para la prevención o retraso de microalbuminuria: ¿es una causa de preocupación?*

### To the Editor,

Microalbuminuria cannot be ignored by cardiologists because it is considered a predictor of coronary artery disease in patients with type 2 diabetes. Angiotensin II receptor blockers (ARB-II) have been accepted nephroprotective agents in patients with type 2 diabetes with microalbuminuria since publication of the Irbesartan Patients with Diabetes and Microalbuminuria (IRMA-2) study.<sup>1</sup> In patients with macroalbuminuria, the Reduction of Endpoints in NIDDM with Angiotensin II Antagonist Losartan (RENAAL)<sup>2</sup> and Irbesartan in Diabetic Nephropathy Trial (IDNT)<sup>3</sup> studies showed a slowing of progression to terminal kidney disease. However, in patients with diabetes with microalbuminuria, the Diabetic Retinopathy Candesartan Trial (DIRECT)<sup>4</sup> showed no significant reduction in microalbuminuria.

Recently, the Randomized Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP) study<sup>5</sup> has been published. Interestingly, it found that the use of olmesartan vs placebo to be associated with a significantly reduced incidence of microalbuminuria (23% relative reduction). However, it also showed

increased incidence of cardiovascular death with olmesartan (15 vs 3 patients;  $P = .01$ ), mainly due to sudden cardiac death (7 patients vs 1) and death from myocardial infarction (5 patients vs 0). Any-cause mortality was unfavorable, but non-significant, for olmesartan (26 vs 15 patients).

In an attempt to clarify this recent concern, we aimed to determine the safety in terms of mortality of ARB-II use in patients with type 2 diabetes with normoalbuminuria, microalbuminuria or macroalbuminuria in a combined analysis.

The present meta-analysis included all randomized placebo-controlled studies of patients with type 2 diabetes and using ARB-II in the intervention group, published in English- or Spanish-language peer-review journals that present mortality data (at least any-cause mortality). We conducted a systematic review of MEDLINE/PubMed and ISI Web-of-Knowledge databases until April 2011. The search terms were *losartan, irbesartan, valsartan, olmesartan, candesartan, eprosartan, telmisartan*, combined with *diabetic nephropathy* and *randomized trial*. We also reviewed meta-analyses and recent review articles.

We calculated the relative risk (RR) with 95% confidence interval using Mantel-Haenszel weighting. We determined heterogeneity using Cochran's Q test and the H- and I-statistics.<sup>2</sup> Publication bias was determined using the Egger and Macaskill method. We also performed an analysis of sensitivity. Statistical analysis was with SPSS 15 and the Domenech JM macro (Macro!MAR for SPSS Statistics, V2010.04.15. UAB).

Of 459 articles, only five met our inclusion criteria<sup>1-5</sup> (1.1%); these included 9603 patients (Table 1). Essentially, the causes of exclusion were: a) nonrandomized design; b) lack of placebo

**Table 1**  
Baseline Characteristics of Patients With Type 2 Diabetes in Each of the Studies Chosen (in the Placebo Group)

	Brenner et al. <sup>2</sup>	Parving et al. <sup>1</sup>	Lewis et al. <sup>3</sup>	Bilos et al. <sup>4</sup>	Haller et al. <sup>5</sup>
Name of study/group	RENAAL	IRMA-2	IDNT	DIRECT-Protect2	ROADMAP
Year of publication	2001	2001	2001	2009	2011
ARB-II studied	Losartan	Irbesartan	Irbesartan	Candesartan	Olmesartan
Total sample size <sup>a</sup>	1513	590	1148	1905	4447
Age, years	60 ± 7	58.3 ± 8.7	58.3 ± 8.2	56.8 ± 7.9	57.8 ± 8.6
Caucasian, %	49.6	98	78	96	100
Men, %	64.8	68.7	71	51	45.3
BMI	29 ± 6	30.3 ± 4.4	30.5 ± 5.9	29.4 ± 4.8	30.9 ± 4.9
Coronary disease, %	22.1	4.5	29 <sup>b</sup>	NR	24.4
Myocardial infarction, %	12.3	1.5	NR	NR	5.4
Stroke or TIA	0.1	3.5	NR	NR	2.2
Peripheral arterial disease, %	NR	4	NR	NR	0.4
Creatinine, μmol/l	168 ± 44.2	88.4 ± 8.8	149.4 ± 50.4	90.1 ± 15.2	77.5 ± 17.1
Glycohemoglobin, %	8.4 ± 1.6	7.1 ± 1.6	8.2 ± 1.7	8.2 ± 1.6	7.7 ± 1.6
Albuminuria <sup>a</sup>	Macroalbuminuria	Microalbuminuria	Macroalbuminuria	Normoalbuminuria	Normoalbuminuria
High blood pressure at enrolment <sup>a</sup>	Yes	Yes	Yes	62%	NR
Mean follow-up, years <sup>a</sup>	3.4	2	2.6	4.7	3.2
Mortality intervention group, n/N	158/751	3/389	87/579	37/949	26/2232
Mortality placebo group, n/N	155/762	1/201	93/569	35/953	15/2215

ARB-II, angiotensin II receptor blockers; BMI, body mass index; NR, not reported; TIA, transitory ischemic accident.

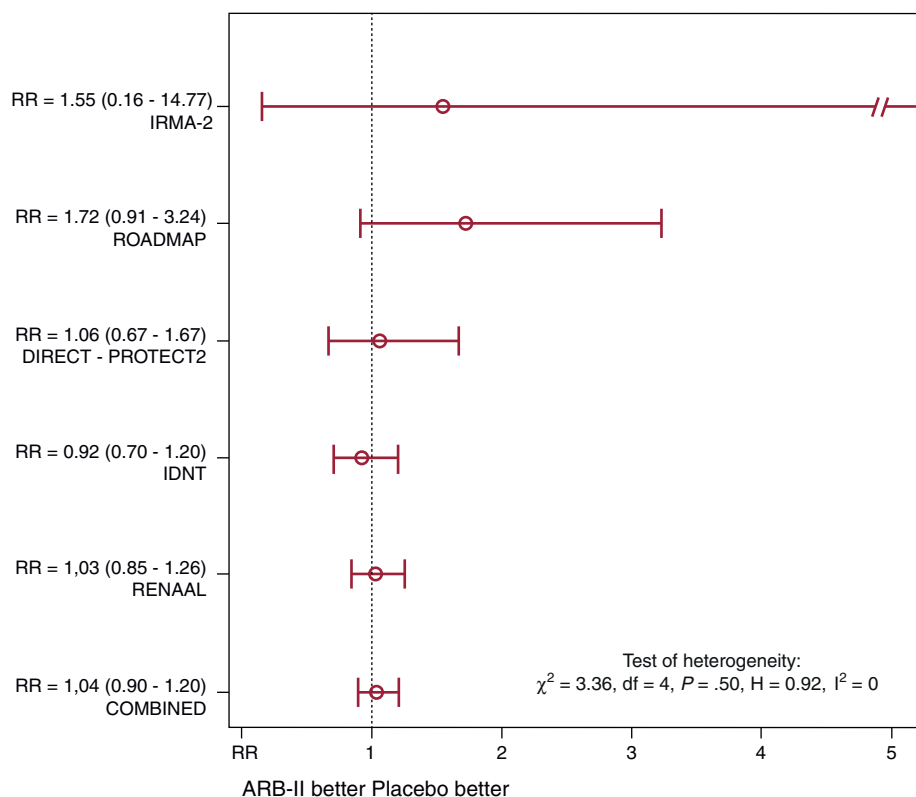
<sup>a</sup> Intervention group with each ARB-II and non-intervention (placebo) group.

<sup>b</sup> Described in the original publication as “history of cardiovascular disease”.

Continuous variables are expressed as mean ± standard deviation and categorical variables as percentage.

group; c) lack of data on mortality, and d) “non-informative” studies (0 mortal events in intervention and control groups). Except for Haller<sup>5</sup>, the remaining articles<sup>1-4</sup> reported no specific individualized data on “cardiovascular-cause” mortality.

Of 4900 patients in the group receiving ARB-II, 311 (6.3%) died during follow-up (of whatever cause) vs 299 of 4700 (6.4%) in the placebo group (Mantel-Haenszel RR = 1.04; *P* = .61) (Fig. 1). Although the studies with lower baseline risk (ROADMAP<sup>5</sup> and



**Figure 1.** Comparative effect of angiotensin II receptor blockers in patients with type 2 diabetes with respect to any-cause death (expressed as relative risk). ARB-II, angiotensin II receptor blockers; RR, relative risk.

IRMA-2<sup>1</sup>) tended to present a less favorable RR in patients receiving ARB-II, there was no evidence of significant heterogeneity. Sensitivity analysis was concordant and we found no publication bias.

The unexpected ROADMAP study<sup>5</sup> findings on increased cardiovascular-cause mortality in patients receiving olmesartan conflicts with recent trials, principally, the ONGoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET)<sup>6</sup> that included 9612 patients with diabetes and reported telmisartan had a beneficial effect similar to that of ramipril—which had previously been shown to reduce myocardial infarction and mortality. It has been argued that some of the excess events occurred in patients with previous ischemic heart disease and in patients in whom olmesartan induced a minimum hypotensive effect or a substantial reduction in blood pressure, raising once more the controversial “J curve” issue with respect to mortality and ischemic heart disease.<sup>5,6</sup>

We conclude that although previous studies have adequately shown that ARB-II use slows kidney disease in a range of patients with type 2 diabetes with different degrees of vascular disease, the present meta-analysis shows no benefits but nor does it show any harm to patients' global survival. Further studies will need to determine whether the conflictive ROADMAP study<sup>5</sup> results are a cause for concern because they reflect a specific effect of olmesartan—which cannot be discounted—or simply a chance finding. This raises the interesting question as to whether microalbuminuria remains a good intermediate variable to predict cardiovascular outcomes.

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## Phenotypic Variability in Marfan Syndrome in a Family With a Novel Nonsense *FBN1* Gene Mutation

### Variabilidad fenotípica del síndrome de Marfan en una familia con una nueva mutación en el gen *FBN1*

To the Editor,

We present a family in which four members were diagnosed by molecular testing as having the Marfan syndrome (MFS), with a highly variable expression. The proband is a 30-year-old man in whom a mild dilatation of the aortic root was detected at the age of 12 years. He underwent cataract surgery when he was 13 and, when he was found to have lens subluxation at the age of 18, he was diagnosed with MFS. At the present time, he is totally blind in his right eye and has scoliosis, arachnodactyly and recurrent patellar dislocation. The diameter of the aortic root is presently 41 mm.

The patient and his partner came to the genetics unit seeking genetic counseling with regard to future offspring. He explained that he had four healthy sisters, that he was the only member of his family with MFS, and that there was no family history of aortic disease or sudden death at a young age. After receiving an explanation of the mode of inheritance—autosomal dominant—and a description of the reproductive options, they were offered prenatal or preimplantation diagnosis once the mutation responsible for the disease had been identified. They were also informed that more than 90% of the patients with MFS may have an *FBN1* gene mutation. We discussed with the couple the limitations to predict the severity of the disease, given that the clinical spectrum ranges from mild bone and joint involvement to severe neonatal forms with fatal cardiovascular disease. After adequate informed

consent, we proceeded to *FBN1* gene sequencing using DNA extracted from peripheral blood. In this study, we detected four single nucleotide polymorphisms (SNP) included in the SNP database (in Entrez databases): rs1018148 (IVS2–102T>C), rs59966849 (IVS28+47–/CATAA), rs2303502 (IVS48+54T>A) and rs363832 (IVS56+17G>C). In addition, we detected two intronic variants not described in the polymorphism databases and, thus, of uncertain significance (IVS25+49delTAAAGA and IVS40–35C>T). In the coding sequences, we identified a heterozygous point mutation in exon 54: E2194X (c.6580G>T) (Fig. 1). It was a premature termination codon (as are 33% of the mutations of this gene) that had not been previously described. This mutation presumably causes the disease as it produces the truncation and loss of 24% of the fibrillin 1, which affects 11 epidermal growth

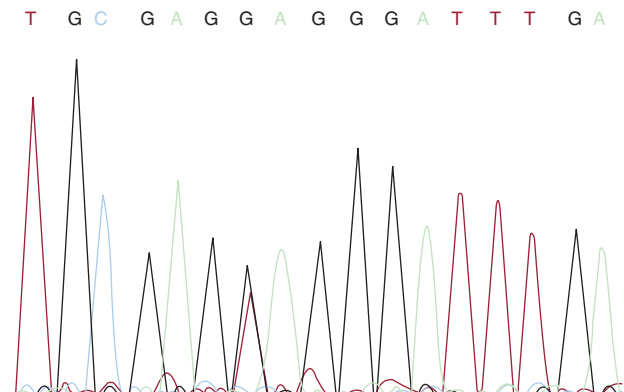


Figure 1. c.6580G >T mutation.