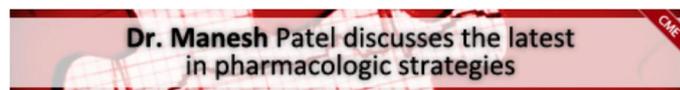


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Albuminuria developing, progressing, despite treatment with ACE inhibitors or ARBs

JULY 2, 2010 | Lisa Nainggolan

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ESH Oslo, Norway - A group of Spanish doctors has discovered that albuminuria appeared to develop or progress in patients attending their hypertension clinic who had been on long-term therapy with ACE inhibitors or angiotensin-receptor blockers (ARBs).

These findings are provocative, given that suppression of the renin-angiotensin system (RAS) with ACE inhibitors or ARBs is considered, together with tight blood-pressure control, as the elective treatment for patients with microalbuminuria, according to the 2009 update of the European Society of Hypertension (ESH) guidelines [1].

"We reviewed 1433 patients who had been on ACE inhibitors or ARBs for a minimum of two years and found, to our surprise, that after observing them for three further years, the percentage presenting with high-normal albuminuria, microalbuminuria, and macroalbuminuria was constantly rising while we maintained RAS suppression," senior author of the research, Dr Luis M Ruilope (Hospital 12 de Octubre, Madrid, Spain), told *heartwire*. The paper was presented at a hotline session during the recent ESH European Meeting on Hypertension 2010 by Ruilope's colleague Dr Cesar Cerezo (Hospital 12 de Octubre).

Doctors at the meeting did not seem to know what to make of these data, and several experts contacted by *heartwire* for comment did not respond. Ruilope said physicians "have, for years, been living with the idea of the positiveness of RAS suppression. I'm not denying any of the good things [about these drugs], but, for some reason, the suppression doesn't last forever."

One senior investigator who has been involved in many trials of ACE inhibitors and ARBs, Dr Salim Yusuf (McMaster University, Hamilton, ON), said he was "not surprised" by the finding that microalbuminuria develops in the presence of ACE inhibition or angiotensin-receptor blockade. "We have known of this for a long time, having observed it in several studies. RAS blockade merely slows things down," he told *heartwire*.

Therapy alteration needed?

There is some debate as to how important albuminuria is as an indicator of cardiovascular and/or renal risk in patients with hypertension. Some consider it a risk marker rather than a risk factor, but most experts agree it should be monitored and that if it is rising while all major risk factors are controlled, this indicates a poor prognosis.

The progression of albuminuria in the Spanish hypertension clinic patients occurred despite the fact that their BP control improved over the course of the three years they were observed. The latter indicates that lack of compliance with therapy is not the explanation for the findings, says Ruilope, who adds that compliance is taken very seriously in his clinic.

He believes a change of therapy might be required to counter the rise in albuminuria seen—for example, dual blockade with ACE inhibitors plus ARBs—although this is a controversial combination not generally recommended for use—or the addition of the direct renin inhibitor aliskiren (Tekturna, Novartis) or an aldosterone blocker such as spironolactone.

Next, his team intends to perform a study comparing these options with placebo, in addition to existing hypertensive therapy, to look at the effects on albuminuria.

Other possible explanations could be that some patients might be nonresponders to RAS suppression with ACE inhibitors or ARBs. Alternatively, there could be a protective effect of certain statins in terms of albuminuria, he said, noting that his team has yet to dissect out the data on statins from their patients.

Changes were even more marked in diabetics



Dr Luis M Ruilope

For some reason, the [RAS] suppression doesn't last forever.



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Dr Cesar Cerezo

In his presentation at the ESH meeting, Cerezo reported that the 1433 patients included in the analysis, who were on average age 60, had all been on ACE-inhibitor or ARB therapy for at least two years when they were first assessed. At this time point, 67.7% of them had normal levels of albuminuria, 11.9% exhibited high-normal values of albuminuria, 16.4% had microalbuminuria, and 4% had macroalbuminuria.

At that time, 54.1% had BP values below 140/90 mm Hg (average BP was 138.3/80.0 mm Hg). All of the patients were followed for three years, during which RAS suppression with ACE-inhibitor or ARB therapy was maintained, while BP control improved so that 56.6% of patients were controlled (average BP 137.6/77.4 mm Hg).

At the end of follow-up, significantly fewer patients were normoalbuminuric, but significantly more presented with high-normal albuminuria, microalbuminuria, and macroalbuminuria.

The changes were seen in nondiabetics as well as diabetics, but were more marked in the latter, Ruilope said, with only 37.5% of diabetics being normoalbuminuric at the end of three years, and 16.5% having macroalbuminuria.

Trends in albuminuria among patients on long-term RAS suppression

Status	At beginning of study period (%)	3 y later (%)
Normoalbuminuria ^a	67.7	54.9
High-normal values of albuminuria ^b	11.9	16.0
Microalbuminuria ^c	16.4	21.6
Macroalbuminuria ^d	4.0	7.5

a. Albumin-to-creatinine ratio [ACR] <10 mg/g for men, <15 mg/g for women

b. ACR 10-20 mg/g for men, 15-30 mg/g for women

c. ACR 20-200 mg/g for men, 30-300 mg/g for women

d. ACR >200 mg/g for men, >300 mg/g for women

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"These results indicate that albuminuria develops in the presence of chronic RAS suppression at adequate doses and progresses continuously. Long-term RAS suppression needs to be revisited in order to control this alteration," Cerezo said.

Ruilope says other research is supportive of this phenomenon, including a paper published in the *European Journal of Heart Failure*, which showed that 40% of patients presenting with heart failure were being treated with an ACE inhibitor, "so, in other words, they developed heart failure while under RAS suppression." His team has also just had a manuscript describing similar HF cases accepted for publication in the *Journal of Hypertension*, he said.

Depending on what is uncovered by further research into this phenomenon, "guidelines may need to be reassessed," he commented.

Ruilope has served as advisor or speaker in the past 12 months for AstraZeneca, Otsuka, Pfizer, Daiichi Sankyo, Takeda, Novartis, and Boehringer Ingelheim. Cerezo has no conflicts of interest to disclose.

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Source

1. Mancia G, Laurent S, Agabiti-Rosei E, et al. Reappraisal of European guidelines on hypertension management: a European Society of Hypertension Task Force document. *J Hypertens* 2009; 27:2121-2157.



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Your comments

- Albuminuria developing, progressing, despite treatment with ACE inhibitors or ARBs
- # 1 of 5 July 3, 2010 02:10 (EDT)
- askin kaplan Albuminurea or Prevention of Micro ablbuminurea
I think the most important should be to prevent rather than treating what has happened to the kidney
- # 2 of 5 July 7, 2010 09:10 (EDT)
- Allen Leier What is it going to take for medicine to learn drugs are not the answer. The goal of every physician should be to get patients off all drug medication as soon as possible. Diet, exercise, and a change in lifestyle are the best solutions. We seem unable to fathom the complexity of the human chemical balance and tampering with it is not the solution. If a patient is not willing to change their lifestyle it is a choice they make and should be allowed to suffer the consequences. Medicine has got them believing we can save them when only they can save themselves.
- # 3 of 5 July 7, 2010 09:43 (EDT)
- Dmitri Vasin Drugs will be needed in most, like it or not.
Allen,
pre-industrial lifestyle with "good" unprocessed food diet and plenty of physical activity had seen life expectancy in the 30s and 40s. I am not aware of any studies of systematic application of the concept in modern times, thus historical evidence do not support improved longevity and health. I do support your sentiment regarding personal responsibility for lifestyle decisions people are making. Indeed advances in medicine, including pharmacotherapy, allow people to make poor choices and make the rest of us to pay for the consequences such as their disability and treatment of chronic diseases.
On the subject of the article:
ACE escape is a phenomenon (measured by rebound of aldosterone which often times exceeds pretreatment levels) known for over 20 years and there is nothing new there. Adding ARB to ACEI provided only temporary delay also. Spironolactone seems to be offering more durable effects as measured by BP, microalbuminuria and hypokalemia effect. Aliskiren also seems to lower aldosterone on the top of ACEI and ARB, but I had already seen cases (small%) of break through of both PRA and Aldo.
To achieve sustained reduction of albuminuria (and thus presumably risk) multimodal interventions with multiple drugs, including statins, ACEI, Aldo antagonists are needed. And, lifestyle interventions help there as well.
- # 4 of 5 July 7, 2010 01:30 (EDT)
- ajay singh unbelivable
1 despite good b.p. control almost to normal levels proteinuria incidence increased after 3 years ??beyond conventional wisdom?
2 not a word about how good diabetes control was in the trial group?presumably proteinuria increased despite good diabetes control implications?? futility of it all?
- # 5 of 5 July 10, 2010 10:38 (EDT)
- Roberto Gabriel Albin this, it isn't a surprise
macro or microalbuminuria because of use of ACE inhibitors in high BP is being described in Medical Clinics of NorthAmerica edited in 1987 about Esencial Hipertension.
this work don't write anything about diabetes control in the group of diabetics.
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