New ONTARGET analysis: Monitor albuminuria to predict CV risk, death

JULY 6, 2010 | Lisa Nainggolan

Oslo, Norway - A new analysis of the large ONTARGET trial presented at the recent **European Society of Hypertension** (ESH) **European Meeting on Hypertension 2010** has shown that big changes in albuminuria predict cardiovascular and renal outcomes and mortality, independent of baseline albuminuria [1].

Dr Roland E Schmieder

"The message to general practitioners is that albuminuria is worthwhile to monitor, because a change in albuminuria tells the physician whether the patient has an increased or decreased risk of cardiovascular and renal events and of actually dying. It is a protein that indicates serious consequences," said **Dr Roland E Schmieder** (University of Erlangen, Germany), who presented the findings during a hotline session.

Schmieder, who is a nephrologist, said that cardiologists in particular have been skeptical of the utility of measuring albumin as a tool for judging the success of treatment. Prior to these data, there was evidence that change in albuminuria was predictive of events and death, but only from a small number of patients in a few studies, he said. The large number of patients in ONTARGET, together with the fact that they are exactly the kind of patients GPs see—high risk or with diabetes—indicates that this result can now be considered "conclusive," he noted.

"These data are crystal clear, and I think we should reassess albuminuria after six months or a year of treatment, to see how successful therapy has been in reducing vascular risk overall. It's a spot urine test, best done in the morning, but it's easily measured everywhere in the world," he stressed during a press conference.

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American Society of Hypertension president, **Dr George Bakris** (University of Chicago Pritzker School of Medicine), said he "would partially agree" with Schmieder's conclusions. "Change in microalbuminuria is not predictive of kidney disease presence, but for cardiovascular risk the data are stronger," he said. Still, change in microalbuminuria is not considered a risk factor, rather a risk marker, "in the same ballpark as [C-reactive protein] CRP—this is why the **FDA** does not acknowledge it as a validated surrogate." Nevertheless, Bakris said he supports monitoring change in albuminuria "to assess for unappreciated CV risk."

And **Dr Luis Ruilope** (Hospital 12 de Octubre, Madrid, Spain) told **heart*wire*** that while he agrees that these ONTARGET data add strength to the call for monitoring albuminuria, he says a number of questions remain to be answered about this new analysis.

Doubling of albuminuria associated with "dramatic" increase in deaths

The landmark **ONTARGET** trial, first reported two years ago, showed that antihypertensive treatment with the angiotensin receptor blocker (ARB) **telmisartan** (Micardis, Boehringer Ingelheim) was "noninferior" to the ACE inhibitor **ramipril** in terms of the primary end point—a composite of cardiovascular death, MI, stroke, or hospitalization for heart failure—in the 25 620

patients enrolled. However, the combination of the two drugs was associated with more adverse events, without an increase in benefit.

In his new analysis, Schmieder was able to include 23 480 patients from the total ONTARGET population, and he and his colleagues examined whether changes in albuminuria in spot urine from baseline—measured in a central laboratory—were related to the incidence of cardiovascular and renal outcomes and total mortality over 32 months of follow-up.

A doubling of albuminuria from baseline to two years, seen in 28% of participants, was associated with a "dramatic" increase in mortality of almost 50% (HR 1.47; $p<0.0001$), Schmieder said, while a decrease in albuminuria (at least halving), noted in 21% of people, was associated with reduced mortality (HR 0.85; $p=0.025$), compared with those with lesser, minor changes in albuminuria, even after adjustment for confounding factors.

Doubling of albuminuria was also associated with significant increases in cardiovascular death (HR 1.54), the primary composite outcome (HR 1.38), and renal outcomes—dialysis or doubling of serum creatinine—(HR 1.54).

However, halving of albuminuria was not so strongly associated with reductions in cardiovascular death (HR 0.88, not significant), composite outcome (HR 0.85; $p=0.0512$), or renal outcomes (no association). But this was likely due to the low number of people who experienced reductions of albuminuria of this magnitude, Schmieder said.

But which patients did experience a fall in albuminuria?

Ruilope said that in order to interpret these results properly it will be important to know whether the reduction in albuminuria was seen across the board, in everybody, or in specific groups—were they found, for example, among the 40% of patients who were ACE-inhibitor-naive before entering the study? The latter question, he says, "has to be explained and is extremely important."

Also, it appears that protein in the urine was only checked "a limited number of times"—namely, at baseline and at two years, he noted, yet definitive conclusions have been drawn from this. And it would be useful to know whether the patients who experienced large increases or reductions in albuminuria were taking statins or not, he said.

When **heart*wire*** put these questions to Schmieder, he said: "No further data and comments can be released. The study is not yet published."

Reassess guidelines on how often to test for albuminuria

Schmieder said, "To illustrate very clearly" what these new results mean in absolute terms, "there would be 20 deaths more in 10 years for a doubling of albuminuria, which is a strong message."

"What we have learned is that albuminuria is some kind of indicator of endothelial dysfunction, a vascular marker, and we can measure it very easily, very cheaply, in the urine," he added.

He said that the 2007 European guidelines on hypertension recommended that microalbuminuria be measured at baseline in every hypertensive patient, and "now with these data, I think we should reassess this parameter after six months or a year of treatment, to see how successful treatment has been in reducing the vascular risk overall."

Bakris disclosed being a consultant or advisor to Abbott, Merck, Gilead, Forest, Novartis, Takeda, CVRx, Boehringer Ingelheim, Servier, and the FDA. He has received grant or research support from GlaxoSmithKline and Forest and has served on speakers' bureaus for Novartis and Forest. Ruilope has served as advisor or speaker in

the past 12 months for AstraZeneca, Otsuka, Pfizer, Daiichi Sankyo, Takeda, Novartis, and Boehringer Ingelheim. Schmieder had not responded to ***heartwire****'s request for disclosures when this article was published.*

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  [*Hypertension* > *Hypertension*; Jun 22, 2010]
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  [*Brain/Kidney/Peripheral* > *Brain/Kidney/Peripheral*; Aug 14, 2008]
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