Microalbuminuria should be Considered in Risk Stratification and Management of Hypertensive Subjects

Agonist

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Arterial hypertension (HT) is a modifiable cardiovascular risk factor, highly prevalent in our environment. (1) Over the years, it has been demonstrated that patients with HT show a significant heterogeneity, presumably due to differences in genetic or environmental factors, which in turn have implications for treatment response, susceptibility to developing target organ damage, and freedom from cardiovascular events. To optimize the management of this population, different stratification methods for patients with HT have been proposed. Microalbuminuria (MA) occupies a prominent place among them. Measuring MA has been strongly recommended as a method of cardiovascular risk stratification for individuals with diabetes mellitus types 1 and 2, because it is an independent predictor of cardiovascular events, microangiopathy and macroangiopathy, and progression to end-stage renal disease in subjects with diabetes. (2) In addition, evidence has been accumulated on the utility of this marker in essential HT even in the absence of diabetes, and it is on this population that we will focus arguments, while its role in patients with diabetes is out of discussion.

It is considered that urinary albumin loss should be < 30 mg/day in patients with normal renal function. When urinary albumin is between 30 and 300 mg/day, there is MA. While there may be a transient increase in this loss (for instance, physical activity), it is in pathological processes that this determination has become relevant in recent years. MA is common in patients with HT: taking into account most of the studies, prevalence of MA in essential HT varies between 5-30%; this divergence is attributed to ethnic differences and exposure to other concomitant risk factors. In accordance, there is a close association between MA and cardiovascular risk factors (hyperglycemia, impaired glucose tolerance, hyperinsulinemia, dyslipidemia, smoking), as well as with the target organ damage (left ventricular hypertrophy and impaired renal function). (3) In addition, patients with MA have higher blood pressure levels, as evidenced by the good correlation between urinary albumin excretion and white-coat blood pressure (BP) values, and in the ambulatory BP monitoring, and they have circadian rhythm disturbances in BP, characterized by reduction of night-time BP (non-dippers). (4, 5) Therefore, we can say that MA is associated with an increased risk profile in patients with essential HT.

MA is considered an independent predictor of fatal and non-fatal vascular events. (6) Consistent with these data, the HOPE and LIFE studies have provided us with important information. The HOPE study analyzed the effect in a high risk population randomly assigned to receive 10 mg of ramipril or placebo. The study inclusion criteria were the following: 55 years of age or older, previous cardiovascular disease or diabetes, in addition to a cardiovascular risk factor. Urinary albumin excretion was measured in 97% of the population (9,043 individuals). MA was detected in 1,140 (32.6%) of the patients with diabetes and in 823 (14.8%) patients without diabetes. After a 4.5-year follow up, the incidence of composite primary endpoint (acute myocardial infarction, stroke or cardiovascular death) showed a relative risk (RR) of 1.83 (CI 95% 1.64-2.05; $p < 0.001$) when comparing patients with MA to those who did not have it at baseline. There was also an increase in mortality from any cause (RR 2.09; CI 95% 1.84-2.38; $p < 0.001$) and in hospitalization due to heart failure (RR 3.23; CI 95% 2.54-4.1; $p < 0.001$) in the same population. These differences were similar in patients with and without diabetes, and remained so even after adjusting these results by age, sex, smoking, hypertension, dyslipidemia, abdominal obesity, and serum creatinine. These results clearly show that MA works like an independent risk predictor of cardiovascular events. Furthermore, the same analysis showed that MA is a continuous variable in predicting cardiovascular risk, increasing the likelihood of events, even within normal limits. (7)

The LIFE study randomized 9,193 patients with HT in stages II or III and left ventricular hypertrophy to initial therapy based either on losartan 50 mg or atenolol 50 mg, to which hydrochlorothiazide and –if necessary– other antihypertensive drugs could be added. Of the total participants, 8,206 samples were available to measure the urinary albumin/creatinine ratio (ACR), in which the incidence of cardiovascular events was assessed at an average follow-up of 4.8 years. Patients with higher ACR at baseline showed increased risk intervals (HR) of 97.7% (CI 95% 66.5-223%; $p < 0.001$) for cardiovascular mortality, 75.2% (CI 95% 54-

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99.4%; p < 0.001) for mortality from any cause, 51% (CI 95% 28.8-76.9%; p < 0.001) for stroke, and 45% (CI 95% 19.9-75.4%; p < 0.001) for myocardial infarction. Again, MA acted as an independent predictor of these events, even after adjustments per left ventricle mass, age, sex, smoking habit, creatinine levels, race, and treatment group within the study. (8) Moreover, a recent subanalysis of this study showed that including MA in a risk score improves the capacity to predict cardiovascular events, compared to traditional score systems (such as Framingham). (9) This justifies the decision to include this marker in risk stratification, which some documents on HT management have adopted. (1, 10)

Another important characteristic of the MA should not be overlooked: its capacity to predict the development of chronic renal failure. While there is a microalbuminuria-macroalbuminuria-renal failure sequence, it was described for patients with diabetes types 1 and 2, and is much less clear in non-diabetic patients with hypertension. In a HOPE substudy, Mann et al showed that the presence of MA predicts the later development of macroalbuminuria (OR 16.7; CI 95% 8.6-32.4); in fact, 5% of the patients with basal MA develop proteinuria or nephropathy. It was also noted that ramipril can prevent this progression. (11)

Why is MA a predictor of renal and cardiovascular risk? Clearly, this small concentration of urinary proteins is not a direct cause that affects progression of atherosclerosis or is conducive to the occurrence of vascular events. However, as discussed, MA is associated with other causal factors, or factors closely related to vascular damage. Moreover, MA shows an increase in renal endothelial permeability and diffuse endothelial dysfunction. Thus, MA is an easily measured marker of other risk factors, as well as of the presence of endothelial dysfunction, which reflects the underlying microvascular or macrovascular damage.

Despite all these data, we are not satisfied with the association between this marker and a particular event to be prevented in order to implement a marker into our daily practice, but we want something else: its implementation must lead to the adoption of behaviors with prognostic impact on our patients. It would be of little use that MA gave us information only about a high-cardiovascular risk population, already defined – to a greater or lesser extent– by other variables. This is where MA becomes more important, since it influences on the choice of antihypertensive therapy. (1, 10) In this regard, angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor type 1 are the drugs indicated due to their antiproteinuric effects. These agents reduce intraglomerular pressure and attenuate glomerular mesangial matrix expansion in animal models of hypertension and diabetes. The net result of the use of these agents is the prevention of glomerulosclerosis, a phenomenon that affects independent of glycemia and blood pressure control. (12) Proteinuria reduction has been reported in several trials of patients with essential HT without diabetes, and showed that this effect is present primarily with the use of ACE inhibitors or AT-1 inhibitors. (11, 13, 14) Moreover, these drugs can reduce the progression to MA and, therefore, the occurrence of chronic renal failure. (11)

In this context, an important question would also be: Is it the same to reduce MA than to reduce cardiovascular events? In patients with MA and diabetes mellitus, MA reduction is clearly associated with reduced risk of cardiovascular events, microangiopathy and macroangiopathy, and mortality. The evidence in essential HT is low in the absence of diabetes. To answer this key question, the LIFE study lets draw some conclusions. This study carried out an interesting subanalysis on the impact of MA reduction on cardiovascular events. Measurement of ACR at baseline and after 1 year of treatment was performed for this purpose. The 8,206 patients who met those criteria were classified into four groups, dichotomizing the ACR values according to the media of that population: group 1, low baseline ACR at one year; group 2, low baseline ACR - high ACR at one year; group 3, high baseline ACR - low ACR at one year; and group 4, high baseline ACR - high ACR at one year. Researchers observed increased incidence of the combined endpoint of stroke, myocardial infarction and cardiovascular death (5.5%, 8.6%, 9.4% and 13.5, respectively). The analysis of the components of the combined endpoint also showed similar results. Since atenolol does not reduce MA significantly, losartan is considered to be largely responsible for that difference. Another important point in this study is that results were independent of the blood pressure levels achieved, thus increasing the relevance of MA in patients with treated and controlled essential HT. The authors conclude their work by recommending to perform MA determination yearly, and to ensure an accurate control of blood pressure and other cardiovascular risk factors in case of hypertension, considering MA as a therapeutic target rather than a risk marker. (14)

Last but not least, the cost-effectiveness relation of measuring MA remains to be analyzed. At this point, in a recent publication, Hoerger et al used a simulation model of costs, in which they analyzed the cost-effectiveness of MA screening in patients with diabetes, with HT but no diabetes, and in the general population. In the model, they considered the use of ACE inhibitors or AT-1 inhibitors in case the test was positive. The study was based on the development of renal failure, but vascular events such as MA complications were also considered. The authors concluded that the screening of patients with diabetes and hypertensive patients without diabetes is favorable from a cost-effectiveness perspective; however, in the general population, this benefit is lost. Although this study was carried out considering the costs of centers in the United States, implementing these research studies in our country may also entail benefits. (15) In conclusion, MA is not only associated with cardiovascular risk and development

of nephropathy, but it is also important in guiding the selection of drugs for the treatment of HT, and in defining the therapeutic targets of blood pressure. This determination is easy to perform, and has a favorable cost-effectiveness result. Finally, in patients with MA, it should be noted that it is convenient not only to reach a normal BP level, but also to normalize urinary albumin losses, transforming MA reduction in a therapeutic target, rather than a risk marker.

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Antagonist

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If a scrutiny is carried out on those who argue that microalbuminuria (MA) should not be used for risk stratification and management of hypertensive patients, I have it clear that I must be one of the few ones in this corner. At the end of this controversy, I hope to have convinced many others that the role of MA is extremely limited and controversial.

All what the agonist has written in this debate seems indisputable. MA is a good marker of future cardiovascular disease (CVD) in patients with hypertension (HT) and diabetes mellitus (DB), (3, 4) and of progressive chronic renal disease that may require dialysis. (5) But it is true and useful, if we are epidemiologists: if you take 100 individuals and verify who have MA in that group, undoubtedly those individuals will have greater chances of developing the events mentioned above. But now, let us consider how it helps us at the office, with concrete patients, each of them with a different cardiovascular (CV) risk.

The first example is about a male patient, aged 55, who consults for the first time with a history of DM, HT and chronic renal failure (CRF). His blood pressure (BP) is now 150/100. Even if he did not provide more data, it would be agreed that, according to all the guidelines, he is a patient with high CV risk (therefore, MA would not be useful for stratification), and that his therapeutic management would include hygiene and dietary measures, BP reduction to < 130/80, statin, glycemia control (Hb gluc < 7), and aspirin (100 mg) once HT is well under control. Once those targets are achieved, **no literature would support stricter targets** if albuminuria remained high. LIFE (6) and RENAAL are the studies most cited as evidence that MA should be followed or reduced as therapeutic target. (7) A substudy of LIFE showed that patients with greater reduction of albuminuria had less events (Figure 1). Therefore, it is recommended to follow the values of MA to confirm that the therapy is being effective, and, if not, "to make further intervention in BP and modifiable risk factors". (6) It should be pointed out that this is not an interventional study about MA, and an association was found: albuminuria was lower in patients who progressed better. If the patients who responded better showed changes in their albuminuria, that does not mean that we should use MA to specify targets of BP or LDL. Moreover, there is no focus on what those further interventions would be, because this was obviously not a study designed for that purpose, and such studies do not exist. Therefore, improvement as a result of further intervention is a supposition. And it must be emphazised that initial BP was 174/98 and final BP was 145/81. If I already know in advance that the target is < 130/80, what is the use of the MA follow-up before achieving that target? If I find that MA is high, I must continue to reduce BP all the same. The other study is a subanalysis of RENAAL, which shows that patients whose albuminuria lowered by 30% at 6 months had fewer events than those who did not have a reduction. (7) Again, this is not an interventional study about albuminuria, and it was carried out in patients with macroalbuminuria who do not correspond to this debate.

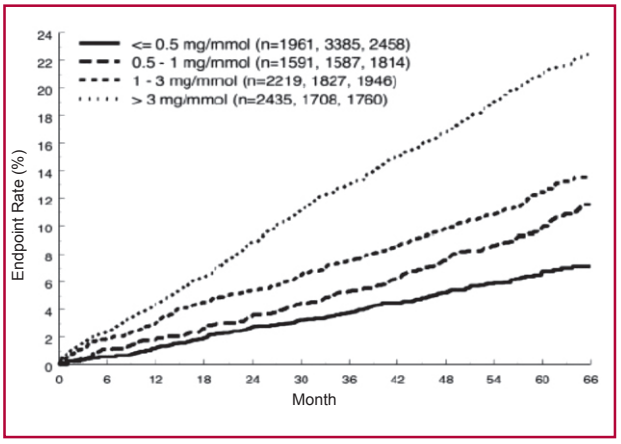

Fig. 1. Different levels of proteinuria during therapy predict the reduction of CV events. LIFE Study. (6)

Therefore, progression of MA could be used to leave a clear conscience that the therapy is working, (6, 7) but never to define BP or LDL targets, or to know what to do if it is not so. The suggestions proposed in some guidelines about further BP or LDL reduction correspond to the experts' opinions, and not to clinical trials which had this question in mind. I think we should try, but until further studies investigate that specific question, they will fall in the area of the art of medicine, rather than in science.

With respect to the initial antihypertensive drug, due to his DB and CRF, nearly all will agree that an ACE inhibitor and an ARB are necessary, and probably all will agree that, with that PA, most probably a combination of drugs will be necessary to reach the proposed target; but I will get back on the issues of RAS blockade and proteinuria in more detail. Therefore, in this particular case in which albuminuria is normal or elevated, it does not alter management, and to ask for it is useless. If this same patient returns a year later and did not take his medication, to ask again for MA (on an annual basis, as most guidelines recommend) will not help in his management either.

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The second example is a patient with moderate CV risk, according to the European Guidelines of HT. (8) It is a 55 year old man, with BP 150/98, active smoker of 20 cigarettes/day and with LDL cholesterol of 180. Management of this patient includes hygiene and dietary measures, BP reduction to < 130/80, statin, stop smoking, and aspirin (100 mg) once BP is well under control. In this case, a high or normal MA does not help to define therapeutic targets either. If the MA was high, it would not be of use to increase risk stratification, and even if it were, it would not alter the treatment plan for that patient. In this scenario, some might argue that if albuminuria was high, the BP or the LDL cholesterol target would be more aggressive, but there is no literature to support that approach in patients with moderate CV risk.

Having eliminated the use of MA in patients with high and moderate CV risk, this biochemical test becomes useless in clinical practice for most hypertensive patients. If we take into account an epidemiological study of Framingham, which stratified patients according to their BP and CV risk, 68 patients out of a total of 4,962 with isolated HT had no additional risk factors. (9)

Finally, these are two examples of patients with low CV risk. A 47 year old woman, postmenopausal, with BP 146/90, no additional risk factors and normal renal function. For this patient, the management would be BP reduction to < 140/90 and hygiene and dietary measures. If albuminuria were found, it might be argued that it increases the risk of CV and renal disease, and therefore –as in the case of all patients with CRF– we should lower BP to < 130/80. In fact, to have MA is not a synonym of CRF, and there are no BP targets set for MA. If it was not intended to start with ACE inhibitors or ARB, finding MA might help to decide for these drugs. We will now see what the real impact of treating this patient with an ACE inhibitor or a statin consists of.

A young man with white-coat BP in borderline (normal AMBP) and no CV risk. Should we ask for MA in the initial study of this patient? If it were elevated, many would argue that ACE inhibitors or ARB should be used in this case to reduce proteinuria. Even though normotensive individuals without DM but with MA have up to three times higher CV risk, the very same authors of Framingham point out that treating it would not necessarily reduce their risk. (10) The PREVEND IT study sheds light on these last two patients (normal or slightly high BP in individuals with MA and low CV risk). (11) A population screening of the PREVEND cohort was carried out, and it showed that 1,439 individuals had MA (15-300 mg/day); most of them were normotensive (there were few hypertensive individuals), and 3.4% had suffered a cardiovascular event. As shown, it was a low CV risk cohort. In a 2 × 2 study, 864 patients were randomized to receive fosinopril 20 mg or placebo, and pravastatin 40 mg or placebo. They had a 4-year follow up, and the primary end point was CV mortality and hospitalization due to CV morbidity. After 4 years, only 45 individuals (5.2%) had a CV event. Fosinopril reduced albuminuria considerably (26%), and there was a non-significant trend towards primary end point reduction. Pravastatin did not reduce albuminuria, and its trend to reduce hard events was even smaller and non-significant. (11) In addition, the study of intermediate or surrogate events (carotid intima/media index) did not show benefits during 4 years of treatment with these drugs commonly used to reduce CV risk. (12)

Several conclusions can be drawn from this study of patients with microalbuminuria and low CV risk. The first one is that this is not a common situation, and the second one is that although we treat them with ACE inhibitors and/or statin for 4 years, there is no great benefit for final or intermediate events. It is true that perhaps the study was underpowered, and that since these are low-risk patients, they should be treated for a long time to see the benefits. But it is also true that the only study in the literature that investigates this point failed to demonstrate therapeutic utility. And if I can do nothing different from the therapeutic point of view, what is the use of performing the biochemical test? I know this last point is arguable because **there is no good evidence**, but we can also make mistakes by extrapolating data from higher risk populations (for example, LIFE).

Another important reason why some physicians are interested in knowing the level of albuminuria is that it might determine which drug to start therapy with. And here it is necessary to dispel a misconception: that albuminuria can only be reduced with drugs that inhibit the renin-angiotensin system (for example, ACE inhibitors and ARB). All BP-lowering drugs can reduce proteinuria because they lower intraglomerular pressure. In 1987, Parving demonstrated that metoprolol, furosemide and hydralazine could reduce proteinuria. (13) With the same level of BP lowering as with other drugs, ACE inhibitors and ARB further reduce proteinuria, and therefore they are the first choice to be used in these situations. And not because those are the only drugs that reduce proteinuria! Furthermore, if still one were to initially treat the patient with ACE inhibitors or ARB –like most physicians in our country do–, this last argument weakens.

Another reason that makes it messy and difficult to use in-office MA is that it is very variable. Many factors can affect its value, and if a patient's MA is measured for 3 days straight, it may easily go from normal to high values. For that reason, clinical studies that assess MA always use the average of two or three consecutive measurements to report the resulting value. In clinical practice, only one measurement is usually required, therefore it is much less reliable.

As can be seen, the real utility of performing in-office MA and acting accordingly has little applicability. In patients with high CV risk, it does not help in stratification or in proposing more aggressive targets for managing BP or LDL. I think this area needs studies

that can provide an answer to the question. And in the few remaining patients with low CV risk, if MA is elevated but one would not start with ACE inhibitors or statin, the therapy is not beneficial at four years. What happens with longer periods of therapy still remains a question mark.

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AGONIST'S REPLY

The role of MA in risk stratification is given by: 1) its value as independent variable, and 2) its inclusion in a risk score improves patients' categorization. In addition, its decrease is associated with reduced risk. However, in clinical practice, risk categorization is as follows: hypertensive patients with low, moderate or high cardiovascular risk, and also with or without MA. For further clarification, I will take as example the first two patients described by the antagonist: both are high risk patients, one for diabetes, chronic renal failure and HT, and the other for risk score (even with normal HDL and triglyceride levels, his cardiovascular risk at 10 years exceeds 20%). Despite being within the same risk category, these patients are different and require different therapy. Similarly, the management of two patients within the same risk category will differ, depending on whether or not they have MA: the presence of MA will enhance the treatment with ACE inhibitors, AT-1 blockers, or both; knowing the relationship between HT and MA, it is reasonable to lower BP values and verify the correct control of other risk factors, follow these patients more closely, especially because of their predisposition to developing macroalbuminuria, etc.

In conclusion, I think that taking MA value as a therapeutic target is as valid as any other target set on the basis of a continuous relation with cardiovascular risk. Or do we have clinical trials that support the search for LDL cholesterol targets? The pathophysiological, clinical, and therapeutic bases that give relevance to this determination are consistent and reasonable, and suggest that waiting for the amount of evidence may lead us to make decisions too late.

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ANTAGONIST'S REPLY

I think the agonist's initial discussion is similar to that used by most physicians when they ask for MA because it predicts CV and renal events. Clearly, this would be the approach of an epidemiologist, not a clinician.

I fully agree with the phrase "its implementation should lead to the adoption of behaviors with prognostic impact on our patients", but I do not agree with the fact that it helps to choose the initial drug. Two drugs are needed when the BP stage is 2-3, one of which is usually an ACE inhibitor or an ARB. If the BP stage is 1, most physicians in Argentina will start with these drugs, without knowing whether or not the patient has MA. I believe MA should be used once therapeutic targets are achieved, to propose stricter targets, but – as mentioned above– this approach has no literature to support it.

Since there is a close relationship among several risk factors, if LVH is found or if the carotid intima-media index is increased, MA will have no value in these patients because the alleged "major risk" has already been found. Therefore, to ask for all those tests

simultaneously is meaningless.

Finally, the LIFE study is worth mentioning again, which is commonly cited as evidence that asking for MA is necessary because it helps to make decisions. This study demonstrated that, in a range of final BP wider than the one suggested by our current guidelines, individuals who lowered MA had less events. If for those physicians who ask for MA with these high blood pressures, verifying that the patient is responding to the treatment is useful to calm their nerves, this should not be grounds to argue that knowing the MA value will help to make decisions, because a better BP target than the one obtained in the study is defined in advance. This study demonstrates association, it does not show how to intervene in MA; therefore, it should not be interpreted as determinant of a therapeutic target.

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