Of course, albuminuria was the characteristic finding in Bright’s disease and was the cause of the ‘coagulable urine’. The prognostic importance of albuminuria was first recognized in diabetic nephropathy in which changes in albuminuria usually precede the decline in renal function. However, albuminuria provides prognostic information in all causes of progressive chronic kidney disease (CKD) and in fact provides a similar amount of information as estimates of kidney function (eGFR) itself [1]. Recent studies have shown that the presence of substantial (or ‘macro-’) albuminuria increases the risk of poor renal outcomes by an order of magnitude [2]. Mechanistically, in renal disease, macroalbuminuria is a marker of glomerular damage and may also be a mediator of subsequent tubular injury [3].

**Albuminuria becomes a cardiovascular risk marker**

More recently, albuminuria has been found to be an independent marker of cardiovascular risk [4]. The recent meta-analysis by the Chronic Kidney Disease Prognosis Consortium has reliably demonstrated this association with macroalbuminuria approximately doubling the risk of cardiovascular death [2]. Albuminuria also has a continuous positive association with non-fatal cardiovascular events which persists after adjustment for traditional risk factors [4]. What is less clear is how much information albuminuria adds to a prognostic model once traditional Framingham risk factors (i.e. sex, age, smoking status, blood pressure, and total and HDL cholesterol) are known. Although it persists as an independent risk factor, this does not mean that its presence (or absence) substantially alters the risk estimated on these other well-established risk factors. Albuminuria may well be a marker of atherosclerotic burden, and reflect the renal endothelial dysfunction that this causes, and—like fundoscopy—it may provide a window into the vascular health of a patient.

**Albuminuria as a modifiable risk factor**

Given its independent association with both renal and cardiovascular risk, the question whether albuminuria is a modifiable risk factor (i.e. whether it has a causal relationship with renal or cardiovascular disease) has been debated. The current NKF KDOQI guidelines recommend albuminuria be monitored and used as a treatment target [5]. Certainly, treatments that reduce albuminuria (e.g. renin–angiotensin system inhibitors) also reduce the risk of poor renal outcomes in populations at high risk of progressive renal disease [6]. Such treatments have also been the subject of large cardiovascular studies which have unequivocally demonstrated their benefit in diabetes and secondary prevention of coronary disease, stroke and heart failure [7]. Furthermore, post-hoc analyses of some of these trials have shown that on-treatment changes in albuminuria predict renal and cardiovascular outcomes. For example, a reduction in albuminuria was found to be negatively predictive of risk of ESRD in a trial of losartan in diabetic nephropathy [8]. Similar results were found with respect to cardiovascular outcomes in the LIFE study comparing losartan with atenolol in hypertension [9].

However, these analyses are not randomized comparisons and are therefore potentially subject to bias and confounding. Such post-hoc comparisons are well known to give misleading answers [10]. Furthermore, the large ONTARGET study showed no additional cardiovascular protection from the combination of telmisartan and ramipril despite additional attenuation in albuminuria progression [11]. In order to answer this question more reliably, the change in albuminuria needs to be measured before randomization, and then, the outcomes can be compared between two properly balanced groups of patients. For the time being, albuminuria is not considered a valid surrogate outcome in trials of progressive CKD (or cardiovascular disease), and further work is required before it can be so [12]. However, as outlined above, it remains a potentially useful risk marker and is the current focus of considerable epidemiological research.

**Albuminuria as a screening tool**

Testing for albuminuria is straightforward and highly acceptable to patients. As elegantly demonstrated by the Prevention of REnal and Vascular ENdstage Disease...
(PREVEND) group from Groningen, Netherlands who have pioneered epidemiological research in albuminuria, large numbers of patients may respond to community-based screening, and the yield is substantial [13]. In the PREVEND cohort of >40 000 people who provided a urine specimen (nearly half of those invited to do so), >7% had evidence of abnormal urinary albumin excretion (defined as >20 mg/L). Increased albuminuria was more common in those with a prior history of vascular disease, and also in those with traditional cardiovascular risk factors. Given its association with both cardiovascular risk and traditional cardiovascular risk factors, the PREVEND group has investigated whether using initial screening by albuminuria can identify a high-risk group who would then benefit from having traditional cardiovascular risk factors measured (and treated as required). This would be an attractive idea given the simplicity (and non-invasiveness) of albuminuria measurement.

In this issue, Özyilmaz et al. have investigated the utility of population-based screening using albuminuria to guide further testing for traditional cardiovascular risk factors (such as blood pressure and lipid fractions) [14]. They found that in their population, 61% of people with urinary albumin concentration (UAC) >20 mg/L were found to have a previously unrecognized cardiovascular risk factor (defined as diabetes mellitus, hypertension or hypercholesterolaemia) compared with only 39% of the whole population. This is not unexpected given the previously described associations between albuminuria and these traditional cardiovascular risk factors. The sensitivity and specificity of UAC >20 mg/L for such a new ‘diagnosis’ were 12% and 96%, respectively. Although the high specificity is impressive (and suggests a very low false-positive rate), the sensitivity is very low. It means that only 12% of new ‘diagnoses’ are discovered using albuminuria screening, or to put it another way, 88% of such ‘diagnoses’ are missed. The sensitivity falls to 8% if a 24-h urine is used to confirm elevated albuminuria, and, as the authors admit, the practicality also makes this approach unattractive.

Özyilmaz et al. acknowledge that 88% of cases are missed, but argue that in the absence of albuminuria, the risk of cardiovascular disease is low enough not to require treatment. However, in the PREVEND cohort, about two-thirds of all people with a history of myocardial infarction (who undoubtedly benefit from intensive lipid- and blood pressure-lowering treatment) had negligible (<10 mg/L) albuminuria, so this claim is hard to substantiate. The authors refer to their own observational data which suggest that patients with low levels of albuminuria do not benefit from antihypertensive therapy. However, this is not supported by large-scale clinical trials of antihypertensive therapy which show no heterogeneity of treatment effect according to baseline albuminuria [7,15]. The absolute benefit will of course be less (because of the lower background risk of cardiovascular disease), but the relative benefit is the same regardless of albuminuria. It is therefore hard to defend the charge that missing almost 90% of new diagnoses of cardiovascular risk factors is a critical weakness in the proposed approach.

Using albuminuria (or indeed any other risk marker) to select a population to screen for and treat cardiovascular risk suffers from Geoffrey Rose’s ‘prevention paradox’: a large number of people at small risk give rise to more cases of disease than the small number who are at a high risk [16]. The majority of people who suffer a myocardial infarction or a stroke are likely to have only modest increases in albuminuria, LDL cholesterol, blood pressure or any other risk marker. How best to reduce the population risk of such diseases (which is what screening aims to do) is controversial and may require a radical redesign of current preventive approaches.

The role of albuminuria in the identification of patients at risk of cardiovascular disease is unresolved. Albuminuria cannot yet be promoted from risk marker to modifiable risk factor or even a screening tool.

Conflict of interest statement. None declared.

References
13. Hildege HL, Janssen WM, Bak AA et al. Microalbuminuria is common, also in a nondiabetic, nonhypertensive population, and an inde-
Rethinking targets of blood pressure and guidelines for hypertension clinical management

Massimo Volpe¹,² and Giuliano Tocci¹

¹Division of Cardiology, II Faculty of Medicine, University ‘La Sapienza’, Sant’Andrea Hospital, Rome, Italy and ²IRCCS Neuromed, Pozzilli, IS, Italy

Correspondence and offprint requests to: Massimo Volpe; E-mail: massimo.volpe@uniroma1.it

Keywords: blood pressure targets; cardiovascular diseases; hypertension guidelines; hypertension management; renal diseases

Introduction

Arterial hypertension is a widely diffuse clinical condition characterized by epidemic proportions, marked impact on national health care systems and a major role in the global burden of cardiovascular (CV) and renal diseases [1]. Hypertension is, in fact, related to an increased risk of developing myocardial infarction, stroke, congestive heart failure, chronic kidney failure and mortality [2]. Effective treatment of hypertension is, in turn, consistently paralleled by a significant reduction of CV and renal morbidity and mortality, independently of age, gender, CV risk profile or concomitant diseases [3]. Despite solid evidence supporting the benefits obtained in hypertensive patients, when an effective antihypertensive strategy achieves the blood pressure (BP) targets currently recommended (i.e. BP levels below 140/90 mmHg in the general population and below 130/80 mmHg in high-risk hypertensive patients, such as those with diabetes mellitus or proteinuria), BP control is poorly achieved in clinical practice [4].

Beyond the concomitant presence of additional CV risk factors and associated clinical conditions, several causes have been advocated for explaining the worldwide poor rates of BP control [5]. Among these factors, poor adherence of patients to therapeutic (pharmacological or non-pharmacological) prescriptions, insufficient physician–patient communications, clinical inertia, lack of knowledge or poor implementation of recommendations proposed by guidelines, sub-optimal antihypertensive drug dosages or insufficient use of combination therapies are those most commonly reported, as they may explain, at least in part, the gap between recommended and achieved rates of BP control at a global level.

Among these factors, however, references to ineffectiveness of hypertension guidelines or objective difficulties to transfer guidelines’ recommendations to daily clinical practice are not usually quoted. On the other hand, in a complex and widespread condition, as arterial hypertension, concise and effective guidelines are definitely needed. In this regard, the rapid innovations of diagnostic options, the availability of newer drugs and novel therapeutic strategies and, most of all, the continuous new scientific findings on the pathophysiology of arterial hypertension, which have been reported over the last 30 years indeed represent a good reason to periodically review the field and provide doctors with a synthetic appraisal of the advances with the consequent recommendations. As an example of the continuous changes, Table 1 reports a number of concepts, statements and treatment options, largely accepted in the 1970s or even in the early 1980s. Today, these concepts look obsolete and have been substantially overwhelmed by new and more solid scientific evidence and substituted by different statements and clinical behaviours.

For these reasons, guidelines remain extremely important for all physicians aware or not of the new scientific achievements and of the suggested modifications in the clinical management and treatment of arterial hypertension. Nonetheless, rethinking the ways to develop guidelines and to translate them to achieve a more effective...