Albuminuria in heart failure: what do we really know?

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Purpose of the review

To describe the role of albuminuria as a risk marker for heart failure and a predictor for treatment effect on heart failure prognosis.

Recent findings

The level of albumin in the urine is a predictor of heart failure in the general population and in patients with cardiovascular risk, such as those with diabetes. Mild elevations of albuminuria, in the microalbuminuria range, appear to be associated with impaired systemic endothelial function. This increases the chance of developing hypertension, diabetes and cardiovascular disease, ultimately leading to heart failure. Higher levels of albuminuria, in the proteinuric range, reflect marked renal pathology, which increases cardiovascular risk due to renal function decline. In patients with established heart failure, microalbuminuria is highly prevalent (30%). Although more frequent in diastolic than systolic dysfunction, it appears to indicate a worse prognosis in the latter class. Diabetes is a multiplier of risk, probably due to bidirectional relationship between diabetes and heart failure. Treatment with drugs that intervene in the renin–angiotensin–aldosterone system (RAAS) lowers albuminuria and is associated with prevention of the onset and worsening of heart failure and other cardiovascular disorders.

Summary

Albuminuria is associated with increased heart failure risk. Lowering of albuminuria using RAAS inhibitors appears to lower the risk for heart failure.

Keywords

albuminuria, diabetes, heart failure, surrogate endpoint

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Introduction

Heart failure is a leading cause of morbidity and mortality in the industrialized world [1–3], and accounts for substantial healthcare costs [4,5]. During the last decade, there have been substantial advances in the management of heart failure, with much improvement in clinical outcomes achieved through pharmacological inhibition of neurohormonal systems [6]. Yet, half of the patients will die within 4 years, underscoring the need for better preventive or therapeutic strategies [7].

Therefore, strong interest has emerged in risk markers for heart failure prediction, such as biomarkers of endothelial dysfunction and inflammation [8,9]. Urinary albumin excretion rate has been shown to predict cardiovascular disease in patients with diabetes [10,11] and hypertension [12,13], as well as in seemingly healthy individuals [14]. Despite its established role as an early marker of cardiovascular risk, the importance of albuminuria in heart failure, the end stage of most cardiovascular diseases, is not clearly established.

This review will discuss recent advances in the understanding of the role of albuminuria in the prediction and prognosis of heart failure, as well as the relation between treatment-induced albuminuria lowering and heart failure prognosis.

The pathophysiological mechanism of albuminuria

The presence of albumin in urine above normal values (>30 mg/day or 20 mg/l) is generally defined as albuminuria. Low levels of albumin in urine, ranging from 30 to 300 mg/day (20 to 200 mg/l) are defined as microalbuminuria. Levels above 300 mg/day (200 mg/l) are defined as macroalbuminuria (also called overt proteinuria/albuminuria). Despite these clear cut-off values, albuminuria is regarded as a continuous variable, as higher values are related to higher risk, even within the defined normal range. Microalbuminuria is highly prevalent in patients with diabetes and hypertension, ranging from 10 to 40% [14,15]. Nevertheless, microalbuminuria is also frequently found in seemingly healthy individuals (5 to 7%) [14,16].

The pathophysiological mechanism of albuminuria and its link with cardiovascular disease is not clearly established, but three main causes have been put forward [17]. First, urinary albumin loss could be a consequence of renal damage. Damage to the glomerulus or proximal tubule may lead to increased filtration or decreased tubular reabsorption of albumin, or both. In turn, the increased albumin filtration damages the glomerulus through increased mesangial protein trafficking, and the proximal tubule through increased burden of albumin reabsorption [18]. This renal damage leads to decreased glomerular filtration and this will lead to compensatory mechanisms, such as activation of the renin–angiotensin–aldosterone system (RAAS), which may subsequently affect the cardiovascular system. The second explanation may be that albuminuria reflects widespread vascular damage induced by common cardiovascular risk factors, and as such higher susceptibility to atherosclerosis and cardiovascular disease [19]. Recently, several studies have shown that there is a common barrier for albumin across the endothelial vascular layer, namely the glycocalyx. This dynamic layer covers peripheral vasculature as well as the fenestrated endothelium of the glomerular vessels [20••]. Differences in systemic glycocalyx are associated with different albuminuria [21]. Thus, increased urine albumin leakage may well be a measure of endothelial damage. The third possible explanation (adding to the second one) is that individuals are born with a variable degree of endothelial function (glycocalyx function). In fact, glycocalyx volume varies within normal individuals [21], and it has been found that albuminuria, in newborns and young individuals, is as variable as in older people. This may indicate that genetic or in-utero factors may determine albuminuria/endothelial function and thus individual susceptibility to cardiovascular risk later in life [17].

A confusing phenomenon in the earlier-mentioned hypothesis is the recent guideline definition of renal dysfunction, in which microalbuminuria is seen as an indicator of renal disease even in the absence of a decreased glomerular filtration rate (GFR) [22]. However, the presence of microalbuminuria is often not associated with renal pathology, and could well be a more general than renal disease indicator. In case of overt proteinuria, we do find damaged glomeruli, tubules and often also renal interstitium, indicating a renal-based albumin leakage.

Albuminuria and risk of heart failure in the general population

Several large prospective cohort studies have shown that increased albuminuria is associated with heart failure onset in various community populations (Table 1 and Fig. 1) [23–25,26••,27–34].

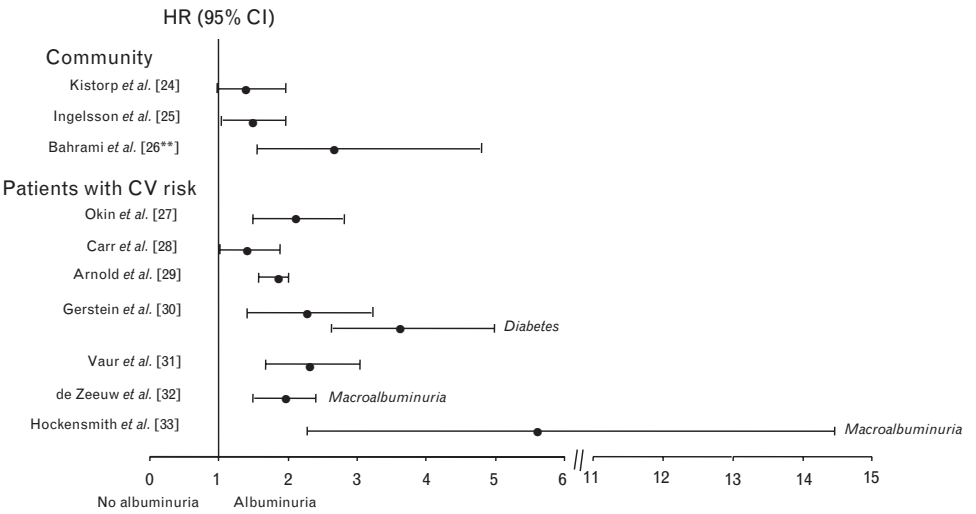
In middle-aged nonhypertensive and nondiabetic individuals, Arnlov *et al.* [23] showed that even low levels of albuminuria, below the microalbuminuria threshold,

Table 1 Albuminuria and risk of new-onset heart failure

Study	Original study name	Study population	*n*	Mean age	Follow-up (years)	New cases HF	Risk of new onset HF/CV events HR/OR
General population							
Arnlov *et al.* [23]	Framingham	Nonhypertensive and nondiabetic	1568	55	6		Low levels of UAE predict first CV event, including HF
Kistorp *et al.* [24]		Older adults	626, 597	68	5	94, 18	Major CV event – HR 2.32 (CI 1.33–4.05); HF – NS
Ingelsson *et al.* [25]		Elderly men	1106	70	9	98	HR 1.49 (CI 1.13–1.98)/ No treatment
Bahrami *et al.* [26••]	MESA	No history of symptomatic CV disease	6814	65	4	79	MA – HR 2.73 (CI 1.56–4.78)
Patients with established CV risk							
Okin *et al.* [27]	LIFE	Hypertension and LVH	7786	67	4.7	231	HR 2.1 (CI 1.5–2.8)
Carr *et al.* [28]	LIFE	Hypertension, LVH and diabetes	1195	60	4.7	76	HR 1.41 (CI 1.08–1.86)
Arnold *et al.* [29]	HOPE	CV disease or diabetes and another CV risk factor	9541	55	4.5	951	HR 1.82 (CI 1.58–2.10)
Gerstein *et al.* [30]	HOPE	CV disease or diabetes and another CV risk factor	9043	≥55	4.5	234, 609	No diabetes – HR 2.20 (CI 1.40–3.26); diabetes – HR 3.70 (CI 2.64–5.17)
Vaur *et al.* [31]	DIABHYCAR	Type 2 diabetes and elevated albumin levels	4912	≥50	4	187	HR 2.30 (CI 1.71–3.09)
de Zeeuw *et al.* [32]	RENAAL	Type 2 diabetes with nephropathy	1513	60	3.4	191	Macroalbuminuria – HR 1.92 (CI 1.54–2.38)
Hockensmith *et al.* [33]		Type 2 diabetes	860	58	5	32	Macroalbuminuria – OR 5.6 (CI 2.2–14.5)
Torffvit *et al.* [34]		Type 1 diabetes	462	47	12	27, 17	CV death – Macroalbuminuria HR 8.2 (CI 2.1–31.7), HF – NS

CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; LVH, left ventricular hypertrophy; MA, microalbuminuria; OR, odds ratio; UAE, urinary albumin excretion.

Figure 1 Albuminuria and risk of heart failure



CI, confidence interval; CV, cardiovascular; HR, heart rate.

predicted the development of a composite of cardiovascular events, including heart failure.

In older nonhospitalized adults, Kistorp *et al.* [24] found that albuminuria above the 80th percentile is a predictor of major cardiovascular events. In a subsample of patients with normal left ventricular ejection fraction (LVEF > 50%), albuminuria was not a significant predictor of heart failure, but in this study only 18 patients developed heart failure. In contrast, Ingelsson *et al.* [25] found in a larger study of elderly men that microalbuminuria increases the risk of heart failure by 50%, but only in individuals without antihypertensive treatment. The lack of predictive effect of albuminuria in patients with antihypertensive treatment was probably because of the small number of patients included in this group. Indeed, several large-scale RCTs have shown that albuminuria is a risk predictor of heart failure irrespective of antihypertensive treatment [27,29]. Albuminuria remained a predictor of heart failure in untreated individuals without myocardial infarction (MI) or diabetes at baseline, irrespective of interim MI, BP levels or other risk markers, such as Cystatin C, C-reactive protein, and NT-proBNP at baseline.

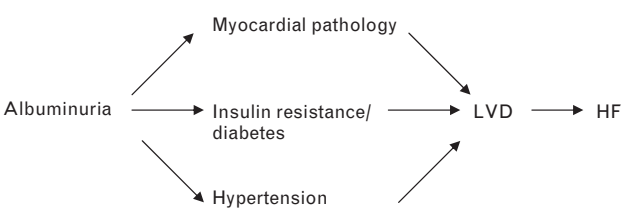
In participants without symptomatic cardiovascular disease, Bahrami *et al.* [26••] showed that microalbuminuria increased by almost three-fold the risk of heart failure after adjustment for multiple risk factors at baseline, and interim MI. However, when LVEF was included in the model, only macroalbuminuria remained an independent predictor. Indeed, patients with low EF have a high risk of developing symptomatic heart failure [35]. On the other hand, the study may indicate that LV dysfunction (LVD) is one of the pathways via which albuminuria leads to increased risk of heart failure. This supposition is supported by Liu *et al.* [36], who showed that albuminuria is associated with LV systolic and diastolic dysfunction and screening for albuminuria may identify individuals with cardiac dysfunction. As albuminuria is an indicator of generalized vascular dysfunction, it may also indicate vascular myocardial pathology that contributes to cardiac dysfunction. However, it may also be that during follow-up albuminuria leads to heart failure via other cardiovascular risk pathways, such as development of insulin resistance/diabetes or hypertension [37,38] (Fig. 2).

In conclusion, albuminuria is a risk predictor for heart failure in the general population, independent of BP levels, diabetes and baseline or interim MI. Albuminuria may lead to heart failure via several pathways, including direct myocardial pathology, as well as development of insulin resistance/diabetes and hypertension.

Albuminuria and risk of heart failure in patients with established cardiovascular risk

Albuminuria was considered initially a marker of uncontrolled BP and diabetes, and as such its predictive capacity was extensively studied in patients with cardiovascular risk (Table 2 and Fig. 1) [27–40,41•,42].

Figure 2 Pathophysiological mechanisms of heart failure in patients with albuminuria



HF, heart failure; LVD, left ventricular dysfunction.

Table 2 Albuminuria in patients with established heart failure

Study	Study population	*n*	Mean age	Results
Cross-sectional studies				
Van de Wal *et al.* [39]	Advanced HF and reduced EF (NYHA III, IV)	94	69	MA in 30% of patients despite ACEI therapy and normal BP; no association of UAE with renal or neurohormonal parameters
Damman *et al.* [40]	HF outpatients with low LVEF	90	40	Patients with HF have structural tubular damage, ↑UAE, and ↓GFR
Orea-Tejeda *et al.* [41•]	Stable HF outpatients (NYHA I–III)	72	63	Prevalence of MA higher in diastolic vs. systolic HF (40 vs. 24%); in systolic HF, MA associated with predictors of worse prognosis
Prospective studies				
Capes *et al.* (SOLVD) [42]	LVEF $\leq$ 0.35 with symptomatic or asymptomatic HF	5487	60	Clinical proteinuria predictor of HF hospitalization (HR 1.81 (CI 1.37–2.41))
Kirstop *et al.* [43••]	Patients with HF with and without diabetes	195	69	Albuminuria predictor of ischemic events in patients with HF and diabetes – HR 2.07 (1.18–3.65)

BP, blood pressure; CI, confidence interval; EF, ejection fraction; GFR, glomerular filtration rate; HF, heart failure; LVEF, left ventricular ejection fraction; MA, microalbuminuria; UAE, urinary albumin excretion.

In patients with hypertension and left ventricular hypertrophy (LVH), Okin *et al.* [27] showed that microalbuminuria increases the risk of heart failure two-fold despite aggressive BP lowering treatment. Furthermore, in a subgroup analysis of the same trial, albuminuria predicted new heart failure hospitalizations in patients with hypertension, LVH and diabetes [28].

In patients with history of cardiovascular disease or diabetes and another cardiovascular risk factor, Arnold *et al.* [29] showed that microalbuminuria increases the risk of developing heart failure two-fold, irrespective of treatment with ramipril. Microalbuminuria predicted the risk of heart failure in both diabetic and nondiabetic individuals, but diabetes amplified the heart failure risk [30].

Three studies performed solely in patients with type 2 diabetes show the predictive capacity of increased albuminuria with regard to heart failure onset. Vaur *et al.* [31] found a logarithmic relationship between level of albuminuria and subsequent development of heart failure; each 10-fold increase in UAE was associated with double risk of heart failure. In patients with type 2 diabetes and nephropathy, de Zeeuw *et al.* [32] showed that patients with high macroalbuminuria have a nearly three-fold higher risk of heart failure compared with patients with low macroalbuminuria. Furthermore, in a cohort of type 2 diabetic patients in which 16 (1.6%) patients had already NYHA I, II HF at baseline, macroalbuminuria remained an independent predictor of heart failure hospitalizations [33]. Finally, in type 1 diabetes patients macroalbuminuria was also associated with development of cardiovascular disease, although not specifically heart failure, probably due to the small number of incident heart failure cases (18 patients) in this cohort [34].

In conclusion, albuminuria at low (microalbuminuria) levels as well as at high (proteinuria) levels is a risk predictor of heart failure in patients with cardiovascular risk, including those with hypertension and diabetes.

Albuminuria in patients with established heart failure

The occurrence of increased albuminuria in heart failure should be considered in the context of underlying disease, as heart failure is the end stage of several cardiovascular disorders, including diabetes. The underlying disease may determine the type of LVD, for example, systolic vs. diastolic, and may also influence the prognosis. In heart failure, the association between albuminuria and renal function as well as other markers of prognosis was studied in three small cross-sectional studies (Table 2) [39,40,41•].

In patients with advanced heart failure and systolic dysfunction, van de Wal *et al.* [39] have shown that microalbuminuria was present in 32% of patients at moderately impaired GFR, indicating that microalbuminuria may be an early indicator of renal damage. Surprisingly, patients with microalbuminuria were not significantly different in clinical (and neurohormonal) parameters from those without microalbuminuria, but they had a nonsignificantly higher prevalence of diabetes. The lack of a significant difference could well be explained by the small sample size, but also by the wide range of medication used in these patients.

The relationship between albuminuria and renal function in patients with systolic heart failure was also elegantly described by Damman *et al.* [40], who showed that patients with heart failure have high levels of albuminuria and low GFR, but also structural tubular damage.

Orea-Tejeda *et al.* [41•] have specifically studied whether microalbuminuria exerts different characteristics in patients with systolic and diastolic dysfunction. They showed that microalbuminuria was overall present in 31% of patients, but more frequently in patients with diastolic than those with systolic heart failure (40 vs. 24%). Furthermore, patients with systolic heart failure and microalbuminuria had a higher prevalence of type 2 diabetes, and other predictors of worse prognosis, such as volume overload, lower serum albumin levels, and high pulmonary artery pressure, whereas in patients with diastolic dysfunction such an association was not observed.

The relationship between diabetes and heart failure is very complex and has a bidirectional nature; patients with diabetes are at high risk of developing heart failure, whereas patients with heart failure are also at high risk of developing insulin resistance and diabetes. This is due to RAAS activation, but also due to reduction of skeletal muscle blood flow in heart failure [44]. Thus, the more severe heart failure, the higher the risk of developing diabetes. In turn, more severe patients will receive more intensive RAAS therapy, closing a vicious circle of diabetes and albuminuria risk. Nevertheless, due to the cross-sectional design of these studies, one cannot say whether diabetes at baseline induced microalbuminuria or heart failure induced diabetes and microalbuminuria. All studies do point to the importance of controlling diabetes and heart failure progression in these patients.

Despite the high prevalence of microalbuminuria in heart failure, only two studies have prospectively studied the relationship between albuminuria and clinical outcomes in heart failure patients (Table 2) [42,43••].

In the SOLVD trial population, which included a large number of patients with LVEF 0.35 or less with symptomatic or asymptomatic heart failure, Capes *et al.* [42] studied the impact of clinical proteinuria on clinical outcomes. At baseline, patients with clinical proteinuria had a significantly higher prevalence of diabetes, higher systolic and diastolic BP, a lower LVEF and more severe (NYHA III, IV) heart failure. After adjustment for these predictors, clinical proteinuria remained an independent predictor of heart failure hospitalizations and mortality.

Kistorp *et al.* [43••] have prospectively studied during a median of 2.5 years whether albuminuria and other biomarkers of endothelial dysfunction at baseline are related to prognosis in patients with heart failure with and without diabetes. The authors found that among the diabetic heart failure patients albuminuria, plasma E-selectin and fasting blood glucose predicted the risk of ischemic events, but this association was not observed in nondiabetic heart failure patients.

In conclusion, microalbuminuria is highly prevalent in patients with heart failure. Although more frequent in diastolic than systolic dysfunction, it appears to indicate a worse prognosis in the latter class. Microalbuminuria is frequently associated with diabetes, and indicates a worse prognosis in patients with heart failure and diabetes than in those with heart failure alone. This is probably due to the bidirectional relationship between diabetes and heart failure.

Effect of treatment that lowers albuminuria on heart failure prevention and prognosis

It is already clearly established that treatment with RAAS inhibitors decreases morbidity and mortality in patients with heart failure [45], but whether this effect is related to the reduction of albuminuria is not clear.

In patients with LV dysfunction, only one study has assessed the effect of therapy on albuminuria and clinical outcomes. Capes *et al.* [42] showed that treatment with an angiotensin-converting enzyme (ACE)-inhibitor prevented clinical proteinuria in diabetic patients with LVD. This effect was not observed in nondiabetic patients, but this may be due to the low incidence of proteinuria in this population and thus insufficient power. Furthermore, treatment with enalapril resulted in a greater reduction of heart failure hospitalizations in diabetic patients than in nondiabetic patients.

In patients with cardiovascular risk, reduction of albuminuria by therapy has been shown to prevent heart failure (Table 3) [29,32,46–48]. Arnold *et al.* [29] showed that treatment with the ACE-inhibitor ramipril reduced the risk of developing heart failure. Although this study had shown that the ACE-inhibitor lowers albuminuria, the authors did not assess whether reduction of heart failure risk was a direct consequence of a treatment-induced decrease in albuminuria. In patients with type 2 diabetes and nephropathy de Zeeuw *et al.* [32] showed that macroalbuminuria reduction with an angiotensin receptor blocker was associated with a reduction in heart failure risk (27% reduction in heart failure risk for every 50% reduction in albuminuria).

Furthermore, several studies have shown that albuminuria reduction is associated with reduction of cardiovascular events. In the LIFE study [46], patients who had an albuminuria greater than the median value, but were able to decrease their albuminuria to less than the median value, had a reduced risk for cardiovascular events. A similar effect was observed in patients with hypertension, LVH and diabetes [47]. The prevention of renal and vascular end-stage disease (PREVEND) study showed that treatment with an ACE-inhibitor resulted in a significant decrease in urinary albumin excretion and a trend

Table 3 Effect of treatment of albuminuria on heart failure prevention

Study	Original study name	Study population	*n*	Drug	Reduction HF risk/CV risk
Arnold JM *et al.* [29]	HOPE	CV disease or diabetes and another CV risk factor	9541	Ramipril vs. placebo	HR 0.77; 0.68–0.87
de Zeeuw D *et al.* [32]	RENAAL	Type 2 diabetes with nephropathy	1513	Losartan vs. placebo	27% reduction in HF risk for every 50% reduction in MA
Ibsen H *et al.* [46]	LIFE	Hypertension and LVH	8206	Losartan vs. atenolol	Patients with UACR above the median able to decrease ACR to less than the median value reduced risk of CV events
Ibsen H *et al.* [47]	LIFE	Hypertension, LVH and diabetes	1063	Losartan vs. atenolol	33 vs.15% reduction in albuminuria with losartan vs. atenolol. Risk of CV events related to in-treatment reduction in UACR
Asselbergs FW *et al.* [48]	PREVEND	Participants with MA	1439	Fosinopril vs. placebo	26% reduction in UAE and 40% reduction in CV mortality and hospitalization (trend)

LVH, left ventricular hypertrophy; MA, microalbuminuria; UACR, urinary albumin to creatinine ratio; UAE, urinary albumin excretion.

toward decrease in cardiovascular events in participants with microalbuminuria from the general population [48].

Conclusion

The role of albuminuria in the development of heart failure appears multifaceted. Mild elevations of albuminuria, in the microalbuminuria range, appear to be associated with impaired systemic endothelial function. This increases the chance of developing hypertension, diabetes and cardiovascular disease, ultimately leading to heart failure. In contrast, higher levels of albuminuria, in the proteinuric range, reflect marked renal pathology. These patients are at high cardiovascular risk due to deranged metabolism associated with GFR decline. Clearly, diabetes is a multiplier of risk both in microalbuminuria and in proteinuria conditions. Treatment with RAAS inhibitors lowers albuminuria and lowers heart failure onset, as well as cardiovascular risk in general. Furthermore, RAAS inhibitors improve outcomes in patients with heart failure and diabetes. Differences in albuminuria levels appear to be a valuable biomarker to predict heart failure risk as well as treatment efficacy. More prospective studies are needed on the mechanism of albuminuria and heart failure prognosis as well as on treatment-induced albuminuria lowering and heart failure risk reduction.

References and recommended reading

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