

# Effects of manidipine vs. amlodipine on intrarenal haemodynamics in patients with arterial hypertension

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## WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Dihydropyridine calcium channel blockers (CCBs) are widely used antihypertensive drugs. Evidence from animal studies indicates there are differences between CCBs in their renal haemodynamic effects suggesting that manidipine reduces, whereas amlodipine increases intraglomerular pressure but data from humans are scarce.

## WHAT THIS STUDY ADDS

- In this study amlodipine was found to increase significantly intraglomerular pressure whereas manidipine decreased intraglomerular pressure in people with essential hypertension. This difference was attributed to significant vasodilation of the afferent arteriole with amlodipine compared with manidipine. This study for the first time has confirmed in humans data from experimental models on the different action of CCBs on dilatatory capacity on efferent and afferent arterioles.

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## AIMS

Intraglomerular pressure is one of the main drivers of progression of renal failure. Experimental data suggest that there are important differences between calcium channel blockers (CCBs) in their renal haemodynamic effects: manidipine reduces, whereas amlodipine increases intraglomerular pressure. The aim of this study was to investigate the effects of manidipine and amlodipine treatment on intraglomerular pressure ( $P_{\text{glom}}$ ) in patients with mild to moderate essential hypertension.

## METHODS

In this randomized, double-blind, parallel group study, hypertensive patients were randomly assigned to receive manidipine 20 mg ( $n = 54$ ) or amlodipine 10 mg ( $n = 50$ ) for 4 weeks. Renal plasma flow (RPF) and glomerular filtration rate (GFR) were determined by constant-infusion input-clearance technique with p-aminohippurate (PAH) and inulin.  $P_{\text{glom}}$  and resistances of the afferent ( $R_A$ ) and efferent ( $R_E$ ) arterioles were calculated according to the model established by Gomez.

## RESULTS

$P_{\text{glom}}$  did not change in the manidipine group ( $P = 0.951$ ), whereas a significant increase occurred in the amlodipine group ( $P = 0.009$ ). There was a significant difference in the change of  $P_{\text{glom}}$  by 1.2 mmHg between the manidipine and amlodipine group ( $P = 0.042$ ). In both treatment arms,  $R_A$  was reduced (manidipine  $P = 0.018$ ; amlodipine  $P < 0.001$ ). The reduction of  $R_A$  was significantly more pronounced with amlodipine compared with manidipine treatment ( $P < 0.001$ ).  $R_E$  increased in both treatment arms (manidipine  $P = 0.012$ ; amlodipine  $P = 0.002$ ), with no difference between the treatment arms. Both CCBs significantly reduced systolic and diastolic blood pressure (BP) (both  $P < 0.001$ ). However, amlodipine treatment resulted in a significantly greater decrease of BP compared with manidipine ( $P < 0.001$ ).

## CONCLUSIONS

In accordance with experimental data after antihypertensive treatment of 4 weeks, intraglomerular pressure was significantly lower with the CCB manidipine than with amlodipine, resulting and explaining their disparate effects on albuminuria.

## Introduction

Hypertension is a major determinant of renal disease progression. Although tight blood pressure (BP) control is an established goal in the treatment of patients with renal disease, it is also well recognized that some antihypertensive drugs have additional effects on renal haemodynamics, potentially affecting the progression of renal disease. Dihydropyridine calcium channel blockers (CCBs) are widely used as both first choice treatment and in combination with other antihypertensive drugs [1]. However, there is still a matter of debate about CCBs and their effects on intrarenal haemodynamics. Repeatedly, experimental models have shown that the potent blood pressure lowering actions of conventional CCBs (e.g. amlodipine) reduce glomerular hyperfiltration and afford renal protection [2, 3]. However, there are also data to demonstrate that the preferential activity of amlodipine on preglomerular vessels, causing mainly dilation of the afferent arteriole, with only modest effects on the efferent arteriole, could also cause an increase in glomerular hyperfiltration and glomerular pressure that could promote renal disease progression [4–6]. In accordance, we have recently evaluated the effect of the conventional CCB amlodipine on renal haemodynamics in hypertensive humans and demonstrated that amlodipine led to glomerular hyperfiltration and an increase in glomerular pressure [7].

Nowadays novel types of CCBs (e.g. manidipine) have been developed, and experimental data suggest that these novel CCBs differ in particular with respect to their effects on intrarenal haemodynamics, demonstrating a relatively greater vasodilatory effect on efferent arterioles [8]. In the hydronephrotic kidney model it was shown that manidipine dilates both afferent and efferent arterioles, although the magnitude on efferent arterioles was less than on afferent arterioles in this particular model of renal injury [9]. Using microdissected renal arterioles, Arima *et al.* have demonstrated that manidipine has dilatory actions on both afferent and efferent arterioles [10]. Another experimental study has clearly demonstrated that manidipine causes vasodilation of the afferent as well as efferent arterioles, thereby leading to a fall of intraglomerular pressure [11].

In contrast to the relative abundance of data derived from animal studies, data in humans are scarce. Studies have focused on effects of CCBs on changes in albuminuria or creatinine clearance, reflecting renal function [12, 13]. To date, no data are available on the effects of different CCBs on intrarenal haemodynamics, in particular on intraglomerular pressure. The objective of the current study was therefore to test whether the experimental data hold true in the clinical setting and the two CCB, manidipine and amlodipine, exert disparate effects on intrarenal haemodynamics and intraglomerular pressure in hypertensive patients.

## Methods

### Study population

This investigator-initiated trial followed a randomized, double-blind, parallel group design in 104 patients with arterial hypertension grade 1–2. Subjects were recruited by advertising in local newspapers in the area of Erlangen-Nürnberg, Germany, and eligible subjects were enrolled consecutively. Written informed consent was obtained prior to study inclusion.

Main inclusion criteria were age between 18 and 65 years, arterial hypertension grade 1 or 2 according to ESH guidelines 2003 and no evidence of significant cardiovascular disease other than hypertension. Main exclusion criteria were secondary arterial hypertension, arterial hypertension grade 3, uncontrolled diabetes mellitus or requiring insulin, concomitant treatment with other antihypertensive drugs or drugs known to affect blood pressure.

The study protocol was approved by the Local Ethics Committee (University of Erlangen-Nürnberg) and the study was conducted in accordance with the Declaration of Helsinki and the principles of 'good clinical practice' (GCP) guidelines.

The study was registered at <http://www.clinicaltrials.gov> (ID: NCT00627952).

### Study design

Participants on antihypertensive medication underwent a wash-out phase for 4 weeks and inclusion and exclusion criteria were rechecked again. Thereafter, baseline measurement of renal haemodynamics was performed using the constant infusion input clearance technique. Then study participants were randomly assigned to receive manidipine 20 mg or amlodipine 10 mg for 28 days and repeated measurements of renal haemodynamics were performed thereafter.

The primary objective of this study was to investigate the effects of a once daily oral dose of manidipine 20 mg, compared with once daily oral dose of amlodipine 10 mg over a 4 week treatment period on intraglomerular pressure in patients with mild to moderate essential hypertension.

### Determination of renal haemodynamics

All clearances were performed at the same time in the morning in a quiet and temperature-controlled room. Renal haemodynamics were determined by the constant infusion input clearance technique with inulin (Inutest, Fresenius, Linz, Austria) and sodium p-aminohippurate (PAH) (Clinalfa, Basel, Switzerland) for glomerular filtration rate (GFR) and renal plasma flow (RPF), respectively, as suggested by Cole *et al.* [14] and repeatedly reported from our laboratory (<http://www.crc-erlangen.de>). In brief, after a bolus infusion of inulin and PAH over 15 min and a subse-

quent constant infusion over 105 min, a steady-state between input and renal excretion of the tracer substances was reached. Duplicate blood samples were collected for the assessment of RPF and GFR. PAH was measured according to previously described methods [15]. Inulin was measured indirectly by converting inulin to fructose and subsequently measuring fructose by an enzymatic method (Boehringer Mannheim, Mannheim, Germany). Each blood sample was measured in duplicate with a coefficient variation of <5%.

### Calculation of renal and intraglomerular haemodynamics

Filtration fraction (FF) was calculated as GFR/RPF and renal blood flow (RBF) as RPF/(1 – haematocrit).

Intraglomerular pressure ( $P_{\text{glom}}$ ) and resistances of the afferent ( $R_A$ ) and efferent ( $R_E$ ) arterioles were calculated according to the model originally established by Gomez [16], which has been discussed by Guidi *et al.* [17] and applied in previous studies [7, 18], as follows:

$$\begin{aligned} P_{\text{glom}} &= \Delta P_F + P_{\text{Bow}} + \pi_G \\ &= (\text{GFR}/K_{\text{FG}}) + P_{\text{Bow}} + (5 \times (C_M - 2)) \\ &= (\text{GFR}/K_{\text{FG}}) + P_{\text{Bow}} + (5 \times ((\text{TP}/\text{FF} \times \ln(1/1 - \text{FF})) - 2)) \end{aligned}$$

In the above equation,  $K_{\text{FG}}$  (gross filtration coefficient) is estimated as  $0.0406 \text{ ml s}^{-1}$  per kidney.  $P_{\text{Bow}}$  (hydrostatic pressure in the Bowman's space) is estimated as 10 mmHg.  $\pi_G$  (oncotic pressure within glomerular capillaries) can be obtained from  $C_M$  (plasma protein concentration within the glomerular capillaries), and calculated from TP (total protein concentration) and FF.

From Ohm's law:

$$R_A = ((\text{MAP} - P_{\text{glom}}) / \text{RBF}) \times 1328$$

$$R_E = (\text{GFR}/K_{\text{FG}} \times (\text{RBF} - \text{GFR})) \times 1328$$

### Measurement of urinary albumin and creatinine

All samples were measured centrally at the biochemistry laboratory of the University of Erlangen-Nürnberg according to established methods. In brief, urinary albumin concentration was measured by a turbidimetric method. The inter-assay coefficient of variation was 3.44%. Creatinine concentration in urine was measured photometrically by the Jaffé method. The inter-assay coefficient of variation was 2.03%.

### Statistical analysis

Normal distribution of data was confirmed by Kolmogorov–Smirnov tests before further analysis. Normally distributed data were compared by paired and unpaired Student's *t*-tests and are expressed as mean  $\pm$  standard deviation (SD). Data of UACR were not normally distributed. Therefore, median and interquartile range are

reported. UACR values were log-transformed before statistical analysis. Where indicated, a multiple stepwise regression analysis with significance levels of 0.05 for entry and 0.10 for removal of a variable at each forward step was conducted. Two-tailed values of  $P < 0.05$  were considered statistically significant. All analyses were performed using SPSS 16.0 (SPSS Inc., Chicago, Illinois, USA).

## Results

Baseline characteristics of participants randomized to the respective CCB (manidipine or amlodipine) are given in Table 1. There were no differences in any of the clinical characteristics between the two groups.

### Intrarenal haemodynamics

The primary endpoint of our study,  $P_{\text{glom}}$ , did not change in the manidipine group ( $69.5 \pm 3.9$  vs.  $69.5 \pm 3.6$  mmHg,  $P = 0.951$ ), whereas a significant increase was noted in the amlodipine group ( $68.6 \pm 4.4$  vs.  $70.2 \pm 4.0$  mmHg,  $P = 0.009$ ). There was a significant difference in the change of  $P_{\text{glom}}$  by 1.2 mmHg between the manidipine and amlodipine group ( $P = 0.042$ , Figure 1).

In both treatment arms  $R_A$  was reduced (manidipine  $3389 \pm 1383$  vs.  $3055 \pm 1192 \text{ dyn s}^{-1} \text{ cm}^{-5}$ ,  $P = 0.018$ ; amlodipine  $2987 \pm 925$  vs.  $2320 \pm 739 \text{ dyn s}^{-1} \text{ cm}^{-5}$ ,  $P < 0.001$ ). The reduction of  $R_A$  was significantly more pronounced with amlodipine compared with manidipine treatment ( $P < 0.001$ ).  $R_E$  increased in both treatment arms (manidipine  $2557 \pm 494$  vs.  $2701 \pm 524 \text{ dyn s}^{-1} \text{ cm}^{-5}$ ,  $P = 0.012$ ; amlodipine  $2488 \pm 505$  vs.  $2737 \pm 590 \text{ dyn s}^{-1} \text{ cm}^{-5}$ ,  $P = 0.002$ ), with no difference between the treatment arms.

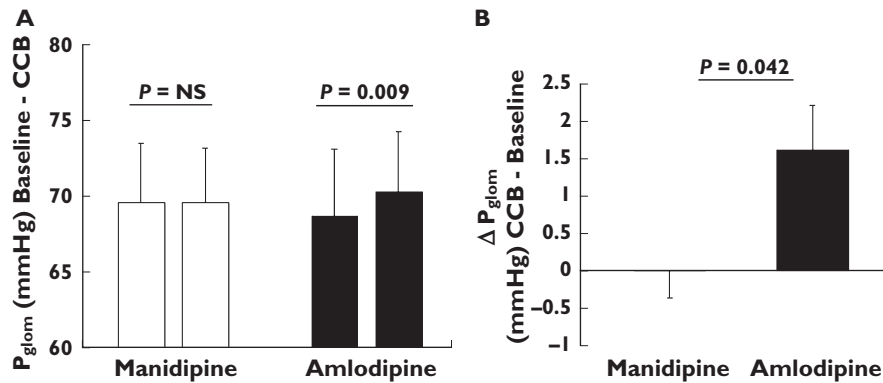
The intraglomerular pressure is mainly the result of the interplay between the efferent and afferent arteriolar resistance. Hence, the ratio of the resistances of the efferent to the afferent arterioles ( $R_E : R_A$ ) are given in Figure 2. Baseline levels did not differ between manidipine and amlodipine groups. In both groups there was an increase of this

**Table 1**

Clinical characteristics (mean  $\pm$  SD) of participants stratified according to assigned calcium channel blocker

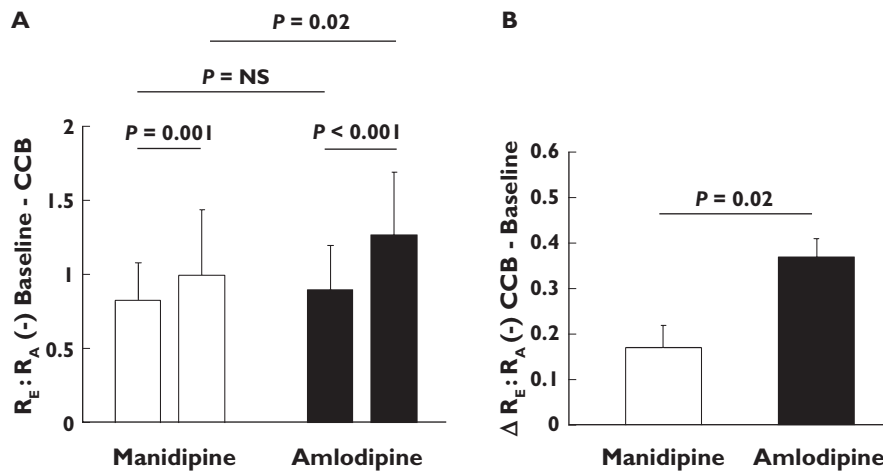
	Manidipine	Amlodipine	<i>P</i> value
Age (years)	50.5 $\pm$ 12	50.7 $\pm$ 9	NS
Gender (M/F)	44/10	41/9	NS
BSA (m <sup>2</sup> )	2.05 $\pm$ 0.2	2.03 $\pm$ 0.2	NS
BMI (kg m <sup>-2</sup> )	27.7 $\pm$ 3.5	27.0 $\pm$ 3.3	NS
Systolic BP (mmHg)	150 $\pm$ 10	148 $\pm$ 9	NS
Diastolic BP (mmHg)	93 $\pm$ 8	93 $\pm$ 9	NS
Heart rate (beats min <sup>-1</sup> )	71 $\pm$ 10	72 $\pm$ 11	NS
UACR (mg g <sup>-1</sup> creatinine)	12.7 $\pm$ 17	14.3 $\pm$ 33	NS

BSA, body surface area; BMI, body mass index; UACR, urinary albumin : creatinine ratio; NS, not significant.



**Figure 1**

A)  $P_{\text{glom}}$  at baseline and after 4 weeks of treatment with CCBs manidipine (white columns) and amlodipine (black columns), a comparison within the CCB groups. B) Change of  $P_{\text{glom}}$  between baseline and 4 weeks of treatment with CCBs manidipine (white column) and amlodipine (black column), a comparison between the CCB groups



**Figure 2**

A) Ratio of the resistances of the efferent and afferent arteriole ( $R_E : R_A$ ) at baseline and after 4 weeks of treatment with CCBs manidipine (white columns) and amlodipine (black columns), a comparison within the CCB groups. B) Change of  $R_E : R_A$  between baseline and 4 weeks of treatment with CCBs manidipine (white column) and amlodipine (black column), a comparison between the CCB groups

ratio (manidipine  $0.83 \pm 0.3$  vs.  $1.0 \pm 0.3$ ,  $P = 0.001$ ; amlodipine  $0.9 \pm 0.3$  vs.  $1.27 \pm 0.4$ ,  $P < 0.001$ ). However, the change of the  $R_E : R_A$  was more pronounced with amlodipine compared with manidipine ( $0.37 \pm 0.04$  vs.  $0.17 \pm 0.05$ ,  $P = 0.002$ ).

### Renal haemodynamics

The RPF was maintained in both treatment groups (manidipine  $616 \pm 141$  vs.  $597 \pm 146$  ml min<sup>-1</sup>,  $P = 0.169$ ; amlodipine  $621 \pm 130$  vs.  $603 \pm 115$  ml min<sup>-1</sup>,  $P = 0.318$ ). Consistent with the findings on intraglomerular haemodynamics, GFR was numerically more increased with amlodipine ( $140 \pm 18$  vs.  $144 \pm 16$  ml min<sup>-1</sup>,  $P = 0.081$ ), than with manidipine ( $141 \pm 18$  vs.  $142 \pm 19$  ml min<sup>-1</sup>,  $P = 0.467$ ).

### Systemic haemodynamics

Baseline systolic and diastolic BP did not differ between manidipine and amlodipine groups. Both CCBs decreased systolic (manidipine  $150 \pm 10$  vs.  $143 \pm 12$  mmHg,  $P < 0.001$ ; amlodipine  $148 \pm 9$  vs.  $133 \pm 10$  mmHg,  $P < 0.001$ ) and diastolic BP (manidipine  $93 \pm 8$  vs.  $90 \pm 7$  mmHg,  $P < 0.001$ ; amlodipine  $93 \pm 9$  vs.  $85 \pm 9$  mmHg,  $P < 0.001$ ). However, BP reduction was significantly less pronounced with manidipine treatment compared with amlodipine treatment (systolic  $-7 \pm 11$  vs.  $-16 \pm 13$  mmHg,  $P < 0.001$ ; diastolic  $-3 \pm 6$  vs.  $-8 \pm 7$  mmHg,  $P < 0.001$ ).

### Urinary albumin : creatinine ratio (UACR)

In accordance with the data on intraglomerular pressure and  $R_E : R_A$ , manidipine treatment resulted in lower UACR

compared with baseline levels (6.0 (4.0–10.0) vs. 4.0 (3.3–9.0) mg g<sup>-1</sup> creatinine,  $P = 0.053$ ), which, however, failed to reach our prespecified statistical significance level. In contrast, amlodipine treatment resulted in a significant increase of UACR compared with baseline levels (5.0 (3.0–10.0) vs. 7.0 (4.0–14.0) mg g<sup>-1</sup> creatinine,  $P = 0.003$ ). There was a significant difference in the change of UACR between the treatment groups, in favour of manidipine ( $P < 0.001$ ).

Since blood pressure changes due to antihypertensive treatment may also lead to alterations in renal perfusion pressure and thereby albumin excretion, we performed further analyses of our data. To assess the influence of MAP changes due to antihypertensive treatment as a potential confounding factor, multiple linear regression analyses were performed. MAP change in response to antihypertensive treatment was not related to the change in log-transformed UACR ( $\beta = 0.164$ ,  $P = 0.167$ ), whereas assigned antihypertensive medication was related to change in log-transformed UACR ( $\beta = 0.541$ ,  $P < 0.001$ ).

### Adverse events

Incidence of peripheral oedema, the most common side effect of antihypertensive therapy with dihydropyridine-type CCBs, was significantly lower with manidipine compared with amlodipine treatment (2 (3.6%) vs. 10 (17.5%),  $P = 0.03$ ). Other typical side effects of antihypertensive therapy with CCBs (e.g. palpitations or flushing) did not differ between manidipine and amlodipine.

## Discussion

The main result of the present study is that in contrast to antihypertensive treatment with manidipine, amlodipine increases  $P_{\text{glom}}$  significantly, resulting in a significant difference in the change of  $P_{\text{glom}}$  between these two CCBs in favour of manidipine. The intraglomerular pressure is mainly the result of the interplay between the efferent and the afferent arteriole, and in line with our data on  $P_{\text{glom}}$  we found a significant increase in the  $R_E : R_A$  ratio, resulting from a more prominent vasodilation of the afferent arteriole with amlodipine compared with manidipine. Therefore, we could translate published data from experimental models that action of CCBs regarding dilatatory capacity on efferent and afferent arterioles varies depending on the used agents [19] for the first time to humans.

The detrimental consequences of an increased glomerular pressure on the progression of renal disease are well known [20]. Conversely, a reduction in  $P_{\text{glom}}$  prevents glomerular hyperfiltration and reduces albuminuria, since the driving force of albuminuria (i.e. the filtration pressure) is reduced. Indeed, we could demonstrate that manidipine treatment resulted in a lower UACR whereas amlodipine significantly increased UACR, with a significant difference in the change of UACR between the two CCB.

This is in line with previous findings in hypertensive patients with metabolic syndrome randomly assigned to manidipine (20 mg) or amlodipine (10 mg). Despite a similar blood pressure reduction, albuminuria was only significantly reduced with manidipine, but not with amlodipine, with a significant difference between treatment arms [21]. Often monotherapy is not sufficient to achieve recommended BP targets, and patients require combination therapy. Recently, a study focusing on combination therapy with CCBs and renin-angiotensin system (RAS)-modulating agents reported disparate effects between different CCBs on albuminuria despite similar effects on BP. In hypertensive diabetic patients with microalbuminuria, despite a maximum dose of a RAS blocker, urinary albumin excretion (UAE) was significantly more reduced with manidipine vs. amlodipine [22].

Since there is a continuous relation between albuminuria and cardiovascular (CV) and renal risk, even at levels of albumin excretion within the normal range [23–26], and its reduction is associated with an improved prognosis [27], it can be postulated that the effect of antihypertensive medication on albuminuria is of importance even in hypertensive patients without concomitant renal disease.

There was a significantly lower incidence of peripheral oedema with manidipine compared with amlodipine treatment (2 vs. 10,  $P = 0.03$ ). This finding is in line with previous studies [22, 28]. Due to its lipophilicity and vaso-selective action, it is postulated that manidipine has a lower degree of baroreflex-induced activation of the sympathetic system, and hence causes a lesser increase of the capillary pressure gradient [29]. This finding has an important clinical impact, since antihypertensive management remains suboptimal in western civilization [30]. One of the reasons is side-effects of antihypertensive medication, a crucial determinant of adherence to prescribed therapy. Therefore, reduction of side effects may translate into better therapy adherence and improved long term BP control, resulting in better CV and renal outcomes.

There are several limitations of our study. In contrast to experimental models, the human renal microcirculation (resistances of the afferent and efferent arteriole and glomerular hydrostatic pressure) cannot be examined directly. Therefore the physiologist Gomez had already in the 1950s developed a model to calculate glomerular haemodynamic parameters from RPF, GFR and total protein concentration (with some assumptions such as the presence of filtration disequilibrium along the glomerular capillaries) [16]. Although based on several assumptions, the Gomez calculations have been repeatedly applied and appear to be reliable in humans without renal disease and normal renal function [7, 18]. In particular, comparisons of intrarenal haemodynamics within one individual, and within short periods of time are considered to be reliable in humans.

Secondly, despite clinical studies [21, 28] showing a comparable BP lowering effects of manidipine 20 mg and amlodipine 10 mg, in our study amlodipine treatment resulted in a significantly greater decrease of BP compared with manidipine treatment. Therefore, multiple regression analysis was performed to determine the impact of BP change on renal haemodynamic parameters. MAP change in response to antihypertensive treatment was not related, whereas assigned antihypertensive medication was related to the change in UACR. This is also strengthened by findings of previous published studies. In the Ramipril Efficacy in Nephropathy 2 (REIN-2) trial, the CCB felodipine was added to ramipril. In contrast to the further blood pressure reduction with the add-on therapy of felodipine, throughout the study urinary protein excretion was similar in both arms [31]. In hypertensive patients with albuminuria, despite maximum dose of RAS blockers, manidipine decreased UAE significantly. There was no correlation between SBP reduction and UAE [32]. Another study compared the effect of manidipine vs. hydrochlorothiazide (HCTZ) in addition to candesartan in hypertensive patients with type 2 diabetes and microalbuminuria. There was no significant difference in achieved BP levels between the treatment arms, whereas UAE rate was further reduced only with manidipine in contrast with no significant change with HCTZ, indicating that the antiproteinuric effect of manidipine is independent of BP reduction [33].

Nevertheless, we cannot rule out that effects seen in this study may have been influenced by the sizable difference in blood pressure reduction between the treatment groups.

We have to consider that multiple comparisons (both within and between the groups) increase the possibility of findings by chance, but may also provide additional exploratory information and in our statistical analysis the primary objective was clearly prespecified.

In summary, we could demonstrate beneficial effects of manidipine compared with amlodipine on the renal microcirculation, specifically a lower intraglomerular pressure and reduced urinary albumin excretion, which may translate into better renal protection.

## Competing Interests

M. Alberici is an employee of Chiesi Farmaceutici S.p.A., Parma, Italy. RES has received grants, lectures and consultancy fees from Chiesi Farmaceutici S.p.A., Parma, Italy.

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