Personal Opinion

Preservation of renal function: the spectrum of effects by calcium-channel blockers

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Abstract The vast majority of animal data derived from models of either remnant kidney or diabetes demonstrate that dihydropyridine (nifedipine-like) calcium-channel blockers (DHPCCBs) effectively reduce arterial pressure but do not significantly affect proteinuria nor prevent development of glomerular scarring. Conversely, the non-DHPCCBs such as diltiazem and verapamil blunt both the rise in proteinuria as well as mesangial matrix expansion and subsequent glomerular scarring in diabetes. Additionally, the non-DHPCCBs markedly attenuate development of glomerular scarring in the remnant kidney model. The primary reasons for these differences between subclasses of CCBs relates to a lack of the following attributes by DHPCCBs: (1) they fail to reduce glomerular membrane permeability which is increased in these models; (2) they fail to affect the synthesis of certain key matrix proteins that perpetuate development of glomerular scarring (this effect may be due to the differential expression of calcium channels within the glomerular mesangium); and (3) the DHPCCBs totally abolish renal autoregulation in these models, an effect not observed with non-DHPCCBs. Taken together with long-term (>3 year) clinical studies, primarily in diabetic nephropathy, it is clear that the non-DHPCCBs seem to offer protection to the kidney not available with DHPCCBs alone, unless systolic arterial pressure is reduced to levels of \( \leq 110 \text{ mmHg} \).

Key words: calcium-channel blockers; glomerular filtration rate; albuminuria; proteinuria; hypertension; glomerulosclerosis

Introduction

Over the past decade there have been significant differences noted between the subclasses of calcium-channel blockers (CCBs) with regard to their effects on surrogate end-points of renal disease progression [1–23]. These end-points include the rate of decline in glomerular filtration rate (GFR) as well as changes in albuminuria and proteinuria. Moreover, in all animal models of diabetic nephropathy as well as the remnant kidney model, DHPCCBs have universally failed to prevent glomerular scarring as well as reduce increases in proteinuria [16,17,20–23]. These changes relate to a failure of DHPCCBs to effect key mechanisms that are altered during the natural history of these disease processes.

The primary factors that may account for differences in renal disease progression as measured by surrogate end-points such as changes in serum creatinine and proteinuria are summarized in Table 1. These include: a variable distribution of calcium channels, divergent effects on glomerular membrane permeability, renal autoregulation as well as mesangial matrix protein expression. This paper will explore these mechanisms in the context of both the natural history of diabetic nephropathy as well as how blockade of different calcium channels may impact on the above mentioned variables. Additionally, this paper will summarize all relevant, long-term, i.e. greater than three years in duration, clinical trials that have evaluated progression of renal disease with the various CCBs. It will place these studies into proper clinical context with regard to their effects on preservation of renal function as well as overall effects on the cardiovascular system.

Differences in calcium-channel distribution

One of the key factors that may explain the divergent renal outcomes observed with CCBs may relate to the variable cellular distribution of a given calcium channel. Clearly there is more than a single calcium channel that these drugs inhibit.

CCBs as a class have quite divergent morphological and to a lesser extent haemodynamic effects on the kidney (Table 1). This is largely due to the fact that they do not inhibit the same calcium channel to achieve their effect. Preliminary classification schemes divide
calcium channels into low-voltage-activated (T-type) and high-voltage-activated types: L-type, dihydropyridine-sensitive, and N-type, \( \omega \)-conotoxin GVIA-sensitive. Experimental use of various toxins has led to the further subclassification of high-voltage-activated channels to P-type, Q-type, and R-type [24]. It is the L-type calcium channel that is abundant in the cardiovascular system and that, within the last few years, has been isolated and cloned. Its subunits have been identified and its amino-acid composition determined [25]. The L-type calcium channels comprise five subunits termed \( z_1, z_2, \beta, \gamma \), and \( \delta \). The \( z_4 \) subunit appears to be responsible for channel opening and voltage dependency and it contains receptors for calcium channel antagonists. These geographically distinct receptors correspond to each of the three different chemical classes of antagonists, exemplified by diltiazem, nifedipine and verapamil. Diltiazem appears to have an inhibitory effect on mitochondrial sodium—calcium exchange that is unique among calcium-channel antagonists [26]. Additionally, calcium channels have an unequal distribution as well as differential binding throughout the neural and cardiovascular systems [27–29]. Hence, a particular subclass of CCBs such as the DHPCCBs will have their own channel to inhibit and subsequently yield different biological effects when compared to other channel blockers.

**Differences in glomerular permeability**

Three recent meta-analyses review studies on renal disease progression in both animal models of diabetes as well as clinical studies of diabetic and non-diabetic renal disease [8,9,23]. These meta-analyses found that non-DHPCCBs and ACE inhibitors had the greatest efficacy for reducing proteinuria. Moreover, it was noted that a strong correlation exists between reductions in proteinuria and an attenuated development of glomerulosclerosis [8,9,23]. All animal studies reviewed for these meta-analyses demonstrate that a reduction in arterial pressure without a blunted rise in proteinuria result in a failure to blunt the progression to glomerular scarring [9,23]. Moreover, all biopsy studies as well as studies that evaluate changes in GFR have demonstrated that antihypertensive agents that fail to reduce proteinuria also fail to significantly alter the natural history of renal disease progression [9,12,16,23,30,31].

One of the primary reasons that albuminuria may correlate with glomerular injury in animal models of diabetes relates to its degree of glycation. The level of blood sugar will determine the amount of glycated albumin in the circulation [32,33]. Glycated albumin has been shown to increase mesangial matrix protein expression and production leading to the morphological changes associated with diabetic nephropathy [34–36]. Thus, increased membrane permeability at the glomerular will increase the likelihood that glycated albumin will be exposed to mesangial cells and subsequently stimulate cellular activity.

A recent randomized, parallel group study with a 2-year follow-up in patients with NIDDM associated nephropathy, supports the concept that non-DHPCCBs reduce membrane permeability, especially to large molecules while DHPCCBs do not manifest calcium exchange that is unique among calcium-channel antagonists [26]. Additionally, calcium channels have an unequal distribution as well as differential binding throughout the neural and cardiovascular systems [27–29].

### Table 1. Factors that help explain the differential effects of calcium channel blockers on renal morphology and function

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Intrarenal factors</th>
<th>CCB effect</th>
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<tr>
<td></td>
<td></td>
<td>DHPCCBs</td>
</tr>
<tr>
<td><strong>A. Albuminuria/proteinuria</strong></td>
<td>( P_{GC} )</td>
<td>( - ) [12]</td>
</tr>
<tr>
<td><strong>B. Mesangial volume expansion</strong></td>
<td>( \dagger ) Glomerular membrane permeability</td>
<td>( - ) [12,38]</td>
</tr>
<tr>
<td>(Diabetes)</td>
<td>( \dagger ) Matrix proteins synthesis (laminin, fibronectin, collagen IV, etc.)</td>
<td>( - ) [20]</td>
</tr>
<tr>
<td><strong>C. Glomerular scarring</strong></td>
<td>( \dagger ) Renal autoregulation</td>
<td>Abolished [17,19]</td>
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<td></td>
<td>(see a + b above)</td>
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**Deereased only if blood pressure markedly reduced.\( P_{GC} \), intraglomerular pressure. *Responses to ACE inhibitors are similar in remnant kidney animal model. Note, however, that renal autoregulatory mechanisms are not affected by ACE inhibitors. **High sodium intake, \( \geq 200 \text{ mEq/day} \) will blunt reductions in glomerular permeability.**
on the glomerular membrane no effect on permeability would be observed by these DHPCCBs. Conversely, if calcium channels associated with diltiazem and verapamil activity were more prevalent this would lead to decreases in permeability associated with non-DHPCCBS. Thus, since increased leakiness to glycated albumin clearly increases glomerular injury, independent of arterial pressure load, non-DHPCCBs may provide unique and independent protection to the kidney, apart from arterial pressure reduction.

Renal autoregulation

Another possible explanation for the differences between dihydropyridine and non-DHPCCBs is their action on renal autoregulation. Renal autoregulation is the inherent ability of the kidney to maintain GFR over a wide range of arterial pressures, thus blunting the pressure load transmitted from the systemic circulation to the glomerular capillary. DHPCCBs abolish this native ability of the kidney to protect itself [17,19,21], thus allowing a linear transmission of pressure into the glomerular capillaries. Therefore, to achieve any protection against glomerular injury with such agents, systolic pressure needs to be reduced to levels of <110 mmHg (Figure 1).

Several studies also demonstrate that chloride ion inhibition reduces renal autoregulatory abilities of the kidney as well as effects on vascular action of angiotensin II [41,42]. Non-DHPCCBs and other antihypertensive agents have either minimal or no significant effects on renal autoregulation [19]. Table 2 summarizes the effects of the different antihypertensive drug classes on renal autoregulation.

Table 2. Summary of antihypertensive agents that reduce autoregulatory ability of the kidney

<table>
<thead>
<tr>
<th>Completely</th>
<th>Partially</th>
<th>Negligibly</th>
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<tbody>
<tr>
<td>Dihydropyridine CCBs</td>
<td>Non-dihydropyridine CCBs</td>
<td>Beta blockers</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>Loop diuretics</td>
<td>Alpha blockers</td>
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Three separate studies using 24-h blood pressure monitoring in a rat remnant kidney model demonstrate that blood pressure reduction with ACE inhibitors does not significantly affect the renal autoregulatory process [17,19,21]. Blood pressure reduction with non-DHPCCBs, while partially interfering with renal autoregulation, still allows some preservation of this inherent protective biological process. Conversely, treatment with DHPCCBs totally obliterates autoregulation and allows for linear association of pressure to be transmit-

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**Fig. 1.** The effects of a given calcium-channel blocker on glomerular scarring over a range of systolic blood pressures. Each line represents the slope of a given group's systolic pressure plotted against the associated amount of scarring observed. Adapted from reference 21. GS, glomerulosclerosis.
ted through the glomerular capillary bed [17,19]. Hence, as was pointed out by Griffin et al. [17] if one is to assume protection of renal morphology and function with a DHPPCCB blood pressure reduction would have to be reduced to a systolic level of <110 mmHg to equal the same level of renal protection associated with a systolic pressure of 140 mmHg observed with an ACE inhibitor. A similar association may be demonstrated when a comparison between dihydropyridine and non-DHPPCCBs is examined (Figure 1). Thus, in addition to a lack of effect on glomerular permeability, dihydropyridine may also abolish the kidneys normal ability to protect itself against the pressure head by obliterating autoregulatory processes.

**Clinical studies**

When one considers the effects of any blood-pressure-lowering agent on preservation of renal function they must consider the following variables: (1) the natural history of the disease being studied, (2) the stage of disease which is present at the time of recruitment into the study, (3) the level of blood pressure reduction as well as the duration of control in each patient evaluated in a given study, (4) and lastly, the sodium intake of the patient especially if the variable being studied is albuminuria or proteinuria. An extensive discussion as to why these factors are critically important in a given study design and their impact on data interpretation is beyond the scope of this paper. The reader, however, is referred to several reviews of these topics [43–47].

In the natural history of diabetic nephropathy, especially that from insulin dependent diabetes mellitus (IDDM), it takes between 3 and 8 years for microalbuminuria to develop [44,45]. Hypertension generally develops in about 40% of IDDM patients and 25% of non-insulin-dependent diabetic (NIDDM) patients [44,45]. All diabetic patients with hypertension will ultimately develop end-stage renal disease requiring dialysis [44,45,48].

The average rate of decline in GFR in such patients ranges from 1.5 to 2.5 ml/min/year in patients treated with ACE inhibitors or non-DHPPCCBs to 10–12 ml/min/year in those whose arterial pressure is uncontrolled [5,6,49,50]. This rate of decline in renal function primarily depends on the level to which blood pressure is reduced as well as the medications used to achieve such a level. Thus it is clear for substantial differences in declines of renal function to be appreciated between different treatment groups the duration of follow-up must be a minimum of 3 years. Unfortunately surrogate end-points of renal disease progression such as changes in proteinuria have been examined in thousands of patients for periods of up to 2 years. Thus, for the previously mentioned reasons, we will only discuss studies that have ‘long-term’ follow-up, i.e. greater than or equal to a 3-year duration.

There are three completed [5,6,51] and three ongoing [14,52,53] long-term studies that address the effects of CCBs on progression of renal disease. These studies are primarily in patients with NIDDM associated nephropathy with one in patients with IDDM associated nephropathy. Moreover, there are no long-term studies, to date, that examine the effects of CCBs in patients with IDDM associated nephropathy.

The completed studies, however, demonstrate a clear benefit when non-dihydropyridine CCBs are used over conventional therapy, i.e. a block on both progression of nephropathy and reduction in proteinuria [5,6]. Specifically, one study of 52 patients with NIDDM-associated nephropathy and hypertension, randomized to either an ACE inhibitor (lisinopril), non-dihydropyridine CCBs (verapamil or diltiazem SR), or a beta blocker (atenolol) and followed for 6 years, demonstrated that the greatest mean rate of decline in creatinine clearance was in the atenolol group (−3.4 ml/min/year/1.73 m²) with no differences between the lisinopril (−1.1 ml/min/year/1.73 m²) and non-dihydropyridine CCB (−1.5 ml/min/year/1.73 m²) groups [5]. Moreover, while the degree of blood-pressure reduction was similar in all groups, proteinuria was reduced to a similar extent only in the lisinopril and the non-dihydropyridine CCB groups. These observations were further exemplified in a 5-year randomized study among African-American patients with NIDDM nephropathy, In this study, verapamil was associated with a 62% slower progression of renal disease when compared to a beta blocker, given similar reductions in arterial pressure [6]. Conversely, studies on NIDDM-associated renal disease progression with dihydropyridine agents have, with one exception, thus far failed to show any significant reduction in albuminuria or slowed progression in nephropathy [54]. The equivalent results on albuminuria reduction and GFR decline between amlodipine and cilazapril were not surprising, however, given the degree of renal disease present in these patients, that is, microalbuminuria with a GFR between 75 and 90 ml/min. Moreover sodium intake, which has been shown to be a critical determinant of albuminuria reduction associated with ACE inhibitor as well as a non-DHPPCCB use [39,55,56], was neither controlled for nor measured. Additionally, Velussi et al. demonstrate a marked reduction in GFR with amlodipine relatively early in the course of the disease process. This observation is contrary to all other published studies that demonstrate 2–10% increase in insulin clearance with DHPPCCBs [12,16].

Sodium intake was also not measured in a separate study by Zucchelli et al. that documents similar effects between a DHPPCCB and an ACE inhibitor on renal survival at 2 years of follow-up [51]. However, this study further documents a greater than fivefold increase in the number of people starting dialysis in third-year follow-up who were randomized to nefedipine. Thus to date there is no meaningful data with DHPPCCBs by which anyone can assess their effect on renal disease progression. Conversely, two previously discussed long-term studies in patients with NIDDM-
associated nephropathy demonstrate similar benefits between an ACE inhibitor and non-DHPCCB on renal disease progression.

CCBs and cardiovascular disease

It is curious, with all the available data from clinical trials on cardiovascular disease, that the DHPCCBs have failed to show any reduction in mortality from ischaemic heart disease [57,58]. Notable is the PRAISE trial, which failed to show a reduction in cardiovascular events among patients with ischaemic heart disease. Moreover, in this trial of over a thousand people with severe heart failure, renal function significantly worsened in 7.7% of patients randomized to the DHPCCB, amiodipine, as compared to the 3.6% in the placebo group, \( P = 0.002 \) [58]. If the effect of amiodipine on tubular secretion of creatinine, however, is similar to other dihydropyridine CCBs, this worsening in renal function may be simply explained by a decreased creatinine secretion induced by the drug and not represent a true worsening of renal function [59]. Interestingly, this lack of benefit on ischaemic heart disease events with DHPCCBs is in contrast to two distinct post myocardial infarction trials that demonstrate non-DHPCCBs significantly reduce mortality and cardiovascular event rates [60,61].

To further draw a distinction between dihydropyridine and non-dihydropyridine CCBs, a recent double-blind placebo-controlled randomized trial in 100 post-myocardial infarction patients with heart failure, demonstrated a significant reduction in cardiovascular event rates, including myocardial infarction, strokes, and death when verapamil was added to an ACE inhibitor as compared to ACE inhibitor alone [62]. This further supports the notion of differential effects by CCBs.

Additional data that attest to the cardiovascular and renal safety of the non-DHPCCBs are derived from the MDRD study. Twenty-six per cent of the 840 patients in this study were receiving CCBs at baseline as compared to 37% who were taking ACE inhibitors [46]. It is also clear that the distribution of those who received the ACE inhibitor or diltiazem SR was similar between blood pressure groups [46]. Thus, while this trial was not statistically powered or designed to detect differences between these agents with regard to renal disease progression, given the numbers and duration of follow-up, there were clearly no safety issues with this non-dihydropyridine CCB when compared to other antihypertensive agents used [Tom Greene PhD, statistician, MDRD study, personal communication]. Thus, as we originally stated, from a renal perspective, non-DHPCCBs are not associated with adverse renal effects and may be beneficial. Taken together, these data suggests that the non-DHPCCBs are both beneficial to the heart as well as the kidneys. Moreover, since the major cause of death in diabetic patients is due to cardiovascular disease, one needs to select carefully from among the CCB subclasses to optimize a given patients cardiorenal profile.

Summary

To date there is insufficient evidence to conclude that one particular CCB should be viewed as having the best overall profile on either the kidney or heart. However, data is growing to support the concept of two specific subclasses of CCBs with regard to their effects on both cardiovascular and renal end-points. Specifically, DHPCCBs generally do not reduce proteinuria nor markedly slow progression of renal disease. Moreover, their effects on diabetic renal disease progression appear to be correlated solely with their ability to lower blood pressure. Conversely non-DHPCCBs slow progression of advanced diabetic renal disease to a degree similar to that observed with an ACE inhibitor. Moreover, their renal benefits do not appear to be related solely to blood-pressure reduction as seen with DHPCCBs.

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