Use of calcium channel blockers to slow the progression of diabetic nephropathy

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Objectives
- Pharmacist objectives:
  - Describe the mechanisms in which calcium channel blockers are proposed to prevent the progression of diabetic nephropathy.
  - Evaluate the utility of calcium channel blockers for prevention/treatment of diabetic nephropathy alone or as an adjunct to renin-angiotensin-aldosterone system blockade based on current evidence.
- Pharmacy technician objectives:
  - Describe the mechanisms in which calcium channel blockers are proposed to prevent the progression of diabetic nephropathy.
  - Discuss the place in therapy of calcium channel blockers for the prevention/treatment of diabetic nephropathy.

Abbreviations
- ACE-inhibitor = angiotensin converting enzyme inhibitor
- ARB = angiotensin receptor blocker
- SCr = serum creatinine
- NE = norepinephrine
- CCB = calcium channel blocker
- Non-DHP = non-dihydropyridine
- DHP = dihydropyridine
- T2DM = type 2 diabetes mellitus
- UACR = urine albumin:creatinine ratio
Diabetes and Nephropathy

- Multiple mechanisms that lead to tissue damage at play
- Standard of care:
  - Control blood glucose
  - Control blood pressure
  - Renin-angiotensin-aldosterone system blockade
    - ACE-inhibitors or ARBs
    - For those with albuminuria

Clinical Case Scenarios

- You have a patient in your clinic with type 2 diabetes mellitus who has confirmed albuminuria. This patient is unable to tolerate ACE-inhibitors or ARBs due to hyperkalemia and increased Scr (doubled) with prior use.

- You have a patient in your clinic with type 2 diabetes mellitus, already on an ACE-inhibitor, with noted progression of diabetic nephropathy.

Calcium channels and the Kidney

- Types of calcium channels that impact kidney function
  - L-type
    - Present in the afferent arteriole
  - T-type
    - Present in the afferent and efferent arteriole
  - N-type
    - Present on sympathetic nerve endings
    - Activation → NE release → renin secretion and decreased renal blood flow
    - Affects both afferent and efferent arterioles

Adapted from www.pulmcrit.org
Can CCB’s provide additional nephroprotection independent of blood pressure lowering?

Not all calcium channel blockers are created equal

- Non-dihydropyridine calcium channel blockers
  - Verapamil, Diltiazem
  - More cardioselective

- Dihydropyridine calcium channel blockers
  - “Traditional” DHP CCB
    - Block L-type calcium channels in vascular smooth muscle → BP lowering
    - Examples: amlodipine, nifedipine, felodipine
  - “Novel” DHP CCB
    - Block N-type or T-type calcium channels in addition to L-type
    - Examples: cilnidipine (L-/N-types), benidipine (L-/T-types), efonidipine (L-/T-types)
    - Not yet available in the U.S.


Non-DHP CCB and Diabetic Nephropathy

- Appear to reduce albuminuria more so than “traditional” DHP CCB
- Thought to reduce glomerular membrane permeability

Conflicting evidence:

- Comparing Non-DHP CCB to DHP CCB
- Non-DHP CCB reduce albuminuria > DHP CCB
- Independent of blood pressure lowering
- Non-DHP added to ACE-Inhibitor
  - No added benefit of non-DHP when added to ACE-inhibitor for prevention of microalbuminuria (BENEDICT-A, BENEDICT-B)
  - Non-DHP added to ACE-Inhibitor (Toto et al 2008)

DHP-CCB and Diabetic Nephropathy

- "Traditional" DHP-CCB
  - Dilate afferent arterioles only
  - Studied: Nifedipine, Amlodipine, Nicardipine, Felodipine, Isradipine, Nisoldipine
  - Overall, no benefit seen for reducing proteinuria with or without ACE-inhibition

- "Novel" DHP-CCB
  - Dilate afferent and efferent arterioles
  - Appear more effective in reducing albuminuria compared to L-type only calcium channel blockers


Evidence with "novel" DHP-CCB: Cilnidipine vs L-type CCB

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Duration</th>
<th>Intervention</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>CLEARED</td>
<td>T2DM UACR &lt;300mg/g</td>
<td>6 months each</td>
<td>Cilnidipine vs L-type CCB</td>
<td>Decreased UACR with cilnidipine vs L-type CCB</td>
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<tr>
<td>Masuda T, et al. 2011</td>
<td>HTN T2DM group</td>
<td>8-9 months each</td>
<td>Cilnidipine vs Amlodipine</td>
<td>UACR lower with cilnidipine use</td>
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<tr>
<td>SAKURA</td>
<td>T2DM UACR 30-300mg/d RAS inhibition</td>
<td>12 months</td>
<td>Cilnidipine vs Amlodipine</td>
<td>UACR decreased more with cilnidipine use vs Amlodipine initially (3 to 6 months) No significant difference seen after 12 months</td>
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Evidence with "novel" DHP-CCB: Cilnidipine + RAS inhibitor vs RAS inhibitor alone

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<tr>
<td>Katayama K, et al. 2006</td>
<td>T2DM UACR &lt;300mg/g</td>
<td>12 months</td>
<td>Valbunat vs valbunat + cilnidipine</td>
<td>Greater UACR reduction in combination group vs valbunat alone</td>
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Evidence with “novel” DHP-CCB: T-type CCB

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<th>Outcome</th>
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<td>Sasaki H, et al. 2009.</td>
<td>T2DM HTN Nephropathy (UACR &gt;300mg/g) On candesartan</td>
<td>12 months Efonidipine vs amlodipine</td>
<td>Decrease in eGFR and increase in UACR with amlodipine No change in renal function with efondipine</td>
<td></td>
</tr>
<tr>
<td>Abe M, et al. 2010.</td>
<td>CKD stages 3-5 UACR ≥300mg/g HTN ~50% diabetic nephropathy On max dose ARB</td>
<td>12 months Benidipine vs Cilnidipine</td>
<td>Decrease in UACR in both groups (no significant difference between groups)</td>
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Clinical Case Scenarios – What are your recommendations?

- You have a patient in your clinic with type 2 diabetes mellitus who has confirmed albuminuria. This patient is unable to tolerate ACE-inhibitors or ARBs due to hyperkalemia and increased SCR (doubled) with prior use.

- You have a patient in your clinic with type 2 diabetes mellitus, already on an ACE-inhibitor, with noted progression of diabetic nephropathy.

Conclusions

- Limited evidence to support use of specific CCBs available in the US for prevention of progression of diabetic nephropathy
- Evidence that blocking N-type and T-type calcium channels provide benefit to prevent or delay progression of diabetic nephropathy
- Novel CCB will hopefully become available in the US that can be utilized for prevention of progression diabetic nephropathy in addition to RAAS inhibition and in those unable to tolerate ACE-inhibitors or ARBs
Assessment Question #1

Blockade of the which calcium channels will lead to dilation of both afferent and efferent glomerular arterioles?

- A. Lyte and C-type
- B. C-type and T-type
- C. N-type and T-type
- D. N-type and C-type

Assessment Question #2

Which of the following calcium channel blockers has shown to decrease urine albumin: creatinine ratio in patients with diabetic nephropathy or at risk for developing diabetic nephropathy?

- A. Amlodipine
- B. Cilnidipine
- C. Nifedipine
- D. Felodipine

References

References