

Specific effects of calcium channel blockers in diabetic nephropathy

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GUIDELINES

- a. **Non-dihydropyridine calcium channel blockers (CCBs) offer a small protective effect on proteinuria in diabetic nephropathy, beyond their antihypertensive action. (Level II Evidence - Type 2 diabetes, small volume). There is no evidence that CCBs influence decline of glomerular filtration rate (GFR) in diabetic nephropathy, beyond their antihypertensive effect. One RCT in hypertensive normoalbuminuric Type 2 diabetic patients shows no benefit of verapamil over placebo in progression to microalbuminuria.**

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV sources)

- **There is insufficient evidence to recommend routine use of dihydropyridine calcium channel blockers (CCBs) in diabetic nephropathy, unless required for antihypertensive action.**
- **There is a small additional benefit on proteinuria from addition of non-dihydropyridine CCBs to angiotensin-converting enzyme inhibitors (ACEIs). (Level III evidence – Type 2 diabetes, small volume)**
- **CCBs are recommended as second-line treatment in diabetic nephropathy, and are frequently required for optimal blood pressure (BP) control. There is a small benefit of non-dihydropyridines over dihydropyridines for protection against progression of proteinuria.**

Background

Calcium channel blocking drugs differ in their effects on glomerular haemodynamics and urinary albumin excretion, both in normal and in disease states. Non-dihydropyridine CCBs reduce albumin excretion. This section questions whether or not CCBs have any specific renoprotective effect, beyond BP lowering, in diabetic renal disease.

Search strategy

Databases searched: The Cochrane Renal Group Specialised Register was searched for randomised controlled trials relating to the prevention of progression of

kidney disease in people with diabetes mellitus Type 1 and Type 2. Specific interventions included antihypertensive therapies, ACE inhibitors, A II receptor antagonists, calcium channel blockers, dietary protein restriction and glucose control, and interventions to control hypercholesterolemia and hyperlipidemia.

Date of search: 16 December 2003.

What is the evidence?

Studies are limited in number, and patient numbers are small. The Benedict trial is the only RCT which provides head-to-head study of CCBs vs ACEI with adequate control of BP (Ruggementi et al 2004). It is adequately controlled and we lack long-term studies with functional endpoints.

Ruggementi et al (2004) studied hypertensive normoalbuminuric Type 2 diabetic patients and showed no benefit of Verapamil over placebo in progression to microalbuminuria, while trandolapril reduced risk of progression to microalbuminuria by 51% compared with verapamil.

Non-dihydropyridine calcium channel blockers offer a small protective effect on proteinuria in diabetic nephropathy, beyond their antihypertensive action. (Level II Evidence - Type 2 diabetes, small volume).

There is no evidence that CCBs influence decline of GFR in diabetic nephropathy, beyond their antihypertensive effect.

Non-dihydropyridine calcium channel blockers in diabetic nephropathy

Type 2 diabetes

Bakris et al (1996): In this study, 52 Type 2 diabetics with hypertension were randomised to lisinopril, verapamil/diltiazem, or beta blockers and followed for a mean of 5.3 years. Endpoint was change in slope of creatinine clearance. Mean arterial pressure was equivalent in all three groups. Functional decline in the atenolol group was greater than the other two groups, and albuminuria decreased with verapamil /diltiazem to an extent similar to lisinopril.

Bakris et al (1997) studied 34 African Americans with renal impairment due to Type 2 diabetes and overt nephropathy randomised to verapamil or atenolol, with additional diuretic in both groups to achieve BP < 140/90 mmHg. After mean follow-up of 54 months, creatinine clearance was better maintained in verapamil group, and proteinuria was less.

Velussi et al (1996) followed 44 hypertensive Type 2 diabetics with normo- or microalbuminuria randomised to either amlodipine or cilozapril for 3 years, and found similar efficacy in the two groups in delaying GFR decline and reducing AER at BP < 140/85 mmHg.

Mosconi et al (1996) performed a 3-phase, parallel group study in 16 hypertensive microalbuminuric patients with Type 2 diabetes and biopsy-proven nephropathy and

slight GFR depression. Both nitrendipine and enalapril treatment groups controlled BP, lowered albuminuria, and preserved GFR over 27 months.

The Benedict trial (Ruggenenti et al 2004) studied 1204 hypertensive (defined as BP > 130/80 mmHg or on antihypertensive therapy) Type 2 diabetics without albuminuria, to assess whether ACEIs and non-dihydropyridine calcium-channel blockers, alone or in combination, prevent microalbuminuria in subjects with hypertension, Type 2 diabetes mellitus, and normal urinary albumin excretion. Patients were randomised to trandolapril 2 mg (T), trandolapril 2 mg plus verapamil 180 SR (T+V), verapamil alone 240 SR (V) or placebo (P) for 3 years. The primary endpoint of development of persistent microalbuminuria was reached in 12% of V, and 10% of placebo patients (NS), and in 6% of each of the T alone and T+V groups ($p = 0.01$, T+V vs P).

Target BP was 120/80 mmHg, achieved if required via prescribed stepwise addition of drugs without RAS blockade action or non-dihydropyridine CCBs. Actual BP was slightly but significantly lower in the T+V group, potentially confounding the outcome. SAEs and numbers on statin therapy were comparable in all groups.

Dihydropyridine calcium channel blockers

There is a significant difference in antiproteinuric effect between dihydropyridines and non-dihydropyridines, despite both being effective antihypertensive agents. This probably relates to differential effect on glomerular permeability (Smith et al 1998). This group randomised 21 hypertensive patients with Type 2 diabetes and nephropathy to either diltiazem CD or nifedipine and followed them 3-monthly for 21 months. Despite similar levels of blood pressure control, proteinuria was reduced only in the diltiazem group, with improvement in glomerular size selectivity. No significant differences in GFR were found.

Addition of non-dihydropyridine calcium channel blockers to ACEI

Evidence that the protective effect of ACEI and of non-dihydropyridine CCBs in Type 2 diabetic nephropathy are additive is limited to the studies of Bakris et al (1998) who reported an open-label, parallel group study of 37 Type 2 diabetics with overt nephropathy, randomised to trandolapril (T), verapamil (V) or combination (T+V). Doses of drug were titrated over 8 weeks to achieve a goal blood pressure of < 140/90 mmHg in all 3 groups. Baseline proteinuria was 1342 ± 284 mg/dl. Proteinuria reduction in the T+V group ($62 \pm 10\%$) was greater than either T alone ($33 \pm 8\%$) or V alone ($27 \pm 8\%$), despite lower doses of both T and V in the T+V group. The mean daily dose of the individual components of T+V (T 2.9 ± 0.8 mg, V 219 ± 21.1 mg) was significantly lower than the dose of either T alone (5.5 ± 1.1 mg/day ($P < 0.01$) or V alone (314.8 ± 46.3 mg, given in two divided doses, $P < 0.01$). GFR did not change over 1 year in any group.

Summary of the evidence

There is no evidence that calcium channel blockade retards renal function deterioration in diabetic nephropathy. Studies have been small and largely confined to Type 2 diabetes. One RCT has indicated superiority of trandolapril over verapamil in preventing progression to microalbuminuria in hypertensive normalalbuminuric Type 2 diabetic patients. This is good evidence that non-dihydropyridine CCBs reduce

proteinuria. However, the clinical benefit of CCBs seem on current data, to be largely confined to their antihypertensive action.

What do the other guidelines say?

Kidney Disease Outcomes Quality Initiative (2004): Nondihydropyridine CCBs consistently demonstrate reduction in proteinuria, alone and when added to ACE inhibitor. It is reasonable to use a combination of ACE inhibitor and/or ARB and non-dihydropyridine CCB in hypertensive patients.

UK Renal Association: No recommendation.

Canadian Society of Nephrology: No recommendation.

European Best Practice Guidelines: No recommendation.

International Guidelines:

Canadian Diabetes Association (2003): The use of non-dihydropyridine CCBs may be considered to reduce urinary albumin excretion in proteinuric hypertensive patients (Grade B, Level 2).

American Diabetes Association (2004): With regards to slowing the progression of nephropathy, the use of DCCBs as initial therapy is not more effective than placebo. Their use in nephropathy should be restricted to additional therapy to further lower blood pressure in patients already treated with ACE inhibitors or ARBs. (B)
In the setting of albuminuria or nephropathy, in patients unable to tolerate ACE inhibitors and/or ARBs, consider the use of non-DCCBs, beta-blockers, or diuretics for the management of blood pressure. (E)

Implementation and audit

No recommendation.

Suggestions for future research

No recommendation.

References

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Appendices

Table 1 Characteristics of included studies

• Study ID (author, year)	N	Study Design	Setting	Participants	Intervention (experimental group)	Intervention (control group)	Follow up (months)	Comments
<i>Bakris et al. 1997</i>	34	Randomised controlled clinical trial	Nephrology clinic	34 African- Americans with diabetic nephropathy	Verapamil	Atenolol	54 mo	
<i>Mosconi et al. 1996</i>	13	Randomised controlled clinical trial	Hospital	13 micro-albuminuric NIDDM patients with mild hypertension and diabetic glomerulopathy	Nitrendipine	Enalapril	27 mo	

Table 2 Quality of randomised trials

Study ID (author, year)	Method of allocation concealment	Blinding			Intention-to-treat analysis	Loss to follow up (%)
		(participants)	(investigators)	(outcome assessors)		
<i>Bakris et al. 1997</i>	Not specified	No	No	Unclear	Yes	14.7
<i>Mosconi et al. 1996</i>	Not specified	Yes	Yes	Unclear	No	18.8

Table 3 Results for dichotomous outcomes

Study ID (author, year)	Outcomes	Intervention group (number of patients with events/number of patients exposed)	Control group (number of patients with events/number of patients not exposed)	Relative risk (RR) [95% CI]	Risk difference (RD) [95% CI]
Bakris et al. 1997	Doubling of serum creatinine	5/18	3/16	1.48 (95%CI: 0.42, 5.24)	0.09 (95%CI: -0.19, 0.37)
Mosconi et al. 1996	From microalbuminuric normo-albuminuric	4/7	4/6	0.86 (95%CI: 0.36, 2.02)	-0.10 (95%CI: -0.62, 0.43)

Table 4 Results for continuous outcomes

Study ID (author, year)	Outcomes	Intervention group (mean [SD])	Control group (mean [SD])	Difference in means [95% CI]
Bakris et al. 1997	Mean change in protein excretion (g/dL)	-1.3 (0.7)	-0.278 (0.382)	-1.02 (95%CI: -1.39, -0.65)
	Rate of decline in creatinine clearance (mg/dL)	-1.7 (0.9)	-3.7 (1.4)	2.00 (95%CI: 1.20, 2.80)
Mosconi et al. 1996	Blood glucose (mg/dL)	99.2 (8.3)	99.7 (11.2)	-0.50 (95%CI: -11.37, 10.37)
	SBP (mmHg)	105.3 (11.7)	146.6 (12.4)	3.70 (95%CI: -9.47, 16.87)
	DBP (mmHg)	84.9 (3.6)	93.7 (7.8)	-8.80 (95%CI: -15.59, -2.01)
	GFR (mL/min/1.73m ²)	81.2 (7.8)	79.9 (17.7)	1.30 (95%CI: -14.00, 16.60)