The development of new-onset type 2 diabetes associated with choosing a calcium channel blocker compared to a diuretic or beta-blocker

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CRD summary
This review concluded that calcium-channel blockers for the treatment of hypertension appear to reduce the risk of developing new-onset type two diabetes mellitus compared with treatment with β-blockers and/or diuretics. However, given the differences between the studies and several potential limitations of the review methodology, the reliability of the authors’ conclusions is unclear.

Authors' objectives
To examine the effects of calcium-channel blockers (CCBs), compared with β-blockers and diuretics, on new-onset type two diabetes mellitus in patients with hypertension.

Searching
MEDLINE, EMBASE, CINAHL and the Cochrane Library were searched from 1966 to December 2006 for publications in English; the search terms were reported. In addition, abstracts and bibliographies of primary and review articles were handsearched.

Study selection
Randomised controlled trials (RCTs) comparing CCBs with β-blocker and/or diuretic treatment in hypertensive patients, and reporting incidences of new-onset type two diabetes mellitus, were eligible for inclusion. The included studies were of hypertensive patients with or without coronary artery disease or cardiovascular risk, the majority of whom were male. Mean ages ranged from 60.3 to 76 years. The interventions included enalapril, lisinopril, felodipine, isradipine, nifedipine with or without atenolol or enalapril, diltiazem, amlodipine with or without perindopril and/or doxazosin, and verapamil with or without hydrochlorothiazide or trandolapril. The controls received conventional drugs, including one or more of the following: atenolol, hydrochlorothiazide, trandolapril, bendroflumethiazide, doxazosin, metoprolol, pindolol, hydrochlorothiazide, amiloride, enalapril, diuretics, β-blockers, chlorthalidone and lisinopril. Where reported, drug doses ranged from 2.5 to 360 mg/day.

It appears that two reviewers screened studies for relevance, but it was unclear how any discrepancies were resolved.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
Dichotomous data on new-onset diabetes mellitus were extracted to calculate relative risk ratios, which were converted into odds ratios (ORs) with 95% confidence intervals (CIs).

The authors did not state how many reviewers extracted the data.

Methods of synthesis
The ORs were pooled using random-effects or fixed-effect models. Subgroup analyses were undertaken to examine the effects of CCB compared with a thiazide diuretic, and to compare different types of CCB (dihydropyridine versus non-dihydropyridine). Sensitivity analyses were also performed to assess the effect of the fixed-effect model on the results and the removal of potential study bias. Statistical heterogeneity was assessed using the $I^2$ test, while publication bias was assessed using funnel plot analysis and Egger's test.

Results of the review
Six RCTs (n=99,006) were included in the review. Sample sizes ranged from 6,321 to 33,357 and mean follow-up
durations ranged from 2.7 to 5.5 years.

CCB was found to reduce the risk of developing new-onset diabetes mellitus compared with β-blockers and/or diuretics (OR 0.81, 95% CI: 0.73, 0.90, p=0.0001). Subgroup and sensitivity analyses did not significantly alter the results.

There was significant statistical heterogeneity for overall effect ($I^2=57\%$) and the subgroup analysis comparing dihydropyridine with β-blocker and/or diuretic ($I^2=62.7\%$). Publication bias was not detected by Egger's test or funnel plots.

**Authors' conclusions**
CCBs for the treatment of hypertension appear to reduce the risk of developing new-onset type two diabetes mellitus compared with treatment with β-blockers and/or diuretics.

**CRD commentary**
The review question was clear and was supported by appropriate inclusion criteria. The literature search was adequate, using four electronic databases and other appropriate sources. Publication bias was not detected. However, publications were restricted to those in English, which means that language bias might have been introduced; together with the fact that no apparent attempt was made to identify unpublished papers, it is possible that potentially relevant papers were missed. Validity was not assessed, which means that the reliability of the subsequent data synthesis is unclear. Furthermore, since the study selection and data extraction processes were unclear, reviewer error or bias cannot be ruled out. Appropriate methods were used to assess and investigate statistical heterogeneity. Sample sizes were large. However, since there was significant statistical heterogeneity among studies, different treatments were used, and the authors mentioned differences in definitions of new-onset diabetes mellitus, it may not have been appropriate to pool the results. Given the above considerations and the potential for reporting bias, the reliability of the authors’ conclusions is unclear.

**Implications of the review for practice and research**
Practice: The authors did not state any implications for practice.

Research: The authors stated that further research is required to evaluate the protective effects of CCBs in developing new-onset diabetes mellitus, in order to determine whether the effects reflect a beneficial effect or a lack of a negative effect.

**Funding**
Not externally funded.

**Bibliographic details**
Kuti E L, Baker W L, White C M. The development of new-onset type 2 diabetes associated with choosing a calcium channel blocker compared to a diuretic or beta-blocker. Current Medical Research and Opinion 2007; 23(6): 1239-1244

PubMedID
17559720

DOI
10.1185/030079907X188044

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Adrenergic beta-Antagonists /adverse effects /therapeutic use; Angiotensin II Type 1 Receptor Blockers /therapeutic use; Angiotensin-Converting Enzyme Inhibitors /therapeutic use; Calcium Channel Blockers /adverse effects
AccessionNumber
12007002414

Date bibliographic record published
30/09/2008

Date abstract record published
01/12/2008

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.