

The Truth About CCBs Ten Years Later

In 1995, it was determined that the use of calcium channel blockers (CCBs) was associated with an increased risk of cardiovascular events and death, which ultimately resulted in heightened fears about the use of CCBs. This article reviews the significant findings of epidemiologic and hypertension studies which followed in the 10 years after these initial claims.

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In March of 1995, a paper was presented at a spring session of the American Heart Association Epidemiology section by Dr. Bruce Psaty. The paper was subsequently published in JAMA.¹ In it, the researcher determined—using a retrospective chart review—that the use of calcium channel blockers (CCBs) was associated with an increased risk of cardiovascular events and death. Upon further assessment, it was clarified that the patients in the study had been taking short-acting formulations of the CCBs and that the analysis had not been adequately examined for coexistent or concomitant medical conditions. Such conditions included resistant hypertension or diabetes that would also contribute to an increased risk of cardiovascular events and to a need for additional antihypertensive therapy (often including CCBs).

This paper spawned an extremely large number of articles in the media. As a result, patients wanted to stop taking their CCBs. In addition, general fears increased as television documentaries were screened ostensibly to inform the public, but they were incorrect in content and conclusion and so slandered the doctors whom they interviewed.

James' case

James, 52, went to see his physician for a check-up.

Past history:

- Overweight
- Does not exercise
- Works as a bartender
- Lifelong non-smoker
- Married with three children



Family history:

- His father, two uncles and one brother have suffered from a premature coronary event

Physical examination:

- BMI is 33
- BP is 174/108 mmHg (average of three readings)
- Pulse rate at 88 bpm
- Fundi test results show arteriovenous nicking
- Heart sounds included an S3. There were no bruits
- There were no other positive physical findings

Initial laboratory tests revealed:

- Elevated serum cholesterol level of 8.5 mmol/L
- Serum triglyceride level of 4.4 mmol/L
- Serum HDL level of 0.8 mmol/L
- CBC and serum electrolyte along with creatinine levels are normal
- EKG changes are consistent with LVH
- Urinalysis is negative

Go to page 34 for a follow-up on James' case

Epidemiology studies

Epidemiology studies usually use data that has been collected over time, often for other purposes such as usual clinical care. The researchers cannot control the reasons for which certain patients are given certain drugs, or why certain patients will follow certain lifestyles of their own choosing. This type of uncontrollability can lead to results that are not confirmed when an interventional study is done, researching the same drug, hormone, vitamin or lifestyle issue. Recently, there have been several examples of the fallibility of epidemiologic studies. As we have come to understand, taking vitamin supplements is not useful in preventing cancer or cardiovascular events, nor does taking estrogen supplements help prevent cardiovascular events. Epidemiologic studies should be seen as hypothesis-generating, but not hypothesis-proving.

Hypertension studies

The randomized-controlled study is considered the strongest design for testing the efficacy of a given intervention, whether it is a drug, a group of drugs, a diet, or a change in lifestyle. A pre-determined number of subjects are randomly placed into a given number of treatment groups and the doctors and nurses, who are administering the study, treat all subjects/patients in a similar manner. They do not know if the subjects are receiving the active substance in their daily pill, the placebo or the control medication.

About the author...

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Several studies assessing the efficacy of various CCBs have been conducted over the past five years.

The INSIGHT trial²

The International Nifedipine Gastrointestinal Transport System Study: Intervention as a Goal in Hypertension Treatment trial compared nifedipine, a slow-release formulation taken once daily, to amiloride and hydrochlorothiazide once daily, in patients with primary hypertension. There was no significant difference in the primary combined endpoint of stroke, heart attack, heart failure and cardiovascular death between the two groups.

Newly-diagnosed diabetes occurred significantly less in the group treated with the slow-release nifedipine (4.3%) compared to the group treated with amiloride and hydrochlorothiazide (5.6%); a 23% reduction ($p = 0.02$).

The NORDIL trial³

In the Nordic Diltiazem trial, over 10,000 patients were randomly placed in a diltiazem or a beta-blocker/diuretic arm and followed for four and a half years. Although there was no significant difference in the primary composite endpoint of MI, stroke and cardiovascular death, there was a significantly lower risk of stroke in the diltiazem arm (20%). This lower rate of stroke was surprising since there was a significantly higher BP in the diltiazem arm (155/89 mmHg and 152/89 mmHg in the beta-blocker/diuretic arm). Stroke is usually very sensitive to long term systolic BP, whereas coronary artery events are related to other risk factors, such as serum cholesterol indices, tobacco smoking and diabetes. This paradoxical result suggests that diltiazem might have a specific stroke-reducing effect.

The ALLHAT trial⁴

The Antihypertensive and Lipid-Lowering Treatment to prevent Heart Attack Trial was designed to evaluate several classes of antihypertensive agents and to compare them to the diuretic, chlorthalidone. In this case, amlodipine was the CCB used. Fifteen thousand patients were given the diuretic, 9,000 were given amlodipine and an additional group of approximately 9,000 patients received lisinopril. Although there were minor differences in BP control, or secondary outcomes, there was not a significant difference between the diuretic arm and the amlodipine arm for the primary outcome or all-cause mortality. By the end of the study, patients were given an average of two drugs each; the second-line therapy would have been either a beta-blocker or other sympatholytic medications, such as clonidine or reserpine. These second-line drug choices were limited by the design of the five-arm study and may not have represented medications commonly used in clinical practice. Hence, it is difficult to know how applicable these results are to the general population.

The VALUE trial⁵

The Valsartan Antihypertensive Long-term Use Evaluation trial was constructed to demonstrate that the angiotensin receptor blocker (ARB) valsartan, would reduce the rate of cardiovascular events, even with similar levels of BP control. The active comparator was amlodipine. A thiazide diuretic was added if the first-line therapy was not

effective in lowering BP to the target level. Fifteen thousand, two-hundred and forty-five patients with a high-risk of cardiovascular events who had hypertension were tested. They were randomized to CCB or ARB therapy and followed for a mean of 4.2 years. In the first year, the patients in the amlodipine arm showed significantly greater BP reduction, with significantly fewer strokes and cardiovascular events. By the end of the study, there was no difference in the primary endpoint of cardiac morbidity and mortality.

The important change to hypertension guidelines that resulted from this study was that high-risk hypertensive patients should have their diagnosis confirmed and treatment promptly initiated (*i.e.*, ideally within a month).

The ASCOT trial⁶

The Anglo-Scandinavian Cardiac Outcomes Trial randomized 19,257 high-risk patients in a two-by-two factorial design to study both statin therapy and to compare amlodipine and angiotensin-converting enzyme (ACE) inhibitor treatment to atenolol and bendroflumethiazide. The hypertension study was stopped after five and a half years of median follow up, at which time an interim analysis had demonstrated a significant 11% reduction in overall mortality in the amlodipine arm. However, there was no difference in the primary endpoint of cardiac morbidity and mortality. As expected, there was a significant 23% reduction in fatal and non-fatal stroke and a 30% reduction ($p < 0.0001$) in patients newly-diagnosed with diabetes taking amlodipine. Although some critics

In the first year of the VALUE study, patients taking a CCB showed greater BP reduction with significantly fewer strokes and cardiovascular events.

More on James

James is at high risk for a cardiovascular event and fits the enrollment criteria for the VALUE⁵ or ASCOT⁶ study.

He has evidence of target organ damage in his optic fundi and heart.

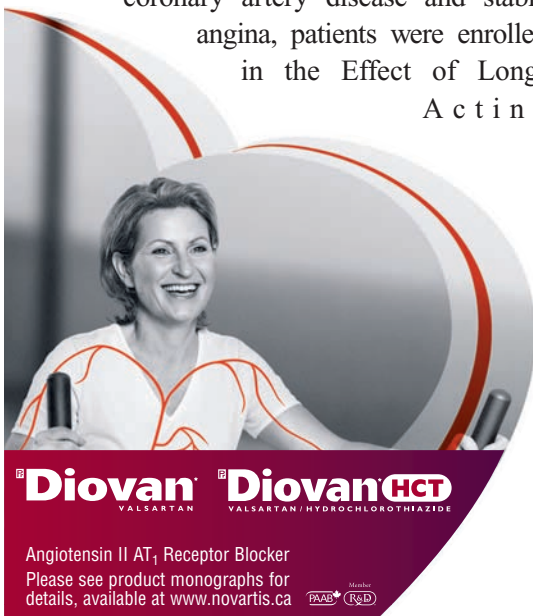
Aggressive reduction of his BP with a CCB, would be an option for him. In addition, he should receive counselling on weight loss as a means to help lower his BP, lipids, as well as his risk of diabetes. He should also receive a statin.

have suggested that the second-line medication, the ACE inhibitor, may have been responsible for the benefit seen in the study, only a small percentage of the patients received it.

Coronary Artery Disease

The ACTION trial⁸

To examine the effects of CCBs in patients with coronary artery disease and stable angina, patients were enrolled in the Effect of Long-Acting



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Nifedipine on Mortality and Cardiovascular Morbidity in Patients with Stable Angina Requiring Treatment trial and were given 60 mg of the once-daily, slow-release formulation nifedipine (n = 3,825 patients), or placebo (n = 3,840 patients) in addition to conventional therapy. Mean follow-up was 4.9 years. The CCB did not affect major cardiovascular event-free survival, but it did reduce the need for coronary interventions and angiography. There was no increase in MIs with the use of the CCB.

The CAMELOT trial⁸

In the two-year long Comparison of Amlodipine vs. Enalapril to Limit Occurrences of Thrombosis trial, 1,991 patients were randomized to amlodipine, 10 mg once daily, or enalapril, 20 mg, once daily, or placebo, once daily. There was a significant 31% reduction in cardiovascular events with amlodipine, but not with enalapril, compared to the placebo. There was no significant difference when comparing amlodipine to enalapril. In the substudy of intravascular ultrasound (IVUS) in 274 patients, it was found that there was a progression of atheroma in the placebo arm, a trend (p = 0.08) towards progression in the enalapril arm and no progression in the amlodipine arm. However, there was no significant difference between the placebo and amlodipine arms according to IVUS.

Concluding Thoughts...

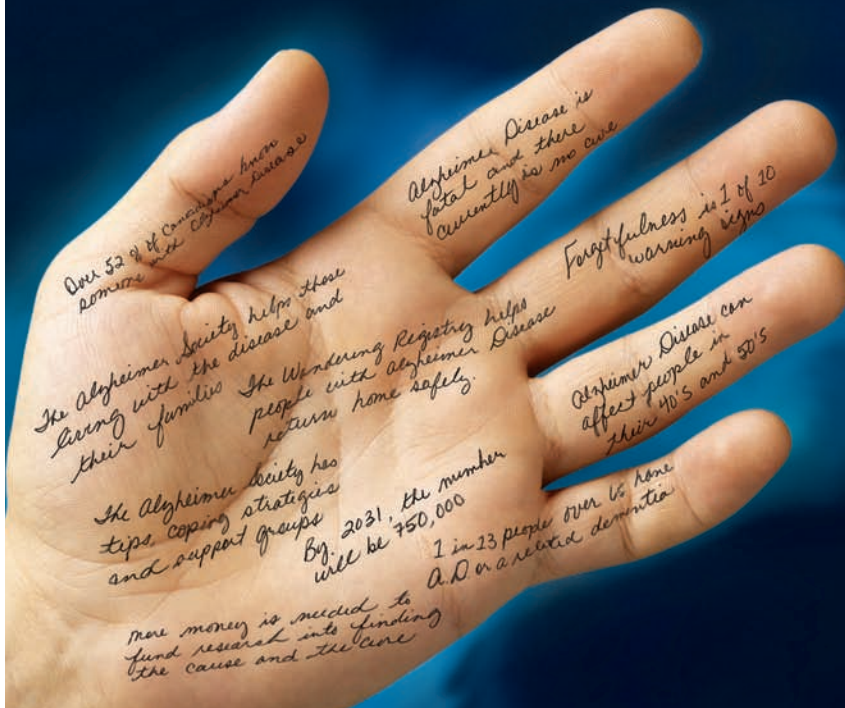
The use of CCBs in prospective randomized trials has demonstrated that **CCBs are safe and effective** in the prevention of cardiovascular events for patients with hypertension or coronary artery disease. The results from studies like those outlined

here have led to the incorporation of long-acting CCBs in the evidence-based hypertension guidelines put forth by the Canadian Hypertension Education Program and other similar groups. 

References

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Remember This...



Remembering is difficult... but even more difficult if you have Alzheimer Disease. A disease, which affects the brain, erases memory, and eventually takes life itself.

The Alzheimer Society provides information, support and funds research into the cause and cure. To find out more contact your local Alzheimer Society.

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