

# Enalapril reduced the risk for new-onset diabetes in left ventricular dysfunction

Vermes E, Ducharme A, Bourassa MG, et al. **Enalapril reduces the incidence of diabetes in patients with chronic heart failure: insight from the Studies Of Left Ventricular Dysfunction (SOLVD).** *Circulation.* 2003;107:1291-6.

## QUESTION

In nondiabetic patients with left ventricular dysfunction, does the angiotensin-converting enzyme (ACE) inhibitor enalapril reduce the risk for new-onset diabetes mellitus more than placebo?

## DESIGN

Randomized {allocation concealed\*}†, blinded (patients, clinicians, data collectors, {outcome assessors, data analysts, and monitoring committee}†),\* placebo-controlled trial with mean 2.9-year follow-up (Studies of Left Ventricular Dysfunction [SOLVD]).

## SETTING

{One of the 83 participating hospitals (Montreal Heart Institute)}†.

## PATIENTS

291 nondiabetic (fasting plasma glucose [FPG] level < 7.0 mmol/L) patients (mean age 56 y, 92% men) from the Montreal Heart Institute who were enrolled in the SOLVD trial, had left ventricular dysfunction (ejection fraction [EF] ≤ 35%), and no history of diabetes. Exclusion criteria were age > 80 years, unstable angina pectoris, myocardial infarction in the previous month, severe pulmonary disease, renal insufficiency

(creatinine level > 177 μmol/L), intolerance to ACE inhibitors, or current ACE inhibitor use. All patients were included in the analysis.

## INTERVENTION

Patients were allocated to enalapril, 5 to 20 mg/d ( $n = 153$ ), or placebo ( $n = 138$ ).

## MAIN OUTCOME MEASURES

Development of new-onset diabetes (FPG ≥ 7.0 mmol/L) at 2 different visits.

## MAIN RESULTS

Analysis was by intention to treat. Fewer patients in the enalapril group developed new-onset diabetes mellitus than did those in the placebo group (Table). In a multivariate analysis, enalapril decreased the risk for diabetes mellitus (hazard ratio 0.22, 95% CI

0.10 to 0.46,  $P < 0.001$ ). In a subgroup with baseline impaired FPG (6.1 to 7.0 mmol/L), fewer patients taking enalapril developed new-onset diabetes mellitus than those taking placebo (Table).

## CONCLUSION

In nondiabetic patients with left ventricular dysfunction, the angiotensin-converting enzyme inhibitor enalapril reduced the risk for new-onset diabetes mellitus.

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\*See Glossary.

†Information provided by author.

## Enalapril vs placebo to prevent new-onset diabetes mellitus in left ventricular dysfunction at mean 2.9 years†

New-onset diabetes	Enalapril	Placebo	RRR (95% CI)	NNT (CI)
All patients	5.9%	22.4%	74% (48 to 87)	7 (5 to 12)
Patients with impaired fasting glucose	3.3%	48%	93% (63 to 99)	3 (2 to 5)

‡Abbreviations defined in Glossary; RRR, NNT, and CI calculated from data in article.

## COMMENTARY

Dysglycemic states, including diabetes, impaired glucose tolerance, and lesser degrees of hyperglycemia, are risk factors for subsequent cardiovascular (CV) events. Moreover, nondiabetic patients at high risk for future CV events are likely to be dysglycemic and have a high risk for future diabetes. Such patients had a rate of new-onset diabetes of 1.2% per year in the placebo arm of the HOPE study (1) and of 3.7% in the metabolically neutral amlodipine arm of the ALLHAT study (2). Once diabetes develops, patients are at high risk for retinopathy, neuropathy, renal disease, and other complications. Thus, strategies to prevent diabetes in high-risk patients are clearly indicated.

Recent clinical trials have shown that diabetes can be prevented or delayed with lifestyle changes, metformin, or acarbose. These trials studied patients with impaired glucose tolerance who had few other risk factors for CV events.

ACE inhibitors may also prevent diabetes. An exploratory analysis of the HOPE study suggested that ramipril may reduce the relative risk for diabetes by 44% in patients at high risk for CV events (1). The ALLHAT study found a 22% reduction in the relative risk for diabetes in hypertensive patients allocated to lisinopril compared with amlodipine (2). The study by Vermes and colleagues reported a similar finding in patients allocated to enalapril.

The hypothesis that ACE inhibitors may reduce diabetes, however, requires confirmation from a large randomized trial. The Diabetes REduction Assessment with ramipril and rosiglitazone Medication trial is randomizing 5000 patients with impaired glucose tolerance or impaired FPG to ramipril, 15 mg/d, or placebo, and the primary outcome is new-onset diabetes or death.

We have now entered the area of diabetes prevention. Ongoing trials will assess the efficacy of interventions that prevent diabetes and also reduce CV risk. In the meantime, activity and diet changes remain the most effective proven approach for preventing diabetes in high-risk patients.

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## References

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