

Candesartan prevented development of diabetes mellitus in heart failure

Yusuf S, Ostergren JB, Gerstein HC, et al. Effects of candesartan on the development of a new diagnosis of diabetes mellitus in patients with heart failure. *Circulation*. 2005;112:48-53.

Clinical impact ratings: Cardiology ★★★★★☆ Endocrinology ★★★★★☆☆

QUESTION

In patients with heart failure, does candesartan prevent development of diabetes mellitus?

METHODS

Design: Prespecified secondary analysis of 3 randomized, placebo-controlled trials (Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity Program [CHARM]).

Allocation: {Concealed}†.*

Blinding: Blinded {clinicians, patients, data collectors, outcome assessors, monitoring committee, manuscript writers, and data analysts}†.*

Follow-up period: Median 3.1 years.

Setting: {618 centers in 26 countries}†.

Patients: 5436 patients (mean age 66 y, 69% men) with symptomatic heart failure who did not have diabetes at baseline came from 3 parallel trials (CHARM-Alternative: patients with left ventricular ejection fraction [LVEF] ≤ 40% who were intolerant of angiotensin-converting enzyme [ACE] inhibitors;

CHARM-Added: patients with LVEF ≤ 40% and receiving an ACE inhibitor; and CHARM-Preserved: patients with LVEF > 40%).

Intervention: Candesartan (incremental doses up to a maximum of 32 mg/d as tolerated) (*n* = 2715) or matching placebo (*n* = 2721).

Outcomes: Development of diabetes and a composite endpoint of diabetes and all-cause mortality.

Patient follow-up: 99.9% (intention-to-treat analysis).

MAIN RESULTS

Candesartan reduced development of diabetes and a composite endpoint of diabetes

and all-cause mortality more than placebo (Table).

CONCLUSION

In patients with heart failure, candesartan reduced development of diabetes and a composite endpoint of diabetes and all-cause mortality.

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*See Glossary.

†Pfeffer MA, Swedberg K, Granger CB, et al. *Lancet*. 2003;362:759-66.

Candesartan vs placebo in patients with heart failure at median 3.1 years†

| Outcomes | Candesartan | Placebo | RRR (95% CI) | NNT (CI) |
|-------------------------|-------------|---------|---------------|----------------|
| Development of diabetes | 6.0% | 7.4% | 21% (4 to 35) | 64 (39 to 351) |
| Composite endpoint§ | 25.5% | 28.6% | 12% (4 to 19) | 29 (19 to 83) |

‡Abbreviations defined in Glossary; RRR, NNT, and CI calculated from hazard ratios and control event rate in article.

§Composite endpoint = diabetes and all-cause mortality.

COMMENTARY

Type 2 diabetes, which is closely linked to obesity and cardiovascular disease, may be preventable through weight control, lifestyle changes, and the use of such drugs as metformin and thiazolidinediones (1). Yusuf and colleagues have added to growing evidence that inhibition of the renin-angiotensin (RA) system, through use of an angiotensin-receptor blocker, can prevent the onset of overt diabetes. The authors did a preplanned subgroup analysis of data from 3 parallel placebo-controlled trials (CHARM) with varying inclusion criteria. Patients had different levels of LVEF, but all had symptomatic heart failure. Diabetes was most convincingly prevented in patients with preserved systolic function, with little benefit observed in those already receiving an ACE inhibitor (suggesting overlap of effect). Detection bias seemed unlikely, and correction for other drug use did not change the conclusions. Because of the complex comorbid conditions involved, it is difficult to tease out which particular patients might benefit most from such intervention. The point, however, may be moot, as most patients should stand to benefit for cardiovascular reasons alone.

The overall 21% relative risk reduction is similar to that reported in other trials, involving almost 40 000 patients (2). Mechanisms of benefit, all speculative, include effects on adipocytes, on insulin delivery and

sensitivity, and on a newly recognized intrapancreatic RA system.

Many studies to date have involved secondary analyses and have included patients with cardiovascular disease for whom RA inhibition might be indicated anyway. For most clinicians, the key question is whether RA inhibition will cost-effectively prevent diabetes in other patients, such as those with impaired glucose tolerance (IGT). Additional answers may come from the NAVIGATOR and DREAM trials, both of which will study the effects of RA inhibition and other preventive approaches in patients with IGT. The results of those trials could really change our practice.

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References

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2. Scheen AJ. Renin-angiotensin system inhibition prevents type 2 diabetes mellitus. Part 1. A meta-analysis of randomised clinical trials. *Diabetes Metab*. 2004;30:487-96.