Differences between candesartan and losartan for heart failure?

Document as included in MAW

A Danish observational study found no statistically significant difference in mortality between patients with heart failure treated with candesartan or losartan. Use of lower doses of these drugs was associated with higher mortality.

Overview and current advice

The NICE guideline for the management of chronic heart failure recommends that an ACE inhibitor is the first choice renin-angiotensin system drug in heart failure. An angiotensin II receptor antagonist (ARB) licensed for heart failure can be considered if the patient develops intolerable side effects with an ACE inhibitor. It can also be used in combination with an ACE inhibitor and a beta-blocker in certain patients on specialist advice. The NICE guideline does not recommend use of a specific ARB, other than to specify using one that is licensed for heart failure. The ARBs licensed for heart failure are losartan, candesartan, and valsartan (which is also licensed for use post-myocardial infarction). The current acquisition cost of generic losartan is considerably less than candesartan. According to the UKMI patent expiry database (password required), patent protection on candesartan in the EU ended on 28/4/2012. However, the Drug Tariff for August 2012 lists candesartan as Category C (drugs which are not readily available as a generic).

A previous observational study using a Swedish registry of patients with heart failure (clinician judged) suggested that losartan was associated with higher mortality in heart failure than candesartan, however, like all observational studies, it had a number of limitations (see MeReC Rapid Review No. 2396).

New evidence

A Danish observational study has reconsidered this issue using a nationwide registry cohort of patients with first-time hospitalisation for heart failure, who were new users of losartan or candesartan.
Overall, after adjustment for multiple confounding factors, losartan was not associated with a statistically significant increased risk of either all-cause mortality (hazard ratio [HR] 1.10, 95% confidence interval [CI] 0.96 to 1.25) or cardiovascular (CV) mortality (HR, 1.14; 95% CI, 0.96 to 1.36) compared with candesartan. Analysis according to the dose of ARB indicated some dose-related effects. Compared with high doses of candesartan (16–32 mg per day), low-dose (12.5 mg per day) and medium-dose losartan (50 mg per day) were associated with increased mortality (HR 2.79, 95% CI 2.19 to 3.55 and HR 1.39; 95% CI 1.11 to 1.73 respectively), whereas use of high-dose losartan (100 mg per day) was not associated with a significantly higher risk (HR 0.71, 95% CI 0.49 to 1.00). Similarly, use of 4 mg per day of candesartan was associated with a statistically significant increased mortality compared with higher doses of candesartan (HR 2.12, 95% CI 1.61 to 2.80).

See the NHS Evidence topic page on heart failure for a general overview of the condition. The NICE Pathway: chronic heart failure brings together all related NICE guidance and associated products on the condition in a set of interactive topic-based diagrams.

**Commentary**

In apparent contrast to a previous observational study, this study found no statistically significant difference in mortality between patients using candesartan or losartan.

Both studies have important limitations. Taken together, it would appear that there is still insufficient evidence to be able to support a firm conclusion of superiority of one drug over the other, although there is a clear signal that higher doses of ARBs may be associated with a reduction in mortality. This new evidence is in line with current NICE guidance for the management of chronic heart failure which states that an ARB licensed for use in heart failure should be used where an ARB is recommended.

Although both studies drew on registry data to provide cohorts for analysis, there were important differences in both the criteria for inclusion in the registry, and on the statistical management of potential confounding factors such as comorbidities, co-medications, and health status markers.

This Danish study provides additional insight into the effects of ARB dosage on mortality. Higher doses were associated with a lower risk of mortality for both losartan and candesartan. Low and medium doses of losartan were associated with higher mortality than high doses of candesartan. In the earlier Swedish study, it is possible that the higher average relative dose among candesartan users, compared with losartan users may have led to an overestimation of the effectiveness of candesartan. In this Danish study, the reduced mortality with higher doses of both ARBs suggests a benefit of using them at a high (target) dose. However, it is not possible to determine from the study whether there are differences in tolerability between drugs, or in the ability to reach target doses.

Although there were no statistically significant differences in mortality between losartan and candesartan in the overall comparison, the HR 95% CIs ranged from 0.96 to 1.25. This means that an increased relative risk as high as 25% for losartan cannot be ruled out. Indeed, these confidence intervals overlap with those of the Swedish study (HR 95% CI 1.23 to 1.65).

Both studies are observational studies, and are subject to many confounding factors. Although in this Danish study, considerable effort to control for differences between groups in baseline characteristics was made, not all potentially confounding factors were recorded and adjusted for and some imbalances inevitably remained. For instance, severity of heart failure, a potentially important confounding factor, was not recorded and it was not possible to fully take this into account. On the other hand, entry on to the Danish registry is based on hospitalisation for heart failure, whilst the criteria for the Swedish registry are less rigorous.

Kate Arnold, Senior Prescribing Adviser, Birmingham and Solihull NHS Cluster.
Study sponsorship

[Add text. Use ‘MEC content’ style.]

References

4. National Prescribing Centre (2011). Observational study suggests candesartan may be preferable to losartan in heart failure. MeReC Rapid Review 2396

About this Medicines Evidence Commentary

Medicines Evidence Commentaries form part of NICE’s Medicines Awareness Service and help contextualise important new evidence, highlighting areas that could signal a change in clinical practice. They do not constitute formal NICE guidance. The opinions of contributors do not necessarily reflect the views of NICE.

Visit Evidence Search

Copyright © 2013 National Institute for Health and Care Excellence. All Rights Reserved.