Efficacy and safety of angiotensin receptor blockers alone and in combination with diuretics in patients with hypertension, heart failure or diabetic nephropathy

This is an excerpt from the full technical report, which is written in Norwegian.

The excerpt provides the report's main messages in English.

No. 24–2008

Review of systematic reviews

kunnskapssenteret

Title	Efficacy and safety of angiotensin receptor blockers alone and in combination with diuretics in patients with hypertension, heart failure or diabetic nephropathy
Norwegian title	Effekt og sikkerhet av angiotensin reseptorblokkere med og uten diuretika hos pasienter med hypertensjon, hjertesvikt eller diabetisk nefropati
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ISBN	978-82-8121-221-3
ISSN	1890-1298
Report	No. 24 – 2008
Project number	405
Type of report	Overview of reviews
No. of pages	64 (84 incl. attachments)
Client	The Norwegian Medicines Agency
Subject heading (MeSH)	Angiotensin Receptor Antagonists; Diuretics; Hypertension; Heart Failure; Diabetic Nephropathies
Citation	Ringerike T, Reikvam, A, Gjertsen MK. Efficacy and safety of angiotensin receptor blockers alone and in combination with diuretics in patients with hypertension, heart failure or diabetic nephropathy. Report from Kunnskapssenteret no. 24–2008. Oslo: Norwegian Knowledge Centre for the Health Services, 2008.

Norwegian Knowledge Centre for the Health Services summarizes and disseminates evidence concerning the effect of treatments, methods, and interventions in health services, in addition to monitoring health service quality. Our goal is to support good decision making in order to provide patients in Norway with the best possible care. The Centre is organized under The Norwegian Directorate for Health, but is scientifically and professionally independent. The Centre has no authority to develop health policy or responsibility to implement policies.

We would like to thank all contributers for their expertise in this project. Norwegian Knowledge Centre for the Health Services assumes final responsibility for the content of this report.

Norwegian Knowledge Centre for the Health Services
Oslo, July 2008

Key messages

Efficacy and safety of angiotensin receptor blockers alone and in combination with diuretics in patients with hypertension, heart failure or diabetic nephropathy

Background: Hypertension increases the risk of developing cardiovascular diseases, in particular myocardial infarction and stroke. Several types of drugs lower blood pressure and angiotensin receptor blockers (ARB) constitute one drug class. These drugs are also found in combination with thiazide diuretics. This report aimed to compare the different drugs within the ARB class with regard to efficacy and safety in patients with hypertension, heart failure and diabetic nephropathy.

Method: The report is an overview of systematic reviews. We have examined the effect of ARB on clinical endpoints like death, cardiovascular events (myocardial infarct, stoke) and end-stage renal disease. We performed systematic searches in Cochrane Library, Centre for Reviews and Dissemination databases, Medline (Ovid) and Embase (Ovid).

Results: We did not identify systematic reviews where drugs within the ARB class were directly compared. Neither did we find systematic reviews in which the combination drugs were compared. This applied to all clinical endpoints and all patient populations examined in this report. Studies that compared the different ARBs with other active drug treatments or with placebo, with use of hard endpoints (death, cardiovascular events, end-stage renal failure), are present but few. For most comparisons with other active treatments significant differences with regard to efficacy have not been reported. Thus these studies could not be used as a basis for trying to undertake an indirect comparison between the different drugs within the ARB class. ARBs appeared to be well tolerated. The adverse events related to the ARBs varied between studies, and there were not sufficient data to determine whether differences existed between the different ARBs concerning specific adverse drug reactions.

Conclusion: It has not been documented that one or several drugs within the class of ARB are more efficacious or safer than the others in patients with hypertension, heart failure or diabetic nephropathy.

Executive summary

Efficacy and safety of angiotensin receptor blockers alone and in combination with diuretics in patients with hypertension, heart failure or diabetic nephropathy

BACKGROUND

Hypertension is a common health problem in Norway. Data from the Norwegian prescription registry indicate that approximately 20 % of the population receive at least one prescription for drugs belonging to the class cardiovascular drugs. Hypertension in itself is not at disease, but hypertension increases the risk of developing cardiovascular diseases. There are several causes of hypertension; both hereditary and environmental factors are involved.

Treatment of hypertension aims at reducing the risk of cardiovascular diseases and early death. High blood pressure is only one of several factors which influence this risk. Other risk factors are smoking, sedentary lifestyle, obesity and blood lipid disorders.

Several types of drugs lower blood pressure, and they act through different mechanisms. This report deals with efficacy and safety of one of these drug classes, the angiotensin receptor blockers (ARB). The report was commissioned by the Norwegian Medicines Agency as part of their evaluation of whether one or a few selected ARBs should be regarded as the first choice ARB for treatment of hypertension, heart failure or diabetic nephropathy.

MANDATE

At present, seven different ARBs are available in Norway: losartan, eprosartan, valsartan, irbesartan, candesartan, telmisartan and olmesartan. All of them are also available in combination with thiazide diuretics (hydrochlorothiazide). The mandate was to evaluate documented effect of the ARBs on morbidity and/or mortality, as compared to other drug treatments or placebo. In addition, we were to examine if the various ARBs differed with regard to blood pressure lowering efficiency. In par-

ticular, we were requested to assess studies which directly compared the different drugs within the ARB class. Quality of life should also be evaluated. Relevant populations were patients with hypertension, heart failure and diabetic nephropathy.

METHOD

This report is an overview of systematic reviews. We also searched for new relevant randomized controlled trials published later than the systematic reviews, to make sure that recent knowledge would not alter the conclusions of the reviews.

We searched systematically for systematic reviews and randomized controlled trials in Cochrane Library, Centre for Reviews and Dissemination databases, Medline (Ovid) and Embase (Ovid).

Two employees at the Norwegian Knowledge Centre for the Health Services examined all identified titles and abstracts. Potentially relevant publications were ordered in full-text and evaluated according to predefined criteria. All included publications were evaluated for quality according to a predefined check-list. Study quality was assigned as high, medium or low. Evaluations were performed independently and disagreements were solved by discussion.

RESULTS

We did not identify systematic reviews dealing with direct comparisons of drugs within the ARB class. Neither did we identify systematic reviews in which the combination drugs were compared. This applied to all outcomes and all patient populations under evaluation in this report.
Results based on studies that compared ARBs with other drug treatments, or with placebo, by use of hard endpoints (death, cardiovascular events, end-stage renal failure) are limited. Only a few of the seven ARBs have been included in randomized controlled trials with the aim of investigating death, cardiovascular death or end-stage renal disease. It has not been documented that ARBs compared to other active treatments are superior in preventing deaths.

For the evaluation of quality of life in patients with hypertension several quality of life instruments have been used and ARBs have been compared to several types of active treatments. This makes it difficult to judge how the different ARBs affect quality of life. For patients with heart failure, the Minnesota Living with Heart Failure (MLHF)-questionnaire has been used. Significant differences between ARBs and the comparator drug were not observed. Comparisons with placebo were done in studies of widely differing size and different questionnaires were used; in general ARBs were equal to or better than placebo. We did not identify studies which evaluated quality of life in patients with diabetic nephropathy.

ARB appeared to be well tolerated. The adverse events related to the ARBs varied between studies, and there were not sufficient data to determine whether differences existed between the different ARBs concerning specific adverse drug reactions.

DISCUSSION

Controlled clinical trials, in which two or more drugs are directly compared, are usually needed for estimation of efficacy and safety of drug treatment. Because direct comparisons between the various ARBs are absent, it is difficult to evaluate them against each other. It could be a possibility to evaluate how ARBs have fared in comparison with other drugs or placebo, and on basis of this try to undertake an indirect comparison of the ARBs. Only few studies have, with use of hard endpoints, compared ARBs to other active treatment. The results do not exhibit an unambiguous pattern. Our conclusion is that the ARBs do not perform better or worse than the comparator drugs. The analyses are complicated by the fact that the studies have used combination of drugs in each study arm. This implies that observed drug effects might be caused by drug combinations and not by a single drug.

Accordingly, the studies are not well suited for evaluation of efficacy and safety of the drugs within the ARB class.

CONCLUSION

We did not find it documented that one or several of the drugs within the class of ARB are more efficacious or safer than the others in patients with hypertension, heart failure or diabetic nephropathy.

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