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HTA-Report | Summary

New-onset diabetes and antihypertensive treatment

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Health political background

Expenses in the statutory health insurance continuously increase due to medical advancement and the demographic development. Due to the increase in health care expenditures it is requested to reduce costs especially for drugs. Therefore, therapeutic approaches which are cost-effective in the short term as well as in the long term should be promoted.
Especially chronic diseases substantially contribute to the continuous increase in health care expenditures, including type-2 diabetes mellitus as one of the most expensive chronic diseases. Arterial hypertension as well as obesity and adiposity present risk factors for the development of type-2 diabetes mellitus. Diabetes mellitus and hypertension often appear in combination.
Numerous analyses have demonstrated that not only hypertension, but also antihypertensive therapies promote the development of type-2-diabetes mellitus. Studies indicate that the application of angiotensin converting enzyme (ACE) inhibitors and angiotensin-receptor-blockers (ARB) lead to less new-onset diabetes compared to beta-blockers, diuretics and placebo. Given that beta-blockers and diuretics impair the glucose metabolism, the metabolic effects of different antihypertensive drugs should be regarded; otherwise not only the disease itself, but also antihypertensive therapies may promote the development of new-onset diabetes. Even though the cost of ACE inhibitors and ARB are higher, the use in patients with metabolic disorders could be cost-effective in the long-term if new-onset diabetes is avoided.

Scientific background

Hypertension is a risk factor for arteriosclerotic vascular diseases. Cohort studies in the 1970ies and 1980ies as well as in the 1990ies show, that both systolic and diastolic blood pressure correlate with the risk of stroke and coronary artery disease. Worldwide, hypertension is responsible for more than 50 % of deaths due to stroke and for about 25 % of deaths due to coronary artery disease. The prevalence decreased in the last decade but is still high and will probably increase due to demographic development: elderly people are often more affected by hypertension than younger people. The lifetime-risk for developing hypertension is nearly 90 % for people older than 55 years of age. In addition, the prevalence of adiposity also associated with hypertension, continue to increase in the industrial countries.
The correlation between systolic blood pressure and the relative risk of stroke is stronger than the relative risk of coronary artery disease, whereas mortality due to coronary artery disease is the dominating consequence of hypertension. Besides systolic and diastolic blood pressure levels and type-2 diabetes mellitus, age, smoking, dyslipedemia, a family history of premature cardiovascular disease (≤ 55 years for men, ≤ 65 years for women),

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abdominal obesity (abdominal girth men ≥ 102 cm, women ≥ 88 cm), as well as fasting plasmaglucose (5.6 to 6.9 mmol/l or 102 to 125 mg/dl) or pathological plasmaglucose levels, are risk factors for cardiovascular diseases. A metabolic syndrome exists if three or more of the following risk factors are present: abdominal obesity, pathological levels of plasmaglucose, blood pressure > 130/85 mmHg, decreased high-density-lipoprotein-cholesterol (HDL-cholesterol) levels and increased levels of triglycerides. The definition of metabolic syndrome changed in the past years. No general accepted definition has been stipulated up to now, which implies that the factors should be regarded separately.

Research questions

The following questions are evaluated within this report: Which classes of antihypertensive agents promote the development or the manifestation of type-2 diabetes mellitus? How high is the incidence of new-onset diabetes during antihypertensive therapy and how is a treatment-induced type-2 diabetes mellitus evaluated clinically? Which agents are therefore cost-effective in the long term? Which ethical, social or legal aspects should be regarded?

Methods

A systematic literature search and a hand search in agreement with the German Health Technology Assessment Agency (DAHTA) of the German Institute of Medical Documentation and Information (DIMDI) were conducted. The search makes no claim to be complete.
Included are studies and systematic reviews with at least ten participants which reported on new-onset diabetes in the course of antihypertensive treatment. The following antihypertensive drugs are focused on: ACE inhibitors, alpha-blockers, ARB, beta-blockers, calcium-channel-antagonists or diuretics. Trials with the higher evidence are preferred however case-control-studies fulfilled the minimum requirements.
The trials had to be published after 1966 (after 2003 for economic publications) in English or German. Trials with less than ten participants, meeting abstracts, editorials or non-systematic reviews/overviews were excluded.
The publications were selected independently by two scientists considering the defined inclusion- and exclusion criteria.

Results

On the basis of the predefined search criteria and the conducted literature search, 2,404 clinical publications, 511 economic as well as 44 ethical and legal and no social publications were identified. After reviewing title and abstracts, 461 medical, 96 economic and one ethical/legal publication were ordered as full texts. Thereof, ten publications are ordered twice, and 13 publications were supplements of already ordered publications. In total, it was not possible to order or download 41 medical publications. Of 96 ordered economic publications, 37 were duplicates and five were not available. Additionally, 33 medical and two economic publications were identified by hand search. They were also assessed on the basis of the inclusion- and exclusion criteria.

Altogether, 34 medical publications fulfilled the inclusion criteria and included six meta-analyses, three systematic reviews, 19 randomised controlled trials, one publication with at least one well-designed controlled study without randomisation, two well-designed quasi-experimental studies and one case-control-study.

Eight publications reported on diuretics and/or beta-blockers, whereas six publications reported on ACE inhibitors alone or in combination with calcium-channel-antagonists. Ten publications dealt with ARB and/or ACE inhibitors and their implications on development of diabetes. Five publications evaluated the role of calcium-channel-antagonists in the development of diabetes mellitus whereas another five publications reported on new-onset diabetes in the course of different antihypertensive drugs compared to no medical therapy. The studies showed a significant difference in the development of type-2 diabetes mellitus in the antihypertensive treatment: a higher incidence of new-onset diabetes was found with diuretics and/or beta-blockers. A possible preventive effect is reported for ACE inhibitors and ARB. Compared to other antihypertensive drugs, these caused the lowest diabetes incidence. Calcium-channel-antagonists were neutral position.

The incidence of a treatment-induced type-2 diabetes depended on the different substance classes. It differed between the various publications. The diabetes incidence in the course of treatment with calcium-channel-antagonists varies from 0.9 % to 2.0 % per year, for ACE inhibitors from 1.0, 1.1 % and 1.7 % per year. The annual incidence with thiaziddiuretics and beta-blockers was partly reported as a combined incidence. It ranged from 1.0 % over 1.1 % to 1.2 %. If only thiaziddiuretics were considered, the incidence amounted to 2.4 % and for beta-blockers from 1.7 % to 3.0 %. The rate of new-onset diabetes differed in the studies because they were sometimes combined with other antihypertensive drugs and no monotherapy was considered. In this respect, it was difficult to assign the annual incidence to the different substance classes. Independent from the substance class, the incidence was estimated at 1.7 % annually.

Furthermore, it is significant that a reduction in insulin sensitivity was responsible for the development of diabetes mellitus. Diabetes mellitus often occurred under insulin resistant conditions like obesity, hypertension, heart failure, and metabolic syndrome. Overall, three identified publications informed about factors promoting new-onset diabetes in the course of an antihypertensive treatment: Hispanic ethnicity or afro-Americans, left-ventricular hypertrophy, stroke or transitoric ischemic attacks (TIA), conditions after coronary revascularisation, hypercholesteremia, high body-mass-index and high systolic blood pressure.

Two publications reported on the cost-effectiveness of ARB as a monotherapy or in combination with calcium-channel-blockers compared to diuretics alone or in combination with beta-blocker. The first publication compared economic outcomes of calcium-channel-blockers and beta-blockers with regard to the development of new-onset diabetes. Treatment with the ARB candesartan lead to savings in total costs of 549 US-Dollar per patient and in incremental costs of 30,000 US-Dollar per diabetes mellitus avoided. In the second publication, costs to the amount of 18,965 Euro in Great Britain and 13,210 Euro in Sweden were quoted for an avoided event. The treatment with calcium-channel-blockers compared to beta-blockers was proven to be more cost-effective.

No publications were identified regarding ethical, social and legal aspects. These aspects are discussed in the following section.

Discussion

The answer of the first medical objective: *which class of antihypertensive agents promotes the development or the manifestation of type-2 diabetes mellitus?* was documented with a high level of evidence. Nevertheless the studies were heterogenic towards inclusion criteria, primary endpoints, and study duration. None of the identified studies were conducted in Germany, which makes the transferability of the results, especially economic results, difficult. Most of the studies were conducted in the United States and the results were not stratified for ethnicity. It was possible to identify whether a drug-induced diabetes mellitus was reversible after discontinuing the drug or changing the substance class. Evidence was given in the STAR-LET study, where patients with new-onset diabetes and antihypertensive therapy with ARB and thiaziddiuretics received normal glucose levels after changing to another combination of antihypertensive drugs. Further studies are required to address this issue thoroughly.

The two identified economic publications let assume that newer antihypertensive drugs (ARB, calcium-channel-blockers) compared to beta-blockers and diuretics are cost-effective in the long term with regard to less new-onset diabetes. For ACE inhibitors, no publications were found. From the medical publications of this report it was concluded that ACE inhibitors cause fewer new-onset diabetes than diuretics and beta-blockers and therefore also lead to cost savings by avoiding diabetes and its complications.

For Germany, no data concerning the cost-effectiveness of antihypertensive drugs with regards to the development of diabetes are available. To assess cost-effectiveness, studies with an adequate duration to also consider cardiovascular events due to hypertension as well as diabetes are required. In a health economic model, the lifetime treatment with antihypertensive drugs should also be regarded to show the costs of the different therapy strategies in comparison to lifetime costs of diabetes mellitus and its complications.

Not only from a medical or economical but also from an ethical viewpoint, it is debateable if it is reasonable to treat patients with diuretics and/or beta-blockers if they have risk factors other than hypertension for developing diabetes mellitus. The antihypertensive therapy aims are avoiding cardiovascular events and cardiovascular mortality. The therapeutic benefit of the antihypertensive treatment has to be weighed against the risk of developing diabetes mellitus. Diabetes itself is also associated with a higher risk for cardiovascular events and leads to death if left untreated. It remains to treat patients at risk for cardiovascular events with drugs, which promote conditions which could again increase this risk. Is it justifiable to treat hypertension and accept the development of diabetes?

According to the guidelines of the German Hypertension League (Deutsche Hochdruckliga e. V.) and the German Society of Hypertension (Deutsche Hypertonie Gesellschaft), diuretics and beta-blockers should not be prescribed for patients with metabolic syndrome or rather with different specific manifestations of the metabolic syndrome.

Regarding legal aspects, non-compliance of these guidelines may be regarded as a treatment error. A treatment error only occurs when the error

leads to impairment (development of diabetes) and the patient is able to prove the causality. This might be difficult, unless the patient was not informed adequately about the possible risk of developing diabetes mellitus in the course of treatment with diuretics and/or beta-blockers.

Conclusions/recommendations

Antihypertensive treatment has a significant influence on the incidence of diabetes mellitus, whereas the incidence is higher for patients treated with diuretics or beta-blockers than for patients treated with calcium-channel-blockers, ACE inhibitors and ARB. This effect is much stronger when both substance classes are used in combination. The results of the identified publications within this report show a medically relevant limitation for the use of diuretics and beta-blockers.

Patients with insulin-resistent states, hypertension, impaired plasmaglucose, obesity and heart failure should preferably be treated with ACE inhibitors and ARB.

Further research is required to confirm the role of ACE inhibitors and ARB in the prevention of type-2 diabetes and to assess the risk for cardiovascular events and mortality due to drug-induced diabetes.

From a health economic point of view, evidence is lacking regarding the cost-effectiveness of the newer antihypertensive drugs in Germany. To gain reliable data, health economic studies and health economic models in a German setting have to be conducted. Based on costs for diabetes mellitus and its complications, the assumption is made that the use of antihypertensive drugs, which cause a lower diabetes incidence, can also be considered cost-effective for the German health care system.