The use of statins in primary prevention
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Background

In developed countries coronary heart diseases are one of the major causes of death. 1999 seventeen per cent of patients in the inpatient sector in Germany have been hospitalised as a result of an affection of the cardiovascular system. 64218 Germans died of a heart attack in the year of 2002. Cardiovascular disease prevention can be achieved either by lifestyle changes or drug therapy. Basically primary and secondary prevention as well as specific and non-specific prevention can be distinguished. In primary prevention risk factors are treated when there is no disease present, whereas secondary prevention aims at inhibiting consequences or recurrence of illness. Specific prevention focuses on strictly selected groups of patients or persons. Recommended guidelines for the primary prevention of cardiovascular diseases (e.g. the Third Report of the National Cholesterol Education Program Expert Panel (ATP III), the guidelines of the German Association of Cardiology, the therapeutic recommendations of the “Arzneimittelkommission der deutschen Ärzteschaft für Koronare Herzkrankheit” as well as the “European guidelines on cardiovascular disease prevention in clinical practice”) at present primarily aim at life-style changes. If no success can be seen cholesterol lowering drug therapy - besides other measures - is advised.

Objectives

The aim of this report is first to investigate the efficacy and effectiveness of statins in primary prevention of cardiovascular and non-cardiovascular events. Secondly economic implications for Germany will be examined - particularly in comparison to existing prevention programs. Finally ethical questions will be considered.

Medical assessment

The individual risk of experiencing cardiovascular events within the next ten years can be determined with the aid of the concept of “global risk”. In this concept individual cardiovascular risk is determined according to certain risk factors like overweight, high blood pressure, lipid dysfunctions, diabetes mellitus, metabolic syndrome, age or sex - independent of patient history. Most recent studies as well as therapeutic guidelines refer to this concept of global risk rather than to previous definitions of primary and secondary prevention. The “Arzneimittelkommission der deutschen Ärzteschaft für Koronare Herzkrankheit” implemented the PROCAM-Risk-Score in its guidelines for the prevention of coronary heart disease, which is based on the data of the Prospective Cardiovascular Münster (PROCAM-) study.

Methods

A systematic literature search was performed in 30 international databases for the period of January 1998 to 2004 which yielded 3704 abstracts. The research strategy included medical, economic as well as ethic and juridical search terms. Eleven publications were added through hand search in ref-
Results

There is no doubt about a correlation between coronary heart disease and the cholesterol level. Studies prove that statins reduce “bad” Low-Density-Lipoprotein (LDL-C) and increase “good” High-Density-Lipoprotein (HDL-C). As statins also have pleiotropic effects adverse effects may occur. These effects may partly be desired. As a result such “adverse events” the risk of stroke can be lowered. This is shown in several statin studies which originally were planned to study the therapeutic effects on coronary heart disease. In principle, also a connection between stroke and LDL-C-level can be found. However previous studies could not prove effects to the extent that was shown for the use of statins in the prevention of coronary heart disease. As positive effects are proved the use of statins for specific primary prevention of cardiovascular diseases - as suggested in guidelines - is recommended. With regard to safety, statins - according to present knowledge - can be seen as safe as long as attention is paid to metabolism of each medicament in case of co-medication.

Diabetes mellitus type 2 is an important risk factor for the development of coronary heart disease. In general patients with diabetes mellitus type 2 should be treated as high risk patients and should take statins for lipid profile modification. Nevertheless, also when taking statins, the risk of suffering from coronary heart disease for patients with diabetes remains high. Regarding the prevention of osteoporosis study results are inconsistent. The use of statins in the primary prevention of osteoporosis cannot be recommended.

Large patient cohorts treated with statins show lower incidences of dementia in several reports. Moreover dementia was shown to be linked with lipid metabolism. However until now there is no direct proof that statins have positive effects in the prevention of dementia.

Economic assessment

The most important outcome parameters of cost-effectiveness-analysis - these are costs per life-years-gained or per quality-adjusted-life-years respectively - are compared. The term “life-years-gained” represents the number of years the treatment group outlives the control group. The term “costs per quality-adjusted-life-years” also takes into account the quality of the life-years gained.

Methods

Different search terms for statins, prevention and disease were linked with economic terms (such as cost-effectiveness, cost-benefit, economics, evaluation). At the end of the selection process eleven studies remained for the economic assessment and 26 studies were included as background literature.
Results

The economic evaluations, which were identified through the literature search, refer to the United States, Canada, the Netherlands, Great Britain and Belgium. For the calculation of the cost-effectiveness-ratio, different parameters were included in each study. Results for the cost-effectiveness of statins show a heterogeneous picture. The range of published cost-effectiveness values per life year gained in primary prevention varies from € 7800 (for the cheapest statin in Great Britain) to approximately € 51000 (on basis of a Dutch study which assumes rather low effectiveness). Overall agreement can be found that treatment of high risk groups is cost effective. For populations with lower coronary risk cost-effectiveness results are inhomogeneous and show a broad range. There was no cost-effectiveness study for Germany. A rough estimate was done to assess the future expenses in Germany in the case of an enlargement of the group of patients receiving statins to include low risk patients. At present costs of drugs per year per patient can be estimated to amount to € 460. When the group of patients receiving statins is extended to include patients with an annual coronary risk of one to three per cent (and assuming current drug prices) the annual statin drug budget of the social health insurance would increase by 50 to 80 % (which means additional expenses between € 700 millions and € 1.1 millions). However, the prices of statins are likely to decrease within the next years. For an exact estimation of the cost-effectiveness-ratio of statins in primary prevention in Germany a model calculation taking into account all relevant parameters would be necessary.

Ethical aspects

Methods

Only one relevant article could be found through the literature search (see above). In the discussion considerations and conclusions of the authors will be summarised.

Results

The above mentioned article addresses the problem of the lack of implementation of medical guidelines in routine clinical practice, as well as the ethical dilemma doctors face in the conflict between the commitment to care for the well-being of patients as best as possible and the pressure of cost saving.

Legal aspects

No relevant articles on legal aspects could be identified through the literature search. This report mainly focuses on the medical and economic assessment of the use of statins in primary prevention. Important legal aspects include questions of reimbursement or medical malpractice.

Discussion

Statins are efficacious and safe drugs for primary as well as for secondary prevention of coronary heart disease. However the potentials for the primary prevention of cardiovascular diseases shown in studies can be reached in routine practice only if the same compliance as in randomised controlled studies is achieved. Compliance (on the part of doctors as well as patients) is an
indispensable precondition for the success of primary preventive interventions.

There is a lack of current studies including relevant alternatives to statin-therapy, for example cost calculations per life year gained due to drug therapy compared with measures that imply counselling/education and diet modification. Moreover the economic studies do not give sufficient basic information and data to generalise their results. For an exact estimation of the cost-effectiveness-ratio of statins in primary prevention in Germany a model calculation using current statin prices and taking into account all relevant parameters like valid epidemiologic and economic data would be necessary.

Regarding ethical consideration three issues arise - the selection of patients (for which patient groups statin treatment should be recommended?), the decision dilemma of doctors between delivering high standard care and the pressure of cost saving and the problem of insufficient compliance (should it be accepted as inherent to the system?). Patients that have no inherited cardiovascular risk factors would not need lipid lowering drugs when realising recommended lifestyle changes. Measures that aim at lifestyle changes moreover are much less expensive than drug therapy. Therefore the question arises if statins should be referred to as “lifestyle medicine”.

Statin treatment in primary prevention means that patients have to be treated for several years. The question arises if it can be expected of healthy individuals to undergo such kind of long term therapy or to what extent this therapy will be accepted by the patient. Nevertheless the issue of compliance arises with regard to (long term) drug therapy as well as with regard to lifestyle changes.

Conclusion

According to current standard of knowledge the use of statins as suggested in guidelines is recommended for specific primary prevention of cardiovascular diseases.

The use of statins for the primary prevention of stroke cannot be recommended at present. Also no recommendations can be made regarding statin therapy for the primary prevention of Alzheimer’s disease or osteoporosis. Compliance regarding all involved actors in the health care system is one of the most important issues. A systematic approach has to be chosen to undermine excessive and inappropriate subscriptions in daily practice and optimize the use of statins. Within this context it is important, that the "right" person gets the "right" medicine.

Regarding the economic perspective published cost-effectiveness-analyses show a heterogeneous picture. The broad range of different assumptions and methodological approaches as well as differences between countries make comparison difficult. For an exact estimation of the cost-effectiveness-ratio of statins in primary prevention in Germany a model calculation taking into account all relevant parameters would be necessary. From the economic point of view monitoring of current statin utilisation - with the aim of a more targeted use - should be prior to an enlargement of the number of recipients.