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Cardiovascular drugs and their ecotoxic effect: a systematic review about garlic as a potential antihypertensive.

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Introduction

Cardiovascular diseases (CVDs) are a group of diseases in which the heart or blood vessels are affected and not functioning properly, such as; heart failure, heart arrhythmias, coronary heart disease and many more implications. Each year around 17.9 million people die from cardiovascular diseases, making it the leading cause of death globally [7]. There is an upward trend in the prevalence of cardiovascular disease and it is estimated that by 2030, 31.7% of all deaths globally will be accountable to cardiovascular diseases [31]. With the rise of the prevalence of cardiovascular diseases, there is also a proportional incline in the use of cardiovascular drugs. 24.5% of the top 200 most prescribed drugs in the United States are cardiovascular medicines [34]. However, with the upsurge of the cardiovascular drugs usage comes another problem; their ecotoxic effect. There is an upward trend in the occurrence of medical waste resulting from cardiovascular drugs in the environment. Cardiovascular drugs are detected in surface waters, reaching up to hundreds of nanograms per liter and in wastewaters concentrations up to a few micrograms per liter are reached. This has a toxic effect on the aquatic organisms resulting in alternations in cardiac physiology and impaired growth, reproduction and lipid metabolism [34]. Cardiovascular drugs are prescribed in large volumes and it is important to get an insight in the drug's indications and pharmacokinetics and their corresponding effect on the ecotoxicity. Therefore, in this thesis this problem regarding the ecotoxic effect of the medical waste of cardiovascular drugs will be more elaborated and will include a systematic review about garlic as a potential blood pressure lowering agent.

ADME criteria for cardiovascular drugs

ADME, which stands for absorption, distribution, metabolism and excretion is a common abbreviation used in pharmacokinetics. These four different parameters are important to understand the effect of a pharmaceutical compound, since by looking at the ADME properties of a drug, the efficacy and safety of a drug can be determined because the four criteria determine the exposure of the drug to the tissue. There are many different types of cardiovascular medicines since there are a lot of different indications. The most common cardiovascular medicines are [35]:

- Anticoagulants (Warfarin&Heparin)
- Diuretics (furosemide)
- Angiotensin-converting enzyme (ACE) inhibitors (lisinopril, enalapril, and benazepril)
- Angiotensin receptor blockers (losartan, candesartan, valsartan)
- beta blockers (bisoprolol, carvedilol, metoprolol)
- Calcium channel blockers (amlodipine, felodipine, lacidipine)
- Antiplatelet medications (aspirin)
- Digoxin

In appendix 1, the ADME criteria for these drugs are displayed.
When looking at all the different drugs in appendix 1, it immediately stands out that a huge proportion of these drugs are cleared renally or via the feces. Therefore, these drugs might end up in the sewerage and may therefore possibly show ecotoxic effects, if present in high concentrations, which should be prevented since this will affect the aquatic wildlife.

Indications and who uses these drugs

Cardiovascular disease is a general term for conditions in which the heart or blood vessels are affected and not functioning properly. There are many different types of CVD with different indications. Therefore, there are myriad different classes of drugs with different mechanisms of actions to treat these particular indications, In the table 1 below, an overview can be seen of the most common medical interventions in CVD and their specific indications. [35]

Drug	Indication
Warfarin	Used for preventive and treatment purposes regarding atrial fibrillation, cardiac vale replacement and used as complementary treatment to reduce mortality, myocardial infarcts and thromboembolic events after a myocardial infarction [10]
Heparin	Used for preventive purposes for embolism in patients suffering from atrial fibrillation and as complementary antithrombin treatment for unstable angina and myocardial infarctions. Also used to prevent the clotting process to happen during surgery [10]
Furosemide	As monotherapy used to treat mild or moderate hypertension. Used as combination therapy for severe hypertensive patients [10]
Lisinopril	Used for treatment of patients suffering from acute myocardial infarction, hypertensive patients (6 years or older) and as a complementary treatment for heart failure. In combination with hydrochlorothiazide, it is used to treat hypertension [10]
Enalapril	Used as monotherapy or as combination therapy for the management of either essential of renovascular hypertension, heart failure and used as preventive treatment of symptomatic heart failure in the case of an asymptomatic left ventricle dysfunction [36]
Benazepril	Used for the treatment for hypertension as monotherapy or in combination with thiazide diuretics [10]
Losartan	Used to treat hypertension in hypertensive patients older than 6 years and to reduce the risk of stroke in patients suffering from hypertension and left ventricular hypertrophy. Often used in combination with hydrochlorothiazide [10]
Candesartan	Used as treatment for hypertensive adults and children from 1-16 years old. It can be used as monotherapy or in combination with other antihypertensives. [6]

Valsartan	Used to treat hypertension to reduce strokes and myocardial infarcts. Also used as medication after a heart attack has occurred to lower the risk of dying [19]
Bisoprolol	Used as monotherapy or in combination with other medication to treat mild to moderate hypertensive patients and is also used to prevent strokes and heart attacks, atrial fibrillation and angina pectoris [10]
Carvedilol	Used to treat mild or severe heart failure, hypertension and dysfunction of the left ventricle [10]
Metoprolol	Used to treat heart failure, myocardial infarction, angina pectoris, hypertension and atrial fibrillations. [10]
Amlodipine	Used as monotherapy or in combination therapy with other hypertensives to treat hypertension, coronary artery disease, angina pectoris [10]
Felodipine	Used to treat mild to moderate hypertensive patients.
Lacidipine	Used as monotherapy or in combination with b-blockers, angiotensin converting enzyme inhibitors and diuretics to treat hypertension [10]
Aspirin	Used as treatment to reduce pain in various conditions. However, it is also used in the treatment of myocardial infarction since it can inhibit the aggregation of platelets [10]
digoxin	Used to treat mild to moderate heart failure in adults and is used in children with heart failure to improve the myocardial contractions [10]

Table 1.Indications for the most common prescribed cardiovascular drugs per class. Anticoagulants (warfarin & Heparin); diuretics (Furosemide); Angiotensin-converting inhibitors (lisinopril, enalapril, benazepril); Angiotensin receptor blockers (losartan, candesartan, valsartan); beta blockers (bisoprolol, carvedilol, metoprolol); Calcium Channel blockers (amlodipine, felodipine, lacidipine); Antiplatelet medication (Aspirin); Digoxin

As can be seen in table 1, there are many different intervention types for specific indications. There are prescription guidelines for the primary treatment of cardiovascular disease formed so that cardiovascular events are being prevented from occurring. These guidelines are formed and followed by clinicians so that patients are treated in the best way possible. These guidelines will also take possible comorbidities of the patients, their age, vulnerability, motivation and possible lifestyle changes into account in the treatment plan [22]. There are standard European guidelines however these guidelines may differ per country. Therefore, the Dutch prescription guideline and the European guideline in the prevention for cardiovascular disease will be summarized and the possible differences between the guidelines will be elaborated.

Dutch prescription guideline cardiovascular disease

According to the Dutch prescription guideline for hypertension, there are several steps followed in the medical treatment of hypertension. **Step 1a** includes the treatment with an Angiotensin converting enzyme (ACE) inhibitor such as enalapril or lisinopril. ACE-inhibitors have the highest preference due to their low costs. Subjects with an impaired renal function (glomerular filtration rate between 10-50 ml/min/1.73m^2) should receive an adjusted dose determined by the clinician. **Step 1b** involves the treatment of an angiotensin receptor blocker since it causes less often coughing problems compared to ACE-inhibitors. Telmisartan, Candesartan, Losartan or Valsartan are the prescribed interventions. There is no need to adjust the dose in the case of a glomerular filtration rate higher than 10ml/min/1.73m^2. **Step 1c** is covered by the treatment with calcium antagonists such as amlodipine or lercanidipine, these are the preferred calcium antagonist due to their lower cost in comparison with other calcium antagonists. In Subjects with atrial fibrillation, Diltiazem or Verapamil are prescribed. Calcium antagonists should not be administered to patients with heart failure. **Step 1d** involves the use of thiazide diuretics such as hydrochlorothiazide or chlortalidone. Preferably, patients that suffered from gout or skin cancers like basal cell or squamous cell carcinoma should not be treated with thiazide diuretics. Thiazides may cause photosensitive reactions and therefore it is advised to pay attention for the amount of exposure to sunlight. **Step 1e** implicates the treatment with beta blockers. Metoprolol succinate, atenolol and bisoprolol are the preferred beta blockers by reason of their lower costs. Beta blockers should not be prescribed in patients who have an elevated risk on developing diabetes, which is the case in obese subjects and beta blockers should also not be the drug of choice in patients with elevated glucose levels. In table 2, all the different treatment steps regarding step 1 and their used medicines and dose according to the Dutch NHG standard CVRM (2019) are presented. [22]

STEP	Prescribed Interventions and dose
1a (ACE-inhibitors)	• Enalapril 1dd 10 mg (elderly 5 mg), • Lisinopril 1 dd 10 mg (elderly 5 mg) • Perindopril 1 dd 4 mg(elderly 2 mg) • Ramipril 1 dd 2.5 mg (elderly 1.25mg)
1b (Angiotensin receptor blockers)	• Telmisartan 1 dd 40 mg (elderly 20 mg) • Candesartan 1 dd 8 mg (elderly 4 mg) • Losartan 1 dd 50 mg (elderly 25 mg) • Valsartan 1 dd 80 mg (elderly 40 mg)
1c (Calcium antagonist)	• Amlodipine 1 dd 5 mg • Lercanidipine 1 dd 10 mg In patients with atrial fibrillation: • Diltiazem mga 1 dd 200 mg • Verapamil mga 1 dd 120 mg.
1d (Thiazide diuretics)	• Hydrochlorothiazide 1 dd 12,5 mg • Chlorthalidone 1 dd 12,5 mg
1e (Betablockers)	• Metoprolol succinate mga 1 dd 50 mg • Atenolol 1 dd 25 mg • Bisoprolol 1 dd 5 mg

Table2.. Used medicines in the first step treatment plan and their corresponding doses according to the Dutch NHG standard CVRM. [22]

Steps 1a till 1e are all approximately equal in the effectivity to lower the blood pressure in hypertensives. However, there are specific situations in which there are preferred interventions to lower the blood pressure, these specific situations are listed below in table 3.

Situation	Preferred intervention(s)
Elevated albuminuria levels (>3 mg/mmol albumin/creatine)	ACE-inhibitors/Angiotensin receptor blockers
Earlier occurrence of a myocardial infarction/ coronary art disease	Betablockers, ACE inhibitors/Angiotensin receptor blockers
Angina Pectoris	Betablockers, calcium antagonists
Heart failure	Angiotensin receptor blockers/ ACE-inhibitors, Betablockers, diuretics, Aldosterone antagonists
Atrium fibrillations	Betablockers, Calcium channel blockers, ACE-inhibitors/Angiotensin receptor blockers, Aldosterone antagonists
Peripheral arterial disease	ACE-inhibitors
Diabetes mellitus	ACE-inhibitors/Angiotensin receptor blockers
Patients with a West- or South -African heritage	Diuretics and Calcium antagonists
Pregnancy	Methyldopa, Labetalol (mixed alpha and beta blocker), Calcium antagonists

Table 3. Preferred intervention guideline in specific situations according to the Dutch NHG standard CVRM (2019) [22]

Step 2 will be used If the interventions from step 1a till 1e are not capable to lower to blood pressure sufficiently. Step 2 concerns combination therapy of two and if needed three different class of drugs, which are listed in step 1a till 1e, so that the blood pressure will be lowered more effectively. Some combinations between the different drugs classes are not recommended since side effects may occur. Betablockers and diuretics are not combined since there is a risk of developing Diabetes Mellitus. ACE-inhibitors and Angiotensin receptor blockers are also not prescribed together since there is an elevated risk in developing kidney failure. If ACE-inhibitors or Angiotensin receptor antagonists are used simultaneously with a diuretic, halve the starting dose or when possible, interrupt the use of the diuretics 2- 3 days in advance before starting with the combination treatment with ACE-inhibitors or Angiotensin receptor antagonists. The use of a combination drug, which include multiple active ingredients can also enhance the patients' compliance in the combination therapy.
Two weeks after the start of the combination therapy, the blood pressure and possible side effects should be evaluated. If the treatment of the combination therapy has an insufficient effect, reconsider the possible secondary causes of the elevated blood pressure like an unhealthy diet or insufficient exercise. If this does not result in a possible way to lower the blood pressure, add another intervention from step 1a till 1e.

If after step 2, the desired effect is still not reached, the doses are elevated in step 3.
The dosages of the interventions from step 1 are increased in small proportions, every two to four weeks until the maximum dose has been reached. The maximum dose of each drug is listed below in table 4.

STEP	Prescribed Interventions and dose
1a (ACE-inhibitors)	• Enalapril 1dd 40 mg (elderly 5 mg), • Lisinopril 1 dd 80 mg (elderly 5 mg) • Perindopril 1 dd 8 mg(elderly 2 mg) • Ramipril 1 dd 10 mg (elderly 1.25mg)
1b (Angiotensin receptor blockers)	• Telmisartan 1 dd 80 mg (elderly 20 mg) • Candesartan 1 dd 32 mg (elderly 4 mg) • Losartan 1 dd 100mg (elderly 25 mg) • Valsartan 1 dd 320 mg (elderly 40 mg)
1c (Calcium antagonist)	• Amlodipine 1 dd 10 mg • Lercanidipine 1 dd 20 mg In patients with atrial fibrillation: • Diltiazem mga 1 dd 400 mg • Verapamil mga 2 dd 240mg.
1d (Thiazide diuretics)	• Hydrochlorothiazide 1 dd 25 mg • Chlorthalidone 1 dd 25 mg
1e (Betablockers)	• Metoprolol succinate mga 1 dd 200 mg • Atenolol 1 dd 100 mg • Bisoprolol 1 dd 20mg

Table 4.. The maximum dose of the used medicines according to the Dutch NHG standard CVRM. [22]

European prescription guideline for cardiovascular disease

According to the European guideline for cardiovascular disease treatment, the preferred drugs for the treatment of hypertension are thiazide like diuretics, Beta blockers, calcium antagonists, ACE-inhibitors and angiotensin receptor blockers are the preferred classes of blood pressure lowering drugs. The use of Beta blockers may induce side effects like an increase in weight, affect the lipid metabolism and will lead to an elevated risk in developing diabetes. Therefore, this is not a first-choice treatment in patients with several metabolic risk factors and in patients that have a higher risk in developing diabetes. Thiazides Diuretics may also induce the chance of developing diabetes and therefore, combination of diuretics and Beta blockers is not preferred according to the European prescription guidelines. Drugs that have a longer duration of action are preferer since the patients' compliance will increase. The use long-acting antihypertensive drugs will also result in a more constant blood pressure with less variability in the blood pressure and therefore the chance of cardiovascular events to happen, will decrease. There five different classes of drugs (Betablocker, calcium antagonist, thiazide diuretics, ACE-inhibitors and Angiotensin like receptor blockers) are all effective in lowering the blood pressure. However, there are some specific conditions in which some drugs are the preferred choice according to the European prescription guideline for cardiovascular disease. An overview of these specific conditions can be seen in table 5 below. [24]

Situation	Preferred intervention(s)
Left-ventricular hypertrophy	ACE-inhibitors, Angiotensin receptor blockers, Calcium antagonists.
Asymptomatic atherosclerosis	Calcium antagonists, ACE-inhibitors
Microalbuminuria	ACE-inhibitors, Angiotensin receptor blockers
Renal dysfunction	ACE-inhibitors, Angiotensin receptor blockers
Earlier occurrence of a Myocardial Infarction	ACE-inhibitors, Betablockers, Angiotensin receptor blockers
Angina pectoris	Betablockers, Calcium antagonists
Heart failure	Diuretics , Betablockers, ACE-inhibitors, Angiotensin receptor blockers, mineralocorticoid receptor antagonists
Aortic aneurysm	Betablockers
Atrial fibrillation: prevention	Angiotensin receptor blockers, ACE-inhibitors, Betablockers, mineralocorticoid receptor antagonists
Atrial fibrillation: rate control	Betablockers, Calcium antagonists
Proteinuria	ACE-inhibitors, Angiotensin receptor blockers
Peripheral artery disease	ACE-inhibitors, Calcium antagonists
Diabetes mellitus	ACE-inhibitors, Angiotensin receptor blockers
Pregnancy	Methyldopa, Betablockers, calcium antagonists
Black individuals	Diuretic, calcium antagonists

Table 5. Preferred intervention guideline in specific situations according to the European guidelines on cardiovascular disease prevention [24]

If medication with one of the preferred drugs classes (thiazide like diuretics, Beta blockers, calcium antagonists, ACE-inhibitors and angiotensin receptor blockers) is not efficacious enough, combination treatment is induced by adding a drug from another class unless side effects do occur or the blood pressure is not lowered more upon addition the second drug. Combination therapy is induced first before elevating the doses since the combination therapy of two drugs is more effective than doubling the dose of a single drug. The combination of a beta blocker and a Diuretic should be avoided where possible since it will induce Diabetes Mellitus. The combination of an ACE-inhibitor and an Angiotensin receptor blocker is also not recommended. 15-20% of patients with hypertension are treated with a combination treatment consisting of three different drugs to control the blood pressure. To increase the patients' compliance, it is favored to add all the three different active ingredients to a single formulation so that the number of pills taken daily will be lower. The most prescribed three combination formulation contains a Renin-angiotensin system blocker with a calcium antagonist and a diuretic combined [24]

Both the Dutch and the European prescription guidelines do use the same classes of drugs as first line treatment for hypertension (thiazide like diuretics, Beta blockers, calcium antagonists, ACE-inhibitors and angiotensin receptor blockers). Unlike the European guideline, does the Dutch guideline state which drugs from the several classes are used and their corresponding dose. The European guideline does not contain this information. A possible reason could be the fact that it may differ per European country which drugs exactly are used and therefore this is not included in the European guideline that precisely. Both guidelines did contain information about the preferred intervention given in specific situations, which can be seen in table 4 and 6. What can be seen from this is the fact that the special situations stated in the Dutch guideline, were all present in the European guideline. However, the European guideline did contain special situations like left-ventricle hypertrophy, asymptomatic atherosclerosis, renal dysfunction, aortic aneurysm and proteinuria for which the Dutch guideline does not have a preferred intervention present for. The rest of the listed special situations from the European guideline were also present in the Dutch guidelines and the preferred interventions per situation were almost the same. The only difference between the two guidelines is that for peripheral artery disease, the European guideline preferers the use of an ACE-inhibitor or a calcium antagonist and the Dutch guideline does only prescribe an ACE-inhibitor in this situation. Both guidelines include the use of combination therapy if the therapy with one active substance does not yield the preferred efficacy. In both guidelines, the combination of a beta blocker and a diuretic and the combination of an ACE-inhibitor and an Angiotensin receptor blocker are not recommended. So, there are some small differences between the two different guidelines but broadly speaking, these guidelines are almost the same in the choice for preferred interventions.

Personalized medicine

By looking deeper into the genetic profile of patients, differences in the patients will be highlighted and on the basis of this genetic profile decisions can be made to make the treatment the most efficacious. By making personalized drugs, the chance of adverse drug events to occur will diminish. These drugs can be personalized by looking at the patient's genetic information by for instance looking at the genomic sequences in their body. There are general prescription guidelines for the treatment of cardiovascular disease however there might be some special cases in which the standard treatments according to these guidelines are not effective and the use of personalized medicine will lead to a more efficacious and safe treatment for the patient which will more prevent adverse drug reactions to occur, which is the United States' fourth leading cause of hospitalization[16]. According to the Dutch and European prescription guidelines for the treatment for cardiovascular disease, the first step consists of the use of an antihypertensive of choice and when not effective, combinations of different antihypertensive drugs are recommended before increasing the doses. By implementing personalized medicine, the quantity of cardiovascular drugs prescribed according to these guidelines will decrease, since the treatment will be more efficacious due to personalized perspectives and therefore the amount of medical waste regarding the use of cardiovascular drugs will decrease even as their ecotoxic effect.

Prevent the use of Cardiovascular drugs

By implementing several lifestyle adjustments, the chance of occurrence of cardiovascular diseases will decrease and therefore also the need of usage of cardiovascular drugs will be lowered and their ecotoxic effect as well. The four most important lifestyle adjustments are; Not smoking, sufficiently exercising, maintaining a healthy bodyweight and following a healthy diet. Living by these rules will lower the chance of developing cardiovascular disease and therefore the use of cardiovascular drugs can be prevented which will is beneficial for the environment. From all these four lifestyle adjustments, smoking has the biggest negative impact on the body's cardiovascular health status. People that smoke almost have a two times higher risk of getting coronary disease and a ten times higher risk of getting peripheral artery disease. People that tend to smoke are also more vulnerable for developing arrhythmias, stroke, loss of left ventricular function, heart failure and cardiac death [5].
Nutrition choices are also a very important factor in the chances of developing cardiovascular disease. The ultimate diet for the prevention of heart disease should contain a lot of fruits, vegetables, nuts, chicken, whole grains, and vegetable oils and does not include a lot of alcohol, red meats, products high in sugar, sodium and trans-fats [14].
The chances of developing cardiovascular disease in people who follow this diet are 50% lower in comparison with people that tend to follow a western diet containing a lot of red or processed meats, refined grains, milk products and a lot of sugar [5].
Saturated fats do affect the blood vascular system in comparison with unsaturated fats and the intake of saturated fats will result in an increased cholesterol levels which will lead to an elevated chance of developing cardiovascular disease. By eating less salt and more foods high in potassium, the risk of developing cardiovascular disease is lowered [14] and therefore also the use of cardiovascular drugs will be prevented. Sufficient physical activity is very important. Physical inactivity has an increase in risk of 45% for the development of coronary art disease, stroke 60% and it results in a 30% more likelihood to develop hypertension. Activities with a moderate intensity are associated with a decline of 26% in the risk of developing cardiovascular disease and high intensity activities will result in a decline of 42% in the risk of developing cardiovascular disease [5]. By implementing sufficient physical activity in the daily life and following a healthy diet, a healthy bodyweight can be achieved. Overweight persons will have an increased chance of getting cardiovascular diseases since they may have higher levels of cholesterol and triglyceride, a higher blood pressure and diabetes [17]. Thus, it is very important to life by a healthy lifestyle and if needed perform lifestyle corrections according to these four factors so that the chance of developing cardiovascular disease will be lowered and thus the use of cardiovascular drugs can be prevented and their ecotoxic effect will be lowered.

Systematic research: Garlic as Green Alternative for Cardiovascular drugs.

Introduction

With the increasing prevalence of cardiovascular disease, the usage of cardiovascular drugs will increase and therefore the ecotoxic effect of these drugs will also increase in the future which will affect the aquatic wildlife. By looking at potential green alternatives, the utilization of cardiovascular drugs might decrease which will lower the environmental damage. There are several natural products with potential antihypertensive effects like fish oil, garlic, hawthorn, olive oil vitamins and minerals and many more [33]. Garlic is one of the most widely used supplements and it may be a promising agent for reducing blood pressure, however the evidence is still limited [21]. In this systematic research, the blood lowering effect of garlic will be assessed and the research question is as follows:
“ What is the evidence for the effect of garlic as blood pressure lowering medication?’’

Methods

Search Strategy

Systematic Research was conducted by using PubMed to look for randomized controlled trials and meta-analysis that did investigate the effect of garlic on the Blood pressure. In the PubMed database was searched with the use of MESH headings, which were as follows: ‘’GARLIC’’, ‘’HYPERTENSION’’ and ‘’BLOODPRESSURE’’. The studies that are included did meet the following criteria: the effect of garlic on the blood pressure is assessed in the study, the intervention did only consist out of garlic and this was compared to a placebo and other cardiovascular drugs, and if the studies were randomized and did contain blood pressure data obtained in human trials.

Search Results

The indicated search strategy did lead to the retrieval of three meta-analysis and two Randomized controlled trials, which were not included in the meta-analysis.

Results

See figure 1, for the flowchart which gives an overview of the search results and the excluded studies and the final studies included in this systematic research.

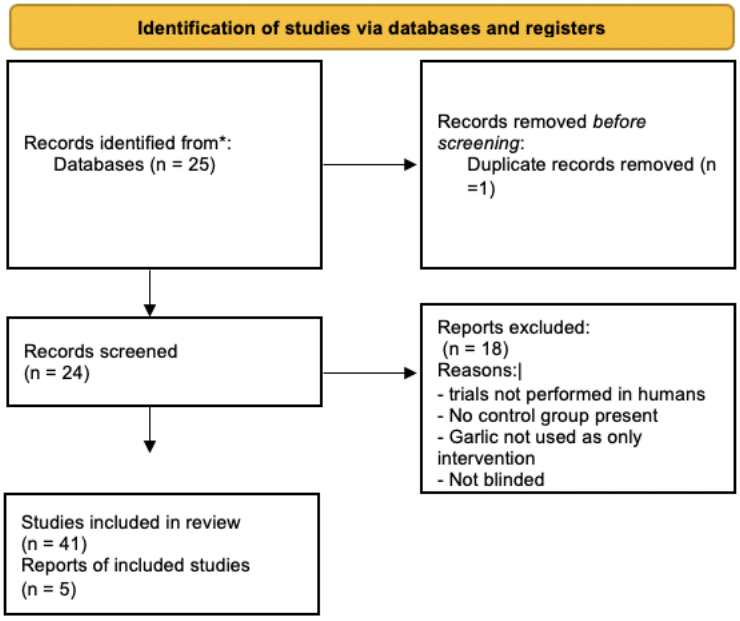

Figure 1. Flow chart systematic research

The first meta-analysis performed by Reid et al, did include 20 trials with garlic-only interventions and a placebo control group that did mention the mean systolic blood pressure, the diastolic blood pressure and corresponding standard derivatives. The outcome of the Meta-analysis is that garlic supplements do lower the systolic blood pressure with a mean difference of 5.1±2.2. mm Hg and the diastolic blood pressure is lowered by a mean difference of 2.6 ± 1.6 mm Hg. After performing subgroup meta-analysis of trials in which the subjects at the start of the treatment were hypertensive or normotensive, a bigger decrease in both the systolic and diastolic blood pressure was observed. For the systolic blood pressure, a decrease of 8.7 ± 2.2 mm Hg was reached after performing subgroup analysis and for the diastolic blood pressure a decrease of 6.1 ± 1.3. mm Hg [25].
The second meta-analysis performed by Wang et al, did include 17 studies and consisted of a total number of patients of 1534 of which 799 in the diastolic blood pressure arm and 735 in the systolic blood pressure arm. According to the analysis, garlic is able to reduce the systolic blood pressure by 3.75 mm Hg in comparison with the control group. Garlic showed to be also more effective in lowering the diastolic blood pressure in comparison with the control group, a reduction of 3.39 mm Hg was observed. Quality evaluation of the included trials was performed by Hang et al. and after the removal of the low-quality trials, a systolic blood pressure reduction of 3.85 mm Hg and a diastolic blood pressure reduction of 1.59 mm Hg were observed. Wang et al. did also perform subgroup analysis in hypertensive and normotensive subjects. This resulted in a systolic blood pressure reduction of 4.4 mm Hg and a diastolic blood pressure reduction of 2.68 mm Hg in hypertensive subjects. Subgroup analysis in normotensive subjects did not results in a noteworthy reduction in both diastolic

and systolic blood pressure between the garlic intervention group and the control group. Wang et al. did also evaluate the dose-response relationship and a maximum antihypertensive effect was obtained with a daily intake of 480 mg garlic after 12 weeks [32]

The third study, Stabler et al. did include two studies in which the effect of a triple daily intake of 200 mg garlic on the blood pressure was determined in comparison with a placebo group. The first included study did only contain 47 hypertensives and a mean systolic reduction of 12 mm Hg was observed and a 9 mm Hg mean reduction for the diastolic blood pressure. In the second study included, the number of people per intervention group was not mentioned but a mean reduction in the systolic blood pressure of 10-11 mm Hg and a reduction of the diastolic blood pressure of 6-8 mm Hg in comparison with the placebo group were observed [30].

Ashraf et al. studied the effect of different doses of garlic on systolic and diastolic blood pressure in hypertensives. A total of 192 Subjects were divided in groups and were administered either 300 mg, 600 mg, 900 mg, 1200 mg , 1500 mg garlic or placebo or 100 mg atenolol (Betablocker) once per day for 24 weeks. In table 7 below, the changes in systolic blood pressure between each intervention group can be seen after 12 and 24 weeks.

Intervention	Week 0	Week 12	Week 24
300 mg Garlic	145.0 ± 0.706	143.4±0.669	142.7±0,644
600 mg Garlic	145.3± 0.792	143.6±0.645	141.0 ±0.577
900 mg Garlic	145.0 ±0.800	141.8±0.706	138.9±0.569
1200 mg Garlic	143.9±0.818	140.8±0.811	137.2±0.861
1500 mg Garlic	145.2±0679	141.6±0.696	137.6±0.587
Atenolol 100 mg	147.8±0.898	139.3±0.896	138.6±0.815
Placebo	130.9±0.892	129.7±0.944	130.7±0.850

Table 7. Changes in systolic blood pressure after 0, 12 and 24 weeks in groups given different doses of garlic, atenolol or placebo [2].

As can be seen in table 7, the groups that were given garlic did all show a significant drop in systolic blood pressure after 0 , 12 and 24 weeks in comparison with the placebo group. In the groups that are given higher doses of garlic(900mg,1200mg,1500mg), a higher reduction in systolic blood pressure was observed. In table 8 below, the changes in diastolic blood pressure between each intervention group can be seen after 12 and 24 weeks.

Intervention	Week 0	Week 12	Week 24
300 mg Garlic	93.15 ± 0.543	91.89±0.540	91.70±0.514
600 mg Garlic	93.11± 0.521	91.74±0.390	89.74 ±0.370
900 mg Garlic	92.79±0.515	90.00±0.617	88,63±0.512
1200 mg Garlic	92.97±0.494	89.75±0.457	86.70±0.598
1500 mg Garlic	91.93±0.446	89.59±0.370	86.96±0.454
Atenolol 100 mg	98.26±0.657	92.04±0.561	89.15±0.494
Placebo	94.33±0.430	95.26±0.418	95.37±0.221

Table 8. Changes in diastolic blood pressure after 0, 12 and 24 weeks in groups given different doses of garlic, atenolol or placebo [2].

As can be seen in table 8, the groups that were given garlic did all show a significant drop in diastolic blood pressure after 0, 12 and 24 weeks in comparison with the placebo group. In the groups that are given higher doses of garlic(900mg,1200mg,1500mg) , a higher reduction in diastolic blood pressure can be been seen. The garlic interventions used, showed a significant and similar reduction in the systolic as diastolic blood pressure in comparison with Atenolol after 12 and 24 weeks [2].

A randomized placebo-controlled trial by Reid et al. Assesses the effect of aged garlic extract on central blood pressure and stiffness of the arteries, which are both, important risk factors for cardiovascular disease. 88 hypertensive subjects did undergo a 12 week during trial in which every day 1.2g aged garlic extract or a placebo was taken. A significant reduction of the systolic blood pressure by 5.0 ± 2.1 mm Hg was observed in comparison to placebo and for the diastolic blood pressure, a reduction of 6.3 ±1.1mm Hg was reached. Subgroup analysis was performed by dividing the subjects into responders and non-responders. A subject was considered as a responder as after garlic treatment, a reduction by more than 3% in systolic or diastolic blood pressure was obtained. After subgroup analysis, in responders a systolic reduction of 11.5 ±1.5 mm Hg and a diastolic reduction of 6.3±1.1. mmHg was observed in comparison to placebo [26].

Discussion

The meta-analysis of Reid et al. indicated that garlic supplements are effective in lowering both the systolic and diastolic blood pressure. The meta-analysis did only include placebo controlled studies that used garlic supplements and reported the mean systolic and diastolic blood pressures and their corresponding standard derivates, from 2008 till 2013. . A strongpoint for this meta-analysis is that it only included placebo-controlled studies so that the efficacy of the garlic treatment could be tested. A downside of this performed meta-analysis is the fact that it is not stated clearly what type of subjects are used, think of age, gender, origin and possible comorbidities were not mentioned. Furthermore, the meta-analysis included different types of garlic supplements namely garlic powder, garlic oil, garlic extract and Japanese powder containing egg yolk. All these different types of garlic supplements could have a different effect on the blood pressure and therefore the determined reduced mean diastolic and systolic blood pressure is a mean value for all these different types of garlic supplements, which is not that accurately since the this could differ between the different types of supplements. Some of the included studies did not report how and by who and how often the blood pressure was measured in the trials, which could have affected the outcomes: A clinician can measure the blood pressure more accurately and if the blood pressure is only measured once instead of taking the mean of multiple measures, there could be measurement bias. After performing subgroup analysis, by classifying the subjects in group of hypertensives or normotensives, a higher reduction in both the systolic and diastolic blood pressure was reached in hypertensives and no significant effect in blood pressure reduction in normotensives was revealed. The meta-analysis performed by Wang et al. showed similar results: a reduction in both the systolic and diastolic blood pressure was caused by the use of garlic in comparison with the placebo group. The meta-analysis did include only randomized controlled trials that investigated the association of the intake of garlic and the blood pressure, so the patients were randomized in either the placebo or intervention group and therefore observer bias was prevented. In this meta-analysis, A Begg rank correlation test and Egger linear regression test were performed to asses that there was no publication bias concerning the use of garlic in relation to blood pressure. A limitation of this meta-analysis is the fact that in some studies that were included, patients were already treated with antihypertensive medicine and when these patients were also given garlic, this may have had an influence on the antihypertensive effect of garlic The trials included in this analysis did also show different garlic supplements used as intervention like garlic powder, extract and oil, which may all affect the blood pressure differently. Some of the included trials did also not describe the process of how and by who the blood pressure was measured precisely, which can lead to bias. There was also no exclusion of subjects with comorbidities, so therefore the blood pressure lowering effects of garlic in these patients may differ, so there is a chance that also here, some bias may have occurred. Heterogeneity did occur and therefore Wang et al. excluded the low-quality trials and this yielded the same outcome, a reduction in both the systolic and diastolic blood pressure and after excluding the low-quality trials, no heterogeneity was found any more. Wang et al. also performed sub-group analysis to check for a difference in the effect of garlic in normotensives and hypertensives. The outcome of the subgroup analysis gave rise to the fact that garlic is effective in lowering the systolic and diastolic blood pressure in hypertensives but no noteworthy reduction in blood pressure in normotensives was found. The outcome of these subgroup analysis is advantageous since garlic only lowers the systolic and diastolic blood pressure in hypertensives and not in normotensives and thus it is more unlikely the use of garlic will result in hypotension in normotensive subjects. Wang et al. did also evaluate the dose-response relationship and a maximum antihypertensive effect was obtained with a daily intake of 480 mg garlic after 12

weeks. The third meta-analysis performed by Stabler et al. did include two studies and also here, blood pressure (systolic and diastolic) reduction did occur upon a three times daily administration of 200 mg garlic in comparison with a placebo group. The included participants were at least 18 years and were diagnosed with primary hypertension. A strongside of this study is that the fact that the participants that were during the trial treated with other hypertensives, were all placed in groups according to their additional therapy. So, people that already took for instance propranolol, were placed in groups with others that also received propranolol. A downside of this performed meta-analysis is the fact that for the first included study, only 47 subjects were used and for the second study included, the number of participants was not mentioned. Another limitation in this study is that there was no assessment of heterogeneity performed. The blinded, placebo-controlled trial performed by Ashraf et al. evaluated the effect of different daily doses of garlic, in comparison with a placebo and a betablocker (Atenolol) on the systolic and diastolic blood pressure in hypertensives. The setup of the trial was single-blind, placebo-controlled trial performed in patients from both sexes in the age rand from 20 till 70 years old with newly diagnosed stage 1 hypertension. The trial was conducted in different primary health care centers located in Karachi, but due to the different locations, there might be alternations in the conduction of the trial per location and thus, there might be some bias involved. For both the systolic and diastolic blood pressure, all groups that were given garlic did show a decrease in blood pressure after 12 and 24 weeks. A significantly higher drop in both the systolic and diastolic blood pressure were found in the groups that were given a higher dose of garlic. A strongpoint from this study is the comparison with a used antihypertensive. The different doses of garlic supplementation did show similar results in comparison with Atenolol in lowering both the systolic and diastolic blood pressure. The randomized placebo-controlled trial by Reid et al. did evaluate the effect of aged garlic extract on the blood pressure and the outcomes are also in accordance, a reduction in blood pressure was established however, there were some subjects that did not respond to the intake of aged garlic extract. Therefore, Reid et al. performed sub-group analysis by dividing the subjects into responders and non-responders. The outcome of the subgroup analysis was an even more significant decrease in both the systolic and diastolic blood pressure in responders in comparison to placebo.
Garlic has shown to have antihypertensive effects and is effective in reducing the both the systolic and diastolic blood pressure. The anti-hypertensive effect of garlic is only significantly present in subjects with existing hypertension, which can be seen as an advantage. The dose-response evaluations of garlic have shown that in higher dosages administered, the blood pressure is lowered more significantly. A comparison has been made with the use of garlic as antihypertensive in comparison with Atenolol, and no clear differences in blood pressure reduction were indicated. Therefore, it can be stated that garlic shows a lot of potential in lowering the blood pressure and can be seen as a potential green alternative for cardiovascular drugs. However, more research should be conducted in which garlic is compared to more antihypertensive drugs, so that the efficacy can be more relatively assessed and a conclusion can be drawn whether garlic may be a suitable green alternative for cardiovascular drugs and if it can possibly be used in combination with cardiovascular drugs for the treatment of hypertension and therefore, the use of cardiovascular disease can possible be reduced which may lead to a reduction in their ecotoxic effects.

Conclusion

The use of garlic has shown to be effective in lowering both the systolic and diastolic blood pressure in hypertensives in comparison to control groups and did not show significant reduction in lowering the blood pressure in normotensives. However, to state that it is a suitable green alternative for cardiovascular drugs, more research should be conducted in which the use of garlic is compared to more antihypertensive drugs so that the efficacy can be more relativized and a conclusion can be drawn whether garlic is a suitable intervention in combination with cardiovascular drugs for the treatment of hypertension and therefore, the use of cardiovascular disease can possible be reduced which may lead to a reduction in the ecotoxic effects of cardiovascular drugs.

General Conclusion

Cardiovascular disease is the leading cause of death globally and it is estimated that the prevalence of cardiovascular disease will only increase in the near future. Therefore, cardiovascular drugs will be used more often, which will increase their ecotoxic effect affecting the aquatic wildlife. The most common drugs used in the treatment of cardiovascular disease are either cleared renally or via the feces and thus these drugs might end up in the sewerage in elevated concentrations, which may be harmful and enhance the ecotoxicity of these drugs. There are different guidelines per country for the medical treatment of cardiovascular disease but these do show resemblance for a huge proportion. By implementing personalized medicines in the treatment for cardiovascular disease, the quantity of cardiovascular drugs prescribed according to these guidelines will decrease, since the treatment will be more efficacious due to personalized perspectives and therefore the amount of medical waste regarding the use of cardiovascular drugs will decrease even as their ecotoxic effect. With lifestyle adjustment such as quit smoking, sufficiently exercising, maintaining a healthy bodyweight and following a healthy diet, cardiovascular disease can be prevented essentially like the use of the corresponding cardiovascular drugs, which will lower the ecotoxicity of these drugs. There is not much literature present about the long-term ecotoxic effects of cardiovascular disease and therefore more research should be conducted to determine the exact impact of these drugs on the environment. Green alternatives for cardiovascular drugs could also decrease the ecotoxicity of the used drugs. The use of garlic has shown to be effective in lowering both the systolic and diastolic blood pressure in hypertensives in comparison to control groups and did not show significant reduction in lowering the blood pressure in normotensives. However, to state that it is a suitable green alternative for cardiovascular drugs, more research should be conducted in which the use of garlic is compared to more antihypertensive drugs so that the efficacy can be more relativized and a conclusion can be drawn whether garlic is a suitable intervention in combination with cardiovascular drugs for the treatment of hypertension and therefore, the use of cardiovascular disease can possible be reduced which may lead to a reduction in the ecotoxic effects of cardiovascular drugs.

Appendices

Drug	Absorption	Distribution	Metabolism	Excretion
Warfarin	Oral bioavailability of almost 100%[10]	Volume of distribution of 0,14L/Kg [10]	Warfarin is metabolized to several hydroxywarfarins by human cytochromes p450 [10]	Mostly excreted as metabolites. There is an renal clearance of 80% and 20% through feces half-life R- warfarin: 37-89 hours (R-warfarin) S-Warfarin: 21-43 hours [10]
Heparin	Not absorbed by Gastrointestinal tract, so administered parenterally [10]	Volume of distribution of 0,05L/Kg . doest not distribute in adipose tissues [10]	Metabolized by the liver and the reticuloendothelial system[10]	Mainly excreted by the reticuloendothelial system. Small proportion unmetabolized heparin also excreted through urinary tract. half-life 1.5 hours[10]
Furosemide	Oral bioavailability varying from 10-90% [10]	Volume of distribution of 0.181L/Kg in healthy subjects and 0,140L/kg in heart failure patients[10]	Mainly metabolized by the kidneys and a small proportion metabolized by the liver[10]	85% clearance by the kidney of which 43% is excreted renally. 50% of the administered dose is among excretion in urine in its unchanged form and the other fraction is metabolized into glucuronide. half-life

				2 hours (drugsbank furosemide)[10]
lisinopril	Oral bioavailability varying from 6-60% [10]	Apparent volume of distribution is 124 L [10]	Not metabolized [10]	Solely excreted via urinary tract. half-life 12.6hours [10]
Enalapril	Oral bioavailability 60% [10]	Volume of distribution varying from 1-2.4L/Kg[12]	60% from the absorbed dose is hydrolyzed by hepatic esterase to enalaprilat [10]	94% of the total dose is excreted by the kidneys as the metabolite (enalaprilat) or as unchanged fraction.
benazepril	Minimum oral bioavailability of 37% [10]	Volume of distribution of 8.7L [3]	Benazepril (prodrug) is primarily metabolized in the liver to benazeprilat by cleaving off the ester group[10]	Both benazepril and benazeprilat are primarily excreted by the kidneys. half-life benazepril: 5,8-11,5 hours benazeprilat: 13-31,6 hours[10]

Drug	**Absorption**	**Distribution**	**Metabolism**	**Excretion**
Losartan	Oral bioavailability 33%[10]	Volume of distribution of 34L and the active metabolite has a volume of distribution of 12 L [11]	Three metabolism pathways; glucuronidation, hydroxilaton and oxidation by various cytochrome P450 enzymes[27]	Excreted via urinary tract, feces as either unchanged drug or as active metabolite. [1] half-life 6-9 hours[10]
Candesartan	Oral bioavailability of 15% after candesartan Cilexetil (prodrug) administration[10]	Volume of distribution of 0.13L/Kg[10]	Candesartan cilexetil (prodrug) is metabolized in the intestinal wall, it undergoes by ester hydrolysis so that Candesartan (Active metabolite) is formed[10]	Mainly excreted via the urinary tract and also a small proportion via bile or feces[13] half-life 9 hours[10]

Valsartan	Oral bioavailability between 10-35%. Intake of food decreases AUC by 40% and Cmax by 50%[28]	Volume of distribution of 17 L [28]	Only a small fraction of Valsartan is metabolized by the liver, the responsible enzyme not known yet[20]	Primarily excreted via the feces as unchanged drug and a small of proportion of approximately 13% is excreted via urine Half-life 6 hours[10]
bisoprolol	Oral bioavailability of 90% and unaffected by food consumption [10]	Volume of distribution of 3.5L/Kg[10]	Transformation into inactive Metabolites is performed by CYP3A4	Excreted via the kidneys and liver. A fraction of approximately 50% of the oral dose is excreted in its unchanged form. Half-life 10-12 hours [10]
carvedilol	Oral bioavailability between 25-35% Absorption is delayed by food [18]	Volume of distribution of 2L/Kg [10]	Metabolized by the liver by aromatic ring oxidation and glucuronidation[11]	
metoprolol	Oral bioavailability of 50% and if administered Intravenously 100%[10]	Volume of distribution of 4.2 L/Kg. can pass the blood-brain barrier[10]	High fraction metabolized by first pass metabolism. Metabolism to a high extent by CYP2D6 and a small proportion by CYP3A4[10]	Excreted by the kidneys. Half-life 3-7 hours [10]

Drug	**Absorption**	**Distribution**	**Metabolism**	**Excretion**
Amlodipine	Oral bioavailability between 64-90%[10]	Volume of distribution of 21L/Kg[10]	Metabolized by the liver into inactive metabolites[10]	Amlodipine metabolites are excreted through the kidneys[4] Half-life 30-50 hours
Felodipine	Undergoes first-pass metabolism which yields a	Volume of distribution of 10L/Kg [10]	Completely Metabolized via the hepatic pathway via cytochrome P40	Metabolites are excreted via the urinary tract. Half-life

	bioavailability of 15% [10]		3A4 into metabolites with no pharmacological activity [10]	Hypertensive patients: 17.5-31.5 hours. elderly hypertensive patients: 19.1-35.9 hours. Healthy subjects: 8.5-19.7 hours [10]
Lacidipine	Oral bioavailability of 10% undergoes first-pass metabolism [10]	Volume of distribution of 4.8L/Kg [10]	Complete hepatically metabolized by CYP3A4-enzymes [10]	70% of the metabolites are excreted through feces and 30% of the metabolites is renally cleared. <u>Half-life</u> 13-19 hours [10]
Aspirin	Bioavailability of 68% [23]	Volume of distribution of 10.5L [23]	In the stomach, bloodstream, intestinal mucosa and primarily in the liver ,metabolized into salicylate. Salicylate is primarily metabolized by the liver via conjugation with either glucuronic acid or glycin, which is the dominant pathway. [23]	Both salicylate and the salicylate metabolites are excreted via the urinary tract. The excretion depending of the pH of the urine, the salicylate will be in its ionized form ranging from 3-80% [23] <u>Half-life</u> Aspirin: 13-19 minutes Salicylate: 3.5-4.5 hours
Digoxin	Oral bioavailability between 50-90% if administered orally with gelatinized capsules, a bioavailability of 100% can be reached.	Volume of distribution of approximately 7L/Kg [8]	The liver metabolized a small proportion of the absorbed digoxin dose by glucuronidation and sulfation [10] and around 8% goes through the entero-hepatic cycle [23]	Primarily excreted via the urinary tract as unchanged fraction(50-70%) The excretion via the urinary tract depends on the glomerular filtration rate. Digoxin can also

	Bacteria located in the colon can form inactive product, which will affect the absorption. Co-medication with antibiotics, which will affect the bacteria, may improve the absorption of digoxin [10]			be excreted via the biliary system. [15] Half-life Healthy subjects: 1.5-2 days. Patients with impaired renal function: 3.5-5 days.

Appendix 1. ADME criteria for the most common prescribed cardiovascular drugs per class. Anticoagulants (warfarin & Heparin); diuretics (Furosemide); Angiotensin-converting inhibitors (lisinopril, enalapril, benazepril); Angiotensin receptor blockers (losartan, candesartan, valsartan); beta blockers (bisoprolol, carvedilol, metoprolol); Calcium Channel blockers (amlodipine, felodipine, lacidipine); Antiplatelet medication (Aspirin); Digoxin [1][4][10][15][23].

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The trends in the use of Beta-blockers & Calcium channel blockers among males and females & betwen subjects aged 40-65 and older than 65 located in the Netherlands: a drug utilization study.

By

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Professor: prof. dr. E. Hak
Topic PTEE3: Reducing medicine waste: a pilot study on preventive cardiovascular drugs
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Introduction

As stated in the systematic research above, there is an increase in the prevalence of cardiovascular disease, which is the leading cause of death globally. Cardiovascular drugs can have an ecotoxic effect resulting from medical waste which may affect the aquatic wildlife resulting in alternations in cardiac physiology and impaired growth, reproduction and lipid metabolism. Therefore, it is important to conduct research in the trends of the volume of prescriptions in the treatment of cardiovascular disease, so that the ecotoxic effect of these drugs can be more assessed and to see whether the volume of drug use has decreased over the last years by e.g., lifestyle modifications or green alternatives so that the ecotoxic effect of these drugs has been possibly lowered throughout the years. In this drug utilization study, an insight will be given at the trends in the annual incidence and prevalence in prescription of two blood pressure lowering agents; Beta-blockers and Calcium Channel blockers, and whether there are differences in prescription of these drugs among age groups older than 65 and younger than 65 and between males and females. The prescription data is retrieved from the iadb database using Structured Query Language (SQL).

Material & Methods

Data retrieval

The data used in this drug utilization study is retrieved from the Interaction Database (IADB), which is a prescription database that includes data from 54 community pharmacies in the Netherlands and contains around 700.000 anonymized patients [1]. The IADB database tracks the various prescriptions that are given to the patients by the community pharmacies over time and the dataset is representative for the whole Dutch population in terms of drug usage[2]. The database contains a lot of information about the patients and their corresponding recipes, however for this utilization study, only the following parameters were selected and used: year, anopat (anonymized patient number), gebdat(birthdate), mv (gender), edat (date of first prescription in IADB), afldat(date the drug was delivered to the patient), ATC(the anatomical therapeutic chemical code for the received drug), nr_start_atcs (amount of different drugs the patient started with). In appendix 1 till 13, all the SQL queries regarding the retrieved information from the iadb database are presented.

Study Population

For this study, only subjects older than 40 were selected since this age group is more likely to have cardiovascular disorders and therefore, the usage of either betablockers or calcium channel blockers will occur more frequently. For the prevalence, all men and woman with a minimal age of 40 at the moment of first prescription of monotherapy consisting of either a Betablocker (ATC=C07) or a Calcium channel blocker (ATC=C08)) were selected from the database. The first prescription of one or more of any of the mentioned agents should have been given for at least 1 year before the start of the study. For the incidence, All men and woman with a minimal age of 40 at the moment of first prescription of monotherapy consisting of either a Betablocker (ATC=C07) or Calcium channel blocker (ATC=C08), after a long time of non-use or for the first time were included. This means that the subjects did not either use betablockers or calcium channel blockers in at least the 365 before the new prescription. Therefore, they must be in the database 365 days before the new prescription. The data retrieved from the database was selected from the period between 1 January 2010 until 31 December 2020. Subjects with Existing comorbidities e.g., diabetes, asthma, cancer etc. were not excluded from this study since these subjects might also suffer from cardiovascular diseases and thereby might use a beta-blocker or a calcium channel blocker and since we are solely interested in the trends in the volume of prescription of these drugs, patients with comorbidities were not left out of this study.

Data Analysis

Effect measures

The prevalence, incidence and relative risk were determined from the database. The prevalence in this case, stands for the proportion of subjects that use either a beta-blocker or a Calcium channel blocker that are 40 years or older during 2010 till 2020. The incidence is the proportion of subjects that are 40 years or older, who start the use of either a Beta-blocker or a Calcium channel blocker during 2010 till 2020. The relative risk compares the prevalence of using either a Beta-blocker or a Calcium channel blocker in 2020 compared to the use in 2010. The relative risk can be lower than 1, which means that the chance of using either a Beta-blocker or a Calcium channel blocker in 2010 is higher than in 2020. A relative risk higher than 1 indicates that the chance of using a Beta-blocker or a Calcium channel blocker in 2020 is higher than in 2010. The prevalence for each year is calculated by dividing the number of new and pre-existing cases of administration of either a beta-blocker (ATC=C07) or a calcium channel blocker (ATC=C08), divided by the total number of study population, which are all people aged 40 and above that are present in the database from1 January 2010 until 31 December 2020. The users of betablockers or calcium channel blockers could be selected due to the ATC codes that correspond to either a betablocker (ATC=C07) or a calcium channel blocker (ATC=C08). The incidence is calculated by dividing the number of first starters of either a beta-blocker (ATC=C07) or a calcium channel blocker (ATC=C08), divided by the population estimates. The relative risk is calculated by dividing the prevalence of 2020 by the prevalence of 2010. The data is stratified by age and gender. Therefore, the prevalence, incidence and relative risk were calculated for two age groups; (<65 years) and (>65 years) and for males and females, to see the trends in use of the two drugs in these different classes of subjects.

Statistics

The 95% confidence interval of the prevalence, incidence and relative risk were calculated for the different effect measures. The 95% CI represent a range of values that contains the true value with 95% certainty. The confidence intervals are calculated with the following formula:

$$p \pm 1{,}96 \times \sqrt{\frac{p \times (1-p)}{n}}$$

In which p can stand for either the prevalence, incidence or relative risk for a certain year and n stands for the denominator, which are all subjects that meet the inclusion criteria for that certain year, which is in this case all men and woman aged 40 and older. The Confidence interval of the relative risk is used to state whether the increase or decrease in prevalence is significant or not. If the relative risk's 95% CI does not include 1, it can be stated that the increase or decrease in prevalence between 2010 and 2020 is significant, if the CI contains a 1, the increase or decrease in prevalence is unsignificant.

For the relative risks, the Chi-squared test is also performed to state whether the decrease or increase in prevalence is significant or not. This test is performed using the Rothman episheet in excel [3]. The Chi-square test is used to compare observed and expected results which are the prevalence in 2020 and the prevalence in 2010 in this case[4]. If the outcome of the Chi-square test has a p value <0,05, then it can be stated that there is a significant difference between the two values. If p>0,05, the difference between the prevalence of 2020 and 2010 is unsignificant.

Results

Annual incidence and prevalence in prescription of Betablockers or Calcium channel blockers

The trends in prevalence and incidence of the use of Beta-blockers or calcium channel blockers in subjects aged 40 or older between 2010 and 2020 are presented below. Figure 1 represents the trends in prevalence of Beta-blockers and Calcium channel blockers and figure 2 illustrates the trends in incidence of Beta-blocker or Calcium channel blocker usage.

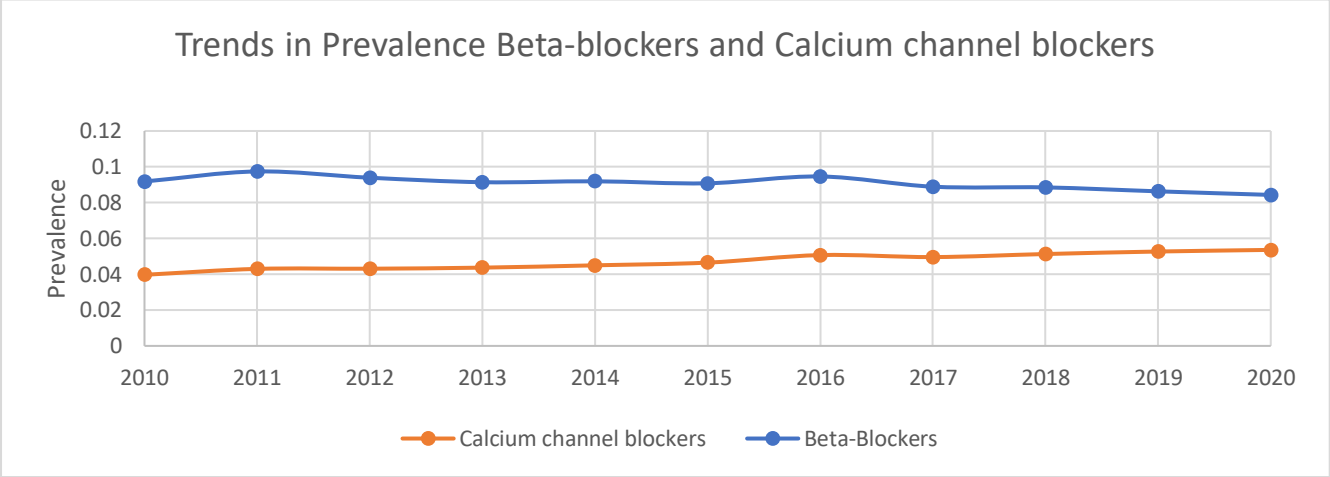


Figure 1. Trends in the prevalence of prescription of Beta-blockers and Calcium channel blockers in subjects aged 40 or older in a period ranging from 2010 till 2020. The prevalence is plotted against the time in years. The blue line represents the prevalence of Beta-Blocker prescription and the orange line represents the prevalence of Calcium channel blocker Prescription.

As can be seen in figure 1, there is an increase in the prevalence of calcium channel blockers from 2010 onwards till 2020, the Relative risk is 1.35 with a 95% CI of 1.33-1.36, leaving 1 out of the CI and therefore it can be stated that the increase is statistically significant. To further test the significance, the P-value of the Chi-square test is <0,05, which also indicates there is a significant increase in prevalence. For the betablockers, an overall decrease can be observed when looking at the prevalence in 2010 compared to 2020. The relative risk for the Beta-blocker is 0.91 with a 95% CI of 0.909-0.927 and a P-value <0,05, which indicates that the decrease in prevalence is statistically significant. When looking at the Beta-blockers is graph 1, for some years like 2011 and 2016, the prevalence increases slightly in comparison with the previous year, so there are fluctuations between the different years but overall, there is a slight decrease in prevalence. When comparing the prevalence of Calcium channel blockers with Betablockers, it can be seen that the prevalence of the Beta-blockers is almost 2 times higher than the prevalence of the Calcium channel blockers. However, the prevalence of the betablockers slightly decreases over the years and the prevalence of the calcium channel blockers shows an increase in prevalence.

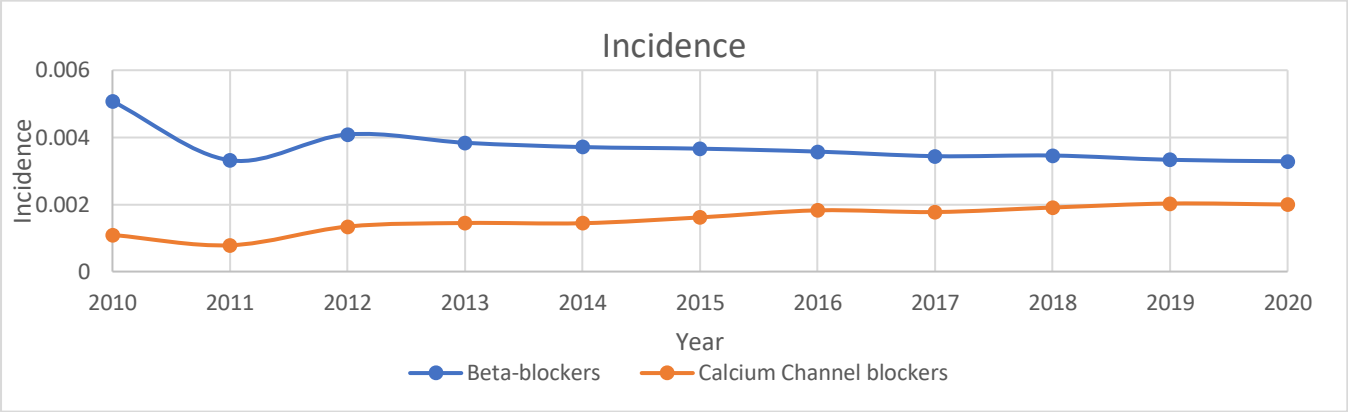


Figure 2. Trends in the incidence of prescription of Beta-blockers and Calcium channel blockers in subjects aged 40 or older in a period ranging from 2010 till 2020. The prevalence is plotted against the time in years. The blue line represents the prevalence of Beta-Blocker prescription and the orange line represents the prevalence of Calcium channel blocker Prescription.

Figure 2, shows that there is a decrease in incidence of Beta-blockers. The incidence drops from 0,005074 in 2010, to 0,003287 in 2020. 2011 is the year in which the incidence did show the highest decrease in comparison with the previous year. An increase in the incidence of calcium channel blockers can be observed. The incidence increases from 0,001093 in 2010, to 0,001998 in 2020. The Beta-blockers incidence is almost 2 times higher in comparison the calcium channel blockers. However, the incidence of the Beta-blockers decreases over the years and the incidence of the Calcium channel Blockers rises.

Age

To determine the trends in prevalence and incidence per age group, the subjects are divided in two age groups: 40-64 years and 65 years and older. Figure 3 and 4 represent both the prevalence and incidence of either a Beta-blocker or a Calcium channel blocker prescription in the age group younger than 65. The prevalence and incidence of the prescription of either a Beta-blocker or a Calcium channel blocker in the age group older than 65 are indicated in figure 5 and 6.

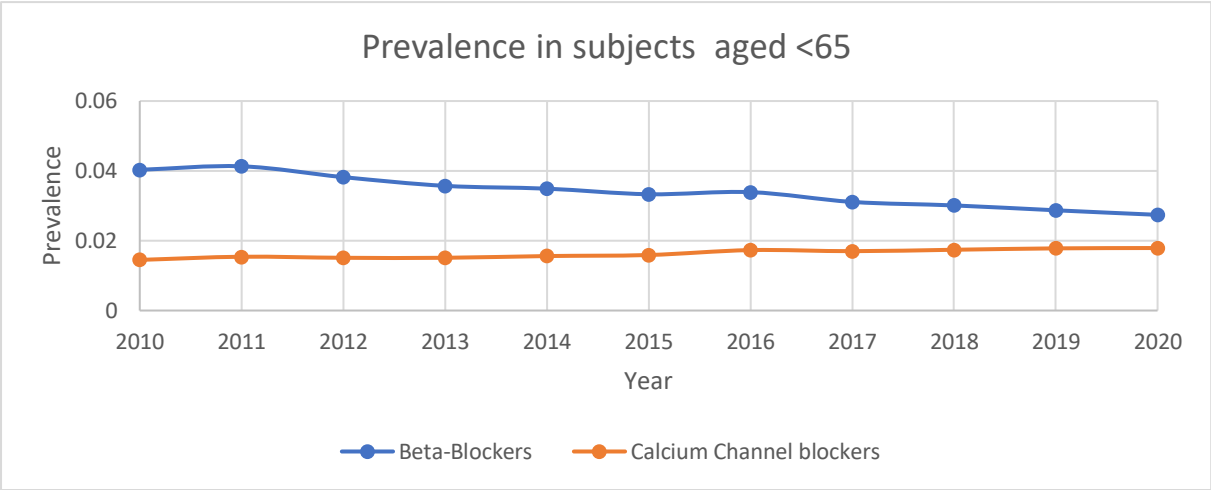


Figure 3. Trends in the prevalence of prescription of Beta-blockers and Calcium channel blockers in subjects aged younger than 65 in a period ranging from 2010 till 2020. The prevalence is plotted against the time in years. The blue line represents the prevalence of Beta-Blocker prescription and the orange line represents the prevalence of Calcium channel blocker Prescription.

Figure 3 shows that there is a decrease in prevalence of Beta-blocker prescription in the period from 2010 till 2020. The relative risk for the Beta-blocker is 0.67 with a 95% CI of 0.669-0.690 and a P-value <0,05, which indicates that the decrease in prevalence is statistically significant for the prevalence of Calcium channel blockers, a slight increase in prevalence can be observed in the period from 2010 till 2020. The relative risk for the Calcium channel blocker is 1.23 with a 95% CI of 1.205-1.26427 and a P-value <0,05, which indicates that the increase in prevalence is statistically significant. When comparing the prevalence of prescription of the Betablockers and Calcium channel blockers, it can be seen that in 2010, the prevalence of the betablockers is more than 2 times higher as the prevalence of prescription of Calcium channel blockers, however the prevalence of the betablockers decreases more than that the prevalence of the Calcium channel blockers increases and therefore, in 2020 the prevalence of the betablockers is only around 1.5 times higher than the Calcium channel blockers prevalence.

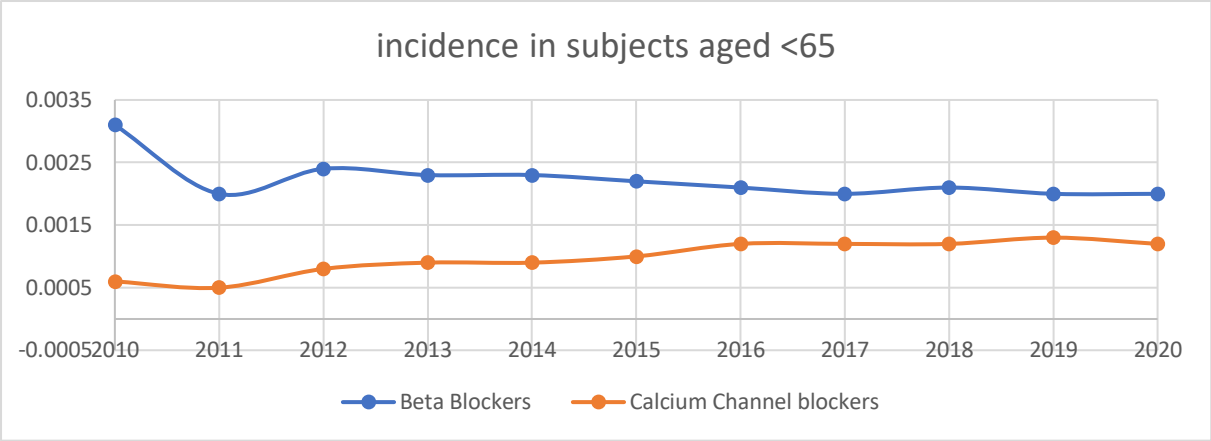


Figure 4. Trends in the incidence of prescription of Beta-blockers and Calcium channel blockers in subjects aged younger than 65 in a period ranging from 2010 till 2020. The incidence is plotted against the time in years. The blue line represents the incidence of Beta-Blocker prescription and the orange line represents the incidence of Calcium channel blocker Prescription.

Figure 4 illustrates a higher incidence of prescription of Betablockers in 2010 in comparison with the other years till 2020. So overall, there is a reduction in incidence in subjects aged younger than 65. For the Calcium channel blockers, the incidence increased over time in subjects aged younger than 65. For all years in the period of 2010 till 2020, the incidence of prescription of Betablockers is higher than the incidence of prescription of Calcium channel blockers in subjects aged younger than 65.

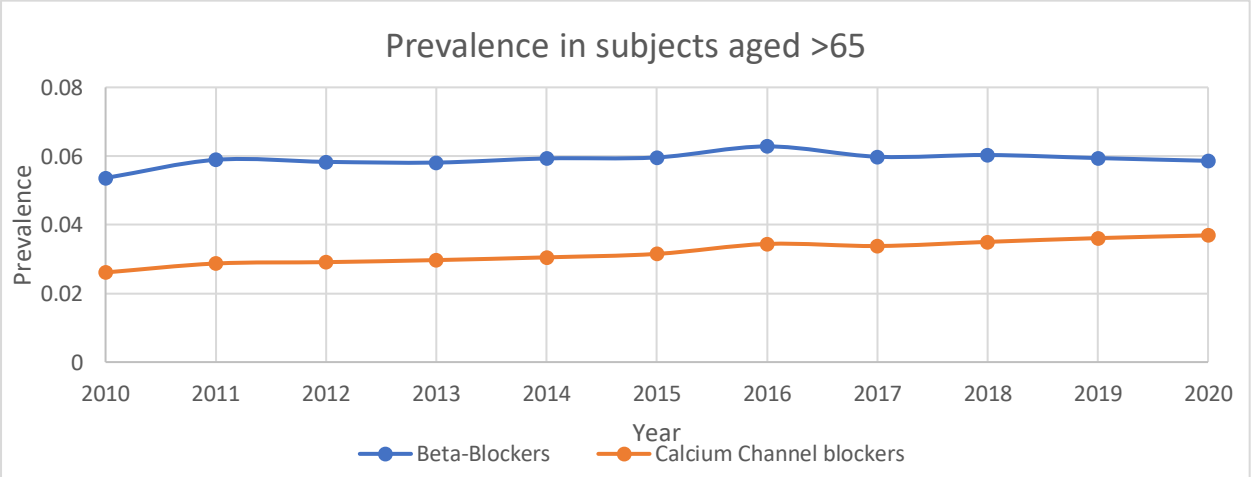


Figure 5. Trends in the prevalence of prescription of Beta-blockers and Calcium channel blockers in subjects aged older than 65 in a period ranging from 2010 till 2020. The prevalence is plotted against the time in years. The blue line represents the prevalence of Beta-Blocker prescription and the orange line represents the prevalence of Calcium channel blocker Prescription.

Figure 5 demonstrates that the prevalence of prescription of Betablockers in subjects aged older than 65 fluctuates around a prevalence value of 0,06. Overall, there is only a minimum increase in prevalence for Betablockers since the prevalence of 2020 is slightly higher than 2010. The relative risk for the Beta-blocker is 1.09 with a 95% CI of 1.079-1.106 and a P-value <0,05, which indicates that the increase in prevalence is statistically significant.
For the calcium channel blockers, an increase in prevalence of prescription can be observed. The relative risk for the Calcium channel blocker is 1.41 with a 95% CI of 1.389-1.438 and a P-value <0,05, which indicates that the increase in prevalence is statistically significant. For all years in the period of 2010 till 2020, the prevalence of prescription of Betablockers is higher than the incidence of prescription of Calcium channel blockers in subjects aged older than 65.

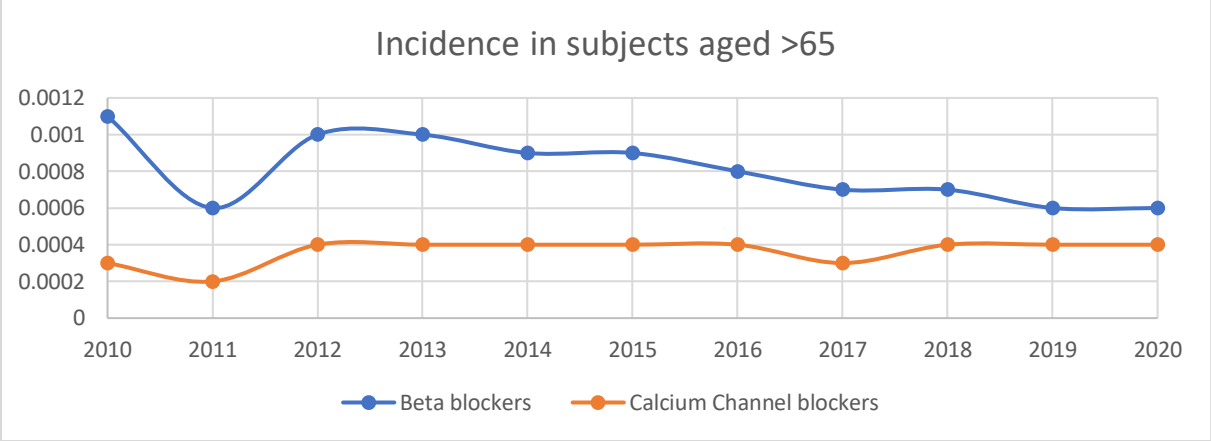


Figure 6. Trends in the incidence of prescription of Beta-blockers and Calcium channel blockers in subjects aged older than 65 in a period ranging from 2010 till 2020. The Incidence is plotted against the time in years. The blue line represents the incidence of Beta-Blocker prescription and the orange line represents the incidence of Calcium channel blocker Prescription.

Figure 6 illustrates a higher incidence of prescription of Betablockers in 2010 in comparison with the other years till 2020. So overall, there is a reduction in incidence in subjects aged older than 65 for these drugs. For the Calcium channel blockers, the incidence increased in the period from 2010 till 2012 to an incidence value of 0,004. From 2012 till 2020, the incidence remains 0,004 except for 2017, in which the incidence was 0,003. During the time period of 2010 till 2020, an increase in incidence is observed for the calcium channel blockers since the incidence of 2020 is higher than the incidence in 2010 for subjects aged 65 years and older. For all years in the period of 2010 till 2020, the incidence of prescription of Betablockers is higher than the incidence of prescription of Calcium channel blockers in subjects aged older than 65.

Gender

To see whether there are differences between males and females in the annual incidence and prevalence in prescription of Beta-blockers and calcium channel blockers, the subjects were divided by gender. Figures 7 and 8 represent the Betablockers' prevalence and incidence between men and woman. Figures 9 and 10 represent the prevalence and incidence of prescription of Calcium channel blockers between men and woman.

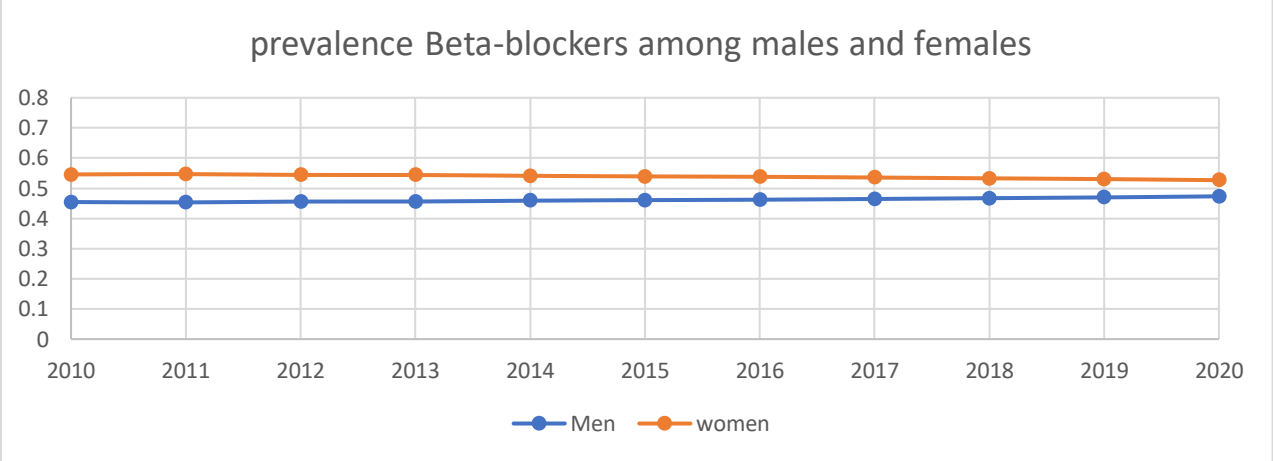


Figure 7. Trends in the prevalence of prescription of Beta- blockers for both man and woman in a period ranging from 2010 till 2020. The prevalence is plotted against the time in years. The blue line represents the prevalence of Beta-Blocker prescription among men and the orange line represents the prevalence of a Beta-blocker Prescription among woman.

As can be seen in figure 7, the prevalence of prescription of Beta-blockers is higher in woman. However, over the years the woman's prevalence slightly decreases.
The relative risk for the Beta-blocker among females is 0.96 with a 95% CI of 0.962-0.968 and a P-value <0,05, which indicates that the decrease in prevalence among females is statistically significant. On the contrary, the men's prevalence does increase slightly in the period from 2010 till 2020. The relative risk for the Beta-blocker among males is 1.04 with a 95% CI of 1.034-1.040 and a P-value <0,05, which indicates that the increase in prevalence is statistically significant. The woman's prevalence is higher for all years in comparison with the men's prevalence in the period from 2010 till 2020.

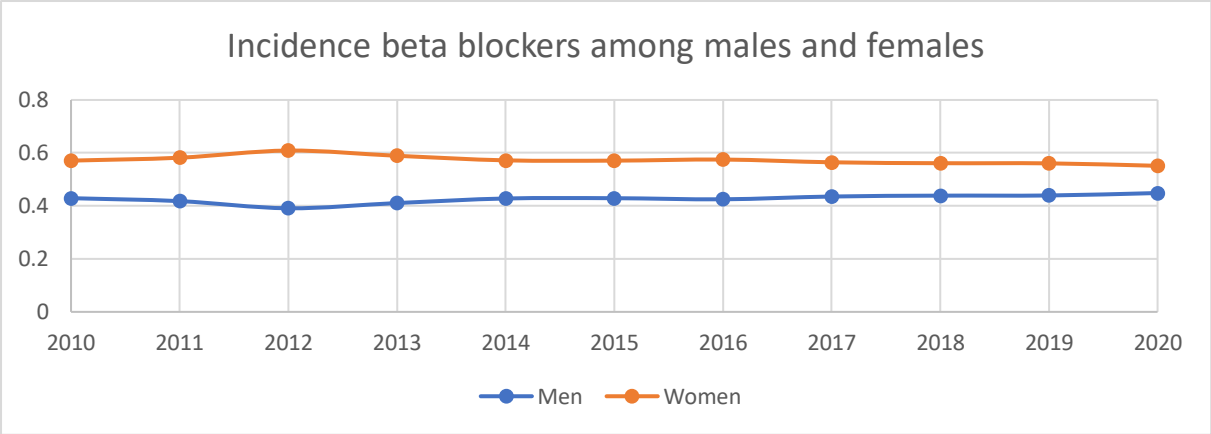


Figure 8. Trends in the incidence of prescription of Beta-blockers for both men and woman, in a period ranging from 2010 till 2020. The Incidence is plotted against the time in years. The blue line represents the incidence of Beta-Blocker prescription among men and the orange line represents the incidence of Beta-Blocker prescription among women.

As can be seen in figure 8, the woman's incidence varies around 0,6 in the period ranging from 2010 till 2020. The males' incidence also fluctuates around 0,4 during this period. The woman's incidence is higher than the men's incidence for every year from 2010 till 2020.

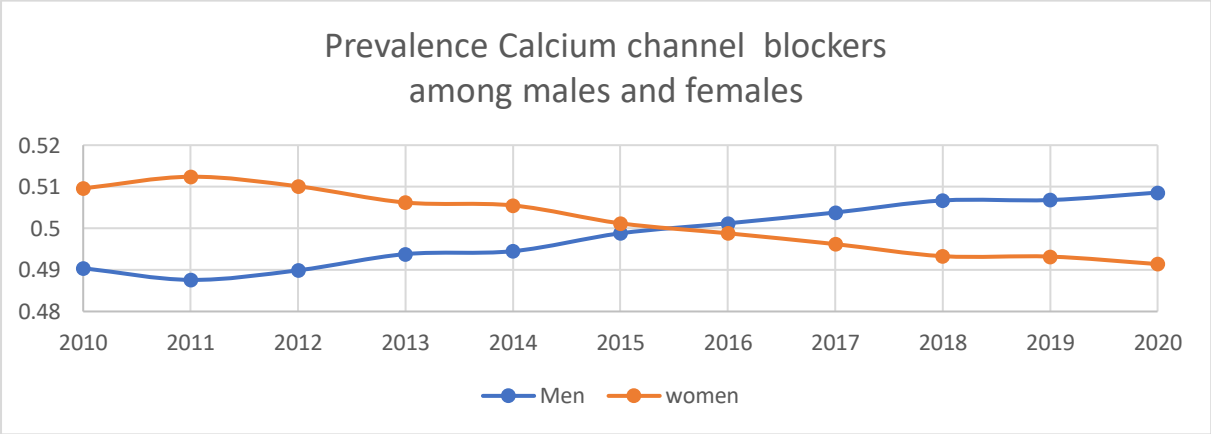
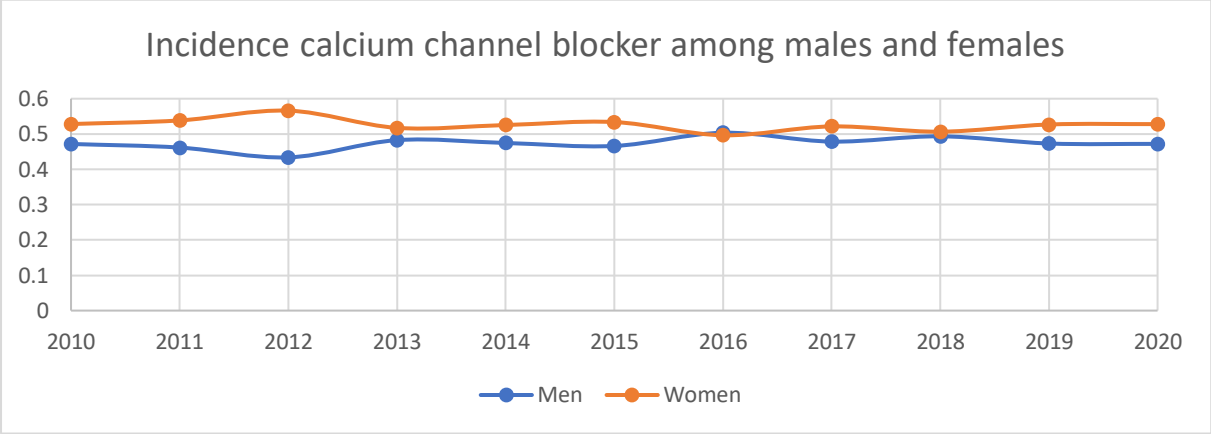


Figure 9. Trends in the prevalence of prescription of Calcium channel blockers for both man and woman in a period ranging from 2010 till 2020. The prevalence is plotted against the time in years. The blue line represents the prevalence of Calcium channel prescription among men and the orange line represents the prevalence of Calcium channel blocker Prescription among woman.

As can be seen in figure 9, the prevalence among woman is in 2010 around 0,51. In the period from 2010 till 2020, the prevalence among woman decreases towards a value of 0,49. The relative risk for the Calcium channel blocker among females is 0.96 with a 95% CI of 0.961-0.967 and a P-value <0,05, which indicates that the decrease in prevalence is statistically significant. The male's prevalence is in 2010 around 0,49. In 2020, the men's prevalence is around 0,51, so the men's prevalence does increase during this period of ten years. The relative risk for the Calcium channel blockers among males is 1.03 with a 95% CI of 1.034-1.040 and a P-value <0,05, which indicates that the increase in prevalence is statistically

significant. In 2010, the females' prevalence is higher than the men's but since the females' prevalence is decreasing and the male's prevalence is increasing, in 2015 the men's prevalence surpasses the females' prevalence.



As can be seen in figure 10, the men and woman's incidence are fluctuating around 0,5.

Discussion

prevalence and incidence of the whole study population

Calcium channel blockers

When looking at the overall prevalence demonstrated in figure 1, it can be seen that there is an increase of 35% in the overall prevalence of the Calcium channel blocker prescription in a period from 2010 till 2020. The incidence of the Calcium channel blockers does also increase over time, which is in line with the increasing prevalence. Since both the prevalence and incidence increase for the Channel blockers, it is expected that in the years after 2020, both the incidence and prevalence will keep following this increasing trend, which is alarming due to the ecotoxicity resulting from the medical waste of these drugs. Therefore, the volume of prescriptions should be more lowered by e.g., green alternatives or lifestyle modifications, which are briefly discussed in the systematic research, so that there will be less medical waste and thereby will possible ecotoxic effects be decreased on the aquatic wildlife.

Beta-Blockers

The prevalence of the prescription Beta-blockers slightly decreases with approximately 9% The incidence of the Beta-blockers also follows the prevalence and shows a decreasing trend in the period from 2010 till 2020. So, it can be stated that there is a decrease over the years in the overall prevalence and people that start using Beta-blockers from 2010 till 2020, which is necessary to reduce the ecotoxic effect of the medical waste resulting from Beta-blockers. However, this decrease is very slightly and therefore higher reductions in prevalence are needed as this is beneficial for the environment and thus even for Beta-blocker users, more lifestyle adjustments or greener alternatives or personalization of medicines is desired.

When comparing the prevalence and incidence of these two drugs, it can be seen that both the Beta-blocker's prevalence and incidence are higher for every year in comparison with the Calcium channel blocker's incidence and prevalence. This is not in accordance with the prescription Guidelines, that are discussed in the systematic report. According to the Dutch guidelines, Calcium channel blockers are preferred as a prescription over Beta-blockers in the treatment of hypertension. This is because the treatment with Beta-blockers is associated with an elevated risk to develop diabetes in obese patients and the treatment is also not preferred in patients that have elevated glucose levels. Therefore, it is expected that the Beta-blockers would have a lower prevalence and incidence in comparison with the Calcium channel blockers, which is not the case.

Age

When comparing the prevalence and incidences of both drugs between the two age groups, it can be seen that the prevalence is higher for both drugs in the older age group consisting of subjects aged older than 65, in comparison with the younger group that includes subjects with an age of 40 till 65. This can be possibly explained by the fact that people in the younger age group are more physical active and live by a healthier lifestyle in comparison with the elder group and thereby possibly have less cardiovascular disorders, which can reduce the volume of prescriptions of antihypertensive drugs. Therefore, more attention should be paid to the age group older than 65, to reduce the volume of prescriptions in these subjects.
On the other hand, the incidence seems to be higher for both drugs in the younger group (40 till 65), so it can be stated that people tend to start using the Beta-blockers and Calcium channel blockers at an age younger than 65. Just like the prevalence and incidence among the whole population, it can also be seen both in the younger and older age group that the Beta-blocker's prevalence and incidence are higher for every year in comparison with the Calcium channel blocker's incidence and prevalence, which is not in line with the Dutch prescription guidelines in the treatment for hypertension.

Gender

Both the prevalence and incidence of prescriptions of Beta-blockers is higher in males than in females. The male's prevalence slightly increases with 4%. The prevalence among females decreases throughout the years with 4%. There are more males that start the prescription in the period from 2010 till 2020 in comparison with the females, since the incidence levels are higher among males. The male's incidence does slightly decrease over the years and the female's incidence does slightly increase. So, it can be stated that the Beta-blocker usage is slightly favored among males. For the Calcium channel blockers, the prevalence was higher in females in 2010. However, the prevalence decreased over time with 4% and the males' prevalence, increased with 4% and therefore in 2015, the prevalence was higher among males than females. So, the Calcium channel blocker usage was more favored among females in 2010 but from 2015 on towards 2020, the calcium channel blocker prescription is more common among men. There incidence levels for both males and females fluctuate around 0.5 so there are no significant differences among the different genders in people that start the prescription of Calcium channel blockers. So, the Beta-blockers usage and start of prescriptions, is more favorable among men. For the Calcium channel blockers, the prevalence was first higher among woman, but from 2015 onwards the prevalence was higher among males. The incidence levels of the Calcium channel blockers did not show a big difference among the different genders, so there are no significant gender differences in starting the prescription of Calcium channel blockers. Thus, it is shown that there are some differences in incidence and prevalence between males in females for both drugs, However, these differences between the different genders are very slightly so in terms of ecotoxicity it cannot be stated that e.g. men cause more ecotoxic effects due to more medical waste than woman.

Strengths and Limitations

A strength of this drug-utilization study is the access and usage of the Iadb database, which provides a large sample size which is representable for the whole Dutch population in terms of drug usage. Another strongpoint is the statistical analysis with the Chi-squared test and 95% confidence interval to state whether the increase or decrease in prevalence was statistically significant or not. However, there are also some limitations in this study.
The Iadb database contains a lot of prescription information of the patients, but the blood pressure is not included in the database and therefore in this study, no distinction in the volume of prescription could be made for the three different stages of hypertension. Another limitation comes in the determination of the Relative risk, which is a comparison of the prevalence of 2010 with the prevalence of 2020. In some cases, the obtained relative risk might not be a good reference point since sometimes the prevalence of 2010 or 2020 might fluctuate with the other years' values and therefore the relative risk is not representative for that specific time period. A solution for this might be to take average values for more years in the start and end of the study in the calculation of the relative risk so that these fluctuations might be corrected.

Follow-up research

In this drug-utilization study, insights are given in the trends in prevalence and incidence of prescriptions for Beta-blockers and Calcium channel blockers in the total population and for different age groups and between males and females. An appropriate follow-up research could investigate how these increases in prevalence and incidence can be lowered in the best way so that the ecotoxicity of the medical waste resulting from this drug will be less. Think of different prescription guidelines that also take this ecotoxic effect of these drugs into account and would focus more on greener alternatives or more physical activity. Another example could be to investigate how this medical waste ends up in the waters and try to prevent this process from happening so that also here, the ecotoxicity will be lowered.

Conclusion

In the period from 2010 till 2020, there is an increase in prevalence and incidence of prescriptions of Calcium channel blockers for the whole population, which is unwanted in terms of ecotoxicity regarding the medical waste of cardiovascular drugs. Therefore, this upward trend in prescriptions for this drug must decline in the future by paying more attention to greener alternatives and lifestyle adjustments like more physical activity, a healthier diet and stop smoking. For the Beta-blockers, it can be seen that there is a slight decrease in both the prevalence and incidence of prescriptions for the whole population, which is beneficial for the ecotoxic effect and a further decrease should be strived for in the future. The prevalence and incidence are higher for Beta-blockers in comparison with Calcium channel blockers, which is not in line with the Dutch prescription guidelines in the treatment for hypertension. When looking at the trends in prevalence and incidence of prescriptions between the two age groups, it can be seen that there is a higher prevalence in the older group consisting of subjects aged older than 65. This can be explained by the fact that these patients are less physical active in comparison with subjects aged 40 till 65 and therefore tend to have more cardiovascular disorders and thus, the volume of prescription will be higher in the older age group. The younger group that includes subject aged 40 till 65, does have higher incidences for both drugs in comparison with the older group (older than 65), so people tend to start the prescription of Beta-blockers and calcium channel blockers more often at an age younger than 65. For both drugs there are some differences in terms of prevalence and incidence between males and females, however these differences are very slightly so in terms of ecotoxicity, no clear conclusion can be given about whether one gender contributes more to the ecotoxicity on the aquatic wildlife than the other. In the future, more attention should be paid on the volume of prescriptions of these drugs and the increasing prevalence and incidences should be reduced. This can be done by using more green alternatives or implementing more lifestyle adjustments, as discussed in the systematic report.

Appendices

Appendix 1

```
SELECT
jaar,
SUM(pop_man + pop_vrouw) pop
FROM popschat
WHERE lftd >= 40
GROUP BY jaar
```

Query that retrieved the data for the Denominator (all men and woman with a minimal age of 40) from the Iadb database

Appendix 2

```
SELECT
jaar,
n,
n/pop
FROM (
SELECT
jaar,
count(distinct anopat) n
FROM recept INNER JOIN patient USING(anopat)
WHERE ATC LIKE "C07%"
AND TIMESTAMPDIFF(YEAR, gebdat, afldat) >= 40
GROUP BY jaar
) a INNER JOIN denom USING(jaar)
```

Query that retrieved the data for the prevalence of Betablocker prescription for every year from the Iadb database

Appendix 3

```
SELECT
jaar,
n,
n/pop
FROM (
SELECT
jaar,
count(distinct anopat) n
FROM recept INNER JOIN patient USING(anopat)
WHERE ATC LIKE "C08%"
AND TIMESTAMPDIFF(YEAR, gebdat, afldat) >= 40
```

```
GROUP BY jaar
) a INNER JOIN denom USING(jaar)
```

Query that retrieved the data for the prevalence of Calcium channel blocker prescription for every year from the Iadb database

Appendix 4

```
SELECT
jaar,
n,
n/pop
FROM (
SELECT
jaar,
count(distinct anopat) n
FROM recept INNER JOIN patient USING(anopat)
WHERE ATC LIKE "C07%"
AND TIMESTAMPDIFF(YEAR, gebdat, afldat) >= 40
AND TIMESTAMPDIFF(YEAR, gebdat, afldat) =< 65
GROUP BY jaar
) a INNER JOIN denom USING(jaar)
```

Query that retrieved the data for the prevalence of Betablocker prescription for every year in subjects aged from 40 till 65 from the Iadb database

Appendix 5

```
SELECT
jaar,
n,
n/pop
FROM (
SELECT
jaar,
count(distinct anopat) n
FROM recept INNER JOIN patient USING(anopat)
WHERE ATC LIKE "C08%"
AND TIMESTAMPDIFF(YEAR, gebdat, afldat) >= 40
AND TIMESTAMPDIFF(YEAR, gebdat, afldat) =< 65
GROUP BY jaar
) a INNER JOIN denom USING(jaar)
```

Query that retrieved the data for the prevalence of Calcium channel blocker prescription for every year in subjects aged from 40 till 65 from the Iadb database

Appendix 6

```
SELECT
jaar,
n,
n/pop
FROM (
SELECT
jaar,
count(distinct anopat) n
FROM recept INNER JOIN patient USING(anopat)
WHERE ATC LIKE "C07%"
AND TIMESTAMPDIFF(YEAR, gebdat, afldat) > 65
GROUP BY jaar
) a INNER JOIN denom USING(jaar)
```

Query that retrieved the data for the prevalence of Beta blocker prescription for every year in subjects aged older than 65 from the Iadb database

Prevalence older than 65 beta blockers

Appendix 7

```
SELECT
jaar,
n,
n/pop
FROM (
SELECT
jaar,
count(distinct anopat) n
FROM recept INNER JOIN patient USING(anopat)
WHERE ATC LIKE "C08%"
```

```
AND TIMESTAMPDIFF(YEAR, gebdat, afldat) > 65
GROUP BY jaar
) a INNER JOIN denom USING(jaar)
```

Query that retrieved the data for the prevalence of Calcium channel blocker prescription for every year in subjects aged older than 65 from the Iadb database

Appendix 8

```
SELECT
jaar,
C09 / pop,
C08 / pop,
C07 / pop
FROM (
SELECT
YEAR(startdat) jaar,
SUM(start_ATCs LIKE "C08%") C08,
SUM(start_ATCs LIKE "C07%") C07
FROM starters
WHERE nr_start_atcs = 1
AND TIMESTAMPDIFF(YEAR, gebdat, edat) >65
GROUP BY jaar
) a INNER JOIN denom USING(jaar)
```

INCIDINCE EFFECT MEASURES
OLDER THAN 65

Query that retrieved the data for the incidence of Calcium channel blocker and Beta-blocker prescription for every year in subjects aged older than 65 from the Iadb database

Incidence older than 65 , beta blockers and calcium channel blockers

Appendix 9

```
SELECT
jaar,
C09 / pop,
```

```
C08 / pop,
C07 / pop
FROM (
SELECT
YEAR(startdat) jaar,
SUM(start_ATCs LIKE "C08%") C08,
SUM(start_ATCs LIKE "C07%") C07
FROM starters
WHERE nr_start_atcs = 1
AND TIMESTAMPDIFF(YEAR, gebdat, edat) >=40
AND TIMESTAMPDIFF(YEAR, gebdat, edat) =<65
GROUP BY jaar
) a INNER JOIN denom USING(jaar)
```

Query that retrieved the data for the incidence of Calcium channel blocker and Beta-blocker prescription for every year in subjects aged 40 till 65 from the Iadb database

Appendix 10

```
SELECT
jaar,
count(*) n,
SUM(mv = 1) nman,
SUM(mv = 2) nvrouw,
ROUND((SUM(mv = 1) / count(*)) * 100,2) perc_nman,
ROUND((SUM(mv = 2) / count(*)) * 100,2) perc_nvrouw

FROM (

SELECT
jaar,
anopat,
mv
FROM recept INNER JOIN patient USING(anopat)
WHERE ATC LIKE "C08%"
AND TIMESTAMPDIFF(YEAR, gebdat, afldat) >= 40
GROUP BY jaar, anopat
) a
GROUP BY jaar
```

PREVALENCE EFFECT MEASURES ash gender diff calcium channel

Query that retrieved the data for the prevalence of Calcium channel blocker prescription for every year among males and females from the Iadb database

Appendix 11

```
SELECT
jaar,
count(*) n,
```

```
SUM(mv = 1) nman,
SUM(mv = 2) nvrouw,
ROUND((SUM(mv = 1) / count(*)) * 100,2) perc_nman,
ROUND((SUM(mv = 2) / count(*)) * 100,2) perc_nvrouw

FROM (

SELECT
jaar,
anopat,
mv
FROM recept INNER JOIN patient USING(anopat)
WHERE ATC LIKE "C07%"
AND TIMESTAMPDIFF(YEAR, gebdat, afldat) >= 40
GROUP BY jaar, anopat
) a
GROUP BY jaar
```

PREVALENCE EFFECT MEASURES ash gender diff calcium channel

Query that retrieved the data for the prevalence of Beta- blocker prescription for every year among males and females from the Iadb database

Appendix 12

```
SELECT
jaar,
count(*) n,
SUM(mv = 1) nman,
SUM(mv = 2) nvrouw,
ROUND((SUM(mv = 1) / count(*)) * 100,2) perc_nman,
ROUND((SUM(mv = 2) / count(*)) * 100,2) perc_nvrouw
FROM (
SELECT
anopat,
mv,
YEAR(startdat)jaar
FROM starters
WHERE nr_start_atcs = 1 AND start_atcs LIKE "C08%"
GROUP BY jaar, anopat
) a
GROUP BY jaar
```

INCIDENCE GENDER CALCIUM

Query that retrieved the data for the incidence of Calcium channel blocker prescription for every year among males and females from the Iadb database

Appendix 13

```
SELECT
jaar,
count(*) n,
SUM(mv = 1) nman,
SUM(mv = 2) nvrouw,
ROUND((SUM(mv = 1) / count(*)) * 100,2) perc_nman,
ROUND((SUM(mv = 2) / count(*)) * 100,2) perc_nvrouw
FROM (
SELECT
anopat,
mv,
YEAR(startdat)jaar
FROM starters
WHERE nr_start_atcs = 1 AND start_atcs LIKE "C07%"
GROUP BY jaar, anopat
) a
GROUP BY jaar
```

INCIDENCE GENDER CALCIUM

Query that retrieved the data for the incidence of Beta-blocker prescription for every year among males and females from the Iadb database

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