Cardiovascular risk in patients with type 2 diabetes treated with insulin in primary care: New user design (the ZODIAC cohort).

Research Project II

Medical Pharmaceutical Sciences – track Pharmaco-Epidemiology

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Abstract

Background: Several reports claim an association between insulin administration and increased cardiovascular risk, just as the association between lipid lowering drugs and an increased level of HbA1c and increased diabetic medication.

Objective: To estimate the cardiovascular risks before and after insulin and to estimate the degree of increase of HbA1c and of increased diabetic medication.

Design: Retrospective observational cohort study with new users design.

Setting: Patients with type 2 diabetes in primary care in the (surrounding area) of Zwolle (ZODIAC study) from 1998 to 2014.

Patients: Patients who were already treated for diabetes in secondary care, patients with insufficient cognitive capabilities or a very short life expectancy were excluded. Patients were enrolled in the study after informed consent. The year in which the patient begins with insulin is defined as T0 (index timepoint).

Methods: Patients were screened annually for laboratory results, medication use, lifestyle aspects and physical parameters. For the lipid lowering association, patients who were treated with lipid lowering drugs at T-1 were excluded. For the assessment of cardiovascular risk, ADVANCE and SCORE were computed from available data for T-1, T0 and T1. These two are risk assessment methods, specific for diabetes and in general respectively. ADVANCE gave points from 0 to 22 that were linked to percentages and SCORE was categorized in low risk, moderate risk and high risk.

ADVANCE was obtained from available data, just as SCORE for the association between insulin administration and cardiovascular risk. For the other association, between the use of lipid lowering drugs and increased diabetic medication, the outcome was defined as the use of insulin and therefore longitudinal relative risks were assessed. Besides, logistic regression was performed to correct for covariates and as cross-sectional analysis. Covariates were age, gender, smoking BMI and systolic blood pressure. Multiple linear regression was performed for HbA1c as outcome and here the model was corrected for the same covariates. These regression analyses were performed for T0.

Results: Significant increase in CVR was found for proxy ADVANCE from 3,0% at T-1 to to 4,3% at T0 and T1. SCORE remained low for the three timestamps, namely 2,81 % at T-1 and 2,82 % at T0 and T1 . So the risk in cardiovascular disease is here not significantly increased. For the other association, the relative risks suggested that lipid-lowering drugs are preventive in the use of insulin (less than 0,5). Contribution of lipid lowering drugs was not found in the multiple linear regression ($p > 0,05$). Contribution of lipid lowering drugs was found in the logistic regression and was negative ($p < 0,05$ and regression coefficient = -0,887).

Limitations: Original ADVANCE could not be obtained due to missing data, medication use (non-diabetic, among which lipid lowering drugs) was only qualitative assessed, numbers of patients getting insulin seemed to be false due to impossibilities.

Conclusions: Low CVRs are found for diabetic patients and these findings were not as expected. Relative risks were surprisingly low since risks above 1 were expected. Regression analyses showed also not expected findings since positive contributions were expected. All these findings are not reliable and further research is needed and recommended.

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Introduction

Background

Diabetes

Diabetes mellitus is derived from the Greek word diabetes meaning siphon - to pass through and the Latin word mellitus meaning honeyed or sweet. This is because in diabetes excess sugar is found in blood as well as the urine. This excess is caused by an insufficient or even absent production of insulin. Insulin is a main hormone in glycemic control and is – amongst others -involved in cellular uptake of glucose from the blood stream and interstitial fluid. With a disbalance between glucose levels and insulin action, blood glucose levels will rise, eventually to a level which surpasses the renal reuptake capacity. When this occurs, increased blood glucose levels will be accompanied by the presence of glucose in the urine. [1]

Insulin is produced in the beta cells in the islets of Langerhans, which are found in the pancreas. There are four types of endocrine cells in these islets, with two of them being the most important in diabetes mellitus, i.e. the insulin producing beta cells and glucagon secreting alpha cells. Glucagon is the antagonizing hormone of insulin. This balance is important for the maintenance and regulation of glucose levels in tissues and in blood. However, in diabetes mellitus insulin can be either absent (type 1 DM) or insufficient (type 2 DM). In the case of T2DM, one often sees a combination of increasing insulin resistance and (relatively) insufficient production of insulin. These two types have different etiologies and interventions/management. Furthermore, there are also other causes of diabetes mellitus, but since they are relatively rare and not part of the presented study, these will not be described in detail. [2]

T1DM and T2DM also have different epidemiologies since their etiology is different. Appendix 1 contains information about these two types of diabetes. Type 1 diabetes is an autoimmune disease while type 2 is more based on issues with lifestyle and aging. Another difference is that type 1 diabetes is treated with insulin, type 2 is treated with insulin only when the person's own insulin production fails to result in acceptable glucose concentrations, and often after a rather prolonged period of adequate reaction on lifestyle measures and diet, and / or oral glucose lowering medication or a GLP-1 analogue. Further on, the focus is on type 2 diabetes and type 1 diabetes is beyond the scope.

Type 2 diabetes, glucose, HbA1c and concomitant medication

For the diagnosis of type 2, at two different days the fasting level of glucose in venous plasma is at least 7.0 mmol/l. Another possibility for diagnosis is a fasting glucose level of at least 7.0 mmol/l or a random glucose level in plasma of at least 11.1 mmol/l combined with symptoms of hyperglycemia. It is recommended to repeat the assessment of the fasting glucose level after three months in the laboratory, also as yearly investigation of the patient. [2]

In type 2 diabetes, the blood glucose level is elevated as mentioned before. The fasting target value of glucose in venous plasma is between 4.5 and 8 mmol/l and the 2 hours postprandial value of glucose in venous plasma is under 9 mmol/l. A short-term high glucose value with a rapid correction has less impact on HbA1c than a chronically increased blood glucose with fewer high peaks. A high fasting glucose value with a good HbA1c can be considered as a momentary outlier or as a starting disorder, but some patients consistently have a relatively high fasting glucose value, while the HbA1c is good. Especially in patients who do not use insulin there is usually a reasonable correlation between the HbA1c and the fasting glucose value. However a single measurement of a high fasting glucose value in non-insulin using T2DM patients does not always have to lead to immediate intensification of treatment. If this value is again too high for the next fasting glucose measurement,

the HbA1c is determined. With an HbA1c below the target value, intensification of the treatment is not necessary and in such patients a more frequent measurement of HbA1c is advisable as a lead for possible adjustment of the medication. A good fasting glucose value with a high HbA1c indicates that the patient may be less well regulated than the fasting value suggests. [2]

The target value of HbA1c depends on age, medication and duration of illness. Therefore, there are four categories:

1. HbA1c target value ≤ 53 mmol / mol: all patients younger than 70, as well as patients aged 70 years and older, provided that they are treated only with lifestyle advice or metformin monotherapy (independent of duration).
2. HbA1c target value 54-58 mmol / mol: patients aged 70 years and older with a duration of illness shorter than 10 years (medication consists at least of metformin plus sulfonylurea).
3. HbA1c target value 54-64 mmol / mol: patients aged 70 years and older with a disease duration of 10 years or longer (medication consists at least of metformin plus sulfonylurea).
4. A higher target value applies to vulnerable elderly people and people with a short life expectancy (arbitrarily: shorter than 5 years). There is no evidence in these patients that a low HbA1c is beneficial for the longer term prognosis. The treatment objective is primarily to prevent symptomatic hypo- or hyperglycemia. Glucose values of 6-15 mmol /l and HbA1c values of 53-69 mmol / mol are acceptable in these patients.

Factors like presence of micro- and/or macrovascular complications, comorbidity, vulnerability, risks of possible hypoglycemia, life expectancy, feasibility, medication side effects, hypoglycemia risk, and motivation of the patient may be reason, in consultation with the patient, to deviate from the advised treatment goals. [2]

Type 2 diabetes is associated with increased cardiovascular risk and therefore not only the glycemic control is the therapeutic target but also control of blood pressure (for which antihypertensive drugs are prescribed) and of lipid profile (for which statins are prescribed), so concomitant medication is common. Patients with type 2 diabetes who have hypertension (systolic blood pressure ≥140 mmHg when < 80 years of age) are usually treated with ACE inhibitors since these drugs have a positive impact on the blood pressure, and are considered to be renoprotective. The lipid profile consists of different lipids (total cholesterol, HDL cholesterol, LDL cholesterol, ratio total cholesterol / HDL cholesterol, triglycerides) and every type has its own target value. When the LDL-C (LDL- cholesterol) is at least 2,6 mmol/l then it is advised to prescribe a statin. Especially LDL-cholesterol (LDL-C) is an important risk factor for cardiovascular diseases. Other ratios and targets may also play a role in the assessment of cardiovascular risk. [3]

Insulin and cardiovascular risk

In the literature, several studies and trials show an increase in cardiovascular risk in type 2 diabetes patients who were treated with insulin. This increase is based on strong dose-dependent associations between the injected dose of insulin and cardiovascular risk. Insulin is associated with for instance weight gain, recurrent hypoglycemias and iatrogenic hyperinsulinemia. Discussion remains, whether the association of increased cardiovascular risk is with hyperinsulinaemia, or with the increased / increasing insulin resistance. Most authors consider the increased / increasing cardiovascular risk to be correlated to degree of insulin resistance: the more severe the insulin resistance, the more severe the cardiovascular risk. [4 5]

Pathological effects associated with insulin resistance are inflammation, atherosclerosis, hypertension, dyslipidemia, heart failure and arrhythmias. Insulin administration is also associated with poorer prognosis and increased mortality. Insulin is known for some adverse effects like hypoglycemia. Hypoglycemia may be recurrent and asymptomatic and can stimulate existing organ damage and also catecholamine release which leads to QT interval prolongation. QT interval prolongation is in turn responsible for arrhythmias and for an increased risk of adverse CV events. Other consequences of recurrent hypoglycemia are baroreceptor paralysis, trophic effects, vasoconstriction, increased platelet aggregation, coagulation, atherosclerosis, ischemic electrocardiogram changes and angina. The heart is relatively insulin resistant and free fatty acids are the prime nutrient for the myocardial muscle so they are promoted for oxidation rather than glucose for energy production in myocardium. Cardiac glucolipotoxicity is increased by insulin treatment in refractory hyperglycemic and hyperlipidemic type II diabetes since the natural barrier of the heart is overridden leading to excessive glucose entry. [4 5]

Another aspect of insulin treatment is iatrogenic hyperinsulinemia that is caused by high levels of exogenous insulin. This type of hyperinsulinemia is linked with insulin resistance, weight gain, increased blood pressure, dyslipidemia, chronic inflammation and beta cell exhaustion. Renal retention of sodium, water and uric acid may also occur. Compensatory hyperinsulinemia is able to manipulate phosphatidylinositol-3-kinase signaling and synthesis of nitric oxide; leading to excessive vasoreactivity, atherosclerosis, hypertension and mitogenicity. Hyperinsulinemia is associated with an increased risk of cardiomyopathy and induced endothelial dysfunction and atherosclerosis because of the production of endothelin and other vascular pro-inflammatory molecules. [4 5]

Assessment of cardiovascular risk

In general practice, cardiovascular risk can be assessed in several ways. Here, three types of risk scores will be discussed. [6] The first one is called “SCORE” and is used for patients below 70 years without diabetes or anamnesis of cardiovascular disease. The second assessment is meant for patients with an anamnesis of cardiovascular disease and is called “SMART RISK SCORE”. The third assessment is “ADVANCE RISK SCORE” and was developed for patients with type II diabetes.

Cardiovascular risk profile

The assessment of cardiovascular risk is performed in patients with potential risk, since performing in patients with low risk is not useful. General practitioners do a combination of opportunistic screening and systematic screening to get a targeted study population based on randomization. So when a patient visits the GP and the GP suspects that he or she has a potential risk, he would likely investigate him. The investigation takes repeatedly place, for instance every 5 years. This investigation is more general and independent from the ZODIAC investigation that is annually.

Patients who will be investigated may have the following characteristics:

- Incriminating anamnesis for premature heart and vascular diseases;
- Presence of risk factors like smoking, obesity, high blood pressure or cholesterol;
- Risk increasing comorbidity, such as chronic kidney damage.

The assessment of cardiovascular risk is based on the measurements of a combination of essential risk factors for atherosclerosis. For this, the anamnesis, physical investigation and laboratory outcomes are relevant:

- Anamnesis: age; sex; smoking; family anamnesis with heart and vascular diseases; nutrition; psychosocial risk factors; alcohol use; physical activity;
- Physical examination: systolic blood pressure; Body Mass Index (BMI) (optional combined measurement of the waist);
- Laboratory outcomes: lipid spectrum (total cholesterol (TC), HDL-C, TC-HDL-ratio, LDL-C, triglycerides); glucose level, creatinine level in serum with (via CKD-EPI-formula) estimated Glomerular Filtration Rate (eGFR); albumin-creatinine ratio in urine.

SCORE

Depending on the estimated risk, the investigation should be repeated for every 5 years or earlier when the risk is near the treatment value. The SCORE gives a 10-years risk of cardiovascular disease. Consequently, the SCORE is estimated for men above 40 years and for women above 50 years. Gender, age, smoking, TC-HDL-ratio and systolic blood pressure are parameters to assess the SCORE. Cardiovascular mortality in 10 years (SCORE) is ranged from 0 to 31 and the risk of illness plus mortality is from 1 to greater than 50.

Different risks are also categorized without quantitative assessment (risk score) for the patients. Patients with very high risk are for instance patients with known heart and vascular diseases, diabetes mellitus with related organ damage, or patients with severe chronic renal damage and a calculated SCORE of at least 10%. Patients with high risk have a single risk factor that is severe increased, like blood pressure or total cholesterol or have diabetes or chronic renal damage. These patients have a SCORE between 5 and 10%. Patients with low risk have a SCORE of less than 5% for 10 years and most of middle-aged people are in this category. In the second appendix, the SCORE assessment is shown in a table, green means low risk, yellow means moderate risk and red means high risk. [3]

ADVANCE

Cardiovascular risk is differently assessed in diabetes patients. For diabetic patients, who do not have atherosclerotic vascular diseases, the ADVANCE risk function is used. . The score consists of 10 clinical parameters which is shown in appendix 3. These clinical parameters reflect the stage and burden of diabetes or morbidity. Obtained points from every parameter are summed up to get the score, which ranges from 0 to 8. The score predicts the 4-years risk of myocardial infarct, stroke or cardiovascular mortality. It is possible to extrapolate the 4-years risk to a 10-years risk with the following formula: risk10 years = 1-(1-risk4 years)^10/4. However, this extrapolation is not valid since every clinical parameter has its own progressive risk pattern and does not take future diseases or morbidities into account. [7]

Lipid lowering drugs and intensification of diabetic medication

Statin treatment is initiated for lowering cholesterol levels in order to reduce CVD risk. [3] However, reports claim that an unfavourable property of statins is elevation of glucose and HbA1c levels. Therefore initiation of statin treatment might lead to an intensification of diabetic treatment. Intensification of diabetic treatment can be assessed in several ways, e.g. changing from medicine or adding a new group of drugs to current treatment. These ways can be ranked to determine the type of intensification. The major intensification is switching from oral medication or combination therapy (both oral medication and insulin) to insulin solely and the minor intensification is changing from medicine or adding a new group of drugs to current treatment.

Objectives

The first focus of this study is to examine the relationship between cardiovascular risk and insulin treatment, since in literature / previous studies a possible association between insulin and cardiovascular risk was found.

The second and the last focus of this study is to discover a difference in intensification of diabetic medication between patients who initiated lipid lowering drug treatment and patients who did not.

Research questions

1. What is the cardiovascular risk in patients newly started with insulin treatment (at T0)?
2. Is there a difference in cardiovascular risk before and after starting with insulin treatment?
3. Do patients who initiated lipid-lowering drugs need more often an intensification of diabetic medication than patients who did not initiate lipid lowering drugs?

Methods

Setting and participants

The population is from the Zwolle Outpatient Diabetes project Integrating Available Care (ZODIAC) study. This prospective observational cohort study investigated the effects of shared care for patients with type 2 diabetes in the Netherlands from 1998 till 2014. This cohort has been expanded several times. In the beginning years, the population consisted of patients from the surrounding area of Zwolle. The area has expanded over the years and also the number of participating general practitioners was increased from 53 in 1998 to 459 in 2008. The patients participated in the study after informed consent and the number of participating patients also increased from 1622 to 27.438 in the same time range. In 2012, the number of patients passed 60.000.

The year in which the patient begins with insulin is defined as T0, which is used as index time point (figure 1). Here, the study period is from T-1 till T+1 since data of other timestamps are less relevant and also poor. [8]

In the Netherlands everyone has a general practitioner and more than 80% of the patients with type 2 diabetes is treated in primary care according to the Dutch General Practitioner Standard (NHG-standaard in Dutch).

Study design

This present retrospective cohort study (based on a recently composed database derived from the general ZODIAC data) offers the possibilities for studies with a before-after design (figure 1), which means that there is a cohort of new insulin user (n=7874) whose data before and insulin treatment are collected and used. Every patient is his own control.

For this study, patients with type 2 diabetes mellitus treated in primary care who are started with insulin (any type) were relevant. Patients who were already treated for diabetes in secondary care, patients with insufficient cognitive capabilities or a very short life expectancy were excluded. Also patients with missing diabetes duration and age at diagnosis were excluded.

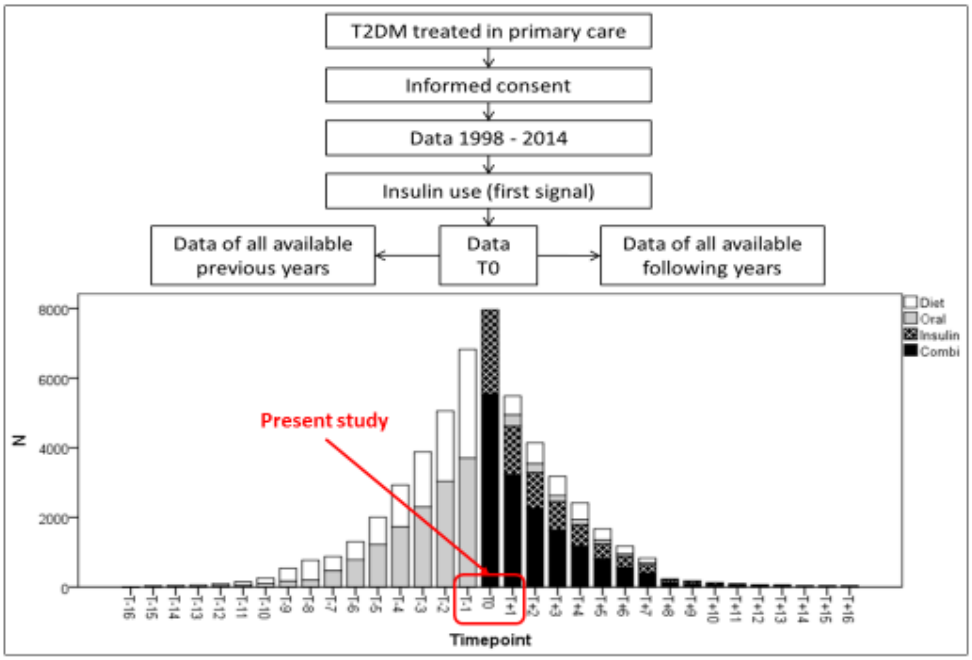

Figure 1: Study design of ZODIAC study

Data collection

Study data were collected by participating general practitioners from patients with type 2 diabetes each year. These data contain biometric, physical, lifestyle and medication information which is obtained by laboratory and physical examination for instance. Measurement units were aligned to allow proper comparison. Some of the laboratory results were converted to a more appropriate unit, like HbA1c from % to mmol/mol. There was thus two ways of assessment of this variable. HbA1c was also assessed in two ways. The old assessment was in % and the new was in mmol/mol. The score table of ADVANCE shows the HbA1c in % but in the Netherlands the HbA1c is measured in mmol/mol. In the dataset however, there were two types of HbA1c. One of the diagnostic results, retinopathy, was needed to recode since this variable had two ways of assessment according to different diagnostic policies. Another variables, which were assessed in two ways, were lifestyle oriented like smoking and exercise due to different diagnostic policies. Smoking needed also to be recoded. Diabetic medication was more specified in different drugs classes like oral, insulin, and combination of these two. These categories are further defined in metformin, sulfonylureas, thiazolidinediones and other classes namely repaglinide, DPP-4 inhibitors, and/or GLP-1 receptor agonists. Insulin medications were categorized into five groups based on their acting time namely short-acting insulin and rapid-acting insulin analogues as first group, intermediate-acting insulin as second group, pre-mixed types as third group, basal insulin analogues as fourth group and

combination as last group. Diabetic medication is also quantitative assessed; the number of oral, insulin and combined were included as variables. For the assessment of insulin use however, the insulin use was not further specified due to lower numbers of patients for the relative risks.

Variables that contain biometric, physical, lifestyle and medication information were important for the assessment of the parameters of the ADVANCE, the SCORE and for the assessment of the intensification of diabetic medication, see figure 2 and 3. Some of these variables are categorical, like antihypertensive drugs and other variables concerning non-diabetic medication (yes or no), including lipid lowering drugs. So for the association between lipid lowering drugs and insulin, the type of lipid lowering drugs is not assessed. In other words, there is only qualitative information about lipid lowering drugs use and different types of diabetic medication. This means that there is no information about the dosage of medication. However, there is no information about the dosage. Other variables are quantitative like age, pulse pressure and HbA1c blood level, in most cases these variables are also normally distributed. Grouping of some quantitative variables was important for the assessment of ADVANCE, like retinopathy.

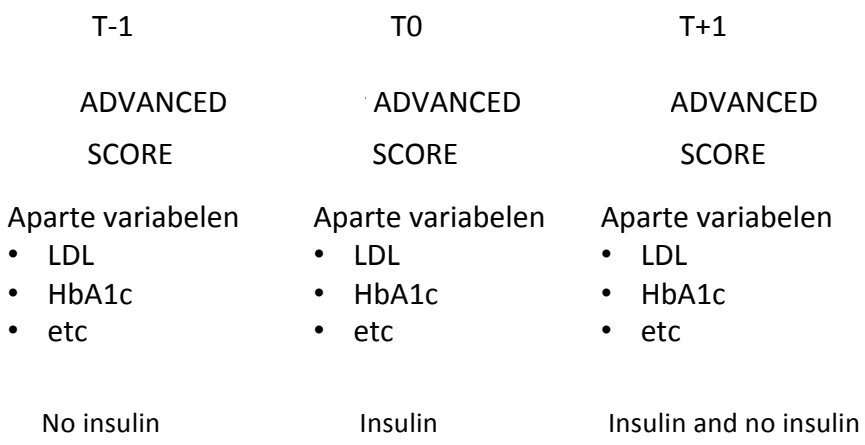

Figure 2: Overview of variables and outcomes for the association between insulin and cardiovascular risk

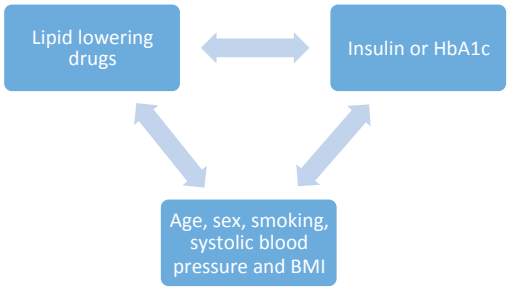

Figure 3: Overview of variables and outcomes for the association between lipid lowering drugs and insulin or HbA1c at T0

Data quality

To describe and consider the data quality, these characteristics are discussed:

- *Validity:* The validity of the study dataset is strong, since some variables were measured in two ways since the policy of assessment was changed. Examples of a variable which were measured in two ways are retinopathy and HbA1c.
- *Accuracy:* Here, the accuracy is moderate since some values of certain variables were not realistic. An example of unrealistic values is a low systolic blood pressure and a high diastolic blood pressure at the same timestamp which will give together a negative pulse pressure. A negative pulse pressure was observed in only 1 case at T0. Therefore, cleaning was initially not needed. Other variables showed however a greater amount of unusual and unexpected values so all kinds of unusual and unexpected values were cleaned.
- *Completeness:* The dataset is unfortunately not complete, most complete values are at T0 and before T-5 and after T+5 data is poor. Therefore the completeness is poor.
- *Consistency:* The consistency is here moderate since collecting data is dependent from general practitioners and therefore there are differences in the amount of values in the variables.
- *Uniformity:* In the study dataset, uniformity is good because there are several units of measures for some laboratory outcomes for example retinopathy and smoking because of changes in diagnostic policy and these are implemented in different variables. [11]

Missing data

Missing data are inevitable, and there is a distinction between missing at random (MAR), missing completely at random (MCAR) and missing not at random (MNAR). There is also a distinction in the patterns of missing data namely monotone, univariate and arbitrary. In longitudinal studies, the monotone pattern is likely to occur due to loss to follow up for instance. It is also likely that the pattern is univariate since the same participants have missing data on one or more variables. There are principled methods to deal with missing data. Multiple imputation, full information maximum likelihood and expectation-maximization method are examples of such methods. [9] In this dataset, missing values were found. However, imputation was not performed.

Endpoints

Complete case analysis

Proxy ADVANCE

The primary endpoint was the proxy ADVANCE score. To get proxy ADVANCE score, a syntax was needed to compute sub scores. The syntax can be found in appendix 4. Some of the parameters in the ADVANCE score table were related and not the same as the variables in the dataset and these are albuminuria, atrial fibrillation and treated hypertension and Non HDL- C, these are translated to albuminkreatratio, beta blockers, antihypertensive drugs and CholtotminHDL in the dataset respectively. Albuminuria is divided in normoalbuminuria, microalbuminuria and macroalbuminuria in the score table of ADVANCE. Normoalbuminuria is an albumin creatinine ratio of below 3 mg/mmol, micro-albuminuria is a ratio from 3 to 30 mg/mmol and macro-albuminuria is a ratio above 30 mg/mmol. [10] Beta-blockers are prescribed for atrial fibrillation, also in case of diabetes. Therefore the variable beta-blockers is a proxy for atrial fibrillation. For Non HDL-C the only variable that is close to its definition is CholtotminHDL, which means the total cholesterol minus HDL-C

resulting non HDL-C. For the three timestamps, 3323, 4372 and 3586 ADVANCE scores were obtained for respectively T-1, T0 and T1.

SCORE

For the SCORE, the patients with known age, gender, smoking habits, systolic blood pressure and TC-HDL ratio were needed. This means that fewer variables were needed than ADVANCE. The SCORES were calculated for the patients whose values were in range of the SCORE table found in figure 1. For the assessment of the SCORE scores, the table of SCORE was translated to a syntax (appendix 5) . For T-1, 3932 SCORES were obtained, for T0 4673 and for T1 3307.

Intensification of diabetic medication and HbA1c

For the association between lipid lowering drugs and insulin, patients who were treated with lipid lowering drugs prior to insulin (i.e. at T-1) were excluded (figure 3). So the cohort differs here, and there are 3721 patients. These patients do not have insulin as medication in T-1. When they start insulin, they are in T0 and they also could have combination therapy. In T1, only oral diabetic medication is also possible besides insulin and combination therapy. The difference in the number of patients who had intensification of diabetic medication is important for the second association. Therefore various crosstabs were assessed. The frequencies that were obtained were necessary for the calculation of relative risks. For the relative risks, the exposure was defined as using lipid-lowering drugs (LLD) and the outcome was defined as using solely insulin. The relative risks were longitudinally assessed. For this, the differences in medication and differences over time were assessed by considering different scenarios like from “using LLD and taking combi medication at T0 (so only exposure in T0) to “using LLD and insulin at T1 (exposure remained, bad outcome). These scenarios are abbreviated as C+ LLD+ at T0 and I+ LLD+ at T1. For relative risks, this T0 group is interesting and numbers of patients getting insulin and still LLD at T1 is considered as exposed and with bad outcome. Non-exposed with bad outcome would be patients from T1 with insulin but without LLD use. Good outcome is combination therapy and/or oral medication at T1. For the relative risks, the relevant frequencies are in bold. There are three possible relative risks that could be obtained: combination versus insulin, oral versus insulin and no insulin versus insulin. Another possible scenario is O- LLD+ at T0 and O+ LLD – at T1, so in T0 the diabetic medication is not oral and in T1 it is decreased to oral medication and no longer LLD. This association is naturally out of interest for the relative risks since there is no insulin at T1.

Another outcome is the difference of HbA1c level at T0 for no-users of lipid lowering drugs versus users. It is important to mention that HbA1c must be corrected for covariates and therefore smoking, gender, age and BMI are integrated in the multiple linear regression model. For the relationship between lipid lowering drugs and the use of insulin these covariates are also integrated in the logistic regression model.

Statistical methods

Descriptive statistics

Continuous variables were given as mean with standard deviation (if normally distributed) or as median with interquartile range. Normality was assessed by visual checking of the Q-Q plots and the coefficients skewness & kurtosis (from -1 to +1).

Inferential statistics

For not normally distributed variables, the Wilcoxon sign rank test was performed to assess the differences in the medians between the timestamps. For other variables, the paired T-test and the McNemar test were used, respectively for continuous and normal variables (HbA1c, DeltaBP, Age at diagnosis and Duration of DM) and categorical variables (sex, antihypertensive drugs, beta blockers and retinopathy).

For ADVANCE and SCORE, the Friedman test was first performed to compare the means at different timestamps, thereafter Wilcoxon signed rank test as post-hoc analysis.

As mentioned earlier, for lipid lowering drugs and insulin crosstabs were made. Moreover, different scenarios were analyzed and relative risks were assessed. Besides the relative risks, regression analyses were performed. Logistic regression was performed for the relationship between lipid lowering drugs and insulin; multiple linear regression was performed for HbA1c as outcome. In multiple linear regression, normality of the outcome variable, homoscedasticity and outliers were checked.

Software

For the results and the outcomes of the first 2 research questions and for the frequencies of the second association, the 26th version of SPSS was used. Medcalc was used for the calculation of relative risks, since this is not possible in SPSS.

Results

Insulin and CVR

For this analysis, patients from ZODIAC cohort were included. These patients had a known duration of diabetes and their age at diagnosis was known.

Descriptive statistics of T-1, T0 and T1

Table 1: Descriptive statistics of T0

Variable	N	%	Mean (SD)	Range (min – max)
Total population	7848	100		
Sex (male)	3669	46,8		
Age			68,8 (11,79)	24 – 100
Smoking (yes, if known)	1170 of 4145	28,2		
Alcohol (yes, if known)	721 of 4135	17,4	0,6 units / day	0 – 20
Exercising (if known)	Insufficient: 3295 of 5441 Sufficient: 2146 of 5441	60,6 39,4		
BMI			30,34 (5,29)	17,2 – 72,7
Height (in cm)			169,96 (10,12)	72 – 205
Diastolic blood pressure			77,32 (10,33)	40 – 125
Systolic blood pressure			139,16 (17,83)	80 – 248
Difference blood pressure			61,89 (15,91)	20 – 163
Metformin use	4778	60,9		
Atrial fibrillation	2977	37,9		
Retinopathy	687 of 5269	13,0		
Treated hypertension	5670	72,2		
HbA1c (mmol/mol)			58,52 (11,23)	30 – 127
Albuminuria			6,95 (38,19)	0 – 1900
Non HDL C			3,2 (1,68)	
Lipid lowering drugs	4670	59,5		

In this table, the patient population at T0 is shown. The mean age and BMI are high, respectively 68,8 and 30,34. This means that about the half is elderly and is obese. There is less missing data compared to T-1 and T1. Sex is always known and here metformin use, atrial fibrillation and hypertension are also known. Metformin use, atrial fibrillation and hypertension are also increased compared to T-1. So it seems that the population's health is deteriorated.

Table 2: Patient characteristics at T-1

Variable	**N**	**%**	**Mean (SD)**	**Range (min – max)**
Total population at T-1	6724	85,39		
Sex (male) at T-1	3195 of 6724	47,5		
Age at T-1			67,8 (11,78)	23 – 99
Smoking at T-1 (yes, if known)	1103 of 4054	27,2		
Alcohol at T-1 (yes, if known)	653 of 4014	16,3	0,6 units / day	0-12
Exercising (if known)	Insufficient: 2740 of 4683 Sufficient: 1943 of 4683	58,5 41,5		
BMI at T-1			30,06 (5,22)	17,5 – 62,5
Height (in cm) at T-1			170,2 (9,95)	110 – 205
Diastolic blood pressure at T-1			78,28 (10,11)	41 – 120
Systolic blood pressure at T-1			140,08 (17,89)	85 – 240
Difference blood pressure at T-1			61,75 (16,21)	17 – 148
Metformin use	3056	44,8		
Atrial fibrillation	1866	27,3		
Retinopathy	455 of 4063	11,2		
Treated hypertension	3638	53,3		
HbA1c (mmol/mol)			59,48 (12,00)	17-127
Albuminuria			5,64 (23,49)	0 – 832
Non HDL C			3,22 (1,14)	
Lipid lowering drugs	3003	44,7		

In this table, characteristics of the patient population in T-1 are shown. In general these patients have comorbidities like atrial fibrillation, hypertension and are obese.

Table 2: Descriptive statistics of T1

	N	%	Mean	Range (min – max)
Total population at T1	5411	68,72		
Sex (male) at T1	2499	46,2		
Age at T1			69,8 (11,78)	25 – 101
Smoking at T1 (yes, if known)	667 of 2608	25,6		
Alcohol at T1 (yes, if known)	465 of 2609	17,8	0,6 units	0 – 12
Exercising	Insufficient: 2182 of 3706Sufficient: 1524 of 3706	58,9 41,1		
BMI at T1			30,48 (5,22)	16,3 – 66,9
Height (in cm) at T1			169,85 (9,87)	110 – 204
Diastolic blood pressure at T1			76,61 (10,08)	40 – 120
Systolic blood pressure at T1			138,80 (17,60)	75 – 230
Difference blood pressure at T1*			62,21 (15,78)	10 – 142
Metformin use	3122	57,7		
Atrial fibrillation	2005	37,1		
Retinopathy	576 of 4236	13,6		
Treated hypertension	3849	71,1		
HbA1c (mmol/mol)			59,48 (12,01)	7 – 110
Albuminuria			6,41 (26,98)	0 – 1170
Non HDL C			3,1 (2,56)	
Lipid lowering drugs	3146	58,1		

Here, missing data is increased again and the health of the patient population seems ameliorated. There are fewer cases who use metformin, other important variables are also decreased but not retinopathy.

In tables 1, 2, and 3, it is important to mention that not every variable is implemented in the table of the score and the values of the variables are not complete. However, some of these variables are also important for the assessment of cardiovascular risk but are not implemented in the ADVANCE risk score table as clinical parameters.

Other analyses for variables apart

Paired T-test

Table 6: Results from the paired T-test

Endpoints	P-value
Pulse pressure T-1 vs. Pulse pressure T0	0,205
HbA1c T-1 vs. HbA1c T0	0,000
Pulse pressure T0 vs. Pulse pressure T1	0,542
HbA1c T0 vs. HbA1c T1	0,000
Pulse pressure T-1 vs. Pulse pressure T1	0,658
HbA1c T-1 vs. HbA1c T1	0,000

Here, only in HbA1c differences are found. For every combination (comparison between timestamps) of this variable, there is difference. Pulse pressure seems to be constant over the three timestamps.

Wilcoxon signed rank test

Table 7: Results of the Wilcoxon signed rank test

Endpoints	P-value (median of p values from imputations)
Albuminuria T-1 vs. T0	0,062
Non HDL-C T-1 vs. T0	0,015
Albuminuria T0 vs. T1	0,000
Non HDL-C T0 vs. T1	0,041
Albuminuria T-1 vs. T1	0,000
Non HDL-C T-1 vs. T1	0,459

In this table, differences were found in both variables. However, no difference was also found; for albuminuria T-1 and T0 and for Non-HDL-C T-1 and T1.

McNemar test

Table 8: results of McNemar test

Endpoints	P-value
Sex T-1 vs. T0	1,000
Hypertension T-1 vs. T0	0,000
Atrial fibrillation T-1 vs. T0	0,000
Retinopathy T-1 vs. T0	0,002
Sex T0 vs. T1	1,000
Hypertension T0 vs. T1	0,000
Atrial fibrillation T0 vs. T1	0,000
Retinopathy T0 vs. T1	0,001
Sex T-1 vs.T1	1,000
Hypertension T-1 vs. T1	0,003
Atrial fibrillation T-1 vs. T1	0,002
Retinopathy T-1 vs.T1	0,000

In this last type of test, all endpoints show significant difference except sex.

Main results: ADVANCE

For the three timestamps, different ADVANCES were calculated. For T-1, the mean ADVANCE was 11,38 for n= 3323. For T0, a higher mean ADVANCE was found, namely 11,83 and n= 4372. The highest mean ADVANCE is found in T1 from n= 3586 and is 12,04.

Friedman test of ADVANCE

Table 9:Descriptive statistics of ADVANCE

Variable	Mean	Std.	Min.	Max.	Mean rank
ADVANCE_T-1	11,3829	2,829	3	21	1,74
ADVANCE_T0	11,8281	2,878	3	21	2,04
ADVANCE_T1	12,0409	2,934	3	21	2,22

Table 10: Results of Friedman test for ADVANCE

N	1588
Chi-square	264,615
Df.	2
P-value	0,000

Wilcoxon signed rank test for ADVANCE

Table 11: Results of Wilcoxon signed rank test

Variables	P value
ADVANCE_T-1 vs. ADVANCE_T0	0,000
ADVANCE_T0 vs. ADVANCE_T1	0,000
ADVANCE_T-1 vs. ADVANCE_T1	0,000

The Friedman test showed a significant difference between the ADVANCES, the ADVANCES are increasing over time and Wilcoxon signed rank test admit the difference between the timestamps. The ADVANCES differ from each other and this means that insulin increases the risk.

Main results: SCORE

Descriptive statistics for SCORE

Table 12: Descriptive statistics for and of SCORE

Variable	T-1	T0	T1
Gender (male)	3195/6724 (47,5%)	3669/7848 (46,8%)	2499/5411 (46,2%)
Age	67,66 (11,69)	68,77 (11,70)	69,77 (11,70)
Smoking	1485/6489 (23,0%)	1707/7709 (22,1%)	1056/5353 (19,7%)
TC-HDL-ratio	3,86 (1,37)	3,87 (1,43)	3,83 (1,39)
Systolic blood pressure	140,08 (17,77)	139,22 (17,72)	138,83 (17,50)
SCORE	2,81 (1,902)	2,81 (1,811)	2,82 (1,794)

In this table, the descriptive statistics of the SCORE patients are shown. In all timestamps, there are more women than men and their average age is almost 70 years. Interestingly, smoking seems to decrease over time and also their systolic blood pressure. However, the TC-HDL-ratio and SCORE remains almost the same. Last but not least, the mean SCORE is low, especially when the mean age is taken into account.

Main results

Friedman test of SCORE

Table 13: Results of Friedman test for SCORE

Variable	**Mean**	**Std.**	**Min.**	**Max.**	**Mean rank**
SCORE_T-1	2,87	1,917	0	18	2,00
SCORE_T0	2,80	1,774	1	15	1,97
SCORE_T1	2,82	1,734	1	9	2,03

Table 14: Results of Friedman for SCORE

N	1726
Chi-square	5,546
Df.	2
P-value	0,062

For the SCORE, Friedman test was performed and the obtained P value is above 0,05 namely 0,062 so this means that there is no significant difference between the SCORES. This means that insulin does not increase CVR according to SCORE.

Lipid lowering drugs and insulin/HbA1c

Overview of descriptive statistics

Table 16: Descriptive statistics of the variables in patients that did not use lipid lowering drugs at T-1

Variable	T-1	T0	T1
N	3721	3721	2569
Sex (male)	1626 (43,7)	1626 (43,7)	1092/2569 (42,5)
Age	68,79 (12,14)	69,79 (12,14)	70,79 (12,14)
Smoking (yes)	762/3527 (21,6)	751/3646 (20,6)	460/2539 (18,1)
Systolic blood pressure	140,58 (17,73)	139,39 (17,45)	138,61 (17,73)
Lipid lowering drugs	0	1447 (38,9)	1079 (42,0)
Oral diabetic medication	1262 (33,9)	0 (0,0)	1550 (60,3)
Insulin	0 (0,0)	1331 (35,8)	2167 (84,4)
Combination	0 (0,0)	2390 (64,2)	2314 (90,1)
Number of oral medication	1: 532 (14,3) 2: 693 (18,6) 3: 37 (1,0)	1: 1589 (42,7) 2: 783 (21,0) 3: 18 (0,5)	1: 1100 (42,8) 2: 444 (17,3) 3: 6 (0,2)
Number of insulins	0: 3721 (100)	1: 3256 (87,5) 2: 463 (12,4) 3: 2 (0,1)	1: 1855 (72,2) 2: 308 (12,0) 3: 4 (0,2)
Number of combination	1: 532 (14,3) 2: 693 (18,6) 3: 37 (1,0)	1: 1120 (30,1) 2: 1581 (42,5) 3: 967 (26,0) 4: 51 (1,4) 5: 2 (0,1)	1: 736 (28,6) 2: 1012 (39,4) 3: 536 (20,9) 4: 29 (1,1) 5: 1 (0,0)
HbA1c	59,40 (12,48)	58,17 (11,30)	57,09 (10,61)

Here, males seem to be underestimated in all timestamps and about one fifth is smoker, the mean age is about 70 and the systolic blood pressure shows a light decrease. Furthermore, the types and number of diabetic medication are shown per timestamp. In T-1, there are no users of insulin, combination and lipid lowering drugs as expected. However, in the numbers of combination, the numbers of patients are the same as that of the numbers of oral medication. In T0, there are no users of oral diabetic medication solely. Patients do use oral medication combined with insulin. There are also patients who use solely insulin, but only one third of the patients. About 2 out of 5 patients do use lipid lowering drugs. In the last timestamp, T1, every patient does receive diabetic medication and 9 out of 10 patients receive combination therapy. Besides, in all timestamps there is a decrease in the number of patients over the increasing number of medication. The last variable, HbA1c, seems to decrease over time.

Table 17: Specified descriptive statistics of T0

Medication at T0		LLD + (% of total)	LLD -	Total
Oral	+	0	0	0
	-	1447 (38,9)	2274 (61,1)	3721
Insulin	+	341 (25,6)	990 (74,4)	1331
	-	1106 (46,3)	1284 (53,7)	2390
Combination	+	1106 (46,3)	1284 (53,7)	2390
	-	341 (25,6)	990 (74,4)	1331
Number of oral	0	341 (25,6)	990 (74,4)	1131
	1	779 (49,0)	810 (51,0)	1589
	2	323 (41,3)	460 (58,7)	783
	3	4 (22,2)	14 (77,8)	18
Number of insulin	1	1234 (37,9)	2022 (62,1)	3256
	2	212 (45,8)	251 (54,2)	463
	3	1 (50,0)	1 (50,0)	2
Number of combination	1	267 (23,8)	853 (76,2)	1120
	2	736 (46,6)	845 (53,4)	1581
	3	419 (43,3)	548 (56,7)	967
	4	23 (45,1)	28 (54,9)	51
	5	2 (100,0)	0 (0,0)	2

In this table, the descriptive statistics are specified by the use of lipid lowering drugs. The endpoint is the number of patients who get combination therapy and LLD at T0, so this table is used for the calculation of relative risks. For every medication type, it seems that the greater proportion does not use LLD. However, the proportion of using lipid lowering drugs is increasing with the number of medication and the proportion of using LLD is 100% for patients who use 5 medications of combination therapy. It is also important to mention that the numbers of patients getting insulin or not is the opposite of patients getting combi therapy or not.

Table 18: Specified descriptives of T1

Medication at T1	LLD + (% of Total)	LLD -	Total
Oral +	69 (46,9)	78 (53,1)	147
Oral -	1010 (41,7)	1412 (58,3)	2422
Insulin +	229 (30,0)	535 (70,0)	764
Insulin -	850 (47,1)	955 (52,9)	1805
Combination +	732 (52,2)	671 (47,8)	1403
Combination -	347 (29,8)	819 (70,2)	1166
Number of oral 0	278 (27,3)	741 (72,7)	1019
1	587 (53,4)	513 (46,6)	1100
2	213 (48,0)	231 (52,0)	444
3	1 (16,7)	5 (83,3)	6
Number of insulin 0	118 (29,4)	284 (70,6)	402
1	795 (42,9)	1060 (57,1)	1855
2	163 (52,9)	145 (47,1)	308
3	3 (75,0)	1 (25,0)	4
Number of combination 0	49 (19,2)	206 (80,8)	255
1	222 (30,2)	514 (69,8)	736
2	518 (51,2)	494 (48,8)	1012
3	272 (50,7)	264 (49,3)	536
4	18 (62,1)	11 (37,9)	29
5	0 (0,0)	1 (100,0)	1

In T1, the distribution of LLD-users differs from that of T0. The proportion of using lipid-lowering drugs is increasing with the number of medication and becomes the greater proportion when the number of medication is high. So the greater proportion is shifting from not users to users of LLD. It is also important to mention that the numbers of patients are decreasing over increasing number of medications so these proportions are possibly less reliable.

Overview of differences over time and medication

Table 21: Scenarios from T-1 to T0

From T-1	To T0	N
O- LLD- (2459)	O- LLD+	1174
	O- LLD-	1285
	C- LLD-	792
	I- LLD-	493
	C+ LLD+	863
	I+ LLD+	311
	C+ LLD-	493
	I+ LLD-	792
	C- LLD+	311
	I- LLD+	863
O+ LLD- (1262)	O- LLD+	273
	O- LLD-	989
	C- LLD-	198
	I- LLD-	791
	C+ LLD+	243
	I+ LLD+	30
	C+ LLD-	791
	I+ LLD-	198
	C- LLD+	30
	I- LLD+	243

In this table, the numbers of patients with difference in diabetic medication and in LLD are shown from T-1 to T0. Due to the exclusion criterion, there are no users of LLD in T-1. In T0, insulin or combination therapy is possible. It is important to mention that the number of patients in T-1 is equal to the first two numbers of patients in T0, also that the number of patients for C- is equal to I+ (LLD is the same for these two) cause not having combi means directly having insulin here. Nearly the half of TO population from not oral users (O- in T-1) is using LLD (1174 of 2459). In T0, there are more patients who use combi and LLD (863) than insulin and LLD (311). There are more users of insulin not taking LLD (792) than users of combi not taking LLD (493). However, only a part of T0 population from oral users (O+ in T-1) is using LLD (273 of 1262). In T0, here are again more users of combi and LLD (243) than insulin and LLD (30). However, there are less users of insulin not taking LLD (198) than users of combi not taking LLD (791). Overall, these numbers are not relevant for the assessment of relative risks since LLD was not used in T-1 (no exposure in T-1).

Table 22: Scenarios From T0 to T1

From T0	To T1	N
C+ LLD- (1284)	O+ LLD+	13
	O+ LLD-	53
	O- LLD+	100
	O- LLD-	699
	C- LLD-	165
	I- LLD-	704
	C+ LLD+	93
	I+ LLD+	5
	C+ LLD-	587
	I+ LLD-	48
	C- LLD+	20
	I- LLD+	108
C+ LLD+ (1106)	O+ LLD+	**47**
	O+ LLD-	**15**
	O- LLD+	621
	O- LLD-	134
	C- LLD-	103
	I- LLD-	**115**
	C+ LLD+	**543**
	I+ LLD+	**23**
	C+ LLD-	**46**
	I+ LLD-	**34**
	C- LLD+	95
	I- LLD+	**645**
I+ LLD- (990)	O+ LLD+	5
	O+ LLD-	8
	O- LLD+	81
	O- LLD-	539
	C- LLD-	511
	I- LLD-	115
	C+ LLD+	37
	I+ LLD+	37
	C+ LLD-	36
	I+ LLD-	432
	C- LLD+	81
	I- LLD+	49
I+ LLD+ (341)	O+ LLD+	4
	O+ LLD-	2
	O- LLD+	208
	O- LLD-	40
	C- LLD-	40
	I- LLD-	21
	C+ LLD+	29
	I+ LLD+	164
	C+ LLD-	2
	I+ LLD-	21
	C- LLD+	183
	I- LLD+	48

Here, the numbers of patients with difference in diabetic medication and in LLD are shown from T0 to T1. These numbers are needed for the calculation of relative risks. These numbers are useful since LLD was used in T0. In T1, oral medication is again possible. Therefore more combinations are obtained. For the first group (C+ LLD- in T0), the biggest well-defined group in T1 is C+ LLD- (587). This means that combination therapy is the greatest group of diabetic medication for this subpopulation of T0 and a fewer patients using combi take LLD (93). The patients getting insulin in T1 is only 53, and 5 of them also taking LLD. Oral medication has small patient numbers, 13 for LLD users and 53 for non-users. So there are more oral patients than insulin patients.

The second group consists of patients who had combination therapy and LLD in T0 (C+ LLD+ at T0) and this group is of interest since this group is exposed to LLD prior outcome (insulin in T1) and only have insulin in T1 (outcome in T1 no outcome in T0). Here again, the biggest well-defined group is C+ LLD+ in T1 (543) so nearly the half of the population from T0 had no change in medication. From 57 insulin users in T1, 23 patients also use LLD. In T1, 62 patients used oral medication and 47 of them also took LLD. This means that for this T0-group, there are more oral medication patients than insulin patients in T1.

The third group consists of insulin users at T0 who did not take LLD. In T1, 37 patients took LLD and insulin and 432 patients remained in the same medication group as in T0. Oral medication was taken by only 13 patients in T1, 5 of them also LLD. Combination therapy was also a small group, 37 of 73 patients also used LLD.

The last group, patients using insulin and LLD in T0, is the smallest group of T0 and has low patients numbers for oral and combination therapy in T1. The numbers are respectively 6 and 31. LLD users from these medication groups are respectively 4 and 29. For insulin, there are 185 users and 164 of them also take LLD.

Main results

Longitudinal relative risks

Table 24:Relative risks of T0 to T1

Outcome	RR (95% CI)
Combination vs. Insulin	**0,0908 (0,0565 – 0,1460)**
Oral vs. Insulin	**0,4735 (0,3228 – 0,6946)**
No insulin vs. Insulin	**0,1509 (0,0917 – 0,2484)**

In this table, the relative risks are shown and these risks are all significantly below 1.The lowest risk was found for combination versus insulin, this risk is less than 0,10. The highest risk was found for oral medication (about 0,5), and logically the third risk would be between these two.

Regression analyses

Multiple linear regression

Multiple linear regression analysis was done for the relationship between lipid lowering drugs and HbA1c. Prediction of HbA1c is possible from age, gender, smoking, BMI and systolic blood pressure.

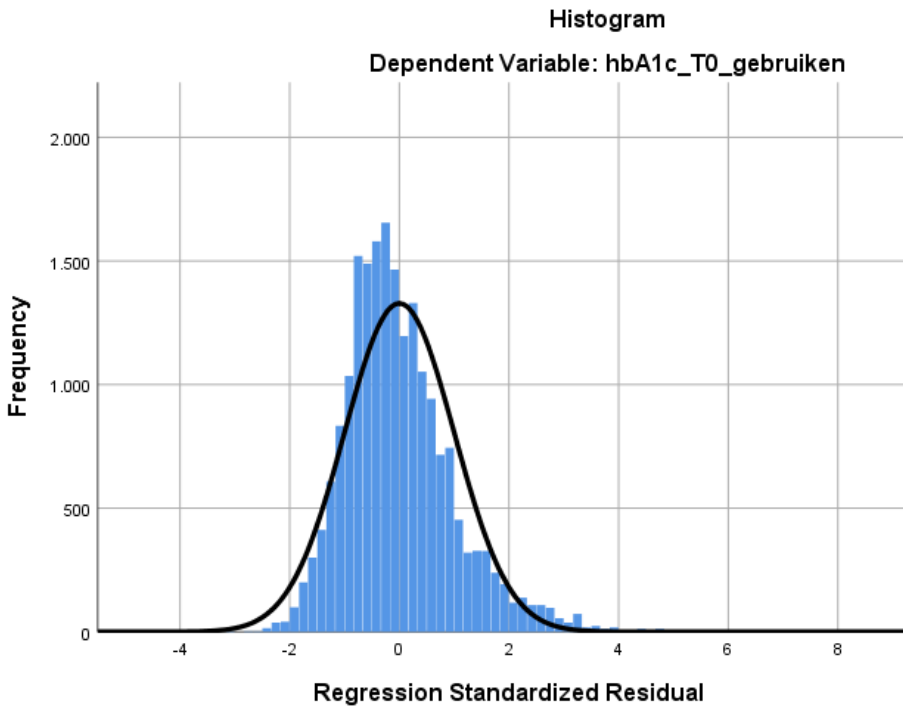

Figure 8: Normality check for HbA1c

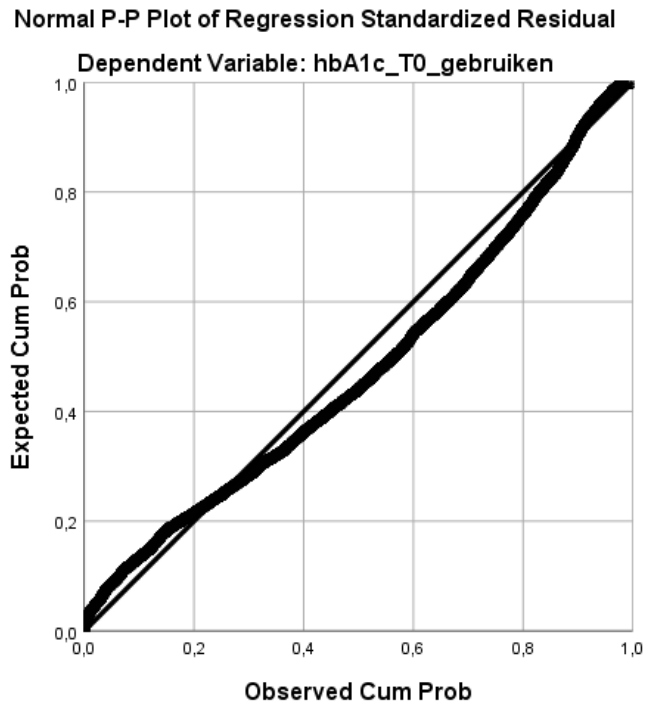

Figure 9: Checking for outliers by P-P plot.

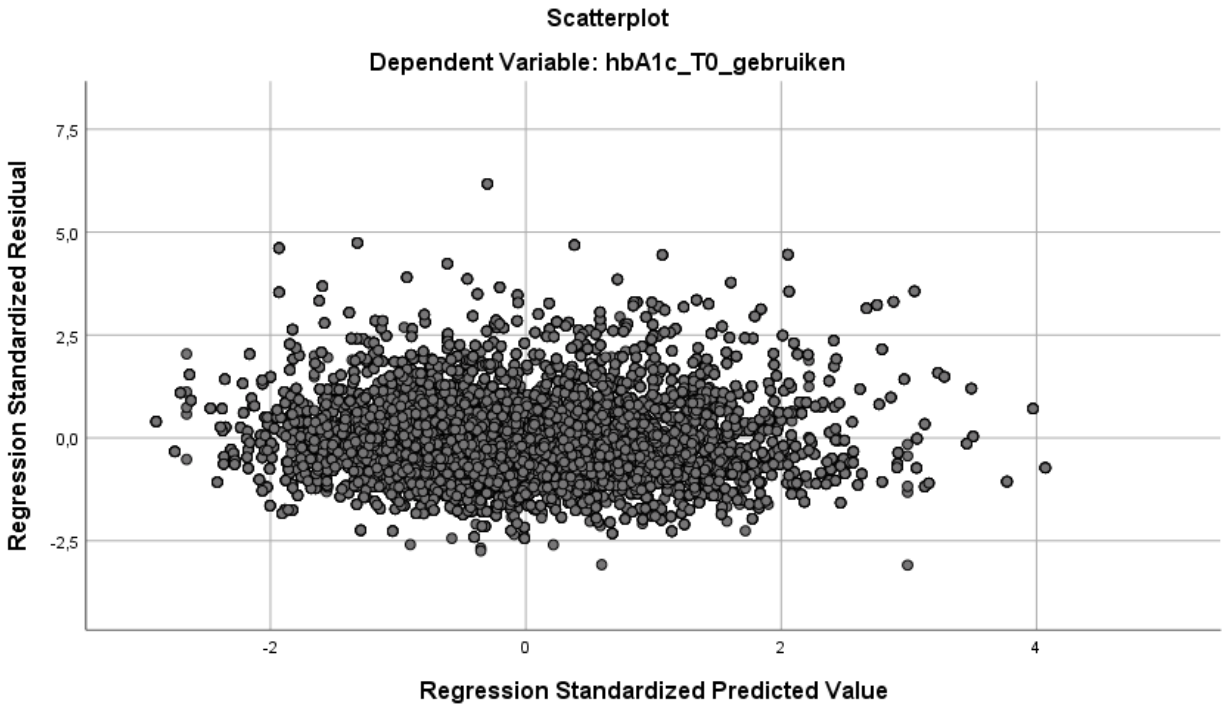

Figure 10: Homoscedasticity check by scatterplot

The figures above show that first HbA1c is normally distributed, second the standardized residuals have a normal distribution and last that the homoscedasticity model is satisfied. These assumptions are needed thus now a regression line can be obtained. The regression line is based on the dependent variables that have significant contribution to the regression model.

Table 23: Results of multiple linear regression on HbA1c, cross-sectional at T0

	Unstandardized coefficients		**Standardized coefficients**		
Model	**B**	**Std. Error**	**Beta**	**t**	**Sig.**
(Constant)	58,023	2,278		25,474	0,000
Lipidenverlagendemiddelen_T0	-0,689	0,403	-0,030	-1,709	0,087
Geslacht_T0	-0,121	0,407	-0,005	-0,297	0,766
Systolischebloeddruk_T0	0,019	0,011	0,030	1,674	0,094
BMI_T0_gebruiken	0,074	0,038	0,036	1,947	0,052
Roken_gebruiken_T0	-0,467	0,499	-0,017	-,0937	0,349
Leeftijd_T0	-0,060	0,017	-0,065	-3,460	0,001

Here the regression coefficients are shown for the regression model and only age seems to be significant ($p < 0,05$), inversely. This means that the regression line for HbA1c is

$Y = 58,023 - 0,06 X$

BMI is borderline significant ($p<0.1$, just as lipid lowering drugs and systolic blood pressure.

It is interesting that smoking, age and the use of lipid lowering drugs have negative regression coefficients since these variables are associated with higher HbA1c.

Logistic regression

Logistic regression analysis was done for the relationship between lipid lowering drugs and insulin. Prediction of getting insulin versus combi is based on odds ratios. These odds ratios were significant for age, gender, BMI, systolic blood pressure and the use of lipid lowering drugs. These odds ratios give information about the factor the risk is increased or not (per unit or classification). So for systolic blood pressure, the odds is 0,993 for every unit increase and for an increase of 10 units the odds would be 0,993^10. The odds ratios are shown in the last column and its significance on its left side and its confidence interval. Gender (being female) and age do positively contribute to the model. Systolic blood pressure, BMI and lipid lowering drugs have significant odds ratios of below 1. This means that taking lipid lowering drugs would likely decrease the risk of getting solely insulin.

Table 24: Results of logistic regression on insulin compared to combination therapy, cross-sectional at T0.

Model	B	Std. Error	df	Sig.	Exp (B) (95% CI)
(Constant)	-0,457	0,417	1	0,274	0,633
LLD_T0	-1,273	0,066	1	0,000	0,280 (0,246 – 0,319)
Geslacht_T0	0,169	0,069	1	0,014	1,185 (1,0355 – 1,355)
Systolischebloeddruk_T0	-0,007	0,002	1	0,001	0,993 (0.989 – 0,997)
BMI_T0_gebruiken	-0,014	0,007	1	0,035	0,986 (0,973 – 0,999)
Roken_gebruiken_T0	0,158	0,084	1	0,060	1,171 (0,994 – 1,380)
Leeftijd_T0	0,022	0,003	1	0,000	1,023 (1,016 – 1,029)
Lichaamsbeweging_gebruiken_T0	-0,097	0,417	1	0,181	0,908 (0,788 – 1,046)

It is important to mention that this model has a low predictive value since the Nagelkerke R square is only 0,139. The Hosmer and Lemeshow had a lower value of 0,087, which means that this model has a poor match of expected and observed values.

Discussion

Key results

This study showed a difference in the proxy ADVANCE risk score, suggesting that there is difference in cardiovascular risk before and after the initiation of insulin therapy. The cardiovascular risk (the proxy total score) was significantly increased when insulin therapy is started compared to previous year (T-1 vs. T0), also a year after insulin started (T-1 vs. T1) and between T0 and T1, which can be seen in table 11. The proxy scores are respectively 11,38, 11,83 and 12,04 and are shown in table 9. These scores are related to four-year risks of major CVD of 4,3 %. These risks seem not to be high for diabetic patients. [3] In the literature, reported prevalence of CVD among diabetic patients is higher, almost 33%. [12] So proxy ADVANCE showed difference in cardiovascular risk before and after insulin, but SCORE did not show that. At T-1 and T0, SCORE was 2,81 and 2,82 at T1 and this means also that in general the diabetic patient is at low risk for CVD , the SCORES are shown in table 12. However, the original coloured chart of SCORE shows a great green part and only the tops of the tables are orange and red. So this means that the age is an important factor to assess the risk and it was also not expected that the mean SCORE scores would be low as the mean ages of the patient population over the timestamps were nearly 70 years. A possible explanation for this could be that the elderly of the patient population are healthy, and that they could have a low systolic blood pressure and a low TC-HDL ratio. In this patient population, there are more women than men and the majority was non-smoker, which could also explain the odd finding. After all, non-smoking women are least likely to get a high SCORE.

Lipid lowering drugs and insulin

For the second association, relative risks were obtained to discover a difference in intensification of diabetic medication between patients who use lipid lowering drugs and patients who do not use lipid lowering drugs. These relative risks were not completely expected. The relative risk for getting solely insulin for example was in all cases significant below 1, while in literature an association between statins and increased insulin resistance is found. [13] [14]

Now, the regression analyses will be discussed. In multiple linear regression, the use of lipid lowering drugs did not affect HbA1c level as this was shown in the table. This is possibly due to the impossibilities mentioned earlier. Only age was able to significantly affect this outcome variable, in a negative way. It was not expected to find a negative regression coefficient for age since a positive association between age and HbA1c is known. Other variables did not contribute to the model and that is obvious since in literature associations were found. Another explanation is the exclusion criterion that resulted in a reduced patient population, if patients were not excluded then more information was available and the model would have more power. Lipid lowering drugs are mostly taken chronically and to exclude patients who used LLD in T-1 will result in a biased proportion of LLD users in T0. In logistic regression, more variables were found that had contribution to the model, including lipid lowering drugs. Other variables are age and systolic blood pressure. According to the model however, using lipid lowering drugs has a negative regression coefficient and an Odds ratio below 1. This means that using lipid lowering drugs is preventive which is possibly invalid due to more possible covariates like diabetes medication. This could explain the low Nagelkerke value.

Limitations

The Advance Risk function is a good method to assess CVR. However, some predictors and clinical parameters are not implemented in its model, like smoking, drinking, waist circumference and

exercising. Smoking is heavily associated with CVD since more than 10% of deaths worldwide from CVD in 2000 is because of smoking. Smoking is not only an independent risk factor, it interacts also with other major risk factors like high serum levels of lipids, untreated hypertension and diabetes mellitus. [15] Smoking increases 2 to 6 times the risk of coronary diseases or stroke and 2 to 4 times the risk of heart failure or peripheral vascular diseases than non-smoking. In one of six deaths as a result of coronary disease, the cause is smoking. That results in 1600 persons per year in the Netherlands. Drinking alcohol has ambiguous effect on CHD. Light or moderate drinking lowers the risk on CHD with 20 to 30% for middle aged people compared to non-drinkers. Excessive drinking leads to a higher risk of CHD and stroke than no or moderate drinking. [16] Measuring waist circumference (WC) is a good predictor of abdominal obesity. Waist circumferences of more than 102 cm for men and 88 cm for women are associated with high health risk. Shields et al found that both in men and women, an increase of 1 cm in WC was linked with 1.07 increase in the odds of having more than 2 CVD risk factors. [17] At last, exercising decreases cardiovascular mortality and prevents from cardiovascular disease. Regularly exercising lowers blood pressure, increases insulin sensitivity and ameliorates lipoprotein profile. [18]

So implementing these parameters will be useful for a better assessment. Three of these parameters were also present in the ZODIAC study, except waist circumference. Data of BMI were collected in the ZODIAC study but according to Shield et al. BMI does not give information about the distribution of body fat. Another limitation of the ZODIAC study is poor information about comorbidities, treated hypertension and atrial fibrillation are for instance found in the variables antihypertensive medication and beta-blockers. Beta-blockers have several indications, one of them is atrial fibrillation, and other indications are heart failure, hypertension, hyperthyroidism and migraine. [19] So there is an overestimation of patients who have atrial fibrillation since not all patients who use beta-blockers have atrial fibrillation.

Another interesting comorbidity is retinopathy. Retinopathy is one of the clinical parameters for ADVNACE This variable was assessed in two ways according to different diagnostic guidelines. It was possible to diagnose the patient as “retinopathy unclear” or “retinopathy indefinable”. These two options were considered as “no retinopathy” but this gives an invalid outcome. In case unclear or indefinable retinopathy, the ophthalmologist should repeat its diagnostic research because the outcome may be due to technical or instrumental error. This means that there is an underestimation of retinopathy in the patient population, patients with unclear retinopathy may have affected eyes.

Hypertension should be treated when the systolic blood pressure exceeds 140 mmHg according to CVRM, however patients are found with hypertension who are not treated with antihypertensive medication. Antihypertensive drugs are on the contrary also given to patients with a normal systolic blood pressure (so below 140 mmHg). So secondary care should be optimized and other clinical parameters should also be checked for such mishaps. Hypertension should be treated since hypertension is worldwide a major risk factor for CVD. In 2010, hypertension was responsible for 9,4 million deaths and 7,0% of disability-adjusted life years worldwide. [3]

A limitation of the ZODIAC study is the limited information about non-diabetic medication. This information is only qualitative, so the dose, type, the frequency and the number of non-diabetic medication are unknown. If this information was complete better assessment was possible for lipid lowering drugs.

Interpretation

Atrial fibrillation had an increasing prevalence between the three timestamps but the highest incidence was found between T-1 and T0 this is due to the power of the data at T0. These increases also have a significant P value of 0,000. Atrial fibrillation, is a comorbidity and therefore it was expected that this would be increasing over time. Retinopathy is a variable that showed a steady increase over the timestamps. It is also very logic that retinopathy is increasing over time since this comorbidity is hard to prevent. So it was expected that retinopathy would increase in prevalence over time. Hypertension also showed a significant increase over time but also with the highest incidence between T-1 and T0 so at T0 there is least missing data. Hypertension was expected to be increasing over time, due to worsened condition of the patients over time. Pulse pressure was nearly constant over time, so the P-value is not significant, not in one timestamp. This was not expected, a higher pulse pressure is associated with cardiac comorbidities like hypertension. HbA1c was significant decreasing over time, which was expected since insulin is a more reliable medicine to lower the HbA1c than oral diabetic medication. Albuminuria seemed to be significant increased over time but the lowest value was found at T0. The decrease of albuminuria from T-1 to T0 was also significant. This was not expected since albuminuria should be persistent increasing, just like retinopathy does. Non-HDL-C is the last variable and this variable showed an decrease over time but the decrease between T0 and T1 was not significant. This may be due to the other effects of insulin, stimulating production of fatty acids in the liver. [20]

It is known that diabetic patients have in general higher risk of CVD than non-diabetic healthy people. [3] Therefore, a low proxy ADVANCE and SCORE were not expected for this population. ADVANCE consists of clinical parameters that were discussed earlier and therefore the proxy ADVANCE is partly under or overestimated. The Dutch based SCORE charts that were used in this study are known to underestimate the CVD risk. The underestimation is due to incorrect multipliers, according to Jørstad et al. [21] They adjusted the multipliers that were needed to convert the SCORE mortality risk to SCORE combined risk. The multipliers to be adjusted were derived from two different national cohorts and were not validated in other large population based studies. Furthermore, these multipliers are based on only three clinical features of nonfatal CVD. The adjusted multipliers were derived from a large prospective population-based cohort in the UK named European Prospective Investigation of Cancer and Nutrition-Norfolk (EPIC-Norfolk). The adjusted multipliers were based on the ratios of fatal CVD to normal CVD and included a broad range of CVD. Another limitation of the SCORE is its simplicity of the variables. SCORE is developed for healthy people with no (anamnesis of) heart or coronary diseases but as earlier mentioned, other variables are also important but not implemented in the method. However, the parameters for the SCORE like TC-HDL ratio is beneficial over 1 type of fat since this ratio does the atherogenic component (plaque forming) in the numerator take into account as well as the anti-atherogenic component in the denominator. (lipoprotein ratios: physiological significance and clinical usefulness in cardiovascular prevention). Systolic blood pressure is a good parameter since it is a better predictor of CVD than diastolic blood pressure. Furthermore, increased diastolic blood pressure is associated with increased systolic blood pressure. An isolated increased diastolic blood pressure is a rare phenomenon while an isolated increased systolic pressure is seen in elderly. [3] So there are limited parameters but they seem to be valid and adaptation of SCORE is needed since underestimation leads to less prevention since more patients will have false low risk.

For the association between lipid lowering drugs and insulin, the obtained relative risks did not show a positive association. However, obtaining relative risks with this study is not fully legitimate since the order of outcome and exposure is not very known. There is just annually check of the patients, so just a point check. This was solved by longitudinal relative risks and still the relative risks were significantly below 1. Relative risks could also be obtained for difference over time and over difference in number of medication. However, this was not done. For the regression analyses, the contribution of lipid lowering drugs was only found in the logistic regression. In the multiple linear regression, contribution of lipid lowering drugs was significantly close. This means that it could be a contribution but when the model was optimized for possibly other covariates like diabetic medication. Then, the contribution would be still negative but perhaps in a different degree because of the regression coefficient (B = -0,689).

Generalizability

The generalizability of this study is moderate, since it is useful to do similar study but with greater population to minimalize impossibilities and to maximize the validity of the results. So further and comprehensive research is needed to minimize bias and to get a clear vision on the use of insulin and lipid lowering drugs and its effects.

Conclusion

In this study, relationship between insulin administration and CVR was investigated. This was done with two risk assessment methods namely SCORE and ADVANCE. SCORE is more general and ADVANCE specific for diabetes patients. These two methods showed low risks for diabetes patients. SCORE remained low before and after insulin (<2,82%) and ADVANCE showed an increase in risk from 11,38 to 12,83 and 12,04 over the timestamps. This study investigated also the relationship between the use of lipid lowering drugs and the intensification of diabetic medication. This was defined as the use of insulin and relative risks were assessed. The relative risks suggested that lipid lowering drugs are preventive in the use of insulin (about 0,5). Besides relative risks, regression analyses were performed. Logistic regression for the relationship between lipid lowering drugs and insulin, multiple linear regression analysis for the relationship between lipid lowering drugs and HbA1c level. Contribution of lipid lowering drugs was found in the logistic regression. This contribution was negative and the model was corrected for covariates. For both parts of the study, further research is needed and recommended.

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Appendices

Appendix 1:

Table 1: Type 1 DM vs. Type 2 DM

	Type 1 DM	Type 2 DM
Epidemiology	**Prevalence:** In 2018, 1.186.400 diabetic patients were known in the Netherlands. 624.900 (52,7%) of them were men and 561.500 (47,3%) are women. Of the total number, 9% has type I DM (10% men and 8% women). The majority of these patients were below 19 years old. Moreover, there is a reverse relationship between diabetes and education level. Among patients with immigration background, the prevalence is higher (at least two times). **Incidence:** 53.600 patients (4,5%) were new, 30.400 of them were male and 23.200 were female. (Volksgezondheidenzorg, 2019) https://www.volksgezondheidenzorg.info/onderwerp/diabetes-mellitus/cijfers-context/huidige-situatie	
Etiology	Autoimmune destruction of beta cells, with polymorphisms in human leukocyte antigen (HLA) and major histocompatibility complex (MHC). So hereditary is known, but environmental factors also for instance certain viruses and bacteria's. Type 1 Diabetes: Etiology, Immunology, and Therapeutic Strategies | Physiological Reviews	Obesity and aging play a key role. So this concerns lifestyle but also genetics (obesity). About 50 polymorphisms involved in type II DM are known. Environmental toxins are considered to be contributing factors. Type 2 Diabetes Mellitus: A Review of Current Trends
Pathophysiology	Hyperglycemia is the main characteristic. Changes in glucose transport, excess fatty acids due to lipid breakdown and pro-inflammatory cytokines are common. This leads to polydipsia, weight loss, nausea and fatigue. Non-enzymatic glycation of proteins and lipids also occur. Glycated hemoglobin can be measured and tested (HbA1c). Microvascular damage in retina, kidneys and peripheral nerves are linked with glycation. These damages can cause blindness, dialysis and amputation respectively. Macrovascular complications include angina pectoris, myocardial infarct and peripheral vascular disease.	
Management	The aim of the treatment is to maintain a good glucose regulation to prevent or minimalize the risk of micro-and macrovascular complications. Changing lifestyle and diet are from the beginning needed to optimize the effectiveness of the treatment and this is also first attempt of the treatment, especially for type 2. Education about the disease to acquire knowledge and insight is also included. https://www.ncbi.nlm.nih.gov/books/NBK551501/	
Intervention	The first step of the insulin scheme involves a short-acting insulin before meals (3 per day) with a (medium) long acting insulin for the night. This is called a basal-bolus insulin scheme. When this is less ideal or too stressful, an alternative scheme with mix-insulin is optional. This mix can be given twice a day or once with a short- or with a long acting insulin. Note: Setting insulin doses is based on blood glucose day curves. The HbA1c gives an impression of the average blood glucose over the past 2 months. The target value of the HbA1c is determined	Metformin is the first choice medicine. Sulfonylureas are added when metformin leads to side effects or maximum dosage is achieved and the glycemic control is still insufficient. Further additions of medicines like insulin, DPP4-inhibitor or GLP1 agonist may be needed. The BMI must be checked since GLP1-agonists have a weight losing effect and is preferable over DPP4-inhibitor if BMI > 35 kg/m^2. These additions may be combined with each other and in case of insulin, intensification is also possible. The preference is once an isophane insulin because of the rich experience and a good

	individually. https://www.farmacotherapeutischkompas.nl/bladeren/indicatieteksten/diabetes_mellitus_type_1	long term safety. Evaluation is always necessary to determine an addition or intensification. Intensification involves the first step of the insulin scheme or once insulin per day with a DPP4-inhibitor or with a GLP1-agonist. Note: all these medications, except insulin, are taken oral. https://www.farmacotherapeutischkompas.nl/bladeren/indicatieteksten/diabetes_mellitus_type_2

Appendix 2:

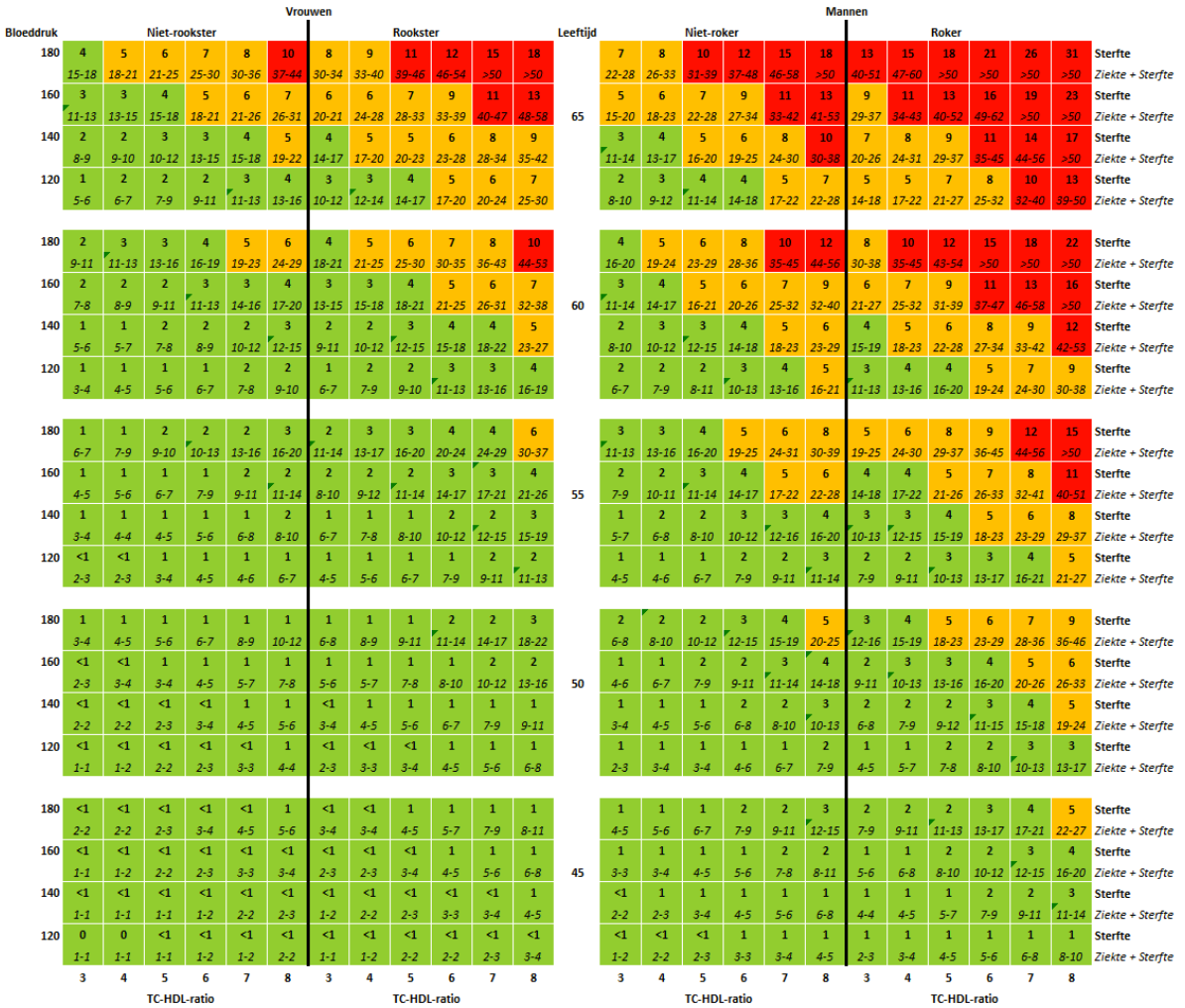
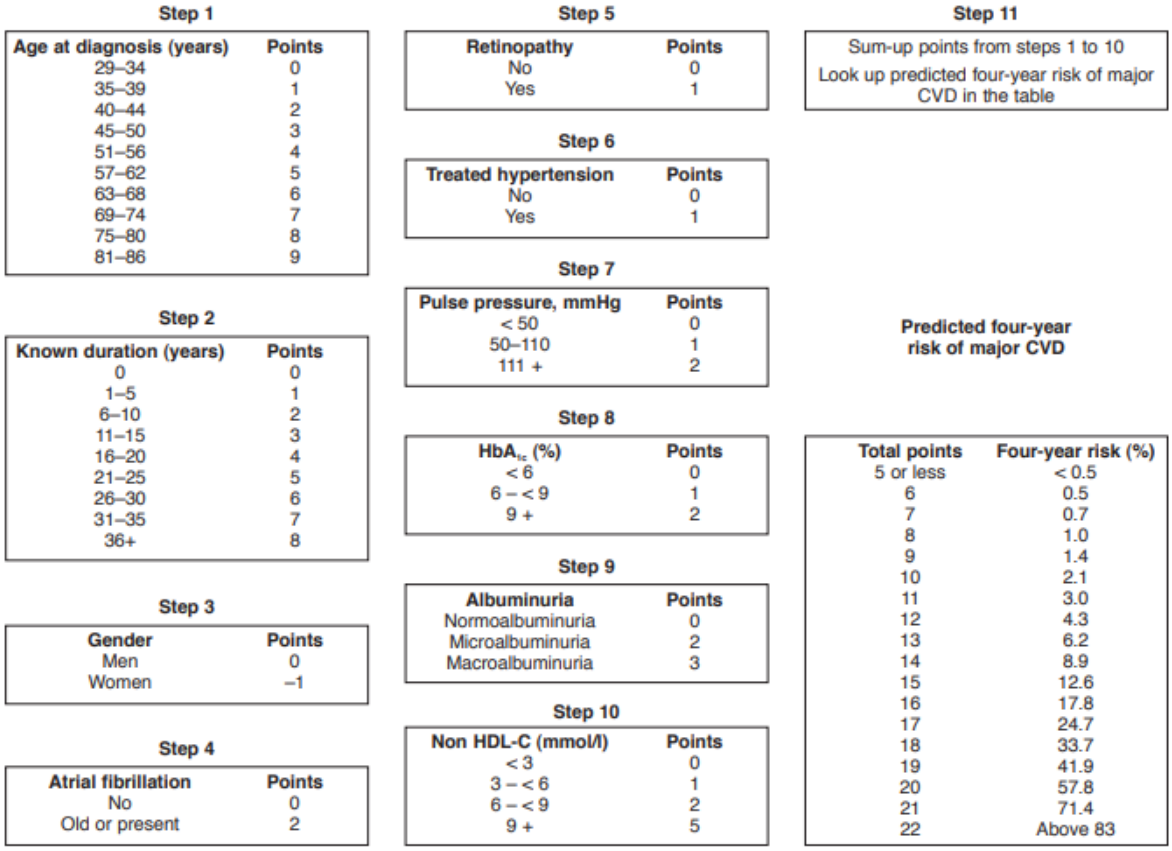


Figure 1: The SCORE table

Appendix 3:



Step 1

Age at diagnosis (years)	Points
29–34	0
35–39	1
40–44	2
45–50	3
51–56	4
57–62	5
63–68	6
69–74	7
75–80	8
81–86	9

Step 2

Known duration (years)	Points
0	0
1–5	1
6–10	2
11–15	3
16–20	4
21–25	5
26–30	6
31–35	7
36+	8

Step 3

Gender	Points
Men	0
Women	–1

Step 4

Atrial fibrillation	Points
No	0
Old or present	2

Step 5

Retinopathy	Points
No	0
Yes	1

Step 6

Treated hypertension	Points
No	0
Yes	1

Step 7

Pulse pressure, mmHg	Points
< 50	0
50–110	1
111 +	2

Step 8

HbA_{1c} (%)	Points
< 6	0
6 – < 9	1
9 +	2

Step 9

Albuminuria	Points
Normoalbuminuria	0
Microalbuminuria	2
Macroalbuminuria	3

Step 10

Non HDL-C (mmol/l)	Points
< 3	0
3 – < 6	1
6 – < 9	2
9 +	5

Step 11

Sum-up points from steps 1 to 10

Look up predicted four-year risk of major CVD in the table

Predicted four-year risk of major CVD

Total points	Four-year risk (%)
5 or less	< 0.5
6	0.5
7	0.7
8	1.0
9	1.4
10	2.1
11	3.0
12	4.3
13	6.2
14	8.9
15	12.6
16	17.8
17	24.7
18	33.7
19	41.9
20	57.8
21	71.4
22	Above 83

Figure 2: Clinical parameters for the assessment of the ADVANCE score

Appendix 4:

Syntax of proxy ADVANCE for T-1

* Encoding: UTF-8.

```
**********************************************************************************
**********************************DIAGNOSESCORE
**********************************************************************************
**********************************


*DiagnoseScore.


FREQUENCIES VARIABLES=

DSG_LeeftijdTenTijdeDiagnose


NUMERIC DiagnoseScore_min1 (F1.0).
```

```
EXECUTE.

IF DSG_LeeftijdTenTijdeDiagnose <=34 diagnosScore_min1 = 0.
IF DSG_LeeftijdTenTijdeDiagnose >=35 AND DSG_LeeftijdTenTijdeDiagnose <=39 DiagnoseScore = 1.
IF DSG_LeeftijdTenTijdeDiagnose >=40 AND DSG_LeeftijdTenTijdeDiagnose <=44 DiagnoseScore = 2.
IF DSG_LeeftijdTenTijdeDiagnose >=45 AND DSG_LeeftijdTenTijdeDiagnose <=50 DiagnoseScore = 3.
IF DSG_LeeftijdTenTijdeDiagnose >=51 AND DSG_LeeftijdTenTijdeDiagnose <=56 DiagnoseScore = 4.
IF DSG_LeeftijdTenTijdeDiagnose >=57 AND DSG_LeeftijdTenTijdeDiagnose <=62 DiagnoseScore = 5.
IF DSG_LeeftijdTenTijdeDiagnose >=63 AND DSG_LeeftijdTenTijdeDiagnose <=68 DiagnoseScore = 6.
IF DSG_LeeftijdTenTijdeDiagnose >=69 AND DSG_LeeftijdTenTijdeDiagnose <=74 DiagnoseScore = 7.
IF DSG_LeeftijdTenTijdeDiagnose >=75 AND DSG_LeeftijdTenTijdeDiagnose <=80 DiagnoseScore = 8.
IF DSG_LeeftijdTenTijdeDiagnose >=81 AND DSG_LeeftijdTenTijdeDiagnose <=86 DiagnoseScore = 9.
EXECUTE.

FREQUENCIES VARIABLES=
DiagnoseScore
/ORDER=ANALYSIS.



*********************************************************************************
**********************************DUURSCORE
*********************************************************************************
*********************************

*DuurScore_min1.

FREQUENCIES VARIABLES=
DSG_DiabetesDuur_Min1

NUMERIC DuurScore_min1 (F1.0).
EXECUTE.
```

```
IF DSG_DiabetesDuur_Min1 = 0 DuurScore_min1 = 0.
IF DSG_DiabetesDuur_Min1 >= 1 AND DSG_DiabetesDuur_Min1 <=5 DuurScore_min1 = 1.
IF DSG_DiabetesDuur_Min1 >= 6 AND DSG_DiabetesDuur_Min1 <=10 DuurScore_min1 = 2.
IF DSG_DiabetesDuur_Min1 >= 11 AND DSG_DiabetesDuur_Min1 <=15 DuurScore_min1 = 3.
IF DSG_DiabetesDuur_Min1 >= 16 AND DSG_DiabetesDuur_Min1 <=20 DuurScore_min1 = 4.
IF DSG_DiabetesDuur_Min1 >= 21 AND DSG_DiabetesDuur_Min1 <=25 DuurScore_min1 = 5.
IF DSG_DiabetesDuur_Min1 >= 26 AND DSG_DiabetesDuur_Min1 <=30 DuurScore_min1 = 6.
IF DSG_DiabetesDuur_Min1 >= 31 AND DSG_DiabetesDuur_Min1 <=35 DuurScore_min1 = 7.
IF DSG_DiabetesDuur_Min1 >35 DuurScore_min1 = 8.
EXECUTE.

FREQUENCIES VARIABLES=
DuurScore_min1
/ORDER=ANALYSIS

**********************************************************************************
**********************************GESLACHTSCORE
**********************************************************************************
**********************************

*GeslachtScore_min1.

FREQUENCIES VARIABLES=
Geslacht_Min1

NUMERIC GeslachtScore_min1 (F1.0).
EXECUTE.

IF Geslacht_min1 = 0 GeslachtScore_min1 = 0.
IF Geslacht_min1 = 1 GeslachtScore_min1 = -1.
EXECUTE.
```

```
FREQUENCIES VARIABLES=
GeslachtScore_Min1
/ORDER=ANALYSIS


********************************************************************************
**********************************BETASCORE
********************************************************************************
**********************************

*BetaScore_min1.

FREQUENCIES VARIABLES=
Bètareceptroblokkerendesympaticolytica_min1

NUMERIC BetaScore_min1 (F1.0).
EXECUTE.

IF Bètareceptroblokkerendesympaticolytica_min1 = 0 BetasScore_min1 = 0.
IF Bètareceptroblokkerendesympaticolytica_min1 = 1 BetasScore_min1 = 2.
EXECUTE.

FREQUENCIES VARIABLES=
BetaScore_Min1
/ORDER=ANALYSIS


********************************************************************************
**********************************RETINOPATHIESCORE
********************************************************************************
**********************************
```

```
*RetinopathieScore_min1.

FREQUENCIES VARIABLES=
Retinopathie_min1

NUMERIC RetinopathieScore_min1 (F1.0).
EXECUTE.

IF Retinopathie_min1 = 0 RetinopathieScore_min1 = 0.
IF Retinopathie_min1 = 1 RetinopathieScore_min1 = 1.
EXECUTE.

FREQUENCIES VARIABLES=
RetinopathieScore_Min1
/ORDER=ANALYSIS

*******************************************************************************
**********************************ANTIHYPERTENSIESCORE
*******************************************************************************
*********************************

*AntihypertensieScore_min1.

FREQUENCIES VARIABLES=
Antihypertensiva_min1


NUMERIC AntihypertensieScore_min1 (F1.0).
EXECUTE.

IF Antihypertensiva_min1 = 0 AntihypertensieScore_min1 = 0.
IF Antihypertensiva_min1 = 1 AntihypertensieScore_min1 = 1.
```

```
EXECUTE.

FREQUENCIES VARIABLES=
AntihypertensieScore_Min1
/ORDER=ANALYSIS

*********************************************************************************
**********************************DELTABPSCORE
*********************************************************************************
*********************************

*DeltaBPScore_min1.

FREQUENCIES VARIABLES=
DeltaBP_min1

NUMERIC DeltaBPScore_min1 (F1.0).
EXECUTE.

IF DeltaBP_min1 < 50 DeltaBPScore_min1 = 0.
IF DeltaBP_min1 >=50 AND DeltaBP_min1 <=110 DeltaBPScore_min1 = 1.
IF DeltaBP_min1 >111 DeltaBPScore_min1 = 2.
EXECUTE.

FREQUENCIES VARIABLES=
DeltaBPScore_Min1
/ORDER=ANALYSIS

*********************************************************************************
**********************************HBA1CSCORE
*********************************************************************************
*********************************
```

```
*HbA1cScore_min1.

FREQUENCIES VARIABLES=
HbA1c_min1_gebruiken

NUMERIC DeltaBPScore_min1 (F1.0).
EXECUTE.
IF HbA1c_min1_gebruiken < 6 HbA1cScore_min1 = 0.
IF HbA1c_min1_gebruiken >=6 AND HbA1c_min1_gebruiken <= 9 HbA1cScore_min1 = 1.
IF HbA1c_min1_gebruiken > 9 HbA1cScore_min1 = 2.
EXECUTE.

FREQUENCIES VARIABLES=
HbA1cScore_Min1
/ORDER=ANALYSIS

*********************************************************************************
**********************************ALBUMINESCORE
*********************************************************************************
**********************************

*AlbumineScore_min1.

FREQUENCIES VARIABLES=
Albuminekreatratio_min1

NUMERIC AlbumineScore_min1 (F1.0).
EXECUTE.

IF Albuminekreatratio_min1 < 3          AlbumineScore_min1 = 0.
IF Albuminekreatratio_min1 >=3 AND Albuminekreatratio_min1 <=30 AlbumineScore_min1 = 2.
```

```
IF Albuminekreatratio_min1 >30 AlbumineScore_min1 = 3.
EXECUTE.

FREQUENCIES VARIABLES=
AlbumineScore_min1
/ORDER=ANALYSIS

************************************************************************************
**********************************CHOLTOTMINHDLSCORE
************************************************************************************
*********************************

*CholtotMinHDLScore_min1.

FREQUENCIES VARIABLES=
CholtotMinHDL_Min1

NUMERIC CholtotMinHDLScore_min1 (F1.0).
EXECUTE.

IF CholtotMinHDL_Min1 < 3 CholtotMinHDLScore_min1 = 0.
IF CholtotMinHDL_Min1 >=3 AND CholtotMinHDL_Min1 <=6 CholtotMinHDLScore_min1 = 1.
IF CholtotMinHDL_Min1 >=7 AND CholtotMinHDL_Min1 <=9 CholtotMinHDLScore_min1 = 2.
IF CholtotMinHDL_Min1 >9 CholtotMinHDLScore_min1 = 5.
EXECUTE.

FREQUENCIES VARIABLES=
CholtotMinHDLScore_min1
/ORDER=ANALYSIS
```

```
*********************************************************************************
**********************************TOTAALSCORE
*********************************************************************************
**********************************
```

```
*TotaalScore_min1.

FREQUENCIES VARIABLES=
DiagnoseScore
DuurScore_min1
GeslachtScore_min1
BetaScore_min1
RetinopathieScore_min1
AntihypertensieScore_min1
DeltaBPScore_min1
HbA1cScore_min1
AlbumineScore_min1
CholtotMinHDLScore_min1

NUMERIC TotaalsScore_min1 (F2.0).
EXECUTE.

COMPUTE TotaalScore_min1 = DiagnoseScore + DuurScore_min1 + GeslachtScore_min1 +
BetaScore_min1 + RetinopathieScore_min1 + AntihypertensieScore_min1 + DeltaBPScore_min1 +
HbA1cScore_min1 + AlbumineScore_min1 + CholtotMinHDLScore_min1.
EXECUTE

FREQUENCIES VARIABLES=
TotaalScore_min1
/ORDER=ANALYSIS
```

```
************************************************************************************
**********************************

*Retinopathie

************************************************************************************
**********************************


*Retinopathie_plus1.


FREQUENCIES VARIABLES=

diabetischeretinopathielinkeroog_gebruiken_plus1

diabetischeretinopathierechteroog_gebruiken_plus1



NUMERIC Retinopathie_plus1 (F1.0).

EXECUTE.


IF diabetischeretinopathielinkeroog_gebruiken_plus1 = 1 OR
diabetischeretinopathierechteroog_gebruiken_plus1 = 1  Retinopathie_plus1 = 1.

IF diabetischeretinopathielinkeroog_gebruiken_plus1 = 0 AND
diabetischeretinopathierechteroog_gebruiken_plus1 = 0 Retinopathie_plus1 = 0.

EXECUTE.


FREQUENCIES VARIABLES=

Retinopathie_plus1

/ORDER=ANALYSIS
```

Appendix 5:
Syntax for SCORE_T-1

**********SCORE_MIN1**********

****

*SCORE_min1.

FREQUENCIES VARIABLES=

Geslacht_min1

Roken_gebruiken_Min1

Totcholgedeelddhdlchol_min1

Systolischebloeddruk_min1

Leeftijd_min1

NUMERIC SCORE_min1 (F1.0).

EXECUTE.

IF Geslacht_min1 = 1 AND Roken_gebruiken_Min1 = 1 AND Totcholgedeelddhdlchol_min1 > 8 AND systolischebloeddruk_min1 >= 181 AND leeftijd_min1 >=56 AND leeftijd_min1 <=60 SCORE_min1 = 3.

IF Geslacht_min1 = 1 AND Roken_gebruiken_Min1 = 1 AND Totcholgedeelddhdlchol_min1 > 7 AND systolischebloeddruk_min1 >= 161 AND leeftijd_min1 >=61 SCORE_min1 = 3.

IF Geslacht_min1 = 1 AND Roken_gebruiken_Min1 = 1 AND Totcholgedeelddhdlchol_min1 > 5 AND systolischebloeddruk_min1 >= 181 AND leeftijd_min1 >=61 SCORE_min1 = 3.

IF Geslacht_min1 = 1 AND Roken_gebruiken_Min1 = 1 AND Totcholgedeelddhdlchol_min1 > 8 AND systolischebloeddruk_min1 >= 181 AND leeftijd_min1 >=61 SCORE_min1 = 3.

IF Geslacht_min1 = 0 AND Roken_gebruiken_Min1 = 1 AND Totcholgedeelddhdlchol_min1 > 8 AND systolischebloeddruk_min1 >= 161 AND leeftijd_min1 >=51 AND leeftijd_min1 <=55 SCORE_min1 = 3.

IF Geslacht_min1 = 0 AND Roken_gebruiken_Min1 = 1 AND Totcholgedeelddhdlchol_min1 > 7 AND systolischebloeddruk_min1 >= 181 AND leeftijd_min1 >=51 AND leeftijd_min1 <=55 SCORE_min1 = 3.

IF Geslacht_min1 = 0 AND Roken_gebruiken_Min1 = 1 AND Totcholgedeelddhdlchol_min1 > 8 AND systolischebloeddruk_min1 >= 141 AND systolischebloeddruk_min1 <=160 AND leeftijd_min1 >=56 AND leeftijd_min1 <=60 SCORE_min1 = 3.

IF Geslacht_min1 = 0 AND Roken_gebruiken_Min1 = 1 AND Totcholgedeelddhdlchol_min1 > 6 AND systolischebloeddruk_min1 >= 161 AND systolischebloeddruk_min1 <=180 AND leeftijd_min1 >=56 AND leeftijd_min1 <=60 SCORE_min1 = 3.

IF Geslacht_min1 = 0 AND Roken_gebruiken_Min1 = 1 AND Totcholgedeelddhdlchol_min1 > 4 AND systolischebloeddruk_min1 >= 181 AND leeftijd_min1 >=56 AND leeftijd_min1 <=60 SCORE_min1 = 3.

IF Geslacht_min1 = 0 AND Roken_gebruiken_Min1 = 1 AND Totcholgedeelddhdlchol_min1 > 7 AND systolischebloeddruk_min1 >= 120 AND systolischebloeddruk_min1 <=140 AND leeftijd_min1 >=61 SCORE_min1 = 3.

IF Geslacht_min1 = 0 AND Roken_gebruiken_Min1 = 1 AND Totcholgedeelddhdlchol_min1 > 6 AND systolischebloeddruk_min1 >= 141 AND systolischebloeddruk_min1 <=160 AND leeftijd_min1 >=61 SCORE_min1 = 3.

IF Geslacht_min1 = 0 AND Roken_gebruiken_Min1 = 1 AND Totcholgedeelddhdlchol_min1 > 4 AND systolischebloeddruk_min1 >= 161 AND systolischebloeddruk_min1 <=180 AND leeftijd_min1 >=61 SCORE_min1 = 3.

IF Geslacht_min1 = 0 AND Roken_gebruiken_Min1 = 1 AND Totcholgedeelddhdlchol_min1 > 3 AND systolischebloeddruk_min1 >= 181 AND leeftijd_min1 >=61 SCORE_min1 = 3.

IF Geslacht_min1 = 0 AND Roken_gebruiken_Min1 = 0 AND Totcholgedeelddhdlchol_min1 > 7 AND systolischebloeddruk_min1 >= 181 AND leeftijd_min1 >= 56 AND leeftijd_min1 <=60 SCORE_min1 = 3.

IF Geslacht_min1 = 0 AND Roken_gebruiken_Min1 = 0 AND Totcholgedeelddhdlchol_min1 > 8 AND systolischebloeddruk_min1 >= 141 AND systolischebloeddruk_min1 <=160 AND leeftijd_min1 >= 61 SCORE_min1 = 3.

IF Geslacht_min1 = 0 AND Roken_gebruiken_Min1 = 0 AND Totcholgedeelddhdlchol_min1 > 7 AND systolischebloeddruk_min1 >= 161 AND systolischebloeddruk_min1 <=180 AND leeftijd_min1 >= 61 SCORE_min1 = 3.

IF Geslacht_min1 = 0 AND Roken_gebruiken_Min1 = 0 AND Totcholgedeelddhdlchol_min1 > 5 AND systolischebloeddruk_min1 >= 181 AND leeftijd_min1 >= 61 SCORE_min1 = 3.

IF Geslacht_min1 = 1 AND Roken_gebruiken_Min1 = 1 AND Totcholgedeelddhdlchol_min1 > 8 AND systolischebloeddruk_min1 >= 181 AND leeftijd_min1 >=51 AND leeftijd_min1 <=55 SCORE_min1 = 2.

IF Geslacht_min1 = 1 AND Roken_gebruiken_Min1 = 1 AND Totcholgedeelddhdlchol_min1 > 8 AND systolischebloeddruk_min1 >= 141 AND leeftijd_min1 >=56 AND leeftijd_min1 <=60 SCORE_min1 = 2.

IF Geslacht_min1 = 1 AND Roken_gebruiken_Min1 = 1 AND Totcholgedeelddhdlchol_min1 > 6 AND systolischebloeddruk_min1 >= 161 AND systolischebloeddruk_min1 <= 180 AND leeftijd_min1 >=56 AND leeftijd_min1 <=60 SCORE_min1 = 2.

IF Geslacht_min1 = 1 AND Roken_gebruiken_Min1 = 1 AND Totcholgedeelddhdlchol_min1 > 4 AND totcholgedeelddhdlchol_min1 <= 8 AND systolischebloeddruk_min1 >= 181 AND leeftijd_min1 >=56 AND leeftijd_min1 <=60 SCORE_min1 = 2.

IF Geslacht_min1 = 1 AND Roken_gebruiken_Min1 = 1 AND Totcholgedeelddhdlchol_min1 > 6 AND systolischebloeddruk_min1 >= 120 AND systolischebloeddruk_min1 <= 140 AND leeftijd_min1 >=61 SCORE_min1 = 2.

IF Geslacht_min1 = 1 AND Roken_gebruiken_Min1 = 1 AND Totcholgedeelddhdlchol_min1 >4 AND systolischebloeddruk_min1 >= 141 AND systolischebloeddruk_min1 <= 160 AND leeftijd_min1 >=61 SCORE_min1 = 2.

IF Geslacht_min1 = 1 AND Roken_gebruiken_Min1 = 1 AND Totcholgedeelddhdlchol_min1 >3 AND totcholgedelddhdlchol_min1 <=7 AND systolischebloeddruk_min1 >= 161 AND systolischebloeddruk_min1 <= 180 AND leeftijd_min1 >=61 SCORE_min1 = 2.

IF Geslacht_min1 = 1 AND Roken_gebruiken_Min1 = 1 AND Totcholgedeelddhdlchol_min1 >3 AND totcholgedelddhdlchol_min1 <=5 AND systolischebloeddruk_min1 >= 181 AND leeftijd_min1 >=61 SCORE_min1 = 2.

IF Geslacht_min1 = 1 AND Roken_gebruiken_Min1 = 0 AND Totcholgedeelddhdlchol_min1 >7 AND systolischebloeddruk_min1 >= 181 AND leeftijd_min1 >=56 AND leeftijd_min1 <=60 SCORE_min1 = 2.

IF Geslacht_min1 = 1 AND Roken_gebruiken_Min1 = 0 AND Totcholgedeelddhdlchol_min1 >8 AND systolischebloeddruk_min1 >= 141 AND systolischebloeddruk_min1 <= 160 AND leeftijd_min1 >=61 SCORE_min1 = 2.

IF Geslacht_min1 = 1 AND Roken_gebruiken_Min1 = 0 AND Totcholgedeelddhdlchol_min1 >6 AND systolischebloeddruk_min1 >= 161 AND systolischebloeddruk_min1 <= 180 AND leeftijd_min1 >=61 SCORE_min1 = 2.

IF Geslacht_min1 = 1 AND Roken_gebruiken_Min1 = 0 AND Totcholgedeelddhdlchol_min1 > 4 AND totcholgedeelddhdlchol_min1 <=8 AND systolischebloeddruk_min1 >= 181 AND leeftijd_min1 >=61 SCORE_min1 = 2.

IF Geslacht_min1 = 0 AND Roken_gebruiken_Min1 = 1 AND Totcholgedeelddhdlchol_min1 > 8 AND systolischebloeddruk_min1 >= 181 AND leeftijd_min1 >=40 AND leeftijd_min1 <= 45 SCORE_min1 =2.

IF Geslacht_min1 = 0 AND Roken_gebruiken_Min1 = 1 AND Totcholgedeelddhdlchol_min1 > 8 AND systolischebloeddruk_min1 >= 141 AND systolischebloeddruk_min1 <=160 AND leeftijd_min1 >=46 AND leeftijd_min1 <= 50 SCORE_min1 =2.

IF Geslacht_min1 = 0 AND Roken_gebruiken_Min1 = 1 AND Totcholgedeelddhdlchol_min1 > 7 AND systolischebloeddruk_min1 >= 161 AND systolischebloeddruk_min1 <=180 AND leeftijd_min1 >=46 AND leeftijd_min1 <= 50 SCORE_min1 =2.

IF Geslacht_min1 = 0 AND Roken_gebruiken_Min1 = 1 AND Totcholgedeelddhdlchol_min1 > 5 AND systolischebloeddruk_min1 >= 181 AND leeftijd_min1 >=46 AND leeftijd_min1 <= 50 SCORE_min1 =2.

IF Geslacht_min1 = 0 AND Roken_gebruiken_Min1 = 1 AND Totcholgedeelddhdlchol_min1 > 8 AND systolischebloeddruk_min1 >= 120 AND systolischebloeddruk_min1 <=140 AND leeftijd_min1 >=51 AND leeftijd_min1 <= 55 SCORE_min1 =2.

IF Geslacht_min1 = 0 AND Roken_gebruiken_Min1 = 1 AND Totcholgedeelddhdlchol_min1 > 6 AND systolischebloeddruk_min1 >= 141 AND systolischebloeddruk_min1 <=161 AND leeftijd_min1 >=51 AND leeftijd_min1 <= 55 SCORE_min1 =2.

IF Geslacht_min1 =0 AND Roken_gebruiken_min1 =1 AND Totcholgedeelddhdlchol_min1 >5 AND totcholgedeelddhdlchol_min1 <=8 AND systolischebloeddruk_min1 >=161 and systolischebloeddruk_min1<=180 and leeftijd_min1 >=51 and leeftijd_min1 <=55 SCORE_min1 =2.

IF Geslacht_min1 =0 AND Roken_gebruiken_min1 =1 AND Totcholgedeelddhdlchol_min1 >=3 AND totcholgedeelddhdlchol_min1 <=7 AND systolischebloeddruk_min1 >=181 and leeftijd_min1 >=51 and leeftijd_min1 <=55 SCORE_min1 =2.

IF Geslacht_min1 =0 AND Roken_gebruiken_min1 =1 AND Totcholgedeelddhdlchol_min1 >6 AND systolischebloeddruk_min1 >=120 and systolischebloeddruk_min1<=141 and leeftijd_min1 >=56 and leeftijd_min1 <=60 SCORE_min1 =2.

IF Geslacht_min1 =0 AND Roken_gebruiken_min1 =1 AND Totcholgedeelddhdlchol_min1 >4 AND totcholgedeelddhdlchol_min1 <=8 AND systolischebloeddruk_min1 >=141 and systolischebloeddruk_min1<=160 and leeftijd_min1 >=56 and leeftijd_min1 <=60 SCORE_min1 =2.

IF Geslacht_min1 =0 AND Roken_gebruiken_min1 =1 AND Totcholgedeelddhdlchol_min1 >=3 AND totcholgedeelddhdlchol_min1 <=6 AND systolischebloeddruk_min1 >=161 and systolischebloeddruk_min1<=180 and leeftijd_min1 >=56 and leeftijd_min1 <=60 SCORE_min1 =2.

IF Geslacht_min1 =0 AND Roken_gebruiken_min1 =1 AND Totcholgedeelddhdlchol_min1 >=3 AND totcholgedeelddhdlchol_min1 <=4 AND systolischebloeddruk_min1 >=181 and leeftijd_min1 >=56 and leeftijd_min1 <=60 SCORE_min1 =2.

IF Geslacht_min1 =0 AND Roken_gebruiken_min1 =1 AND Totcholgedeelddhdlchol_min1 >=3 AND totcholgedeelddhdlchol_min1 <=7 AND systolischebloeddruk_min1 >=120 and systolischebloeddruk_min1<=140 and leeftijd_min1 >=61 SCORE_min1 =2.

IF Geslacht_min1 =0 AND Roken_gebruiken_min1 =1 AND Totcholgedeelddhdlchol_min1 >=3 AND totcholgedeelddhdlchol_min1 <=6 AND systolischebloeddruk_min1 >=141 and systolischebloeddruk_min1<=160 and leeftijd_min1 >=61 SCORE_min1 =2.

IF Geslacht_min1 =0 AND Roken_gebruiken_min1 =1 AND Totcholgedeelddhdlchol_min1 >=3 AND totcholgedeelddhdlchol_min1 <=4 AND systolischebloeddruk_min1 >=161 and systolischebloeddruk_min1<=180 and leeftijd_min1 >=61 SCORE_min1 =2.

IF Geslacht_min1 =0 AND Roken_gebruiken_min1 =0 AND Totcholgedeelddhdlchol_min1 > 8 AND systolischebloeddruk_min1 >=181 and leeftijd_min1 >=46 and leeftijd_min1 <=50 SCORE_min1 =2.

IF Geslacht_min1 =0 AND Roken_gebruiken_min1 =0 AND Totcholgedeelddhdlchol_min1 >7 AND systolischebloeddruk_min1 >=161 and systolischebloeddruk_min1<=180 and leeftijd_min1 >=51 and leeftijd_min1 <=55 SCORE_min1 =2.

IF Geslacht_min1 =0 AND Roken_gebruiken_min1 =0 AND Totcholgedeelddhdlchol_min1 >6 AND systolischebloeddruk_min1 >=181 and leeftijd_min1 >=51 and leeftijd_min1 <= 55 SCORE_min1 =2.

IF Geslacht_min1 =0 AND Roken_gebruiken_min1 =0 AND Totcholgedeelddhdlchol_min1 >8 AND systolischebloeddruk_min1 >=120 and systolischebloeddruk_min1<=140 and leeftijd_min1 >=56 and leeftijd_min1<=60 SCORE_min1 =2.

IF Geslacht_min1 =0 AND Roken_gebruiken_min1 =0 AND Totcholgedeelddhdlchol_min1 >7 AND systolischebloeddruk_min1 >=141 and systolischebloeddruk_min1<=160 and leeftijd_min1 >=56 and leeftijd_min1<=60 SCORE_min1 =2.

IF Geslacht_min1 =0 AND Roken_gebruiken_min1 =0 AND Totcholgedeelddhdlchol_min1 >5 AND systolischebloeddruk_min1 >=161 and systolischebloeddruk_min1<=180 and leeftijd_min1 >=56 and leeftijd_min1<=60 SCORE_min1 =2.

IF Geslacht_min1 =0 AND Roken_gebruiken_min1 =0 AND Totcholgedeelddhdlchol_min1 >4 and totcholgedeelddhdlchol_min1 <=7 AND systolischebloeddruk_min1 >=181 and leeftijd_min1 >=56 and leeftijd_min1<=60 SCORE_min1 =2.

IF Geslacht_min1 =0 AND Roken_gebruiken_min1 =0 AND Totcholgedeelddhdlchol_min1 >7 AND systolischebloeddruk_min1 >=120 and systolischebloeddruk_min1<=140 and leeftijd_min1 >=61 SCORE_min1 =2.

IF Geslacht_min1 =0 AND Roken_gebruiken_min1 =0 AND Totcholgedeelddhdlchol_min1 >5 AND totcholgedeelddhdlchol_min1 <=8 and systolischebloeddruk_min1 >=141 and systolischebloeddruk_min1<=160 and leeftijd_min1 >=61 SCORE_min1 =2.

IF Geslacht_min1 =0 AND Roken_gebruiken_min1 =0 AND Totcholgedeelddhdlchol_min1 >=3 AND totcholgedeelddhdlchol_min1 <=7 and systolischebloeddruk_min1 >=161 and systolischebloeddruk_min1<=180 and leeftijd_min1 >=61 SCORE_min1 =2.

IF Geslacht_min1 =0 AND Roken_gebruiken_min1 =0 AND Totcholgedeelddhdlchol_min1 >=3 AND totcholgedeelddhdlchol_min1 <=5 and systolischebloeddruk_min1 >=181 and leeftijd_min1 >=61 SCORE_min1 =2.

IF Geslacht_min1 =1 AND Roken_gebruiken_min1 =0 AND Totcholgedeelddhdlchol_min1 >=3 and systolischebloeddruk_min1 >=120 and leeftijd_min1 >=40 and leeftijd_min1<=55 SCORE_min1 =1.

IF Geslacht_min1 =1 AND Roken_gebruiken_min1 =0 AND Totcholgedeelddhdlchol_min1 >=3 AND systolischebloeddruk_min1 >=120 and systolischebloeddruk_min1<=180 and leeftijd_min1 >=56 and leeftijd_min1<=60 SCORE_min1 =1.

IF Geslacht_min1 =1 AND Roken_gebruiken_min1 =0 AND Totcholgedeelddhdlchol_min1 >=3 AND totcholgedeelddhdlchol_min1 <=7 and systolischebloeddruk_min1 >=181 and leeftijd_min1 >=56 and leeftijd_min1<=60 SCORE_min1 =1.

IF Geslacht_min1 =1 AND Roken_gebruiken_min1 =0 AND Totcholgedeelddhdlchol_min1 >=3 and systolischebloeddruk_min1 >=120 and systolischebloeddruk_min1<=140 and leeftijd_min1 >=61 SCORE_min1 =1.

IF Geslacht_min1 =1 AND Roken_gebruiken_min1 =0 AND Totcholgedeelddhdlchol_min1 >=3 and totcholgedeelddhdlchol_min1<=8 and systolischebloeddruk_min1 >=141 and systolischebloeddruk_min1<=160 and leeftijd_min1 >=61 SCORE_min1 =1.

IF Geslacht_min1 =1 AND Roken_gebruiken_min1 =0 AND Totcholgedeelddhdlchol_min1 >=3 and totcholgedeelddhdlchol_min1<=6 and systolischebloeddruk_min1 >=161 and systolischebloeddruk_min1<=180 and leeftijd_min1 >=61 SCORE_min1 =1.

IF Geslacht_min1 =1 AND Roken_gebruiken_min1 =0 AND Totcholgedeelddhdlchol_min1 >=3 and totcholgedeelddhdlchol_min1<=4 and systolischebloeddruk_min1 >=181 and leeftijd_min1 >=61 SCORE_min1 =1.

IF Geslacht_min1 =1 AND Roken_gebruiken_min1 =1 AND Totcholgedeelddhdlchol_min1 >=3 and systolischebloeddruk_min1 >=120 and leeftijd_min1 >=40 and leeftijd_min1<=50 SCORE_min1 =1.

IF Geslacht_min1 =1 AND Roken_gebruiken_min1 =1 AND Totcholgedeelddhdlchol_min1 >=3 AND systolischebloeddruk_min1 >=120 and systolischebloeddruk_min1<=180 and leeftijd_min1 >=51 and leeftijd_min1<=55 SCORE_min1 =1.

IF Geslacht_min1 =1 AND Roken_gebruiken_min1 =1 AND Totcholgedeelddhdlchol_min1 >=3 AND totcholgedeelddhdlchol_min1 <=8 and systolischebloeddruk_min1 >=181 and leeftijd_min1 >=51 and leeftijd_min1<=55 SCORE_min1 =1.

IF Geslacht_min1 =1 AND Roken_gebruiken_min1 =1 AND Totcholgedeelddhdlchol_min1 >=3 and systolischebloeddruk_min1 >=120 and systolischebloeddruk_min1<=140 and leeftijd_min1 >=56 and leeftijd_min1 <=60 SCORE_min1 =1.

IF Geslacht_min1 =1 AND Roken_gebruiken_min1 =1 AND Totcholgedeelddhdlchol_min1 >=3 and totcholgedeelddhdlchol_min1<=8 and systolischebloeddruk_min1 >=141 and systolischebloeddruk_min1<=160 and leeftijd_min1 >=56 and leeftijd_min1<=60 SCORE_min1 =1.

IF Geslacht_min1 =1 AND Roken_gebruiken_min1 =1 AND Totcholgedeelddhdlchol_min1 >=3 and totcholgedeelddhdlchol_min1<=6 and systolischebloeddruk_min1 >=161 and systolischebloeddruk_min1<=180 and leeftijd_min1 >=56 and leeftijd_min1<=60 SCORE_min1 =1.

IF Geslacht_min1 =1 AND Roken_gebruiken_min1 =1 AND Totcholgedeelddhdlchol_min1 >=3 and totcholgedeelddhdlchol_min1<=4 and systolischebloeddruk_min1 >=181 and leeftijd_min1 >=56 and leeftijd_min1<=60 SCORE_min1 =1.

IF Geslacht_min1 =1 AND Roken_gebruiken_min1 =1 AND Totcholgedeelddhdlchol_min1 >=3 and totcholgedeelddhdlchol_min1<=6 and systolischebloeddruk_min1 >=120 and systolischebloeddruk_min1<=140 and leeftijd_min1 >=61 SCORE_min1 =1.

IF Geslacht_min1 =1 AND Roken_gebruiken_min1 =1 AND Totcholgedeelddhdlchol_min1 >=3 and totcholgedeelddhdlchol_min1<=4 and systolischebloeddruk_min1 >=141 and systolischebloeddruk_min1<=160 and leeftijd_min1 >=61 SCORE_min1 =1.

IF Geslacht_min1 =0 AND Roken_gebruiken_min1 =0 AND Totcholgedeelddhdlchol_min1 >=3 and systolischebloeddruk_min1 >=120 and leeftijd_min1 >=40 and leeftijd_min1<=45 SCORE_min1 =1.

IF Geslacht_min1 =0 AND Roken_gebruiken_min1 =0 AND Totcholgedeelddhdlchol_min1 >=3 AND systolischebloeddruk_min1 >=120 and systolischebloeddruk_min1<=180 and leeftijd_min1 >=46 and leeftijd_min1<=50 SCORE_min1 =1.

IF Geslacht_min1 =0 AND Roken_gebruiken_min1 =0 AND Totcholgedeelddhdlchol_min1 >=3 AND totcholgedeelddhdlchol_min1 <=8 and systolischebloeddruk_min1 >=181 and leeftijd_min1 >=46 and leeftijd_min1<=50 SCORE_min1 =1.

IF Geslacht_min1 =0 AND Roken_gebruiken_min1 =0 AND Totcholgedeelddhdlchol_min1 >=3 and systolischebloeddruk_min1 >=120 and systolischebloeddruk_min1<=180 and leeftijd_min1 >=51 and leeftijd_min1 <=55 SCORE_min1 =1.

IF Geslacht_min1 =0 AND Roken_gebruiken_min1 =0 AND Totcholgedeelddhdlchol_min1 >=3 and totcholgedeelddhdlchol_min1<=7 and systolischebloeddruk_min1 >=161 and systolischebloeddruk_min1<=180 and leeftijd_min1 >=51 and leeftijd_min1 <=55 SCORE_min1 =1.

IF Geslacht_min1 =0 AND Roken_gebruiken_min1 =0 AND Totcholgedeelddhdlchol_min1 >=3 and totcholgedeelddhdlchol_min1<=6 and systolischebloeddruk_min1 >=181 and leeftijd_min1 >=51 and leeftijd_min1 <=55 SCORE_min1 =1.

IF Geslacht_min1 =0 AND Roken_gebruiken_min1 =0 AND Totcholgedeelddhdlchol_min1 >=3 and totcholgedeelddhdlchol_min1<=8 and systolischebloeddruk_min1 >=120 and systolischebloeddruk_min1 <=140 and leeftijd_min1 >=56 and leeftijd_min1 <=60 SCORE_min1 =1.

IF Geslacht_min1 =0 AND Roken_gebruiken_min1 =0 AND Totcholgedeelddhdlchol_min1 >=3 and totcholgedeelddhdlchol_min1 <=7 and systolischebloeddruk_min1 >=141 and systolischebloeddruk_min1 <=160 and leeftijd_min1 >=56 and leeftijd_min1<=60 SCORE_min1 =1.

IF Geslacht_min1 =0 AND Roken_gebruiken_min1 =0 AND Totcholgedeelddhdlchol_min1 >=3 AND totcholgedeelddhdlchol_min1 <=5 and systolischebloeddruk_min1 >=161 and systolischebloeddruk_min1<=180 and leeftijd_min1 >=56 and leeftijd_min1<=60 SCORE_min1 =1.

IF Geslacht_min1 =0 AND Roken_gebruiken_min1 =0 AND Totcholgedeelddhdlchol_min1 >=3 AND totcholgedeelddhdlchol_min1 <=4 and systolischebloeddruk_min1 >=181 and leeftijd_min1 >=56 and leeftijd_min1<=60 SCORE_min1 =1.

IF Geslacht_min1 =0 AND Roken_gebruiken_min1 =0 AND Totcholgedeelddhdlchol_min1 >=3 and totcholgedeelddhdlchol_min1 <=7 and systolischebloeddruk_min1 >=120 and systolischebloeddruk_min1<=140 and leeftijd_min1 >=61 SCORE_min1 =1.

IF Geslacht_min1 =0 AND Roken_gebruiken_min1 =0 AND Totcholgedeelddhdlchol_min1 >=3 and totcholgedeelddhdlchol_min1<=5 and systolischebloeddruk_min1 >=141 and systolischebloeddruk_min1<=160 and leeftijd_min1 >=61 SCORE_min1 =1.

IF Geslacht_min1 =1 AND Roken_gebruiken_min1 =1 AND Totcholgedeelddhdlchol_min1 >=3 and systolischebloeddruk_min1 >=120 and systolischebloeddruk_min1<=180 and leeftijd_min1 >=40 and leeftijd_min1<=45 SCORE_min1 =1.

IF Geslacht_min1 =1 AND Roken_gebruiken_min1 =1 AND Totcholgedeelddhdlchol_min1 >=3 and totcholgedeelddhdlchol_min1<=8 and systolischebloeddruk_min1 >=181 and leeftijd_min1 >=40 and leeftijd_min1<=45 SCORE_min1 =1.

IF Geslacht_min1 =1 AND Roken_gebruiken_min1 =1 AND Totcholgedeelddhdlchol_min1 >=3 and systolischebloeddruk_min1 >=120 and systolischebloeddruk_min1<=140 and leeftijd_min1 >=46 and leeftijd_min1<=50 SCORE_min1 =1.

IF Geslacht_min1 =1 AND Roken_gebruiken_min1 =1 AND Totcholgedeelddhdlchol_min1 >=3 and totcholgedeelddhdlchol_min1<=8 and systolischebloeddruk_min1 >=141 and systolischebloeddruk_min1<=160 and leeftijd_min1 >=46 and leeftijd_min1 <=50 SCORE_min1 =1.

IF Geslacht_min1 =1 AND Roken_gebruiken_min1 =1 AND Totcholgedeelddhdlchol_min1 >=3 and totcholgedeelddhdlchol_min1<=7 and systolischebloeddruk_min1 >=161 and systolischebloeddruk_min1<=180 and leeftijd_min1 >=46 and leeftijd_min1<=50 SCORE_min1 =1.

IF Geslacht_min1 =1 AND Roken_gebruiken_min1 =1 AND Totcholgedeelddhdlchol_min1 >=3 and totcholgedeelddhdlchol_min1<=5 and systolischebloeddruk_min1 >=181 and leeftijd_min1 >=46 and leeftijd_min1 <=50 SCORE_min1 =1.

IF Geslacht_min1 =1 AND Roken_gebruiken_min1 =1 AND Totcholgedeelddhdlchol_min1 >=3 and totcholgedeelddhdlchol_min1<=8 and systolischebloeddruk_min1 >=120 and systolischebloeddruk_min1 <=140 and leeftijd_min1 >=50 and leeftijd_min1<=55 SCORE_min1 =1.

IF Geslacht_min1 =1 AND Roken_gebruiken_min1 =1 AND Totcholgedeelddhdlchol_min1 >=3 and totcholgedeelddhdlchol_min1<=6 and systolischebloeddruk_min1 >=141 and systolischebloeddruk_min1<=160 and leeftijd_min1 >=50 and leeftijd_min1<=55 SCORE_min1 =1.

IF Geslacht_min1 =1 AND Roken_gebruiken_min1 =1 AND Totcholgedeelddhdlchol_min1 >=3 and totcholgedeelddhdlchol_min1<=5 and systolischebloeddruk_min1 >=161 and systolischebloeddruk_min1<=180 and leeftijd_min1 >=50 and leeftijd_min1 <=55 SCORE_min1 =1.

IF Geslacht_min1 =1 AND Roken_gebruiken_min1 =1 AND Totcholgedeelddhdlchol_min1 >=3 and totcholgedeelddhdlchol_min1<=6 and systolischebloeddruk_min1 >=120 and systolischebloeddruk_min1<=140 and leeftijd_min1 >=56 and leeftijd_min1<=60 SCORE_min1 =1.

IF Geslacht_min1 =1 AND Roken_gebruiken_min1 =1 AND Totcholgedeelddhdlchol_min1 >=3 and totcholgedeelddhdlchol_min1<=4 and systolischebloeddruk_min1 >=141 and systolischebloeddruk_min1 <=160 and leeftijd_min1 >=56 and leeftijd_min1 <=60 SCORE_min1 =1.

FREQUENCIES VARIABLES=

SCORE_min1

/ORDER=ANALYSIS.