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ARTICLE

Additive effects of glycaemia and dyslipidaemia on risk of cardiovascular diseases in type 2 diabetes: an observational study from the Swedish National Diabetes Register

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Abstract
Aims/hypothesis The study aimed to assess the relative importance of the control of HbA_{1c} and total cholesterol/HDL-cholesterol ratio (TC/HDL) on risk of cardiovascular disease (CVD).
Methods In 22,135 participants with type 2 diabetes (age 30–75 years, 15% with previous CVD) followed for 5 years, baseline and annually updated mean HbA_{1c} and TC/HDL were analysed and also categorised in combinations of quartiles. Outcomes were fatal/non-fatal CHD, stroke, CVD and total mortality.
Results In all participants, HRs per 1 SD increase in updated mean HbA_{1c} or TC/HDL using Cox regression analysis were 1.13 (95% CI 1.07, 1.19) and 1.31 (1.25, 1.37) for CHD, 1.15 (1.06, 1.24) and 1.25 (1.17, 1.34) for stroke, 1.13 (1.08, 1.18) and 1.29 (1.24, 1.34) for CVD (all $p<0.001$), and 1.07 (1.02, 1–13; $p=0.01$) and 1.18 (1.12, 1.24; $p<0.001$) for total mortality, respectively, adjusted for clinical characteristics and traditional risk factors. The p value for the interaction between HbA_{1c} and TC/HDL was 0.02 for CHD, 0.6 for stroke and 0.1 for CVD. Adjusted mean 5-year event rates in a Cox model, in combinations of quartiles of updated mean TC/HDL and HbA_{1c} (lowest <3.1 mmol/l and 5.0–6.4% [31–46 mmol/mol]; <3.1 mmol/l and ≥7.8% [≥62 mmol/mol]; ≥4.6 mmol/l and 5.0–6.4% 31–46 mmol/mol; and highest ≥4.6 mmol/l and ≥7.8% [≥62 mmol/mol]), were 4.8%, 7.0%, 9.1% and 14.5% for CHD, and 7.1%, 9.9%, 12.8% and 19.4% for CVD, respectively. Adjusted HRs for highest vs lowest combinations were 2.24 (1.58–3.18) for CHD and 2.43 (1.79–3.29) for CVD ($p<0.001$).
Conclusions/interpretation Hyperglycaemia and hyperlipidaemia were less than additive for CHD and additive for other endpoints, with the lowest risk at lowest combination levels and a considerable increase in absolute risk at high combination levels.

Keywords Cardiovascular disease · Diabetes mellitus · Dyslipidaemia · Hyperlipidaemia · HbA_{1c}

Abbreviations

ACCORD	Action to Control Cardiovascular Risk in Diabetes
ADVANCE	Action in Diabetes and Vascular Disease
CVD	Cardiovascular disease
ICD	International Classification of Diseases
IFCC	International Federation of Clinical Chemistry
MI	Myocardial infarction
NDR	Swedish National Diabetes Register
TC	Total cholesterol
UKPDS	UK Prospective Diabetes Study
VADT	Veterans Affairs Diabetes Trial

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Introduction

Dyslipidaemia is one of the major risk factors for CHD, as has been demonstrated in individuals with type 2 diabetes in large studies such as the UK Prospective Diabetes Study (UKPDS) [1, 2]. Total and LDL-cholesterol have been consistently associated with CHD risk in multiple clinical investigations [1]. The total cholesterol/HDL-cholesterol ratio (TC/HDL) is nowadays commonly used as the preferred risk factor among various lipid measures for analysing the association with cardiovascular disease (CVD) [3], as was also used in the UKPDS regarding the association with both CHD [4, 5] and stroke [6] in individuals with type 2 diabetes.

HbA_{1c} is a well-established risk factor for microvascular diabetic complications [7, 8] and also for CVD in type 1 diabetes [9, 10]. Previous epidemiological studies have shown a positive association between HbA_{1c} and risk of CVD in type 2 diabetes [8, 11–13], although some large randomised clinical trials have not been able to show that intensive hypoglycaemic treatment is beneficial with regard to CVD risk [14–16]. However, the long-term follow-up of the UKPDS found, after 10 years, significant risk reductions of 15% for myocardial infarction (MI) and 13% for total mortality with intensive glucose therapy compared with conventional therapy during the initial 10 years [17]. A recent observational Swedish National Diabetes Register (NDR) study also found significant risk reductions of 20% for CHD and 16% for CVD when comparing individuals with type 2 diabetes with a baseline mean HbA_{1c} of 6.5% (48 mmol/mol) vs a mean of 7.5% (59 mmol/mol) when followed for 6 years. In addition, the study demonstrated no increased risks of CHD, CVD or total mortality at low HbA_{1c} levels in all participants, as well as in subgroups with a longer duration of diabetes or a history of CVD [18].

The STENO-2 multiple risk factor intervention trial in type 2 diabetes has shown increased benefit by targeting several risk factors simultaneously [19]. However, it remains uncertain whether combined treatment of dyslipidaemia, for example as manifested by TC/HDL, and glycaemia can be performed simultaneously to obtain maximum benefit with regard to the risks of CHD and CVD.

Against this background, we assessed the relative importance of TC/HDL and HbA_{1c} as risk factors for fatal/non-fatal CHD, stroke and CVD in an observational study of individuals with type 2 diabetes from a national diabetes register. As macrovascular complications represent a major cause of mortality in type 2 diabetes, with MI and stroke accounting for about 80% of all deaths [20], we also assessed the combined effect of control of TC/HDL and HbA_{1c} on risks of fatal CVD and total mortality in a sample in which 15% of participants had a history of CVD.

Methods

The Swedish NDR The NDR was initiated in 1996 as a tool for local quality assurance and feedback in diabetes care. Annual reporting to the NDR is carried out by trained physicians and nurses via the Internet or via clinical records databases, with information collected during patient visits to hospital outpatient clinics and primary healthcare centres nationwide. All participants included agreed by informed consent to register before inclusion. The Regional Ethics Review Board at the University of Gothenburg approved this study. Several reports concerning trends in risk factor control and risk prediction in the NDR have previously been published [21–25].

Participants This study consisted of 22,135 female and male participants with type 2 diabetes registered on the NDR who had data available for all analysed variables, with baseline visits in 2002–2003 and follow-up until December 2007. About 20% of participants registered on the NDR were excluded because of missing data. The inclusion criteria were age range 30–75 years, HbA_{1c} ≥5% (≥31 mmol/mol), BMI ≥18 kg/m^2 and plasma creatinine <150 μmol/l. A history of CVD was present in 15%, a history of heart failure in 4% and atrial fibrillation in 3% of participants.

The definition of type 2 diabetes was treatment with diet only, treatment with oral hypoglycaemic agents only, or age of onset of diabetes ≥40 years and treatment with insulin alone or combined with oral agents. Only 0.4% of participants had an age of onset <30 years, and 2% had an age of onset <40 years.

Examinations at baseline Clinical characteristics at baseline in 2002–2003 were age, duration of diabetes, sex, HbA_{1c} value, total cholesterol, HDL-cholesterol, TC/HDL, LDL-cholesterol, triacylglycerol, weight, height, smoking status, systolic blood pressure, cumulative microalbuminuria, plasma creatinine, type of hypoglycaemic treatment, and use of antihypertensive drugs and lipid-lowering drugs. BMI (kg/m^2) was calculated as weight/height^2. A smoker was defined as a participant who smoked one or more cigarettes per day, who smoked tobacco using a pipe, or who had stopped smoking within the previous 3 months. The Swedish standard for blood pressure recording, used in the NDR, is the mean value (mmHg) of two supine readings (Korotkoff I–V) with a cuff of appropriate size, after at least 5 min of rest.

Laboratory analyses of HbA_{1c} and blood lipids were carried out at local laboratories, and HbA_{1c} analyses were quality-assured nationwide by regular calibration with the HPLC Mono S method (Amersham Biosciences, Stockholm, Sweden). In this study, all HbA_{1c} values (Mono S %) were

converted to the DCCT values (%) using the formula: $HbA_{1c}(DCCT)=0.923\times HbA_{1c}(Mono\ S)+1.345$; $R^2=0.998$ [26], and also expressed as HbA_{1c} (International Federation of Clinical Chemistry [IFCC]) in millimoles per mole. Microalbuminuria was defined as cumulative (micro- or macroalbuminuria), based on a urinary albumin excretion >20 μg/min in two out of three consecutive tests.

HbA_{1c} and TC/HDL were measured both at baseline and over time as an updated mean of annual measurements, calculated for each individual from baseline to each year of follow-up, with the last observation carried forward for missing data. In case of an event during follow-up, the period for estimating updated mean HbA_{1c} or updated mean TC/HDL was from baseline to the year before this event occurred. Otherwise, this period was from baseline to the censor year.

Follow-up and definition of endpoints All participants were followed from the baseline examination until a first cardiovascular event or death, or otherwise, until the censor date of 31 December 2007. The endpoints used in this study were: non-fatal or fatal CHD, non-fatal or fatal stroke, non-fatal or fatal CVD, fatal CVD and total mortality. Non-fatal CHD was defined as non-fatal MI (ICD-10 code I21; www.who.int/classifications/icd/en/), unstable angina (ICD-10 code I20.0), percutaneous coronary intervention and/or coronary artery bypass grafting. Fatal CHD was defined as ICD-10 codes I20–I25. Stroke was defined as non-fatal or fatal cerebral infarction, intracerebral haemorrhage or unspecified stroke (ICD-10 codes I61, I63, I64 and I67.9). A CVD event was the composite of CHD and/or stroke, whichever came first, and the same definition was used for a history of CVD before baseline.

Atrial fibrillation diagnosed before or at baseline was defined as ICD-10 code I48, and a history of heart failure was defined as ICD-10 code I50, both used as covariates in all regression analyses.

All events were retrieved by data linkage with the Swedish Cause of Death and Hospital Discharge Registers, which is a reliable validated alternative to revised hospital discharge and death certificates [27, 28].

Statistical methods Baseline characteristics are presented as means±SD or frequencies in Table 1. Cox regression analysis was used to estimate HRs with 95% CIs for the outcomes per 1 SD increase in baseline TC/HDL and HbA_{1c}, or in updated mean TC/HDL and HbA_{1c} included as strictly time-dependent covariates (Table 2). The proportional hazards assumption was confirmed for all covariates with the Kolmogorov-type supremum test using re-sampling, and with the test of all time-dependent covariates simultaneously introduced. Interactions between baseline TC/HDL and HbA_{1c}, and between updated mean TC/HDL and HbA_{1c}, were analysed with Wald χ^2 values at maximum likelihood estimation, and a non-significant interaction was defined as $p>0.05$ (Table 2).

A Cox regression analysis model was also used to estimate 5-year event rates (1–survival rate) for the outcomes, where model output was the adjusted 5-year event rate for each participant, adjusted for covariates as given in Table 2. Stratification was then performed to achieve adjusted mean 5-year event rates for category combinations by lower or higher quartiles of updated mean TC/HDL, and by lower or higher quartiles of updated mean HbA_{1c} (Fig. 1, Table 3). Subgrouping of event rates by sample intervals has also been used in the Framingham studies [29].

All statistical analyses were performed with SAS version 9.1.3 (SAS Institute, Cary, NC, USA). A p value of <0.05 using a two-sided test was considered statistically significant.

Table 1 Baseline characteristics in 22,135 female and male participants with type 2 diabetes, aged 30–75 years

Variable	All patients
Clinical features	
Age (years)	62±9
Diabetes duration (years)	8±7
HbA_{1c}(DCCT), %	7.3±1.2
HbA_{1c}(IFCC), mmol/mol	56±13
TC (mmol/l)	5.06±1.0
HDL-cholesterol (mmol/l)	1.31±0.4
Ratio TC/HDL	4.13±1.2
LDL-cholesterol (mmol/l)	2.98±0.9
Triacylglycerol (mmol/l)	1.69±0.8
Systolic blood pressure (mmHg)	142±18
BMI (kg/m^2)	29.4±5.1
Male sex	13,060 (59.0)
Smoking	3,766 (17.0)
Albuminuria (urinary albumin >20 μg/min)	4,628 (20.9)
Atrial fibrillation	705 (3.2)
History of cardiovascular disease	3,386 (15.3)
History of congestive heart failure	919 (4.2)
Treatment	
Antihypertensive drugs	13,617 (61.5)
Lipid-lowering drugs	9,451 (42.7)
Hypoglycaemic treatment	
Diet only	5,086 (23.0)
Oral agents only	8,471 (38.3)
Oral agents and insulin	4,001 (18.1)
Insulin only	4,577 (20.6)

Data are means±SD, or frequencies *n* (%)

Table 2 HRs in 22,135 individuals with type 2 diabetes per 1 SD increase in baseline or updated mean values of TC/HDL or HbA_{1c}

Outcome	Type of predictor	Endpoints (*n*)	TC/HDL		HbA_{1c}		*p* for interaction
			HR (95% CI)	*p* value	HR (95% CI)	*p* value	
Fatal/non-fatal CHD	Baseline	1,607	1.19 (1.13, 1.25)	<0.001	1.10 (1.04, 1.16)	<0.001	0.02
	Updated mean	1,607	1.31 (1.25, 1.37)	<0.001	1.13 (1.07, 1.19)	<0.001	0.02
Fatal/non-fatal stroke	Baseline	742	1.16 (1.08, 1.25)	<0.001	1.09 (1.01, 1.18)	0.03	0.7
	Updated mean	742	1.25 (1.17, 1.34)	<0.001	1.15 (1.06, 1.24)	<0.001	0.6
Fatal/non-fatal CVD	Baseline	2,249	1.18 (1.13, 1.23)	<0.001	1.09 (1.04, 1.14)	<0.001	0.05
	Updated mean	2,249	1.29 (1.24, 1.34)	<0.001	1.13 (1.08, 1.18)	<0.001	0.1
Fatal CVD	Baseline	693	1.16 (1.08, 1.25)	<0.001	1.15 (1.06, 1.24)	<0.001	0.8
	Updated mean	693	1.28 (1.20, 1.38)	<0.001	1.18 (1.10, 1.28)	<0.001	0.5
Total mortality	Baseline	1,667	1.05 (1.01, 1.11)	0.03	1.07 (1.01, 1.12)	0.02	0.8
	Updated mean	1,667	1.18 (1.12, 1.24)	<0.001	1.07 (1.02, 1.13)	0.01	0.09

HRs were adjusted for age, diabetes duration, sex, systolic blood pressure, BMI, smoking, albuminuria >20 μg/min, antihypertensive drugs, lipid-lowering drugs, type of hypoglycaemic treatment, atrial fibrillation, history of CVD and history of heart failure

Results

Baseline characteristics for all 22,135 participants with type 2 diabetes are given in Table 1. The age range was 30–75 years, with mean age and duration of diabetes 62 years and 8 years, respectively. A history of CVD was present in 15%, and a history of heart failure in 4%. Lipid-lowering drugs were given to 43% of participants. Treatment with oral hypoglycaemic agents only, insulin combined with oral hypoglycaemic agents and insulin only was given to 38%, 18% and 21% of individuals. The median (25th–75th percentiles) of updated mean TC/HDL was 4.0 (3.25–4.89)mmol/l and of HbA_{1c} was 7.07% (6.42–7.90%) (54 [47–63]mmol/mol).

Events In all participants, 1,607, 742, 2,249 and 1,667 events of fatal/non-fatal CHD, fatal/non-fatal stroke, fatal/non-fatal CVD and total mortality, respectively, occurred, based on 93,254 person-years during a mean 4.8 years of follow-up. In the four combinations of lowest or highest quartiles of updated mean TC/HDL and HbA_{1c} given in Table 3, the corresponding number of person-years of observation was 5,770, 5,329, 6,223 and 6,567, respectively.

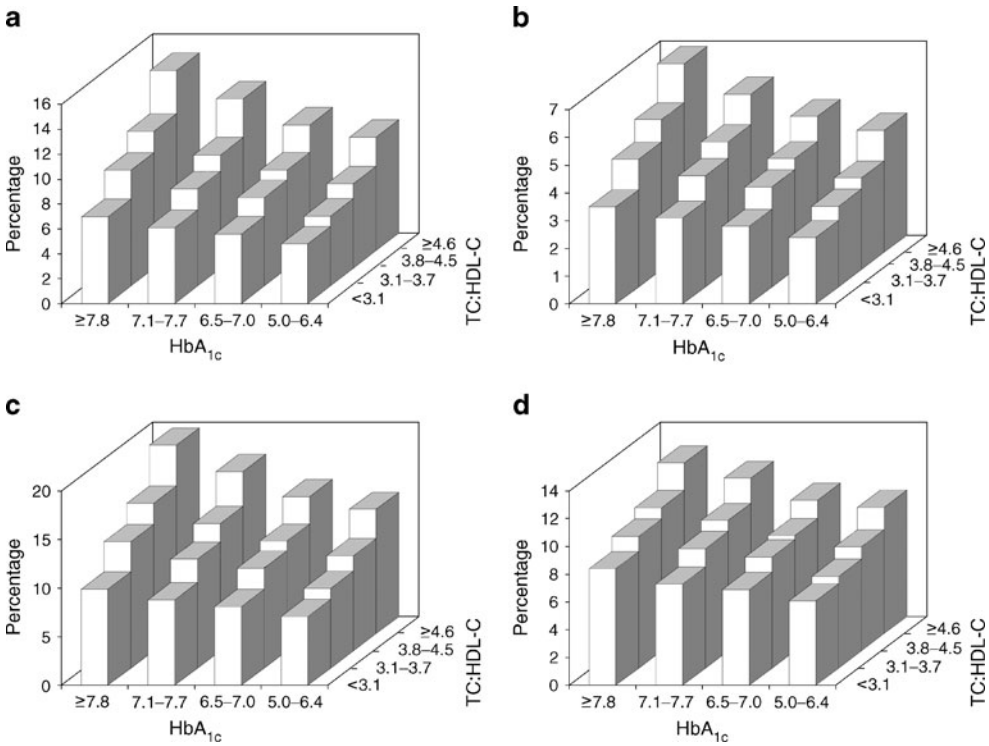

Fig. 1 Mean event rates, adjusted as in Table 3, of outcomes in 22,135 individuals with type 2 diabetes. Values are for 16 different combinations of updated mean HbA_{1c} (mmol/l) and updated mean ratio of TC/HDL. **a** Fatal/non-fatal CHD, (**b**) fatal/non-fatal stroke, (**c**) fatal/non-fatal cardiovascular disease and (**d**) total mortality. All trends of mean event rates by increasing HbA_{1c} per quartile of TC/HDL, and by increasing TC/HDL per quartiles of HbA_{1c} were significant ($p<0.001$). HDL-C, HDL-cholesterol. To convert values for HbA_{1c} in per cent to millimoles per litre, subtract 2.15 and multiply by 10.929

Table 3 Mean event rates for the four lowest or highest combinations of quartiles of updated mean TC/HDL and quartiles of updated mean HbA_{1c}

Variable	Updated mean TC/HDL				Highest/lowest category combination	
	<3.1 mmol/l		≥4.6 mmol/l			
	HbA_{1c} 5.0–6.4% (31–46 mmol/mol)	HbA_{1c} ≥7.8% (≥62 mmol/mol)	HbA_{1c} 5.0–6.4% (31–46 mmol/mol)	HbA_{1c} ≥7.8% (≥62 mmol/mol)	HR (95% CI)	*p* value
HbA_{1c}(DCCT) (mean±SD), %	6.1±0.3	8.6±0.7	6.1±0.3	8.8±0.9		
HbA_{1c}(IFCC) (mean±SD), mmol/mol	43±4	70±7	43±3	72±10		
TC/HDL (mean±SD)	2.7±0.3	2.6±0.4	5.4±0.8	5.5±0.8		
Endpoints						
Fatal/non-fatal CHD						
Number (*n*)	1,418	1,405	1,221	1,626		
Events (*n*) (%)	57 (4.0)	84 (6.0)	127 (10.4)	191 (11.8)		
Event rate (mean±SD), %	4.8±3.5	7.0±5.4	9.1±7.6	14.5±10.8	2.24 (1.58, 3.18)	<0.001
Fatal/non-fatal stroke						
Number (*n*)	1,403	1,406	1,204	1,630		
Events, *n* (%)	23 (1.6)	46 (3.3)	43 (3.6)	96 (5.9)		
Event rate (mean±SD), %	2.4±1.9	3.5±2.9	4.4±4.5	6.8±6.1	3.11 (1.80, 5.37)	<0.001
Fatal/non-fatal CVD						
Number (*n*)	1,411	1,380	1,219	1,611		
Events, *n* (%)	76 (5.4)	124 (9.0)	161 (13.2)	262 (16.3)		
Event rate (mean±SD), %	7.1±5.0	9.9±7.2	12.8±9.8	19.4±13.1	2.43 (1.79, 3.29)	<0.001
Fatal CVD						
Number (*n*)	1,411	1,407	1,208	1,624		
Events, *n* (%)	24 (1.7)	44 (3.1)	46 (3.8)	88 (5.4)		
Event rate (mean±SD), %	2.0±3.1	3.6±5.4	3.7±6.5	6.8±9.6	2.35 (1.37, 4.06)	0.002
Total mortality						
Number (*n*)	1,411	1,407	1,208	1,624		
Events, *n* (%)	88 (6.2)	123 (8.7)	126 (10.4)	170 (10.5)		
Event rate (mean±SD), %	6.1±5.7	8.4±7.8	9.1±9.4	12.3±11.4	1.54 (1.12, 2.12)	0.008

Mean event rates and HRs were adjusted for age, duration of diabetes, sex, systolic blood pressure, BMI, smoking, albuminuria >20 μg/min, antihypertensive drugs, lipid-lowering drugs, type of hypoglycaemic treatment, atrial fibrillation, history of CVD and history of heart failure

HRs in all participants Table 2 gives adjusted HRs for the outcomes per 1 SD increase in updated mean TC/HDL or HbA_{1c} in all 22,135 participants. Adjustments were made for age, duration of diabetes, sex, systolic blood pressure, BMI, smoking, albuminuria >20 μg/min, type of hypoglycaemic treatment, antihypertensive drugs, lipid-lowering drugs, atrial fibrillation, history of CVD and history of heart failure. HRs were higher with TC/HDL as a predictor than with HbA_{1c} as a predictor, and were also higher with updated mean values of the two predictors than with baseline values.

HRs with updated mean TC/HDL and HbA_{1c} values were 1.31 (1.25–1.37) and 1.13 (1.07–1.19) for fatal/non-fatal CHD; 1.25 (1.17–1.34) and 1.15 (1.06–1.24) for fatal/non-fatal stroke; 1.29 (1.24–1.34) and 1.13 (1.08–1.18) for fatal/non-fatal CVD; 1.28 (1.20–1.38); and 1.18 (1.10–1.28) for fatal CVD (all $p<0.001$). HRs for total mortality were 1.18 (1.12–1.24; $p<0.001$) and 1.07 (1.02–1.13; $p=0.01$), respectively.

A subgroup analysis in 18,749 participants with no history of CVD showed similar HRs for all endpoints concerning both baseline and updated mean TC/HDL and HbA_{1c} values.

Interaction tests The test for interaction indicated that the effects on both baseline and updated mean TC/HDL and HbA_{1c} were less than additive for fatal/non-fatal CHD (Wald $\chi^2=5.7$, $p=0.02$), and additive for other outcomes, with Wald χ^2 for the interaction ranging from 0.5 to 2.8, and p values ranging from 0.1 to 0.8 for fatal/non-fatal stroke, fatal/non-fatal CVD, fatal CVD and total mortality (see Table 2).

Mean event rates in category combinations Figure 1 shows 5-year mean rates of the outcomes, adjusted for covariates as in Table 2 in a Cox model, in 16 category combinations of quartiles of updated mean TC/HDL and quartiles of updated mean HbA_{1c}. The number of participants in each of the 16 category combinations ranged from 1,219 to 1,611, with a mean number of 1,383 participants. The quartiles of updated mean TC/HDL were <3.1, 3.1–3.7, 3.8–4.5 and ≥4.6 mmol/l, and the quartiles of updated mean HbA_{1c} were 5.0–6.4% (31–46 mmol/mol), 6.5–7.0% (47–53 mmol/mol), 7.1–7.7% (54–61 mmol/mol) and ≥7.8% (≥62 mmol/mol). Gradually increasing mean 5-year rates for all outcomes, CHD, stroke, CVD and total mortality were observed as exposure to TC/HDL and HbA_{1c} increased. A somewhat stronger effect of increasing TC/HDL for each quartile of HbA_{1c} was seen, compared with the effect of increasing HbA_{1c} for each quartile of TC/HDL. There was no sign of increased risk for the outcomes in the lowest combined quartiles of TC/HDL and HbA_{1c}, concerning CHD, stroke, CVD as well as total mortality.

Table 3 gives events and mean 5-year event rates of the outcomes for four category combinations of the lowest and the highest quartiles of updated mean TC/HDL and HbA_{1c}. Mean TC/HDL and HbA_{1c} were 2.7 mmol/l and 6.1% (43 mmol/mol) in category combination 1, 2.6 mmol/l and 8.6% (70 mmol/mol) in category combination 2, 5.4 mmol/l and 6.1% (43 mmol/mol) in category combination 3 and 5.5 mmol/l and 8.8% (72 mmol/mol) in category combination 4.

Across these four category combinations of updated mean TC/HDL and HbA_{1c}, mean 5-year event rates increased from 4.8%, 7.0% and 9.1% to 14.5% for fatal/non-fatal CHD; from 2.4%, 3.5% and 4.4% to 6.8% for fatal/non-fatal stroke; from 7.1%, 9.9% and 12.8% to 19.4% for fatal/non-fatal CVD; from 2.0%, 3.6% and 3.7% to 6.8% for fatal CVD; and from 6.1%, 8.4% and 9.1% to 12.3% for total mortality, respectively.

The adjusted HR with the highest-category combination of updated mean TC/HDL and HbA_{1c}, compared with the lowest, was 2.24 (1.58–3.18) for fatal/non-fatal CHD, 3.11 (1.80–5.37) for fatal/non-fatal stroke, 2.43 (1.79–3.29) for fatal/non-fatal CVD (all $p<0.001$), 2.35 (1.37–4.06) for fatal CVD ($p=0.002$) and 1.54 (1.12–2.12) for total mortality ($p=0.008$).

Discussion

This observational study of 22,135 individuals with type 2 diabetes followed for 5 years found that the effect of increasing updated mean TC/HDL on the risk of fatal/non-fatal CHD, stroke and CVD was higher than the effect of increasing updated mean HbA_{1c}, although the risk increases caused by both risk factors were strongly significant when adjusted for clinical characteristics, drug treatments and other traditional risk factors. The risk increase for fatal/non-fatal CHD was 31% per 1 SD increase of TC/HDL and 13% per 1 SD increase of HbA_{1c}, with values of 25% and 15% for fatal/non-fatal stroke, and 29% and 13% for fatal/non-fatal CVD, respectively (Table 2).

The findings here of higher risk increases for fatal/non-fatal CHD with TC/HDL than with HbA_{1c} seem to be in accordance with findings from the UKPDS 23 and UKPDS 56 studies concerning individuals with newly developed type 2 diabetes. Cox regression analysis in the UKPDS 23 trial [2] analysing the risk of fatal/non-fatal MI, and using LDL-cholesterol and HDL-cholesterol instead of the TC/HDL ratio, disclosed that these two lipid measures were entered before HbA_{1c} at stepwise regression. The HRs for the highest third, compared with the lowest third, were higher with LDL-cholesterol, at 2.11 ($p<0.001$), and decreased HDL-cholesterol, at 1.75 ($p=0.009$), than with HbA_{1c}, which gave a value of 1.71 ($p=0.01$). UKPDS 56 [4], analysing the risk of fatal/non-fatal MI, found a higher estimate for a 1-unit increase in logarithmically transformed TC/HDL than for a 1%-unit increase in HbA_{1c}. Surprisingly, in the UKPDS 60 study [6], analysing the risk of fatal/non-fatal stroke using Cox regression analysis in individuals with newly developed type 2 diabetes, HbA_{1c} was not found to be a significant risk factor, whereas TC/HDL was a strong risk factor ($p=0.009$). However, UKPDS 35 [8] found a 13% risk increase for stroke per 1%-unit increase in HbA_{1c} ($p=0.03$). Other studies have also found elevated TC and decreased HDL-cholesterol as risk factors for stroke in individuals with type 2 diabetes [30], and elevated TC/HDL as a risk factor for stroke in the general population [31, 32].

With each distribution of updated mean TC/HDL or updated mean HbA_{1c} divided into quartiles, it was also demonstrated in the current study that combinations of quartiles increased the prediction of risk of CHD, stroke, CVD and total mortality over the use of any single quartile of TC/HDL or HbA_{1c}. Participants with higher levels of both TC/HDL and HbA_{1c} were at greater risk than those with an increase in just one of these risk factors, and at much greater risk than those who had neither of the factors raised (Fig. 1). For example, those with a combination of the highest quartiles of TC/HDL and HbA_{1c}, compared with those with a combination of the lowest quartiles of TC/HDL and HbA_{1c}, had a 2.2-fold increased risk of CHD, a 3.1-fold increased risk of stroke, and a 2.4-fold increased risk of CVD (Table 3).

Figure 1 also shows that there was no increased risk of CHD, stroke, CVD and total mortality with low levels of TC/HDL or HbA_{1c}. The combination of the lowest quartiles had a TC/HDL value <3.1, with a mean of 2.7, and a HbA_{1c}

range of 5.0–6.4% (31–46 mmol/mol), with a mean of 6.1% (43 mmol/mol). This category combination also demonstrated the lowest mean 5-year rate for all outcomes.

Furthermore, Fig. 1 demonstrates that the relative increase in mean CVD rate from HbA_{1c} quartiles 1 to 4 was 39% within TC/HDL quartile 1, while higher within TC/HDL quartile 4, it was 51%. Correspondingly, the relative increase from TC/HDL quartiles 1 to 4 was 81% within HbA_{1c} quartile 1, whereas higher within HbA_{1c} quartile 4, it was 99%.

Even if HbA_{1c} is a weaker predictor than lipids, as underlined in a recent review [33] and currently under debate [34–36], HbA_{1c} has an obviously strong effect on outcomes risk, even more so with increasing lipid levels. The absolute risk should be emphasised [33, 36]. The absolute increase in CVD risk in the current study was 5% with HbA_{1c} quartile 4 compared with HbA_{1c} quartile 1 in participants within TC/HDL quartiles 2 or 3 when followed for 5 years, and the corresponding absolute increase in risk was as much as 7% in participants within TC/HDL quartile 4 (Fig. 1). This was seen here in participants with a mean duration of diabetes of 8 years, as in the Action in Diabetes and Vascular Disease (ADVANCE) [14], Action to Control Cardiovascular Risk in Diabetes (ACCORD) [15] studies and Veterans Affairs Diabetes Trial (VADT) [16].

The effects of TC/HDL and HbA_{1c} on risk of fatal/non-fatal stroke, fatal/non-fatal CVD, fatal CVD and total mortality were found to be additive using Cox regression analysis, with non-significant p values for interaction (Table 2). However, these effects were less than additive for fatal/non-fatal CHD, with $p=0.02$ for interaction. This may be due to pre-existing cardiac tissue damage, which may to some extent prevent further deterioration when combined with high values of both TC/HDL and HbA_{1c}.

This observational study allowed for an analysis of participants during daily treatment at hospital and primary care clinics nationwide during recent years, with no exclusion criteria regarding risk factors, thus representing what actually took place in routine clinical practice. A major strength of the study is the large number of participants and person-years involved. Laboratory analyses of HbA_{1c} allowed for calibration to a standard. The capture of data on the outcomes was based on reliable and validated national registers of morbidity and mortality. Unmeasured confounding may exist because of unmeasured covariates. However, substantial adjustments were made for age, sex, duration, drug treatments and several traditional cardiovascular risk factors, including albuminuria, representing microangiopathy, as well as atrial fibrillation, history of CVD and heart failure.

In conclusion, this large observational study of individuals with type 2 diabetes has demonstrated progressive risk increases for CVD and total mortality with increased levels of TC/HDL and HbA_{1c}, and with the lowest risk in the group with the lowest level of both variables. Less than additive effects of the combination of HbA_{1c} and TC/HDL levels were found for CHD, and additive effects for other endpoints. In accordance with the STENO-2 multiple risk factor intervention trial [19], our findings indicate that optimal treatment of both HbA_{1c} and TC/HDL is important in order to reduce the risks of CVD and mortality in type 2 diabetes.

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Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

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