Research: Epidemiology

Variation in prescribing of lipid-lowering medication in primary care is associated with incidence of cardiovascular disease and all-cause mortality in people with screen-detected diabetes: findings from the *ADDITION-Denmark* trial

R. K. Simmons[1], A. H. Carlsen[2], S. J. Griffin[1,3], M. Charles[2], J. S. Christiansen[4], K. Borch-Johnsen[5], A. Sandbæk[2] and T. Lauritzen[2]

[1]MRC Epidemiology Unit, University of Cambridge School of Clinical Medicine, Cambridge, UK, [2]School of Public Health, Section of General Practice, University of Aarhus, Aarhus, Denmark, [3]Primary Care Unit, Cambridge Institute of Public Health, Cambridge, UK, [4]Department of Endocrinology and Diabetes, Aarhus University Hospital, Aarhus and [5]Holbæk Hospital, Holbæk, Denmark

Abstract

Aims   To examine variation between general practices in the prescription of lipid-lowering treatment to people with screen-detected Type 2 diabetes, and associations with practice and participant characteristics and risk of cardiovascular events and all-cause mortality.

Methods   Observational cohort analysis of data from 1533 people with screen-detected Type 2 diabetes aged 40–69 years from the *ADDITION-Denmark* study. One hundred and seventy-four general practices were cluster randomized to receive: (1) routine diabetes care according to national guidelines (623 individuals), or (2) intensive multifactorial target-driven management (910 individuals). Multivariable logistic regression was used to quantify the association between the proportion of individuals in each practice who redeemed prescriptions for lipid-lowering medication in the two years following diabetes diagnosis and a composite cardiovascular disease (CVD) outcome, adjusting for age, sex, prevalent chronic disease, baseline CVD risk factors, smoking and lipid-lowering medication, and follow-up time.

Results   The proportion of individuals treated with lipid-lowering medication varied widely between practices (0–100%). There were 118 CVD events over 9431 person-years of follow-up. For the whole trial cohort, the risk of CVD was significantly higher in practices in the lowest compared with the highest quartile for prescribing lipid-lowering medication [adjusted odds ratio (OR) 3.4, 95% confidence interval (CI) 1.6–7.3]. Similar trends were found for all-cause mortality.

Conclusions   More frequent prescription of lipid-lowering treatment was associated with a lower incidence of CVD and all-cause mortality. Improved understanding of factors underlying practice variation in prescribing may enable more frequent use of lipid-lowering treatment. The results highlight the benefits of intensive treatment of people with screen-detected diabetes (Clinical Trials Registry No; NCT 00237549).

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Correspondence to: Torsten Lauritzen. E-mail: tl@alm.au.dk

Introduction

The cardioprotective benefits of lipid-lowering treatment are well established among people with clinically diagnosed diabetes. Lipid-lowering treatments are associated with a

> **What's new**
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> - Despite the well-established cardioprotective benefits of lipid-lowering treatment in Type 2 diabetes, evidence suggests large variations in statin use in primary care.
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> - Variation may be particularly high among people with screen-detected diabetes because general practitioners (GPs) might be reluctant to prescribe cardioprotective drugs for asymptomatic patients.
>
> - There was wide variation in the prescription of lipid-lowering treatment among people with screen-detected diabetes in Danish primary care; more frequent prescription of lipid-lowering treatment was associated with a lower incidence of cardiovascular disease and all-cause mortality.
>
> - More work is needed to improve understanding of the factors underlying practice variation in prescribing in order to encourage GPs to offer lipid-lowering treatment to this high-risk group.

25% reduction in relative risk in fatal and non-fatal cardiovascular disease (CVD), regardless of the starting level of cholesterol [1]. The UK National Institute for Health and Care Excellence (NICE) recommends prescription of a statin to all individuals with Type 2 diabetes who are 40 years or older, unless the cardiovascular risk from non-hyperglycaemia-related factors is low [2]. However, evidence suggests large variation in the use of statins in primary care [3], which is often unrelated to levels of cardiovascular risk. Patient, physician and practice-level factors can influence statin prescribing for CVD prevention, although previous research suggests that the prescribing behaviour of doctors is likely to contribute most to any variation [4–7].

Variations in lipid-lowering treatment may be particularly high among people with newly diagnosed diabetes. Research suggests that general practitioners (GPs) may be reluctant to prescribe cardioprotective drugs for asymptomatic patients [8], for whom the burden of treatment may seem greater than the burden of the disease [9]. Individuals detected earlier in the disease trajectory may, therefore, have reduced access to potentially beneficial treatment. With the advent of national screening programmes, a growing number of people will fall into this category.

The *ADDITION* study is a multi-centre cluster-randomized trial evaluating cardiovascular outcomes in people with screen-detected diabetes. Intensive treatment was associated with a non-significant 17% reduction in risk of cardiovascular events over five years in the intensive group [10]. In the Danish arm of the *ADDITION* study, we have access to information about individual participants' redeemed prescriptions through the Danish National Prescription Registry. We aimed to characterize the variation in lipid-lowering treatment among people with screen-detected diabetes, and to examine associations with practice and participant characteristics as well as cardiovascular outcomes and all-cause mortality during 6.5 years of follow-up.

Participants and methods

Study design

ADDITION-Denmark consists of two phases, a pragmatic screening programme and a cluster-randomized trial comparing the effects of intensive multifactorial therapy with routine care among individuals with screen-detected Type 2 diabetes. Full details of the study are published elsewhere (Clinical Trials Registry No; NCT 00237549) [10]. Ethical approval was granted by the Region Midt Ethical Committee, Denmark. All participants provided informed consent.

In total, 175 practices (85 randomized to routine care and 90 randomized to intensive treatment) in five counties (Copenhagen, Aarhus, Ringkoebing, Ribe and South Jutland) carried out the screening programme and identified individuals with undiagnosed prevalent diabetes who were subsequently included in the treatment phase of the study. Population-based stepwise screening programmes among people aged 40–69 years without known diabetes, were undertaken between 2001 and 2006. In total, 163 185 individuals registered with participating practices were sent a validated risk score questionnaire [11] with an invitation to visit their family doctor for stepwise diabetes testing if they had a risk score ≥ 5 (maximum 15 points). The risk score was developed using the Danish Inter99 population. Sensitivity for predicting undiagnosed diabetes varied from 68.9 to 77.0%, and specificity from 68.8 to 78%, using four different cut-off points [11]. External validation using the chosen cut-point of ≥ 5 was completed using data from 1028 individuals in a pilot for the *ADDITION* study and revealed a sensitivity of 76.0% [95% confidence interval (CI): 58.3–90.3) and specificity of 72.2% (95% CI: 69.3–75.1) for diabetes. Individuals were diagnosed with diabetes according to 1999 WHO criteria and were subsequently managed according to the treatment regimen to which their practice was allocated: routine care or intensive treatment. General practitioners (GPs) assessed patients against exclusion criteria: an illness with a life expectancy of < 12 months, housebound, pregnancy or lactation, or psychological or psychiatric problems that were likely to invalidate informed consent. Overall, 1533 eligible participants with screen-detected diabetes agreed to take part.

Intervention

The characteristics of the interventions to promote intensive treatment have been described previously [10]. Further

details are available at the study website (http://www.addition.au.dk/). We aimed to educate and support GPs, practice nurses and participants in target-driven management (using medication and promotion of healthy lifestyles) of hyperglycaemia, blood pressure and cholesterol, based on the stepwise regimen used in the Steno–2 study [12]. Targets included HbA$_{1c}$ < 53 mmol/mol (7.0%), blood pressure ≤ 135/85 mm Hg, cholesterol < 5 mmol/l without ischaemic heart disease or < 4.5 mmol/l with ischaemic heart disease, and prescription of aspirin to those treated with anti-hypertensive medication. In accordance with the Heart Protection Study [13], the treatment algorithm included a recommendation to prescribe a statin to all patients with a cholesterol level ≥ 3.5 mmol/l. GPs in the intensive treatment group were advised to start lipid-lowering treatment within four weeks of the diagnosis of diabetes. In the routine care group, participants received the standard pattern of diabetes care according to current recommendations [14].

Measurement and endpoints

Health assessments at baseline included biochemical and anthropometric measures and were undertaken by centrally trained staff following standard operating procedures. All biochemical measures were analysed in two regional laboratories. Standardized self-report questionnaires were used to collect information on lifestyle habits. We also collected relevant data from Danish national registries and linked information using the unique civil registration number. Prescription data were obtained from the Danish National Prescription Registry, which contains information on all prescription drugs redeemed at Danish community pharmacies. Lipid-lowering medication was defined as any ATC-group code C10. Data on education, income and cohabitation status were retrieved from Statistics Denmark. Education was categorized according to UNESCO's *International Standard Classification of Education* [15]. Income was equivalence-weighted on the basis of the OECD-modified scale [16] in which the first adult in the household is given a weight of 1, the second adult is given a weight of 0.5 and each child is given a weight of 0.3. Cohabitation status was categorized into two groups: single and cohabiting. Information on prevalent chronic disease, including ischaemic heart disease (ICD–10 I20.0–25.9), stroke (ICD–10 I60.0–69.8) and cancer (ICD–10 C00.0–97.9), was retrieved from the Danish National Patient Registry, which covers all hospitalizations in Denmark.

Individuals were followed for a mean of 6.5 years. The primary outcome was time to first cardiovascular event after diagnosis of diabetes, including cardiovascular mortality, cardiovascular morbidity (non-fatal myocardial infarction and non-fatal stroke), revascularization and non-traumatic amputation. The secondary outcome was all-cause mortality. The Danish Civil Registration System and the Danish National Patient Register was searched on 31 December 2009 for deaths and for ICD–10 codes for cardiovascular events (I08–I77), surgical procedures concerning amputations (chapters KNFQ, KNHQ, KNDQ, KNCQ) and revascularizations (chapters KF and KP of the NOMESCO Classification of Surgical Procedures. Sundhedsstyrelsen and Munksgaard, Copenhagen, 2005). All events were independently adjudicated by two members of a local endpoint steering committee according to an agreed protocol using standardized case report forms.

Statistical analysis

For each general practice, we calculated the proportion of individuals who redeemed at least three prescriptions of lipid-lowering medication within the first two years of diagnosis, of which the first was redeemed in the first year after diagnosis. These data were displayed in a ranked bar chart and divided into quartiles. Baseline practice and participant characteristics of the trial cohort were described by treatment group quartile. Practice screening intensity was calculated as the median number of patients in the target population who were screened for diabetes divided by the median number of participants in the target population. We compared practice and participant characteristics across quartiles using Kruskal–Wallis tests and chi-squared tests (where appropriate). Logistic regression was used to quantify the association between quartiles of proportions of individuals with screen-detected diabetes in practices who were prescribed lipid-lowering treatment and (1) risk of the composite CVD outcome and (2) risk of all-cause mortality among people with screen-detected diabetes. All models were adjusted for age, sex, previous ischaemic heart disease, previous stroke, previous cancer, prescription of lipid-lowering medication prior to diagnosis (according to the same definition used above), smoking, baseline values for HbA$_{1c}$, total cholesterol, systolic blood pressure, diastolic blood pressure and BMI and follow-up time. Models were run in the whole trial cohort and separately by trial group. We also examined the same associations (with quartiles of prescribed medication) using a Cox proportional hazards model. We ran an individual participant level analysis exploring the association between lipid-lowering prescribing (yes/no) and CVD incidence, adjusting for the same confounders listed above and accounting for clustering by general practice. Sensitivity analyses were conducted to examine whether the overall result remained the same after excluding practices with only one or two participants. All data were analysed using Stata Version 12.0 (STATA Corp., College Station, TX, USA).

Results

One GP practice with four participants was excluded due to missing information on GP characteristics. We subsequently excluded 20 individuals who experienced a CVD endpoint or died in the first two years of follow-up. Table 1 shows

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Table 1 Baseline practice and participant characteristics in the *ADDITION-Denmark* trial cohort (*n* = 1509) by quartile of proportion of individuals prescribed lipid-lowering treatment

Characteristics	Treatment intensity				P-value*
	Quartile 1 (highest)	Quartile 2	Quartile 3	Quartile 4 (lowest)	
Practice					
Number	42	45	43	44	
Median number of patients per practice in the target population (IQR) (A)	656 (555–901)	888 (598–1456)	728 (522–1224)	720 (618–956)	0.174
Prescribed lipid-lowering medication, % (range)					N/A
Whole trial cohort	86.7 (73.3–100)	56.0 (40.9–69.2)	30.0 (21.1–40.0)	6.2 (0–20)	
Intensive treatment	87.8 (76.9–100)	68.7 (54.3–76.5)	36.4 (21.1–50.0)	5.8 (0–20)	
Routine care	79.7 (57.1–100)	45.3 (35.0–53.8)	28.3 (21.1–33.3)	6.5 (0–20)	
Median number of *ADDITION* trial participants per practice (IQR)	6 (3–12)	10 (6–16)	7 (4–13)	5 (2–7.5)	< 0.001
Median number of patients in the target population screened per practice (IQR) (B)	151 (91–196)	157 (111–211)	146 (89–192)	120 (86–166)	0.122
Screening intensity (B/A) (%)	20.7	18.9	17.4	16.4	0.034
Median number of GPs per practice (range)	1 (1–5)	1 (1–6)	1 (1–6)	1 (1–4)	0.158
Participants					
Number	328	550	387	244	
Mean age at diagnosis (SD), years	59.6 (3.5)	59.7 (2.9)	59.6 (2.7)	58.8 (5.0)	0.657
Men, %	53.4	57.1	53.8	66.0	0.054
Education					0.942
> 15 years, *n* (%)	43 (13.4)	84 (15.4)	55 (14.6)	31 (12.9)	
10–15 years, *n* (%)	159 (49.4)	256 (47.1)	180 (47.8)	113 (46.9)	
< 10 years, *n* (%)	120 (37.3)	204 (37.5)	142 (37.7)	97 (40.3)	
Income					0.976
> 80 percentile, *n* (%)	67 (20.4)	112 (20.4)	75 (19.4)	48 (19.7)	
20–80 percentiles, *n* (%)	197 (60.1)	331 (60.2)	229 (59.2)	142 (58.2)	
< 20 percentile, *n* (%)	64 (19.5)	107 (19.5)	83 (21.5)	54 (22.1)	
Cohabiting (%)	66.7	72.9	67.1	69.8	0.613
Mean BMI (SD), kg/m²	30.9 (2.9)	31.2 (1.8)	31.4 (2.2)	31.2 (3.2)	0.797
Current smoker (%)	31.1	32.3	45.5	26.3	0.001
Prevalent ischemic heart disease (%)	11.1	10.4	8.1	3.0	0.004
Prevalent stroke (%)	3.2	2.3	3.9	1.2	0.127
Prevalent cancer (%)	2.5	4.4	5.7	1.5	0.014
Charlson comorbidity index ≥ 1 (%)	13.0	12.5	11.2	9.9	0.718
Mean HbA$_{1c}$, mmol/mol	48.6	49.7	51.9	50.8	0.112
Mean HbA$_{1c}$, %	6.6 (0.7)	6.7 (0.6)	6.9 (0.5)	6.8 (1.1)	0.112
Mean total cholesterol (SD), mmol/l	5.5 (0.6)	5.6 (0.4)	5.7 (0.5)	5.5 (0.7)	0.237
Mean systolic blood pressure (SD), mmHg	141.4 (7.3)	144.8 (8.1)	144.7 (9.7)	146.6 (14.9)	0.145
Mean diastolic blood pressure (SD), mmHg	84.3 (5.5)	85.7 (4.1)	85.9 (4.0)	86.7 (6.4)	0.192
Modelled CVD risk ≥ 5 points (%)**	50.6	59.0	60.5	61.3	0.191
Number of CVD events, *n* (%)	14 (4.3)	38 (6.9)	42 (10.9)	24 (9.8)	0.005
All-cause mortality, *n* (%)	30 (9.1)	46 (8.4)	33 (8.5)	21 (8.6)	0.983
Median person-years of follow-up (IQR)	6.1 (4.0–7.0)	6.4 (5.8–6.8)	6.7 (6.0–7.5)	7.5 (6.4–7.9)	< 0.001

*For group differences from the Kruskal-Wallis equality-of-populations rank test, chi-squared test or ANOVA test.
**Modelled CVD risk was computed using the SCORE model.

baseline practice (*n* = 174) and participant (*n* = 1509) characteristics by quartile of lipid-lowering treatment. The mean (SD) age was 59.6 (6.9) years; 57% were male and the mean BMI was 31.2 kg/m^2. The median [interquartile range (IQR)] number of participants per practice in the target population was 720 (584–1070).

Treatment variation

Figure 1 shows the proportion of participants who redeemed lipid-lowering medication within the first two years of diagnosis in each GP practice. Proportions varied widely from 0% to 100% in both study groups. However, lipid-lowering treatment was prescribed significantly more frequently in the intensive treatment group than the routine care group [intensive treatment: median (IQR): 64.7% (33.3–75.0); routine care: 33.3% (23.1–50.0), *P* < 0.001].

Practice- and participant-level factors associated with variation

Compared with practices with low levels of prescribing of lipid-lowering medication, higher prescribing practices had screened more of their eligible population and had greater numbers of people with screen-detected diabetes (Table 1). Practices were similar for all other examined characteristics.

Participant characteristics were similar across the treatment quartiles for most socio-demographic and clinical characteristics (Table 1). Compared with individuals in the bottom quartile for lipid-lowering prescribing, those in the

top quartile were more likely to have a history of ischaemic heart disease.

Association between treatment variation and CVD events

One hundred and eighteen people experienced a CVD event (8%) over 9431 person-years of follow-up, with the highest number of events in the practices who prescribed lipid-lowering medication to the fewest individuals. Table 2 shows the crude and adjusted ORs for the association between quartiles of proportion of people prescribed lipid-lowering treatment in practices and risk of CVD events. When examining the whole trial cohort, the risk of CVD was significantly higher in practices in the lowest quartile compared with the highest quartile for prescribing of lipid-lowering medication (adjusted OR 3.4, 95% CI 1.6–7.3). The association between lipid-lowering prescribing and CVD events was stronger in the routine care than the intensive treatment group; the odds of CVD increased as the prescription of lipid-lowering medication decreased. There was a significant trend in OR over the four quartiles (*P* < 0.001).

Association between treatment variation and all-cause mortality

One hundred and thirty participants died over 6.5 years of follow-up. When examining the whole trial cohort, all-cause mortality was significantly higher in practices in the lowest quartile compared with the highest quartile for prescribing of lipid-lowering medication (adjusted OR 2.9, 95% CI 1.1–
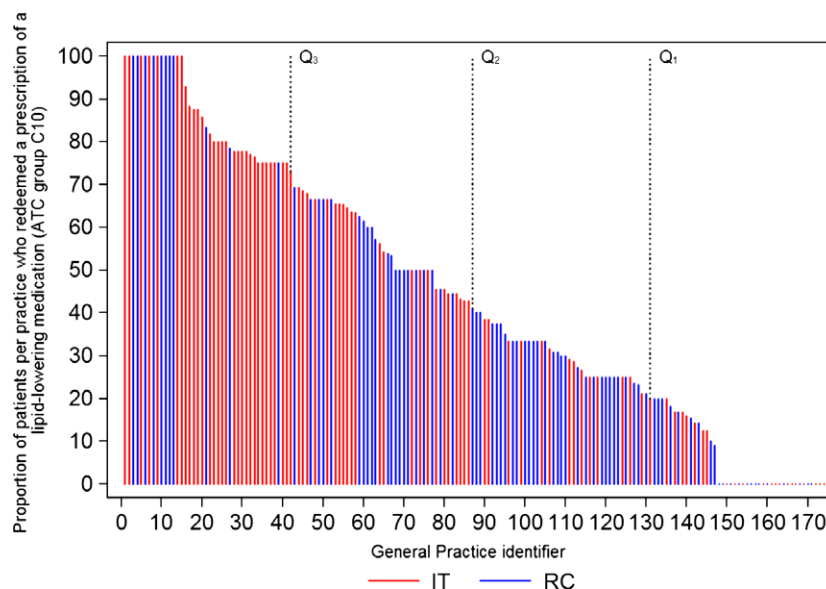
FIGURE 1 Ranked bar chart showing the proportion of *ADDITION-Denmark* participants in each general practice who redeemed at least three prescriptions of lipid-lowering medication within the first 2 years of diagnosis, of which the first was redeemed within the first year from diagnosis. The bars are divided into quartiles. Intensive treatment (IT) practices are indicated by red bars and routine care (RC) practices by blue bars.

Table 2 Crude and adjusted odds ratios for the association between lipid-lowering treatment group, a composite CVD endpoint and all cause-mortality by trial group in *ADDITION-Denmark*

Groups of lipid-lowering treatment	Mean proportion prescribed lipid-lowering treatment (range)	Crude OR for incident CVD (95% CI)	Adjusted* OR for incident CVD (95% CI)	Crude OR for all-cause mortality (95% CI)	Adjusted OR for all-cause mortality (95% CI)*
Overall Cohort					
1 (comparison)	86.7 (73.3–100)	1	1	1	1
2	56.0 (40.9–69.2)	1.7 (0.9–3.0)	1.9 (1.0–3.8)	0.9 (0.5–1.5)	1.4 (0.6–3.3)
3	30.0 (21.1–40.0)	2.7 (1.5–5.1)	3.2 (1.5–6.7)	0.9 (0.5–1.6)	1.6 (0.7–3.8)
4	6.2 (0–20.0)	2.4 (1.3–4.6)	3.4 (1.6–7.3)	0.9 (0.5–1.7)	2.9 (1.1–7.8)
Intensive Treatment Group					
1 (comparison)	87.8 (76.9–100)	1	1	1	1
2	68.7 (54.3–76.5)	2.2 (1.0–4.8)	2.8 (1.3–6.9)	1.4 (0.8–2.6)	3.5 (1.2–9.7)
3	36.4 (21.1–50.0)	2.9 (1.2–6.7)	3.2 (1.1–9.1)	1.3 (0.7–2.5)	4.5 (1.2–15.9)
4	5.8 (0–20.0)	1.9 (0.7–4.7)	2.8 (1.0–7.9)	0.6 (0.2–1.5)	1.8 (0.5–7.0)
Routine Care Group					
1 (comparison)	79.7 (57.1–100)	1	1	1	1
2	45.3 (35.0–53.8)	0.5 (0.2–1.4)	0.7 (0.2–2.0)	0.7 (0.3–2.1)	1.3 (0.3–4.8)
3	28.3 (21.1–33.3)	2.6 (1.1–6.1)	4.7 (1.8–12.2)	1.4 (0.5–3.4)	3.2 (1.0–9.9)
4	6.5 (0–20.0)	2.2 (0.9–5.5)	4.7 (1.6–14.0)	1.8 (0.8–4.3)	7.3 (2.0–26.7)

OR, odds ratio.
*OR adjusted for age, sex, prevalent ischaemic heart disease, stroke and cancer, use of lipid-lowering drugs before screening, smoking, HbA$_{1c}$, total cholesterol, systolic blood pressure, diastolic blood pressure, BMI and follow-up time.

7.8). Similar trends were observed in the routine care and the intensive treatment groups.

Sensitivity analyses

When using Cox regression there was a significant association between treatment variation and CVD events in the whole trial cohort, but not in the routine care and intensive treatment groups when analysed separately. There was no association between treatment variation and all-cause mortality in either trial group using Cox regression, although results were in the expected direction of effect. In an individual participant-level analysis, all-cause mortality was significantly lower among individuals prescribed lipid-lowering treatment compared with those who were not (adjusted OR 0.58; 95% CI 0.35–0.97). There was no association between lipid-lowering treatment and CVD events at the individual level (adjusted OR 0.69; 95% CI 0.44–1.08). After excluding practices with one or two participants, the overall results remained the same.

Discussion

We observed a large variation in the prescribing of lipid-lowering medication, even among GPs in intensive treatment practices who were advised to prescribe lipid-lowering treatment within the first four weeks of a diagnosis of diabetes. The variation did not appear to be explained by participant levels of modifiable cardiovascular risk because most practice and participant characteristics were similar across the treatment quartiles. However, it appeared that GPs were recommending medication to patients with pre-existing ischaemic heart disease and that practitioners who were enthusiastic about screening were also more likely to prescribe lipid-lowering medication. In both trial groups and in the overall cohort, the odds of incidence of the composite CVD endpoint and all-cause mortality increased as the proportion of participants' prescribed lipid-lowering medication in each practice decreased. The associations were independent of age, sex, prevalent chronic disease, lipid-lowering prescription prior to diagnosis, baseline CVD risk factors and follow-up time. There was an association between prescription of lipid-lowering treatment and all-cause mortality, but not CVD events, at the individual level. The strength of this association may reflect residual confounding, for example, lipid-lowering treatment may be reserved for those patients at highest risk in the low prescribing practices.

Our findings suggest that Danish GPs, even those self-selecting to participate in a randomized controlled trial, do not routinely prescribe lipid-lowering drugs to patients with screen-detected diabetes. Although education and target-setting in the intensive treatment compared with the routine care group were associated with an increased frequency of lipid-lowering treatment, there was still room

for improvement. Studies from individuals with established diabetes also suggest that prescribing of lipid-lowering drugs is below recommended levels. An examination of the quality of diabetes care in Aarhus County, Denmark, showed that the proportion of the population redeeming lipid-lowering medication was 18% in 2000, rising to 38% in 2003 [17]. Baseline data from a cluster randomized controlled trial of electronic feedback of treatment status in Danish primary care in 2007 reported that 45% of people with diabetes redeemed a prescription for lipid-lowering mediation [18]. These findings are broadly comparable with the proportion of individuals prescribed a statin in the routine care group in *ADDITION-Denmark* between 2001 and 2006 (33%). The under-utilization of lipid-lowering treatment has also been reported in a number of other health systems that recommend the prescription of lipid-lowering medication to certain high-risk groups including the UK, Ireland and Germany [19–21]. Our results suggest, for the first time, that the lack of adherence to guidelines may have consequences for the clinical outcome for individuals with screen-detected Type 2 diabetes.

Previous research suggests that the prescribing behaviour of doctors is likely to be the biggest factor contributing to the variation in statin prescribing for CVD prevention in primary care [4–7]. Qualitative research shows that GPs face a variety of barriers to initiating statin treatment and instigating CVD prevention more generally. These include differing treatment targets and difficulties in prioritizing patients for treatment and in interpreting primary prevention risk assessment tools [4,22,23]. There are also fears about cost, increased workload, and adherence to treatment, as well as concerns about medicalization and adverse effects on patient health behaviours [4]. The results from our study should also be considered in light of national interest and uncertainty about screening and early treatment for diabetes in Denmark. Articles in the national and international press have suggested that diabetes screening is unnecessary and that the health system is over-medicalizing its citizens [24–27]. These factors may have contributed to GPs being reluctant to prescribe lipid-lowering treatments to asymptomatic patients at an early stage in the course of the disease, and to patients being reluctant to redeem such prescriptions [28]. Future work might collect data on a wider range of potential determinants of prescribing to investigate this issue in more detail. It may also be useful to compare our results with countries like the UK who have a direct financial incentive to prescribing.

Strengths and limitations

Participants were recruited from a large, representative, population-based sample from five different counties in Denmark. There was 99.9% endpoint ascertainment and all CVD events were independently adjudicated. Prescription data were obtained from the Danish National Prescription Registry, which captures all prescription drugs dispensed at community pharmacies. We were able to adjust for a wide range of potential confounders, using information collected from participants at their baseline visit and data retrieved from Statistics Denmark and the Danish National Patient Registry.

In terms of limitations, this was a post-hoc research question using observational data from a trial cohort. Adjustment for age, sex, prevalent chronic disease, baseline cardiovascular risk factors and follow-up time did not alter the association between treatment variation and incident CVD. This makes it unlikely that participant-level comorbidity and differences in follow-up time confounded the observed association and that general-practice-level factors are most likely responsible for the variation in treatment. However, we cannot rule out the possibility of confounding by intention, e.g. practices prescribing more lipid-lowering medication may also encourage more lifestyle changes and prescribe more nicotine replacements, anti-hypertensive and glucose-lowering medication, which may also be linked to the outcomes. Although we showed that higher prescribing practices had screened more of their eligible population and had greater numbers of participants with screen-detected diabetes, we were not able to examine the importance of other general practice factors such as: the age and gender of GPs, the number of GPs per practice and number of other healthcare providers per practice. The recruitment of general practices was not random, potentially limiting the generalizability of our results. However, we covered a large geographical area and participating practices were nationally representative for key characteristics [10]. We do not have data on individuals who were prescribed lipid-lowering medication but chose not to pick it up at their community pharmacy. However, evidence from a trial nested within *ADDITION-Denmark* suggests that compliance rates were very high (close to 100%) [29]. Given that individuals who do not redeem their prescriptions are more likely be to those with higher HbA_{1c} values and complications of diabetes [30], this might have led to an under-estimation of the inverse association between prescribing lipid-lowering medication and incident CVD. We could not ascertain whether the low proportions of participants prescribed lipid-lowering treatments in some practices might be due to individuals being started on lipid-lowering treatment but experiencing side effects and then stopping them.

Conclusion

We found a wide variation between practices in the prescription of lipid-lowering treatment among individuals with screen-detected diabetes and demonstrated a significant association between the frequency of lipid-lowering treatment and CVD and all-cause mortality – both being favourably influenced by more frequent treatment. More work is needed to improve understanding of the factors

underlying practice variation in prescribing in order to encourage GPs to offer lipid-lowering treatment and other preventive interventions to this high-risk group. These results lend support to the benefits of treatment early in the course of the disease. In tailoring treatment decisions to individuals with screen-detected Type 2 diabetes, consideration should be given to the possibilities of both over- and under-treatment.

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