Original Research

The effect of guideline revisions on vascular complications of type 2 diabetes

Ralph Heijmans, Sunny S. Singh, Aloysius G. Lieverse, Eric J.G. Sijbrands and Mandy van Hoek

Abstract

Background: The aim of this study was to investigate the impact of implementation and revision of the 'Diabetes Mellitus type II' guideline by the Dutch College of General Practitioners (DCGP) on the prevalence and incidence of macrovascular and microvascular complications.
Methods: The DiaGene study is a case-control study ($n = 1886$ patients of type 2 diabetes) with extensive, retrospectively collected complication data, as well as prospective follow up of complications. The study incorporates all lines of diabetes care. Cases were divided into categories according to the date of onset of diabetes and publication dates of the DCGP. Logistic regression models were used to investigate the associations between guideline version and complications. To investigate a possible trend between guideline version and complications, the 'guideline category' was also used as a continuous variable. All models were adjusted for clinical covariables.
Results: The 1999 and 2006 guidelines versions were associated with significantly lower risk of retinopathy than the group that started without a guideline [OR 0.32 (95% CI 0.14–0.72, $p = 0.006$) and 0.31 (95% CI 0.11–0.91, $p = 0.034$), respectively]. A significant trend in reduction of peripheral artery disease (PAD) over the guideline versions was found, adjusted for age, sex and diabetes duration (odds ratio (OR) 0.70, 95% CI 0.51–0.97, p trend = 0.029) and for retinopathy in all models (OR = 0.52, 95% CI 0.37–0.73, p trend < 0.001).
Conclusions: The introduction of the first diabetes guideline and subsequent revisions have reduced the risk of macrovascular and microvascular complications of type 2 diabetes, most strongly in diabetic retinopathy. This indicates that real-time diabetes care has improved over time.

Keywords: diabetes care, diabetic retinopathy, guideline, macrovascular complications, microvascular complications, type 2 diabetes

Introduction

Type 2 diabetes is one of the most prevalent chronic diseases in the Netherlands and exposes patients to a high risk of developing macrovascular and microvascular complications.[1,2] Guidelines have been developed and repeatedly updated to implement evidence-based care to prevent vascular complications.[3–6] Unfortunately, to the best of the authors' knowledge no trials have been performed on the efficacy of the guideline nor the revised versions. In the DiaGene study, long-term follow up was available covering a period from no guideline up until to multiple revised versions. Therefore, the authors had the unique opportunity to determine the real-time efficacy of the evolving diabetes guideline, with the expectation that promoting structured diabetes care reduced the risk of vascular complications of type 2 diabetes.

Risk factors of macrovascular and microvascular complications in type 2 diabetes include hyperglycemia,[1] hypertension,[7] lifestyle,[8] smoking, and hypercholesterolemia.[9] In addition to preventing acute complications of type 2 diabetes, the objective of treatment is to reduce morbidity

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and mortality by preventing or delaying vascular complications.[10] Therefore, diabetes guidelines aim at regulating blood glucose levels and influencing the cardiovascular risk factors by controlling blood pressure, blood lipid levels, and improving lifestyle behavior.[6]

The Dutch College of General Practitioners (DCGP)[3] published their first guideline 'Diabetes Mellitus type II' in 1989. This guideline contained evidence-based recommendations for primary care concerning diagnosis, treatment, and support of patients with type 2 diabetes aimed at a uniform approach to diabetes care.[5] In order to meet new standards and to integrate new scientific evidence, the diabetes guideline has been updated three times, in 1999, 2006, and 2013.[4–6] Guidelines on treatment of type 2 diabetes in secondary healthcare were not available in the Netherlands until 2013.[11] Therefore, the guidelines of the DCGP were also used in hospitals.

In a small number of studies, the effect of up to date worldwide and local diabetes guidelines on medical diabetes therapy has been determined.[12–14] The guideline revisions were associated with a significantly increased use of antidiabetic medication. Apparently, the treatment recommendations were quickly put into clinical practice.[12–14] However, the effect of diabetes guidelines on patient's clinical outcomes has not been investigated directly.

In the DiaGene study, the authors investigated the efficacy of the implementation and revision of the guideline 'Diabetes Mellitus type II' of the DCGP on macrovascular and microvascular complications.

Materials and methods

Study design
The design of the DiaGene study has been described previously.[15] The DiaGene study is an all lines of healthcare case-control study with prospective follow up, designed to investigate the etiology of type 2 diabetes and its vascular complications. Data was collected in the cities of Eindhoven and Veldhoven, the Netherlands. The majority of patients with type 2 diabetes in the area of Eindhoven, both primary care and outpatient clinic, were approached for inclusion. Type 2 diabetes was diagnosed according to the guidelines of the WHO and the American Diabetes Association.[16,17] In total, 1886 patients with type 2 diabetes were included in the study. Written informed consent was obtained from all participants. This study was approved by the Medical Ethics Committee of the Erasmus MC and the local Ethics Committees of the hospitals in Eindhoven.

Definitions of macrovascular and microvascular complications
The definitions of macrovascular and microvascular complications have previously been described in more detail.[15] Ischemic heart disease (IHD) was defined as myocardial infarction or percutaneous coronary intervention/coronary artery bypass graft (PCI/CABG). Ischemic cerebral disease (ICD) included cerebrovascular accident or transient ischemic attack. Peripheral arterial disease (PAD) was defined as an ankle-brachial index below 0.80 or below 0.90 with typical complaints, any intervention to treat PAD or the self-reported presence of intermittent claudication. IHD, ICD, and PAD were all derived from medical records and questionnaires. Diabetic retinopathy was scored and graded according to the report of an ophthalmologist and fundus photography. Diabetic nephropathy was defined as microalbuminuria [albumin/creatinine ratio (ACR) ≥ 2.5 for men or ≥ 3.5 for women] present at two of three consecutive measurements, or when high micro-albuminuria or macro-albuminuria was present at one measurement (ACR ≥ 12.5 for men or ≥ 17.5 for women). Diabetic neuropathy was defined by a podiatrist, neurologist or the patient's treating physician. Prospective follow up for macrovascular and microvascular endpoints, according to the definitions above, was performed through the medical charts of all hospitals in the region of Eindhoven. Questionnaires were sent to the primary care patients, who were not under treatment in the local hospitals, to reduce the chance of missing a vascular event.

In the authors' analyses, data on complications during baseline and follow up were merged, and classified as follows: patients with complications at baseline and/or during follow up were qualified as having complications, patients without complications at baseline and during follow up were qualified as having no complications, patients with missing data at baseline or during follow up but with known complications on either two moments were qualified as having complications,

and patients with missing data at baseline and no complications during follow up were qualified as missing. Finally, patients with no complications at baseline and missing data during follow up were qualified as having no complications. The latter mainly belonged to primary care and failed to respond to the prospective questionnaire. For all of these patients, a screening of hospital records inside the region was performed. However, as this system may not be foolproof, the authors additionally randomly contacted 40 of these patients and found complications at follow up in 5% indicating an overall acceptable error in the study of <2.1% misclassification.

Exposure to guideline groups
The date of birth and age of onset of type 2 diabetes were used to determine the year of onset of type 2 diabetes. Subsequently, as a measure for treatment according to versions of the guideline, all cases were divided into categories in alignment with the publications of the DCGP guideline 'Diabetes Mellitus type II' as follows: patients with onset diabetes before 1989 in category 1, patients with onset diabetes during or after 1989 and before 1999 in category 2, patients with onset diabetes during or after 1999 and before 2006 in category 3, and patients with onset diabetes during or after 2006 and before 2013 in category 4. There were no patients in the DiaGene study with the onset of type 2 diabetes after 2012. These categories reflect groups of people that have progressed through and have been treated according to the subsequent guidelines for a certain period in each category. As explained in the following, to reduce confounding by the age and duration of diabetes, the authors adjusted the logistic models accordingly.

Statistical methods
To compare baseline variables between the four guideline categories, the one-way analysis of variance (ANOVA) test was applied for continuous variables with a normal distribution and the chi-squared test for categorical variables.

Logistic regression models were used to investigate the associations between the macrovascular and microvascular complications as outcome variables and the guideline categories as the exposure variable. To investigate a possible trend between guideline version and complications, the 'guideline category' was also used as a continuous variable in the regression models.

Two models were conducted. The basic model 1, was adjusted for sex, age, and duration of type 2 diabetes and an extended model 2 was additionally adjusted for body mass index (BMI) and smoking. Statistical analyses were performed using IBM SPSS Statistics, version 25.

Results

Baseline characteristics
Baseline characteristics of cases, which were divided among the four categories according to guideline version, are listed in Table 1. A total of 120 cases were excluded because the date of onset diabetes could not be determined, leaving a total of 1766 patients for analyses. There was a significant difference in age, HbA1c, HDL-cholesterol, non-HDL-cholesterol, smoking, and the prevalence of all macrovascular and microvascular complications between guideline versions. The distribution of sex was not different over the guideline categories.

Association between guideline version and vascular complications
The results of the logistic regression analyses for the basic and extensive models are listed in Table 2. Compared with the reference category 'no guideline', the odds ratio (OR) of having IHD, ICD, or PAD did not differ significantly in all guideline categories in the basic and extensive models.

With regard to the microvascular complications diabetic nephropathy and neuropathy, the OR in both models did not differ significantly in the guideline categories compared with the 'no guideline' category. For diabetic retinopathy, in the most extensive model, the 1999 and 2006 guideline categories were associated with a lower significant ORs of 0.32 (95% CI 0.14–0.72, $p = 0.006$) and 0.31 (95% CI 0.11–0.91, $p = 0.034$), respectively.

Effect of guideline updates on vascular complications
In Table 3 trend associations between guideline versions and vascular complications are sted. PAD was significantly reduced overall guideline versions in model 1 (OR 0.70, 95% CI 0.51–0.97,

Table 1. Baseline characteristics.

Variable	No guideline	Guideline 1989	Guideline 1999	Guideline 2006	p value
	n = 242	*n* = 579	*n* = 757	*n* = 188	
Age (years)	70.4 ± 9.1	66.1 ± 9.6	63.4 ± 10.7	61.1 ± 11.6	<0.001
Sex (male count (%))	129 (53.3)	300 (51.8)	411 (54.3)	111 (59.0)	0.377
Duration of type 2 diabetes (years)	26.2 ± 6.8	13.1 ± 3.2	4.9 ± 2.4	1.0 ± 1.0	<0.001
BMI (kg/m^2)	30.3 ± 5.4	30.9 ± 5.9	30.4 ± 5.2	29.9 ± 5.0	0.123
HbA1c (mmol/mol)	57.49 ± 10.89	56.98 ± 12.31	50.90 ± 10.62	50.10 ± 11.95	<0.001
HbA1c (%)	7.41 ± 1.00	7.36 ± 1.13	6.81 ± 0.97	6.73 ± 1.09	<0.001
HDL-cholesterol (mmol/l)	1.25 ± 0.39	1.17 ± 0.32	1.16 ± 0.31	1.11 ± 0.29	<0.001
Non-HDL-cholesterol (mmol/l)	2.84 ± 0.75	3.06 ± 0.89	3.17 ± 0.89	3.40 ± 1.01	<0.001
Current smoker (%)	28 (13.1)	100 (18.9)	125 (18.1)	31 (18.3)	0.045
Former smoker (%)	120 (56.3)	285 (53.9)	392 (56.8)	109 (64.5)	
Never smoked (%)	65 (30.5)	144 (27.2)	173 (25.1)	29 (17.2)	
Ischemic heart disease (%)	37.9	36.1	25.3	30.3	<0.001
Ischemic cerebral disease (%)	24.2	15.1	14.4	13.1	0.003
Peripheral artery disease (%)	22.9	20.7	13.4	10.3	<0.001
Nephropathy (%)	51.9	43.5	37.7	30.1	<0.001
Retinopathy (%)	69.0	44.5	13.7	12.0	<0.001
Neuropathy (%)	76.5	59.7	63.3	48.7	<0.001

Unless stated otherwise, mean (±SD) are given.
BMI, body mass index; Hba1c, hemoglobin A1c; HDL, high-density lipoprotein.

p trend = 0.029). No other significant trends were found for macrovascular complications.

With regard to microvascular complications, a significant trend in reduction of diabetic retinopathy was found overall guideline categories in model 1 (OR 0.56, 95% CI 0.41–0.77, *p* trend < 0.001) and model 2 (OR 0.52, 95% CI 0.37–0.73, *p* trend < 0.001). No significant trends were found for other microvascular complications.

Discussion

In this study, the authors found a significant risk reduction of 69% of diabetic retinopathy when patients started their treatment in a more recent DCGP type 2 diabetes guideline. In addition, the authors detected a significant overall trend in lower odds for PAD and diabetic retinopathy when starting treatment in a more recent DCGP guideline.

The authors' results demonstrate that diabetes care has improved over time. The authors presume these effects can be explained by two factors. First, guideline implementation eliminates the uncertainty of clinicians with regards to treatment method, avert outdated practices and improve the consistency of care.[18] Second, guideline revisions reflect the scientific development of type 2 diabetes care over the years, which is

Table 2. Guideline categories and the association with vascular complication risk.

	Guideline 1989				Guideline 1999				Guideline 2006			
	Model 1		Model 2		Model 1		Model 2		Model 1		Model 2	
	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
IHD	1.19 (0.71–1.98)	0.509	0.94 (0.53–1.65)	0.824	0.77 (0.38–1.58)	0.480	0.54 (0.25–1.17)	0.116	1.09 (0.46–2.59)	0.846	0.74 (0.29–1.90)	0.528
ICD	0.56 (0.31–1.02)	0.060	0.61 (0.32–1.17)	0.137	0.53 (0.23–1.22)	0.136	0.58 (0.24–1.43)	0.238	0.48 (0.17–1.35)	0.164	0.55 (0.18–1.69)	0.296
PAD	1.00 (0.56–1.80)	0.993	0.94 (0.49–1.78)	0.848	0.63 (0.28–1.42)	0.264	0.59 (0.24–1.43)	0.242	0.48 (0.17–1.36)	0.167	0.48 (0.16–1.50)	0.208
Nephropathy	0.92 (0.56–1.50)	0.726	0.78 (0.46–1.34)	0.373	0.79 (0.40–1.57)	0.503	0.75 (0.36–1.58)	0.451	0.60 (0.26–1.38)	0.227	0.50 (0.20–1.27)	0.146
Retinopathy	0.93 (0.55–1.58)	0.800	0.89 (0.50–1.57)	0.683	0.33 (0.16–0.72)	0.005*	0.32 (0.14–0.72)	0.006*	0.39 (0.14–1.03)	0.057	0.31 (0.11–0.91)	0.034*
Neuropathy	0.71 (0.37–1.37)	0.308	0.75 (0.37–1.53)	0.434	1.14 (0.45–2.90)	0.776	1.27 (0.48–3.39)	0.632	0.75 (0.21–2.66)	0.660	0.71 (0.19–2.71)	0.618

Model 1 adjusted for sex, age, and duration of type 2 diabetes.
Model 2 additionally adjusted for body mass index, and smoking.
ICD, ischemic cerebral disease; IHD, ischemic heart disease; PAD, peripheral arterial disease.
*p value <0.05

Table 3. Odds ratios (ORs) and associated *p* values after trend logistic regression analyses.

	Guideline category (model 1)		Guideline category (model 2)	
	OR (95% CI)	*p* trend	OR (95% CI)	*p* trend
Ischemic heart disease	0.93 (0.71–1.20)	0.567	0.84 (0.63–1.11)	0.218
Ischemic cerebral disease	0.88 (0.64–1.22)	0.448	0.91 (0.65–1.29)	0.599
Peripheral arterial disease	0.70 (0.51–0.97)	0.029	0.71 (0.50–1.00)	0.053
Nephropathy	0.82 (0.64–1.06)	0.126	0.83 (0.63–1.09)	0.173
Retinopathy	0.56 (0.41–0.77)	<0.001	0.52 (0.37–0.73)	<0.001
Neuropathy	1.16 (0.80–1.69)	0.441	1.17 (0.79–1.73)	0.446

Model 1 adjusted for sex, age, and duration of type 2 diabetes.
Model 2 additionally adjusted for BMI and smoking.

expected to improve clinical outcomes, although the findings were not entirely consistent with the observations, upon which these revisions are based.

The DCGP published the first type 2 diabetes guideline in 1989.[3] This guideline contained recommendations for the diagnosis and treatment of type 2 diabetes in primary care. The main goals of treatment in this guideline were the regulation of blood glucose levels and the reduction of body weight. Of note, the precise treatment targets of blood sugar and body weight remained unclear. In 1999, the first revision was published.[4] An important change was the advice to regulate glucose levels more intensively based on the UKPDS 33 study,[19] in which intensive blood glucose control substantially decreased the risk of the microvascular but not of the macrovascular complications. Therefore, the authors expected a decrease of microvascular complication risk following the introduction of the 1999 guideline. This was only partly the case. For diabetic retinopathy, the authors found a significant risk reduction in the 1999 guideline category, but no significant risk reduction for nephropathy and neuropathy. Another important change in this 1999 revision was the treatment advice for hypertension and lipid metabolism disorders. Thiazide diuretics, angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, and cholesterol synthesis inhibitors (statins) were prescribed according to risk scores based on the UKPDS 38[7] and the 4S study.[20] The UKPDS 38 study demonstrated that tight blood pressure control decreased the risk of ICD. Our results, however, did not show a significant change in ICD after implementation

of the 1999 guideline. Tight blood pressure control was also associated with a reduced risk of diabetic retinopathy, but not of diabetic nephropathy and neuropathy, which corresponds to the authors' results. The 4S study revealed that cholesterol-lowering simvastatin decreased the risk of IHD events in high-risk patients and type 2 diabetes was considered as cardiovascular risk equivalent.[21,22] However, IHD risk did not improve in the authors' analysis, but a significant trend for better prevention of PAD over the guideline versions was found. Finally, in the 1999 guideline, recommendations were formulated for the detection of patients with diabetes in high-risk populations. This may have decreased the delay between the onset and the diagnosis of diabetes, leading to an early start of treatment and, as a consequence, improved the prevention of vascular complications, as found for PAD and retinopathy in our study.

In 2006, the second revision was published.[5] Based on the Heart Protection Study,[23] prescriptions of statins to all patients with type 2 diabetes was recommended. In this study, however, no significant further risk reduction in IHD and ICD risk was found when treatment was started according to the 2006 guideline. This guideline version also emphasized the importance of protecting renal function and diagnosing diabetic neuropathy. In this study, no changes in nephropathy and neuropathy risk were observed.

According to the authors' findings, it can be concluded that guideline implementation and revisions have prevented PAD and diabetic retinopathy in the study patients with type 2 diabetes.

There are advantages and disadvantages of this study to consider to aid in the interpretation of the findings. An advantage of this study is the meticulous collection of phenotypic, medications, and risk factor data. In addition, to the best of the authors' knowledge, this is the first time the effects of diabetes guidelines on patient's clinical outcomes have been investigated in a real-world clinical setting. Although guidelines are based on scientific insights obtained by epidemiologic reports and large controlled trials and changes in prescription of anti-hyperglycemic drugs after revision of guidelines have been examined,[12–14] to the best of the authors' knowledge, no study has been carried out that directly investigates the effect of guideline implementation and revision on type 2 diabetes complications. Although this study was performed with great care, some limitations need to be considered. First, diabetic neuropathy data was only available for patients that were under surveillance in the hospitals. This reduced the power for the analyses as well as generalizability to nonhospital patients. Second, owing to the characteristic features of a cohort study, patients of the 'no guideline' category were also exposed to the first, second, and third guideline. The authors' main analyses, therefore, compared patients treated without a guideline which followed treatment according to 1989, 1999, and 2006 guidelines with patients treated according to 1989, 1999, and 2006 guidelines. It is possible that the effect of treatment without guideline or treatment according to an earlier guideline is compensated by exposure to later guidelines. This may have reduced the estimates of the efficacy of the guidelines in these analyses. In addition, the characteristics of a cohort study also entail a possible selection bias: one could argue that the sickest individuals from the oldest guideline categories have not been included in our study. As a consequence, the number of events in the older guideline groups may have been underestimated. Despite this, the authors still found significant improvement in PAD and retinopathy after implementing and updating the guideline. Third, the duration of diabetes and age are important risk factors for developing complications. It is therefore essential to adjust the models accordingly. However, diabetes duration and age are also directly associated with guideline category. Adjustment for diabetes duration and age could, therefore, lead to an underestimation of the effect of guideline implementation. Despite these

adjustments, the authors were still able to show the effects of PAD and diabetic retinopathy in the main analysis. Fourth, a proportion of the DiaGene study consists of secondary care patients. The original type 2 diabetes guideline and further revisions published by the DCGP were aimed at primary care. Guidelines regarding secondary care treatment were not available until 2013.[11] The majority of the patients in this study initially started their treatment in primary care and the DCGP guidelines have also been used for treatment in secondary care. Finally, the authors cannot exclude the fact that the socio-economic developments since 1989 also played a role. Model 2 was additionally adjusted for smoking and BMI at inclusion, to adjust for lifestyle factors. However, residual lifestyle effects cannot be excluded. Furthermore, the fact that the BMI of some participants changes significantly over time cannot be excluded. Although BMI was highly stable in the vast majority of participants of a number of long-term follow-up studies.[24,25]

To conclude, this study shows that for patients with type 2 diabetes, guideline adjustments through the years have significantly reduced PAD and retinopathy. This indicates that real-time diabetes care has improved over time. Future studies should be directed at investigating the effect of guideline implementation in other diseases. In addition, in future diabetes guideline studies, when exact dates of complications are available, associations between complication incidence rate among different guideline categories can give an even more accurate estimate of guideline update effects.

Author note
RH analyzed and completed the database, wrote and reviewed/edited manuscript.

SS maintained the DiaGene study database, analyzed the data, wrote and reviewed/edited the manuscript.

AL collected and designed the DiaGene study and reviewed and edited the manuscript.

ES collected and designed the DiaGene study, initiated the research question, and reviewed and edited the manuscript.

MH coordinated the analyses, initiated the research question, collected data, designed the DiaGene study, and wrote, reviewed, and edited the manuscript.

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