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Prescribing practices and clinical predictors of glucose-lowering therapy within the first year in people with newly diagnosed Type 2 diabetes

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What's new?

- This nationwide prospective cohort study describes real-life prescribing practices and predictors of glucose-lowering therapy within the first year following Type 2 diabetes mellitus diagnosis in Denmark.
- Within one year after diabetes debut, 74% of patients were on a glucose-lowering drug, and 12% received combination therapy.
- Presence of comorbidity, young age, central obesity and poor baseline glucose control were important predictors, both of receiving any glucose-lowering therapy and of receiving combination therapy.

Abstract

Aim To examine prescribing practices and predictors of glucose-lowering therapy within the first year following diagnosis of Type 2 diabetes mellitus in a clinical care setting.

Methods We followed people enrolled in the Danish Centre for Strategic Research in Type 2 Diabetes (DD2) cohort from outpatient hospital clinics and general practices throughout Denmark in 2010–2013. We used Poisson regression to compute age- and gender-adjusted risk ratios (RRs).

Results Among 1158 new Type 2 diabetes mellitus patients, 302 (26%) did not receive glucose-lowering therapy within the first year, 723 (62%) received monotherapy [685 (95%) with metformin], and 133 (12%) received more than one drug. Predictors of receiving any vs. no therapy and combination vs. monotherapy were: age < 40 years [RR: 1.29 (95% CI: 1.16–1.44) and 3.60 (95% CI: 2.36–5.50)]; high Charlson Comorbidity Index [RRs: 1.20 (95% CI: 1.05–1.38) and 2.08 (95% CI: 1.16–3.72)]; central obesity [RRs: 1.23 (95% CI: 1.04–1.44) and 1.93 (95% CI: 0.76–4.94)];

fasting blood glucose of ≥ 7.5 mmol/l [RRs: 1.25 (95% CI: 1.10–1.42) and 1.94 (95% CI: 1.02–3.71)]; and HbA_{1c} ≥ 59 mmol/mol (≥ 7.5%) [RR: 1.26 (95% CI: 1.20–1.32) and 2.86 (95% CI: 1.97–4.14)]. Weight gain ≥ 30 kg since age 20, lack of physical exercise and C-peptide of < 300 pmol/l also predicted therapy.

Conclusions Comorbidity, young age, central obesity and poor baseline glycaemic control are important predictors of therapy one year after Type 2 diabetes mellitus debut.

Introduction

In current treatment guidelines for Type 2 diabetes mellitus, glucose-lowering therapy is recommended as early as possible after diagnosis to achieve near normoglycaemia [1–3]. Nonetheless, 50–58% of people with Type 2 diabetes mellitus apparently remained without medication related to frailty in the first year after diagnosis in the UK and Sweden [4,5]. Surprisingly little is known on treatment patterns of glucose-lowering drugs shortly after diagnosis of Type 2 diabetes mellitus in real-world clinical care settings. Although metformin has become the undisputed first drug of choice [1], the available treatment armamentarium for intensified therapy has expanded considerably [2,6] and it is unknown how this relates to current treatment practices.

The initiation and choice of glucose-lowering therapy for people with Type 2 diabetes mellitus should follow an individualized approach based on clinical evaluation and should consider individual factors, such as: age, functional status, pre-existing comorbidity and biochemical phenotype of the person; and drug factors, such as: safety, effectiveness and tolerability [3,4]. Younger people with Type 2 diabetes mellitus are expected to tolerate and receive more intensive therapy compared with older and frail people, yet real-life data on associations among age, comorbidity and treatment

choices are sparse. As per current guidelines [3], stepwise intensification, and combination therapy if necessary, is recommended as soon as HbA_{1c} is above target levels. Because the risk of microvascular complications depends on the overall glycaemic burden over time [7], early initiation of glucose-lowering therapy in most people with Type 2 diabetes mellitus is recommended [3,8]. Hence, investigation of baseline individual factors that predict the need of therapy and intensification of therapy in real life is warranted.

In this cohort study, we examined prescribing practices of glucose-lowering drugs in a real-world clinical care setting, and examined the predictors of receiving monotherapy, combination therapy or no glucose-lowering therapy at all, within the first year following diagnosis of Type 2 diabetes mellitus.

Methods

Setting and participants

We conducted this cohort study within the nationwide cohort of the Danish Centre for Strategic Research in Type 2 Diabetes (DD2). The DD2 project has been enrolling people with newly diagnosed Type 2 diabetes mellitus throughout Denmark from general practitioners (GPs) since 2009 and from hospital specialist outpatient clinics since 2010. The details of implementation and logistics of the DD2 project have been described previously [9]. In Denmark, ~ 80% of patients with Type 2 diabetes mellitus are diagnosed, followed and treated by their GP at one of Denmark's ~ 2000 general practices, whereas ~ 20% of patients with Type 2 diabetes mellitus are referred to one of ~ 40 hospital specialist outpatient clinics for follow-up and treatment. National guidelines do not

recommend systematic screening for diabetes, but recommend testing for diabetes in adults with clinical symptoms suggestive of diabetes (polydipsia, polyuria, weight loss, etc.), and in asymptomatic adults with certain risk factors (high risk of cardiovascular disease, family history, diabetogenic drugs, etc.) [10]. Recruitment to the DD2 project is an ongoing process with recruitment from hospital clinics currently being ahead of that from GPs in primary care. During our study period, 23 hospital outpatient clinics and 140 general practices throughout Denmark were actively enrolling patients. Thus, our study population geographically represents people with Type 2 diabetes mellitus from all over Denmark, from urban and rural settings, and from various types of hospitals and general practices, but currently over-samples patients followed by hospital specialists, constituting approximately two-thirds of patients in this study.

Data recorded in the DD2 project include each patient's unique central person registry (CPR) number, the DD2 enrolment date, demographic details, detailed interview and clinical examination data provided by GPs or hospital specialists at time of enrolment, and fasting blood samples reports. The unique CPR number, provided to each Danish resident at birth or upon immigration, enables linkage of the DD2 cohort with data from various Danish medical and administrative registries [11]. The flowchart in Fig. 1 demonstrates the selection process of our study cohort. For this study, to focus on DD2 patients with true newly diagnosed Type 2 diabetes mellitus, we selected only those who had no records of either glucose-lowering drug prescriptions or hospital contacts with Type 2 diabetes mellitus more than six months before the DD2 enrolment date (see Results section).

Data on glucose-lowering drug prescriptions

The Danish National Prescription Registry is an administrative database that gathers patient-, drug- and prescriber-related information and contains complete data on all prescription medications

dispensed from community pharmacies and hospital-based community pharmacies throughout Denmark since 2004 [12]. The drugs are coded according to the anatomical therapeutic chemical (ATC) classification system. In Denmark, glucose-lowering drugs are available by prescription from monopolized pharmacies only.

From the Danish National Prescription Registry, we retrieved information on all glucose-lowering drugs dispensed to patients enrolled in the study during the first 365 days after the DD2 enrolment date (ATC codes used in this study are listed in the Appendix).

Data on predictor variables

From the DD2 database, we collected data on gender, age, central obesity and self-reported lifestyle factors including alcohol intake, regular physical activity and weight gain ≥ 30 kg since the age of 20 years [9]. We obtained a complete hospitalization history for all patients' major coexisting diseases as included in the Charlson Comorbidity Index using the Danish National Registry of Patients [13]. The Danish National Registry of Patients contains information on discharges from Danish acute care, non-psychiatric hospitals since 1977, and all hospital outpatient clinics and emergency department visits since 1995 [14]. Based on hospital diagnosis codes, we computed a Charlson Comorbidity Index score for each patient [15], defining three comorbidity levels: low (score of 0), medium (score of 1–2) and high (score of ≥ 3). Diabetes was excluded from the Charlson Comorbidity Index score because it constituted the index disease of our study cohort. In the DD2 biobank, blood samples were analysed for the first ~ 1000 consecutive patients enrolled. After applying eligibility criteria (as shown in Fig. 1), we were able to retrieve information on fasting blood glucose, alanine aminotransferase and C-reactive protein from the DD2 biobank for a subcohort of 547 of our study patients. Information on the first recorded HbA1c available after the

enrolment date was collected by linkage with the Danish Diabetes Database for Adults and was available for a subcohort of 812 of our study patients [16].

Statistical analysis

After following all patients for one year, we described glucose-lowering drug treatment at one year following enrolment. The main glucose-lowering drug categories in our study were: no glucose-lowering drug prescription filled within one year, and one or more glucose-lowering drug prescriptions filled within one year. We further categorized those with glucose-lowering therapy into monotherapy (only one type of glucose-lowering drug prescribed within one year) and combination therapy (more than one type of glucose-lowering drug prescribed within one year). We then used Poisson regression analysis with robust error variance to calculate crude and age- and gender-adjusted risk ratios (RRs) with 95% confidence intervals (CIs) to test the association between patient-related factors and receiving glucose-lowering therapy during the first year after Type 2 diabetes mellitus debut. Among patients who received glucose-lowering therapy within one year, we conducted similar analyses to calculate crude and adjusted RRs of receiving combination therapy and patient-related factors associated with it.

All analyses were performed using SAS version 9.2 (SAS Institute, Inc., Cary, NC, USA).

Patients registration and sample collection for the DD2 cohort have been approved by the National Committee on Health Research Ethics (Denmark) (record number S-20100082) and permission to use health registry data is obtained from the Danish Data Protection Agency (record number 2008-58-0035). After receiving detailed oral and written information approved by the National Committee on Health Research Ethics (Denmark), patients volunteered to participate in the DD2 study and

signed a written informed consent document.

Results

Overall patient characteristics

Table 1 shows baseline demographic, clinical, lifestyle and biochemical characteristics of the study cohort. Of the 1158 patients with newly diagnosed Type 2 diabetes mellitus, 57% were men and the majority (66%) had been enrolled from hospital outpatient clinics. Of the patients, 302 (26%) did not receive any glucose-lowering drugs within the first year after diagnosis, 723 (62%) received monotherapy and 133 (12%) received combination therapy. Those who did not receive any glucose-lowering therapy were older [median age: 64, interquartile range (IQR): 57–70 years) than those who received monotherapy (median age: 60, IQR: 53–66 years) or combination therapy (median age: 55, IQR: 47–63 years). Figure 2 shows the individual glucose-lowering drug regimens prescribed during the first year. Among the 856 glucose-lowering drug users, 685 patients (80% of all users; 95% of the 723 monotherapy users) received metformin monotherapy. Within the first year, insulin was used by 6% (51/856), incretin-based therapies by 11% [94/856; 6% dipeptidyl peptidase-4 (DPP-4) inhibitors, and 5% glucagon-like peptide-1 (GLP-1) receptor agonist] and sulfonylureas by 5% (43/856), either alone or in combination.

Factors predicting initiation of glucose-lowering therapy

Table 2 presents crude and adjusted RRs of receiving glucose-lowering therapy in the first year following Type 2 diabetes mellitus diagnosis. The likelihood of receiving glucose-lowering therapy was higher in patients who were < 40 years old (adjusted RR: 1.29, 95% CI: 1.16–1.44) and in those who were 40 – 59 years old (adjusted RR: 1.16, 95% CI: 1.08–1.24), compared with those who were

60+ years old. Patients with a high comorbidity level (Charlson Comorbidity Index score ≥ 3) were more likely to initiate glucose-lowering therapy (adjusted RR: 1.20, 95% CI: 1.05–1.38) compared with those having low comorbidity (Charlson Comorbidity Index score of 0). Central obesity (adjusted RR: 1.23, 95% CI: 1.04–1.44), weight gain ≥ 30 kg since 20 years of age (adjusted RR: 1.10, 95% CI: 1.03–1.18), and lack of regular physical exercise (adjusted RR: 1.07, 95% CI: 1.01–1.15) also increased the likelihood of initiating glucose-lowering therapy during the first year following Type 2 diabetes mellitus diagnosis. We observed a higher likelihood of receiving glucose-lowering therapy in patients with Type 2 diabetes mellitus who had a high baseline fasting blood glucose (≥ 7.5 mmol/l; adjusted RR: 1.25, 95% CI: 1.10–1.42) compared with those who had fasting blood glucose < 6.5 mmol/l, and in those with HbA_{1c} ≥ 59 mmol/mol (≥ 7.5%) (adjusted RR: 1.26, 95% CI: 1.20–1.32) compared with those who had HbA_{1c} < 59 mmol/mol (<7.5%).

Factors predicting combination therapy

Table 3 illustrates crude and adjusted RRs of receiving combination therapy (133, 16% of all treated) compared with monotherapy (723, 84% of all treated) within the first year of Type 2 diabetes mellitus diagnosis. Patients with Type 2 diabetes mellitus < 40 years were substantially more likely to receive combination therapy (adjusted RR: 3.60, 95% CI: 2.36–5.50) compared with those who were 60+ years old. Patients with a moderate or high comorbidity level (Charlson Comorbidity Index score of 1–2 or ≥ 3) were more likely to receive combination therapy (adjusted RR: 1.19, 95% CI: 0.81–1.74; and 2.08, 95% CI: 1.16–3.72, respectively) than those with low comorbidity (Charlson Comorbidity Index score of 0). The likelihood of receiving combination therapy vs. monotherapy was also materially increased in patients with central obesity (adjusted RR: 1.93, 95% CI: 0.76–4.94). By contrast, alcohol overuse was associated with decreased likelihood of combination therapy

(adjusted RR: 0.23, 95% CI: 0.06–0.88). In the subsample with biobank information, patients with a baseline fasting blood glucose ≥ 7.5 mmol/l (adjusted RR: 1.94, 95% CI: 1.02–3.71), alanine aminotransferase > 45/70 IU/l for women/men (adjusted RR: 1.44, 95% CI: 0.71–2.90), and a C-peptide < 300 pmol/l were more likely to receive combination therapy within one year of diagnosis (adjusted RR: 3.02, 95% CI: 1.22–7.46). Furthermore, in this study, patients with HbA_{1c} ≥ 59 mmol/mol (≥ 7.5%) were more likely to receive combination therapy (adjusted RR: 2.86, 95% CI: 1.97–4.14) than those with HbA_{1c} < 59 mmol/mol (<7.5%).

Discussion

Within the first year after Type 2 diabetes mellitus diagnosis, 74% of patients in our clinical practice setting had initiated glucose-lowering therapy, of whom 88% received monotherapy, almost always with metformin. We found that a large variety of different combination therapies was used during the first year, likely reflecting the current large treatment armamentarium. Young age, presence of comorbidity at baseline, central obesity, large weight gain before diagnosis, lack of physical exercise and level of baseline hyperglycaemia were important factors associated with receiving glucose-lowering therapy. In addition to these factors, a low C-peptide was associated with combination therapy within the first year after diagnosis.

In parallel with the introduction of more individualized treatment guidelines in Type 2 diabetes mellitus, the relatively strongest focus on early and intensive glucose-lowering therapy should be given to patients with Type 2 diabetes mellitus with a short disease duration such as those included in the present DD2 cohort [2,3,10,17,18]. Accordingly, a large proportion (74%) of our study cohort received glucose-lowering drugs in the first year of Type 2 diabetes mellitus diagnosis. The large

proportion (88%) with monotherapy is similar to findings in an ongoing study based on Danish administrative prescription data, in which 91% of 38 418 adults with incident treated Type 2 diabetes mellitus during 2000 to 2012 started therapy with a single glucose-lowering drug [19]. In contrast to our findings, a considerably lower proportion (42%) of people initiated glucose-lowering drugs in the first year among 9158 people with newly diagnosed Type 2 diabetes mellitus in 2003–2005 in the UK [4,5]. In comparison, in the Danish Type 2 diabetes mellitus cohort from the multicentre Anglo-Danish-Dutch Study of Intensive Treatment in People With Screen-Detected Diabetes in Primary Care (ADDITION) study, 57% patients received glucose-lowering drugs during the 6 years of follow-up [20]. The higher treatment proportion in our cohort compared with some previous studies may be explained in part by the difference in timing of the studies, which makes a comparison of results difficult due to changing treatment guidelines. Additionally, the prescribing behaviour of GPs compared with specialists may influence the findings [21]. Because the DD2 cohort was in its early phase of enrolment in 2010-2013, recruitment from hospital clinics was ahead of that from GPs and our results may refer to more severe cases of Type 2 diabetes mellitus than the average in Denmark [22].

Young age predicted both any therapy and combination therapy in our study. This is in agreement with a study of 10 743 people with newly diagnosed Type 2 diabetes mellitus from the USA who were followed for 2 years, where the median time to start glucose-lowering therapy in people older than 65 years was > 2 years compared with 350 days in people younger than 65 years [23]. Our results may reflect compliance with newer guidelines in which more stringent glycaemic control is emphasized in people < 65 years of age without comorbidities at diabetes debut [3,24]. However, our finding that presence of comorbidities at diabetes debut also predicted any therapy and combination therapy during the first year is important and may reflect clinicians' appropriate focus on people with

Type 2 diabetes mellitus who present with complications already at diagnosis. A survey study from the UK identified possible reasons for not treating or not giving intensified (combination) therapy to older individuals with diabetes, namely: general frailty, concerns regarding the safety of glucose-lowering drugs, concerns regarding treatment burden to the patient, and impaired cognitive or physical function of the patient [25]. In accordance, although with limited statistical precision, we observed that individuals with alcohol overuse had decreased likelihood of receiving combination treatment during the first year, which might reflect similar physician concerns than for elderly people.

A recent study based on The Health Improvement Network Database in the UK [26], found young age (reported $P < 0.001$) and higher BMI ($P < 0.033$) as predictors of increased deterioration in glycaemic control between 6 months and 2 years after Type 2 diabetes mellitus diagnosis. This corroborates with our findings on young age and obesity, since deteriorated glycaemic control is the main indicator to initiate or intensify glucose-lowering therapy. Obesity is associated with higher insulin resistance and increased blood glucose [27], and in a previous study of 23 729 people with Type 2 diabetes mellitus from Italy, obesity was also associated with receiving combination therapy (odds ratio: 1.19, 95% CI: 1.12–1.28) [28]. Finally and expectedly, having high fasting blood glucose at baseline was a strong predictor of therapy within the first year, and low levels of C-peptide – reflecting insulinopenic Type 2 diabetes mellitus patients – were strongly associated with combination therapies, likely including insulin in many cases.

Strengths and limitations

A main strength of our study is its comprehensive and detailed assessment of clinical data among patients with newly diagnosed Type 2 diabetes mellitus with close to 100% completeness for

demographic and clinical characteristics and prescription data [22]. Our study also has some limitations. First, our descriptive data likely apply to people with more advanced Type 2 diabetes mellitus than the average in Denmark, because 66% of our patients were enrolled from hospital outpatient clinics. Second, in our cohort with short-term follow-up some patients who received two or more different glucose-lowering drug prescriptions may represent individuals who shifted from one type of glucose-lowering drug to another, rather than used two or more drugs simultaneously in combination. Third, the fact that only 17% of our patients had an early $HbA_{1c} \geq 59$ mmol/mol ($\geq 7.5\%$), compared with 53% having pre-treatment $HbA_{1c} \geq 59$ mmol/mol ($\geq 7.5\%$) among people with Type 2 diabetes mellitus who started glucose-lowering drugs in an ongoing population-based study [19], is likely related to many of our cohort already having started treatment before HbA_{1c} measurement. Finally, we did not take into account survival within the first year after enrolment, yet observed mortality during the first year in our study cohort was low (six patients, ~ 0.5%).

Conclusions

In conclusion, in this study from a Danish real-world clinical care setting, we observed that within one year after Type 2 diabetes mellitus diagnosis, 74% were on a glucose-lowering drug, almost universally with metformin, whereas 12% received combination therapy. Presence of comorbidity, young age, central obesity and poor baseline glycaemic control were important patient-related predictors, both of receiving any glucose-lowering therapy and of receiving combination therapy.

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Competing interests

The Department of Clinical Epidemiology, Aarhus University Hospital, receives funding for other studies from companies in the form of research grants to (and administered by) Aarhus University.

Author contributions

JSC, HBN, HTS and JR participated in designing the DD2 cohort. JR, JSN, SF, AV, IB, JSC, HBN, HTS and RWT conceived of the study. IB was responsible for the biochemical analyses. ES, AM, RWT and HTS participated in the design of the study and KB performed the statistical analysis. AM initially drafted the article, with help by ES and RWT. All other authors have critically reviewed the manuscript. All authors contributed substantially, revised the manuscript for intellectual content, and approved the final version to be submitted. AM and RWT are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis

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FIGURE 1 Flowchart showing the study cohort selection process.

FIGURE 2 Glucose-lowering drugs prescribed during the first year after Type 2 diabetes diagnosis in patients enrolled in the DD2 study. DPP-4, dipeptidyl peptidase-4 inhibitors; GLP1, glucagon-like peptidase-1 analogue; SU, sulfonylurea.

Appendix

World Health Organization International Classification of Diseases 8th Edition (ICD-8) and 10th Edition (ICD-10) codes and Anatomical Therapeutical Chemical classification system (ATC) codes used in this study

Glucose-lowering drugs

- *Insulin and analogues*

  ATC-codes: A10Axxx

- *Metformin*

  ATC-codes: A10BAxx

- *Sulfonylureas*

  ATC-codes: A10BBxx

- *Dipeptidyl peptidase 4 (DPP-4) inhibitors*

  ATC-codes: A10BHxx

- *Glucagon-like peptide 1 (GLP-1) analogue*

  ATC-codes: A10BX04. A10BX05. A10BX07. A10BX10

- *Maglitinides*

  ATC-codes: A10BX02. A10BX03. A10BX08

- *Other glucose-lowering drugs*

  ATC-codes: A10BFxx (alpha glucosidase inhibitor). A10BGxx (Thiazolidinedione)

- *Combination tablets*

  ATC-codes: A10BDxx

Table 1 Baseline characteristics of 1158 patients with newly diagnosed Type 2 diabetes

Characteristics	Total* (%) *N* = 1158
Gender	
Women	499 (43)
Men	659 (57)
Age (years)	
< 40	54 (5)
40–59	471 (41)
≥ 60	633 (54)
Charlson Comorbidity Index score (without diabetes)	
0	808 (70)
1–2	285 (25)
3+	65 (5)
Central obesity†	
No	91 (13)
Yes	1064 (87)
Weight gain since 20 years of age	
< 30 kg	498 (51)
≥ 30 kg	474 (49)
Regular physical exercise	
Yes	461 (40)
No	697 (60)
Alcohol consumption	
≤ 14/21 alcoholic drinks/week for women/men	1080 (93)
> 14/21 alcoholic drinks/week for women/men	77 (7)
Study enrolment site‡	
Hospital outpatient clinic	584 (66)
General practice	298 (34)
Fasting blood glucose (mmol/l)§	
< 6.5	168 (31)
≥ 6.5 to < 7	110 (20)
≥ 7 to < 7.5	91 (17)
≥ 7.5	176 (32)
HbA1c (mmol/mol)§	
< 59 (< 7.5%)	678 (83)
≥ 59 (≥ 7.5%)	134 (17)
C-peptide (pmol/l)§	
≥ 300	526 (96)
< 300	21 (4)
Glutamic acid decarboxylase antibody§	
Negative	535 (98)
Positive	12 (2)
Alanine aminotransferase (IU/l)§	
≤ 45/70 for women/men	492 (92)
> 45/70 for women/men	42 (8)
C-reactive protein (mg/l) §	
≤3mg/L	326 (60)
>3 mg/L	217 (40)

* Numbers do not add up to total for all characteristics because of missing information.
† Central obesity = Waist circumference > 94 cm for men and > 80 cm for women.
‡ Information on enrolment site is available for a subcohort of 882 patients.
§ Data available from Danish Diabetes Database for Adults for a subcohort of 812 patients.

Table 2 Risk ratios of receiving glucose-lowering therapy compared with no glucose-lowering therapy in the first year following Type 2 diabetes diagnosis

	No glucose-lowering therapy	Any glucose-lowering therapy	Risk ratios (95% CI)	
	n = 302	*n* = 856	Crude	Age- and gender-adjusted
Gender				
Women	138 (28)	361 (72)	1.00 (referent)	1.00 (referent)
Men	164 (25)	495 (75)	1.04 (0.97–1.11)	1.03 (0.96–1.10)
Age (years)				
< 40	6 (11)	48 (89)	1.30 (1.16–1.44)	1.29 (1.16–1.44)
40 59	97 (21)	374 (79)	1.16 (1.08–1.24)	1.16 (1.08–1.24)
≥ 60	199 (31)	434 (69)	1.00 (referent)	1.00 (referent)
Study enrolment site*				
Hospital outpatient clinic	117 (20)	467 (80)	1.27 (1.15–1.40)	1.21 (1.10–1.33)
General practice	110 (37)	188 (63)	1.00 (referent)	1.00 (referent)
Charlson Comorbidity Index score †				
0	220 (27)	588 (73)	1.00 (referent)	1.00 (referent)
1–2	69 (24)	216 (76)	1.04 (0.96–1.13)	1.10 (1.02–1.19)
3+	13 (20)	52 (80)	1.10 (0.97–1.25)	1.20 (1.05–1.38)
Central obesity‡				
No	37 (41)	54 (59)	1.00 (referent)	1.00 (referent)
Yes	263 (25)	801 (75)	1.27 (1.07–1.51)	1.23 (1.04–1.44)
Weight gain since 20 years of age (kg)				
< 30	146 (29)	352 (71)	1.00 (referent)	1.00 (referent)
≥ 30	96 (20)	378 (80)	1.13 (1.05–1.21)	1.10 (1.03–1.18)
Regular physical exercise				
Yes	137 (30)	324 (70)	1.00 (referent)	1.00 (referent)
No	165 (24)	532 (76)	1.09 (1.01–1.17)	1.07 (1.01–1.15)
Alcohol consumption				
≤ 14/21 alcoholic drinks/week for women/men	280 (26)	801 (74)	1.00 (referent)	1.00 (referent)
> 14/21 alcoholic drinks/week for women/men	22 (29)	55 (71)	0.96 (0.83–1.12)	0.96 (0.84–1.11)
Fasting blood glucose (mmol/l)§				
< 6.5	59 (35)	109 (65)	1.00 (referent)	1.00 (referent)
≥ 6.5 to < 7	33 (30)	77 (70)	1.08 (0.91–1.279	1.06 (0.90–1.25)
≥ 7 to < 7.5	22 (24)	69 (76)	1.17 (1.00–1.37)	1.16 (0.99–1.35)
≥ 7.5	26 (15)	150 (85)	1.31 (1.16–1.49)	1.25 (1.10–1.42)
HbA1c (mmol/mol)¶				
< 59 (< 7.5%)	164 (24)	514 (76)	1.00 (referent)	1.00 (referent)
≥ 59 (≥ 7.5%)	2 (1)	132 (99)	1.30 (1.24–1.36)	1.26 (1.20–1.32)
C-peptide (pmol/l)§				
≥ 300	134 (26)	392 (74)	1.00 (referent)	1.00 (referent)
< 300	6 (29)	15 (71)	0.96 (0.73–1.26)	0.99 (0.76–1.30)
Glutamic acid decarboxylase antibody §				
Negative	137 (26)	398 (74)	1.00 (referent)	1.00 (referent)
Positive	3 (25)	9 (75)	1.01 (0.72–1.40)	0.94 (0.64–1.39)
Alanine aminotransferase (IU/l)§				
≤ 45/70 for women/men	131 (27)	361 (73)	1.00 (referent)	1.00 (referent)
> 45/70 for women/men	5 (12)	37 (82)	1.20 (1.06–1.36)	1.15 (1.01–1.30)
C-reactive protein (mg/l)§				
≤ 3	92 (28)	234 (72)	1.00 (referent)	1.00 (referent)
> 3	47 (22)	170 (78)	1.09 (0.99–1.20)	1.05 (0.95–1.15)

*Information on enrolment site available for a subcohort of 882 patients.
† Diabetes was not included in Charlson Comorbidity Index score.
‡ Central obesity = Waist circumference > 94 cm for men and > 80 cm for women.
§ Data available from DD2 biobank for a subcohort of 547 patients.
¶ Data available from Danish Diabetes Database for Adults for a subcohort of 812 patients.

Table 3 Risk ratios of receiving combination therapy compared with monotherapy in 856 patients with newly diagnosed Type-2 diabetes who were treated with glucose-lowering drugs

	Monotherapy	Combination therapy	Risk ratios (95% CI)	
	n = 723	*n* = 133	Crude	Age- and gender-adjusted
Gender				
Women	306 (85)	55 (15)	1.00 (referent)	1.00 (referent)
Men	417 (84)	78 (16)	1.03 (0.75–1.42)	1.02 (0.75–1.39)
Age (years)				
< 40	28 (58)	20 (42)	3.62 (2.37–5.53)	3.60(2.36–5.50)
40–59	311 (83)	63 (17)	1.46 (1.04–2.06)	1.46 (1.03–2.06)
≥ 60	384 (88)	50 (12)	1.00 (referent)	1.00 (referent)
Study enrolment site*				
Hospital outpatient clinic	388 (79)	79 (17)	1.87 (1.14–3.07)	1.74 (1.07–2.81)
General practice	171 (91)	17 (9)	1.00 (referent)	1.00 (referent)
Charlson Comorbidity Index score †				
0	497 (85)	91 (15)	1.00 (referent)	1.00 (referent)
1–2	185 (86)	31 (14)	0.93 (0.64 – 1.35)	1.19 (0.81 – 1.74)
3+	41 (79)	11 (21)	1.37 (0.78 – 2.39)	2.08 (1.16 – 3.72)
Central obesity‡				
No	50 (93)	4 (7)	1.00 (referent)	1.00 (referent)
Yes	673 (84)	128 (16)	2.16 (0.83 – 5.61)	1.93 (0.76 – 4.94)
Weight gain since 20 years of age (kg)				
< 30	303 (86)	49 (14)	1.00 (referent)	1.00 (referent)
≥ 30	313 (83)	65 (17)	1.24 (0.88 – 1.74)	1.13 (0.80 – 1.58)
Regular physical exercise				
Yes	275 (85)	49 (15)	1.00 (referent)	1.00 (referent)
No	448 (84)	84 (16)	1.04 (0.76–1.44)	1.02 (0.75–1.40)
Alcohol consumption				
≤ 14/21 alcoholic drinks/week for women/men	670 (84)	131 (16)	1.00 (referent)	1.00 (referent)
> 14/21 alcoholic drinks/week for women/men	53 (96)	2 (4)	0.22 (0.06–0.87)	0.23 (0.06–0.88)
Fasting blood glucose (mmol/l)§				
< 6.5	98 (90)	11 (10)	1.00 (referent)	1.00 (referent)
≥ 6.5 to < 7	74 (96)	3 (4)	0.39 (0.11–1.34)	0.43 (0.12–1.52)
≥ 7 to < 7.5	66 (96)	3 (4)	0.43 (0.12–1.49)	0.47 (0.14–1.58)
≥7.5 mmol/L	118 (79)	32 (21)	2.11 (1.12–4.00)	1.94 (1.02–3.71)
HbA_{1c} (mmol/mol)¶				
< 59 (<7.5%)	458 (89)	56 (11)	1.00 (referent)	1.00 (referent)
≥ 59 (≥ 7.5%)	86 (65)	46 (35)	3.2 (2.28–4.50)	2.86 (1.97–4.14)

	Monotherapy	Combination therapy	Risk ratios (95% CI)	
	n = 723	*n* = 133	Crude	Age- and gender-adjusted
C-peptide (pmol/l)§				
≥ 300	347 (89)	45 (11)	1.00 (referent)	1.00 (referent)
< 300	11 (73)	4 (27)	2.32 (0.96–5.62)	3.02 (1.22–7.46)
Glutamic acid decarboxylase antibody §				
Negative	350 (88)	48 (12)	1.00 (referent)	1.00 (referent)
Positive	8 (89)	1 (11)	0.92 (0.14–5.96)	0.87 (0.14–5.40)
Alanine aminotransferase (IU/l)§				
≤ 45/70 for women/men	320 (89)	41 (11)	1.00 (referent)	1.00 (referent)
> 45/70 for women/men	30 (81)	7 (19)	1.67 (0.80–3.44)	1.44 (0.71–2.90)
C-reactive protein (mg/l) §				
≤ 3	210 (90)	24 (10)	1.00 (referent)	1.00 (referent)
> 3	146 (86)	24 (14)	1.38 (0.81–2.34)	1.15 (0.67–1.97)

* Information on enrolment site available for a subcohort of 882 patients.
†Diabetes was not included in Charleson Comorbidity Index score.
‡ Central obesity = Waist circumference > 94 cm for men and > 80 cm for women.
§ Data available from DD2 biobank for a subcohort of 547 patients.
¶ Data available from Danish Diabetes Database for Adults for a subcohort of 812 patients.

Figure 1:

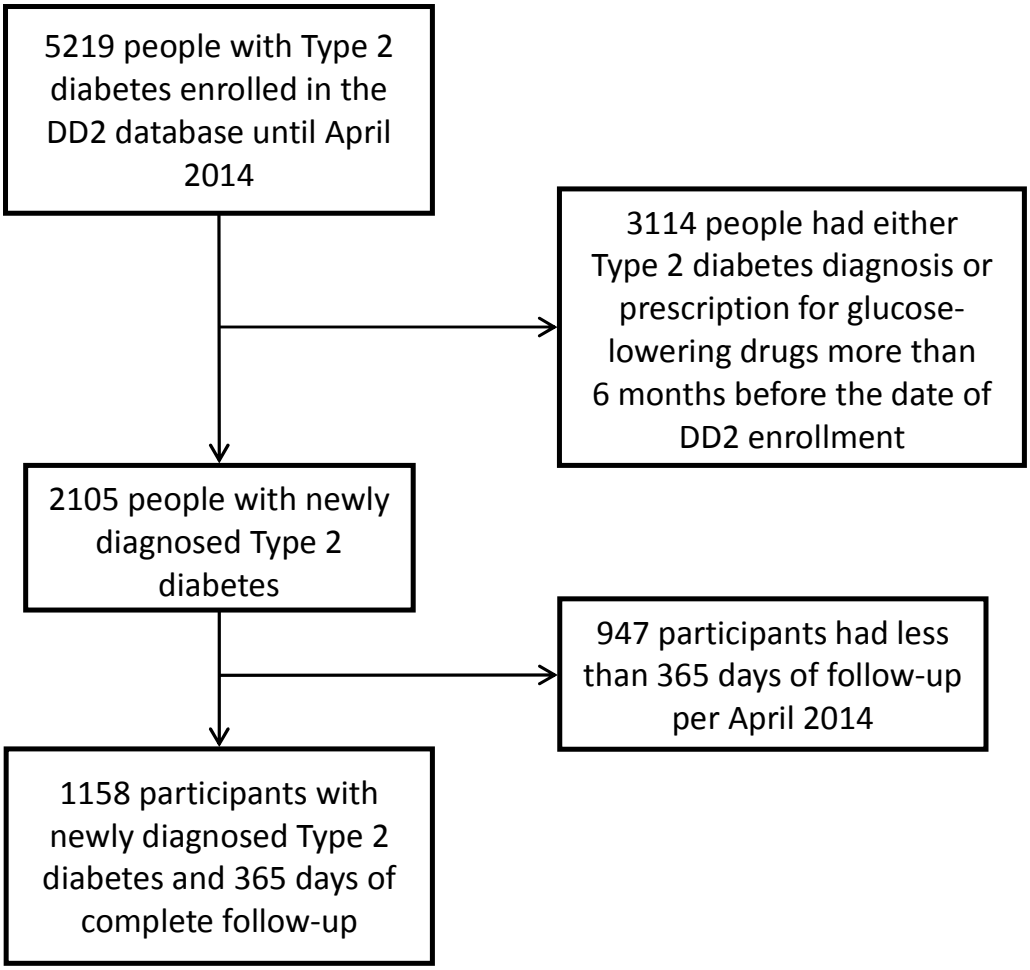

Figure 2.