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ARTICLE

Early glycaemic control in metformin users receiving their first add-on therapy: a population-based study of 4,734 people with type 2 diabetes

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Abstract
Aims/hypothesis The aims of this work were to assess glycaemic control in metformin users receiving their first add-on glucose-lowering therapy and to examine the real-life effectiveness of different add-on drugs.
Methods We carried out a population-based cohort study using healthcare databases in northern Denmark during 2000–2012. We included 4,734 persons who initiated metformin monotherapy and added another glucose-lowering drug within 3 years. Attainment of recommended HbA_{1c} goals within 6 months of add-on was investigated, using Poisson regression analysis adjusted for age, sex, baseline HbA_{1c}, diabetes duration, complications and Charlson Comorbidity Index.
Results Median metformin treatment duration at intensification was 12 months (interquartile range [IQR] 4–23 months) and pre-intensification HbA_{1c} was 8.0% (IQR 7.2–9.2%) (64 [IQR 55–77] mmol/mol). Median HbA_{1c} dropped 1.2% (13 mmol/mol) with a sulfonylurea (SU) add-on, 0.8% (9 mmol/mol) with a dipeptidyl peptidase-4 (DPP-4) inhibitor, 1.3% (14 mmol/mol) with a glucagon-like peptide-1 (GLP-1) receptor agonist, 0.9% (10 mmol/mol) with other non-insulin drugs and 2.4% (26 mmol/mol) with insulin. Compared with SU add-on, attainment of HbA_{1c} <7% (<53 mmol/mol) was higher with GLP-1 receptor agonists (adjusted RR [aRR] 1.10; 95% CI 1.01, 1.19) and lower with DPP-4 inhibitors (aRR 0.94; 95% CI 0.89, 0.99), other drugs (aRR 0.86; 95% CI 0.77, 0.96) and insulin (aRR 0.88; 95% CI 0.77, 0.99). The proportion of metformin add-on users who attained HbA_{1c} <7% (<53 mmol/mol) increased from 46% in 2000–2003 to 59% in 2010–2012, whereas attainment of HbA_{1c} <6.5% (<48 mmol/mol) remained 30% among patients aged <65 years without comorbidities.
Conclusions/interpretation Among early type 2 diabetes patients receiving their first metformin add-on treatment, HbA_{1c} reduction with different non-insulin drugs is similar to, and comparable with, that observed in randomised trials, yet 41% do not achieve HbA_{1c} <7% (<53 mmol/mol) within 6 months.

Keywords Antidiabetic agents · Clinical quality · Comparative effectiveness · Glucose-lowering therapy · Glycaemic control · HbA_{1c} · Hypoglycaemic agents · Metformin · Pharmacoepidemiology · Type 2 diabetes

Abbreviations

aRR	Adjusted relative risk
CCI	Charlson Comorbidity Index
DPP-4	Dipeptidyl peptidase-4
eGFR	Estimated GFR
GLD	Glucose-lowering drug
GLP-1	Glucagon-like peptide-1
IQR	Interquartile range
SU	Sulfonylurea

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Introduction

Metformin monotherapy is currently the recommended initial glucose-lowering drug (GLD) for most patients with type 2 diabetes, with addition of a second GLD if HbA_{1c} targets are not achieved. Glucose-lowering treatment options have expanded considerably [1] yet the number of head-to-head trials comparing GLDs is limited and there is little evidence to guide clinicians' choice of add-on therapy [2]. Adding a non-insulin second-line GLD to metformin was found to reduce HbA_{1c} levels by approximately 1% in clinical trials [3] and an individualised treatment approach following metformin initiation is currently recommended [4]. In real-world type 2 diabetes populations, who may differ from clinical trial participants in some characteristics (e.g. age, comorbidities and compliance with medications [5]), little is known about success rates when older and newer GLDs are used to intensify metformin therapy.

We aimed to assess the quality of glycaemic control in a large population-based cohort of incident metformin users receiving their first add-on glucose-lowering therapy. We examined the association of calendar time with achieved glycaemic control and compared the reduction of HbA_{1c} for different add-on GLDs.

Methods

Setting and study population We conducted this cohort study in northern Denmark during 2000–2012. We used linkage of existing population-based medical databases covering 1.8 million inhabitants or 30% of Denmark's population, as described in more detail elsewhere [6]. The cohort included individuals who redeemed a first-time GLD prescription (codes A10A, A10B) of metformin monotherapy (no GLD prescription other than metformin within the first 14 days) between 1 January 2000 and 31 December 2012 and who had at least 12 months of baseline data. Metformin exposure time was estimated as the quantity filled at each prescription collection, divided by the minimum daily dose used in clinical practice (500 mg), plus another 100 days to avoid falsely assumed termination of treatment due to non-compliance [7].

The treatment-intensification cohort consisted of metformin-exposed patients, who added another GLD within the first 3 years and had at least one HbA_{1c} value recorded within 12 months before and within 3–6 months after the add-on prescription date in a regional laboratory information system research database [6] (for patient flow, see electronic supplementary material [ESM] Fig. 1).

Add-on drugs Metformin add-on therapies examined were sulfonylurea (SU), dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, other non-insulin GLDs and insulin. The first intensification drug defined add-on exposure and subsequent changes were ignored, an approach similar to intention-to-treat analyses.

HbA_{1c} outcomes Baseline HbA_{1c} was defined as the most recently measured HbA_{1c} value within 12 months prior to the intensification date. We assessed the HbA_{1c} level achieved between 2 and 6 months (60–180 days) following the intensification date. If there were several HbA_{1c} measurements, the value closest to day 180 was used. HbA_{1c} was analysed by either the HPLC method or immunoassays on automated equipment.

Patient characteristics We obtained data from medical databases on 19 major disease categories included in the Charlson Comorbidity Index (CCI) based on patients' entire hospital contact history within 5 years before the intensification date. We separately ascertained contacts and/or prescription history for mental disorders and alcoholism-related disorders (see ESM Table 1 for codes), and for any macrovascular or microvascular diabetes complication [6] including prior clinical biochemical indication of renal disease (2 days with estimated glomerular filtration rate [eGFR] $\leq$60 ml min^{-1} $[1.73\ m]^{-2}$ and/or 2 days with urinary albumin above the cut-off for microalbuminuria). The duration of healthcare-system-recorded diabetes was the time between the first-ever GLD prescription/hospital diagnosis of diabetes and the therapy intensification date.

Statistical analysis For each metformin add-on therapy group, we computed absolute reduction in median HbA_{1c} from baseline, as well as proportions of patients and RRs with 9%CIs of achieving HbA_{1c} <6.5% (<48 mmol/mol) and <7.0% (<53 mmol/mol) with SU add-on as reference category. RRs were adjusted by Poisson regression for predefined factors (age [≤60 years, 61–70 years, >70 years], sex, diabetes duration [≤1 year, >1 year], macrovascular complications [yes/no], microvascular complications [yes/no], CCI level [0, ≥1] and baseline HbA_{1c} [≤7.5%, 7.6–9.0%, >9.0%]). Analyses of HbA_{1c} <6.5% (<48 mmol/mol) were restricted to a subgroup of 'healthy' intensification patients (i.e. aged <65 years, CCI=0, no diabetes complications, no mental or alcoholism-related disorders), for whom providers might reasonably suggest a stringent HbA_{1c} goal [4]. Pre-intensification HbA_{1c} values and proportions attaining HbA_{1c} <7% (<53 mmol/mol) and, among 'healthy' patients, <6.5% (<48 mmol/mol), were assessed by calendar year periods. The study was approved by the Danish Data Protection Agency (J. no. 2013-41-1924) and needed no further ethics approval according to Danish law.

Table 1 Characteristics of 4,734 incident metformin users at the time of treatment intensification

Variable	Add-on medication to metformin					
	Sulfonylurea (*n*=2,484)	DPP-4 inhibitor (*n*=1,262)	GLP-1 RA (*n*=329)	Insulin (*n*=377)	Other GLD add-on (*n*=282)	Total (*N*=4,734)
Sex						
Female	983 (39.6)	460 (36.5)	118 (35.9)	154 (40.8)	139 (49.3)	1,854 (39.2)
Male	1,501 (60.4)	802 (63.5)	211 (64.1)	223 (59.2)	143 (50.7)	2,880 (60.8)
Median age at add-on, years	59.0	59.6	54.2	54.4	58.9	58.6
Age group						
<30 years	16 (0.6)	15 (1.2)	6 (1.8)	13 (3.4)	3 (1.1)	53 (1.1)
≥30–59 years	1,310 (52.7)	632 (50.1)	209 (63.5)	220 (58.4)	148 (52.5)	2,519 (53.2)
≥60–70 years	742 (29.9)	414 (32.8)	99 (30.1)	84 (22.3)	86 (30.5)	1,425 (30.1)
>70 years	416 (16.7)	201 (15.9)	15 (4.6)	60 (15.9)	45 (16.0)	737 (15.6)
Year of add-on commencement						
2000–2003	293 (11.8)	0 (0)	0 (0)	20 (5.3)	23 (8.2)	336 (7.1)
2004–2006	604 (24.3)	0 (0)	0 (0)	77 (20.4)	105 (37.2)	786 (16.6)
2007–2009	919 (37.0)	455 (36.1)	42 (12.8)	137 (36.3)	132 (46.8)	1,685 (35.6)
2010–2012	668 (26.9)	807 (63.9)	287 (87.2)	143 (37.9)	22 (7.8)	1,927 (40.7)
Add-on baseline HbA_{1c}, %	8.0 (7.3–9.2)	7.6 (7.0–8.6)	8.0 (7.2–9.2)	9.6 (7.9–11.0)	7.9 (7.2–9.1)	8.0 (7.2–9.2)
Add-on baseline HbA_{1c}, mmol/mol	64 (56–77)	60 (53–70)	64 (55–77)	81 (63–97)	63 (55–76)	64 (55–77)
Add-on baseline HbA_{1c} group						
<6.5% (<48 mmol/mol)	99 (4.0)	69 (5.5)	26 (7.9)	10 (2.7)	20 (7.1)	224 (4.7)
6.5–6.9% (48–52 mmol/mol)	244 (9.8)	184 (14.6)	27 (8.2)	21 (5.6)	28 (9.9)	504 (10.6)
7–7.4% (53–57 mmol/mol)	446 (18.0)	269 (21.3)	55 (16.7)	26 (6.9)	53 (18.8)	849 (17.9)
7.5–7.9% (59–63 mmol/mol)	408 (16.4)	239 (18.9)	55 (16.7)	38 (10.1)	42 (14.9)	782 (16.5)
8.0–8.9% (64–74 mmol/mol)	548 (22.1)	261 (20.7)	75 (22.8)	56 (14.9)	60 (21.3)	1,000 (21.1)
9.0–9.9% (75–85 mmol/mol)	342 (13.8)	130 (10.3)	37 (11.2)	67 (17.8)	37 (13.1)	613 (12.9)
≥10.0% (≥86 mmol/mol)	397 (16.0)	110 (8.7)	54 (16.4)	159 (42.2)	42 (14.9)	762 (16.1)
Diabetes duration						
<1 year	1,152 (46.4)	536 (42.5)	118 (35.9)	185 (49.1)	101 (35.8)	2,092 (44.2)
1–2 years	636 (25.6)	333 (26.4)	107 (32.5)	72 (19.1)	84 (29.8)	1,232 (26.0)
2–3 years	445 (17.9)	280 (22.2)	71 (21.6)	79 (21.0)	60 (21.3)	935 (19.8)
≥3 years	251 (10.1)	113 (9.0)	33 (10.0)	41 (10.9)	37 (13.1)	475 (10.0)
Hospital outpatient clinic diagnosis of diabetes ≤1 year before add-on	430 (17.3)	168 (13.3)	104 (31.6)	143 (37.9)	33 (11.7)	878 (18.5)
Followed in hospital outpatient clinic in the year after add-on	416 (16.7)	143 (11.3)	60 (18.2)	104 (27.6)	54 (19.1)	777 (16.4)
Any macrovascular diabetes complication	361 (14.5)	169 (13.4)	56 (17.0)	75 (19.9)	45 (16.0)	706 (14.9)
Any microvascular diabetes complication	700 (28.2)	317 (25.1)	92 (28.0)	148 (39.3)	73 (25.9)	1,330 (28.1)
Neurological complications	29 (1.2)	4 (0.3)	2 (0.6)	9 (2.4)	0 (0)	44 (0.9)
Eye complications	261 (10.5)	103 (8.2)	31 (9.4)	69 (18.3)	28 (9.9)	492 (10.4)
Renal complications	24 (1.0)	8 (0.6)	3 (0.9)	11 (2.9)	3 (1.1)	49 (1.0)
Microalbuminuria	317 (12.8)	164 (13.0)	63 (19.1)	58 (15.4)	33 (11.7)	635 (13.4)
eGFR ≤60 ml min^{-1} (1.73 $m)^{-2}$	222 (8.9)	89 (7.1)	10 (3.0)	41 (10.9)	23 (8.2)	385 (8.1)
CCI score (excluding diabetes)[a]						
0	1,977 (79.6)	1,036 (82.1)	268 (81.5)	276 (73.2)	227 (80.5)	3,784 (79.9)
1	333 (13.4)	141 (11.2)	43 (13.1)	51 (13.5)	37 (13.1)	605 (12.8)
2	130 (5.2)	65 (5.2)	8 (2.4)	22 (5.8)	13 (4.6)	238 (5.0)
≥3	44 (1.8)	20 (1.6)	10 (3.0)	28 (7.4)	5 (1.8)	107 (2.3)
Previous myocardial infarction	61 (2.5)	31 (2.5)	8 (2.4)	15 (4.0)	13 (4.6)	128 (2.7)
Cerebrovascular disease	105 (4.2)	32 (2.5)	13 (4.0)	17 (4.5)	10 (3.5)	177 (3.7)
Peripheral vascular disease	56 (2.3)	25 (2.0)	7 (2.1)	14 (3.7)	2.1 (0.7)	104 (2.2)
Chronic heart failure	73 (2.9)	30 (2.4)	5 (1.5)	16 (4.2)	3 (1.1)	127 (2.7)

Table 1 (continued)

Variable	Add-on medication to metformin					
	Sulfonylurea (*n*=2,484)	DPP-4 inhibitor (*n*=1,262)	GLP-1 RA (*n*=329)	Insulin (*n*=377)	Other GLD add-on (*n*=282)	Total (*N*=4,734)
Atrial fibrillation	123 (5.0)	61 (4.8)	12 (3.6)	17 (4.5)	14 (5.0)	227 (4.8)
Hypertension	438 (17.6)	226 (17.9)	74 (22.5)	90 (23.9)	48 (17.0)	876 (18.5)
Chronic obstructive pulmonary disease	128 (5.2)	60 (4.8)	13 (4.0)	37 (9.8)	13 (4.6)	251 (5.3)
Cancer	79 (3.2)	49 (3.9)	11 (3.3)	23 (6.1)	8 (2.8)	170 (3.6)
Renal disease	15 (0.6)	4 (0.3)	2 (0.6)	7 (1.9)	4 (1.4)	32 (0.7)
Rheumatic disease	43 (1.7)	16 (1.3)	4 (1.2)	13 (3.4)	5 (1.8)	81 (1.7)
Osteoarthritis	179 (7.2)	97 (7.7)	30 (9.1)	35 (9.3)	27 (9.6)	368 (7.8)
Osteoporosis/fracture	28 (1.1)	16 (1.3)	5 (1.5)	7 (1.9)	2 (0.7)	58 (1.2)
History of infections requiring hospitalisation	380 (15.3)	167 (13.2)	55 (16.7)	75 (19.9)	39 (13.8)	716 (15.1)
Obesity	253 (10.2)	98 (7.8)	65 (19.8)	67 (17.8)	40 (14.2)	523 (11.0)
Alcoholism	20 (0.8)	6 (0.5)	3 (0.9)	6 (1.6)	0 (0)	35 (0.7)
Mental disorders	608 (24.5)	344 (27.3)	96 (29.2)	114 (30.2)	78 (27.7)	1,240 (26.2)
Previous hypoglycaemia	2 (0.1)	2 (0.2)	0 (0)	0 (0)	1 (0.4)	5 (0.1)
Any macroangiopathy	380 (15.3)	175 (13.9)	56 (17.0)	80 (21.2)	46 (16.3)	737 (15.6)
Thrombocyte aggregation prophylaxis	946 (38.1)	499 (39.5)	130 (39.5)	146 (38.7)	111 (39.4)	1,832 (38.7)
Statin	1,593 (64.1)	947 (75.0)	257 (78.1)	242 (64.2)	196 (69.5)	3,235 (68.3)
Any antihypertensive treatment	1,772 (71.3)	948 (75.1)	245 (74.5)	252 (66.8)	215 (76.2)	3,432 (72.5)
ACE inhibitor	1,025 (41.3)	538 (42.6)	149 (45.3)	147 (39.0)	119 (42.2)	1,978 (41.8)
ATII antagonist	559 (22.5)	355 (28.1)	81 (24.6)	82 (21.8)	73 (25.9)	1,150 (24.3)
Oral steroids	193 (7.8)	92 (7.3)	26 (7.9)	59 (15.6)	18 (6.4)	388 (8.2)
Marital status						
Unmarried	432 (17.4)	227 (18.0)	83 (25.2)	92 (24.4)	42 (14.9)	876 (18.5)
Widowed	244 (9.8)	110 (8.7)	20 (6.1)	32 (8.5)	31 (11.0)	437 (9.2)
Divorced	332 (13.4)	176 (13.9)	46 (14.0)	56 (14.9)	49 (17.4)	659 (13.9)
Married	1,476 (59.4)	749 (59.4)	180 (54.7)	197 (52.3)	160 (56.7)	2,762 (58.3)

Data are shown as *n* (%) or as median (IQR)

[a] The CCI includes 19 major disease categories, ascertained from each individual's complete hospital contact history within 5 years before the date of add-on glucose-lowering treatment. Diabetes was excluded, see text

ACE, angiotensin-converting enzyme; ATII, angiotensin II; GLP-1 RA, GLP-1 receptor antagonist

Results

Patient characteristics Among 4,734 metformin monotherapy initiators with add-on therapy and available HbA_{1c} measurements (ESM Fig. 1), 52% (2,484) added an SU, 27% (1,262) a DPP-4 inhibitor, 7% (329) a GLP-1 receptor agonist (298 liraglutide, 31 exenatide), 6% (282) another non-insulin GLD and 8% (377) insulin. At the time of therapy intensification, the median age was 59 years (IQR 50–66 years), 20% had CCI comorbidities other than diabetes, duration of metformin use was 12 months (IQR 4–23 months) and median baseline HbA_{1c} prior to add-on therapy was 8.0% (IQR 7.2–9.2%) (64 [IQR 55–77] mmol/mol) (Table 1).

Among patients who received SU add-on, median age was 59 years, median HbA_{1c} was 8.0% (64 mmol/mol) and 20% had CCI comorbidities (Table 1). Corresponding figures appeared similar for patients who were intensified with DPP-4 inhibitors (60 years, 7.6% [60 mmol/mol] and 18%), GLP-1 receptor agonists, although younger (54 years, 8.0% [64 mmol/mol] and 19) and other GLDs (59 years, 7.9% [63 mmol/mol] and 20%). Patients who received insulin add-on were younger, had higher baseline HbA_{1c} and more comorbidity (54 years, 9.6 (81 mmol/mol), and 27%).

HbA_{1c} reduction with add-on therapy Overall, median HbA_{1c} dropped from 8.0% (64 mmol/mol) at baseline to 6.8% (51 mmol/mol) within 2–6 months after commencement of add-on therapy, corresponding to a reduction of 1.2% (13 mmol/mol). Absolute reductions were 1.2% (13 mmol/mol) (from 8.0 to 6.8% [64 to 51 mmol/mol]) for SU add-on, 0.8% (9 mmol/mol) (from 7.6 to 6.8% [60 to 51 mmol/mol]) for DPP-4 inhibitors, 1.3% (14 mmol/mol) (from 8.0 to 6.7% [64 to 50 mmol/mol]) for GLP-1 receptor agonists including 1.3% (14 mmol/mol) (from 7.9 to 6.6% [63

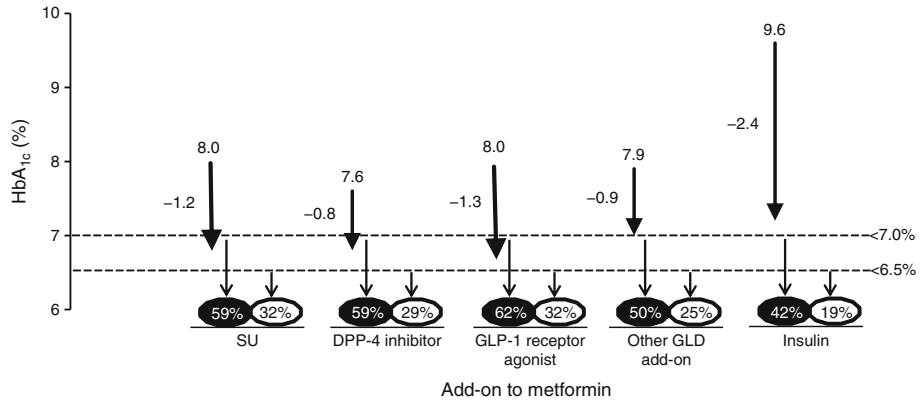

Fig. 1 Absolute reduction in median HbA_{1c} observed before and after add-on therapy. Large arrows show baseline HbA_{1c} (%) and absolute reduction in HbA_{1c} (%) from baseline to 2–6 months after treatment. The figure also shows the crude proportion of all patients (%) reaching glycaemic targets of HbA_{1c} <7.0% (<53 mmol/mol) (black ellipses) and/or HbA_{1c} <6.5% (<48 mmol/mol) in patients <65 years with no comorbidities (white ellipses). To convert values for HbA_{1c} in % into mmol/mol, subtract 2.15 and multiply by 10.929

to 49 mmol/mol]) for liraglutide, 0.9% (10 mmol/mol) (from 7.9 to 7.0% [63 to 53 mmol/mol]) for other non-insulin GLDs and 2.4% (26 mmol/mol) (from 9.6 to 7.2% [81 to 55 mmol/mol]) for insulin add-on (Fig. 1 and ESM Table 2). Overall, 2,704 (57%) of all 4,734 metformin users who received add-on therapy reached an HbA_{1c} <7% within 2–6 months, while 466 (30%) of 1,558 patients <65 years without recorded complications or comorbidities attained an HbA_{1c} <6.5% (ESM Table 2).

Compared with SU add-on, attainment of HbA_{1c} <7% (<53 mmol/mol) was higher with GLP-1 receptor agonists (adjusted RR [aRR] 1.10; 95% CI 1.01, 1.19), including liraglutide (aRR 1.12; 95% CI 1.03, 1.22), and lower with DPP-4 inhibitors (aRR 0.94; 95% CI 0.89, 0.99), other non-insulin GLDs (aRR 0.86; 95% CI 0.77, 0.96) and insulin (aRR 0.88; 95% CI 0.77, 0.99) (Fig. 2 and ESM Table 2). Similar differences in attainment of an HbA_{1c} target <6.5% (<48 mmol/mol) appeared among type 2 diabetes patients aged <65 years without complications or comorbidities (Fig. 2 and ESM Table 2), as well as in analyses restricted to the 2007–2012 period (n=3,612 patients) (ESM Table 3), yet due to the smaller populations these estimates were statistically imprecise.

HbA_{1c} over calendar time The proportion of all metformin users who attained HbA_{1c} targets of <7% (<53 mmol/mol) and <6.5% (<48 mmol/mol), respectively, after add-on therapy increased from 46% and 26% in 2000–2003 to 59% and 29% in 2010–2012. This apparent time trend was associated with decreasing pre-intensification HbA_{1c} values over time (ESM Fig. 2). Corresponding proportions for metformin users aged <65 years without comorbidities who attained HbA_{1c} <6.5% (<48 mmol/mol) remained around 30% with a slightly decreasing tendency (ESM Fig. 3). The median HbA_{1c} level achieved in 2010–2012 was 6.8% (IQR 6.4–7.4%) (51 [IQR 46–57] mmol/mol) in all metformin add-on users and was identical at 6.8% (IQR 6.4–7.4%) (51 [IQR 46–57] mmol/mol) in metformin add-on users aged <65 years without comorbidities.

Discussion

Among real-world metformin users with short diabetes duration (0 to ≤3 years) who receive first add-on treatment, reduction in median HbA_{1c} was approximately 1% and comparable

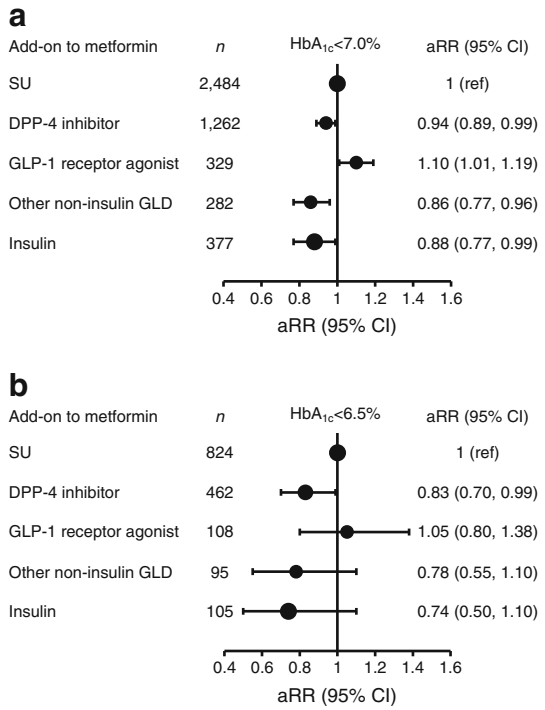

Fig. 2 aRRs for attaining HbA_{1c} targets of <7% (<53 mmol/mol) in all patients (**a**) and <6.5% (<48 mmol/mol) in patients <65 years with no comorbidities (**b**) 2–6 months after intensification. RR was adjusted for age, sex, diabetes duration, macrovascular type 2 diabetes complications, microvascular type 2 diabetes complications, CCI score and baseline HbA_{1c}

with that observed in randomised clinical trials [5]. Differences between add-on treatment regimens were modest, and HbA_{1c} reductions with add-on of DPP-4 inhibitors (0.8%, 9 mmol/mol), SU (1.2%, 13 mmol/mol) and GLP-1 receptor agonists (1.3%, 14 mmol/mol) were similar. Nonetheless, 41% of patients in the most recent years did not achieve an HbA_{1c} <7% (<53 mmol/mol) within 6 months.

The absolute HbA_{1c} reduction with insulin add-on therapy may be overestimated as it is positively correlated with baseline HbA_{1c} level, which was 1.5–2% (17–22 mmol/mol) higher [3]. In contrast, the absolute HbA_{1c} reduction was similar for SU and GLP-1 receptor agonist add-on, although the aRR for reaching HbA_{1c} <7% (<53 mmol/mol) was slightly higher with GLP-1 receptor agonists. Adjusted estimates for reaching HbA_{1c} targets with insulin tended to be lower, possibly related to some of the challenges that patients experience with early insulin administration in real life [8]. Nonetheless, our finding of similar HbA_{1c} levels achieved with insulin and other GLDs despite different HbA_{1c} baseline levels suggest that physicians choose effective therapy for patients with poor baseline glycaemic control, in accordance with guidelines [4, 8].

Few, if any, comparable population-based studies have focused on early glycaemic control in metformin initiators after intensification. Across 11 US health systems, in 2005–2009, 48% achieved an HbA_{1c} <7% (<53 mmol/mol) among a subgroup of 3,135 patients who initiated monotherapy and then added an oral agent within 12 months [9], which is comparable with the findings of the current study.

It is encouraging that an increasing share of patients reach HbA_{1c} <7% (<53 mmol/mol) after therapy intensification. This may be related to decreasing pre-intensification HbA_{1c} levels over time, likely reflecting closer follow-up and earlier treatment [6]. Nonetheless, it is of concern that more than 70% of early metformin users aged <65 years without recorded complications or comorbidities did not reach an HbA_{1c} level of <6.5% (<48 mmol/mol) as recommended by treatment guidelines and 25% still had an HbA_{1c} level of >7.4% (>57 mmol/mol) after intensification (upper quartile). One likely explanation is that half the patients in our cohort had HbA_{1c} ≥8.0% (≥64 mmol/mol) (median) and 25% had HbA_{1c} ≥9.2% (77 mmol/mol) (upper quartile) at the start of add-on therapy. Alternatively, the number, the dose or the efficacy of the drugs employed prior to intensification may not have fully matched the individual needs of each patient. As the greatest potential for prevention exists early in type 2 diabetes before complications have emerged [4], future observational studies should examine possible reasons why many patients do not attain recommended HbA_{1c} targets following intensification.

Study strengths include a population-based design within the comprehensive Danish public healthcare system and, accordingly, our data reflect actual clinical practice in diabetes care. A limitation was that HbA_{1c} measurements within the right time frame were available only for two-thirds of potentially eligible patients. Moreover, prescription redemption is only a marker of actual drug consumption. Finally, although a wide range of confounding factors were assessed, imperfectly measured, unmeasured (e.g. BMI, beta cell function, lifestyle and socioeconomic measures) or unknown factors still may have affected risk estimates.

In conclusion, the observed glucose-lowering effects in real life are similar for different add-on drug options and comparable with those observed in randomised trials. Still, a substantial proportion of patients with type 2 diabetes in the community setting who receive intensification of metformin monotherapy do not achieve currently recommended HbA_{1c} targets.

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Duality of interest Two of the co-authors (ESB and CLH) are employees of Novo Nordisk Scandinavia AB. As co-authors, they contributed to the design and reporting of the study. By contract, however, the Department of Clinical Epidemiology at Aarhus University had control of the data and retained final authority over design, content and interpretation of the analyses. RWT, LMB, MS, LP, HN and SPJ have reported no personal duality of interest. The Department of Clinical Epidemiology is involved in studies with funding from various companies as research grants to (and administered by) Aarhus University, including the present study. Moreover, the Department of Clinical Epidemiology is a member of the Danish Centre for Strategic Research in Type 2 Diabetes (DD2), supported by the Danish Agency for Science (grant no. 09-067009 and 09-075724). DD2 also is supported by the Danish Health and Medicines Authority, the Danish Diabetes Association and an unrestricted donation from Novo Nordisk A/S. Partners in the DD2 project are listed on the project website at www.DD2.nu. The authors have no non-financial interests that may be relevant to the submitted work.

Contribution statement RWT, LMB, ESB, CLH and SPJ conceived and designed the study. Funding was obtained by RWT, LP, ESB, CLH and SPJ. RWT, LP and SPJ supervised the study. Data was acquired by RWT, LMB, LP and SPJ and was analysed and interpreted by all authors. Statistical analysis was performed by LMB and LP. RWT, ESB, CLH and SPJ drafted the manuscript and LMB, MS, LP and HN critically revised it for important intellectual content. All authors gave final approval of the version to be published. RWT had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis and is the guarantor.

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