Appendix

A. Data cleaning and processing

Overall, the dataset used for this study consisted of 24,322 observations (i.e., prescription blocks) for 8,983 individuals. For the purpose of this study, we focused on people with type 2 diabetes. As there were some inconsistencies in the recording of diabetes type at study entry, we excluded people diagnosed with diabetes before age 35, or prescribed insulin less than a year after diagnosis. This excluded 2,062 observations of 841 participants who probably had type 1 diabetes. We also excluded individuals if they had received an anti-diabetes drug within six months of their first recorded prescription of any other medication, since it is likely these people were not observed from the beginning of their therapy onwards (967 individuals with 2,970 observations). We also excluded participants where date of diagnosis was missing (8 individuals with 9 observations), or where prescriptions were observed before the reported date of diagnosis (7 individuals with 8 observations). Finally, we excluded 4 observations for one person who received gliquidone, since we were not able to derive the costs for this drug. The final sample consisted of 7,159 individuals and 19,269 observed prescription blocks. We included individuals on rosiglitazone due to its important role in the past and because it is still being prescribed in the U.S. However, since rosiglitazone was withdrawn from the market in the UK, we provide data on costs and treatment duration for therapies involving rosiglitazone (Tables B.2 and B.3) separately for a sample (6,137 individuals and 15,057 observations) that excluded participants receiving rosiglitazone as well as a full sample. We do not provide separate data for frequencies, since our data do not allow us to conclude which therapies are being prescribed after the withdrawal of rosiglitazone for individuals who would have received the drug in the past.

The costs of medication therapy were derived from the Prescription Cost Analysis England 2014. For each drug type recorded in the GoDARTS data, we calculated an average price per dose unit across all brands, dosages and package sizes weighted by their prescribed volume in 2014. This weighted average price per dose unit was then multiplied by the mean daily dose recorded in the data to obtain daily average costs of the treatment and the total cost of the treatment (i.e., the daily average costs multiplied by the length of treatment). Since there was no valid dose information for Liraglutide prescriptions, we assumed that individuals were prescribed 1.2 mg daily following the guidelines of the National Institute for Health and Care Excellence. For all other drugs with missing dose data we imputed average daily doses using the mean values for the respective drug. All in all, we imputed data for 4,072 out of 19,269 observations (21.1%). It should be noted that we only included the costs of the drug itself, and have not included the costs of additional equipment such as needles, test strips or monitors.

B. Supplementary Tables

Table S.1: Cohort characteristics

	Mean	SD
Number of individuals	7,159	
Age at diagnosis (years)	59.3	10.7
Length of follow-up (years)	10.0	5.2
Number of prescribed drugs	2.4	1.2
Women (%)	44.8%	0.2
Average annual therapy costs (£)	241	284
BMI at first prescription	31.5	6.1
Smoked (%)	63.6%	0.2
Average Hba1c (%)	7.6	0.9
Diagnosis year (range)	1998 (1955-2013)	
Recruitment year (range)	2005 (1998-2012)	
Duration of diabetes at recruitment (years)	6.3	5.7

Source: GoDARTS.

Table S.2: First-line therapies

First-line therapy	Frequency	Time to therapy (years)	Average cost per day (£)	Duration of therapy (years)	Average cost of treatment (£)
Metformin	59.83%	2.64	0.12	3.74	159.97
Sulphonylurea	33.90%	2.82	0.13	3.48	130.92
Insulin	3.53%	9.99	2.72	8.30	8,089.66
Metformin & Sulphonylurea	1.63%	6.14	0.38	4.40	621.14
Thiazolidinedione[*]	0.36%	2.81 *(2.86)*	0.48 *(0.06)*	2.74 *(2.40)*	498.29 *(56.50)*
Metformin & Thiazolidinedione[*]	0.18%	4.74 *(3.29)*	0.69 *(0.17)*	3.52 *(0.55)*	983.38 *(34.64)*
Acarbose	0.17%	4.06	0.28	1.03	105.01
9 different therapies with frequencies <0.1% were omitted (overall 0.4% of the sample).					

[*]: *The figures provided include all TZDs. Figures excluding individuals on rosiglitazone are given in parentheses.*

Source: GoDARTS, Prescription Cost Analysis England 2014. Therapy lines are defined as any combinations of drugs prescribed on the same day. Average costs per day are calculated based on a weighted average price of all drugs prescribed in the NHS England in 2014 and the mean daily dose of the individual. The average cost of treatment is derived from the average cost per day and the duration of the respective prescription.
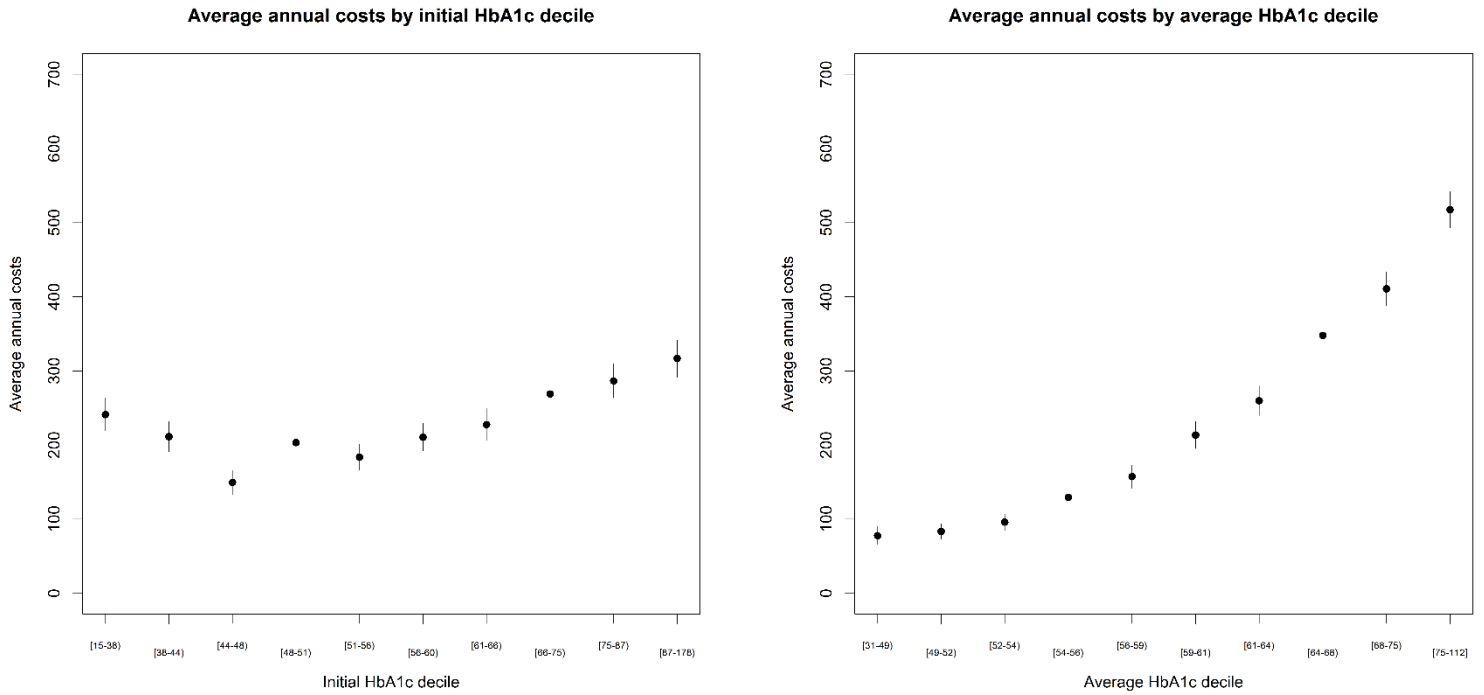
Second-line therapy	Frequency	% of people with a gap of >=90 days between therapies	Gap between 1st & 2nd line therapies (years)	Average cost per day (£)	Duration of therapy (years)	Average cost of treatment (£)
A. Switch to another drug						
DPP4 inhibitors	0.13%	71.43%	1.04	1.35	0.70	351.48
Insulin	2.66%	64.29%	1.58	2.43	5.56	4,858.83
Metformin	5.16%	81.55%	2.31	0.12	3.01	129.13
Sulphonylurea	6.57%	61.74%	1.41	0.13	2.83	113.17
Thiazolidinedione[*]	0.44%	43.48% *(20.00%)*	0.42 *(0.18)*	0.61 *(0.06)*	2.69 *(1.76)*	733.47 *(34.37)*
B. Drug added to firstline therapy						
Acarbose & Metformin	0.29%	0.00%	-	0.32	0.90	124.60
Acarbose & Sulphonylurea	0.40%	0.00%	-	0.37	1.13	174.55
DPP4 inhibitor & Metformin	3.64%	0.00%	-	1.47	1.57	830.31
DPP4 inhibitor & Metformin & Sulphonylurea	0.23%	0.00%	-	1.57	0.98	585.87
DPP4 inhibitor & Sulphonylurea	0.38%	0.00%	-	1.41	1.15	598.33
GLP-1 RA & Metformin	0.38%	0.00%	-	2.32	2.35	1,921.40
Insulin & Metformin	1.90%	0.00%	-	2.61	3.62	3,428.83
Insulin & Metformin & Sulphonylurea	0.30%	0.00%	-	2.88	0.14	149.27
Insulin & Sulphonylurea	2.65%	0.00%	-	2.61	0.33	419.82
Meglitinide & Metformin	0.21%	0.00%	-	0.55	3.50	715.85
Metformin & Sulphonylurea	61.91%	0.34%	2.08	0.24	3.37	285.69
Metformin & Sulphonylurea & Thiazolidinedione[*]	0.57%	0.00% *(0.00%)*	- *(-)*	0.70 *(0.36)*	2.31 *(1.82)*	694.81 *(241.95)*
Metformin & Thiazolidinedione[*]	8.74%	0.00% *(0.00%)*	- *(-)*	0.53 *(0.18)*	3.09 *(2.66)*	657.61 *(171.86)*
Sulphonylurea & Thiazolidinedione[*]	3.06%	1.24% *(2.04%)*	0.36 *(0.18)*	0.64 *(0.06)*	2.52 *(1.76)*	582.16 *(34.37)*
10 different therapies with frequencies <0.1% were omitted (overall 0.4% of the sample).						

[*]: The figures provided include all TZDs. Figures excluding individuals on rosiglitazone are given in parentheses.

[+]: After excluding individuals on rosiglitazone, there were no observations for this combination of drugs in the data.

Source: GoDARTS, Prescription Cost Analysis England 2014. Therapy lines are defined as any combinations of drugs prescribed on the same day. Average costs per day are calculated based on a weighted average price of all drugs prescribed in the NHS England in 2014 and the mean daily dose of the individual. The average cost of treatment is derived from the average cost per day and the duration of the respective prescription.

Figure S.1

Average annual costs by initial HbA1c decile

Average annual costs

Initial HbA1c decile

Average annual costs by average HbA1c decile

Average annual costs

Average HbA1c decile

Deciles in %:

Left panel: [3.56,5.64), [5.64,6.16), [6.17,6.50), [6.50,6.85), [6.85,7.25), [7.25,7.60), [7.69,8.20), [8.20,9.00), [9.00,10.13), [10.13,18.40]

Right panel: [5.00,6.60), [6.60,6.88), [6.88,7.09), [7.09,7.29), [7.29,7.51), [7.51,7.74), [7.74,8.02), [8.02,8.39), [8.39,8.99), [8.99,12.40]

Source: GoDARTS, Prescription Cost Analysis England 2014. The dots mark average costs per year for all persons within the corresponding groups. The lines show 95% confidence intervals. The groups are based on deciles of the first (or average) observed HbA1c measurement. Figure 2 shows that baseline HbA1c levels are not associated with costs with the exception of individuals at the upper end of the distribution. There is a strong association between average HbA1c decile and annual therapy costs.

Median values and interquartile ranges

Table S.4: Duration and costs of first-line therapy

	Therapy at diagnosis (%)	Time to therapy (years)	Annual cost of therapy (£)	Duration of therapy (years)
Overall sample (n=7,159)	7.25%	1.55 [0.19,4.35]	37.72 [30.84,55.74]	2.88 [1.16,5.37]
A. Gender				
Men (n=3,953)	7.03%	1.72 [0.2,4.6]	37.72 [30.84,56]	2.9 [1.19,5.34]
Women (n=3,206)	7.52%	1.4 [0.18,4.15]	37.72 [30.84,55.38]	2.85 [1.12,5.43]
B. Smoking status				
Smoked (n=4,098)	7.98%	1.36 [0.15,4.02]	37.72 [30.84,53.88]	2.78 [1.09,5.25]
C. BMI				
BMI<30 (n=2,825)	4.99%	2.05 [0.31,5.21]	37.72 [26.18,52.36]	3 [1.24,5.64]
BMI≥30 (n=3,362)	6.37%	1.52 [0.26,4.01]	39.39 [35.79,54.87]	2.79 [1.14,5.04]
D. Year of diagnosis				
Before 2000 (n=3,259)	4.45%	2.77 [0.45,6.68]	40.09 [28.2,57.59]	3.08 [1.21,5.92]
From 2000 onwards (n=3,900)	9.59%	0.88 [0.09,2.91]	37.72 [31.43,51.19]	2.72 [1.11,5.01]
E. Age at diagnosis				
<50 (n=1,406)	5.48%	2.09 [0.31,5.8]	44.31 [37.72,64.12]	2.35 [0.95,4.82]
50-54 (n=942)	7.01%	1.8 [0.29,4.91]	43.28 [33.48,56.58]	2.7 [1.09,5.23]
55-59 (n=1,209)	6.70%	1.84 [0.25,4.75]	39.83 [32.06,55.53]	2.81 [1.15,5.12]
60-64 (n=1,231)	7.80%	1.37 [0.14,4.1]	37.72 [30.84,52.81]	3.09 [1.28,5.6]
65-69 (n=1,098)	8.56%	1.22 [0.12,3.9]	37.72 [30.06,51.84]	2.99 [1.12,5.6]
≥70 (n=1,273)	8.25%	1.17 [0.13,3.49]	37.72 [26.18,44.31]	3.28 [1.42,5.87]
F. Initial HbA1c values				
1st quartile (n=1,496)	4.48%	3.42 [0.98,6.51]	37.72 [27.95,52.36]	3.28 [1.32,5.99]
2nd quartile (n=1,425)	4.91%	2.21 [0.69,4.18]	37.72 [27.38,48.28]	3.34 [1.36,5.41]
3rd quartile (n=1,438)	6.82%	0.93 [0.16,2.55]	37.72 [31.1,52.36]	2.91 [1.32,5.25]
4th quartile (n=1,453)	14.18%	0.23 [0.03,0.96]	43.74 [32.05,56.58]	2.1 [0.8,4.43]
G. Average HbA1c values				
1st quartile (n=1,453)	6.13%	2.12 [0.24,5.23]	37.72 [28.29,46.8]	4.3 [1.83,7.27]
2nd quartile (n=1,453)	6.54%	1.53 [0.23,3.97]	37.72 [29.64,50.29]	3.75 [1.69,6.09]
3rd quartile (n=1,453)	8.33%	1.31 [0.15,3.38]	37.72 [30.17,55.54]	2.69 [1.1,4.64]
4th quartile (n=1,453)	9.36%	0.74 [0.08,2.7]	43.74 [32.13,57.19]	1.73 [0.7,3.21]

Source: GoDARTS, Prescription Cost Analysis England 2014. Initial HbA1c quartiles in mmol/mol: [16, 46); [46, 55); [55, 69); [69, 178). Average HbA1c quartiles in mmol/mol: [36, 53); [53, 58); [58, 65); [65, 112). Initial HbA1c quartiles in %: [3.6, 6.4); [6.4, 7.2);, [7.2,8.5); [8.5,18.4). Average HbA1c quartiles in %: [5.4, 7.0); [7.0, 7.5); [7.5, 8.1); [8.1, 12.4). Column 1 gives the percentage of persons that received their first prescription at the time of their diagnosis. Columns 2-4 report median values and interquartiles ranges (in brackets).

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Table S.5: Duration and costs of second-line therapy

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	Second-line therapy observed (%)	Therapy substitution (%)	Gap >=90 days (%)	Gap between 1st & 2nd line therapies (years)	Duration of therapy	Annual cost therapy
Overall (n=5,254)	73.39%	15.32%	7.74%	1.1 [0.15,2.15]	2.19 [0.72,4.56]	81.25 [60.88,132.6]
A. Gender						
Men (n=2,890)	73.11%	14.15%	7.06%	1.08 [0.15,2.08]	2.31 [0.82,4.54]	81.45 [62.17,128.77]
Women (n=2,364)	73.74%	16.75%	8.58%	1.11 [0.14,2.2]	2.05 [0.62,4.57]	80.8 [59.55,142.01]
B. Smoking status						
Smoked (n=3,042)	74.23%	14.40%	7.22%	1.07 [0.15,2.21]	2.2 [0.75,4.53]	80.63 [61.03,125.19]
C. BMI						
BMI<30 (n=1,953)	69.13%	17.15%	8.25%	1.08 [0.16,2.08]	2.11 [0.62,4.5]	77.33 [57.37,123.69]
BMI>30 (n=2,468)	73.41%	12.56%	5.98%	0.96 [0.12,1.77]	2.11 [0.75,4.22]	82.75 [63.36,144.05]
D. Year of diagnosis						
Before 2000 (n=2,697)	82.76%	18.28%	10.83%	1.16 [0.17,2.35]	2.73 [0.81,5.54]	82.3 [61.39,138.57]
From 2000 onwards (n=2,557)	65.56%	12.20%	5.15%	0.75 [0.12,1.79]	1.87 [0.65,3.74]	79.34 [60.07,129.28]
E. Age at diagnosis						
<50 (n=1,185)	84.28%	16.37%	10.81%	1.33 [0.6,2.56]	2.02 [0.66,4.31]	90.07 [64.9,259.73]
50-54 (n=759)	80.57%	11.86%	5.94%	0.86 [0.12,1.83]	2.34 [0.95,4.52]	88.52 [65.13,161.17]
55-59 (n=924)	76.43%	14.50%	8.11%	1.12 [0.18,2.48]	2.35 [0.83,4.56]	82.75 [62.12,125.19]
60-64 (n=917)	74.49%	15.59%	7.55%	0.93 [0.12,1.64]	2.48 [0.85,4.85]	77.37 [58.27,122.28]
65-69 (n=765)	69.67%	14.77%	6.83%	1.01 [0.1,2.08]	2.24 [0.7,4.98]	76.97 [58.29,127.48]
≥70 (n=704)	55.30%	18.61%	6.28%	0.6 [0.11,1.96]	1.83 [0.43,4.07]	68.89 [51.42,98.56]
F. Initial HbA1c values						
1st quartile (n=1,074)	71.79%	17.50%	10.09%	1.43 [0.47,3.07]	2.15 [0.72,4.6]	77.37 [56.62,122.75]
2nd quartile (n=1,024)	71.86%	17.29%	8.07%	1.01 [0.12,1.88]	2.15 [0.65,4.12]	76.65 [56.58,129.81]
3rd quartile (n=1,180)	82.06%	14.41%	7.44%	0.78 [0.09,1.94]	2.3 [0.82,4.59]	80.02 [59.58,132.5]
4th quartile (n=1,270)	87.41%	9.29%	5.23%	0.93 [0.13,1.67]	2.43 [0.86,4.95]	82.75 [63.9,121.45]
G. Average HbA1c values						
1st quartile (n=715)	49.21%	24.90%	9.02%	1.17 [0.2,2.85]	2.32 [0.58,4.73]	68.56 [49.7,116.52]
2nd quartile (n=1,103)	75.91%	13.24%	6.33%	0.84 [0.1,2.05]	2.59 [0.98,5.32]	73.42 [57.97,114.89]
3rd quartile (n=1,336)	91.95%	11.38%	7.09%	1.08 [0.16,1.92]	2.61 [0.88,4.89]	81.45 [60.61,122.49]
4th quartile (n=1,394)	95.94%	12.70%	8.47%	1.07 [0.15,1.82]	1.77 [0.64,3.55]	87.7 [65.27,143.31]

Source: GoDARTS, Prescription Cost Analysis England 2014. Initial HbA1c quartiles in mmol/mol: [16, 46); [46, 55); [55, 69); [69, 178]. Average HbA1c quartiles in mmol/mol: [36, 53); [53, 58); [58, 65); [65, 112]. Initial HbA1c quartiles in %: [3.6, 6.4); [6.4, 7.2);, [7.2,8.5); [8.5,18.4]. Average HbA1c quartiles in %: [5.4, 7.0); [7.0, 7.5); [7.5, 8.1); [8.1, 12.4]. Column 1 gives the percentage of people for whom a switch in therapy is observed. Column 2 shows the percentage of people for whom the 2nd line therapy consisted of a substitution of drugs instead of the addition of a new drug. Columns 4-6 provide median values and interquartile ranges (in brackets).

Table S.6: Regression of therapy outcomes on baseline characteristics

	First-line therapy			Second-line therapy	
Variable	Time to therapy	Duration	Cost per day	Duration	Cost per day
Age at diagnosis (reference category: <50)					
50-54	-163.049*	45.347	-0.008	-22.284	0.002
	(65.438)	(52.076)	(0.023)	(52.457)	(0.039)
55-59	-212.678***	-15.278	-0.053**	22.598	-0.094**
	(60.133)	(48.116)	(0.018)	(51.726)	(0.032)
60-64	-325.225***	88.786	-0.048**	70.109	-0.061
	(59.718)	(51.206)	(0.018)	(54.559)	(0.037)
64-69	-414.751***	-0.996	-0.050**	2.438	-0.052
	(59.604)	(53.001)	(0.017)	(56.994)	(0.039)
>70	-411.084***	82.913	-0.063***	-87.313	-0.140***
	(57.246)	(52.589)	(0.017)	(56.515)	(0.039)
BMI between 25.00 and 29.99 kg/m²	-124.982	16.983	-0.011	98.779	-0.120**
	(70.871)	(58.899)	(0.021)	(59.950)	(0.045)
BMI between 30.00 and 39.99 kg/m²	-283.057***	-51.281	-0.019	102.157	-0.099*
	(69.155)	(57.338)	(0.021)	(58.448)	(0.044)
BMI over 40.00 kg/m²	-551.578***	-14.823	-0.008	-24.59	0.016
	(80.311)	(73.809)	(0.027)	(71.048)	(0.056)
Women	-67.856*	34.295	0.011	-17.542	-0.013
	(32.108)	(31.300)	(0.009)	(33.409)	(0.022)
Smoking at baseline	-82.796*	-114.040***	0.003	7.197	0.001
	(34.184)	(32.279)	(0.010)	(33.893)	(0.023)
Diagnosis ≥2000	-838.733***	-376.393***	-0.052***	-447.346***	0.006
	(37.578)	(35.385)	(0.010)	(35.912)	(0.022)
Initial HbA1c values (reference category: 1st quartile)					
2nd quartile	-334.150***	89.083*	-0.036*	46.745	0.027
	(48.894)	(43.725)	(0.015)	(47.871)	(0.033)
3rd quartile	-723.331***	166.387***	-0.034*	177.645***	0.027
	(48.895)	(45.418)	(0.016)	(48.221)	(0.032)
4th quartile	-1013.391***	171.061***	-0.034*	358.566***	-0.052
	(50.844)	(48.740)	(0.017)	(50.358)	(0.031)
Average HbA1c values (reference category: 1st quartile)					
2nd quartile	-158.831***	-298.665***	-0.012	103.534	-0.038
	(45.600)	(49.104)	(0.009)	(54.412)	(0.033)
3rd quartile	-279.759***	-734.805***	0.014	-22.667	0.014
	(48.794)	(47.755)	(0.014)	(52.303)	(0.034)
4th quartile	-368.808***	-1074.575***	0.044**	-327.883***	0.058
	(50.849)	(49.934)	(0.014)	(52.248)	(0.037)
Constant	2742.245***	2042.405***	0.247***	1194.238***	0.606***
	(106.884)	(83.008)	(0.034)	(79.198)	(0.059)
Sigma	1131.958***	1085.900***	0.327***	1002.325***	0.661***
	(22.738)	(14.098)	(0.028)	(15.736)	(0.018)
N	5,187	5,187	5,187	3,929	3,929

Source: GoDARTS, Prescription Cost Analysis England 2014. Time to therapy and duration of therapy in days. Costs are given in £. Initial HbA1c quartiles in mmol/mol: [16, 46); [46, 55); [55, 69); [69, 178). Average HbA1c quartiles in mmol/mol: [36, 53); [53, 58); [58, 65); [65, 112). Initial HbA1c quartiles in %: [3.6, 6.4); [6.4, 7.2);, [7.2,8.5); [8.5,18.4). Average HbA1c quartiles in %: [5.4, 7.0); [7.0, 7.5); [7.5, 8.1); [8.1, 12.4). The table shows regression coefficients from a Tobit regression of therapy duration and costs on baseline characteristics. Robust standard errors are shown in parentheses. *** p<0.001; ** p<0.01; * p<0.05.

Variable	First-line therapy			Second-line therapy	
	Time to therapy	Duration	Cost per day	Duration	Cost per day
Age at diagnosis (reference category: <50)					
50-54	-155.295*	45.046	-0.008	-20.557	0
	(62.592)	(52.162)	(0.024)	(52.652)	(0.039)
55-59	-206.310***	-17.246	-0.054**	21.484	-0.097**
	(57.448)	(48.160)	(0.018)	(51.920)	(0.032)
60-64	-316.692***	86.138	-0.049**	69.645	-0.062
	(57.095)	(51.384)	(0.018)	(54.711)	(0.037)
64-69	-402.020***	-8.811	-0.052**	2.949	-0.057
	(56.707)	(53.133)	(0.018)	(57.335)	(0.039)
>70	-386.381***	85.191	-0.063***	-93.555	-0.135***
	(53.865)	(52.741)	(0.017)	(56.709)	(0.039)
BMI between 25.00 and 29.99 kg/m²	-274.808	-58.962	-0.041	115.904	-0.135*
	(145.362)	(108.368)	(0.048)	(101.836)	(0.068)
BMI between 30.00 and 39.99 kg/m²	-528.949***	-179.416	-0.041	171.084	-0.163*
	(141.911)	(106.684)	(0.048)	(100.773)	(0.066)
BMI over 40.00 kg/m²	-947.151***	-123.331	-0.033	77.484	-0.168*
	(168.549)	(145.348)	(0.063)	(134.347)	(0.080)
Women	-227.691**	-6.562	0.028	60.061	-0.002
	(70.164)	(60.141)	(0.024)	(62.730)	(0.036)
Smoking at baseline	-168.310*	-206.597***	-0.015	9.857	-0.05
	(75.594)	(62.573)	(0.024)	(64.011)	(0.038)
Diagnosis ≥2000	-1347.040***	-656.204***	-0.095	-295.762*	-0.133
	(164.212)	(127.306)	(0.052)	(123.104)	(0.091)
Initial HbA1c levels (reference category: 1st quartile)					
2nd quartile	-335.972***	90.467*	-0.037*	42.677	0.031
	(47.347)	(43.837)	(0.015)	(48.200)	(0.034)
3rd quartile	-704.064***	165.059***	-0.035*	172.981***	0.031
	(47.087)	(45.388)	(0.016)	(48.444)	(0.032)
4th quartile	-928.704***	173.727***	-0.035*	350.326***	-0.045
	(47.954)	(48.767)	(0.017)	(50.648)	(0.031)
Average HbA1c levels (reference category: 1st quartile)					
2nd quartile	-159.543***	-296.209***	-0.011	102.745	-0.035
	(43.535)	(49.176)	(0.009)	(54.465)	(0.033)
3rd quartile	-270.640***	-732.946***	0.014	-23.359	0.014
	(46.458)	*(47.731)*	*(0.014)*	*(52.322)*	*(0.034)*
4th quartile	-369.609***	-1072.671***	0.044**	-330.477***	0.06
	(48.129)	(49.943)	(0.014)	(52.325)	(0.037)

Interaction effects:

Diagnosis≥2000 & BMI between 25.00 and 29.99 kg/m²	261.305	129.201	0.049	-38.747	0.029
	(153.839)	(125.935)	(0.050)	(122.096)	(0.091)
Diagnosis ≥2000 & BMI between 30.00 and 39.99 kg/m²	438.701**	212.732	0.035	-132.682	0.116
	(149.590)	(122.792)	(0.049)	(119.145)	(0.088)
Diagnosis≥2000 & BMI over 40.00 kg/m²	649.162***	181.102	0.041	-173.452	0.297**
	(177.089)	(166.152)	(0.063)	(153.794)	(0.108)
Diagnosis≥2000 & Women	257.261***	65.058	-0.027	-133.94	-0.021
	(74.893)	(69.461)	(0.024)	(71.611)	(0.045)
Diagnosis≥2000 & Smoking at baseline	139.92	144.770*	0.029	0.654	0.088
	(80.120)	(72.044)	(0.025)	(73.374)	(0.047)
Constant	3043.099***	2211.778***	0.274***	1118.708***	0.678***
	(170.023)	(121.784)	(0.059)	(111.754)	(0.078)
N	5,187	5,187	5,187	3,929	3,929

Source: GoDARTS, Prescription Cost Analysis England 2014. Time to therapy and duration of therapy in days. Costs are given in £. Initial HbA1c quartiles in mmol/mol: [16, 46); [46, 55); [55, 69); [69, 178). Average HbA1c quartiles in mmol/mol: [36, 53); [53, 58); [58, 65); [65, 112). Initial HbA1c quartiles in %: [3.6, 6.4); [6.4, 7.2);, [7.2,8.5); [8.5,18.4). Average HbA1c quartiles in %: [5.4, 7.0); [7.0, 7.5); [7.5, 8.1); [8.1, 12.4). The table shows regression coefficients from a linear regression of therapy duration and costs on baseline characteristics. Robust standard errors are shown in parentheses. *** p<0.001; ** p<0.01; * p<0.05.

Sensitivity analyses

The estimated associations between baseline characteristics and time to first-line therapy as well as duration of therapy could be affected by censoring or the limited duration of follow-up. The duration of first- and second-line therapy recorded in the data is affected by censoring, since some individuals had not completed their respective therapy-line during the period covered in the data. Similarly, some patients will not have started first-line therapy before the end of the study. However, this did not result in censored observations. Instead, the affected observations are missing from the dataset, since the data contained only individuals with at least one prescription of an anti-diabetic drug. Therefore, we used different methods to address these two potential problems in a sensitivity analysis.

Censoring

For the duration of first- and second-line therapy, we re-analyzed the data using survival models, which address the issue of censoring. For the purpose of this study, we defined observations as censored if the recorded end date of the therapy line occurred after December 31, 2013, since most patients have been observed up to this date. Therapy lines that were completed before this date were treated as uncensored. Completed therapy lines include both cases where the patient moved on to another therapy as well as cases where the patient died. We analyzed duration of first- and second-line therapy using Cox proportional hazard regression models and Weibull survival models. Table S.8 below shows the results.

The analysis of first-line therapy included 1,235 censored observations, while the analysis of second-line therapy included 488 censored observations. The results from the Cox regression model and the Weibull survival model are qualitatively very similar. For the duration of first-line therapy, there are some differences between the estimates from the survival models and the estimates from a linear regression (Table 3). For example, in both the Cox and Weibull

regression model, individuals aged 50-54 or 60 and above at diagnosis have a significant hazard ratio (HR) below 1, i.e., their first-line therapies are longer, while in the linear regression model the estimates are not significant. Similarly, individuals with a BMI between 30 and 39.99 kg/m^2 have a hazard ratio above 1, i.e., their first-line therapy is significantly shorter. However, the survival models also confirm our findings from the linear regression models. In particular, individuals diagnosed from the year 2000 onwards have a shorter therapy duration (HR>1), and initial HbA1c levels are associated with longer first-line therapy (HR<1), whereas average HbA1c values are associated with shorter first-line therapy (HR>1). Similarly, individuals diagnosed from the year 2000 onwards have a shorter duration of second-line therapy (HR>1), and initial HbA1c levels are associated with longer second-line therapy. In contrast to the estimates from our linear regression models, average HbA1c levels within the 4th quartile are not significantly associated with duration of second-line therapy. All in all, we conclude that the survival models confirm our conclusions drawn from the   linear   regression   models.

Table S.8: Censored regression of therapy outcomes on baseline characteristics

Variable	First-line therapy duration		Second-line therapy duration	
	Cox regression	Weibull model	Cox regression	Weibull model
Age at diagnosis (reference category: <50)				
50-54	0.782*	0.789*	1.111	1.109
	(0.082)	(0.079)	(0.178)	(0.177)
55-59	1.002	0.997	1.131	1.129
	(0.094)	(0.090)	(0.169)	(0.167)
60-64	0.750**	0.765**	0.987	0.997
	(0.075)	(0.073)	(0.149)	(0.150)
64-69	0.721**	0.724**	0.884	0.892
	(0.076)	(0.074)	(0.148)	(0.148)
>70	0.600***	0.595***	0.818	0.817
	(0.062)	(0.060)	(0.150)	(0.149)
BMI between 25.00 and 29.99 kg/m²	1.138	1.138	0.955	0.964
	(0.134)	(0.129)	(0.164)	(0.164)
BMI between 30.00 and 39.99 kg/m²	1.402**	1.385**	0.986	0.988
	(0.159)	(0.150)	(0.167)	(0.165)
BMI over 40.00 kg/m²	1.078	1.082	0.934	0.931
	(0.159)	(0.153)	(0.218)	(0.216)
Women	0.882*	0.902	1.009	1.018
	(0.053)	(0.052)	(0.094)	(0.094)
Smoking at baseline	1	0.997	0.91	0.914
	(0.060)	(0.057)	(0.087)	(0.086)
Diagnosis >2000	3.005***	2.664***	4.022***	3.811***
	(0.223)	(0.181)	(0.462)	(0.417)
Initial HbA1c values (reference category: 1st quartile)				
2nd quartile	0.919	0.934	1.038	1.039
	(0.074)	(0.072)	(0.137)	(0.136)
3rd quartile	0.706***	0.733***	0.666**	0.667**
	(0.061)	(0.061)	(0.091)	(0.091)
4th quartile	0.769**	0.823*	0.531***	0.538***
	(0.068)	(0.070)	(0.075)	(0.075)
Average HbA1c values (reference category: 1st quartile)				
2nd quartile	1.553***	1.471***	1.031	1.035
	(0.116)	(0.106)	(0.144)	(0.143)
3rd quartile	2.558***	2.310***	1.167	1.164
	(0.212)	(0.181)	(0.159)	(0.157)
4th quartile	2.632***	2.368***	1.087	1.075
	(0.264)	(0.227)	(0.177)	(0.173)
N	5,187	5,187	3,929	3,929
Censored observations	1,235	1,235	488	488

Source: GoDARTS, Prescription Cost Analysis England 2014. Duration of therapy in days. Costs are given in £. Initial HbA1c quartiles in mmol/mol: [16, 46); [46, 55); [55, 69); [69, 178). Average HbA1c quartiles in mmol/mol: [36, 53); [53, 58); [58, 65); [65, 112). Initial HbA1c quartiles in %: [3.6, 6.4); [6.4, 7.2);, [7.2,8.5); [8.5,18.4). Average HbA1c quartiles in %: [5.4, 7.0); [7.0, 7.5); [7.5, 8.1); [8.1, 12.4). The table shows hazard ratios from a survival model. Robust standard errors are shown in parentheses. *** $p<0.001$; ** $p<0.01$; * $p<0.05$.

Limited follow-up duration

As described above, individuals are only included in the dataset once first-line therapy has been initiated. However, some individuals will receive first-line medication therapy only after several years of diet and exercise. Therefore, the limited duration of follow-up for some individuals could bias the result. In particular, individuals with a very long time to first-line therapy are likely to be underrepresented in the group of people diagnosed from 2000 onwards, and consequently the estimated association between year of diagnosis and time to first-line therapy might be downward-biased. The estimates for costs and duration of therapy might also be affected by these systematic differences in cohort composition, although the direction of the bias is less clear.

Therefore, we conducted a sensitivity analysis where we restricted the sample to individuals with at least five years of follow-up (i.e., people diagnosed before the year 2009), and we limited follow-up duration to 15 years. These restrictions should ensure that follow-up duration is more comparable between different cohorts. We excluded people for whom first-line therapy was observed after 15 or more years following diagnosis. If individuals were on first-line therapy (or second-line therapy, respectively) after 15 years of follow-up, we recoded duration of therapy to match the difference between 15 years and time to therapy. If second-line therapy was observed for a person, but only after 15 or more years, we excluded this individual for all analyses of second-line therapy.

The results are shown in Table S.9. Limiting the follow-up duration led to the exclusion of between 157 and 222 observations for each analysis. A comparison with Table 3 in the manuscript shows that most of our conclusions are confirmed by this sensitivity analysis. While the differences in time to therapy initiation are smaller than the reductions reported in Table 3, they are still sizable and statistically significant. Costs per day for first-line therapy

are significantly lower for individuals diagnosed from 2000 onwards, and duration of second-line therapy is significantly shorter for these people.

Table S.9: Regression of therapy outcomes on baseline characteristics using limited follow-up data

Variable	First-line therapy			Second-line therapy	
	Time to therapy	Duration	Cost per day	Duration	Cost per day
Age at diagnosis (reference category: <50)					
50-54	-30.79	59.087	-0.01	-60.725	-0.014
	(54.787)	(49.707)	(0.024)	(53.398)	(0.036)
55-59	-93.394	11.383	-0.053**	12.747	-0.069*
	(49.238)	(45.983)	(0.018)	(53.482)	(0.032)
60-64	-166.933***	117.315*	-0.048**	62.566	-0.036
	(49.837)	(49.033)	(0.019)	(56.611)	(0.037)
64-69	-247.097***	50.343	-0.051**	-14.161	-0.031
	(49.517)	(51.440)	(0.018)	(58.250)	(0.038)
>70	-239.964***	152.314**	-0.063***	-100.241	-0.119**
	(47.602)	(52.352)	(0.018)	(58.303)	(0.038)
BMI between 25.00 and 29.99 kg/m²	-88.1	55.059	-0.013	141.650*	-0.143**
	(59.942)	(57.098)	(0.022)	(63.725)	(0.048)
BMI between 30.00 and 39.99 kg/m²	-212.260***	0.559	-0.019	136.510*	-0.114*
	(58.530)	(55.744)	(0.022)	(61.859)	(0.047)
BMI over 40.00 kg/m²	-423.268***	61.124	-0.008	17.398	0.02
	(70.043)	(73.001)	(0.029)	(74.964)	(0.059)
Women	-50.138	40.975	0.012	-23.477	-0.016
	(27.932)	(30.538)	(0.010)	(34.488)	(0.022)
Smoking at baseline	-68.920*	-102.915**	0.001	20.855	0.014
	(29.136)	(31.432)	(0.010)	(35.041)	(0.022)
Diagnosis ≥2000	-641.946***	-239.191***	-0.052***	-444.395***	0.038
	(32.402)	(33.447)	(0.010)	(37.385)	(0.021)
Initial HbA1c values (reference category: 1st quartile)					
2nd quartile	-295.328***	108.443*	-0.036*	47.032	0.025
	(43.788)	(42.759)	(0.015)	(49.969)	(0.033)
3rd quartile	-683.487***	174.568***	-0.034*	192.447***	0.021
	(42.859)	(44.049)	(0.016)	(50.103)	(0.031)
4th quartile	-912.688***	170.871***	-0.032	385.600***	-0.05
	(44.432)	(47.931)	(0.017)	(52.642)	(0.030)
Average HbA1c values (reference category: 1st quartile)					
2nd quartile	-136.533***	-258.202***	-0.013	128.050*	-0.041
	(40.508)	(48.053)	(0.009)	(57.213)	(0.034)
3rd quartile	-252.565***	-660.871***	0.013	-21.321	-0.005
	(41.608)	(46.400)	(0.014)	(54.905)	(0.033)
4th quartile	-314.568***	-985.535***	0.041**	-340.038***	0.044
	(44.845)	(48.740)	(0.014)	(55.108)	(0.037)
Constant	2362.011***	1778.702***	0.247***	1156.415***	0.574***
	(84.542)	(78.649)	(0.035)	(87.723)	(0.062)
N	4,980	5,030	5,030	3,733	3,707
Excluded observations	207	157	157	196	222

Source: GoDARTS, Prescription Cost Analysis England 2014. Time to therapy and duration of therapy in days. Costs are given in £. Initial HbA1c quartiles in mmol/mol: [16, 46); [46, 55); [55, 69); [69, 178). Average HbA1c quartiles in mmol/mol: [36, 53); [53, 58); [58, 65); [65, 112). Initial HbA1c quartiles in %: [3.6, 6.4); [6.4, 7.2);, [7.2,8.5); [8.5,18.4). Average HbA1c quartiles in %: [5.4, 7.0); [7.0, 7.5); [7.5, 8.1); [8.1, 12.4). The table shows regression coefficients from a linear regression of therapy duration and costs on baseline characteristics. Robust standard errors are shown in parentheses. *** $p<0.001$; ** $p<0.01$; * $p<0.05$.