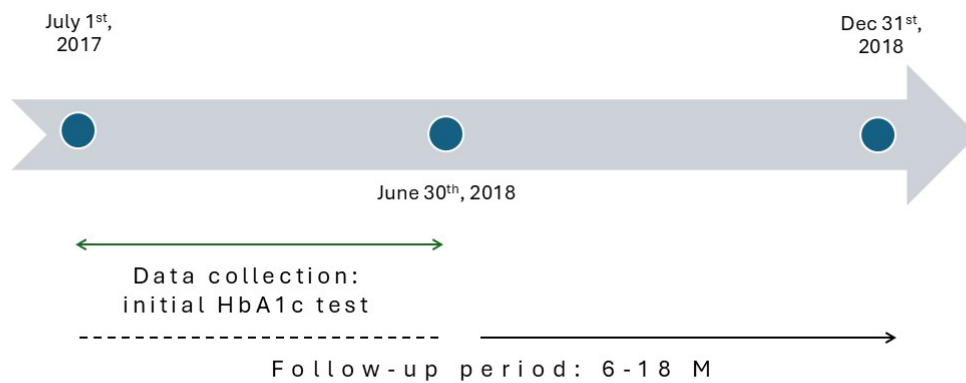


Supplementary Figure 1. Analysis timeline.



Inclusion criteria:

- T2DM patients
- Age 18-80
- HbA1c > 8% despite being on 2 OADs

Exclusion criteria:

- T1DM patients
- Pregnant women
- Treated with injectable therapies
- Advanced comorbid conditions

Outcome: Within 6–18 months after index HbA1c, prescription of a third antidiabetic drug is considered a successful treatment intensification

Abbreviations: M: Months; T2DM: Type 2 Diabetes Mellitus; OADs: Oral Anti Diabetics; T1DM: Type 1 Diabetes Mellitus.

Supplementary Table 1. Laboratory test results.

Lab Test	8.0% < HbA1c ≤ 9.0%	HbA1c > 9.0%	p- value
	(N = 282) Average ± SD	(N = 272) Average ± SD	
Hemoglobin (g/dL)	13.4 ± 1.5	13.7 ± 1.5	0.033
Glucose (mg/dL)	173.3 ± 34.4	233.0 ± 65.4	<0.001
HbA1c (%)	8.5 ± 0.3	10.4 ± 1.2	<0.001
eGFR (mL/min/1.73 m ²)	93.2 ± 19.0	95.6 ± 16.7	0.119
Total cholesterol (mg/dL)	164.8±40.8	179.8 ± 81.0	0.007
LDL-C (mg/dL)	89.3 ± 32.8	94.2 ± 38.3	0.138
NON-HDL (mg/dL)	124.5 ± 37.9	134.0 ± 45.1	0.009
HDL-C (mg/dL)	41.7 ± 10.0	42.3 ± 11.8	0.513
Triglycerides (mg/dL)	175.5 ± 111.2	203.6 ± 141.2	0.011
Serum Creatinine(mg/dL)	0.81 ± 0.29	0.76 ±0 .22	0.013
UACR (mg/gr)	86.4 ± 272.6	83.2 ± 224.5	0.880
UACR (mg/gr) Median [IQR]	14.47 [0-48.86]	14.14 [0-42.45]	

Abbreviations: SD: Standard Deviation; eGFR: Estimated Glomerular Filtration Rate; LDL-C: Low-Density Lipoprotein Cholesterol-calculated; HDL-C: High-Density Lipoprotein Cholesterol, UACR: Urine Albumin Creatinine Ratio; IQR: Interquartile Range

Supplementary Table 2. Baseline medications.

Medication	8.0% < HbA1c ≤ 9.0% (N = 282)	HbA1c > 9.0% (N = 272)	p- value
Metformin	275 (97.5)	264 (97.1)	0.739
Sulfonylurea	63 (22.3)	71 (26.1)	0.301
Repaglinide	50 (17.7)	52 (19.2)	0.659
DPP4 inhibitors	148 (52.5)	135 (49.8)	0.531
SGLT2 inhibitors	22 (7.8)	23 (8.5)	0.778
Pioglitazone	3 (1.1)	0	0.088
Acarbose	0	0	
ACE/ARB's	208 (78.5)	200 (80.3)	0.608
Statins	242 (91.3)	230 (92.4)	0.664
Ezetimibe	32 (12.1)	21 (8.5)	0.190
Aspirin	157 (55.7)	152 (55.9)	0.961
Fibrates	22 (24.4)	32 (42.7)	0.013
Other BP medication	134 (50.6)	127 (51.2)	0.884
Medication compliance (Average ± SD)	70.5 ± 24.5	70.4 ± 24.7	0.993

Abbreviations: DPP4: Dipeptidyl Peptidase 4; SGLT2: Sodium-Glucose co-transporter 2; ACE: Angiotensin-Converting Enzyme; ARB: Angiotensin II Receptor Blocker; BP: Blood Pressure

Supplementary Table 3. Prescription of third medication in patients managed by GPs (N = 518).

Medication	8.0% < HbA1c ≤ 9.0% (N = 268)	HbA1c > 9.0% (N = 250)	p- value
Third medication prescribed, n (%)	127 (47.4)	146 (58.4)	0.012
Any oral medication n (%) (from intensification group)	99 (79.2)	78 (53.4)	<0.001
Metformin	2 (1.6)	0	0.128
Sulfonylurea	8 (6.3)	4 (2.7)	0.151
Repaglinide	16 (12.6)	10 (6.8)	0.105
DPP4 inhibitors	21 (16.5)	15(10.3)	0.056
SGLT2 inhibitors	47 (37.0)	45 (30.8)	0.180
Pioglitazone	5 (3.9)	5 (3.5)	0.819
Acarbose	0	1 (0.7)	0.351
Any Insulin / FRC	15 (11.8)	48 (32.9)	<0.001
Basal	13 (10.2)	38 (26.0)	<0.001
Premixed	0	0	-
Basal bolus	1 (0.8)	5 (3.5)	0.139
Prandial	0	2 (1.4)	0.186
FRC	1 (0.8)	3 (2.1)	0.386
Any insulin	14 (11.2)	45 (31.3)	<.001
GLP1RA	13 (10.2)	24 (16.4)	0.137

Abbreviations: GP: General Practitioner; DPP4: Dipeptidyl Peptidase 4; SGLT2: Sodium-Glucose co-transporter 2; FRC: Fixed Ratio Combination; GLP1RA: Glucagon-Like Protein 1 Receptor Agonist

Supplementary Table 4. Multivariable Cox proportional hazards model for time to treatment intensification in patients managed by GPs (N = 518).

Predictor	HR (95% CI)	p value
Baseline HbA1c >9% (vs 8–9%)	1.42 (1.11–1.81)	0.005
Arab ethnicity (vs Jewish)	0.76 (0.58–0.98)	0.038
Age (per year)	1.00 (0.98–1.01)	0.783
Male sex (vs female)	0.94 (0.73–1.23)	0.670
BMI (kg/m ²)	0.99 (0.97–1.02)	0.592
Diabetes duration (per year)	0.98 (0.95–1.01)	0.234
Ischemic heart disease	1.47 (1.10–1.96)	0.009
Cerebrovascular disease (CVA/TIA)	0.94 (0.67–1.30)	0.694
Heart failure	0.94 (0.50–1.79)	0.854
Diabetic retinopathy	1.24 (0.87–1.78)	0.228
Diabetic nephropathy	2.04 (1.28–3.24)	0.003
Diabetic neuropathy	1.26 (0.86–1.85)	0.230

Adjusted hazard ratios (aHRs) with 95% confidence intervals (CIs) are shown for factors associated with time from the index HbA1c measurement to treatment intensification.

Abbreviations: GP: General Practitioner; HR: Hazard Ratio; BMI: Body Mass Index; CVA: Cerebrovascular Accident; TIA: Transient Ischemic Attack

Supplementary Table 5. Multivariable logistic regression model for receipt of treatment intensification in patients managed by GPs (N = 518).

Predictor	OR (95% CI)	p value
Baseline HbA1c >9% (vs >8–9%)	1.72 (1.19–2.47)	0.004
Arab ethnicity (vs Jewish)	0.57 (0.39–0.85)	0.005
Age (per year)	0.99 (0.97–1.01)	0.334
Male sex (vs female)	0.82 (0.55–1.21)	0.320
BMI (kg/m ²)	1.00 (0.96–1.04)	0.976
Diabetes duration (per year)	0.99 (0.94–1.04)	0.666
Ischemic heart disease	1.90 (1.19–3.04)	0.007
Cerebrovascular disease (CVA/TIA)	1.17 (0.69–1.99)	0.561
Heart failure	1.05 (0.36–3.02)	0.932
Diabetic retinopathy	1.63 (0.91–2.93)	0.099
Diabetic nephropathy	2.21 (0.93–5.29)	0.074
Diabetic neuropathy	1.56 (0.82–2.95)	0.172

Adjusted odds ratios (aORs) with 95% confidence intervals (CIs) are shown for factors associated with undergoing treatment intensification.

Abbreviations: GP: General Practitioner; OR: Odds Ratio; BMI: Body Mass Index; CVA: Cerebrovascular Accident; TIA: Transient Ischemic Attack

Supplementary Table 6. Multivariable logistic regression model for injectable versus oral intensification among intensified patients in patients managed by GPs (N = 518).

Predictor	OR (95% CI)	p value
Baseline HbA1c >9% (vs 8–9%)	3.20 (1.81–5.67)	<0.001
Arab ethnicity (vs Jewish)	1.96 (1.09–3.54)	0.025
Age (per year)	0.97 (0.93–1.00)	0.046
Male sex (vs female)	1.19 (0.65–2.19)	0.566
BMI (kg/m ²)	1.06 (1.00–1.13)	0.033
Diabetes duration (per year)	1.08 (1.00–1.17)	0.051
Ischemic heart disease	0.81 (0.41–1.61)	0.552
Cerebrovascular disease (CVA/TIA)	1.39 (0.64–3.01)	0.407
Heart failure	2.23 (0.50–9.86)	0.291
Diabetic retinopathy	0.37 (0.15–0.91)	0.030
Diabetic nephropathy	0.80 (0.27–2.38)	0.686
Diabetic neuropathy	1.44 (0.60–3.45)	0.414

Adjusted odds ratios (aORs) with 95% confidence intervals (CIs) are shown for factors associated with receiving injectable therapy (vs oral therapy) as the intensification regimen among patients who underwent treatment intensification.

Abbreviations: GP: General Practitioner; OR: Odds Ratio; BMI: Body Mass Index; CVA: Cerebrovascular Accident; TIA: Transient Ischemic Attack

Supplementary Table 7. Associations between patients' characteristics and type of third anti-diabetes agent in patients managed by GPs (N = 518).

Characteristics	HbA1c group ¹	Oral agents	p-value	Insulin / FRC	p-value	GLP1RA	p-value	Sglt2 inhibitor	p-value
Males/Females, n (%)	1	64/35 (80.0/77.8)	0.769	10/5 (12.5/11.1)	0.819	6/7 (7.5/15.6)	0.157	33/14 (41.3/31.1)	0.261
	2	45/31 (54.2/50.8)	0.687	32/16 (38.6/26.2)	0.121	10/14 (12.0/23.0)	0.083	25/18 (30.1/29.5)	0.937
Age, Mean±SD (prescribed vs. not prescribed)	1	64.8±9.0 62.0±11.6	0.196	59.5±11.4 64.9±9.2	0.041	65.1±10.5 64.1±9.5	0.732	63.9±9.1 64.4±9.9	0.777
	2	62.4±10.0 61.0±10.2	0.402	59.5±11.3 62.8±9.3	0.066	61.7±9.0 61.8±10.4	0.971	63.0±7.9 61.2±10.9	0.270
Jews/Arabs, n (%)	1	72/27 (81.8/73.0)	0.266	7/8 (8.0/21.6)	0.032	10/3 (11.4/8.1)	0.586	33/14 (37.5/37.8)	0.972
	2	47/29 (58.8/45.3)	0.108	20/28 (25.0/43.8)	0.018	14/10 (17.5/15.6)	0.764	27/16 (33.8/25.0)	0.254

¹ 8.0% < HbA1c ≤9.0% = Group 1, HbA1c >9.0% = Group 2

Abbreviations: GP: General Practitioner; FRC: Fixed Ratio Combination; GLP1RA: Glucagon Like Protein 1 Receptor Agonist; SGLT2: Sodium-Glucose co-transporter 2

Supplementary Table 8. Associations between patients' comorbidities and type of third anti-diabetes agent in patients managed by GPs (N = 518).

Comorbidities	HbA1c	Oral	p-	Insulin /	p-	GLP1RA	p-	Sglt2	p-
Yes/No, n (%)	group	agents	value	FRC	value		value	inhibitor	value
Heart failure	1	5/94 (83.3/79.0)	0.798	1/14 (16.7/11.8)	0.718	0/13 (0/10.9)	0.392	3/44 (50.0/37.0)	0.520
	2	2/74 (33.3/53.6)	0.330	3/45 (50.0/32.6)	0.376	2/22 (33.3/15.9)	0.263	2/41 (33.3/29.7)	0.849
Ischemic heart disease	1	27/72 (81.8/78.3)	0.666	3/12 (9.1/13.0)	0.549	3/10 (9.1/10.9)	0.774	17/30 (51.5/32.6)	0.054
	2	28/48 (57.1/50.5)	0.451	13/35 (26.5/36.8)	0.214	11/13 (22.4/13.7)	0.181	19/24 (38.8/25.3)	0.093
Stroke/Transient ischemic attack	1	26/73 (78.8/79.3)	0.946	6/9 (18.2/9.8)	0.203	2/11 (6.1/12.0)	0.341	12/35 (36.4/38.0)	0.864
	2	12/64 (35.3/58.2)	0.019	13/35 (38.2/31.8)	0.488	9/15 (26.5/13.6)	0.079	6/37 (17.6/33.6)	0.075
Peripheral artery disease	1	8/91 (80.0/79.1)	0.948	2/13 (20.0/11.3)	0.417	0/13 (0/11.3)	0.261	5/42 (50.0/36.5)	0.399
	2	2/74 (40.0/53.2)	0.560	2/46 (40.0/33.1)	0.748	1/23 (20.0/16.5)	0.839	1/42 (20.0/30.2)	0.624
Retinopathy	1	14/85 (73.7/80.2)	0.520	3/12 (15.8/11.3)	0.581	2/11 (10.5/10.4)	0.984	6/41 (31.6/38.7)	0.556
	2	19/57 (73.1/48.3)	0.022	6/42 (23.1/35.6)	0.220	2/22 (7.7/18.6)	0.175	11/32 (42.3/27.1)	0.126
Nephropathy	1	8/91 (72.7/79.8)	0.580	1/14 (9.1/12.3)	0.756	2/11 (18.2/9.6)	0.376	6/41 (54.5/36.0)	0.224
	2	6/70 (60.0/52.2)	0.635	2/46 (20.0/34.3)	0.354	2/22 (20.0/16.4)	0.769	3/40 (30.0/29.9)	0.992
Neuropathy	1	15/84 (68.2/81.6)	0.161	4/11 (18.2/10.7)	0.326	3/10 (13.6/9.7)	0.584	8/39 (36.4/37.9)	0.895
	2	8/68 (36.4/55.7)	0.094	10/38 (45.5/31.1)	0.190	4/20 (18.2/16.4)	0.836	5/38 (22.7/31.1)	0.427

¹ 8.0% < HbA1c ≤ 9.0% = Group 1, HbA1c > 9.0% = Group 2

Abbreviations: GP: General Practitioner; FRC: Fixed Ratio Combination; GLP1RA: Glucagon Like Protein 1 Receptor Agonist; SGLT2: Sodium-Glucose co-transporter2

Supplementary Table 9. HbA1c reduction in patients managed by GPs (N = 518).

Intensification	HbA1c Baseline	HbA1c Repeated test	p-value	Target HbA1c (<7%) after intervention. n (%)	p-value
8.0% < HbA1c ≤ 9.0% (N = 87)	8.6±0.3	8.2±1.1	0.002	14 (16.1)	0.153
HbA1c > 9.0% (N = 79)	10.4±1.2	8.9±1.5	<0.001	7 (8.8)	
No intensification					
8.0% < HbA1c ≤ 9.0% (N = 83)	8.4±0.3	8.3±1.0	0.190		
HbA1c > 9.0% (N = 65)	10.3±1.0	9.7±1.7	0.001		

HbA1c reduction in both groups, with and without treatment intensification. Analysis was stratified by baseline HbA1c (>8.0–9.0% and >9.0%). Having target HbA1c <7% is shown in patients with treatment intensification.

Abbreviations: GP: General Practitioner.

Supplementary Table 10. Drop in HbA1c after diverse types of third anti-diabetic agents in patients managed by GPs (N = 518).

Group	Treatment Type	Change in HbA1c (mean ± sd, n)	Index HbA1c (mean ± sd, n)	HbA1c After Intensification (mean ± sd, n)	P-value
Oral Agents	8.0% ≥ HbA1c ≤ 9.0%	0.3 ± 1.1 (n = 65)	8.6 ± 0.3 (n = 84)	8.2 ± 1.0 (n = 65)	0.620
Insulin / FRC	8.0% ≥ HbA1c ≤ 9.0%	0.2 ± 1.3 (n = 8)	8.6 ± 0.3 (n = 84)	8.3 ± 1.2 (n = 8)	0.620
GLP1RA	8.0% ≥ HbA1c ≤ 9.0%	0.7 ± 1.2 (n = 11)	8.6 ± 0.3 (n = 84)	7.9 ± 1.1 (n = 11)	0.620
Oral Agents	HbA1c > 9.0%	1.6 ± 1.3 (n = 45)	10.4 ± 1.2 (n = 78)	8.9 ± 1.2 (n = 45)	0.376
Insulin / FRC	HbA1c > 9.0%	1.4 ± 2.0 (n = 17)	10.4 ± 1.2 (n = 78)	8.9 ± 2.0 (n = 17)	0.376
GLP1RA	HbA1c > 9.0%	1.11 ± 1.4 (n = 16)	10.4 ± 1.2 (n = 78)	9.2 ± 1.6 (n = 16)	0.376

Abbreviations: GP: General Practitioner; FRC: Fixed Ratio Combination; GLP1RA: Glucagon Like Protein 1 Receptor Agonist; SGLT2: Sodium-Glucose co-transporter2