Appendix

Appendix Table 1. Baseline characteristics of the NHANES-III diabetic population

	N	% missing	Mean*	SE†
Age, years		-	56.2	12.4
Female	4,475,455	-	56.4	2.3
Race: White	6,358,116	-	80.2	1.7
Black	1,284,824	-	16.2	1.1
Other	288,188	-	3.6	1.0
Hispanic ethnicity	763,197	-	9.6	1.1
Age at time of diagnosis, years		7.5	47.5	13.5
Time since diagnosis, years		7.5	9.8	8.8
Risk factors:				
HDL, mg/dl		15.5	46.3	16.9
Total cholesterol, mg/dl		13.5	220.4	52.0
LDL, mg/dl		72.3	140.1	43.5
A1c, %		12.9	7.7	2.1
Systolic blood pressure, mmHg		1.7	133.5	19.4
Diastolic blood pressure, mmHg		1.8	75.5	10.2
Medications:				
Statin	313,435	-	4.0	1.3
Non-statin:	461,041	-	5.8	1.2
Fibrate	428,217	-	5.4	1.1
Bile acid sequestrant	32,823	-	0.4	0.3
Sulfonylurea	3,390,451	-	42.7	2.6
Insulin	1,870,341	-	23.6	2.3
Thiazide	2,029,944	-	25.6	1.7
ACE inhibitor	1,191,999	-	15.0	1.4
Beta blocker	1,029,406	-	13.0	1.7
Calcium channel blocker	1,371,441	-	17.3	1.7

Note. All statistics are weighted to reflect national estimates. The total diabetic population between the ages of 30 and 75 was 7,931,128.
* Means are reported for continuous variables. Percentages are reported for binary variables.
† SE=standard error. Standard deviations are reported for continuous variables.

Appendix Table 2. Model parameters, LDL

	Mean relative change in LDL (%)*	SE relative change in LDL (%)	CV (%)	Back titration (%)	All-cause discontinuation (%)
SMV20	-32.1	1.0	40.4	-	7.3
SMV40	-7.7	1.2	40.4	-	-
ATV40	-20.1	3.9	40.4	6.5**	2.7**
ATV80	-12.1	4.7	40.4	6.5**	2.7**
SMV80/EZE10	-5.7	1.7	40.4	-	-

*We constrained treatment effects to be homogeneous in magnitude for drugs from a common therapeutic class by calculating each subject's response percentile for each drug class initiated, and requiring all subsequent treatments to have matching response percentiles.
**Back-titration rate from high dose to moderate dose observed in IDEAL trial was 13%; discontinuation from high dose was 5.4% [1].
Sources: Relative changes: Calculated from [2; 3]. CV: Calculated from mean reductions and SE or SD (all on relative scale) and averaged across 16 treatment groups: [4-10]. All-cause discontinuation from SMV20: averaged across 5 treatment groups [11-15].

Appendix Table 3. Model parameters, A1c

	# treatment groups	# patients	Mean absolute change	Mean relative change (%)	CV (%)	All-cause discontinuation (%)
Intensify SUL*	-	-	-0.67	-7.5	34.3	7.0‖
Intensify INS*	-	-	-0.76	-8.8	40.2	13.3‖
naïve → Add MET	4	1004	-1.22	-14.5	36.7	22.6
INS → Add MET	2	93	-1.35	-12.5	36.7**	22.6**
SUL → Add MET	8	2460	-0.92	-6.4	76.3	24.0
naïve → Add SUL	4	714	-1.33	-14.9	34.3	14.0
MET → Add SUL	7	1471	-0.68	-8.9	45.0	19.6
naïve → Add TZD	9	744	-1.03	-11.8	52.9	19.9
INS → Add TZD	2	312	-1.00	-11.0	52.9**	19.9**
MET → Add TZD	6	1090	-0.90	-9.7	46.5	17.8
SUL → Add TZD	9	1999	-1.20	-12.9	22.7	16.6
Add INS	9	2521	-1.51	-17.6	40.2	26.6††

* We assumed patients on sulfonylurea or insulin at baseline were on sub-maximal doses, and were thus titrated to higher doses. For subjects on both sulfonylurea and insulin at baseline, we assumed the maximum dose of sulfonylurea was being used, and we only intensified insulin. The efficacy of intensifying sulfonylurea and insulin were assumed to be 50% of the efficacy of beginning sulfonylurea and adding insulin to oral therapy, respectively. We assumed no discontinuation from this step, but rather back-titration rates would be equivalent to half the discontinuation rate associated with beginning each therapy. CVs were assumed to be the same as sulfonylurea monotherapy and the same as adding insulin to oral therapy, respectively.

** Assumed same CV and discontinuation rate as monotherapy due to inadequate numbers of studies or inadequate sample sizes in available studies.

†† Used discontinuation rate on insulin in UKPDS [16] due to extremely low average rate across 9 treatment groups (9.0%)

|| Back-titration rate to baseline dose.

CVs used in sensitivity analysis were: Intensify SUL: 22.0%, Intensify INS: 21.1%, naïve → Add MET: 25.7%, INS → Add MET: 25.7%, SUL → Add MET: 76.3%, naïve → Add SUL: 22.0%, MET → Add SUL: 39.0%, naïve → Add TZD: 26.0%, INS → Add TZD: 26.0%, MET → Add TZD: 36.7%, SUL → Add TZD: 17.7%, Add INS: 21.1%.

Sources for all parameters: naïve → Add MET: [17-19]; INS → Add MET: [20; 21]; SUL → Add MET: [17; 18; 22-25]; naïve → Add SUL: [17; 26-28]; MET → Add SUL: [17; 22; 29-31]; naïve → Add TZD: [32-35]; INS → Add TZD: [36]; MET → Add TZD: [37-40]; SUL → Add TZD: [41-47]; Add INS: [48-51].

Appendix Table 4. Model parameters, blood pressure

	Mean absolute change		Mean relative change (%)		SE relative change (%)		CV (%)		All-cause discontinuation (%)
	SBP	DBP	SBP	DBP	SBP	DBP	SBP	DBP	
THI	8.8	4.4	5.7	4.5	0.2	0.2	43.9	56.0	12.7
ACE	8.5	4.7	5.5	4.8	0.2	0.2	64.2	71.7	10.5
BBL	9.2	6.7	6.0	6.9	0.2	0.2	55.7	57.1	11.6
CCB	8.8	5.9	5.7	6.1	0.1	0.2	65.5	53.5	15.3
THI2*	1.5	0.6	1.0	0.6	0.04	0.03	43.9	56.0	-
ACE2*	1.5	1.0	1.0	1.1	0.03	0.04	64.2	71.7	-
BBL2*	1.9	1.1	1.3	1.2	0.05	0.04	55.7	57.1	-
CCB2*	2.9	2.0	2.0	2.2	0.05	0.06	65.5	53.5	-

* Twice standard dose

Note: Relative efficacy of 2nd, 3rd, and 4th drug classes added to existing therapy was: 84.0%, 70.6%, 59.3% (systolic), and 65.0%, 42.2%, 27.5% (diastolic).

CVs used in sensitivity analysis for systolic reductions were: 26.7% (THI), 37.1% (ACE), 43.2% (BBL), and 40.9% CCB, and for diastolic reductions: 33.4% (THI), 34.6% (ACE), 25.1% (BBL), and 33.0% (CCB).

Sources: Mean changes and SE: [52]; CV THI: [53-63]; ACE: [53; 54; 56-59; 62; 64-71]; BBL: [53-55; 57-59; 64; 72-75], CCB: [53; 54; 56-60; 64; 66; 70; 71; 75-78]. All-cause discontinuation: [79].

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