Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: TODAY Study Group. A clinical trial to maintain glycemic control in youth with type 2 diabetes. N Engl J Med 2012;366:2247-56. DOI: 10.1056/NEJMoa1109333.

Table of Contents

APPENDIX A. Listing of the TODAY Study Group

The following individuals and institutions constitute the TODAY Study Group (* indicates principal investigator or director):

CLINICAL CENTERS Baylor College of Medicine: S. McKay*, B. Anderson, C. Bush, S. Gunn, M. Haymond, H. Holden, S.M. Jones, N. Kamath, S. McGirk, B. Schreiner, S. Thamotharan, M. Zarate **Case Western Reserve University:** L. Cuttler*, E. Abrams, T. Casey, W. Dahms (deceased), A. Davis, A. Haider, C. Ievers-Landis, B. Kaminski, M. Koontz, S. MacLeish, P. McGuigan, S. Narasimhan, D. Rogers **Children's Hospital Los Angeles:** M. Geffner*, V. Barraza, N. Chang, B. Conrad, D. Dreimane, S. Estrada, L. Fisher, E. Fleury-Milfort, S. Hernandez, B. Hollen, F. Kaufman, E. Law, V. Mansilla, D. Miller, C. Muñoz, R. Ortiz, A. Ward, K. Wexler, Y.K. Xu, P. Yasuda **Children's Hospital of Philadelphia:** L. Levitt Katz*, R. Berkowitz, S. Boyd, B. Johnson, J. Kaplan, C. Keating, C. Lassiter, T. Lipman, G. McGinley, H. McKnight, B. Schwartzman, S. Willi **Children's Hospital of Pittsburgh:** S. Arslanian*, F. Bacha, S. Foster, B. Galvin, T. Hannon, A. Kriska, I. Libman, M. Marcus, K. Porter, T. Songer, E. Venditti **Columbia University Medical Center:** R. Goland*, R. Cain, I. Fennoy, D. Gallagher, P. Kringas, N. Leibel, R. Motaghedi, D. Ng, M. Ovalles, M. Pellizzari, K. Robbins, D. Seidman, L. Siegel-Czarkowski, P. Speiser **Joslin Diabetes Center:** L. Laffel*, A. Goebel-Fabbri, M. Hall, L. Higgins, J. Keady, M. Malloy, K. Milaszewski, L. Orkin **Massachusetts General Hospital:** D.M. Nathan*, A. Angelescu, L. Bissett, C. Ciccarelli, L. Delahanty, V. Goldman, O. Hardy, M. Larkin, L. Levitsky, R. McEachern, D. Norman, D. Nwosu, S. Park-Bennett, D. Richards, N. Sherry, B. Steiner **Saint Louis University:** S. Tollefsen*, S. Carnes, D. Dempsher, D. Flomo, V. Kociela, T. Whelan, B. Wolff **State University of New York Upstate Medical University:** R. Weinstock*, D. Bowerman, S. Bristol, J. Bulger, J. Hartsig, R. Izquierdo, J. Kearns, R. Saletsky, P. Trief **University of Colorado Denver:** P. Zeitler* (Steering Committee Chair), N. Abramson, A. Bradhurst, N. Celona-Jacobs, M. Downey, J. Higgins, M. Kelsey, G. Klingensmith, K. Nadeau, T. Witten **University of Oklahoma Health Sciences Center:** K. Copeland* (Steering Committee Vice-Chair), E. Boss, R. Brown, J. Chadwick, L. Chalmers, S. Chernausek, A. Hebensperger, C. Macha, R. Newgent, A. Nordyke, D. Olson, T. Poulsen, L. Pratt, J. Preske, J. Schanuel, S. Sternlof **University of Texas Health Science Center at San Antonio:** J. Lynch*, N. Amodei, R. Barajas, C. Cody, D. Hale, J. Hernandez, C. Ibarra, E. Morales, S. Rivera, G. Rupert, A. Wauters **Washington University in St Louis:** N. White*, A. Arbeláez, D. Flomo, J. Jones, T. Jones, M. Sadler, M. Tanner, A. Timpson, R. Welch **Yale University:** S. Caprio*, M. Grey, C. Guandalini, S. Lavietes, P. Rose, A. Syme, W. Tamborlane

COORDINATING CENTER George Washington University Biostatistics Center: K. Hirst*, S. Edelstein, P. Feit, N. Grover, C. Long, L. Pyle

PROJECT OFFICE National Institute of Diabetes and Digestive and Kidney Diseases: B. Linder*

CENTRAL UNITS Central Blood Laboratory (Northwest Lipid Research Laboratories, University of Washington): S.M. Marcovina*, J. Harting **DEXA Reading Center (University of California at San Francisco):** J. Shepherd*, B. Fan, L. Marquez, M. Sherman, J. Wang **Diet Assessment Center (University of South Carolina):** M. Nichols*, E. Mayer-Davis, Y. Liu **Echocardiogram Reading Center:** J. Lima*, S Gidding, J. Puccella, E. Ricketts **Fundus Photography Reading Center:** R. Danis*, A. Domalpally, A. Goulding, S. Neill, P. Vargo **Lifestyle Program Core (Washington University):** D. Wilfley*, D. Aldrich-Rasche, K. Franklin, C. Massmann, D. O'Brien, J. Patterson, T. Tibbs, D. Van Buren

OTHER Hospital for Sick Children, Toronto: M. Palmert **Medstar Research Institute, Washington DC:** R. Ratner **Texas Tech University Health Sciences Center:** D. Dremaine **University of Florida:** J. Silverstein

APPENDIX B. Study Design Details and Overview of the Lifestyle Program

Participants were recruited from the clinical populations of the various sites as well as outreach to other sizable nearby pediatric clinics. Participants meeting eligibility criteria at screening (see below) entered a 2-6 month single blind run-in period designed to: (1) provide uniform and high-quality standard diabetes education (SDE) to all patients and their family members; (2) titrate the dose of metformin (single-blind) as tolerated to a target dose of 1000 mg twice a day, with a minimum dose for randomization of 500 mg twice a day; (3) discontinue all other diabetes medications; (4) document adherence to medication by pill count and study visit attendance. To proceed to randomization, participants had to demonstrate 80% medication adherence for 6 weeks, have no more than 2 missed study visits, maintain an HbA1c $\leq$ 8% for a minimum of 2 months on metformin alone, and demonstrate mastery of SDE. Successful run-in participants who provided appropriate informed consent and assent were randomized 1:1:1 to (1) metformin alone, (2) metformin plus rosiglitazone, or (3) metformin plus an intensive lifestyle intervention.

Major Eligibility Criteria for the TODAY Trial

Major inclusion criteria were:

1. Aged10-17 years inclusive at randomization.
2. Diagnosis of T2D by standard laboratory criteria (9) for less than 2 years by the time of randomization. For asymptomatic patients with a normal fasting glucose but elevated two-hour glucose during an OGTT, HbA1c must be $\geq$ 6%. Subjects being treated with diabetes medication for whom diagnostic serum glucose documentation was not available were eligible if HbA1c was $\geq$ 8% at the time of diagnosis.
3. BMI $\geq 85^{th}$ percentile.
4. Fasting C-peptide at screening > 0.6 ng/mL and absence of pancreatic autoimmunity (both GAD and ICA512).
5. A family member or adult closely involved in the daily activities of the child must consent to participate in the child's treatment. The inclusion of a parent or caregiver has been shown to be important to the success of lifestyle change (10), particularly in ethnic minority groups (11). In addition, parental weight change is associated with child weight change (12).
6. Fluency in English or Spanish due to the intensive personal interactions required for in the run-in and lifestyle intervention.
7. Signed parental informed consent form and minor child informed assent form.

Major exclusion criteria were:

1. Creatinine clearance < 70 mL/min.
2. Any hepatic transaminase > 2.5 the upper limit of normal.
3. Diabetic ketoacidosis at any time after diagnosis except for a single episode related to a significant medical illness.
4. Use of various medications: (a) inhaled glucocorticoids at dose above 1000 mcg daily fluticasone equivalent, (b) oral glucocorticoids within the last 60 days or more than 20 days during the past year, (c) medication(s) known to affect insulin sensitivity or secretion within the last 30 days, (d) medication(s) known to cause weight gain within the last 30 days, (e) anabolic steroids within the past 60 days, (f) weight-loss medication(s) within the last 30 days or participation in a formal weight-loss program, or (g) medication(s) known to affect the metabolism of study drug.
5. Presence of various conditions despite appropriate medical therapy: (a) systolic blood pressure $\geq$ 150 mmHg or diastolic blood pressure $\geq$ 95 mmHg, (b) abnormal lipid levels (total cholesterol > 300 mg/dL, LDL > 190 mg/dL or triglycerides > 800 mg/dL), (c) hematocrit < 30% or hemoglobin < 10 gm/dL.
6. Abnormal reticulocyte count or HbA1c chromatogram indicating abnormal hemoglobin variants other

than heterozygosity for S and C.
7. Genetic syndrome or disorder known to affect glucose.
8. Inability of either participant or family member to comprehend the grade level used in the intervention materials.
9. Females who are pregnant, planning to become pregnant within two years of enrollment, or who admit sexual activity without appropriate contraception.
10. Physical limitations preventing participant from being randomized to the lifestyle intervention.
11. Other significant organ system illness or condition (including psychiatric or developmental disorder) that, in the opinion of the investigator would prevent full participation.

Participants were recruited and enrolled over a four-year period and treated and followed for a minimum of 2 years and maximum of 6 years. The primary outcome was time to treatment failure, defined in one of two ways: (1) all regularly scheduled HbA1c values ≥ 8% over a 6-month period or (2) the inability to wean from temporary insulin therapy within 3 months following acute metabolic decompensation. Participants reaching the primary outcome were treated with insulin is instituted as add-on therapy, in addition to continuation of metformin. The study provided treatment of dyslipidemia, hypertension, and microalbuminuria following specified algorithms.

Overview of the Lifestyle Program

The lifestyle program was designed to work with pharmacotherapy to improve diabetes control in youth 10 to 17 years of age through sustained, moderate weight loss (7-10% of initial body weight or the equivalent for youth still growing in height). Primary behavior-change targets included energy balance behaviors (dietary and physical activity) and family involvement/support. The program promoted small, successive changes in participant's dietary and physical activity behaviors through the use of evidence-based behavior change strategies such as self-monitoring (recording target behaviors on forms called "Lifestyle Logs" and graphing weight changes), goal setting, reinforcement for goal achievement, stimulus control, social support, problem solving, and motivational techniques. Trained interventionists called PALs (Personal Activity/nutrition Leaders) administered the program. PALs were supervised by a psychologist on the site study team.

Diet modification. The program used a calorie deficit diet, modified for use with youth with type 2 diabetes, called the Traffic Light Plan, which is an adaptation of Goldfield and Epstein's Traffic Light Diet (Goldfield GS, Epstein LH. Management of obesity in children. New York: Guilford Press; 2002). In the Traffic Light Diet, foods are assigned colors of the traffic light depending upon their nutritional quality. For example, foods containing 5 or more grams of fat, sugary cereals, energy-dense, non-nutritious snacks, and soft drinks are classified as RED (Stop and think) foods. The Traffic Light Plan for the program was designed in close collaboration with TODAY study dietitians and diabetes educators in order to help families make healthier food choices and decrease calorie consumption to within 1200 to 1500 calories, adjusted upward depending upon baseline weight. Participants were encouraged to decrease the number of RED foods consumed daily and to increase the consumption of nutritious foods identified by the traffic light colors GREEN (Go – highly nutritious, low calorie-dense foods), or YELLOW (Caution – good for you but watch portion sizes; nutritious higher calorie foods or "starchy" foods). A "free-choice" approach to changing eating habits and behaviors built upon existing preferences. For example, rather than "prescribing" particular foods, PALs listened to the participants to lean about preferences, traditions, and beliefs that impacted eating habits. Using this information, PALs assisted participants in making gradual adjustments to existing patterns of behavior to promote healthy lifestyle behaviors.

Physical activity modification. The physical activity target was 200 minutes per week of moderate-vigorous intensity activity for most participants and up to 300 minutes per week for those participants who entered the study already engaging in some regular, physical activity. Participants were encouraged

to engage in more lifestyle activities such as walking pets, biking to school, and using stairs instead of elevators, as well as to increase involvement in planned, moderate- to higher-intensity activities. Activities were categorized using a green-yellow-red traffic light color scheme according to intensity, similar to that used to classify foods in the Traffic Light Plan. Beyond the general focus on aerobic activity, strength training through the use of resistance bands was also introduced.

Family support. A supportive family member was identified to partner with each TODAY participant and attend study visits. In the lifestyle program, the adult and the youth each had time to work alone with their PAL. Families were taught to use praise and to develop a family-based reward system to shape and reinforce changes in dietary and physical activity behaviors. In addition to supporting the youth's lifestyle behavior changes through positive reinforcement, the adult partner was also encouraged to engineer a home environment conducive to healthy lifestyle behaviors and to involve all members of the household in support of the youth's behavior change efforts. Overweight adults were encouraged to make personal efforts to lose weight but were not required to do so.

Treatment duration and dose. The lifestyle program took a chronic care approach to weight control, treating participants for a minimum of two years. The program was composed of three treatment phases that varied in terms of intensity of treatment contact and in terms of the types of educational materials used to support behavior change targets. The first phase was Lifestyle Change (LC) which began at randomization and lasted for 6-8 months. During the LC phase, participants attended weekly in-person sessions lasting 60-90 minutes and including time for education regarding healthy eating, physical activity, and family support as well as the teaching and practice of behavior and cognitive-behavioral change techniques to facilitate weight loss. The second phase was Lifestyle Maintenance (LM) that lasted another 6-8 months. The LM phase was characterized by a decrease in the frequency of in-person contacts to bi-weekly, lasting about 60 minutes each, and education and behavior change targets centered on the introduction of weight maintenance skills such as self-monitoring of weight, relapse prevention, and the enlistment of peer support in weight control efforts. The third phase was Continued Contact (CC) that lasted until the end of the TODAY trial. In-person contacts, lasting 45 to 60 minutes each, occurred monthly for the first 12 months and quarterly thereafter. Participants were encouraged to take an increasingly active role in identifying barriers to weight control and applying problem-solving skills within and between visits to improve healthy lifestyle behaviors.

Educational materials. Educational materials were developed for the TODAY study to support the lifestyle program treatment goals. New behavior change lessons were provided to program participants each week during the LC phase (a total of 24 lessons), twice per month in the LM phase (12 lessons), and once a month for twelve months followed by once every three months in the CC phase. The program materials were presented to families in a standard order in the LC and LM phases. In the CC phase, families chose specific lesson materials from a "library" of topics depending upon each family's needs. To accommodate the developmental and cognitive differences between the youth and the adult, two similar, yet slightly different versions of program materials were developed. Adults received information such as positive parenting techniques and the importance of being a role model for healthy lifestyle behaviors. The materials also incorporated interactive exercises and quizzes to engage participants in the learning process and to assess mastery of the information.

Adjustments in treatment dose and addressing barriers to behavior change. Given naturally occurring disruptions such as vacation or illness, families were allowed up to 8 months in the LC and LM phases to receive the intended educational materials before moving on to the next phase. Transition between phases was determined by time from randomization, not by mastery of material or attainment of behavioral goals. However, behavior change information and the opportunity to practice the skills needed to acquire healthy lifestyle goals were introduced in novel ways during each phase of the program. Thus, participants who did not master a concept or acquire a dietary or physical activity goal during an earlier

phase had opportunities to learn the necessary skills in later phases of the intervention. For participants who experienced weight gain or were still overweight and requested additional support to focus on further weight loss in the later phases, the frequency of in-person visits could be temporarily increased for 4-8 weeks. In addition to adjusting treatment dose as a means of overcoming barriers to the achievement of behavior change goals, PALs could also utilize a "toolbox" of strategies, equipment, services, or goods needed for overcoming barriers to meeting treatment goals. Up to $150.00 was available annually per TODAY family.

APPENDIX C. Baseline Characteristics* of 699 Participants, Overall and by Treatment Group

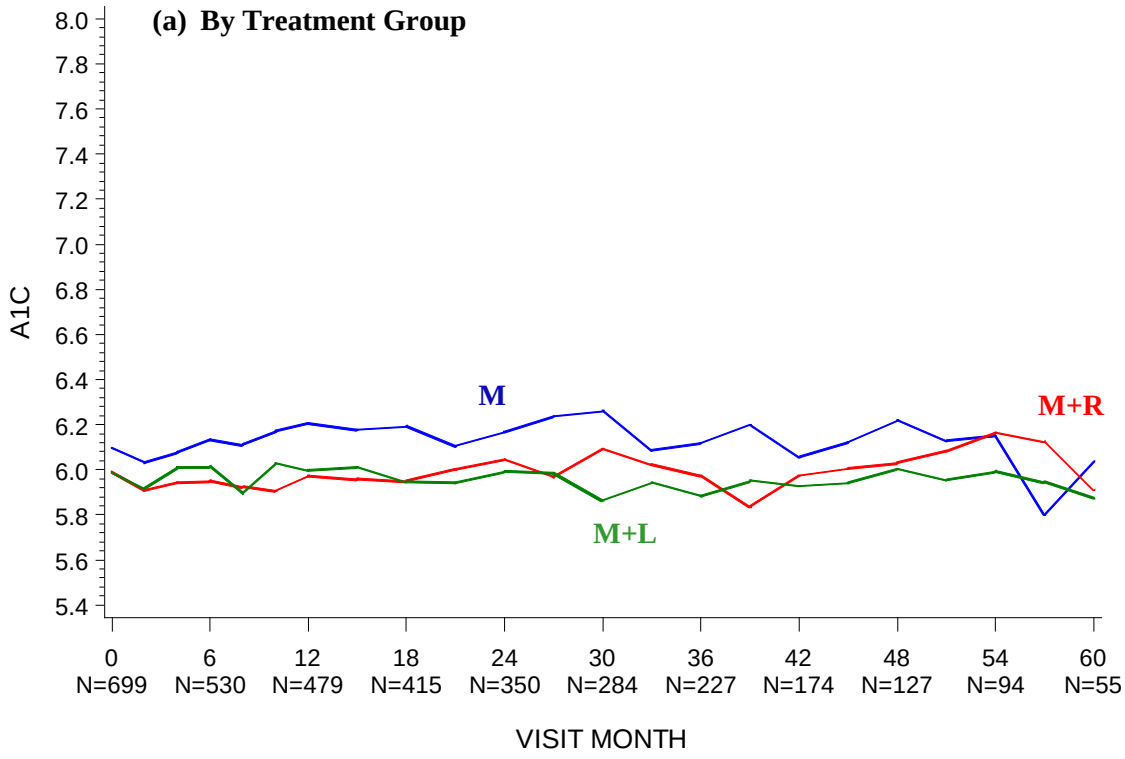
Characteristics	Overall (n=699)	Treatment Group M (n=232)	M+R (n=233)	M+L (n=234)	p†
Age (years)	14.0 (2.0)	14.1 (1.9)	14.1 (2.1)	13.8 (2.0)	.26
Tanner stage 4 or 5	88.0%	88.8%	88.8%	86.3%	.63
BMI Z-score	2.23 (0.47)	2.27 (0.45)	2.22 (0.49)	2.18 (0.46)	.12
Percent overweight‡	78.9 (37.3)	82.1 (38.3)	79.1 (38.1)	75.6 (35.3)	.18
Duration of diabetes (months)	7.8 (5.8)	7.8 (6.0)	8.0 (5.7)	7.6 (5.8)	.78
Female sex	64.7%	62.9%	65.2%	65.8%	.79
Race/ethnicity					.65
White Non-Hispanic	20.3%	21.1%	20.2%	19.7%	
Black Non-Hispanic	32.5%	33.2%	27.5%	36.7%	
Hispanic	39.7%	39.2%	43.3%	36.7%	
American Indian	5.9%	5.2%	6.9%	5.6%	
Asian	1.6%	1.3%	2.1%	1.3%	
Household income					.17
< $25,000	41.5%	38.9%	41.9%	43.6%	
$25,000-49,999	33.7%	39.9%	29.8%	31.3%	
> $49,999	24.8%	21.2%	28.3%	25.1%	
Parent/guardian highest level education					.55
12^{th} grade or less	26.5%	26.2%	26.3%	27.1%	
High school graduate/GED/business/technical	25.1%	24.9%	21.5%	28.8%	
Some college/associates degree	31.8%	33.6%	34.2%	27.5%	
Bachelors degree or higher	16.6%	15.3%	18.0%	16.6%	
Nuclear family history of diabetes	59.6%	57.5%	58.8%	62.5%	.53
Nuclear family + grandparents history of diabetes	89.5%	92.5%	88.5%	87.3%	.16

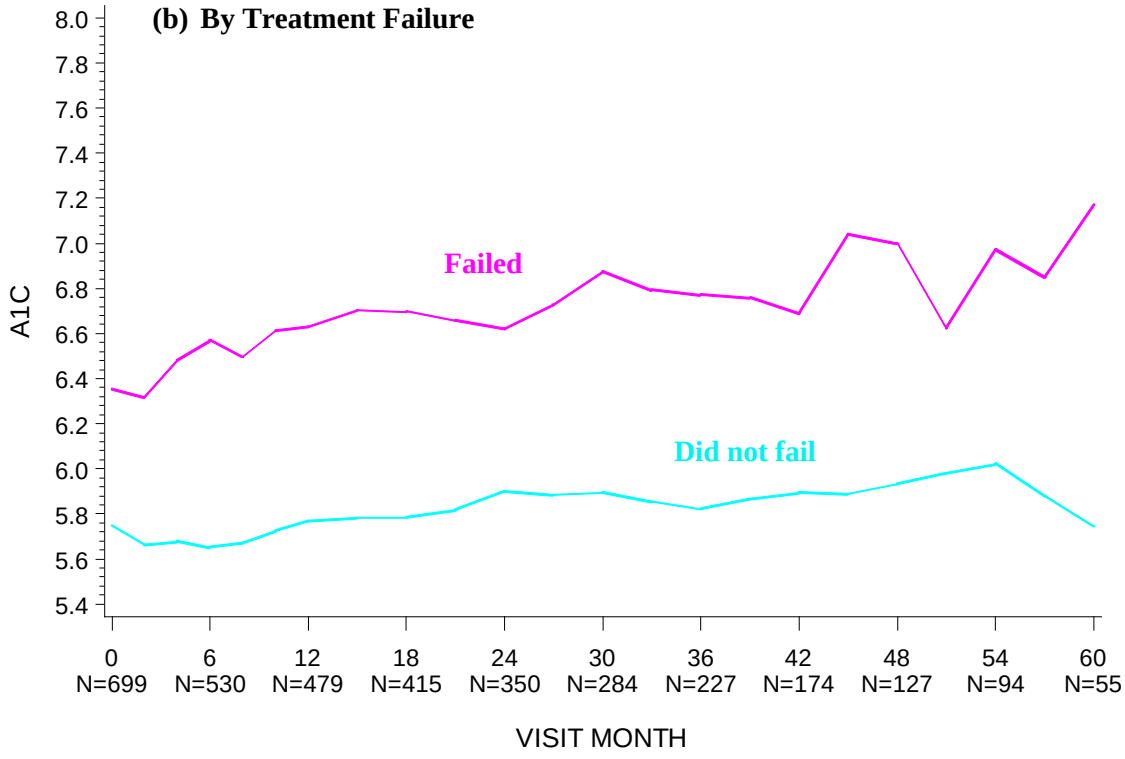
* Values expressed as mean (SD) or percent (%).
† P-values based on analysis of variance or chi-square.
‡ Percent overweight calculated as BMI minus BMI at 50th percentile for age and sex in the numerator, divided by 50th percentile, and multiplied by 100%.

APPENDIX D. Reason for Failure and Median Time to Failure by Treatment Group

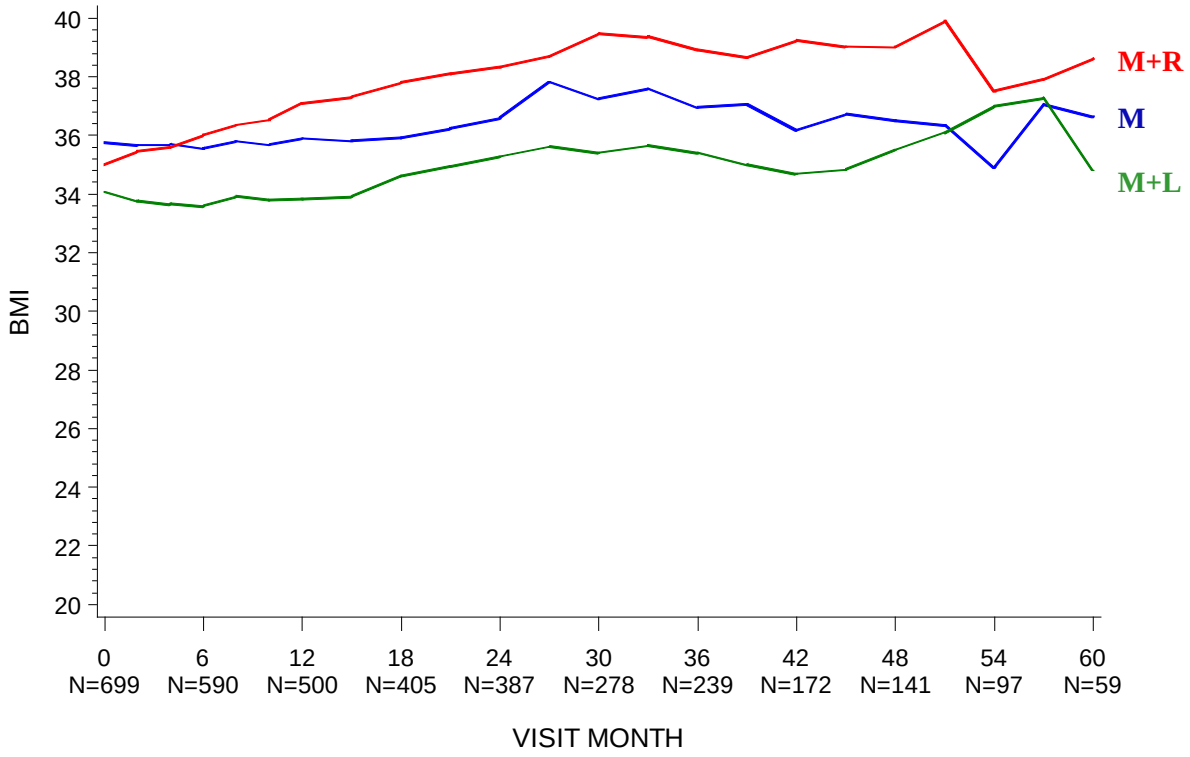
	Metformin alone	Metformin + rosiglitazone	Metformin + lifestyle	p-value
Reason for failure (%)				0.29
Persistent elevation of A1c	84.2%	75.6%	78.9%	
Metabolic decompensation	15.8%	24.4%	21.1%	
Median time to failure (months)	10.3	12.0	11.8	0.63

APPENDIX E. Figures of Mean A1c Over Time in Study (all values prior to failure)

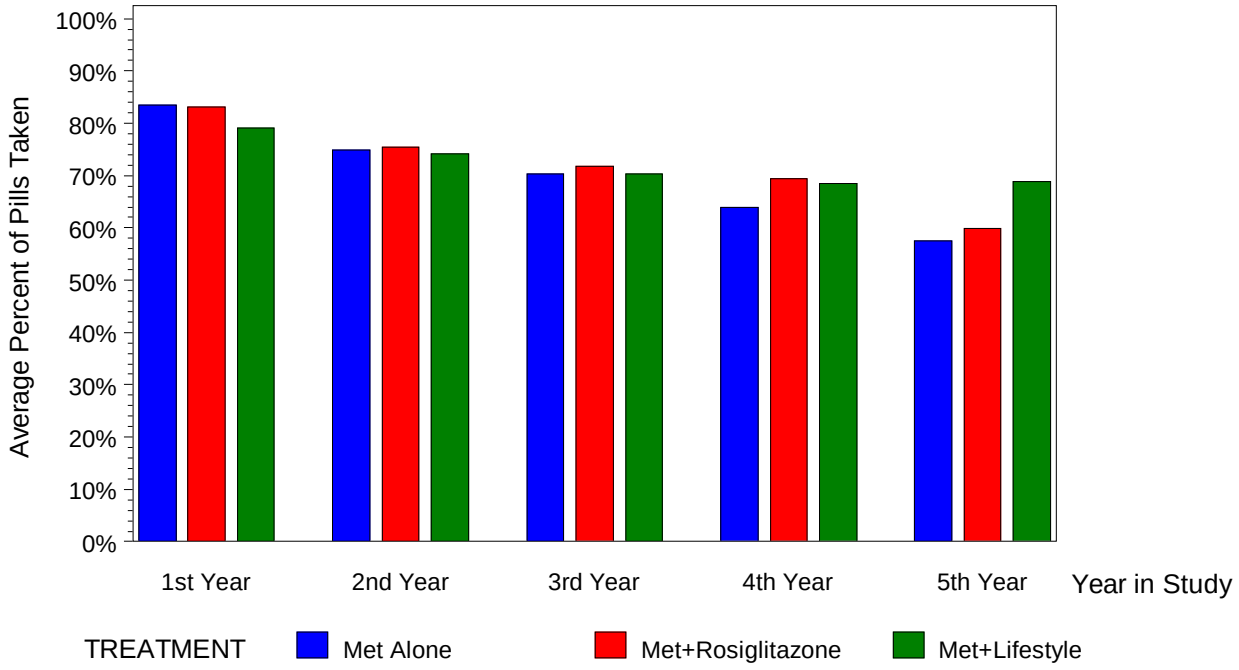




APPENDIX F. Figure of Mean BMI Over Time in Study by Treatment Group (all values prior to failure)



APPENDIX G. Medication Adherence Over Time in Study by Treatment Group



APPENDIX H. Secondary Outcomes at Baseline and 24 Months by Treatment Group

	M		M+R		M+L	
	N	50th (25th, 75th)	N	50th (25th, 75th)	N	50th (25th, 75th)
Total cholesterol (mg/dL)						
Baseline	231	141 (124, 163)	233	146 (125, 167)	234	145 (127, 162)
Month 24	193	153 (135, 178)	187	154 (126, 179)	203	153 (130, 171)
LDL (mg/dL)						
Baseline	230	83 (68, 101)	231	80 (68, 106)	233	84 (69, 100)
Month 24	193	88 (73, 110)	186	84.5 (67, 108)	203	88 (69, 104)
HDL (mg/dL)						
Baseline	230	36 (31, 43)	231	38 (33, 44)	233	38 (34, 44)
Month 24	193	39 (33, 46)	187	40 (34, 49)	203	40 (35, 46)
Triglycerides (mg/dL)						
Baseline	231	99 (70, 147)	233	98 (67, 138)	234	87.5 (63, 128)
Month 24	193	102 (72, 158)	187	104 (68, 168)	203	92 (64, 148)
Urine albumin/creatinine (mg/g)						
Baseline	231	7 (4, 15)	230	6 (4, 13)	231	6 (4, 10)
Month 24	194	7 (4, 15)	183	7 (4, 19)	200	6 (4, 14)
1/fasting insulin (mL/μU)						
Baseline	228	.036 (.025, .050)	228	.040 (.028, .064)	231	.040 (.027, .067)
Month 24	167	.037 (.023, .061)	157	.049 (.031, .068)	167	.039 (.027, .064)
Insulinogenic index*						
Baseline	220	1.02 (.47, 1.98)	223	.92 (.47, 1.58)	221	.87 (.47, 1.89)
Month 24	150	.75 (.33, 1.39)	147	.83 (.28, 1.38)	155	.71 (.26, 1.69)
Systolic blood pressure						
Baseline	232	114 (106.5, 122)	233	113 (106, 121)	234	112 (105, 120)
Month 24	200	114 (107.5, 123.5)	192	115.25 (109, 122.5)	209	114 (108.5, 121)
Diastolic blood pressure						
Baseline	232	66.5 (60.75, 72.25)	233	67 (61.5, 72)	234	65 (61, 71)
Month 24	200	68 (62.75, 73.75)	192	69.75 (64.5, 74.5)	209	68 (62, 74)
DEXA fat mass (kg)†‡						
Baseline	157	34.2 (26.9, 39.4)	160	32.3 (26.1, 40.6)	170	31.5 (25.5, 38.3)
Month 24	130	35.2 (29.5, 42.1)	123	38.3 (29.4, 46.4)	134	33.2 (25.3, 39.0)
DEXA lean mass (kg)†						
Baseline	157	55.6 (46.8, 63.3)	160	55.1 (45.3, 63.0)	170	53.1 (44.6, 61.6)
Month 24	130	55.2 (48.9, 66.0)	123	57.5 (49.3, 64.8)	134	53.7 (47.1, 61.5)

Results expressed as median (25^{th} and 75^{th} percentiles)

* Insulinogenic index was calculated as $(I_{30\ mins} - I_{0\ mins}) / (G_{30\ mins} - G_{0\ mins})$; differences in either numerator or denominator < 0 were set to missing.

† DEXA scans could not be obtained on participants weighing more than 300 pounds (136 kg), the upper limit in size set by the machine manufacturers. Scans were considered invalid if a body part (e.g., arm, leg) was completely off or partially off the scanner, there was hand-hip overlap, or there was motion or movement during the scan.

‡ Significant change from baseline across treatment groups ($p<.05$); pairwise comparison showed M+R significantly different from M+L.