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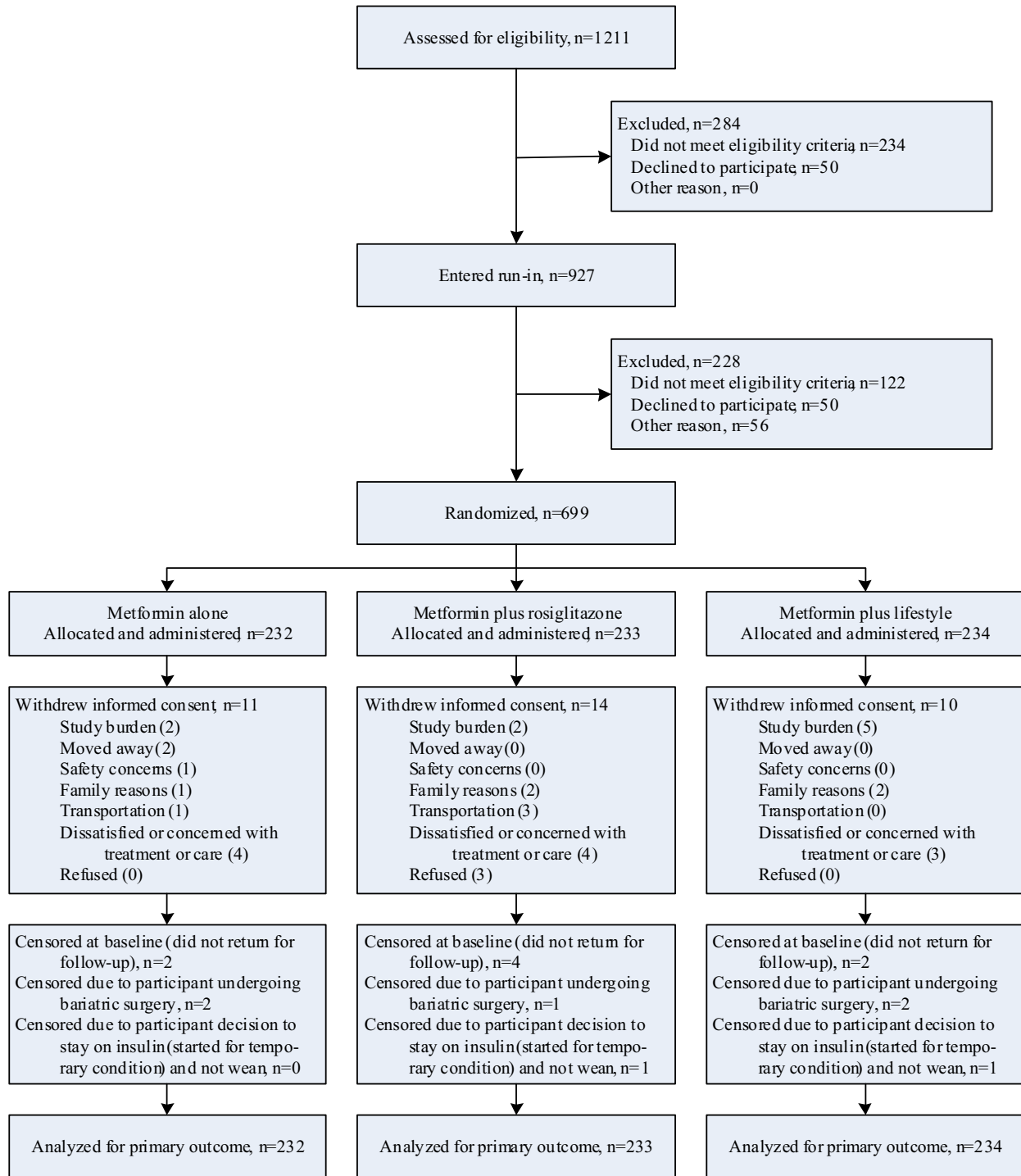
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TODAY CONSORT Diagram



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Definitions and Study-Specific Responses to Targeted Adverse Events (AEs)

Anemia may be an adverse effect of either metformin or rosiglitazone. Hemoglobin and hematocrit were determined at baseline, 2 months, 6 months, and annually after the first year. Anemia was defined as a hematocrit <30.0%, hemoglobin <10 mg/dL, a decline in hematocrit by 4 percentage points from the baseline visit, or a decline of hemoglobin by 2 g/dL from the baseline visit. If anemia was detected, a CBC with differential was performed within one month. If anemia was confirmed, a vitamin B12 level, examination of the blood smear, and other tests (as indicated) were performed at the discretion of the physician to help determine the etiology of the anemia. These additional tests were not collected for analysis as part of the protocol. Vitamin B12 and/or iron supplementation were administered as clinically indicated. If anemia persisted for more than 6 months despite appropriate therapy, the doses of rosiglitazone and metformin were reduced, and hemoglobin and hematocrit were rechecked in 3 months. If anemia was not resolved after 3 months, rosiglitazone was stopped and metformin reduced again. If at any time the hematocrit was less than 27%, rosiglitazone was discontinued and the metformin dose reduced. If anemia persisted despite the lowest study dose of metformin and no rosiglitazone, the study medical consultant was contacted to discuss what action to take, if any.

If anemia resolved, the participant's study medication doses were titrated up to their prior doses one step at a time as long as anemia did not recur. If anemia did recur, a permanent reduction in dose of both study medications was implemented.

Renal impairment increases the risk of lactic acidosis associated with metformin. Serum creatinine was determined at baseline and annually. Creatinine clearance (CrCl) was calculated using the Cockcroft-Gault formula.

$$\text{CrCl} = [(140 - \text{age}) \times \text{IBW in kg}] \div (72 \times \text{Cr}_s \text{ in mg/dL}) \text{ for boys}$$

$$\text{CrCl} = [(140 - \text{age}) \times \text{IBW in kg}] \div (85 \times \text{Cr}_s \text{ in mg/dL}) \text{ for girls}$$

where Cr_s = serum creatinine and IBW=ideal body weight.

If CrCl was <70 mL/minute per 1.73 m² or the Cr_s was >1.5 mg/dL, study medication was discontinued for 2 weeks and the CrCl repeated. If the repeat CrCl was ≥ 70 mL/minute per 1.73 m² and the serum creatinine was ≤ 1.5 mg/dL, study medication was resumed. If the repeat CrCl was again <70 mL/minute per 1.73 m² or Cr_s >1.5 mg/dL, or if CrCl fell again to <70 mL/minute per 1.73 m², study medication was permanently discontinued.

Hepatotoxicity increases the risk of metformin-associated lactic acidosis and drugs of the thiazolidinedione class (but not rosiglitazone) have been associated with hepatotoxicity. SGPT/ALT and SGOT/AST were obtained every two months for the first year and every three months thereafter. If ALT and AST were <1.5 times the upper limit of normal (X ULN), no actions or change in monitoring were implemented. If either ALT or AST increased to 1.5-2.5 X ULN, study medication was continued and ALT and AST were repeated within two weeks. Blood was also obtained for hepatitis A, B, and C titers, which were run and reported if the repeated AST and/or ALT were >1.5 X ULN. Also, if ALT and/or AST were still >1.5 X ULN, an evaluation to rule out liver disease (other than NAFLD) was done locally. The minimum expected evaluation included ceruloplasmin, alpha-1 antitrypsin phenotype, ANA, anti-smooth muscle antibody, anti-LKM antibody, iron, and TIBC, if these had not been previously done. These evaluations were reviewed locally and by the Safety and Monitoring Committee (SMC). Gastroenterology (GI) consultation was obtained, as indicated. If hepatitis titers were positive for hepatitis B or C or the evaluation for liver disease was abnormal (other than for NAFLD), study medications were discontinued. If hepatitis titers were positive for hepatitis A, study medication was

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continued unless ALT and/or AST rose to >2.5 X ULN. For ALT and/or AST 1.5-2.5 X ULN while still on study medication, ALT and AST were repeated monthly for six months, and if stable (that is, not >2.5 X ULN) during that time, routine monitoring was resumed.

If either ALT or AST or both were >2.5 X ULN at any time after randomization, study medication was stopped immediately, pending further evaluation. ALT and AST were repeated in 2 weeks. If the AST/ALT were still elevated, evaluation for hepatitis and other liver disease was obtained, as above, if it had not already been done.

- 1.If the ALT and AST repeated at two weeks returned to <1.5 X ULN, study medication (metformin and/or rosiglitazone) and routine transaminase monitoring was resumed.

- 2.If the repeat ALT and AST decreased to 1.5-2.5 X ULN, study medication was resumed and monitoring continued as above for this transaminase level; that is, monthly for six months, and if stable, routine monitoring was resumed.

- 3.If the ALT and/or AST was still >2.5 X ULN, the participant remained off study medication for as long as the AST and/or ALT were >2.5 X ULN.

If AST and ALT subsequently decreased to <2.5 X ULN, and if the evaluation for liver disease revealed an identifiable and reversible cause of transaminase elevation (for example, hepatitis A or viral disease), then study medication was resumed and AST/ALT were monitored monthly for six months. However, if AST and ALT decreased to <2.5 X ULN, and the evaluation for liver disease did not reveal an identifiable and reversible cause of transaminase elevation, rosiglitazone was permanently discontinued. Metformin could be resumed with monthly monitoring for six months. If AST or ALT increased to >2.5 X ULN a second time without an identifiable and reversible cause of transaminase elevation, then study medication (both rosiglitazone and metformin) were permanently discontinued.

Gastrointestinal symptoms are a common occurrence with metformin. To minimize GI side effects, as part of run-in, metformin was gradually increased to 1,000 mg BID in steps of 500 mg/day every week. At randomization, participants were continued on the highest tolerable dose of metformin. If GI side effects developed after randomization and were mild, the participants were encouraged to remain on the study medication. If GI side effects were moderate or difficult to tolerate, metformin (but not rosiglitazone) was reduced by 500 mg per day. If symptoms persisted, additional reductions of metformin were recommended. If GI symptoms resolved, metformin was restarted and re-escalated by 500 mg per day each week until reaching the previously tolerated dose. If, after re-escalation of the metformin dose, moderate to severe GI symptoms returned, metformin was permanently decreased to the tolerable dose.

Edema and fluid retention may be a side effect of rosiglitazone. Edema was considered clinically significant if there was pitting edema above the participant's ankle. If clinically significant edema occurred, rosiglitazone was temporarily discontinued. An evaluation for potential causes of edema was conducted. If edema resolved and no contraindication for rosiglitazone was identified, rosiglitazone was resumed at the previous dose. If a second episode of clinically significant edema occurred after restarting rosiglitazone, rosiglitazone was permanently discontinued for the duration of the study.

Macular edema was reported as a potential adverse effect of rosiglitazone [Idris I, Warren G, Donnelly R. Association between thiazolidinedione treatment and risk of macular edema among patients with type 2 diabetes. *Arch Intern Med.* 2012; 172:1005-1011]. All TODAY participants had a routine visual acuity test of each eye with their eyeglasses performed either at the 4-month or 6-month visit and annually. Participants who reported visual problems, had deterioration of visual acuity of two lines or greater on the Snellen chart in either or both eyes, or had clinically significant peripheral edema were

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referred for an ophthalmology examination, including dilated funduscopy. If ophthalmologic examination indicated clinically significant macular edema, rosiglitazone was discontinued. This did not occur in any participant.

Heart failure was defined based on clinical evidence or an echocardiogram. If clinical evidence of heart failure occurred, the participant was referred to a cardiologist. In addition, if peripheral edema (see definition above) was noted, cardiology evaluation including an echocardiogram, if indicated, was recommended. If there was clinical or echocardiographic evidence of heart failure, study drug was discontinued.

Weight gain is a potential adverse effect of rosiglitazone and is also a part of the underlying problem in adolescents and young adults with type 1 diabetes. If the weight gain was considered to be unacceptably excessive or resulted in a 10% or greater increase in BMI (kg/m^2) since the most recent scheduled study visit, this was considered an adverse event (AE), and the study dietitian and/or CDE met with the participant (and family, if appropriate) for 1-2 extra visits to implement additional dietary or other interventions. Excessive weight gain was considered a continuous and cumulative event. Each additional episode of a 10% or greater increase in BMI since the most recent scheduled study visit represented a new AE.

Recurrent mild hypoglycemia was defined as more than two episodes per week or more than five episodes per month of symptomatic hypoglycemia with documented blood glucose <60 mg/dL, but not meeting the criteria for severe hypoglycemia. If the TODAY study staff felt that repeated mild hypoglycemia was clinically significant, this was discussed with the SMC to determine if any action was warranted.

Psychological adverse events were defined as either 1) a score >18 on the Beck Depression Inventory (BDI) or 2) a score >15 on the Children's Depression Inventory (CDI) or 3) a response to item 14 of the BDI or item 9 of the CDI that indicated thoughts of suicide, specifically, a response of 'I have thoughts of killing myself, but I would not carry them out', 'I would like to kill myself', or 'I would kill myself if I had the chance'.

Definitions of TODAY Study-Specific Serious Adverse Events (SAEs)

SAEs were identified by self-report. At clinic visits, participants were probed about events since the last visit or they contacted study staff between visits to report an event. In addition to the usual categories of SAEs (life threatening, hospitalization or prolongation of hospitalization, disability, birth of a child with a congenital anomaly, events resulting from an overdose of study medication, and events requiring an intervention to prevent a SAE), the TODAY study defined three additional study-specific SAEs.

Severe hypoglycemia was defined as documented or clinically suspected hypoglycemia that needed to be treated with glucagon, required assistance from a third party to resolve the event, loss of consciousness, or seizure. This definition required that the participant *needed* assistance, not that the participant simply received assistance, and required clinical assessment by the study team that the participant would not have been able to take care of the problem him or herself because of the low blood sugar and not for some other reason (e.g., fear, laziness). The site MD or PI needed to evaluate this distinction.

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In case of a severe hypoglycemic episode in the absence of insulin therapy, the study medication was adjusted downward using a specified algorithm, with reductions in rosiglitazone occurring first and subsequent reductions in metformin only if hypoglycemia recurred after reduction of rosiglitazone. If there were no additional severe hypoglycemic events and HbA1c was $>6\%$, study medication was returned to previous dose level. If there were no additional severe hypoglycemic events and HbA1c was $\leq 6\%$, the decreased dose of study medication was continued. If a second severe hypoglycemic event occurred, study medication dose was decreased for the duration of the trial. If more than 2 severe hypoglycemic events occurred in the same participant in the absence of insulin, rosiglitazone was permanently discontinued and metformin was permanently decreased by 500 mg/day. For participants who had severe hypoglycemia while taking insulin, the insulin dose was adjusted as appropriate before any change in the other study medication(s) was made.

Diabetic ketoacidosis (DKA) was defined as an episode of symptoms associated with DKA (nausea, vomiting, abdominal pain, polyuria, dehydration) with positive urine ketones or blood ketones ≥ 4.0 mM and acidosis with serum bicarbonate ≤ 15 mmol/L and/or pH < 7.3 .

Lactic acidosis was defined as a blood lactate > 5.0 mM associated with a low blood pH and an elevated anion gap on standard electrolytes.