SUPPLEMENTARY DATA

SUPPLEMENTAL MATERIALS

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Supplemental Table S1 – Clamp-derived endpoints on original scales. Statistical analyses presented in the accompanying manuscript were performed on logarithmically transformed data. Prior to taking logs, a constant of 1.06 was added to the ACPRg because of negative values in this β-cell response variable. ACPRg, acute C-peptide response to glucose; ACPRmax, arginine-stimulated maximal c-peptide response; GDR, glucose disposal rate; M/I, glucose disposal rate (M) divided by steady state insulin (I); SS, steady state. Data are presented as mean±SD for normally distributed variables or geometric mean [95% confidence interval] for non-normally distributed variables.

	Glargine Followed by Metformin			**Liraglutide Plus Metformin**		
	Baseline N=67	Month 12 N=64	Month 15 N=65	Baseline N=68	Month 12 N=54	Month 15 N=53
GDR (mmol/kg/min)	0.021±0.010	0.022±0.014	0.023±0.012	0.021±0.009	0.046± 0.022	0.022± 0.010
M/I ($x10^{-5}$ mmol/kg/min per pmol/L)	2.81 [0.65, 12.14]	3.02 [0.59, 15.45]	3.38 [0.61, 18.84]	2.92 [0.75, 11.31]	2.33 [0.52, 10.50]	3.49 [0.90, 13.54]
SS C-peptide (nmol/L)	4.01 [1.91, 8.42]	3.88 [1.85, 8.10]	3.58 [1.54, 8.33]	4.06 [2.09, 7.89]	7.04 [3.09, 16.08]	3.73 [1.87, 7.44]
ACPRg (nmol/L)	1.75 [0.96, 3.16]	1.88 [1.06, 3.32]	1.68 [0.91, 3.09]	1.77 [0.99, 3.16]	2.68 [1.28, 5.60]	1.68 [0.99, 2.83]
ACPRmax (nmol/L)	4.78 [1.83, 12.52]	4.69 [1.93, 11.43]	4.32 [1.58, 11.80]	4.93 [2.27, 10.73]	3.38 [1.18, 9.67]	4.58 [2.21, 9.48]
	Metformin Alone			**Placebo**		
	Baseline N=65	Month 12 N=56	Month 15 N=56	Baseline N=67	Month 12 N=59	Month 15 N=58
GDR (mmol/kg/min)	0.022±0.009	0.025±0.011	0.023±0.014	0.022±0.010	0.022±0.013	0.023±0.012
M/I ($x10^{-5}$ mmol/kg/min per pmol/L)	3.26 [0.81, 13.07]	3.90 [0.86, 17.63]	3.53 [0.67, 18.49]	3.30 [0.69, 15.74]	3.72 [0.92, 15.12]	3.63 [0.95, 13.84]
SS C-peptide (nmol/L)	3.86 [1.98, 7.55]	3.90 [1.88, 8.08]	3.65 [1.94, 6.87]	3.88 [1.86, 8.12]	3.59 [1.70, 7.57]	3.60 [1.72, 7.53]
ACPRg (nmol/L)	1.77 [0.98, 3.17]	1.93 [1.09, 3.40]	1.68 [0.84, 3.34]	1.72 [0.99, 2.98]	1.69 [0.89, 3.22]	1.68 [0.86, 3.26]
ACPRmax (nmol/L)	4.83 [1.98, 11.74]	4.47 [1.96, 10.21]	4.61 [2.00, 10.66]	5.04 [2.06, 12.32]	4.53 [1.71, 12.01]	4.45 [1.56, 12.71]

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Supplemental Table S2 – Targeted AEs during 12 months of active treatment and 3 months of treatment withdrawal

	Glargine followed by metformin	Liraglutide with metformin	Metformin Alone	Placebo
Any low blood sugar	8 (12%)	1 (1%)	3 (5%)	5 (7%)
Skin rash	6 (9%)	1 (1%)	3 (5%)	4 (6%)
GI symptoms	12 (18%)	28 (41%)	23 (35%)	10 (15%)
Diabetes symptoms	2 (3%)	0	0	4 (6%)
Serious Adverse Events (through M15)	• Hospital admission for chest pain • Two hospital admissions for chest pain and tightness	• Kidney stone removal • Elective spinal decompression surgery • Episode of vertigo • Motor vehicle accident w/head injury • Cholelithiasis/ Cholecystitis • Hospitalization for pain control related to chronic back pain • Sepsis due to scalp cellulitis	• Left knee total arthroplasty • Hospitalization for food poisoning • Hospitalization for pneumonia, bronchitis, respiratory infection • Hospitalization for earaches and numbness • Surgical relief of carpal tunnel nerve pain	• Hospitalization due to diminishing ability to support weight and ambulate • Hospitalization for asthma attack • Foot surgery for arthritis

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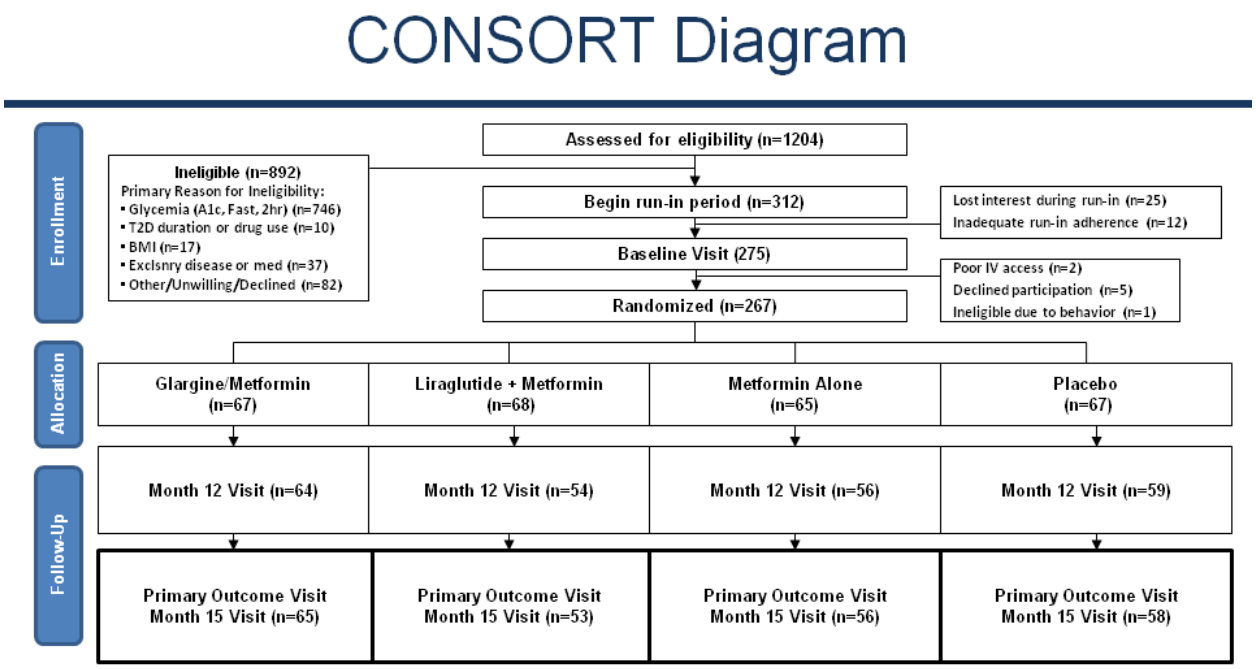
Supplemental Figure S1 – CONSORT Diagram for RISE Adult Medication Study



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Supplemental Figure S2 – IGT Subset of the Study Cohort. Vector Plot Demonstrating Effects of Study Interventions on β-Cell Function: Co-Primary Outcomes (Steady-State C-peptide and ACPRmax) and Secondary Outcome (ACPRg) Paired with Insulin Sensitivity (M/I). Model-based changes over time from baseline to 12 and 15 months for the clamp-based C-peptide responses (steady-state C-peptide, ACPRmax, ACPRg), each plotted with insulin sensitivity quantified as M/I. The black line depicts the joint relationship between each β-cell response and insulin sensitivity at baseline for the full cohort, with the mean value at baseline for the full cohort indicated by the black box with 0. The dotted lines to boxes at Months 12 and 15 show the trajectory of values from baseline to Month 12 of intervention and then to Month 15 (3 months following discontinuation of the intervention). Groups are presented as metformin alone in brown, glargine followed by metformin in green, liraglutide and metformin in purple and placebo in blue. The ellipses depict the 95% confidence bands around the points at Months 12 and 15; where these ellipses overlap the solid black line the value is not statistically different from the baseline. Values above the black line represent improved β-cell function and values below the line represent worsened β-cell function. The 4-group comparisons were significantly different at Month 12, with liraglutide plus metformin different from the other treatments, but there were no differences across the groups at Month 15.

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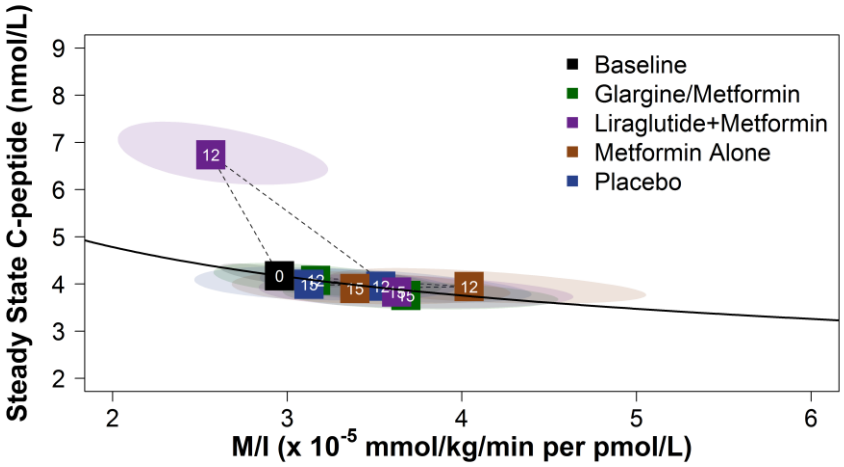

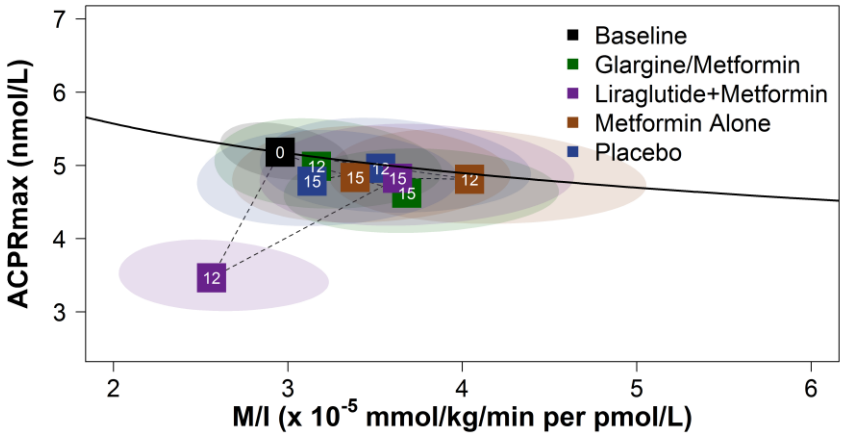

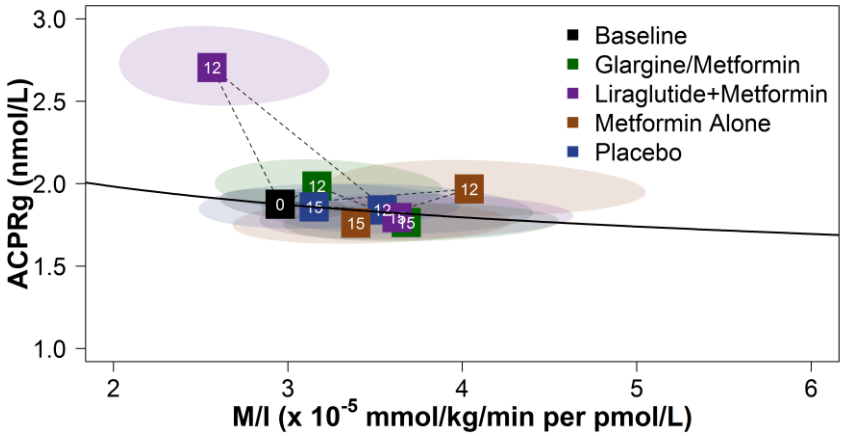

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Appendix 2: Glargine Adjustment Algorithm

For participants randomized to glargine followed by metformin, once-daily insulin glargine was initiated in the evening (between 9:00 PM and 11:00 PM) based on weight (0.25 units/kg for participants with IGT; 0.4 units/kg for participants with type 2 diabetes) and titrated over one month, based on daily fasting morning (between 6:00 AM and 9:00 AM) self-monitoring blood glucose (SMBG), to achieve a fasting blood glucose of 4.4-5.0 mmol/L. Capillary glucose monitoring was performed using FreeStyle Lite glucose meter systems (Abbott Laboratories, Chigago IL). Participants worked with study staff to adjust the glargine dose every 2-3 days. Using capillary glucose readings from the most recent 3 days, the dose of glargine was adjusted according to the following algorithm:

If 2 of last 3 fasting SMBG (or average if < 3)	**Glargine Dose Adjustment**
<2.8 mmol/L	Decrease by the greater of 10% or 8 units
2.8-3.8 mmol/L	Decrease by the greater of 5% or 5 units
3.9-4.4 mmol/L	Decrease by 5 units
4.4-4.9 mmol/L	No adjustment
5.0-5.5 mmol/L	Increase by the greater of 10% or 5 units
5.5-6.1 mmol/L	Increase by the greater of 20% or 10 units
6.1-6.6 mmol/L	Increase by the greater of 25% or 15 units
≥6.7 mmol/L	Increase by the greater of 30% or 20 units

Following 3 months of insulin treatment, insulin glargine was discontinued, and metformin was initiated and titrated as described above.

Study staff monitored medication adherence by auditing returned medication every three months. For glargine, the projected consumption based on prescribed dosing as above was compared to total consumption, measuring returned medication by volume and calculating total consumption by subtracting units returned from units dispensed.

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Appendix 3: Safety Surveillance Plan

Participants with type 2 diabetes and those randomized to glargine were asked to perform SMBG daily and whenever they had symptoms of hypoglycemia or hyperglycemia or felt ill for any reason. They were asked to report abnormal readings to clinic staff, who inquired about symptoms and requested that the participant check urine ketones. If symptoms and/or ketones were present, the participant was brought to the research clinic for interim assessment using the following algorithm:

- If participants experienced acute metabolic decompensation, rescue therapy with insulin was to be initiated. Acute metabolic decompensation was defined as hyperglycemia (plasma glucose >16.6 mmol/L accompanied by symptoms (e.g., vomiting, dehydration, lethargy) and/or moderate or large urinary ketones. Participants with diabetic ketoacidosis (DKA) were to be referred for emergent care. (No participants experienced acute metabolic decompensation.)
- If HbA1c was ≥9% (75 mmol/mol) without acute metabolic decompensation or DKA, therapy was invigorated (using frequent telephone contact and/or visits to encourage optimal medication adherence and lifestyle choices) and HbA1c was repeated within 2 weeks. If HbA1c was still ≥9% (75 mmol/mol), final outcome measurements were obtained within 2 weeks of confirmation, after which rescue therapy was initiated.
- If HbA1c was ≥8% (64 mmol/mol) but <9% (75 mmol/mol) at any visit, therapy was invigorated. HbA1c was obtained within six weeks and, if it was confirmed ≥8% (64 mmol/mol), final outcome measurements were obtained within two weeks, after which rescue therapy was initiated.
- If HbA1c was ≥7% (53 mmol/mol) but <8% (64 mmol/mol) at any visit, therapy was invigorated. HbA1c was obtained at the next quarterly visit and, if it was ≥7% (53 mmol/mol) but <8% (64 mmol/mol), frequent contact was maintained.

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Appendix 4: Statistical Analysis Plan

Often the Disposition Index (DI) – insulin sensitivity * insulin response – is used as an overall measure of β-cell function that appropriately accounts for the reciprocal relationship of insulin sensitivity and the β-cell's insulin response. In these analyses, the DI assumes that the product of the two variables is constant within an individual at a given time, such that changes in insulin sensitivity would be mirrored by a proportional change in the insulin response. This implies that all points along the line represent the same level of metabolic function. In many instances, this relationship has been demonstrated to be a rectangular hyperbola (by definition, the slope of the log-log relationship equal to -1.0); however, in others this relationship has just been assumed. The power calculations for RISE were based on the DI using data provided by several investigators who used methodologies that differed from those used in RISE.

During protocol development, there was concern that relationships underlying this constant depend on the actual measures of peptide (insulin or C-peptide) released by the β-cell. In particular, the slope of the log-log relationship between secretion and sensitivity might not be equal to -1.0 for the C-peptide measures chosen for RISE, as had been observed in prior studies based on insulin. Therefore, the protocols specifically stated that the primary outcomes would be based on two different C-peptide responses (steady state and maximal) adjusted for insulin sensitivity, defined as the glucose disposal rate divided by steady-state insulin (M/I) during the hyperglycemic clamp. However, given the likely possibility that the relationship may not be a rectangular hyperbola, the protocol did not specify details of the approach to be used for the primary outcome analysis, as a decision would be based on evaluation of the baseline data.

During analysis of the pediatric and adult baseline data, we found that the DI (i.e. sensitivity x secretion) is sometimes paradoxically lower in pediatric participants than adult participants, despite the fact that the insulin sensitivity vs. C-peptide curves describing the relationship between these two variables appears higher in children. This contradictory finding is, at least in part, due to the fact that the range of values for insulin sensitivity among children is narrow compared to that of adults, i.e., children are more insulin-resistant than adults. Further, the log-log slopes of insulin sensitivity vs. C-peptide responses are not equal to -1 in children or adults (or overall). Although the untransformed data show a clear inverse relationship typical of a hyperbolic curve, the slopes for each of the primary outcome measures on the log scale is approximately -0.3; this is a hyperbola but not a square hyperbola. Thus, the approach of performing the primary outcome analysis comparing treatment groups after washout, with a test of difference in DI at Month 15 adjusted for baseline, needed to be reassessed.

Several options were considered, including a simple linear regression model (on a log scale) of C-peptide (and insulin) release as a function of insulin sensitivity, with a term for treatment group and adjusting for both variables at baseline. However, this was also deemed inappropriate because that model would estimate the difference in C-peptide (and insulin) release between groups assuming that there was no difference in insulin sensitivity between groups. Rather, we want to account for movement of both variables simultaneously without forcing a specific relationship between them. This can be accomplished by performing the primary outcome analysis using two separate models: insulin sensitivity at Month 15 vs.

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treatment arm (adjusted for baseline) and C-peptide (or insulin) release at Month 15 vs. treatment arm (adjusted for baseline), where the two models are fit simultaneously using Seemingly Unrelated Regression techniques[1-3]. This provides an estimate of the treatment group difference in insulin sensitivity, as well as the treatment group difference in the release of the β-cell peptides, while allowing for correlation among the insulin sensitivity and peptide release measures. This yields an estimate of the joint covariance structure of the two models and allows a joint statistical test of both variables using a 2-DF chi-square test of the treatment arm difference in each model. Thus, we will be able to test whether both the insulin sensitivity and C-peptide (and insulin) release variables are different across treatment groups at Month 15, adjusted for their baseline value.

This approach provides a clear answer to the question of whether the baseline-adjusted Month 15 result differs by treatment. However, given that an underlying reciprocal relationship is expected, it is possible that a significant difference could be found between groups, but that this represents a proportional shift without a specific difference in peptide release adjusted for sensitivity. In other words, the data points could lie on a different part of a shared relationship curve, such that the difference between groups represents a mutually compensated change in secretion and sensitivity terms without a separate underlying change in β-cell function. Therefore, if the results of the two-model analysis are significant, indicating a baseline-adjusted difference by treatments, further analysis will evaluate the patterns of change in either or both variables within each group.

For the Adult Medication Study, the two primary outcomes measuring β-cell function after 3-months of washout will be assessed. In order to maintain a study-wide α=0.05, a closed testing procedure will be used to assess the primary outcome[4]. The closed testing procedure is a method of hierarchical testing that tests higher-order comparisons before allowing lower-level comparisons, thus controlling the type I error and preserving power. First, β-cell function will be compared across the four treatment groups using an analysis of covariance model, adjusted for baseline β-cell function. From this model, the overall test of equality across the four treatment groups will be computed. If that overall test is significant at the α=0.05 level, then each of the four possible sets of three interventions will be compared in four separate analysis of covariance models. The final significance testing of any set of two treatment groups is only undertaken if the p-values for each of the two 3-intervention tests that include a particular two intervention group are both $p<0.05$. For example, for interventions I_1, I_2, I_3 and I_4, the first analysis of variance test I_{1234} assesses whether there are any differences among the four groups. If the overall test across the four groups is not significant, testing concludes and no treatment group is declared different from any other. Alternately, if that initial 4-group test is significant at the α=0.05 level, four separate analysis of covariance models with combinations I_{123}, I_{124}, I_{134} and I_{234} are tested. The comparison I_{12} is only tested if both I_{123} and I_{124} are significant at $p<0.05$ and so forth. The closed testing procedure is chosen as the primary outcome analysis to maintain an overall study-wide α=0.05, while preserving power and allowing each set of interventions to be compared under pre-specified circumstances. The two primary outcomes will be analyzed separately with a total type I error probability of 0.05 for each, i.e. without an adjustment for two separate outcomes.

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