# Supplementary Appendix

Mortality in the Glycemia Reduction Approaches in Type 2 Diabetes (GRADE) Study: A Comparative Effectiveness Randomized Clinical Trial

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Figure S1. GRADE Study Enrollment and Mortality by Randomized Treatment Group



3<sup>rd</sup> row: Treatment allocation by group. Percentages are the proportion of participants randomized to each treatment group of the total cohort.

4<sup>th</sup> row: Percentages are the proportion of people who died in each randomized treatment group.

# Table S1. GRADE Definitions<sup>1</sup> for Cause of Death

Code	Definition/Notes
Sudden death <sup>2</sup>	<ul> <li>Death may only be classified as sudden if patient was seen alive and clinically stable ≤24 hours before being found dead and without any evidence supporting a specific non-cardiovascular cause of death</li> </ul>
Evidence of CVD <sup>3</sup>	<ul> <li>History of cardiovascular disease (CVD) and absence of other known cause</li> <li>If a sudden death occurs AND another cause cannot be identified AND the patient is known to have CVD, the death will be classified as CVD death by convention (immediate cause = sudden death and underlying cause = evidence of CVD).</li> </ul>
MACE death <sup>4</sup>	<ul> <li>Death known to be due to MI or stroke</li> <li>Includes deaths within 30 days of MI or stroke         <ul> <li>MI is defined as any event with acute rise and fall in troponin level with at least 1 value &gt;99<sup>th</sup> percentile of URL and at least one of the following: 1) symptoms of myocardial ischemia; 2) new or presumed new STTW changes or LBBB; 3) new Q waves; 4) imaging evidence of new loss of myocardium or regional wall motion abnormality; 5) intracoronary thrombus on angiography or biopsy</li> <li>Stroke is defined as an acute episode of focal or global neurologic dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction lasting ≥24 hours</li> </ul> </li> </ul>
Hypoglycemia	<ul> <li>Required provision of available documentation</li> <li>Severe hypoglycemia was defined as documented or clinically suspected hypoglycemia that meets at least one of these criteria:         <ul> <li>Requires assistance from a third party to resolve the event</li> <li>Needs to be treated with glucagon or intravenous glucose</li> <li>Results in injury to the participant or others</li> <li>Includes loss of consciousness or seizure</li> </ul> </li> </ul>
Hyperglycemic crisis	<ul> <li>Diabetic ketoacidosis or hyperosmolar hyperglycemic syndrome</li> </ul>

Diabetes-related	If underlying cause is diabetic nephropathy		
Cancer death	Type of cancer adjudicated using Cancer Adjudication		
	Form		
End-stage renal			
death (ESRD)			
Respiratory	COPD or other		
Pneumonia	Cause should be specified		
Infection	<ul> <li>Type of infection should be specified</li> </ul>		
Dementia			
Chronic liver			
disease (CLD)			
Accident	<ul> <li>Type of accident should be specified</li> </ul>		
Suicide			
Overdose			
Unknown⁵ or	<ul> <li>For patients not observed alive within 24 hours of death</li> </ul>		
Undetermined			
Other	Specify cause of death		

<sup>1</sup>Definitions based on:

Hicks KA, Mahaffey KW, Mehran R, Nissen SE, Wiviott SD, Dunn B, Solomon SD, Marler JR, Teerlink JR, Farb A, Morrow DA, Targum SL, Sila CA, Hai MTT, Jaff MR, Joffe HV, Cutlip DE, Desai AS, Lewis EF, Gibson CM, Landray MJ, Lincoff AM, White CJ, Brooks SS, Rosenfield K, Domanski MJ, Lansky AJ, McMurray JJV, Tcheng JE, Steinhubl SR, Burton P, Mauri L, O'Connor CM, Pfeffer MA, Hung HMJ, Stockbridge NL, Chaitman BR, Temple RJ, Standardized Data Collection for Cardiovascular Trials I. 2017 Cardiovascular and Stroke Endpoint Definitions for Clinical Trials. Circulation 2018;137:961-972

GRADE Definitions of Cardiovascular Causes of Death:

- <sup>2</sup> **Sudden death**: Death was classified as sudden if patient *was seen alive* and clinically stable less than 24 hours before being found dead without any evidence supporting a specific non-cardiovascular cause of death.
- <sup>3</sup> Evidence of CVD death: A history of CVD and absence of other known causes. If a sudden death occurs AND another cause cannot be identified AND the patient is known to have CVD, the death will be classified as CVD death by convention. [This would be classified as Immediate Cause=Sudden Death (01) and Underlying Cause=Evidence of CVD (02)]. Also termed **Presumed CVD death in text and figure 1**.
- <sup>4</sup> MACE death: A death known to be due to a myocardial infarction (MI) or a stroke including death with 30 days of an MI or stroke. A MACE death was separated out of CVD by GRADE protocol. By GRADE convention, these were listed individually as MACE death
- <sup>5</sup> **Unknown** or Undetermined: Death was classified as undetermined if the patient *was NOT seen alive* less than 24 hours of being found dead and the cause of death was unknown.

The difference between MACE death and presumed CVD death is that MACE death is *known* to be MACE death, for example, by autopsy, death after witnessed stroke, or death after an episode of chest pain with ECG showing ST elevations.

### Supplementary Methods S1. Description of GRADE Outcomes Adjudication Process

GRADE appointed an Outcomes Subcommittee to determine events, classifications, and adjudication procedures for study outcomes and definitions for events. Designated outcome events were adjudicated by 12 experienced endocrinologists and primary care physicians and 1 expert cardiologist (external to the study, who served as a cardiovascular consultant). Event reviews were conducted by paired adjudicators masked to participant ID and treatment assignment. A tiebreaker was conducted if the two original adjudicators did not agree on the event classification. No adjudicator was assigned to an event from their own site to preserve the independence to the review process. The Coordinating Center at The George Washington University assigned events for review and determined whether a tie breaker was needed. The Outcome Subcommittee met a minimum of twice per year during the trial to discuss sample event cases, review evidence needed for case review, and review event definitions. The cardiovascular consultant was available throughout the trial to provide guidance on CV events and definitions and discuss cases for review. If insufficient information was available for classifying an event, the event was classified as "undetermined" cause of death. All deaths were adjudicated for immediate and underlying cause of death.

	Alive	Died
Participant Vital Status (%)	4,893	153
Age at baseline visit (years)	57.0 ± 9.9	$63.3 \pm 8.7$
Sex		
Male	3,083 (63.0%)	127 (83.0%)
Female	1,811 (37.0%)	26 (17.0%)
Race		
Black	967 (19.8%)	33 (21.6%)
White	3,207 (65.5%)	107 (69.9%)
All others	720 (14.7%)	13 (8.5%)
Ethnicity		
Non-Hispanic	3,939 (81.1%)	138 (90.8%)
Hispanic	915 (18.9%)	14 (9.2%)
BMI (kg/m²)	34.3 ± 6.8	33.7 ± 6.8
Duration of diabetes (years)	4.2 ± 2.7	4.3 ± 2.8
HbA1c (%) at baseline	7.5 ± 0.5	$7.4 \pm 0.4$
HbA1c (mmol/mol)	58.4 ± 5.3	57.7 ± 4.9
Hypertension	3,538 (72.3%)	132 (86.3%)
Systolic blood pressure (mmHg)	128.3 ± 14.7	131.1 ± 17.1
Diastolic blood pressure (mmHg)	77.3 ± 9.8	77.4 ± 10.7
Total cholesterol (mg/dL)	164.0 ± 37.9	156.1 ± 32.7
HDL (mg/dL)	43.5 ± 10.6	42.0 ± 10.5
LDL (mg/dL)	90.7 ± 31.7	86.7 ± 29.7
Triglycerides (mg/dL)	154.4 ± 122.7	139.8 ± 76.8
Framingham Risk Score	23.3 ± 15.3	34.9 ± 16.5
Urine ACR median/IQR (mg/g)	6.3 [3.0, 16.7]	8.9 [4.1, 31.2]
Urine ACR≥30 mg/g	760 (15.6%)	40 (26.1%)

# Table S2. Summary of Baseline Characteristics of GRADE Participants by End ofStudy Vital Status

For quantitative variables, the table reports means and standard deviations, except for urine ACR which has a skewed distribution and for which the table shows median and quartiles. For binary and categorical variables, the table shows number and percentage within each column.

Table S3.	. Types	of Cancer	Deaths in	ו GRADE
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Cancer type	N, deaths
Single Cancer Type	
Lung	10
Pancreas	8
Unknown	6
Kidney	3
Other	2
Liver	2
Esophagus	2
Bladder	2
Stomach	1
Lymphoma	1
Colon	1
CNS/brain	1
Multiple Cancer Types <sup>1</sup>	
Pancreas and Bladder	1
Bladder and Lymphoma	1

<sup>1</sup> The two participants whose underlying cause of death listed more than one type of cancer are not included in the counts for single cancer types.

	Glargine	Glimepiride	Liraglutide	Sitagliptin
Cancer	12	13	7	9
Presumed CVD	10	10	6	10
Unknown	6	2	2	6
Other		3	4	5
Infection	4	4	2	1
MACE	3	1		2
Chronic Liver Disease	3	1∎		2 💷
Respiratory	2	2		1
Pneumonia		2	2	1
Accident	1∎	2	1	1
Suicide	1		1	1
End Stage Renal		1∎	2	
Overdose		2		
Sudden				1
Dementia				1

## Figure S2. Graphical Table of Underlying Cause of Death by Treatment Group

The table shows the number of deaths from each underlying cause. The rows are ordered by frequency of cause of death in the entire cohort. The 10 participants who died with underlying COVID (infection/pneumonia) are shown in red.

### Figure S3. CART Analysis

Each of the four decision trees below models the risk of death using the Classification and Regression Tree (CART) method. The method automatically picks the subset of variables to be included in the final model and selects data-derived cutoffs for each variable.

For example, for all-cause mortality the method selected the Framingham score with a cutoff of 24 as the only variable in the final model. The numbers at the bottom of the tree are the crude rates of death per 10,000 person years. The final tree is selected as the one with the smallest cross-validated error from a 100-fold cross-validation.

Thus, participants with a baseline Framingham score under 24 (left branch of the tree) have a crude rate of 26.0 death per 10,000 person-years. Participants with a baseline Framingham score of 24 or above (right branch of the tree) have a crude rate of 110.6 deaths per 10,000 person-years, i.e. 110.6/26=4.6 times the rate in the lower risk group.

The Framingham score was selected as the only variable in the final model for all-cause deaths, cardiovascular-cause deaths, and cancer deaths. Note that since the cutoffs are derived from the data, the Framingham score has different cutoffs for different causes of death. For the remaining causes combined, the final model also contains a single variable, age, with the highest risk in the oldest age group (>59 years).





Kuhn, Lisa, et al. "The process and utility of classification and regression tree methodology in nursing research." *Journal of Advanced Nursing* 70.6 (2014): 1276-1286.