Supplementary materials

Methods

Supplementary Table 1. Outcomes from the emulated trials
PRONOUNCE trial
Primary: time to first occurrence of a major adverse cardiovascular event, a composite endpoint defined as all-cause death, nonfatal myocardial infarction, or nonfatal stroke **Secondary:** all-cause death, nonfatal myocardial infarction, or nonfatal stroke
GRADE trial
Primary: time to primary metabolic failure, calculated as days to hemoglobin A1c (HbA1c) ≥7% while receiving the assigned medication, with eligibility for outcome ascertainment starting at month 3 after the index date (analogous to the first quarterly HbA1c assessment in GRADE). **Secondary** The secondary outcomes were time to secondary metabolic failure (calculated as days to HbA1c >7.5% while receiving the assigned medication); time to tertiary metabolic failure/insulin initiation; proportions of patients experiencing primary, secondary, and tertiary metabolic failure at 1 and 2 years; number of emergency department visits or hospitalizations for hypoglycemia; incidence of end-stage kidney disease, retinopathy, treatment of retinopathy, peripheral neuropathy, MACE and its components, unstable angina requiring hospitalization or revascularization, heart failure hospitalization, pancreatitis, pancreatic or thyroid cancer, any cancer (except non-melanoma skin cancer), all-cause mortality, and all-cause hospitalization. The HbA1c outcomes were modified from the GRADE trial, where confirmation of an elevated result with a repeat HbA1c was required, as this is not done in routine care.

As previously described,[1, 2] inclusion and exclusion for the trials were identified from ClinicalTrials.gov and published trial protocols and were applied to beneficiaries included in OLDW. The date of an individual's first fill of the drugs of interest was defined as the index date (i.e., new-user design). Patients were required to have at least 6 months of continuous enrollment with medical and pharmacy coverage before the index date. Sociodemographic variables, comorbidities, and medication use during the baseline 6-month period were recorded. Variables were defined by the presence of a claim with eligible diagnosis codes, procedure codes, and prescriptions.

Results

Supplementary Table 2. Comparison of the PROUNOUNCE trial and emulated trial cohorts

	PRONOUNCE trial cohort	Emulated trial cohort			
Characteristics	**Total (N=544)**	**Definition of characteristics (if different) or clarification**	**Total (N=2226)**	**SMD**	**All SMDs < 0.20**
1. Age		**Ascertainable**			
mean ± SD, years	73.2 ± 7.2		75.0 ± 7.5	0.24	No
2. Race, n (%)	541/544 (99.5)	**Partially ascertainable**: OLDW combined race and ethnicity into a single variable	2023/2226 (90.9)		
American Indian or Alaska Native	2 (0.4)		-	-	-
Asian	8 (1.5)		51 (2.5)	0.06	No

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	PRONOUNCE trial cohort	**Emulated trial cohort**			
Characteristics	**Total (N=544)**	**Definition of characteristics (if different) or clarification**	**Total (N=2226)**	**SMD**	**All SMDs < 0.20**
Black or African American	28 (5.2)		415 (20.5)	0.42	
White	503 (93.0)		1557 (77.0)	0.62	
3. Ethnicity, n (%)[a]	540/544 (99.3)	**Partially ascertainable**: OLDW combined race and ethnicity into a single variable. The number of Not Hispanic or Latino participants are inferred based on the total number of participants, the number of Hispanic or Latino participants, and the Unknown participants	2129/2226 (95.6)		
Hispanic or Latino	30 (5.6)		106 (4.8)	0.04	Yes
Not Hispanic or Latino	510 (94.4)		2023 (90.9)	0.13	
Unknown			97 (4.4)		
4. Weight		**Not ascertainable**			
mean ± SD, kg	86.55		-	-	-
5. Body mass index, n (%)	541/544	**Not ascertainable**	-	-	-
Mean ± SD, kg/m^2	28.48		-	-	-
6. Smoking status, n (%)		**Partially ascertainable:** Although OLDW has diagnosis codes for current smoking, which is likely incomplete, other smoking data are likely even more incomplete)			
Current	82 (15.1)		403 (18.1%)	0.08	Yes
Former	211 (38.8)		-	-	-
Never	141 (25.9)		-	-	-
7. Baseline blood pressure, n (%)		**Not ascertainable**			
diastolic >90 or systolic >140, mm Hg	184 (33.8)		-	-	-
8. Total serum cholesterol		**Partially ascertainable:** Only 571 (25.7%) patients captured in OLDW	571/2226 (25.7)		
mean ± SD, mmol/L	4.1 ± 1.09		8.9 ± 2.14	2.83	No
9. Type 2 diabetes					
n (%)	175 (32.2)	**Ascertainable**	875 (39.3)	0.15	Yes

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	PRONOUNCE trial cohort	**Emulated trial cohort**			
Characteristics	**Total (N=544)**	**Definition of characteristics (if different) or clarification**	**Total (N=2226)**	**SMD**	**All SMDs < 0.20**
10. N-Terminal prohormone B-type natriuretic peptide, n (%)	529/544	**Not ascertainable**: Only 3 patients captured in OLDW	-	-	-
Mean ± SD, pg/mL	670.2 ± 2479		-	-	-
11. High-sensitivity C-reactive protein, n (%)	534/544	**Partially ascertainable:** Only 42 (1.9) patients captured in OLDW	42/2226 (1.9)		
Mean ± SD, mg/dL	0.6308 ± 1.8		0.6 ± 1.0	0.02	Yes
12. Troponin T, n (%)	524/544	**Not ascertainable**	-	-	-
Mean ± SD, pg/mL	18.21 ± 17.71		-	-	-
Prostate cancer therapy history, n (%)					
13. Radiotherapy, n (%)	73 (13.4)	**Ascertainable:** Prior radiotherapy (within 6 months before index date)	36 (1.6)	0.46	No
14. Radical prostatectomy, n (%)	64 (11.8)	**Ascertainable**	51 (2.3)	0.38	No
15. Hormonal therapy, n (%)	44 (8.1)	**NA**: This was an exclusion criteria	NA	NA	NA
16. Other, n (%)	24 (4.4)	**NA:** No information provided in PRONOUNCE Trial	-	-	-
17. Gleason score, n (%)		**Not ascertainable**			
2–4	3 (0.6)		-	-	-
5–6	67 (12.3)		-	-	-
7–10	472 (86.8)		-	-	-
18. Stage of prostate cancer, n (%)		**Not ascertainable**: Only baseline metastatic cancer can be captured in OLDW			
Localized	271 (49.8)		-	-	-
Locally advanced	143 (26.3)		-	-	-
Metastatic	111 (20.4)		497 (22.3%)	0.05	Yes
Not classifiable	19 (3.5)		-	-	-
19. Testosterone, n (%)	543/544 (99.8)	**Partially ascertainable:** Only 122 (5.5%) patients captured in OLDW	122/2226 (5.5)		
Median (25th, 75th), ng/dL	330.0 (250, 416)		293.5(182.0, 436.0)	NA	NA
Mean ± SD, ng/dL	332 ± 123.39		326.3 (219.4)	0.03	Yes

Supplementary Table 2. Comparison of the PROUNOUNCE trial and emulated trial cohorts					
	PRONOUNCE trial cohort	**Emulated trial cohort**			
Characteristics	**Total (N=544)**	**Definition of characteristics (if different) or clarification**	**Total (N=2226)**	**SMD**	**All SMDs < 0.20**
20. Prostate specific antigen, n (%)	543/544 (99.8)	**Partially ascertainable:** Only 846 (38%) patients captured in OLDW	846/2226 (38.0)		
Mean ± SD, ng/mL	17.1 (20.0)		64.9 (304.7)	0.22	No
Median (25th, 75th), ng/mL	12.8 (5.8, 32.7)		11.0 (5.8, 27.3)	NA	NA
Cardiac disorders, n (%)	472/544 (86.8)				
21. Myocardial infarction	252 (46.3)	**Ascertainable**	812 (36.5)	0.20	No
22. Coronary carotid, or iliofemoral revascularization	393 (72.2)	**Ascertainable**	2038 (91.6)	0.52	No
23. Coronary, carotid, or iliofemoral stenosis >50% by angiography, n (%)	228 (41.9%)	**Not ascertainable**	-	-	-
24. Carotid stenosis >50% by ultrasound, n (%)	35 (6.4)	**Not ascertainable**	-	-	-
25. Ankle-brachial index <0.9, n (%)	75 (13.8)	**Not ascertainable**	-	-	-
26. Atrial fibrillation, n (%)	102 (18.8)	**Ascertainable**	386 (17.3)	**0.04**	**Yes**
27. Dyslipidemia, n (%)	197 (36.2)	**Ascertainable**	1671 (75.1)	0.85	No
28. Hypertension, n (%)	467 (85.8)	**Ascertainable**	1743 (78.3)	**0.20**	**Yes**
Concomitant medications, n (%)					
29. Cardiovascular medications	530 (97.4)	**Partially ascertainable:** PRONOUNCE Trial protocol did not list specific drugs, so we used: Benazepril, Captopril, Enalapril, Fosinopril, Lisinopril, Moexipril, Perindopril, Quinapril, Ramipril, Trandolapril, Azilsartan, Candesartan, Eprosartan, Irbesartan, Losartan, Olmesartan, Telmisartan, Valsartan, Sacubitril-valsartan, Aliskiren, Bendroflumethiazide, Chlorothiazide, Chlorthalidone, Hydeochlorothiazide, Indapamide, Methyclothiazide, Metolazone, Bumetanide, Ethcrynate Sodium, Ethacrynic acid,	1804 (81.0)	0.55	No

Supplementary Table 2. Comparison of the PROUNOUNCE trial and emulated trial cohorts					
	PRONOUNCE trial cohort	**Emulated trial cohort**			
Characteristics	**Total (N=544)**	**Definition of characteristics (if different) or clarification**	**Total (N=2226)**	**SMD**	**All SMDs < 0.20**
		Furosemide, Torsemide, Amiloride, Triamterene, Eplerenone, Spironolactone, Atenolol, Betaxolol, Bisoprolol, Metoprolol Tartrate, Metoprolol Succinate, Nebivolol, Nadolol, Propranalol, Acebutolol, Pindolol, Timolol, Carvedilol, Labetalol, Esmolol, Sotalol, Amlodipine, Felodipine, Isradipine, Nicardipine, Nifedipine, Nisoldipine, Clevidipine, Torsemide, Nimodipine, Diltiazem, Verapamil, Doxazosin, Prazosin, Terazosin, Alfuzosin, Clonidine, Methyldopa, Guanfacine, Hydralazine, Minoxidil, Guanethidine, Tolazoline, Sodium Nitroprusside, Phenoxybenzamine Hydrochloride, Phentolamine, Fenoldopam, Acetazolamide, Methazolamide			
30. Lipid-modifying agents	458 (84.2)	**Partially ascertainable:** PRONOUNCE Trial protocol did not list specific drugs, so we used statin and non-statin lipid lowering medications	1779 (80.0)	**0.11**	Yes
31. Agents acting on the renin-angiotensin system	396 (72.8)	**Partially ascertainable**: PRONOUNCE Trial protocol did not list specific drugs, so we used angiotensin-converting-enzyme inhibitors/angiotensin II receptor blockers	1179 (53.0)	0.42	No

Supplementary Table 2. Comparison of the PROUNOUNCE trial and emulated trial cohorts					
	PRONOUNCE trial cohort	**Emulated trial cohort**			
Characteristics	**Total (N=544)**	**Definition of characteristics (if different) or clarification**	**Total (N=2226)**	**SMD**	**All SMDs < 0.20**
32. β-Blockers	374 (68.8)	**Partially ascertainable**: PRONOUNCE Trial protocol did not list specific drugs, so we used: Atenolol, Betaxolol, Bisoprolol, Metoprolol Tartrate, Metoprolol Succinate, Nebivolol, Nadolol, Propranalol, Acebutolol, Pindolol, Timolol, Carvedilol, Labetalol, Esmolol, Sotalol	1154 (51.8)	0.35	No

[a] Ethnicity is assigned by an external vendor who uses a rule-based system that combines analysis of first names, middle names, surnames, and surname prefixes and suffixes with geographic criteria. Optum Labs then assigns these ethnicity values into one of five compliance-determined race/ethnicity code values: W (Non-Hispanic White), B (Non-Hispanic Black), H (Hispanic), A (Asian), and U (Unknown).
mm Hg, millimeters of mercury; mmol/L, millimole per liter; ng/mL, nanograms per milliliter; OLDW, OptumLabs Data Warehouse; pg/mL, picograms per milliliter; SD, standard deviation;

Supplementary Table 3. Comparison of GRADE trial and emulated trial cohorts					
	GRADE Trial cohort	**Trial emulation cohort**			
Characteristics	**Total (N = 5,047)***	**Definition of characteristics (if different) or clarification**	**Total (N=7540)**	**SMD**	**All SMDs <0.20**
1. Age		**Ascertainable**			
mean ± SD, years	57.2 ±10.0		61.9 ±11.0	0.45	No
N (%) age group, years					
<45	619 (12.3)		539 (7.1)	0.18	
45–59	2327 (46.1)		2447 (32.5)	0.28	
≥60	2101 (41.6)		4554 (60.4)	0.38	
2. Sex, n (%)		**Ascertainable**			
Male sex	3210 (63.6)		3868 (51.3)	0.25	No
3. Race, n (%)		**Partially ascertainable**: OLDW combined race and ethnicity into a single variable			
White	3,314 (65.7)		4870 (64.6)	0.02	Yes
African American or Black	1,000 (19.8)		969 (12.9)	0.19	
Asian	182 (3.6)		479 (6.4)	0.13	
AI/AN	137 (2.7)		-	-	-
Native Hawaiian or other Pacific Islander	28 (0.6)		-	-	-
Other or more than one race	319 (6.3)		-	-	-
Unknown or not reported	67 (1.3)		284 (3.8)	0.16	
4. Ethnicity, n (%)		**Partially ascertainable**: OLDW combined race and ethnicity into a single variable			
Hispanic/Latino	929 (18.4)		938 (12.4)	0.17	Yes
Not Hispanic/Latino	4077 (80.8)		-	-	-
Unknown/not reported	41 (0.8)		-	-	-
5. Education completed, n (%)		**Partially ascertainable:** education has high rates of missingness in OLDW			
<High school	364 (7.2)		52 (0.7)	0.34	No
High school graduate	1039 (20.6)		2128 (28.2)	0.18	
Some college	1463 (29.0)		4042 (53.6)	0.52	
≥College degree	2180 (43.2)		1220 (16.2)	0.62	
Unknown			98 (1.3)		
6. Duration of diabetes		**Not ascertainable**			
Mean ± SD, years	4.2 ± 2.8		-	-	-
Median (IQR)	3.8 (1.9, 6.4)		-	-	-
7. Screening metformin dose		**Not ascertainable**			
Mean ± SD, mg/day	1575.5 ± 525.2		-	-	-
8. Baseline metformin dose		**Not ascertainable:** the number of tablets issued for metformin do not necessarily			
Mean ± SD, mg/day	1944.2 ± 204.5		-		

		correspond to the dose because patients receive a full prescription up front.			
9. Family history of any first-degree relatives with diabetes,					
N (%)	3522 (69.8)	**Not ascertainable**	-	-	-
Medical history, n (%)					
10. Heart attack/stroke, n (%)	330 (6.5)	**Ascertainable**	631 (8.4)	0.07	Yes
11. Retinopathy, n (%)	49 (1.0)	**Ascertainable**	362 (4.8)	0.23	No
12. Neuropathy, n (%)	1,083 (21.5)	**Ascertainable**	907 (12.0)	0.26	No
13. Hypertension, n (%)	3,360 (66.6)	**Ascertainable**	5637 (74.8)	0.18	Yes
14. Elevated blood lipids, n (%)	3,646 (72.2)	**Ascertainable**	5620 (74.5)	0.05	Yes
Current medications, n (%)					
15. Blood pressure medications	3495 (69.2)	**Partially ascertainable**: GRADE Trial did not list specific drugs, so we used cardiac medications	6023 (79.9)	0.25	No
16. Lipid-lowering medications	3317 (65.7)	**Partially ascertainable**: GRADE Trial did not list specific drugs, so we used statin and non-statin lipid lowering medications	6180 (82.0)	0.38	No
17. Statin	3209 (63.6)	**Ascertainable**	5163 (68.5)	0.10	Yes
18. Aspirin	2288 (45.3)	**Not ascertainable**: Data for only 34 patients captured in OLDW and aspirin can be over the counter	-	-	-
19. Depression/anxiety medication(s), n (%)†	472/2502 (18.9)†	**Not ascertainable**	-	-	-
20. Smoking status, n (%)					
Current	695 (13.8)	**Partially ascertainable:** Although OLDW has diagnosis codes for current smoking, which is likely incomplete, other smoking data are likely	382 (5.1)	0.30	No
Former	1617 (32.0)		-	-	-
Never	2735 (54.2)		-	-	-

		even more incomplete			
21. Weight, mean ± SD, kg	100.0 ± 22.3	**Not ascertainable**	-	-	-
22. BMI, mean ± SD, kg/m²	34.3 ± 6.8	**Not ascertainable**	-	-	-
23. Blood pressure		**Not ascertainable**	-	-	-
Systolic, mean ± SD, mmHg	128.3 ± 14.7		-	-	-
Diastolic, mean ± SD, mmHg	77.3 ± 9.9		-	-	-
N (%) <140/90 mmHg	3,802 (75.3)		-	-	-
N (%) <130/80 mmHg	2,172 (43.0)		-	-	-
Laboratory tests*					
24. HbA1c					
Mean ± SD, %	7.5 ± 0.5	**Partially ascertainable**	7.6 ± 0.5	0.20	Yes
Mean ± SD, mmol/L	58 ± 5.3		NA	NA	NA
N (%) <7%	725 (14.4)		NA	NA	NA
25. Cholesterol, n (%)					
Mean ± SD, mg/dL	163.8 ± 37.8	**Partially ascertainable:** Data for 4860 (64.5%) patients were captured in OLDW	172.0 ± 39.4	0.21	No
Mean ± SD, mmol/L	4.2 ± 0.98		NA	NA	NA
26. Triglycerides		**Partially ascertainable:** Data for 4860 (64.5%) patients were captured in OLDW			
Mean ± SD, mg/dL	154.0 ± 121.6		185.4 ± 115.2	0.27	No
Mean ± SD, mmol/L	1.7 ± 1.4		NA	NA	NA
27. HDL, n (%)		**Partially ascertainable:** Data for 4812 (63.8%) patients were captured in OLDW			
Mean ± SD, mg/dL	43.4 ± 10.6		45.6 ± 12.5	0.19	Yes
Mean ± SD, mmol/L	1.1 ± 0.3		NA	NA	NA
28. LDL, n (%)		**Partially ascertainable:** Data for 4741 (62.9%) patients were captured in OLDW			
Mean ± SD, mg/dL	90.5 ± 31.7		90.9 ± 33.0	0.01	Yes
Mean ± SD, mmol/L	2.3 ± 0.8		NA	NA	NA
N (%) <100 mg/dL	3,348 (66.3)		NA	NA	NA
29. UACR, n (%)		**Partially ascertainable**: Data for only 1554 (20.6%) patients were captured in OLDW			
Medium (Q1, Q2), mg/g	6.4 (3.1, 16.9)		11.0 (5.5, 29.4)		
N (%) <30 mg/g creatinine	4241 (84.1)		1169 (75.2)	0.22	No
30. Fasting glucose, n (%)		**Not ascertainable:** Data for only 136 (1.8%) patients			
Mean ± SD, mg/dL	151.5 ± 30.9		-	-	-
Mean ± SD, mmol/L	8.4 ± 1.7		NA	NA	NA

		captured in OLDW (research lab)			
31. eGFR, n (%)		**Partially ascertainable:** Data for 5340 (70.8%) patients were captured in OLDW			
Mean ± SD, mL/min/1.73 m^2	95.3 ± 16.9		84.9 ± 17.9	0.60	No
N (%) <60 mL/min/1.73 m^2	121 (2.4)		510 (9.5)	0.30	
32. Serum creatinine, n (%)		**Partially ascertainable:** Data for 5340 (70.8%) patients were captured in OLDW	5340/7540 (70.8)		
Mean ± SD, mg/dL	0.83 ± 0.2		0.88 (0.20)	0.25	No
33. Fasting C-peptide, n (%)		**Not ascertainable**: Data for only 60 (0.8%) patients were captured in OLDW (research labs)			
Mean ± SD. nmol/L	1.34 ± 0.6		-	-	-
34. Fasting insulin, pmol/L	129.4 ± 95.4	**Not ascertainable**: Data for only 5 (0.1%) patients were captured in OLDW (research labs)	-	-	-
Fasting insulin, mU/L)	21.6 ± 15.9		-	-	-

*N was 5,047 except for depression/anxiety medication question (see next note).
†This question was added after the study started and was answered by 2,498 participants at baseline. Of these, 472 participants answered "yes" and 2,032 participants answered "no": 472/2,502 = 0.19.
mm Hg, millimeters of mercury; mmol/L, millimole per liter; ng/mL, nanograms per milliliter; OLDW, OptumLabs Data Warehouse; SD, standard deviation; UACR, urinary albumin to-creatinine ratio.

Discussion

In the original GRADE analysis plan, a discrete time logistic regression model was proposed to estimate event rates across time and be flexible to non-proportional hazards. However, in the primary publication for the GRADE trial,[3] the analysis was changed to a restricted mean survival time, which cannot be directly compared with the estimates from the trial emulation following the original analysis plan. Similarly, the PRONOUNCE trial specified prior hormonal therapy (unless terminated at least 12 months prior to trial) as an exclusion criterion on ClinicalTrials.gov, but ultimately did not use it as an exclusion criterion in the published results. Therefore, our emulation excluded these patients, which accounted for 8.1% of the published PRONOUNCE trial's population. This underscores the importance of updating ClinicalTrials.gov and maintaining transparent study protocols and data sharing plans.

References

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2. Deng Y, Polley EC, Wallach JD, et al. Emulating the GRADE trial using real world data: retrospective comparative effectiveness study. *BMJ* 2022; 379: e070717. 20221003. DOI: 10.1136/bmj-2022-070717.
3. Nathan DM, Lachin JM, Balasubramanyam A, et al. Glycemia Reduction in Type 2 Diabetes - Glycemic Outcomes. *N Engl J Med* 2022; 387: 1063-1074. DOI: 10.1056/NEJMoa2200433.