Supplementary material

Supplementary Table 1. List of items for the construction of a Frailty Index based on the ADVANCE Study data (N=11140)

	Items	Scoring	Variable name	Missing	Note
1	HbA1c	< 8.2%: 0 ≥ 8.2%: 1	Recode from HBA1C	54 (0.5%)	Use the cut-off point of 75th percentile.
2	Currently treated hypertension	No: 0 Yes: 1	HYPER	0	
3	Systolic blood pressure	< 157.50 mmHg: 0 ≥ 157.50 mmHg: 1	Recode from SBP	1 (0.01%)	Use the cut-off point of 75th percentile
4	Diastolic blood pressure	< 87.50 mmHg: 0 ≥ 87.50 mmHg: 1	Recode from DBP	1 (0.01%)	Use the cut-off point of 75th percentile
5	Atrial fibrillation	No: 0 Yes: 1	AF, ECG	13 (0.1%)	Combine history of AF and ECG
6	Stroke or TIA	No: 0 Yes: 1	STROKE, TIA	0	Combine stroke and TIA
7	Heart failure	No: 0 Yes: 1	HF	0	
8	Chronic kidney disease	GFR≥60 ml/min: 0 GFR<60 ml/min: 1	CREATININE, AGE, SEX, WEIGHT	47 (0.4%)	Calculate from creatinine, age, weight, gender
9	Hospitalisation due to unstable angina	No: 0 Yes: 1	ANGINA	0	
10	Myocardial infarction	No: 0 Yes: 1	MI	0	
11	CABG/PTCA	No: 0 Yes: 1	CABG	0	
12	Q wave on ECG	No: 0 Yes: 1	Q_WAVES	18 (0.2%)	
13	Peripheral revascularisation (angioplasty or surgery)	No: 0 Yes: 1	REVASC	0	
14	Amputation secondary to vascular disease	No: 0 Yes: 1	AMPUTATION	0	
15	Chronic ulceration on leg/foot	No: 0 Yes: 1	Recode from ULCER_L and ULCER_R	1 (0.01%)	
16	HDL cholesterol	≥ 1 mmol/l: 0 < 1 mmol/l: 1	HDL_CHOL	14 (0.1%)	Use the cut-off point of 25th percentile
17	LDL cholesterol	< 3.70 mmol/l: 0 ≥ 3.70 mmol/l: 1	LDL-CHOL	121 (1.1%)	Use the cut-off point of 75th percentile
18	Triglyceride	< 2.30 mmol/l: 0 ≥ 2.30 mmol/l: 1	TRIGLYC	15 (0.1%)	Use the cut-off point of 75th percentile

19	Suspected Dementia	No: 0 Yes: 1	DEMENTIA	1 (0.01%)	
20	Cognition problem based on MMSE	MMSE≥25: 0 MMSE 21-24: 0.5 MMSE <21: 1	Recode from MMSE	8 (0.1%)	
21	Blindness	No: 0 Yes: 1	BLINDNESS	0	
22	Other eye problems (Retinal photocoagulation therapy, macular oedema, proliferative retinopathy)	No: 0 Yes: 1	RETINAL, MACULAR_O EDEMA, PROLIF_RETI NO	0	
23	Polypharmacy (use≥5 drugs)	No: 0 Yes: 1	Variables related to medications	0	We calculate the total number of medications and choose the cut point of 5
24	Underweight	No: 0 Yes: 1	Recode from BMI	4 (0.04%)	Recode from BMI <18.5
25	High waist circumference	No: 0 Yes: 1	Recode WAIST	6 (0.1%)	Defined as: Waist Cx ≥102 in men, ≥88 in women
26	Sedentary	No: 0 Yes: 1	Recode from EXERCISE_MI LD=0 and EXERCISE_M ODR=0	0	Defined as the number of times spent for moderate and mild exercise last week ="0"
27	Need help with everyday activities	No: 0 Yes: 1	HELP	0	
28	Currently drink alcohol once a week or more	No: 0 Yes: 1	CURR_DRINK ER	0	
29	EQ5D Mobility: problems in walking about	Have no problem: 0 Have some problem: 0.5 Unable to walk: 1	MOBILITY	59 (0.5%)	
30	EQ5D Self-care: problems with washing or dressing	Have no problem: 0 Have some problem: 0.5 Unable to wash/dress: 1	PERSONAL_C ARE	59 (0.5%)	
31	EQ5D Usual Activities: problems doing usual activities	Have no problem: 0 Have some problem: 0.5 Unable to do: 1	ACTIVITIES	59 (0.5%)	
32	EQ5D Pain/Discomfort:	No pain/discomfort: 0	PAIN	59 (0.5%)	

		Some pain/discomfort: 0.5 Extreme pain/discomfort: 1			
33	EQ5D Anxiety/Depression	No anxiety/depression: 0 Anxiety/depression to some extent: 0.5 Extreme anxiety/depression: 1	ANXIETY	59 (0.5%)	
34	Poor self-rated health	No: 0 Yes: 1	Recode from HEALTH_SCALE	62 (0.6%)	Use the cut point of the lowest 25th of the self-rated health scale (<70)

All 34 variables were present in 10828 participants, missingness occurred in 312 participants (Missing 1 variable: 208 participants; Missing 2 variables: 39 participants; Missing 3 variables: 5 participants; Missing 4 variables: 1 participant; Missing 6 variables: 58 participants; Missing 8 variables: 1 participant)

Supplementary Table 2. Unadjusted rates (95% CI) per 1000 person years for outcomes in ADVANCE study participants by glucose intervention

Events	Intensive glucose control group (n=5571)	Standard control group (n=5569)	P-value
Primary study outcomes:			
Combined macrovascular and microvascular events	40.49 (38.06, 43.06)	45.09 (42.52, 47.81)	0.013
Microvascular events	20.50 (18.82, 22.33)	23.70 (21.89, 25.67)	0.015
Macrovascular events	21.51 (19.79, 23.37)	22.81 (21.04, 24.73)	0.319
Secondary study outcomes:			
All-cause mortality	18.62 (17.05, 20.32)	19.92 (18.30, 21.68)	0.278
Cardiovascular mortality	9.48 (8.38, 10.72)	10.82 (9.64, 12.14)	0.123
Severe hypoglycaemia	5.67 (4.83, 6.66)	3.05 (2.46, 3.80)	<0.001

Supplementary Table 3. Unadjusted rates (95% CI) per 1000 person years for outcomes in ADVANCE study participants by blood pressure lowering treatment
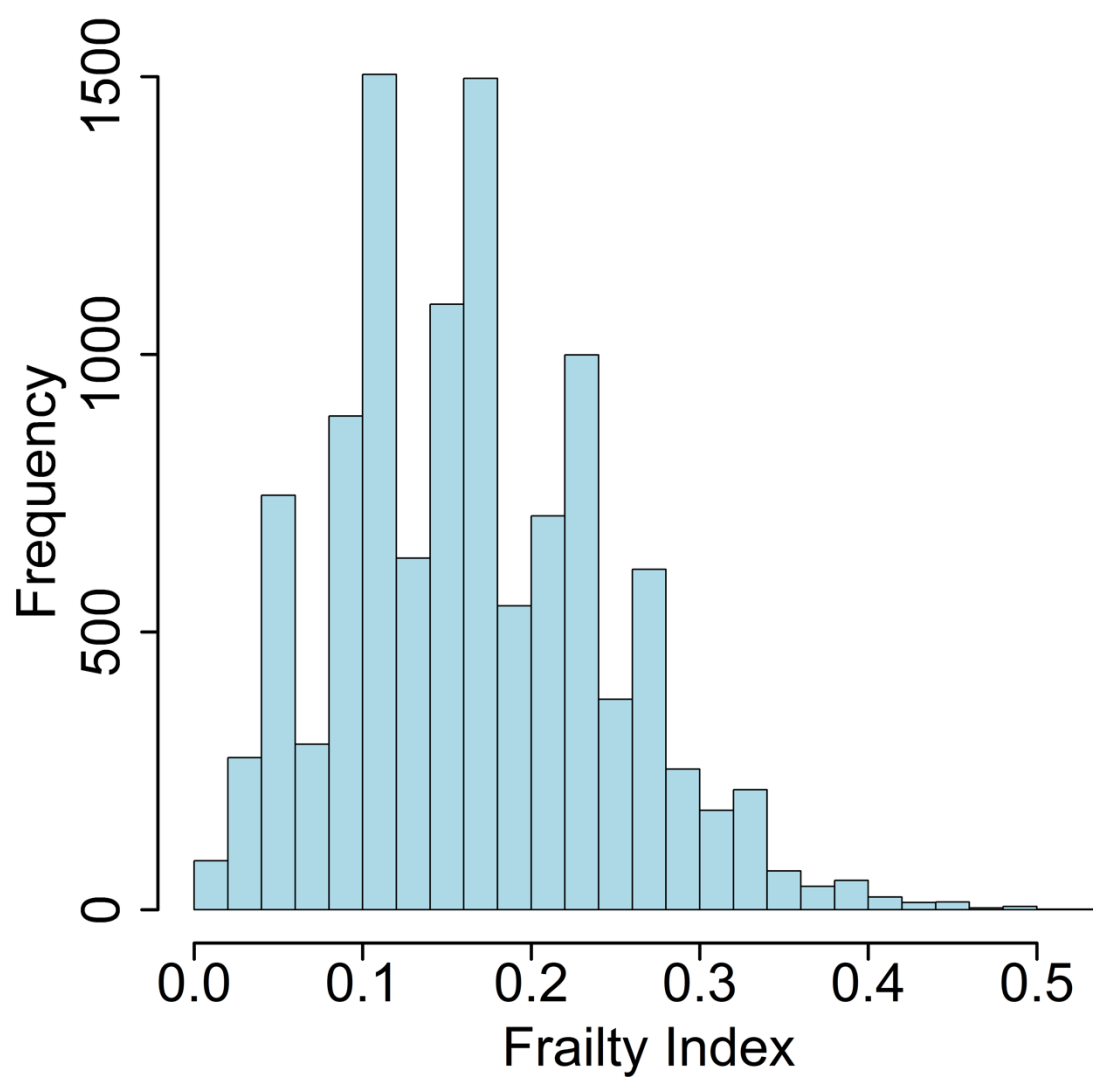
Events	BP lowering treatment (n=5569)	Placebo (n=5571)	P-value
Primary study outcomes:			
Combined macrovascular and microvascular events	38.13 (35.67, 40.77)	41.98 (39.38, 44.75)	0.042
Microvascular events	18.95 (17.26, 20.81)	20.77 (18.99, 22.72)	0.165
Macrovascular events	20.58 (18.81, 22.50)	22.47 (20.62, 24.49)	0.163
Secondary study outcomes:			
All-cause mortality	17.00 (15.42, 18.73)	19.75 (18.04, 21.62)	0.026
Cardiovascular mortality	8.81 (7.69, 10.08)	10.80 (9.56, 12.20)	0.028

Supplementary Table 4: Subgroup analysis on the effect of frailty on outcomes, by age group
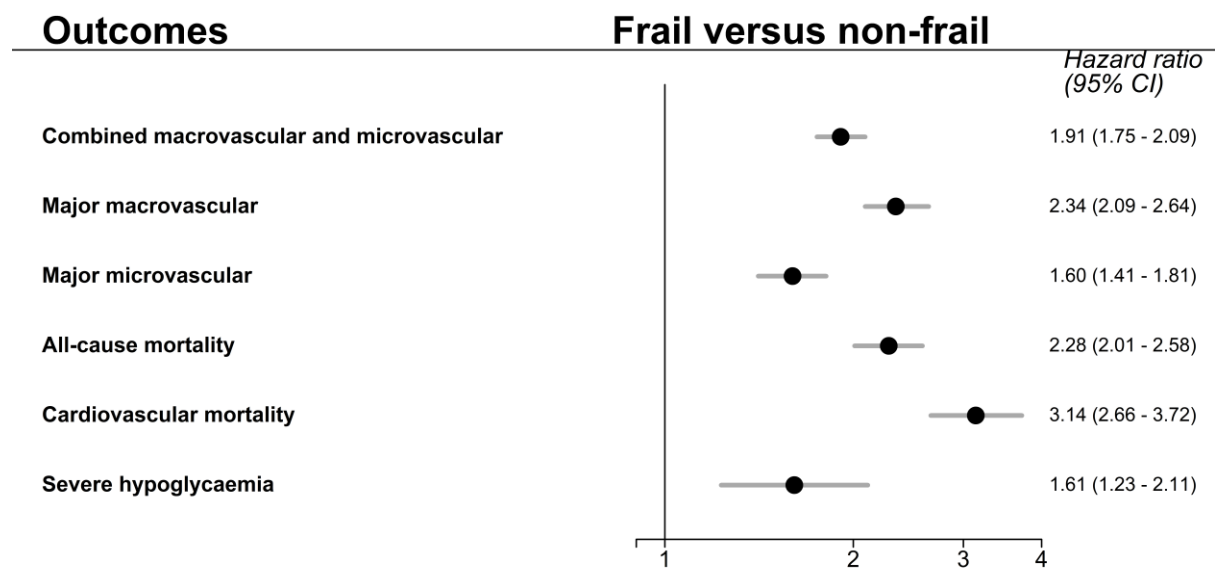
Outcome & subgroup	HR (95%CI)	P value for interaction
Combined major macrovascular and microvascular		
<65 years	1.61 (1.39, 1.87)	0.001
≥65 years	2.16 (1.93, 2.41)	
All-cause mortality		
<65 years	2.47 (1.90, 3.20)	0.629
≥65 years	2.30 (2.00, 2.64)	
Severe hypoglycaemia		
<65 years	1.23 (0.71, 2.14)	0.215
≥65 years	1.82 (1.33, 2.49)	

Supplementary Table 5: Subgroup analysis for the association of randomised treatments on outcomes by age group in frail and non-frail participants

Outcome & subgroup	Frail		Not frail		Comparison
	HR (95%CI)	P value for interaction	HR (95%CI)	P value for interaction	P value for 3-way interaction
Intensive glucose control vs standard control					
Combined major macrovascular and microvascular					
<65 years	1.14 (0.90, 1.45)	0.308	0.74 (0.62, 0.88)	0.079	0.062
≥65 years	0.98 (0.83, 1.17)		0.91 (0.79, 1.04)		
All-cause mortality					
<65 years	1.01 (0.69, 1.47)	0.507	0.87 (0.61, 1.24)	0.767	0.492
≥65 years	1.17 (0.94, 1.45)		0.82 (0.68, 0.99)		
Severe hypoglycaemia					
<65 years	8.10 (1.86, 35.24)	0.049	2.65 (1.37, 5.15)	0.127	0.277
≥65 years	1.71 (1.03, 2.85)		1.46 (0.99, 2.15)		
Blood pressure lowering treatment vs placebo					
Combined major macrovascular and microvascular					
<65 years	0.90 (0.70, 1.17)	0.541	0.96 (0.80, 1.16)	0.166	0.182
≥65 years	1.00 (0.83, 1.20)		0.81 (0.70, 0.94)		
All-cause mortality					
<65 years	0.91 (0.61, 1.36)	0.869	0.87 (0.59, 1.30)	0.548	0.590
≥65 years	0.94 (0.75, 1.19)		0.76 (0.62, 0.93)		

Supplementary Figure 1. The distribution of the Frailty Index in participants of the ADVANCE Trial

Outcomes   Frail versus non-frail

	Hazard ratio (95% CI)
Combined macrovascular and microvascular	1.91 (1.75 - 2.09)
Major macrovascular	2.34 (2.09 - 2.64)
Major microvascular	1.60 (1.41 - 1.81)
All-cause mortality	2.28 (2.01 - 2.58)
Cardiovascular mortality	3.14 (2.66 - 3.72)
Severe hypoglycaemia	1.61 (1.23 - 2.11)

Supplementary Figure 2. The unadjusted hazard ratios of frailty (frail versus non-frail) on the study outcomes (all treatment groups combined)