

ONLINE-ONLY SUPPLEMENTAL MATERIAL

Intensive risk factor management and cardiovascular autonomic neuropathy in type 2 diabetes: the ACCORD Trial

Yaling Tang, MD, MMSc^{1,2}, Hetal Shah, MD, MPH^{1,2}, Carlos Roberto Bueno Junior, PhD¹, Xiuqin Sun, MD^{1,3}, Joanna Mitri, MD, MS^{1,2}, Maria Sambataro, MD⁴, Luisa Sambado, PhD⁴, Hertz C. Gerstein, MD, MSc⁵, Vivian Fonseca⁶, Alessandro Doria, MD, PhD, MPH^{1,2*} and Rodica Pop Busui, MD, PhD^{7*}

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Acknowledgments concerning the original ACCORD trial

Members of the ACCORD DSMB included Antonio M. Gotto Jr. (chair), Kent Bailey, Dorothy Gohdes, Steven Haffner, Roland Hiss, Kenneth Jamerson, Kerry Lee, David Nathan, James Sowers, and LeRoy Walters. The following companies provided study medications, equipment, or supplies: Abbott Laboratories (Abbott Park, IL), Amylin Pharmaceuticals (San Diego, CA), AstraZeneca (Wilmington, DE), Bayer (Tarrytown, NY), Closer Healthcare (Tequesta, FL), GlaxoSmithKline (Philadelphia, PA), King Pharmaceuticals (Bristol, TN), Merck (Whitehouse Station, NJ), Novartis (East Hanover, NJ), NovoNordisk (Princeton, NJ), Omron Healthcare (Schaumburg, IL), Sanofi (Bridgewater, NJ), Schering-Plough (Kenilworth, NJ), and Takeda Pharmaceuticals (Deerfield, IL). None of these companies had an interest or bearing on this study.

Supplemental Figure Legends

Supplementary Figure 1. Distribution of follow-up months at the end of the ACCORD glycemic trial intervention (date of transition of participants from the intensive arm to standard treatment).

Supplementary Figure 2. Prevalence of CAN during the ACCORD study. **A.** Prevalence of CAN in the overall ACCORD cohort by glycemic treatment. **B.** Prevalence of CAN in the ACCORD-BP cohort by treatment. **C.** Prevalence of CAN in the ACCORD Lipid cohort by treatment.

Supplementary Figure 3. Effects of interventions in ACCORD on SDNN, and rMSSD. The primary model was adjusted by fixed effects including trial assignments, seven clinical center networks, and time after randomization, prior CVD events, baseline SDNN, rMSSD correspondingly. The full model was adjusted by additional baseline characteristics as fixed effects, namely age, gender, diabetes duration, HbA1c, body mass index (BMI), height, alcohol, cigarettes, systolic and diastolic blood pressure, low density lipoprotein cholesterol (LDLc), triglycerides, and high density lipoprotein cholesterol (HDLc), urinary albumin/creatinine ratio (UACR) and use of thiazolidinediones (TZDs), insulin, beta-blockers, ACE inhibitors/ARB, statins. Both models included participants as random effects.

Supplementary Table 1. Baseline Characteristics of participants excluded vs. included.

Baseline characteristic	All participants		
	Excluded (N=2,976)	Included (N=7,275)	P-value
Female	1,040 (34.9)	2,912 (40.0)	<0.0001
Age (years)	63.8 ± 7.0	62.3 ± 6.5	<0.0001
DM duration (years)	11.1 ± 7.8	10.7 ± 7.5	0.02
BMI (kg/m ²)	32.3 ± 5.5	32.2 ± 5.4	0.68
Waist (cm)	107.3 ± 13.8	106.5 ± 13.6	0.01
Height (cm)	170.7 ± 9.7	169.9 ± 9.8	0.0004
HbA1c (%)	8.31 ± 1.02	8.27 ± 1.00	0.05
Fasting glucose (mg/dL)	173.0 ± 54.6	175.0 ± 52.9	0.09
SBP (mmHg)	136.6 ± 16.9	136.0 ± 16.3	0.06
DBP (mmHg)	74.3 ± 10.7	74.9 ± 10.1	0.01
LDL (mg/dL)	104.6 ± 33.2	104.8 ± 33.0	0.79
HDL (mg/dL)	41.8 ± 11.6	41.8 ± 11.0	0.93
Women	47.6 ± 12.4	46.7 ± 11.9	0.03
Men	38.7 ± 9.8	38.5 ± 9.0	0.51
Total cholesterol (mg/dL)	181.4 ± 40.4	183.5 ± 40.1	0.01
Triglycerides (mg/dL)*	149 (101 – 219)	158 (108 -231)	<0.0001
eGFR (ml/min/1.73 m ²)	88.6 ± 22.8	90.8 ± 22.5	<0.0001
UACR (mg/mmol)*	1.7 (0.8 – 6.2)	1.3 (0.7 -4.2)	<0.0001
Previous CV event †	1,193 (40.1)	2,416 (33.2)	<0.0001
Report of retinopathy	338 (13.3)	717 (11.2)	0.01
Current smoker	408 (13.7)	839 (11.5)	0.002
Insulin therapy	1,089 (36.7)	2,493 (34.4)	0.02
Previous smoker	1,375 (53.9)	3,239 (50.9)	0.01
Intensive glycemic arm	1,532 (51.5)	3,596 (49.4)	0.06
BP trial	1,393 (46.8)	3,349 (45.9)	0.41
Intensive BP arm	707 (50.8)	1,655 (49.6)	0.45
Lipid trial	1,583 (53.2)	3,936 (49.1)	0.41
Fenofibrate	777 (49.1)	1,988 (50.5)	0.33

DM, diabetes mellitus; BMI, body mass index; HbA1c, Hemoglobin a1c; SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; UACR, urine albumin-to-creatinine ratio; CV, cardiovascular. Except where noted, data are means ± SD for continuous variables and counts (%) for categorical data. * Medians (IQR). †Prior cardiovascular event: In ACCORD, this includes secondary prevention status or history of myocardial infarction, stroke, angina and/or ischemic changes (ECG) on Graded Exercise Tolerance Test or positive imaging, coronary revascularization procedures or other revascularization procedures at baseline.

Supplementary Table 2. Number of CAN evaluations by trial assignment group.

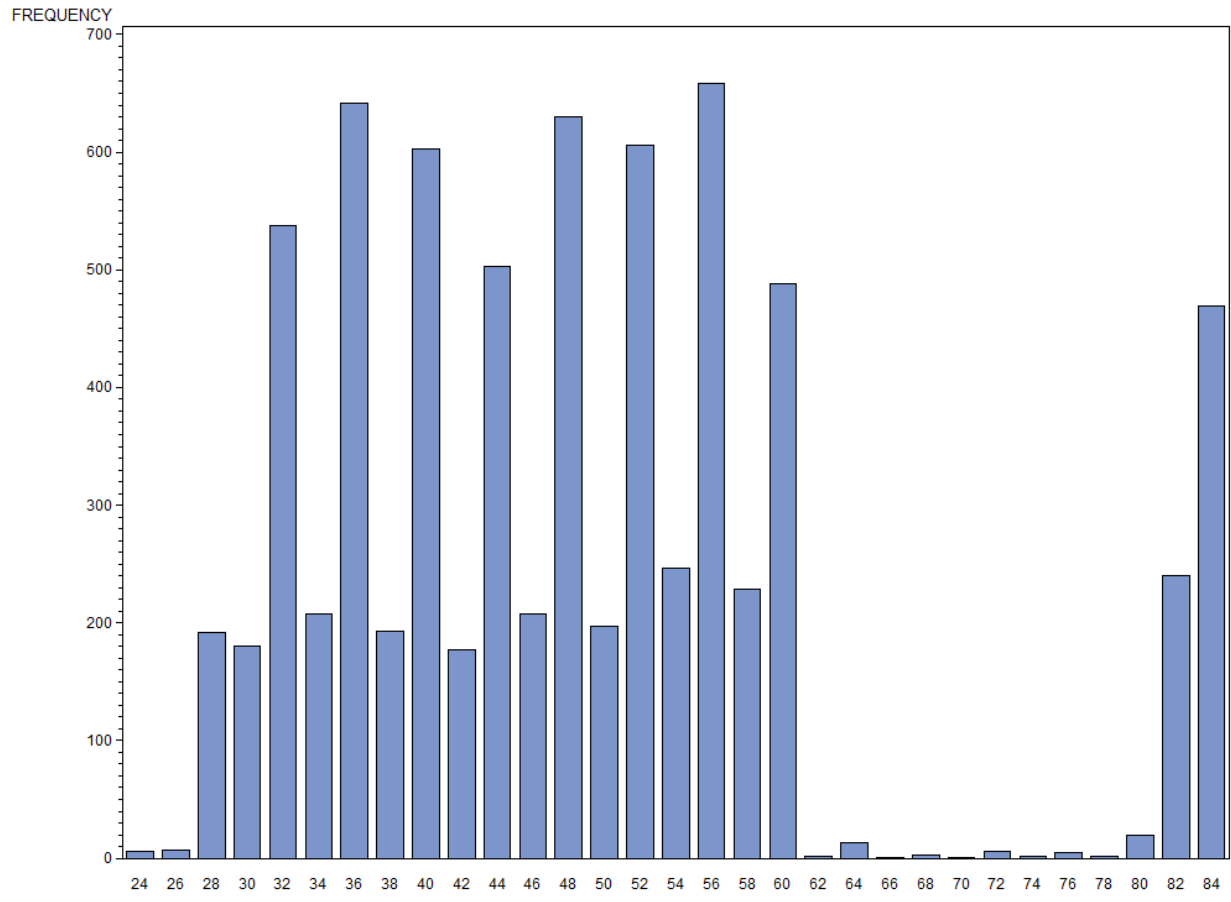
Total number of CAN evaluation	Glycaemia trial		BP trial		Lipid trial	
	Intensive	Standard	Intensive	Standard	Fenofibrate	Placebo
	(N=4,055)	(N=4,093)	(N= 1,855)	(N= 1,884)	(N = 2,224)	(N = 2,185)
1*	459 (11.32)	414 (10.11)	200 (10.78)	199 (10.56)	236 (10.61)	238 (10.89)
2	622 (15.34)	607 (14.83)	256 (13.80)	264 (14.01)	362 (16.28)	347 (15.88)
3	1,328 (32.75)	1,386 (33.86)	609 (32.83)	601 (31.90)	755 (33.95)	749 (34.28)
4	1,496 (36.89)	1,516 (37.04)	724 (39.03)	741 (39.33)	774 (34.80)	773 (35.38)
5	150 (3.70)	170 (4.15)	66 (3.56)	79 (4.19)	97 (4.36)	78 (3.57)

*873 participants had CAN evaluation only at baseline. These participants were not included in this study.

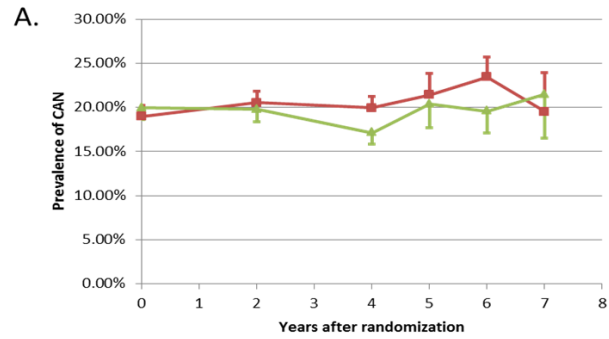
Supplementary Table 3. Effects of interventions in ACCORD on CAN adjusted by time-dependent cardiovascular events.

CVD event used for adjustment	Definition	Intensive glycemic control vs. standard glycemic control		Intensive BP control vs. standard BP control		Fenofibrate + statin vs. placebo + statin	
		OR (95%CI)	P-value	OR (95%CI)	P-value	OR (95%CI)	P-value
ACCORD primary outcome	Non-fatal myocardial infarction, non-fatal stroke, or death from cardiovascular causes.	0.840 (0.747 - 0.945)	0.004	0.752 (0.633 – 0.895)	0.001	0.915 (0.781 – 1.073)	0.27
Non-fatal myocardial infarction		0.840 (0.747 – 0.944)	0.003	0.752 (0.633 – 0.894)	0.001	0.915 (0.781 – 1.073)	0.27
Congestive heart failure	Fatal or hospitalization-requiring congestive heart failure	0.838 (0.746 – 0.942)	0.003	0.753 (0.633 – 0.895)	0.001	0.920 (0.785 – 1.078)	0.30
Expanded macrovascular events	Primary outcome events plus any revascularization or hospitalization for heart failure	0.841 (0.748 – 0.945)	0.004	0.756 (0.635 – 0.899)	0.002	0.925 (0.789 – 1.078)	0.34
Major coronary events	Fatal coronary heart disease (CHD), non-fatal MI, or unstable angina.	0.840 (0.747 – 0.945)	0.004	0.752 (0.632 – 0.894)	0.001	0.917 (0.782 – 1.074)	0.28

Supplementary Figure 1. Distribution of follow-up months at the transition date.

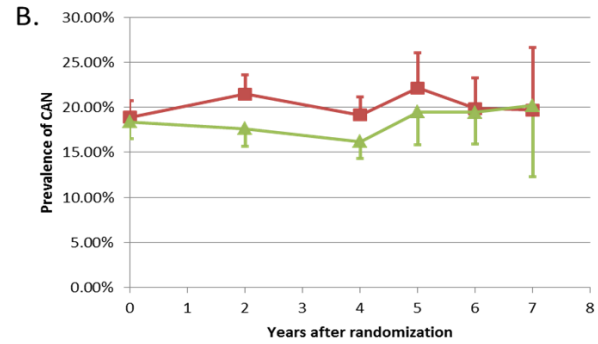


Supplementary Figure 2. Prevalence of CAN in ACCORD study.



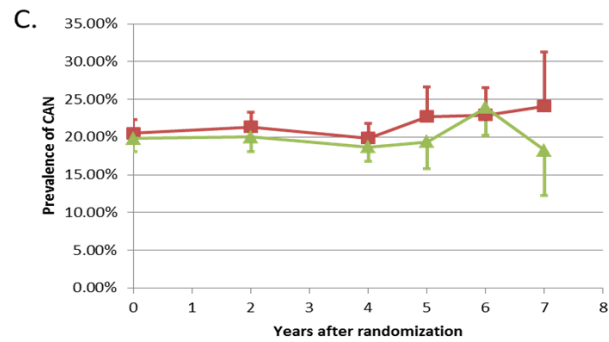
— standard glyceric arm — intensive glyceric arm

Years	0	2	4	5	6	7
Events/N						
Standard	698/3,679	650/3,166	641/3,211	719/915	807/1,054	210/261
Intensive	717/3,596	611/3,089	538/3,146	182/894	191/976	26/261
OR (95%CI)		0.92 (0.81,1.05)	0.80 (0.70,0.91)	0.93 (0.74,1.18)	0.78 (0.63,0.97)	1.07 (0.68,1.67)
P		0.23	0.0009	0.56	0.03	0.78



— Standard BP control — Intensive BP control

Years	0	2	4	5	6	7
Events/N						
Standard	318/1,685	311/1,448	282/1,473	97/438	103/519	25/127
Intensive	304/1,655	253/1,437	234/1,444	89/457	92/173	20/99
OR (95%CI)		0.76 (0.63, 0.92)	0.81 (0.66, 0.98)	0.82 (0.59,1.15)	0.99 (0.72, 1.37)	0.97 (0.48, 1.95)
P		0.005	0.03	0.26	0.95	0.93

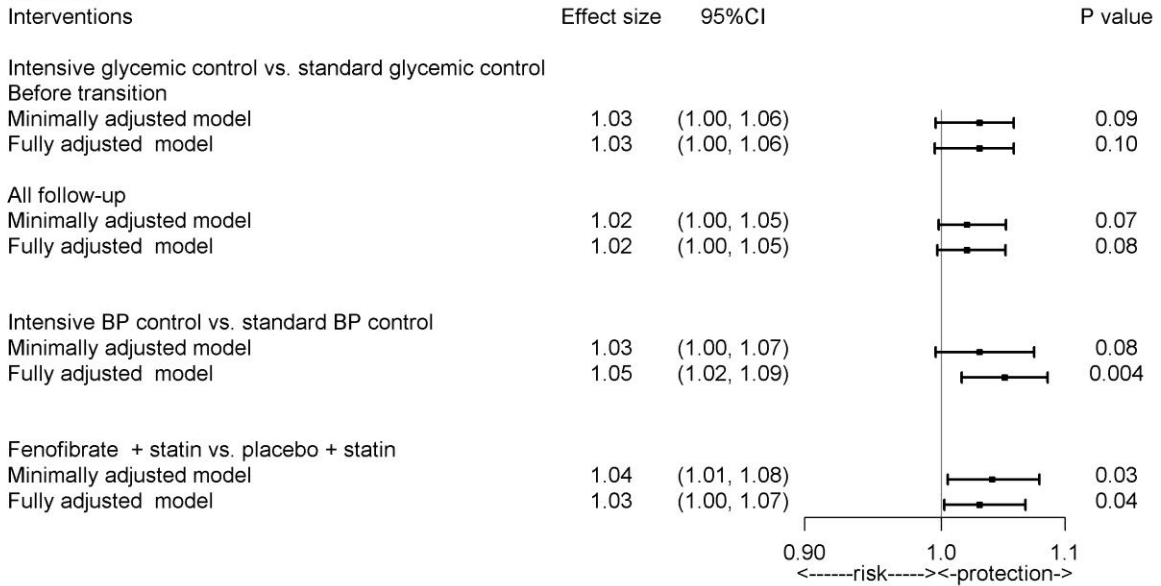


— Placebo — Fibrate

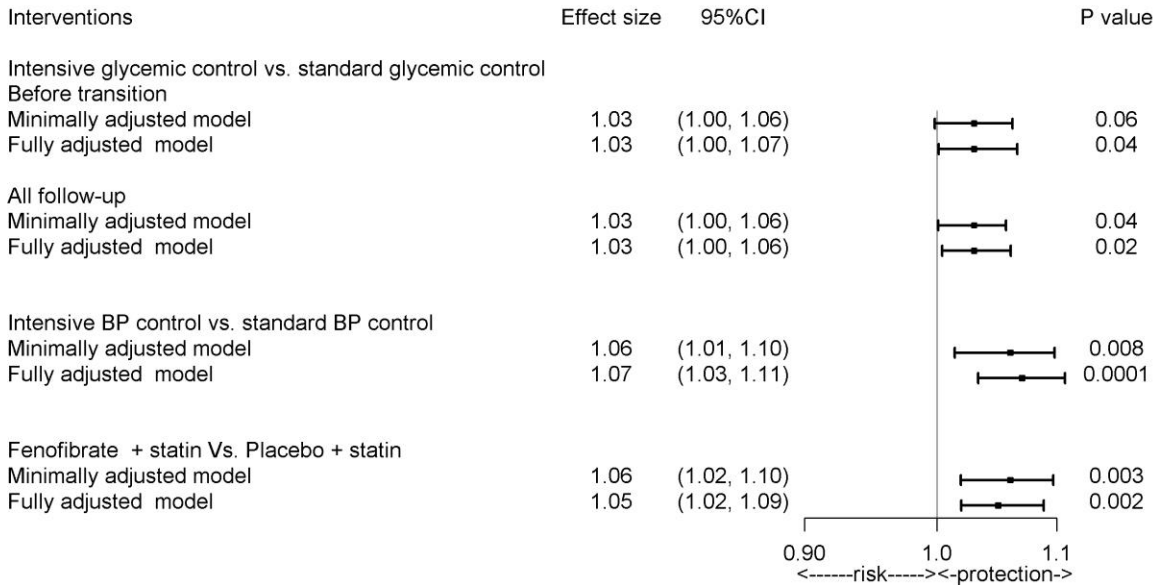
Years	0	2	4	5	6	7
Events/N						
Placebo	399/1,947	356/1,666	340/1,710	101/444	119/519	33/137
Fenofibrate	394/1,988	341/1,704	323/1,730	91/470	124/519	29/159
OR (95%CI)		0.90 (0.75, 1.07)	0.92 (0.77, 1.09)	0.84 (0.61, 1.18)	1.04 (0.77, 1.41)	0.76 (0.42, 1.38)
P		0.24	0.33	0.32	0.78	0.37

Supplementary Figure 3. Effects of interventions in ACCORD on SDNN, and rMSSD.

A. SDNN



B. rMSSD



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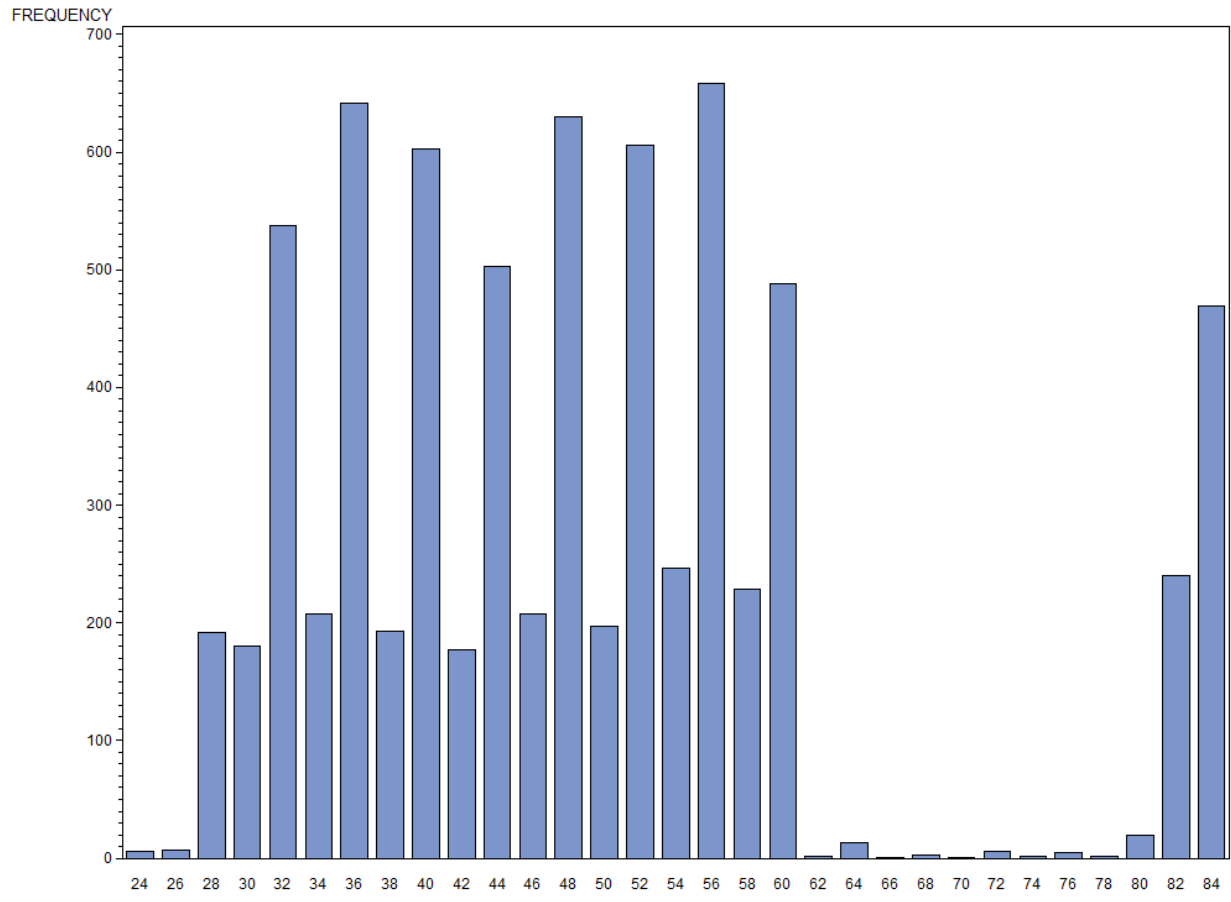
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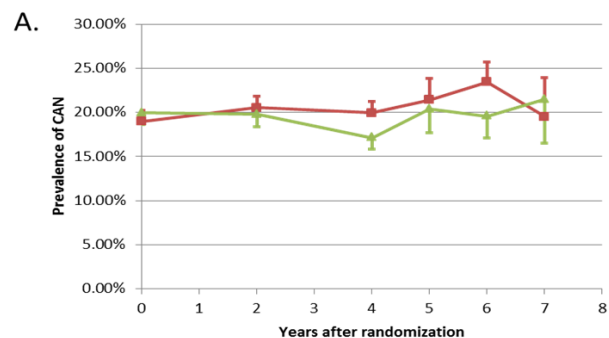
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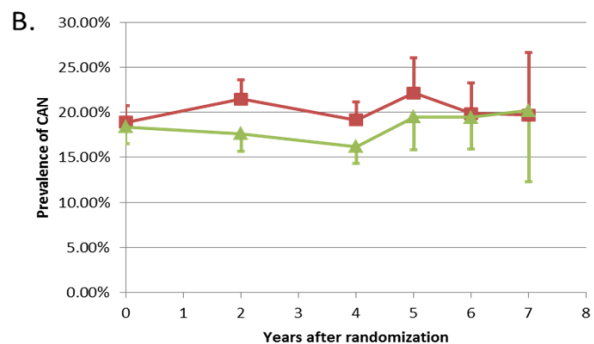


Supplementary Figure 2. Prevalence of CAN in ACCORD study.



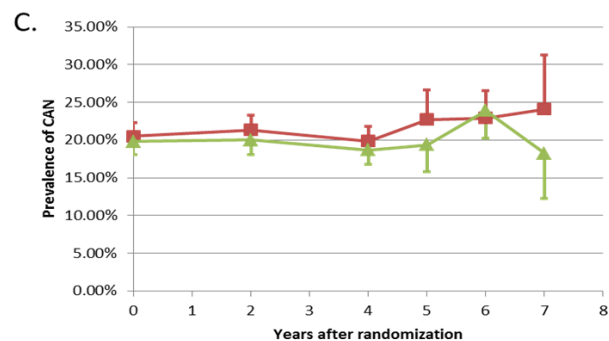
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OR (95%CI)		0.92 (0.81,1.05)	0.80 (0.70,0.91)	0.93 (0.74,1.18)	0.78 (0.63,0.97)	1.07 (0.68,1.67)
P		0.23	0.0009	0.56	0.03	0.78



— Standard BP control — Intensive BP control

Years	0	2	4	5	6	7
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OR (95%CI)		0.76 (0.63, 0.92)	0.81 (0.66, 0.98)	0.82 (0.59,1.15)	0.99 (0.72, 1.37)	0.97 (0.48, 1.95)
P		0.005	0.03	0.26	0.95	0.93

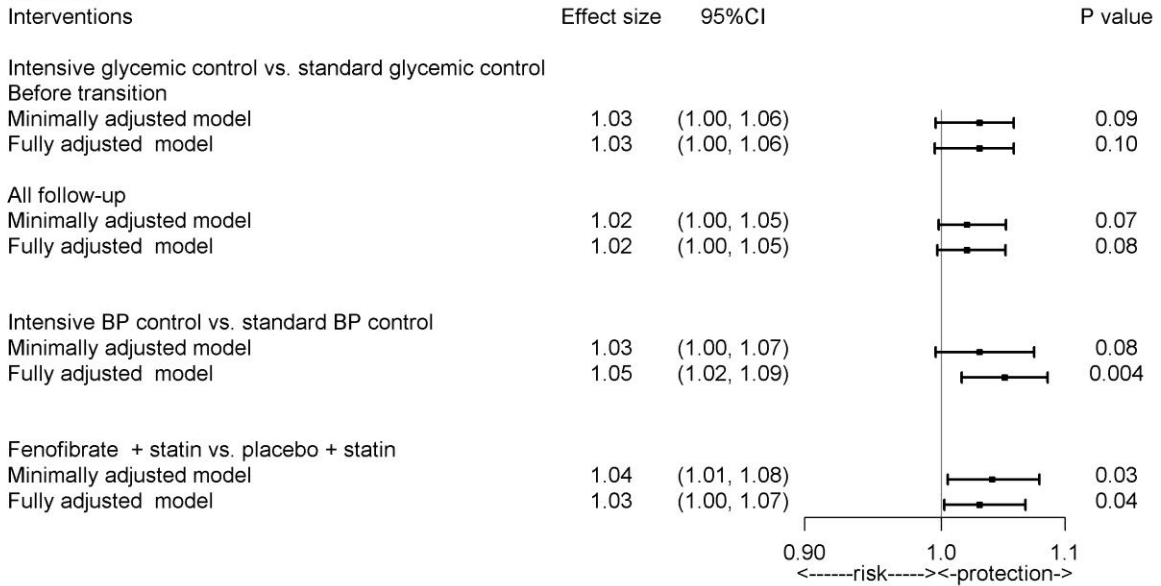


— Placebo — Fibrate

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Placebo	399/1,947	356/1,666	340/1,710	101/444	119/519	33/137
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OR (95%CI)		0.90 (0.75, 1.07)	0.92 (0.77, 1.09)	0.84 (0.61, 1.18)	1.04 (0.77, 1.41)	0.76 (0.42, 1.38)
P		0.24	0.33	0.32	0.78	0.37

Supplementary Figure 3. Effects of interventions in ACCORD on SDNN, and rMSSD.

A. SDNN



B. rMSSD

