Supplemental Material

Table S1. Association between Time in Systolic Blood Pressure Target Range with Clinical Outcomes across Treatment Arm.

	n / N (%)	Unadjusted model		Fully adjusted model	
		HR (95% CI)	*P* value	HR (95% CI)	*P* value
In Spironolactone					
Primary endpoint					
1-SD increment	260/1606 (16.2)	0.79 (0.70, 0.90)	<0.001	0.82 (0.71, 0.95)	0.006
TTR groups					
0-25%	90/490 (18.4)	1.00 (Ref)	-	1.00 (Ref)	-
>25-50%	56/240 (23.3)	1.35 (0.97, 1.89)	0.077	1.11 (0.79, 1.57)	0.551
>50-75%	50/277 (18.1)	0.95 (0.67, 1.34)	0.775	0.76 (0.53, 1.09)	0.141
>75-100%	64/599 (10.7)	0.56 (0.41, 0.77)	<0.001	0.65 (0.46, 0.91)	0.013
All-cause mortality					
1-SD increment	222/1606 (13.8)	0.83 (0.73, 0.95)	0.007	0.82 (0.71, 0.95)	0.008
TTR groups					
0-25%	73/490 (14.9)	1.00 (Ref)	-	1.00 (Ref)	-
>25-50%	43/240 (17.9)	1.27 (0.87, 1.85)	0.215	1.03 (0.70, 1.51)	0.895
>50-75%	44/277 (15.9)	1.03 (0.71, 1.50)	0.859	0.86 (0.59, 1.26)	0.445
>75-100%	62/599 (10.4)	0.68 (0.49, 0.96)	0.026	0.70 (0.49, 0.99)	0.047
Cardiovascular death					
1-SD increment	137/1606 (8.5)	0.79 (0.67, 0.93)	0.006	0.78 (0.65, 0.94)	0.010
TTR groups					
0-25%	49/490 (10.0)	1.00 (Ref)	-	1.00 (Ref)	-
>25-50%	28/240 (11.7)	1.23 (0.77, 1.95)	0.392	1.04 (0.64, 1.68)	0.875
>50-75%	26/277 (9.4)	0.91 (0.57, 1.47)	0.710	0.84 (0.52, 1.37)	0.482
>75-100%	34/599 (5.7)	0.56 (0.36, 0.87)	0.009	0.57 (0.35, 0.91)	0.018
HF hospitalization					

1-SD increment	158/1606 (9.8%)	0.78 (0.67, 0.91)	0.002	0.83 (0.69, 0.99)	0.042
TTR groups					
0-25%	53/490 (10.8)	1.00 (Ref)	-	1.00 (Ref)	-
>25-50%	37/240 (15.4)	1.52 (0.99, 2.31)	0.051	1.21 (0.78, 1.87)	0.390
>50-75%	32/277 (11.6)	1.03 (0.67, 1.60)	0.881	0.76 (0.48, 1.21)	0.246
>75-100%	36/599 (6.0)	0.54 (0.35, 0.82)	0.004	0.67 (0.43, 1.06)	0.088
In Placebo					
Primary endpoint					
1-SD increment	277/1588 (17.4)	0.76 (0.67, 0.86)	<0.001	0.78 (0.67, 0.90)	<0.001
TTR groups					
TTR = 0-25%	116/565 (20.5)	1.00 (Ref)	-	1.00 (Ref)	-
TTR >25-50%	55/223 (24.7)	1.27 (0.92, 1.75)	0.144	1.16 (0.83, 1.63)	0.381
TTR >50-75%	49/249 (19.7)	0.95 (0.68, 1.33)	0.756	0.93 (0.65, 1.33)	0.696
TTR >75-100%	57/551 (10.3)	0.49 (0.36, 0.67)	<0.001	0.55 (0.39, 0.79)	0.001
All-cause mortality					
1-SD increment	218/1588 (13.7)	0.81 (0.71, 0.93)	0.002	0.76 (0.65, 0.89)	<0.001
TTR groups					
0-25%	86/565 (15.2)	1.00 (Ref)	-	1.00 (Ref)	-
>25-50%	45/223 (20.2)	1.42 (0.99, 2.03)	0.059	1.24 (0.85, 1.79)	0.266
>50-75%	37/249 (14.9)	0.98 (0.66, 1.43)	0.900	0.82 (0.55, 1.23)	0.330
>75-100%	50/551 (9.1)	0.60 (0.43, 0.85)	0.004	0.56 (0.39, 0.82)	0.003
Cardiovascular death					
1-SD increment	140/1588 (8.8)	0.80 (0.68, 0.95)	0.009	0.77 (0.63, 0.93)	0.006
TTR groups					
TTR = 0-25%	57/565 (10.1)	1.00 (Ref)	-	1.00 (Ref)	-
TTR >25-50%	27/223 (12.1)	1.29 (0.81, 2.04)	0.281	1.16 (0.72, 1.87)	0.535
TTR >50-75%	25/249 (10.0)	0.99 (0.62, 1.59)	0.984	0.89 (0.54, 1.46)	0.646

TTR >75-100%	31/551 (5.6)	0.56 (0.36, 0.87)	0.010	0.55 (0.34, 0.88)	0.013
HF hospitalization					
1-SD increment	184/1588 (11.6)	0.76 (0.66, 0.88)	<0.001	0.82 (0.68, 0.98)	0.031
TTR groups					
TTR = 0-25%	78/565 (13.8)	1.00 (Ref)	-	1.00 (Ref)	-
TTR >25-50%	34/223 (15.2)	1.15 (0.77, 1.72)	0.499	1.04 (0.68, 1.59)	0.873
TTR >50-75%	34/249 (13.7)	0.97 (0.65, 1.45)	0.890	1.00 (0.65, 1.56)	0.989
TTR >75-100%	38/551 (6.9)	0.49 (0.33, 0.71)	<0.001	0.61 (0.39, 0.96)	0.031

Table S2. Association Between Time in Target Range and Primary End Point across Different Regions.

	n / N	Unadjusted model		Fully adjusted model	
		HR (95% CI)	*P* value	HR (95% CI)	*P* value
Americas region (including US, Canada, Argentina and Brazil)					
1-SD increment	409/1573	0.87 (0.79, 0.96)	0.006	0.89 (0.80, 0.99)	0.026
TTR Groups					
0-25%	152/542	Reference	-	Reference	-
>25-50%	91/291	1.19 (0.92, 1.55)	0.186	1.13 (0.87, 1.47)	0.371
>50-75%	84/339	0.82 (0.63, 1.07)	0.136	0.85 (0.64, 1.12)	0.244
>75-100%	82/401	0.73 (0.56, 0.95)	0.021	0.74 (0.56, 0.97)	0.040
Russia and Georgia					
1-SD increment	128/1621	0.76 (0.65, 0.89)	0.001	0.96 (0.73, 1.26)	0.781
TTR Groups					
0-25%	54/513	Reference	-	Reference	-
>25-50%	20/172	1.09 (0.65, 1.82)	0.747	1.65 (0.90, 3.00)	0.105
>50-75%	15/187	0.73 (0.41, 1.30)	0.286	1.20 (0.62, 2.33)	0.588
>75-100%	39/749	0.51 (0.33, 0.76)	0.001	0.96 (0.50, 1.82)	0.897

Table S3. Association between Time in Target Range and Primary End Point among Patients with

Hypertension.

	n / N	Unadjusted model		Fully adjusted model	
		HR (95% CI)	*P* value	HR (95% CI)	*P* value
1-SD increment	497/2920	0.75 (0.68, 0.83)	<0.001	0.82 (0.74, 0.91)	<0.001
Groups					
0-25%	301/1456	Reference	-	Reference	-
>25-50%	95/584	0.78 (0.62, 0.98)	0.031	0.71 (0.56, 0.89)	0.003
>50-75%	55/369	0.65 (0.49, 0.87)	0.004	0.75 (0.56, 1.00)	0.052
>75-100%	46/511	0.42 (0.31, 0.57)	<0.001	0.60 (0.44, 0.82)	0.002

Table S4. Association Between Time in Target Range and Primary End Point Using Data from 4 Weeks to 4 Months.

	n / N	Unadjusted model		Fully adjusted model	
		HR (95% CI)	*P* value	HR (95% CI)	*P* value
1-SD increment	511/3078	0.77 (0.71, 0.84)	<0.001	0.82 (0.74, 0.90)	<0.001
Groups					
0-25%	209/1076	Reference	-	Reference	-
>25-50%	91/397	1.22 (0.95, 1.55)	0.121	1.07 (0.83, 1.38)	0.595
>50-75%	74/375	1.02 (0.79, 1.33)	0.864	0.99 (0.75, 1.30)	0.940
>75-100%	137/1230	0.55 (0.44, 0.68)	<0.001	0.64 (0.50, 0.81)	<0.001

Table S5. Association Between Time in Target Range and Primary End Point Using Data from Baseline to

12 Months.

	n / N	Unadjusted model		Fully adjusted model	
		HR (95% CI)	*P* value	HR (95% CI)	*P* value
1-SD increment	374/2935	0.76 (0.69, 0.84)	<0.001	0.81 (0.71, 0.92)	0.001
Groups					
0-25%	136/866	Reference	-	Reference	-
>25-50%	95/565	1.05 (0.81-1.36)	0.718	1.00 (0.76, 1.33)	0.985
>50-75%	59/522	0.68 (0.50, 0.93)	0.014	0.65 (0.47, 0.90)	0.010
>75-100%	84/982	0.51 (0.39, 0.67)	<0.001	0.64 (0.47, 0.87)	0.005

Figure S1. Selection of Study Population.


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┌─────────────────────────────────────────┐
│ 3,455 patients were randomized in TOPCAT │
└─────────────────────────────────────────┘
                    │
                    │          ┌──────────────────────────────────────────────┐
                    │          │ •  40 had less than three systolic blood     │
                    ├─────────▶│    pressure measurements.                     │
                    │          │ •  103 primary outcomes happened during      │
                    │          │    first four months.                         │
                    │          │ •  8 had missing covariate data.              │
                    │          └──────────────────────────────────────────────┘
                    ▼
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│ 3,194 patients were included in the study│
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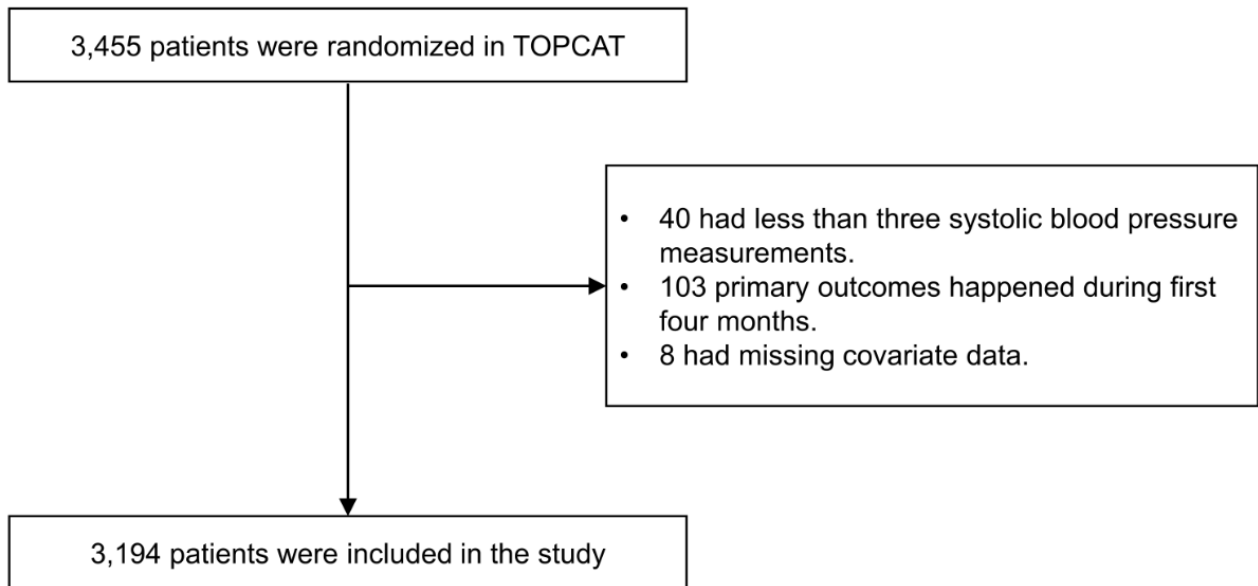
Figure S2. Survival Estimate Across Cardiovascular Outcome According to Time in Target Range Thresholds .