Dapagliflozin In Patients Hospitalized with COVID-19

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on behalf of DARE-19 Investigators

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DApagliflozin in REspiratory failure in patients with COVID-19

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Disclosures

- Research Grants:
  - AstraZeneca, Boehringer Ingelheim
- Clinical Trial Leadership/Consultant:
  - AstraZeneca, Applied Therapeutics, Amgen, Bayer, Boehringer-Ingelheim, Eli Lilly, Janssen, Merck (Diabetes), Novo Nordisk, Sanofi, Vifor Pharma
- DARE-19 Trial was funded by AstraZeneca

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Trial Leadership and Data Analysis

- Investigator-initiated Trial
  - Sponsored by Saint Luke's Mid America Heart Institute
  - Performed in collaboration with AstraZeneca and George Clinical
- Executive Committee
  - Mikhail Kosiborod (Chair), Otavio Berwanger, Gary Koch, Felipe Martinez, Omar Mukhtar, Subodh Verma, Russell Esterline (AZ), Jan Oscarsson (AZ), Anna Maria Langkilde (AZ)
- Data Analysis
  - Fengming Tang, Kensey Gosh, Philip G. Jones (Saint Luke's)
  - Samvel Gasparyan, Joan Buenconsejo, Olof Bengtsson (AZ)
- Independent Data and Safety Monitoring Board
  - James DeLemos (Chair), Robert Guigliano, Carolyn Lam, Ralph D'Agostino Jr

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Background and Rationale

- Patients hospitalized with Covid-19 and cardiometabolic risk factors are at high risk for multi-organ failure and death
- There is a dearth of efficacious therapies that reduce the risk of major clinical events, and large unmet clinical need for additional treatment options
- SGLT2i provide organ protection in patients with chronic cardiometabolic conditions (T2D, HF, CKD) and favorably affect a number of pathophysiologic pathways disrupted during acute illness, such as Covid-19

CKD, chronic kidney disease; HF, heart failure; SGLT2i, sodium-glucose co-transporter-2 inhibitors; T2D, type 2 diabetes.

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Objectives

- We hypothesized that dapagliflozin may reduce the risk of multi-organ failure and death, and improve recovery in patients that are hospitalized with Covid-19 and have cardiometabolic risk factors

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Patient Population

- Key Inclusion Criteria
  - Hospitalization with confirmed/ suspected SARS-CoV-2 for ≤4 days
  - O_2 saturation of ≥94% on ≤5 L/min
  - CXR findings c/w Covid-19
  - ≥1 risk factor (HTN, Type 2 Diabetes, ASCVD, HF, CKD)
- Key Exclusion Criteria
  - Critical illness on presentation
  - eGFR <25 mL/min/1.73m^2
  - Type 1 Diabetes
  - Prior diabetic ketoacidosis

ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HF, heart failure; HTN, hypertension.

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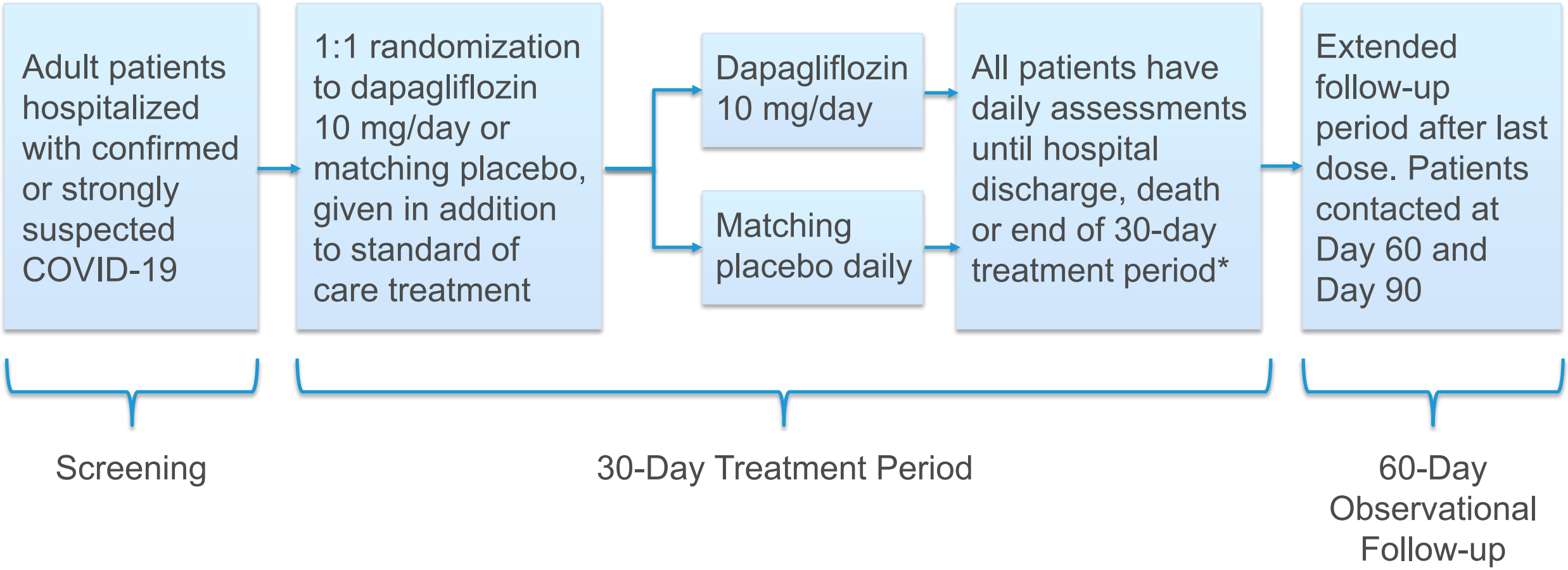
DARE-19 Design



*Discharged patients asked to attend telephone visits at Day 15 and Day 30.

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Dual Primary Endpoints

- Prevention - time to first major clinical event
  - Respiratory (invasive or non-invasive mechanical ventilation)
  - Cardiovascular (pressor, inotropes, new or worsened HF, sustained VT/ VF, resuscitated cardiac arrest)
  - Kidney (doubling of creatinine or initiation of dialysis)
  - Death from any cause
- Recovery - hierarchical composite ranking each patient using the following order
  - Death
  - Organ failure
  - Clinical status if still hospitalized at Day 30
  - Time to hospital discharge before Day 30

HF, heart failure; VT/VF, ventricular tachycardia/ventricular fibrillation.

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DARE-19 Trial

1250 Patients – 7 Countries – 95 Sites

North America:

Canada	4
US	287
Mexico	118

Western Europe:

UK	2

Asia:

India	50

South America:

Brazil	762
Argentina	27

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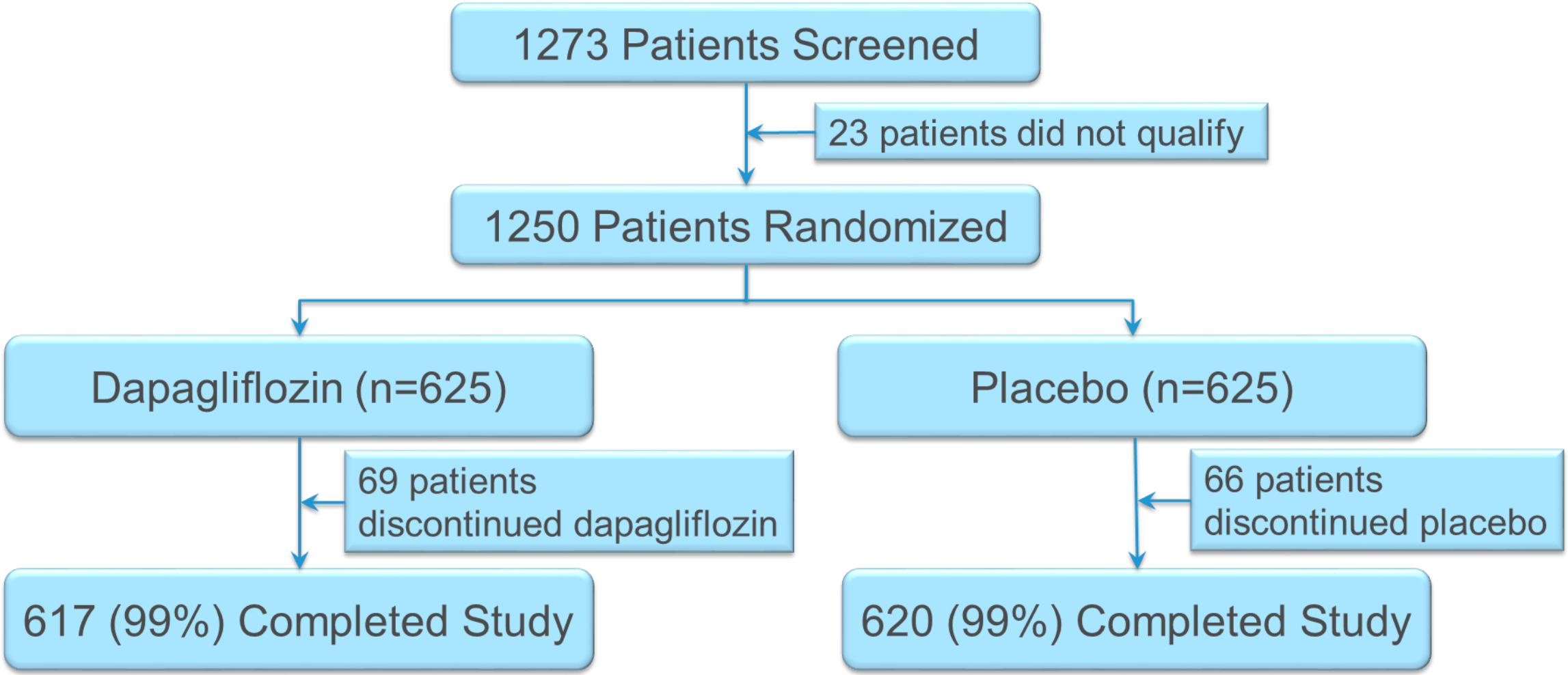
Patient Disposition



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Baseline Characteristics

	Dapagliflozin (N=625)	Placebo (N=625)
Mean age, years	61	62
Female, %	42	44
Inclusion risk factors, %		
Type 2 diabetes	50	52
Heart failure	7	7
Hypertension	84	85
ASCVD	15	17
CKD	6	7
Mean heart rate, beats/min	79	80
Mean systolic blood pressure, mm/Hg	127	127
Mean oxygen saturation, %	96	95
Positive SARS-CoV-2 test, %	93	92
Medication at screening, %		
ACEi/ARB	36	35
Statin	20	23
Insulin	36	35
Remdesivir	18	18
Systemic Steroids	29	31

ACEi/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease.

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Primary Outcome of Prevention: Organ Failure or Death from Any Cause

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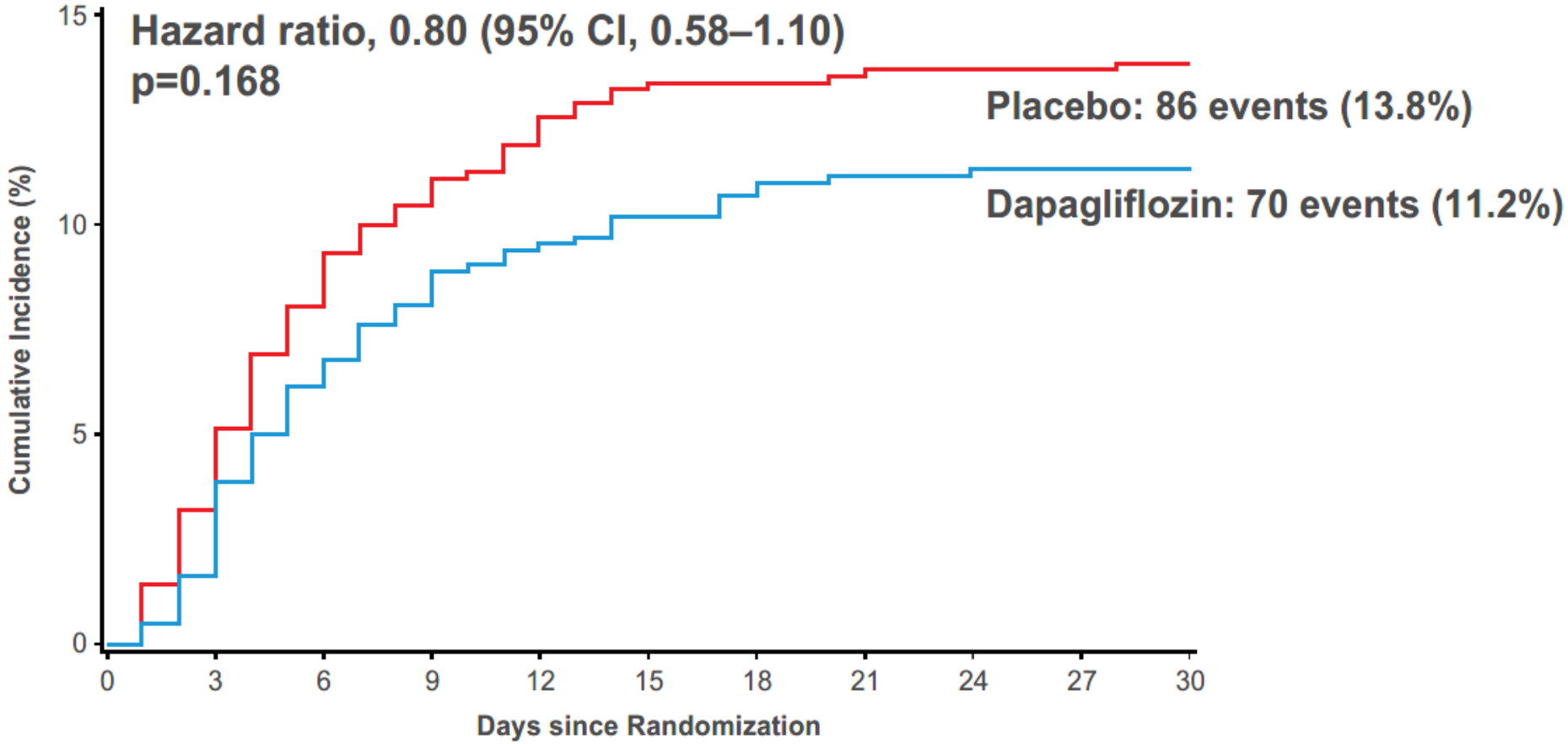
Time to Organ Failure or Death



No. at Risk											
Dapagliflozin	625	610	579	567	559	554	551	548	548	547	546
Placebo	625	601	570	555	546	538	537	536	535	535	534

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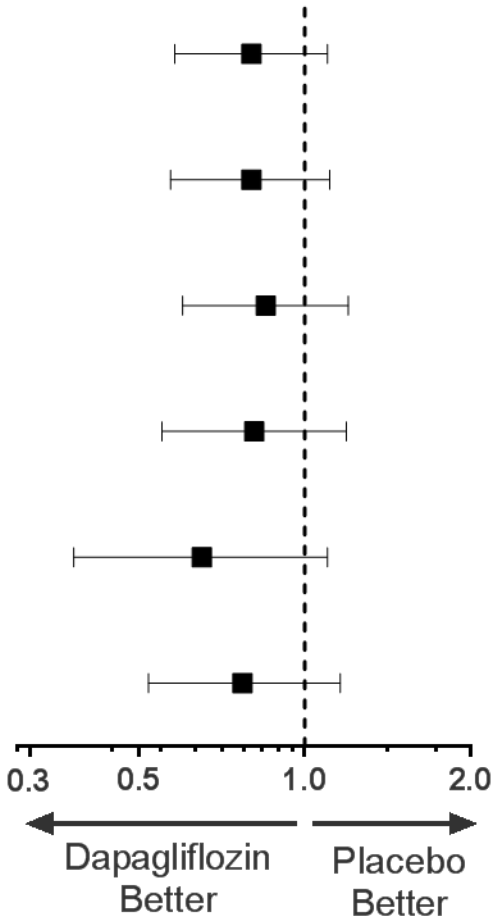
Primary Outcome of Prevention - Components

Outcome, n	Dapagliflozin (N=625)	Placebo (N=625)	Hazard ratio
Primary composite outcome	**70**	**86**	**0.80 (0.58, 1.10)**
New or worsening organ dysfunction	64	80	0.80 (0.57, 1.11)
Respiratory decompensation*	58	70	0.85 (0.60, 1.20)
Cardiac decompensation†	47	58	0.81 (0.55, 1.19)
Kidney decompensation‡	24	35	0.65 (0.38, 1.10)
Death from any cause	41	54	0.77 (0.52, 1.16)



*Respiratory decompensation requiring initiation of mechanical ventilation, and/or initiation of extracorporeal membrane oxygenation. †Includes new or worsening congestive heart failure, requirement for vasopressor therapy and/or inotropic or mechanical circulatory support, or ventricular tachycardia or fibrillation. ‡Doubling of s-Creatinine or initiation of renal-replacement therapy.

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Primary Outcome: Recovery

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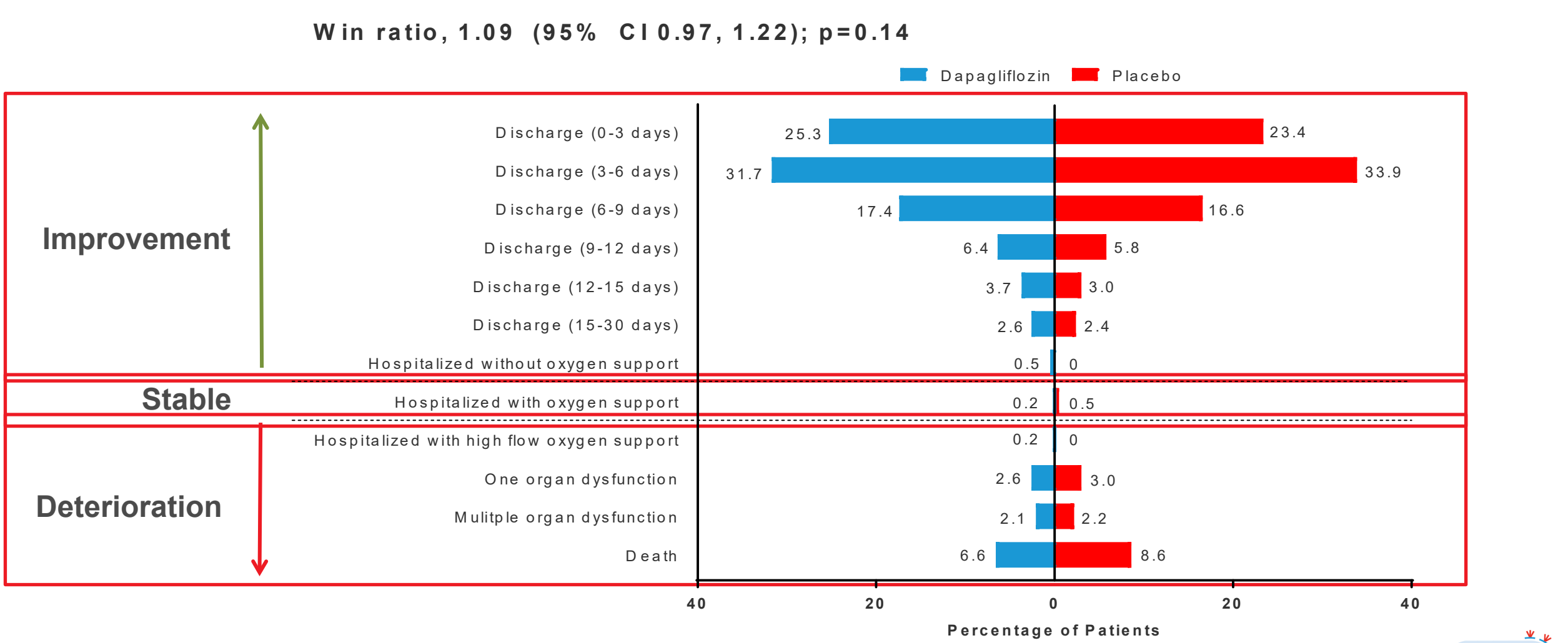
Primary Outcome of Recovery (Hierarchical Composite Endpoint)



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Key Secondary Outcomes

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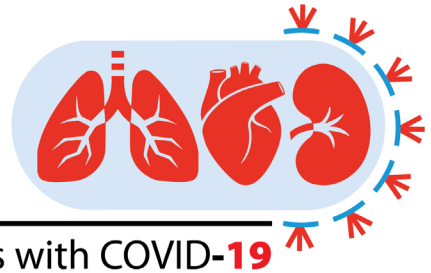

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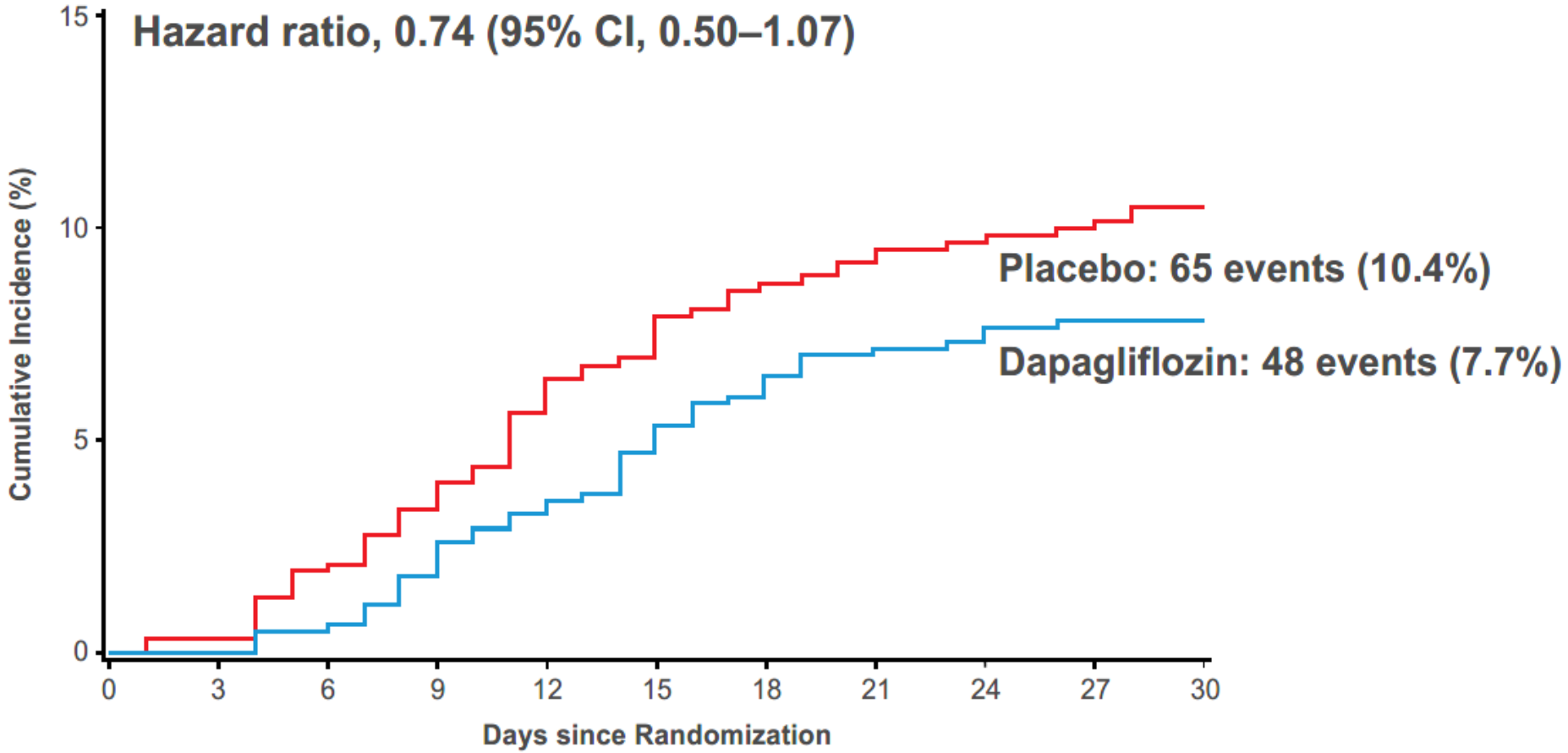
Composite Kidney Endpoint



No. at Risk											
Dapagliflozin	625	618	612	603	594	585	576	570	568	565	564
Placebo	625	619	608	599	585	577	567	563	560	558	555

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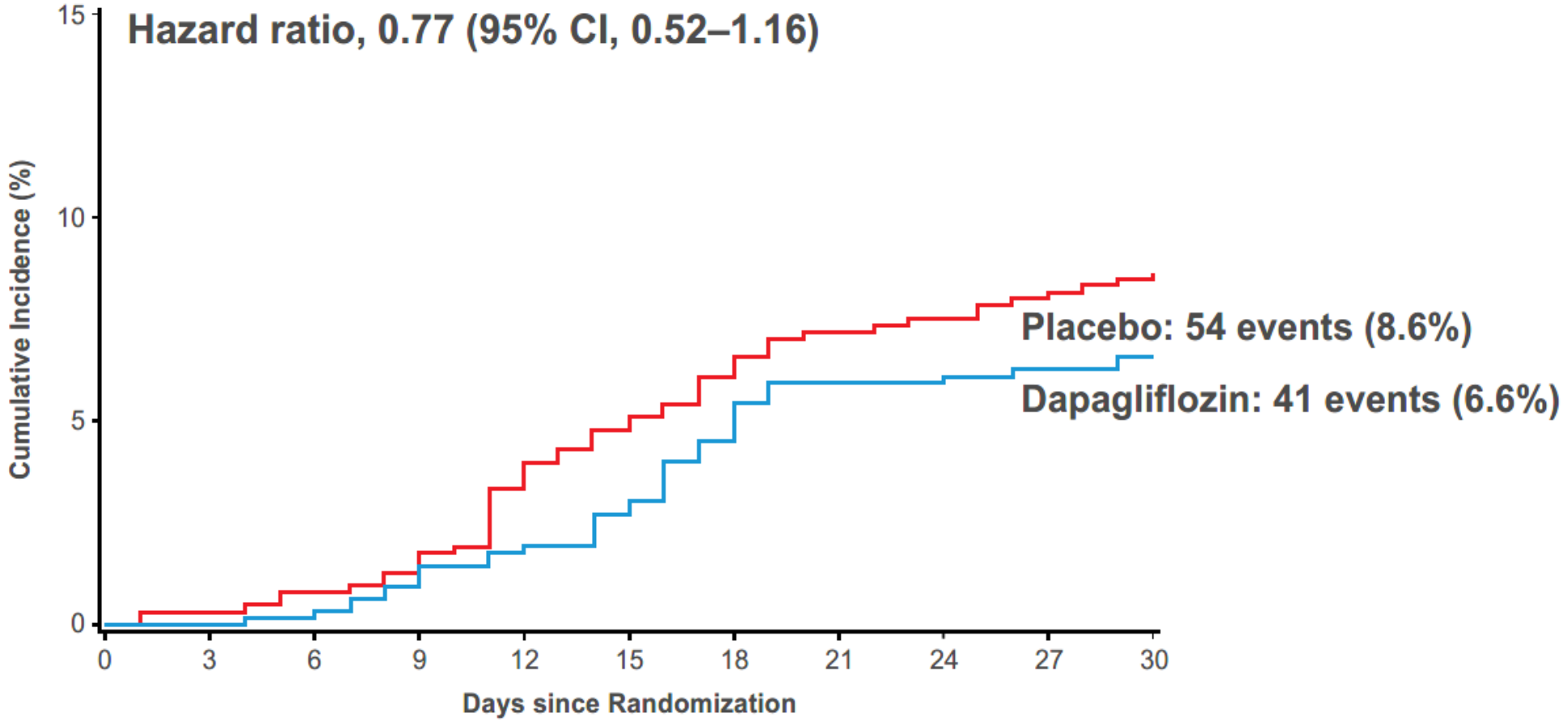
All-cause Mortality



No. at Risk											
Dapagliflozin	625	624	622	617	612	606	595	586	586	584	581
Placebo	625	623	620	617	604	595	587	580	578	575	572

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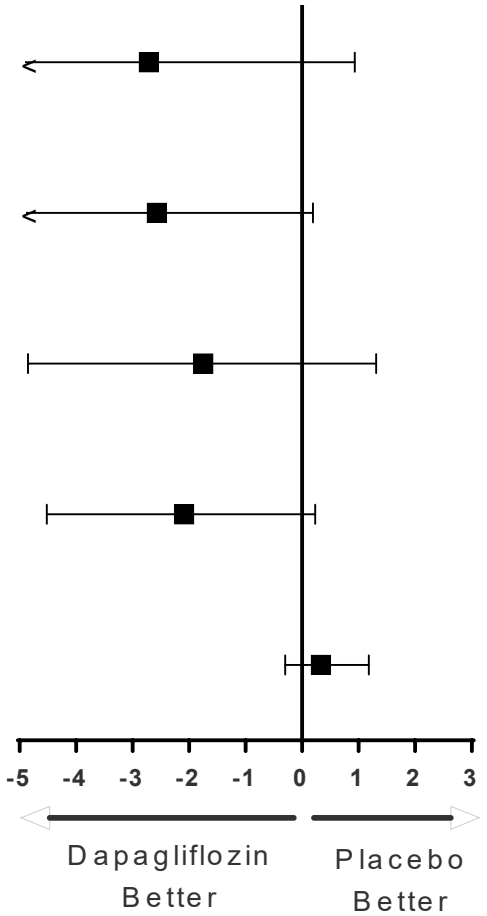
Safety

Events, n	Dapagliflozin (N=613)	Placebo (N=616)	Risk difference
Any severe AE*	65	82	-2.71 (-6.37, 0.93)
AE with the outcome of death	32	48	-2.57 (-5.41, 0.19)
Discontinuation due to AE	44	55	-1.75 (-4.85, 1.31)
Acute kidney injury	21	34	-2.09 (-4.52, 0.23)
Diabetic ketoacidosis	2	0	0.33 (-0.30, 1.18)



*Including death
AE, adverse event.

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Summary and Conclusions

- In DARE-19 Trial which evaluated patients hospitalized with Covid-19 and cardiometabolic risk factors, treatment with dapagliflozin did not achieve statistical significance for the dual primary endpoints
- Numerically fewer patients treated with dapagliflozin experienced organ failure and death - consistent across components (respiratory, cardiovascular, kidney complications and death)
- Dapagliflozin was well tolerated, with numerically fewer serious adverse events than placebo

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Practice Implications

- DARE-19 - first trial that evaluated SGLT2i in patients with acute illness, patient population with the highest risk ever tested with this class
- Given the lack of data, there were concerns that using SGLT2i in Covid-19 could increase the risk of AKI and ketoacidosis
- This fueled recommendations from some groups to stop SGLT2i in patients with Covid-19, even if they had conditions in which this class has been proven to produce substantial benefits (T2D, HF)
- In DARE-19, rates of serious adverse events (including AKI) were numerically lower with dapagliflozin than placebo, and only two non-severe events of DKA were reported
- Our results do not support discontinuation of SGLT2i in a setting of Covid-19, as long as patients are monitored

AKI, acute kidney injury; CKD, chronic kidney disease; DKA, diabetic ketoacidosis; HF, heart failure; SGLT2i, sodium-glucose co-transporter-2 inhibitors; T2D, type 2 diabetes.

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Research Implications

- DARE-19 raises a hypothesis that SGLT2i may afford organ protection in other types of acute illness

- This should be evaluated in future trials

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We thank all patients, investigators and their teams, and collaborators for their participation in the trial and extraordinary efforts under the most difficult of circumstances due to the ongoing pandemic

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