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Hierarchical Composite Endpoints: Definition and Analysis Using the Win Ratio (with ties!)

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Disclaimer

The authors of this presentation are AstraZeneca employees, but the contents of this presentation do not necessarily reflect the viewpoints of AstraZeneca.

Abstract

The global pandemic caused by coronavirus disease 2019 (COVID-19) has created challenges for researchers across the globe and incentives to accelerate development of new therapies. An important therapeutic goal of a successful COVID-19 treatment in hospitalized patients is recovery, usually defined in a fixed period of time, e.g. 30 days. Recovery in the simplest form is the outcome of discharge from hospital analyzed using time-to-event analysis methods or a responder analysis with a specific threshold for defining recovery based on the improvement in clinical status compared to baseline. A more comprehensive endpoint that includes patient recovery is the ordinal scale endpoint suggested by WHO that includes multiple clinical states (death and cure) and evaluation of the effect is done on the full range of outcomes. The ordinal scale endpoint includes a full range of outcomes ranked by clinical importance that are between "death" and "cure" so as to represent meaningful patient states. In this presentation we will discuss the definition of hierarchical composite endpoints (HCE) in COVID-19 setting and how they differ from WHO defined ordinal endpoints. As an analysis method we advocate the use of win ratio (WR) methods. The win ratio is a general method of comparing locations of distributions of two independent, ordinal random variables which can be estimated using distribution-free methods, based on the theory of U-statistics. We will discuss also the key considerations when designing new trials based on HCE and win ratio analysis.

https://ww2.amstat.org/meetings/biop/2021/onlineprogram/AbstractDetails.cfm?AbstractID=303509

The presentation is based on

- *Gasparyan SB, Kowalewski EK, Folkvaljon F, Bengtsson O, Buenconsejo J, Adler J, Koch GG "**Power and sample size calculation for the win odds test: application to an ordinal endpoint in COVID-19 trials**". Journal of Biopharmaceutical Statistics, (Sep 2021), https://doi.org/10.1080/10543406.2021.1968893*

- *Kosiborod MN, Esterline R, Furtado RH, Oscarsson J, Gasparyan SB, Koch GG, Martinez F, Mukhtar O, Verma S, Chopra V, Buenconsejo J. "**Dapagliflozin in patients with cardiometabolic risk factors hospitalised with COVID-19 (DARE-19): a randomised, double-blind, placebo-controlled, phase 3 trial**". The Lancet Diabetes & Endocrinology, (2021 Sep 1); 9 (9): 586-94. https://doi.org/10.1016/S2213-8587(21)00180-7*

Agenda

1. Hierarchical composite endpoints (HCE)
2. Ordinal COVID-19 endpoints and HCE
3. Win ratio with ties (Win/Mann-Whitney odds)
4. DARE-19: Dapagliflozin in inpatient COVID-19 setting

#1

Hierarchical composite endpoints (HCE)

Hierarchical Composite Endpoints (HCE)

- Unlike usual composite endpoints, the HCE combines clinical events with different severity not as equal contributors to the composite, but assigns ranks based on severity.
- The ranked nature of composite allows combining the analysis of clinical improvement with clinical deterioration.
- For example, in Heart Failure, the HCE usually combines information on potential improvement in symptoms and on the occurrence of worsening heart failure events into a single metric.
- An important aspect of HCE is that the occurrence of worsening heart failure events preempts changes in symptoms; that is, the ranks are hierarchical and need to be tested in an ordered sequence (unlike usual ordinal endpoints).

*Packer M "**Proposal for a new clinical end point to evaluate the efficacy of drugs and devices in the treatment of chronic heart failure**". Journal of cardiac failure, (2001); 7(2): 176-182.*

*Packer M "**Development and evolution of a hierarchical clinical composite end point for the evaluation of drugs and devices for acute and chronic heart failure: a 20-year perspective**". Circulation, (2016); 134 (21), 664-1678.*

HCE Examples –DAPA-HF trial (Dapagliflozin, Heart Failure)

The following are recent examples in Heart Failure studies where HCE has been used.

- DAPA-HF (Secondary endpoint)
  - Composite of all-cause mortality and change from baseline to 8 months in the total symptom score on the Kansas City Cardiomyopathy Questionnaire (KCCQ-TSS), scored on a scale from 0 to 100, with a higher score indicating fewer symptoms.
  - Given death was an intercurrent event, death was assigned the worst possible outcome in this setting, hence making this a composite measure with ordinal scale.
  - Analyzed using a win ratio with ties handled as 0.5 wins, which resulted in win ratio of 1.18 (1.11, 1.26), P<0.001.

*McMurray JJ, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, ..., Langkilde AM "**Dapagliflozin in patients with heart failure and reduced ejection fraction**". New England Journal of Medicine, (2019); 381 (21), 1995-2008.*

*Gasparyan SB, Folkvaljon F, Bengtsson O, Buenconsejo J, Koch GG "**Adjusted win ratio with stratification: calculation methods and interpretation**". Statistical Methods in Medical Research, (2020); 30(2), 580-611.*

HCE Examples –EMPULSE trial (Empagliflozin, Acute Heart Failure)

- EMPULSE (Primary endpoint)
  - Clinical benefit, a composite of
    I. death
    II. time to first heart failure event
    III. number of heart failure events (including HHFs, urgent heart failure visits and unplanned outpatient visits),
    IV. change from baseline in KCCQ-TSS after 90 days of treatment.
  - Hierarchical nature of the endpoint is more apparent since if a patient has HHF before Day 90, then instead of Day 90 KCCQ-TSS score, HHF are used for ranking this patient.
  - Analyzed using a win ratio (without ties, ties are expected to be few).

*Tromp J, Ponikowski P, Salsali A, Angermann CE, Biegus J, Blatchford J, Collins SP, Ferreira JP, Grauer C, Kosiborod M, Nassif ME "**Sodium–glucose co-transporter 2 inhibition in patients hospitalized for acute decompensated heart failure: rationale for and design of the EMPULSE trial**". European Journal of Heart Failure, (2021).*

#2

COVID-19 Ordinal Scale and Hierarchical Composite Endpoints

Endpoints for COVID-19

Contains Nonbinding Recommendations

COVID-19: Developing Drugs and Biological Products for Treatment or Prevention
Guidance for Industry[1]

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA office responsible for this guidance as listed on the title page

A minimal common outcome measure set for COVID-19 clinical research

*WHO Working Group on the Clinical Characterisation and Management of COVID-19 infection**

Clinical research is necessary for an effective response to an emerging infectious disease outbreak. However, research efforts are often hastily organised and done using various research tools, with the result that pooling data across studies is challenging. In response to the needs of the rapidly evolving COVID-19 outbreak, the Clinical Characterisation and Management Working Group of the WHO Research and Development Blueprint programme, the International Forum for Acute Care Trialists, and the International Severe Acute Respiratory and Emerging Infections Consortium have developed a minimum set of common outcome measures for studies of COVID-19. This set includes three elements: a measure of viral burden (quantitative PCR or cycle threshold), a measure of patient survival (mortality at hospital discharge or at 60 days), and a measure of patient progression through the health-care system by use of the WHO Clinical Progression Scale, which reflects patient trajectory and resource use over the course of clinical illness. We urge investigators to include these key data elements in ongoing and future studies to expedite the pooling of data during this immediate threat, and to hone a tool for future needs.

Lancet Infect Dis 2020; 20: e192–97
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This online publication has been corrected. The corrected version first appeared at thelancet.com/infection on August 12, 2020

*Members listed at end of paper

Perspective

CLINICAL TRIALS

Clinical Trials
1–11

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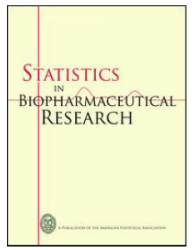
Endpoints for randomized controlled clinical trials for COVID-19 treatments

Lori E Dodd[1], Dean Follmann[1], Jing Wang[2], Franz Koenig[3], Lisa L Korn[4], Christian Schoergenhofer[5], Michael Proschan[1], Sally Hunsberger[1], Tyler Bonnett[2], Mat Makowski[6], Drifa Belhadi[7,8], Yeming Wang[9,10], Bin Cao[9,10], France Mentre[7,8] and Thomas Jaki[11,12]



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Statistics in Biopharmaceutical Research

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Statistical Opportunities to Accelerate Development for COVID-19 Therapeutics

Fanni Natanegara , Névine Zariffa , Joan Buenconsejo , Ran Liao , Freda Cooner , Divya Lakshminarayanan , Samiran Ghosh , Jerald S. Schindler & Margaret Gamalo

COVID-19 related ordinal endpoints (WHO, remdesivir) – fixed timepoint

Ordinal Scale for Clinical Improvement

Patient State	Descriptor	Score
Uninfected	No clinical or virological evidence of infection	0
Ambulatory	No limitation of activities	1
	Limitation of activities	2
Hospitalized Mild disease	Hospitalized, no oxygen therapy	3
	Oxygen by mask or nasal prongs	4
Hospitalized Severe Disease	Non-invasive ventilation or high-flow oxygen	5
	Intubation and mechanical ventilation	6
	Ventilation + additional organ support – pressors, RRT, ECMO	7
Dead	Death	8

Not hospitalized, no limitations of activities	1
Not hospitalized, limitation of activities, home oxygen requirement, or both	2
Hospitalized, not requiring supplemental oxygen and no longer requiring ongoing	3
Medical care (used if hospitalization was extended for infection-control reasons)	
Hospitalized, not requiring supplemental oxygen but requiring ongoing medical care (Covid-19–related or other medical conditions)	4
Hospitalized, requiring any supplemental oxygen	5
Hospitalized, requiring noninvasive ventilation or use of high-flow oxygen devices	6
Hospitalized, receiving invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)	7
Death	8

*"**WHO R&D blueprint novel coronavirus (COVID-19) therapeutic trial synopsis**", (2020) https://www.who.int/blueprint/priority-diseases/key-action/COVID-19_Treatment_Trial_Design_Master_Protocol_synopsis_Final_18022020.pdf*

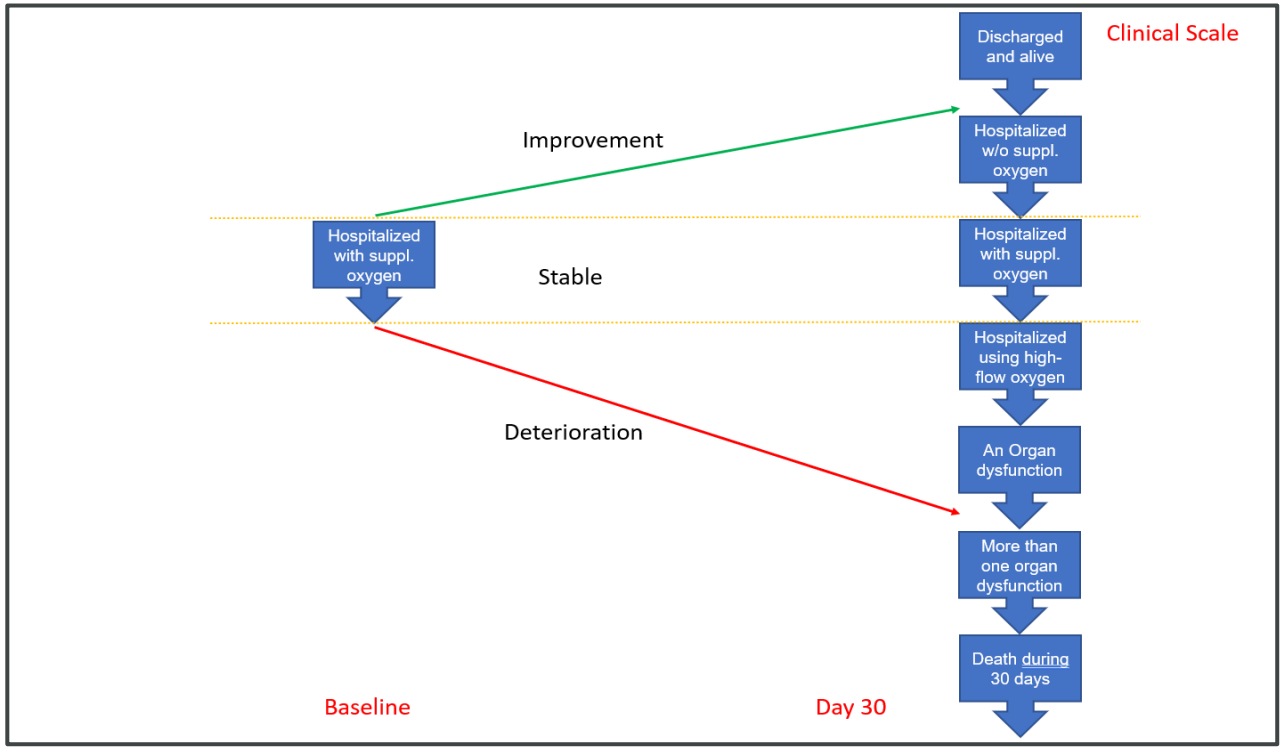
*Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, Hohmann E, Chu HY, Luetkemeyer A, Kline S, Lopez de Castilla D "**Remdesivir for the treatment of Covid-19**". New England Journal of Medicine, (2020); 383(19), 1813-1826.*

Ordinal Scale and HCE

WHO 8-point ordinal scale

Not hospitalized, no limitations of activities	1
Not hospitalized, limitation of activities, home oxygen requirement, or both	2
Hospitalized, not requiring supplemental oxygen and no longer requiring ongoing	3
Medical care (used if hospitalization was extended for infection-control reasons)	
Hospitalized, not requiring supplemental oxygen but requiring ongoing medical care (Covid-19–related or other medical conditions)	4
Hospitalized, requiring any supplemental oxygen	5
Hospitalized, requiring noninvasive ventilation or use of high-flow oxygen devices	6
Hospitalized, receiving invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)	7
Death	8

Fit for purpose Hierarchical Composite Endpoint



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Recovery HCE in DARE-19

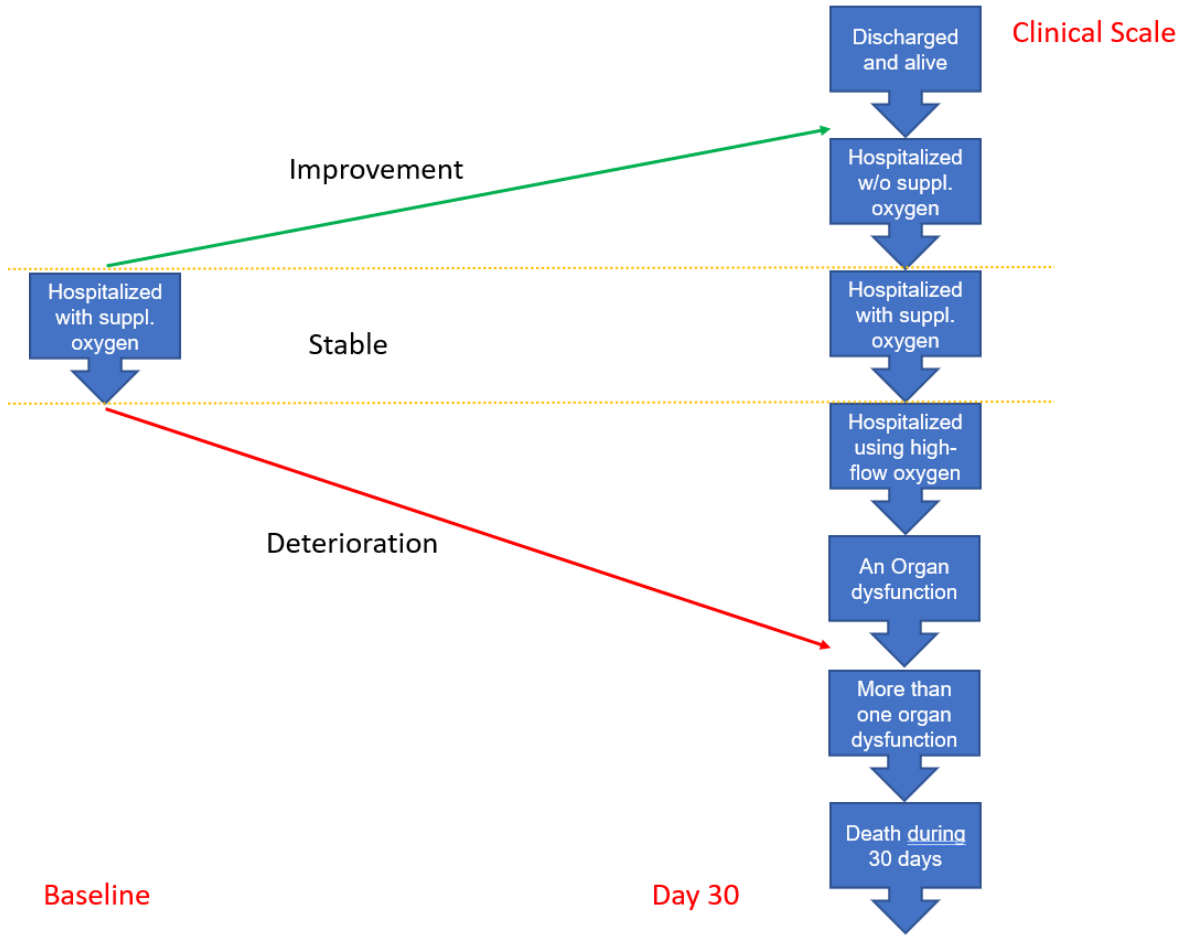
I. **Patients alive at the end of follow up (Day 30), without primary composite event and are discharged from hospital before Day 30** [*Ranking within this cohort will be based on the time to discharge, with patients being discharged later getting a worse rank*]

II. **Patients without primary composite event but hospitalized at the end of follow-up (Day 30),** [*Ranking within this cohort, from worse to better, includes patients on high-flow oxygen devices, patients requiring supplemental oxygen, and patients not requiring supplemental oxygen*]

III. **Patients who did not die but have more than one new or worsened organ dysfunction events**, [*Ranking within this cohort will be based on the number of events, with higher number getting a worse rank*]

IV. **Patients who did not die but have only one new or worsened organ dysfunction event,** [*Ranking within this cohort will be based on the timing of the event, with patients having the event sooner getting a worse rank. Type of organ dysfunction will not be considered*]

V. **Patients dying during the study**, [*Ranking within this cohort will be based on the timing of the event, with patients dying sooner getting a worse rank*]



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Key Considerations on defining Recovery in DARE-19

Ordinal scale and "recovery" HCE

- Two important differences (based on the mode of action of dapagliflozin) between the ordinal scale endpoint and the suggested HCE are the following:

  1. The ordinal scale endpoints are assessed at a prespecified timepoint (for example, at Day 15), HCE uses severity of all events that a patient experiences during the 30 days of follow-up.
  2. The HCE takes into account in-hospital worsening of COVID-19 and not only the eventual discharge from hospital.

- Therefore, the HCE is a recovery endpoint with a stricter definition of recovery. ***Recovery*** is represented on the clinical scale as ***improvement in clinical status*** compared to baseline:

  1. Discharge from hospital before day 30 without in-hospital worsening and alive at Day 30; or
  2. Still in hospital at Day 30, but without in-hospital worsening during the 30 days of hospitalization and without oxygen support.

  It combines disease specific events and events related to dapagliflozin's mode of action.

*Kosiborod M, Berwanger O, Koch GG, Martinez F, Mukhtar O, Verma S, Chopra V, Javaheri A, Ambery P, Gasparyan SB, Buenconsejo J "**Effects of dapagliflozin on prevention of major clinical events and recovery in patients with respiratory failure because of COVID-19: Design and rationale for the DARE-19 study**". Diabetes, Obesity and Metabolism, (2021 Apr); 23(4): 886-96.*

#3

Win ratio with ties (Win/Mann-Whitney odds)

Win ratio with ties (Win/Mann-Whitney odds)

- The concept of Win Ratio was introduced by Pocock et al. in 2012.
- It is a statistic for comparison of two independent ordinal endpoints.
- Each patient in the active group is compared to each patient in the placebo group to decide the "winner" (the endpoint with lower or higher ordinal value).
- The total number of "wins" of the active group is divided by total number of "wins" of the placebo group forming the win ratio statistic.
- Ties were disregarded in calculating the win ratio statistic.
- Dong et al. (2020) suggested to include ties as half wins, forming the win odds statistic.
- Comparison of outcomes works without controversies if the follow-up is the same.

*Pocock SJ, Ariti CA, Collier TJ, Wang D "**The win ratio: A new approach to the analysis of composite endpoints in clinical trials based on clinical priorities**". European Heart Journal, (2012); 33 (2): 176–182.*

*Dong G, Hoaglin DC, Qiu J, Matsouaka RA, Chang YW, Wang J, Vandemeulebroecke M "**The win ratio: On interpretation and handling of ties**". Statistics in Biopharmaceutical Research, (2020); 12 (1): 99–106.*

Hypothesis test for the win odds

- It is more convenient to work with win odds, because
  - If the number of ties is high, it will have a lower value than the WR, hence in the analysis it will account for patients who do not experience improvement in the active group.
  - If we denote the win probability (WP) as the total number of wins, plus half of the ties of the active group divided by total number of comparison, then

$$WO = \frac{WP}{1-WP} \text{ or } WP = \frac{WO}{WO+1}$$

    and the alternative hypothesis can be easily written as WP>0.5 which corresponds to WO>1 (the null hypothesis is WO=1 or WP=0.5)
  - This gives the advantage of estimating WP (using U-statistics) and then transforming its SE to get the SE of $\log(\text{WO})$ as $\frac{SE}{WP*(1-WP)}$.
  - WO>1 corresponds to a shift of active distribution with respect to the placebo distribution, in the "right" direction (to the right if higher ordinal values correspond to a better outcome/winning, or to the left, in the opposite case).
- For the review of advantages of the win odds see Brunner (2021)

*Brunner EM, Vandemeulebroecke M, Tobias M "**Win odds: An adaptation of the win ratio to include ties**". Statistics in Medicine, (2021); 40 (14):3367–3384.*

*Hoeffding W "**A class of statistics with asymptotically normal distribution**". The Annals of Mathematical Statistics, (1948); 19 (3):293–325.*

Designing trials based on the win odds

- Gasparyan et al. (2021) provided power and sample size calculation formulas for the win odds.
- It requires only specification of the alternative value for the win odds to calculate the sample size for given power.
- To infer the "true" WO to design the study simulations can be useful, if the endpoint contains components of different types and no prior data on the same endpoint are available.

Table 1. Sample size based on the win odds test.

Win odds	Win probability	Power = 80%	Power = 90%
1.10	0.5238	4616	6179
1.15	0.5349	2151	2879
1.20	0.5455	1267	1696
1.25	0.5556	848	1135
1.30	0.5652	616	824
1.35	0.5745	472	632
1.40	0.5833	377	505
1.45	0.5918	311	416
1.50	0.6000	262	351

*Gasparyan SB, Kowalewski EK, Folkvaljon F, Bengtsson O, Buenconsejo J, Adler J, Koch GG "**Power and sample size calculation for the win odds test: application to an ordinal endpoint in COVID-19 trials**" Journal of Biopharmaceutical Statistics, Sep 2021, https://doi.org/10.1080/10543406.2021.1968893*

Power of WO as a function of sample size

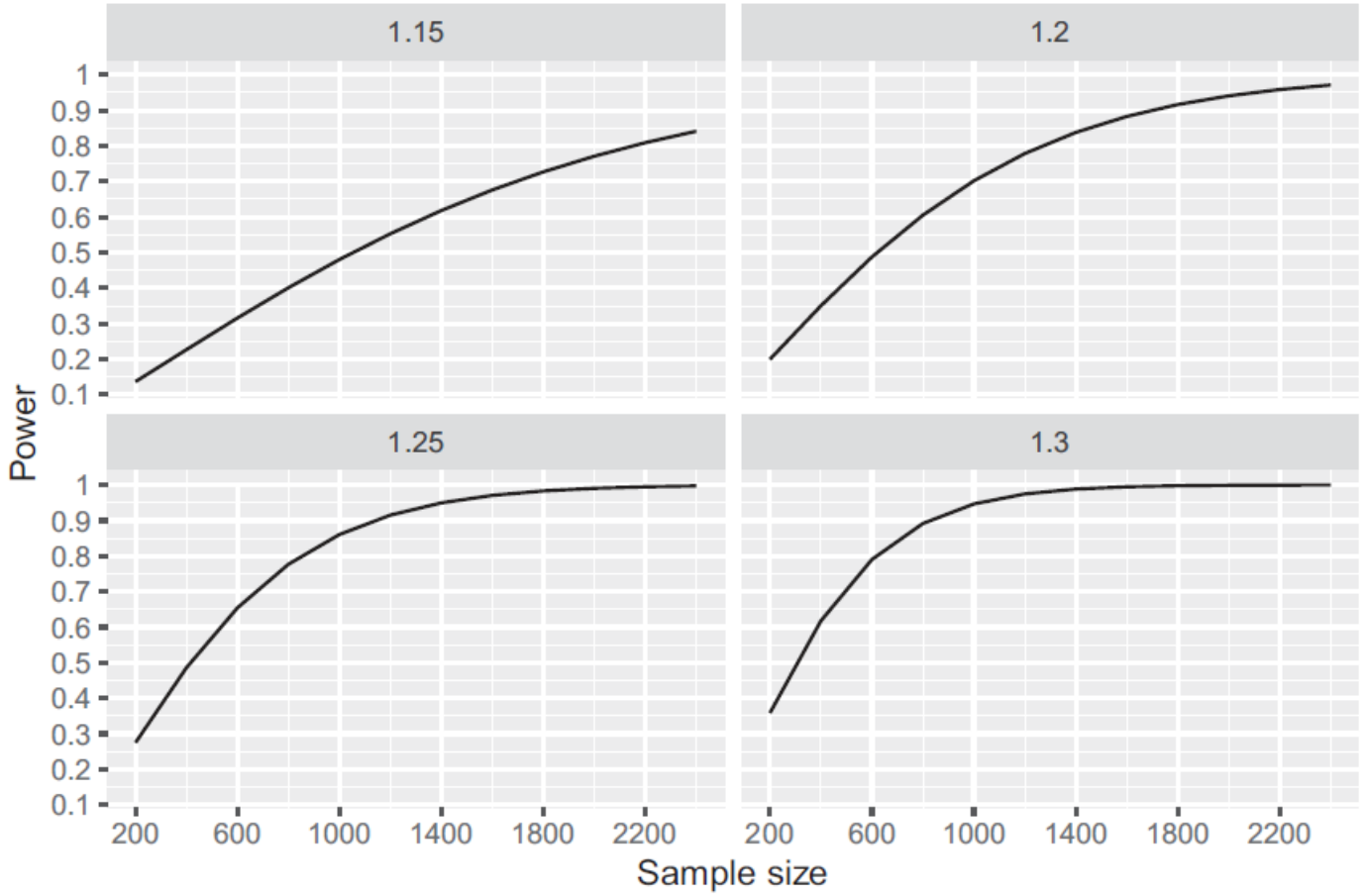
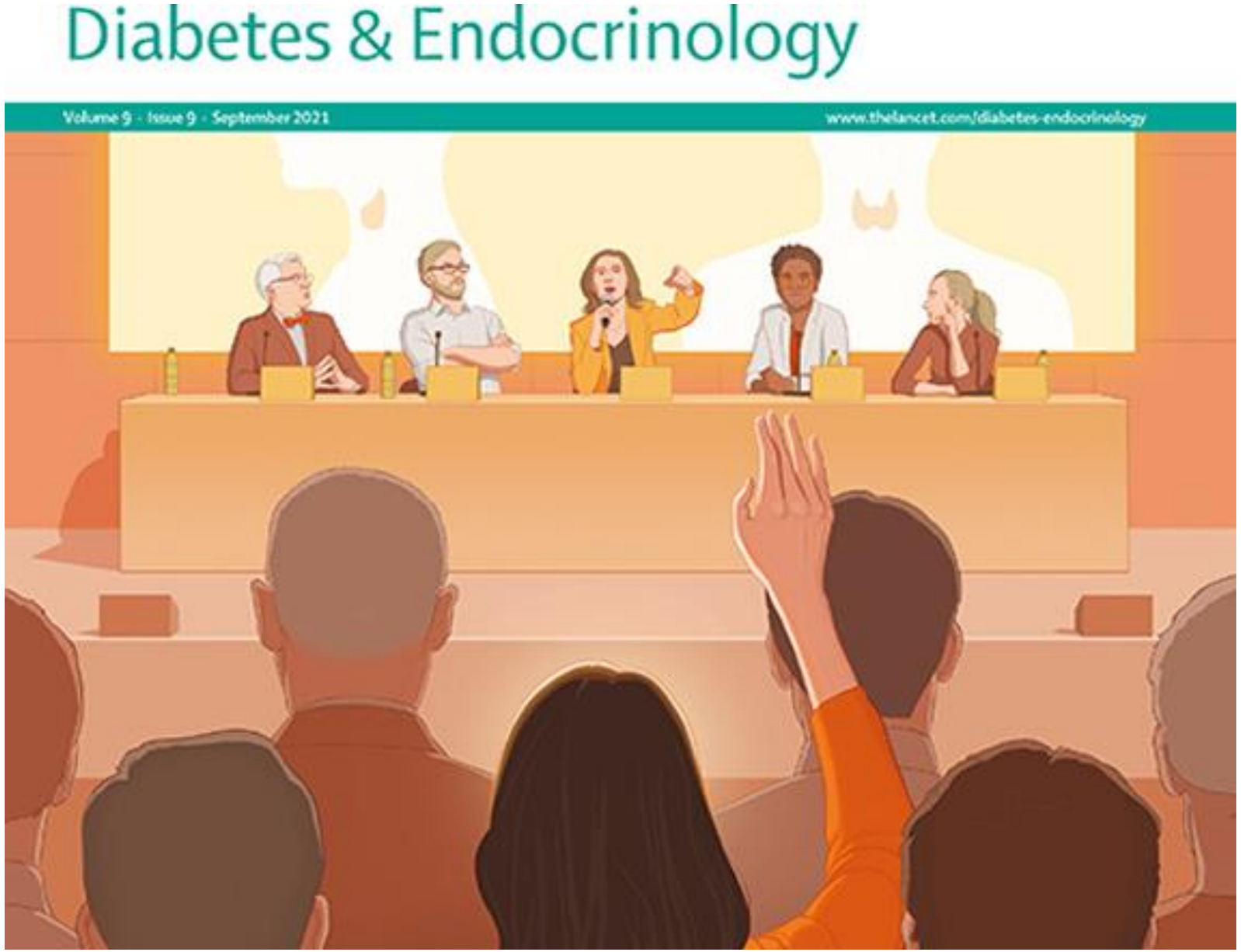


Figure 1. Win odds test power as a function of sample size, for the win odds values 1.15, 1.2, 1.25, 1.3.

*Gasparyan SB, Kowalewski EK, Folkvaljon F, Bengtsson O, Buenconsejo J, Adler J, Koch GG "**Power and sample size calculation for the win odds test: application to an ordinal endpoint in COVID-19 trials**" Journal of Biopharmaceutical Statistics, Sep 2021, https://doi.org/10.1080/10543406.2021.1968893*

#4
DARE-19: Dapagliflozin in inpatient COVID-19 setting



Design of DARE-19

- Dapagliflozin in patients with cardiometabolic risk factors hospitalised with COVID-19 (DARE-19) was a randomized, double-blind, placebo-controlled, phase 3 trial with sample size of 1250.
- DARE-19 had dual primary endpoints of prevention, analyzed as a time-to-event endpoint, and recovery (which we have seen already!), analyzed using Win Odds (WO).
- The study was powered for WO=1.23 and it was estimated that approximately 1200 patients will be needed to attain 80% power.
- The minimal detectable WO was 1.15.

*Kosiborod MN, Esterline R, Furtado RH, Oscarsson J, Gasparyan SB, Koch GG, Martinez F, Mukhtar O, Verma S, Chopra V, Buenconsejo J. "**Dapagliflozin in patients with cardiometabolic risk factors hospitalised with COVID-19 (DARE-19): a randomised, double-blind, placebo-controlled, phase 3 trial**" The Lancet Diabetes & Endocrinology, (2021 Sep 1); 9 (9): 586-94, https://doi.org/10.1016/S2213-8587(21)00180-7*

DARE-19 – Estimand of the recovery endpoint

An estimand is a precise description of the treatment effect reflecting the clinical question posed by a given clinical trial objective.
The attributes below are used to construct the estimand, defining the treatment effect of interest.

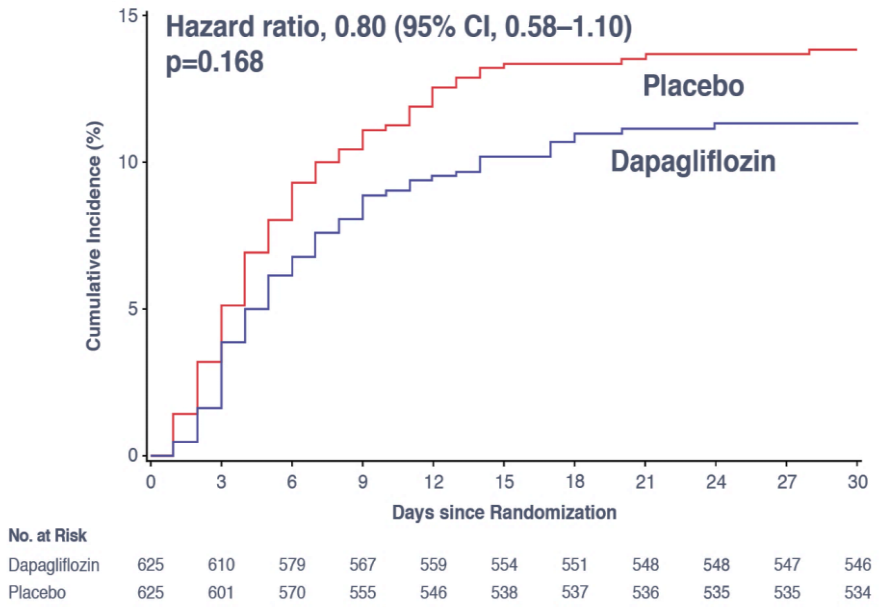
- Treatment = Dapagliflozin + Standard of Care
- Population = Hospitalized patients with COVID-19 and cardio-renal-metabolic risk factors
- The Endpoint = Hierarchical Composite Endpoint of Recovery (which measures change in clinical status compared to baseline)
- Population-level summary = win odds (the odds that a randomly selected patient in the dapagliflozin group will have a better change in clinical status than a randomly selected patient in the placebo group)

Discharge from hospital is an important intercurrent event, since organ dysfunction is not defined after discharge (only death after discharge is included in the composite). This intercurrent event is handled using the composite strategy by including the composite.

Since recovery is defined as improvement in clinical status compared to baseline, then the treatment effect can be characterized as ***improvement of chances of recovery***.

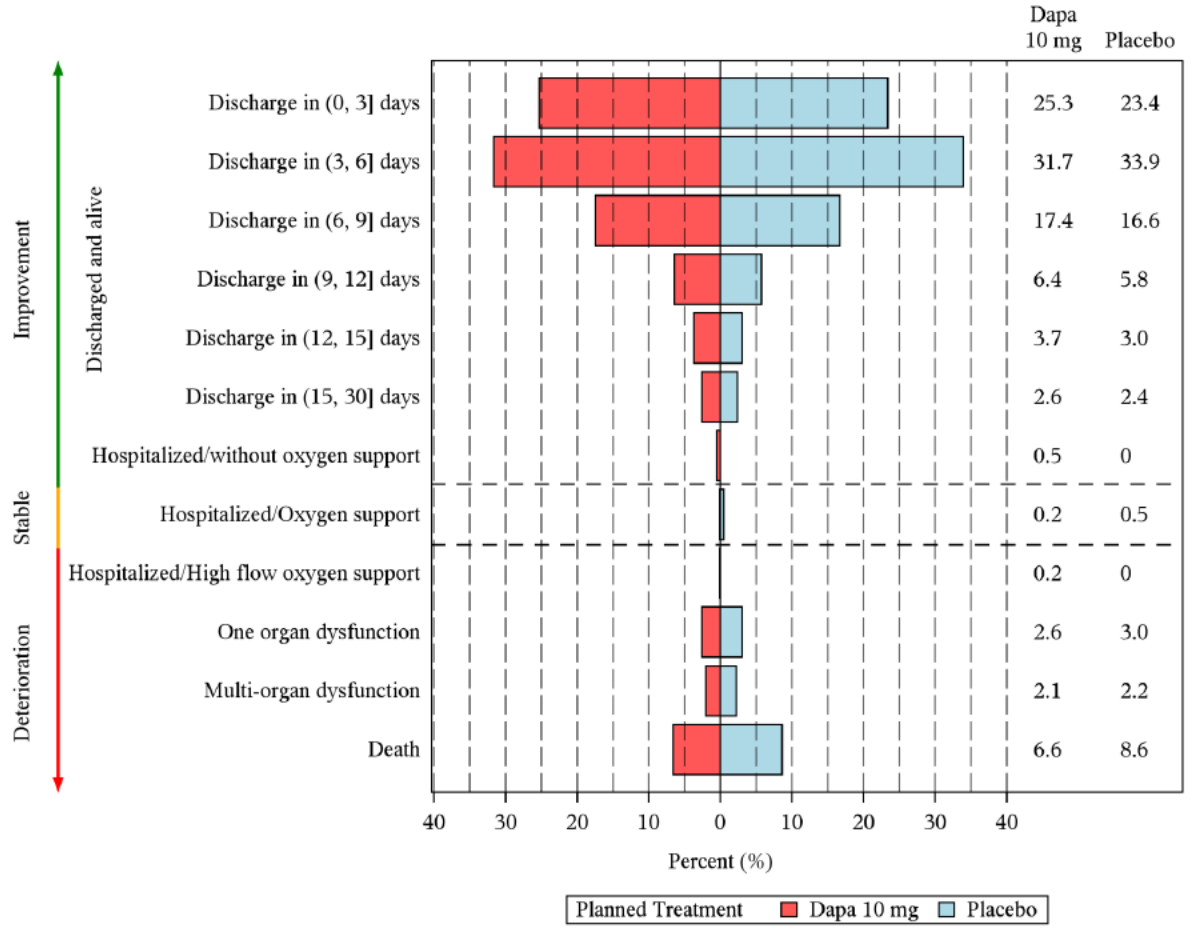
DARE-19 – Dual Objectives – Prevention and Recovery

Prevention endpoint



Recovery hierarchical composite endpoint

WO: 1.09 (95% CI 0.97, 1.22) P=0.136



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Interpretation

- The effect of dapagliflozin on change in clinical status of patients hospitalized with COVID-19 is characterized by a WO 1.09 (95% CI 0.97, 1.22) .
- Hence the odds that a randomly selected patient in the dapagliflozin group will have a better change in clinical status than a randomly selected patient in the placebo group is 1.09, which is not significantly different from WO=1.
- The minimal detectable WO was 1.15, which was considered the clinically meaningful threshold (corresponding to NNT=15 – Number of patients needed to be treated by dapagliflozin compared to being treated with placebo to get one patient with a better change in clinical status).
- Therefore, dapagliflozin did not show an improvement on the recovery in the COVID-19 setting

Recovery is improvement in clinical status compared to baseline.

Conclusion

- HCE are flexible endpoints that can be constructed in different disease areas and for drugs with different mode of actions, as a clinically meaningful measure of patient's condition.

- COVID-19 is a recent example where HCE can be used to construct a measure of patient’s clinical status.

- HCE can be analyzed using win/Mann-Whitney odds (win ratio with ties), which does not require distributional assumptions for estimation (including the proportionality assumption).

- Win odds can be used for designing new trials and provides a clinically meaningful treatment effect estimate as defined by the estimand framework.

THANK YOU!!!

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