CHASING SUMMER:
TOP 5 TRIALS OF 2021-22
"THE EBM WOODSTOCK OF OUR GENERATION"

PRESENTED BY:

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DISCLOSURES & SPECIAL THANKS

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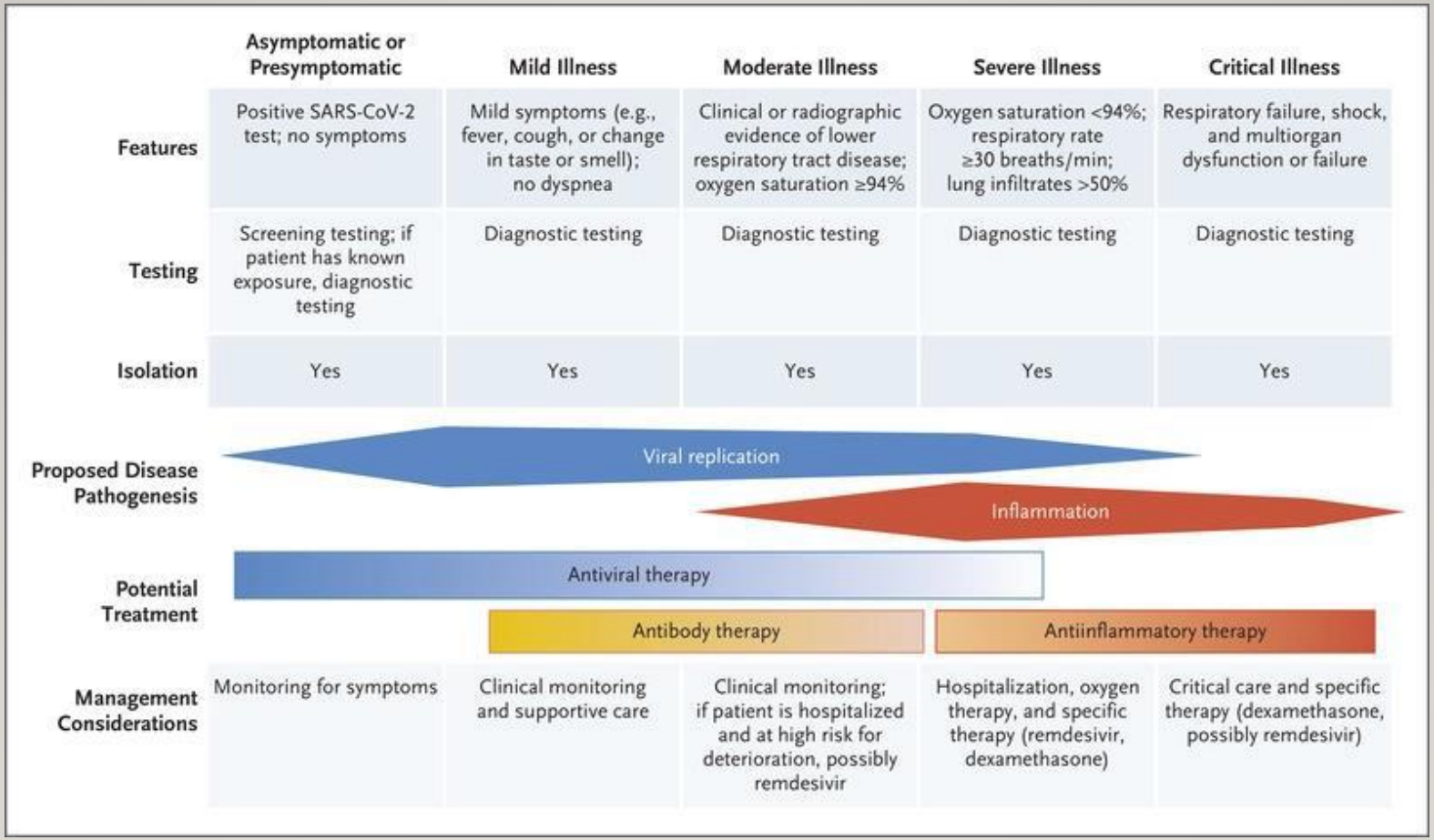
PINETREE:
EARLY REMDESIVIR TO PREVENT PROGRESSION TO SEVERE COVID-19 IN OUTPATIENTS

BACKGROUND

- Remdesivir is a prodrug inhibitor of the SARS-CoV-2 RNA polymerase
- Previous phase 3 trial found both a 10 day and 5 day course of remdesivir shortened recovery time in patients hospitalized with COVID
- Theory is that early treatment of viral infections improves clinical outcomes and reduces mortality



NEJM 2020;383:1757-1766

AUTHOR'S QUESTION

- Does the use of remdesivir in symptomatic, non-hospitalized patients with Covid-19 who are at high risk for disease progression prevent hospitalization?

METHODS

- Patients randomly assigned in 1:1 ratio to receive remdesivir (200 mg on day 1, 100 mg on days 2-3) vs placebo
- Eligibility:
  - Patients 12 years and older with **at least one pre-existing risk factor for progression to severe COVID** or **were 60 years or older**
  - At least one ongoing symptom consistent with COVID, with onset of first symptom within 7 days before randomization
  - COVID infection confirmed by molecular diagnostic assay within 4 days prior to screening
- Risk factors included:
  - Hypertension, Cardiovascular or cerebrovascular disease, Diabetes mellitus, Obesity, Immune compromise, Chronic mild or moderate kidney disease, Chronic liver disease, Chronic lung disease, Current cancer, Sickle cell disease
- Patients were **not eligible** if they were receiving or were expected to receive supplemental oxygen or hospital care at the time of screening, had a previous hospitalization for Covid-19, had previously received treatment for Covid-19 (including investigational agents), or had **received a SARSCoV-2 vaccine**

METHODS

- Trial was ended early due to a decrease in the incidence of SARS-CoV-2 infections, ethical concerns regarding assigning patients to placebo in the context of increased access to emergency-use–authorized treatments
- Of the 1264 patients expected to enroll, only 562 (44.5%) had undergone randomization and had begun the trial regimen prior to the early stoppage

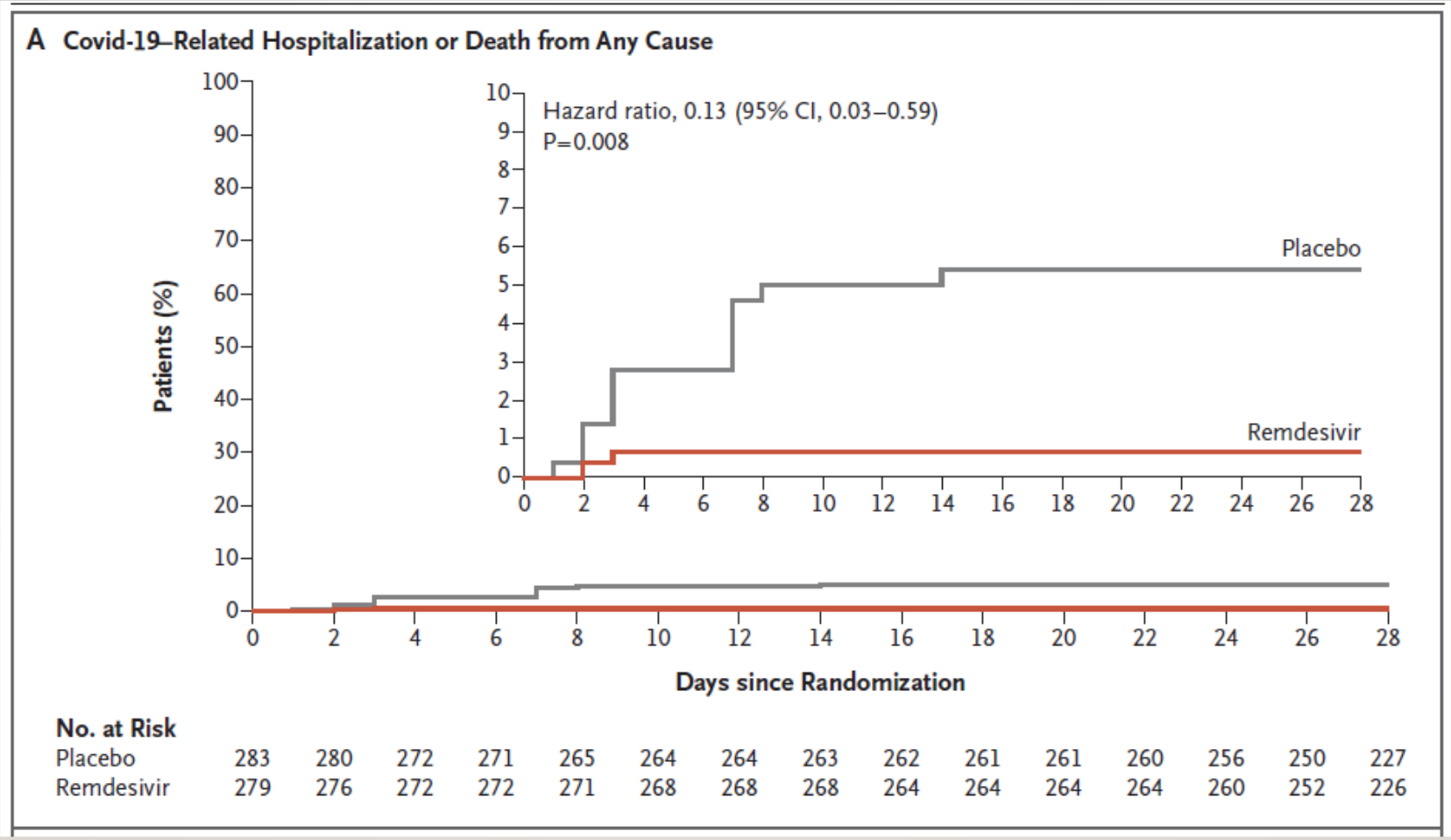
Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Remdesivir (N=279)	Placebo (N=283)	Total (N=562)
Age — yr	50±15	51±15	50±15
Age category — no. (%)			
≥60 yr	83 (29.7)	87 (30.7)	170 (30.2)
<18 yr	3 (1.1)	5 (1.8)	8 (1.4)
Female sex — no. (%)	131 (47.0)	138 (48.8)	269 (47.9)
Residence in the United States — no. (%)	264 (94.6)	267 (94.3)	531 (94.5)
Race or ethnic group — no. (%)†			
White	228 (81.7)	224 (79.2)	452 (80.4)
Black	20 (7.2)	22 (7.8)	42 (7.5)
American Indian or Alaska Native	15 (5.4)	21 (7.4)	36 (6.4)
Asian, Native Hawaiian, or Pacific Islander	7 (2.5)	7 (2.5)	14 (2.5)
Hispanic or Latinx	123 (44.1)	112 (39.6)	235 (41.8)
Other	3 (1.1)	2 (0.7)	5 (0.9)
Body-mass index	31.2±6.7	30.8±5.8	31.0±6.2
Coexisting conditions — no. (%)			
Diabetes mellitus	173 (62.0)	173 (61.1)	346 (61.6)
Obesity	154 (55.2)	156 (55.1)	310 (55.2)
Hypertension	138 (49.5)	130 (45.9)	268 (47.7)
Chronic lung disease	67 (24.0)	68 (24.0)	135 (24.0)
Current cancer	12 (4.3)	18 (6.4)	30 (5.3)
Cardiovascular or cerebrovascular disease	20 (7.2)	24 (8.5)	44 (7.8)
Immune compromise	14 (5.0)	9 (3.2)	23 (4.1)
Chronic kidney disease, mild or moderate	7 (2.5)	11 (3.9)	18 (3.2)
Chronic liver disease	1 (0.4)	1 (0.4)	2 (0.4)
Residence in skilled nursing facility — no. (%)	8 (2.9)	7 (2.5)	15 (2.7)
Median duration of symptoms before first infusion (IQR) — days	5 (3–6)	5 (4–6)	5 (3–6)
Median time since RT-PCR confirmation of SARS-CoV-2 (IQR) — days	2 (1–3)	3 (1–4)	2 (1–4)
Mean SARS-CoV-2 RNA nasopharyngeal viral load — $\log_{10}$ copies/ml‡	6.31±1.75	6.28±1.79	6.29±1.77

N Engl J Med 2022; 386:305-315

RESULTS

- 562 patients underwent randomization
- Remdesivir reduced
  - COVID-19 related hospitalization or death from any cause by day 28 (**NNT 22,** hazard ratio 0.13, 0.03-0.59, p=0.008, **statistically significant difference**)
  - COVID-19 related medical visit by day 28 **(**NNT 15, hazard ratio 0.19, 0.07-0.56)
- No patients died by day 28



N Engl J Med 2022; 386:305-315

RESULTS

- 34.8% in the remdesivir group vs 25.0% in the placebo group reported alleviation of symptoms by day 14 (hazard ratio, 1.41; 95% CI, 0.73 to 2.69, **no difference**)
- The **time-weighted average change in viral load from baseline to day 7 did not differ substantially between the two groups**
- Adverse effects lower in remdesivir group vs placebo (42.3% vs 46.3%)
  - Serious adverse effects lower in remdesivir group (1.8% vs 6.7%)
  - Non-serious A/E (<5%) included nausea, headache, cough

AUTHOR'S CONCLUSION

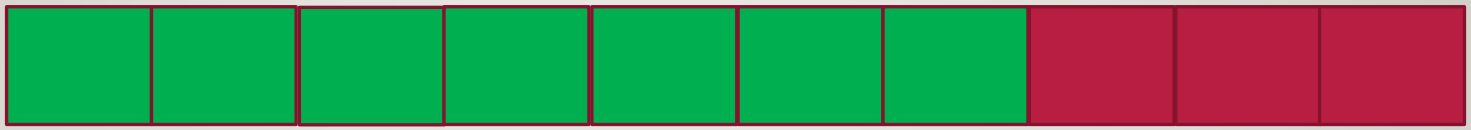
- "Among non-hospitalized patients who were at high risk for Covid-19 progression, a 3-day course of remdesivir had an acceptable safety profile and resulted in an 87% lower risk of hospitalization or death than placebo."

CRITICAL APPRAISAL

- Merits
  - Randomized and double blinded design scheme. Concealed allocation. No loss to follow-up
  - One of the few trials that attempted to characterize "high risk" factors for patients developing poor outcomes from COVID illness.
  - Robust primary efficacy endpoint – composite of hospitalization and death
- Flaws
  - Not true ITT (modified ITT), excluded 22 patients, potentially impacts results due to small # of events in trial
  - Younger patients (only 1/3 of patients in each group over the age of 60)
  - Trial enrollment stopped early, severely underpowered, only half of expected patients randomized
  - COVID variant mismatch with current environment, cases generally milder (no deaths, were some incidental cases?)
  - Immunocompromised, Black, Asian, chronic liver, CKD, cancer patients under-represented
  - **Did not include vaccinated patients**

SOUNDCHECK!

- Risk of Bias



- Clinical Applicability

- Practical Applicability

CLINICAL PEARLS

- Unclear benefit of remdesivir against current COVID Omicron variant and its subvariants
- Unclear benefit of remdesivir for prevention to progression to severe COVID disease in the setting of a vaccinated individual
- No impact on mortality with 3 day course of remdesivir
- Likely benefit > risk in the co-morbid population, with an emphasis on diabetics, hypertensive, and obese patients to receive a short course of remdesivir to prevent hospitalization
- Study could also be extrapolated to benefit high risk patients hospitalized for non-COVID reasons or nosocomial COVID to prevent further disease progression

POISE-3:
TRANEXAMIC ACID IN PATIENTS UNDERGOING NONCARDIAC SURGERY

BACKGROUND

- Tranexamic acid (TXA) is an antifibrinolytic drug previously shown to reduce incidence and severity of bleeding in patients undergoing C-section, cardiac surgery, and orthopedic surgeries
- Limited data in TXA use for patients undergoing non-orthopedic non-cardiac surgeries
- Trials previously run have not been large enough to establish whether TXA increases risk of thrombotic events in noncardiac surgery

AUTHOR'S QUESTION

- In patients undergoing noncardiac surgery who are at risk for bleeding and cardiovascular events, does tranexamic acid result in a lower incidence of life-threatening bleeding, major bleeding, or bleeding into a critical organ than placebo, and is it noninferior to placebo with respect to the incidence of major cardiovascular complications within 30 days?

METHODS

- Patients randomly assigned to receive TXA (1g IV bolus) or placebo at start and end of surgery
  - Included use of partial factorial design of hypotension-avoidance vs hypertension avoidance strategy
- Eligible patients were 45 years of age or older, undergoing inpatient noncardiac surgery, and at risk for bleeding and cardiovascular complications
- Patients were excluded if they were undergoing cardiac surgery or intracranial neurosurgery, if a physician planned to administer systemic TXA during surgery, or if the patient had a CrCl < 30 ml/min
- Due to a financial deficit, the trial recruitment stopped early after at least 9500 patients had undergone randomization

Table 1. Baseline Characteristics of the Patients, Type of Surgery, and Medications.*

Characteristics	Tranexamic Acid (N=4757)	Placebo (N=4778)
Age — yr	69.5±9.5	69.3±9.4
Male sex — no./total no. (%)	2669/4755 (56.1)	2681/4778 (56.1)
Eligibility criteria met — no. (%)	4742 (99.7)	4766 (99.7)
NT-proBNP ≥200 ng/liter	574 (12.1)	552 (11.6)
History of coronary artery disease	1410 (29.6)	1466 (30.7)
History of peripheral artery disease	714 (15.0)	722 (15.1)
History of stroke	400 (8.4)	388 (8.1)
Undergoing major vascular surgery	541 (11.4)	544 (11.4)
Risk criteria		
Met ≥3 of 9 criteria	3988 (83.8)	4003 (83.8)
Undergoing major surgery†	3741 (78.6)	3798 (79.5)
Undergoing urgent or emergency surgery	555 (11.7)	540 (11.3)
Age ≥70 yr	2611 (54.9)	2588 (54.2)
Current diabetes for which medication is taken	1749 (36.8)	1812 (37.9)
Preoperative serum creatinine level >175 μmol/liter	57 (1.2)	73 (1.5)
History of congestive heart failure	674 (14.2)	671 (14.0)
History of transient ischemic attack	282 (5.9)	247 (5.2)
History of hypertension	4293 (90.2)	4321 (90.4)
History of smoking within 2 yr before surgery	1131 (23.8)	1128 (23.6)
Other medical history — no. (%)		
Atrial fibrillation	478 (10.0)	445 (9.3)
Active cancer	1311 (27.6)	1360 (28.5)
Surgery — no./total no. (%)		
Any procedure	4729/4757 (99.4)	4740/4778 (99.2)
General‡	1769/4729 (37.4)	1773/4740 (37.4)
Orthopedic	1083/4729 (22.9)	1063/4740 (22.4)
Vascular	699/4729 (14.8)	700/4740 (14.8)
Urologic	598/4729 (12.6)	624/4740 (13.2)
Spinal	237/4729 (5.0)	206/4740 (4.3)
Gynecologic	162/4729 (3.4)	171/4740 (3.6)
Thoracic	127/4729 (2.7)	146/4740 (3.1)
Low-risk	39/4729 (0.8)	34/4740 (0.7)
Plastic	14/4729 (0.3)	23/4740 (0.5)
Data missing on type of procedure performed	1/4729 (<0.1)	0/4740
No procedure performed	27/4757 (0.6)	35/4778 (0.7)
Data missing on whether patient underwent surgery	1/4757 (<0.1)	3/4778 (0.1)
Medication taken within 24 hr before surgery — no. (%)		
Therapeutic-dose thrombin or factor Xa inhibitor	22 (0.5)	28 (0.6)
Therapeutic-dose vitamin K antagonist	6 (0.1)	8 (0.2)
Therapeutic-dose intravenous or subcutaneous antithrombotic agent	58 (1.2)	44 (0.9)

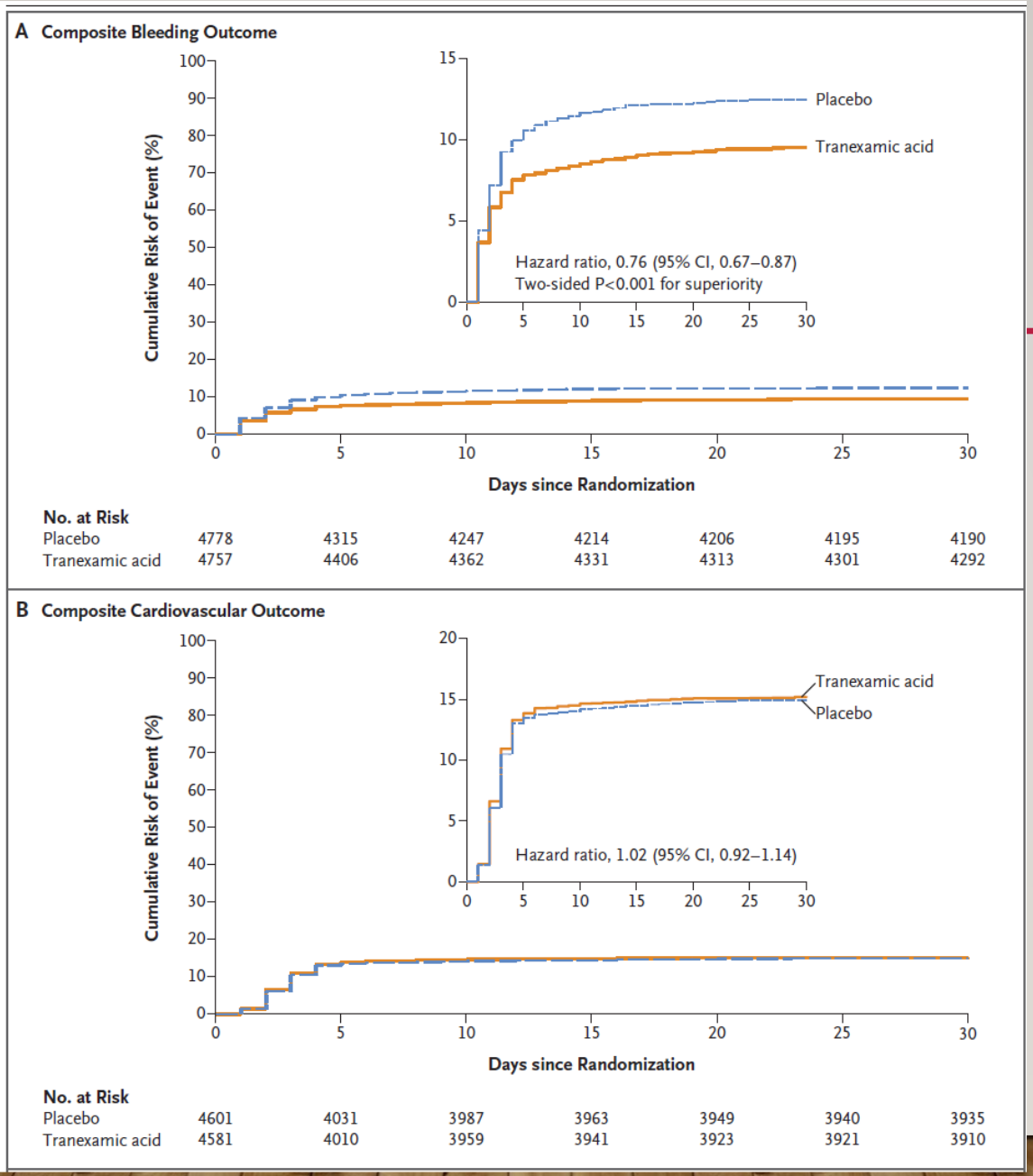
Table 1. (Continued.)

Characteristics	Tranexamic Acid (N=4757)	Placebo (N=4778)
Prophylactic-dose anticoagulant	753 (15.8)	757 (15.8)
Aspirin	638 (13.4)	634 (13.3)
P2Y12 inhibitor	88 (1.8)	84 (1.8)
Nonsteroidal antiinflammatory drug	266 (5.6)	267 (5.6)
Cyclooxygenase-2 inhibitor	132 (2.8)	158 (3.3)

N Engl J Med 2022; 386:1986-1997

RESULTS

- 9535 patients underwent randomization
- For primary efficacy outcomes, TXA reduced (vs placebo)
  - Composite bleeding outcome event at day 30 (**NNT 38**, hazard ratio 0.76, 0.67-0.87, two-sided p<0.001, **statistically significant difference for superiority)**
    - Life-threatening bleeding: 1.6% vs. 1.7%
    - Major bleeding: 7.6% vs. 10.4%
    - Bleeding into a critical organ: 0.3% vs. 0.4%
- For primary safety outcomes, TXA **did NOT achieve noninferiority vs placebo (HR 1.02, 0.92-1.14, p=0.04) for composite CV outcome**
  - Myocardial injury after noncardiac surgery (MINS): 12.8% vs. 12.6%
  - Non-hemorrhagic stroke: 0.5% vs. 0.3%
  - Symptomatic proximal venous thromboembolism: 0.7% vs. 0.6%



N Engl J Med 2022; 386:1986-1997

RESULTS

- Secondary outcomes
  - Hypotension-avoidance vs hypertension-avoidance strategy **(no statistical difference)**
    - MINS 12.7% vs. 12.8% (p = 0.84)
    - Myocardial infarction: 1.4% vs. 1.2% (p = 0.41)
    - Stroke: 0.5% vs. 0.5% (p > 0.99)
    - Vascular mortality: 0.7% vs. 0.6% (p = 0.88)
    - All-cause mortality: 1.3% vs. 1.1% (p = 0.46)
- Other Secondary and Tertiary outcomes (of interest) for TXA vs placebo:
  - Bleeding independently associated with death after noncardiac surgery (8.7% vs 11.3%, hazard ratio 0.76, 0.67-0.87)
  - Transfusion (of at least 1 unit packed red cells) (9.4% vs 12%, odds ratio 0.77, 0.68-0.88)

AUTHOR'S CONCLUSION

- "Among patients undergoing noncardiac surgery, the incidence of the composite bleeding outcome was significantly lower with tranexamic acid than with placebo. Although the between-group difference in the composite cardiovascular outcome was small, the noninferiority of tranexamic acid was not established."

CRITICAL APPRAISAL

- Merits
  - Patients analyzed to groups to which they were randomized, non-inferiority margins clearly defined. Non inferiority hypothesis evaluated in per-protocol population, while other analyses done via ITT.
  - 30 day follow up completed for 99.9% of patients
  - Robust representation of different types of noncardiac surgeries (general, orthopedic, vascular)
  - Robust representation of results in addition to primary results (including MINs, non-hemorrhagic stroke, thrombosis, bleeding independent of noncardiac surgery).
- Flaws
  - Patients were not very co-morbid at baseline (NT-proBNP ≥ 200 in only 10%, a third of each group had CAD, low percentages of PAD, stroke, only a third of each group had diabetes. Low rates of A fib)
  - Trial stopped early due to financial deficit from slowed recruitment during COVID
  - Inability to identify perioperative thrombotic complications

SOUNDCHECK!

- Risk of Bias

- Clinical Applicability

- Practical Applicability

CLINICAL PEARLS

- TXA bolus administration during noncardiac surgery consistently results in less bleeding when compared to placebo, but increases cardiovascular events slightly
  - May have major impact on urgent and emergent surgeries
- No benefit with hypotension avoidance strategy to reduce major vascular outcomes in patients at risk of vascular events
  - Further questions raised with trial on safety of withholding hypertensives prior to surgery, is there any difference to blood pressure targets prior to surgery
- Unclear benefit of TXA in more co-morbid patients undergoing surgery

EMPEROR-PRESERVED:
EMPAGLIFLOZIN IN HEART FAILURE WITH A PRESERVED EJECTION FRACTION

BACKGROUND

- Therapeutic options for patients with heart failure and preserved ejection fraction (HFpEF) are limited, unlike heart failure with reduced ejection fraction (HFrEF)
- Some benefits reported with mineralocorticoid-receptor antagonists and neprilysin inhibitors
- Sodium-glucose cotransporter 2 (SGLT2) inhibitors reduce development and progression of heart failure in patients with reduced ejection fraction, with or without T2DM
- Post hoc analyses of dapagliflozin in T2DM indicated that SGLT2 inhibition may not reduce the incidence of serious adverse outcomes in patients with HFpEF

RECOMMENDATION

11. We recommend an SGLT2 inhibitor, such as dapagliflozin or empagliflozin, be used in patients with HFrEF, with or without concomitant type 2 diabetes, to improve symptoms and quality of life and to reduce the risk of HF hospitalization and/or CV mortality (Strong Recommendation; High-Quality Evidence).
12. We recommend an SGLT2 inhibitor, such as empagliflozin, canagliflozin, or dapagliflozin be used for treatment of patients with type 2 diabetes and atherosclerotic CV disease to reduce the risk of HF hospitalization and death (Strong Recommendation; High-Quality Evidence).
13. We recommend an SGLT2 inhibitor, such as dapagliflozin, be used in patients with type 2 diabetes who are older than 50 years with additional risk factors for atherosclerotic CV disease to reduce the risk of HF hospitalization (Strong Recommendation; High-Quality Evidence).
14. We recommend SGLT2 inhibitors such as canagliflozin or dapagliflozin be used in patients with albuminuric renal disease, with or without type 2 diabetes, to reduce the risk of HF hospitalization and progression of renal disease (Strong Recommendation; High-Quality Evidence).

Values and preferences. These recommendations place weight on the results from large randomized, placebo-controlled trials that consistently showed a benefit of SGLT2 inhibitor treatment on HF prevention and treatment among patients with and without type 2 diabetes.

Can J Cardiol . 2021 Apr;37(4):531-546

AUTHOR'S QUESTION

- What are the the effects of SGLT2 inhibition with empagliflozin on major heart failure outcomes in patients with heart failure and a preserved ejection fraction?

METHODS

- Patients randomly assigned 1:1 to receive either placebo or empagliflozin (10 mg per day)
- Eligible patients were men or women, 18 years of age or older, who had New York Heart Association functional class II–IV chronic heart failure and a left ventricular ejection fraction of more than 40%.
  - The protocol required patients to have an NT-proBNP > 300 pg per milliliter or, for patients with atrial fibrillation at baseline, an NT-proBNP > 900 pg per milliliter.
- Patients were excluded if they had a disorder that could change their clinical course (independent of heart failure) or if they had any condition that might jeopardize patient safety

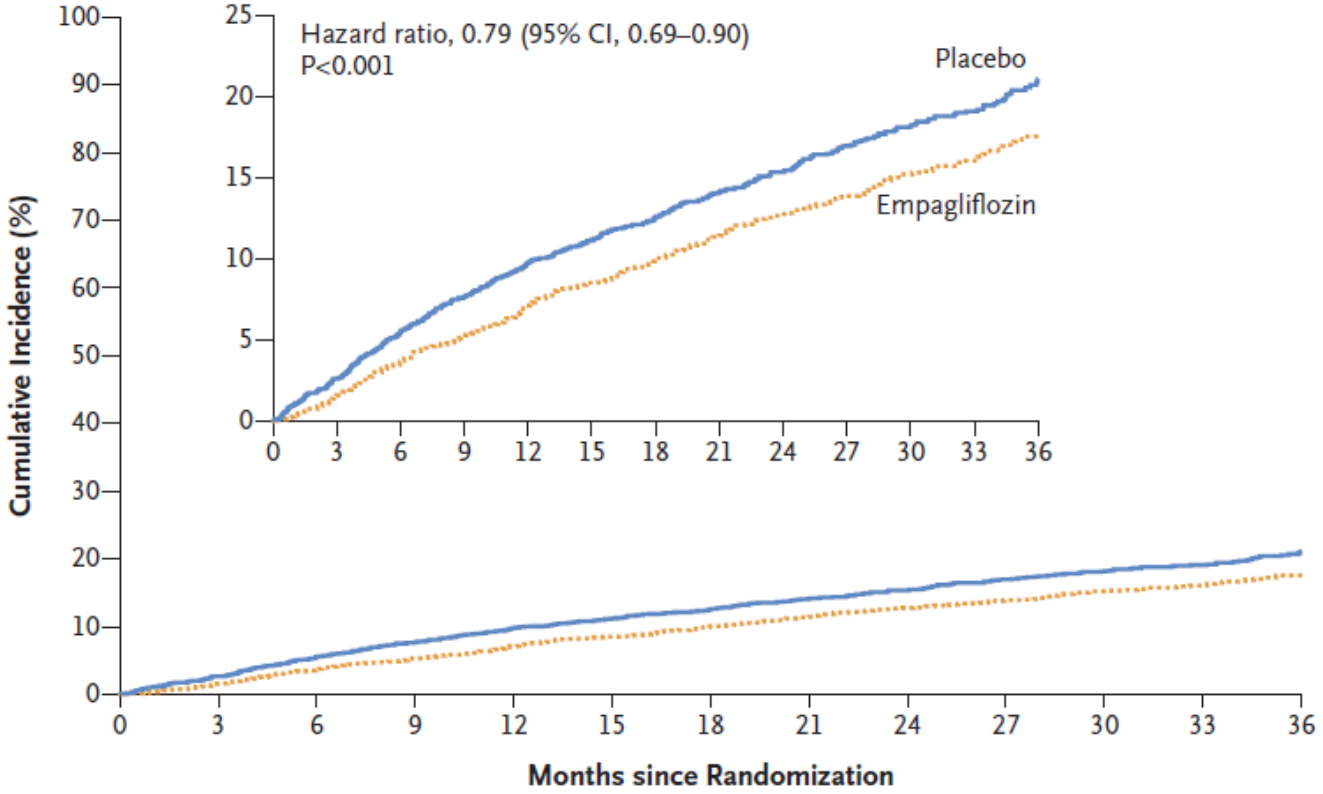
Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Empagliflozin (N=2997)	Placebo (N=2991)
Age — yr	71.8±9.3	71.9±9.6
Female sex — no. (%)	1338 (44.6)	1338 (44.7)
Race — no. (%)†		
White	2286 (76.3)	2256 (75.4)
Black	133 (4.4)	125 (4.2)
Asian	413 (13.8)	411 (13.7)
Other or missing	165 (5.5)	199 (6.7)
Geographic region — no. (%)		
North America	360 (12.0)	359 (12.0)
Latin America	758 (25.3)	757 (25.3)
Europe	1346 (44.9)	1343 (44.9)
Asia	343 (11.4)	343 (11.5)
Other	190 (6.3)	189 (6.3)
NYHA functional classification — no. (%)		
Class I	3 (0.1)	1 (<0.1)
Class II	2432 (81.1)	2451 (81.9)
Class III	552 (18.4)	531 (17.8)
Class IV	10 (0.3)	8 (0.3)
Body-mass index‡	29.77±5.8	29.90±5.9
Heart rate — beats per minute	70.4±12.0	70.3±11.80
Systolic blood pressure — mm Hg	131.8±15.6	131.9±15.7
Left ventricular ejection fraction		
Mean left ventricular ejection fraction — %	54.3±8.8	54.3±8.8
Left ventricular ejection fraction >40% to <50% — no. (%)§	995 (33.2)	988 (33.0)
Left ventricular ejection fraction ≥50% to <60% — no. (%)	1028 (34.3)	1030 (34.4)
Left ventricular ejection fraction ≥60% — no. (%)	974 (32.5)	973 (32.5)
Median NT-proBNP (interquartile range) — pg/ml	994 (501–1740)	946 (498–1725)
Heart failure category — no. (%)		
Ischemic	1079 (36.0)	1038 (34.7)
Nonischemic	1917 (64.0)	1953 (65.3)
Cardiovascular history — no. (%)		
Hospitalization for heart failure during previous 12 mo	699 (23.3)	670 (22.4)
Atrial fibrillation	1543 (51.5)	1514 (50.6)
Diabetes mellitus	1466 (48.9)	1472 (49.2)
Hypertension	2721 (90.8)	2703 (90.4)
Mean eGFR — ml/min/1.73 m^2	60.6±19.8	60.6±19.9
eGFR <60 ml/min/1.73 m^2 — no./total no. (%)	1504/2997 (50.2)	1484/2989 (49.6)

N Engl J Med 2021; 385:1451-1461

RESULTS

- 5988 patients randomized
  - 2/3 patients had LVEF > 50% (median LVEF 54%)
  - Half of patients had diabetes in each group
- Empagliflozin reduced (vs placebo)
  - Composite outcome event at 26 months(death from CV causes or hospitalization for heart failure) (**NNT 30**, hazard ratio 0.79, 0.69-0.9, p<0.001), **statistically significant difference**
    - **Hospitalization for heart failure (hazard ratio 0.71, 0.6-0.83)**
    - Death from CV causes (hazard ratio 0.91, 0.76-1.09)
  - Benefit similar among patients with or without T2DM



No. at Risk

Placebo	2991	2888	2786	2706	2627	2424	2066	1821	1534	1278	961	681	400
Empagliflozin	2997	2928	2843	2780	2708	2491	2134	1858	1578	1332	1005	709	402

Figure 1. Primary Outcome, a Composite of Cardiovascular Death or Hospitalization for Heart Failure.

The estimated cumulative incidence of the primary outcome in the two groups is shown. The inset shows the same data on an expanded y axis.

N Engl J Med 2021; 385:1451-1461

RESULTS

- Select secondary Outcomes for empagliflozin vs placebo:
  - Total hospitalizations: 407 vs. 541 ($p < 0.001$)
  - Change in mean eGFR slope/year: -1.25 vs. -2.62 ($p < 0.001$)
  - Composite renal outcome 3.6% vs. 3.7% ($p > 0.05$)
  - All-cause mortality: 13.4% vs. 14.2% (HR 0.92, 0.77-1.10, $p > 0.05$)
- Safety Outcomes
  - Less serious adverse events occurred in empagliflozin group vs placebo (47.9% vs 51.6%)
  - Adverse events leading to discontinuation of treatment higher in empagliflozin group (19.7% vs 18.4%)
  - Uncomplicated genital and UTI infections, hypotension more common in patients treated with empagliflozin

RESULTS

- Pooled analysis of EMPEROR-Reduced and EMPEROR-Preserved (n=9718)
  - Renal outcomes (decrease in eGFR or renal replacement therapy)
    - 2.8% vs. 3.5% for empagliflozin vs. placebo, with significant heterogeneity ($p = 0.016$ for interaction)
  - Outcomes stratified by Ejection Fraction
  - 33% had EF 41-49%, 67% had EF equal to/over 50%
    - Primary endpoint for empagliflozin vs. placebo
      - For EF ≥50%: 6.7% vs. 8.0% ($p = 0.024$)
      - For EF 41-49%: 7.2% vs. 10% ($p = 0.002$)
    - Total HF hospitalizations for
      - EF ≥50%: 4.5% vs. 5.7% ($p = 0.013$)
      - EF 41-49%: 3.8% vs. 6.5% ($p < 0.001$)

AUTHOR'S CONCLUSION

- "Empagliflozin reduced the combined risk of cardiovascular death or hospitalization for heart failure in patients with heart failure and a preserved ejection fraction, regardless of the presence or absence of diabetes."

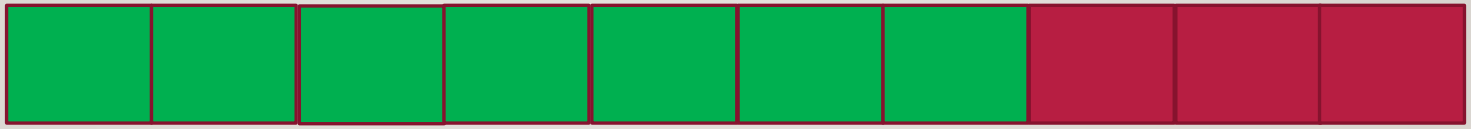
CRITICAL APPRAISAL

- Merits
  - Concealed randomization, double blinded
  - Patients analyzed to groups they were assigned using ITT
  - Well balanced treatments and controls, representation of older population with co-morbidities (including diabetes and renal dysfunction)
  - Robust composite endpoint of CV outcomes, hospitalization, and death. Robust subgroup analyses of different heart failure classes, patients with A fib, and previous heart failure hospitalizations
- Flaws
  - Patient population analyzed seemed to have less severe heart failure. Only 20% in each group were hospitalized in the last 12 months, and most had Class II heart failure
  - High treatment discontinuation rate (23%), significant loss of power, and high rate of discontinuation may have driven effect size towards null hypothesis

SOUNDCHECK!

- Risk of Bias

- Clinical Applicability



- Practical Applicability

CLINICAL PEARLS

- Benefit of empagflozin in HFpEF mainly driven by reduction in hospitalizations, not mortality.
- Improvement in GFR seen in HFpEF patients, but not renal outcomes
  - Pooled analysis of EMPEROR-Reduced and EMPEROR-Preserved suggests renal benefit primarily seen in HFrEF patients
- Empagflozin seems to benefit patients with clinically lower severity HFpEF patients, but outcomes were robust irrespective of baseline EF
- Benefit for SGLT2 inhibitors seen in heart failure patients independent of diabetes
  - However, half of study population were diabetics, benefit may still be diabetes driven?

LOVIT:
INTRAVENOUS VITAMIN C IN ADULTS WITH SEPSIS IN THE INTENSIVE CARE UNIT

BACKGROUND

- Sepsis defined as life-threatening organ dysfunction caused by a dysregulated host response to infection.
- Mainstay treatment includes antimicrobial therapy, source control and organ support
- Theory is that antioxidant effects of vitamin C may reduce tissue injury induced by oxidative stress.
  - Vitamin C cannot be synthesized by humans and is characterized by low levels in critically ill
- Recent meta-analyses suggest overall evidence supporting use of vitamin C therapy in patients is of low certainty

SURVIVING SEPSIS CAMPAIGN BUNDLES

TO BE COMPLETED WITHIN 3 HOURS:

1) Measure lactate level
2) Obtain blood cultures prior to administration of antibiotics
3) Administer broad spectrum antibiotics
4) Administer 30 mL/kg crystalloid for hypotension or lactate ≥4mmol/L

TO BE COMPLETED WITHIN 6 HOURS:

5) Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure (MAP) ≥ 65 mm Hg
6) In the event of persistent arterial hypotension despite volume resuscitation (septic shock) or initial lactate ≥4 mmol/L (36 mg/dL):
   - Measure central venous pressure (CVP)*
   - Measure central venous oxygen saturation ($Scvo_2$)*
7) Remeasure lactate if initial lactate was elevated*

*Targets for quantitative resuscitation included in the guidelines are CVP of ≥8 mm Hg, $Scvo_2$ of ≥70%, and normalization of lactate.

Intensive Care Med. 2013 Feb;39(2):165-228

AUTHOR'S QUESTION

- Will a high dose of vitamin C reduce the risk of death or persistent organ dysfunction at 28 days in adults with sepsis who were receiving vasopressor therapy in the intensive care unit (ICU)?

METHODS

- Patients randomly assigned to receive either vitamin C (50 mg/kg IV bolus q6h for remainder of ICU stay up to 96 hours) vs placebo
- Eligible patients were adults who had been in the ICU for no longer than 24 hours, who had proven or suspected infection as the main diagnosis, and who were receiving a vasopressor.
- Exclusion criteria included contraindications to vitamin C, receipt of open label vitamin C, or expected death/withdrawal of life-sustaining therapy within 48 hours.
- Administration of glucocorticoids and thiamine performed at discretion of treating teams
    - Previous single center study that found a benefit with a treatment combination of IV vitamin C, hydrocortisone, and thiamine

METHODS

- Organ failure was measured by means of the score on the Sequential Organ Failure Assessment (SOFA).
  - Grades the function of six organ systems (CNS, cardiovascular, respiratory, coagulation, liver, renal function)
  - Can be scored up to 24, with higher scores indicating worse clinical outcomes
- Patients' disease severity rated on the Acute Physiology and Chronic Health Evaluation (APACHE) II.
  - Scores range from 0 to 71, with higher scores indicating an increased risk of death.

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Vitamin C (N=429)	Placebo (N=433)†
Age — yr	65.0±14.0	65.2±13.8
Female sex — no. (%)	151 (35.2)	173 (40.0)
Admission type — no. (%)‡		
Medical	350 (81.6)	369 (85.2)
Emergency surgery	69 (16.1)	59 (13.6)
Elective surgery	10 (2.3)	5 (1.2)
APACHE II score§	24.2±7.4	24.1±7.9
SOFA score¶	10.2±3.4	10.1±3.7
Score on Clinical Frailty Scale‖	3.8±1.4	3.9±1.4
1 to 4 — no. (%)	312 (72.7)	308 (71.3)
≥5 — no. (%)	117 (27.3)	124 (28.7)
Primary site of infection — no. (%)**		
Pulmonary	145 (33.8)	159 (36.7)
Gastrointestinal or intra-abdominal	133 (31.0)	112 (25.9)
Blood	55 (12.8)	59 (13.6)
Skin or soft tissue	55 (12.8)	62 (14.3)
Urinary	49 (11.4)	55 (12.7)
Central nervous system	2 (0.5)	4 (0.9)
Other	30 (7.0)	27 (6.2)
SARS-CoV-2 positive — no. (%)††	37 (8.6)	26 (6.0)
Lactate — mmol/liter‡‡	3.4±3.2	3.0±2.8
Vitamin C — μmol/liter§§	20.6±70.6	19.1±39.7
Septic shock definition met — no./total no. (%)¶¶	195/327 (59.6)	183/326 (56.1)
Time from ICU admission to randomization — hr	12.9±8.2	12.3±6.7
Treatment — no. (%)		
Glucocorticoid‖‖	199 (46.4)	196 (45.4)
Mechanical ventilation	294 (68.5)	283 (65.4)
Renal-replacement therapy	46 (10.7)	42 (9.7)
Vasopressor infusion***	428 (99.8)	433 (100)

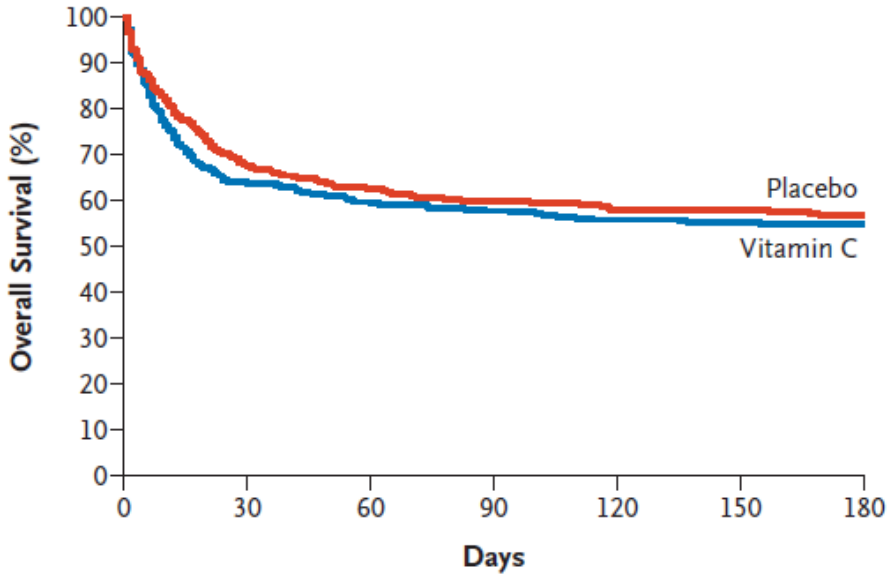
N Engl J Med 2022; 386:2387-2398

RESULTS

- Total of 872 patients randomized
- Vitamin C increased (vs placebo)
  - Primary composite outcome of death or persistent organ dysfunction at day 28 (receipt of vasopressors, invasive mechanical ventilation, or new renal-replacement therapy): **NNH 17**, hazard ratio 1.21, 1.04-1.40, p=0.01, **statistically significant for harm**
  - Analysis adjusted for prespecified baseline characteristics (hazard ratio 1.15, 0.9-1.47)

RESULTS

- Secondary Outcomes
  - At 28 days, death occurred in 35.4% of the vitamin C group and 31.6% in the placebo group (hazard ratio1.17; 95% CI, 0.98 to 1.40, **no difference**).
  - No differences between groups in SOFA scores, biomarkers, 6-month survival, or health related quality of life
- No differences in prespecified safety outcomes (Stage III AKI, acute hemolysis, hypoglycemia)
  - In the vitamin C group, one patient had a severe hypoglycemic episode, and another had a serious anaphylaxis event.



No. at Risk							
Placebo	433	289	265	254	246	245	241
Vitamin C	429	267	248	240	230	227	226

Figure 2. Kaplan–Meier Analysis of Survival at 6 Months.

Shown is the percentage of patients who were alive at the 6-month follow-up (226 patients [54.2%] in the vitamin C group and 241 [56.6%] in the placebo group), which was a secondary outcome in the trial.

N Engl J Med 2022; 386:2387-2398

AUTHOR'S CONCLUSION

- "In adults with sepsis receiving vasopressor therapy in the ICU, those who received intravenous vitamin C had a higher risk of death or persistent organ dysfunction at 28 days than those who received placebo."

CRITICAL APPRAISAL

- Merits
  - Largest RCT on topic to date, median enrollment time of 12 hours after ICU admission, high protocol adherence
  - ITT analysis performed for primary outcome, subgroups pre-specified
  - Robust composite endpoint of death (the hot topic!) and persistent organ dysfunction
  - Long term follow-up with secondary outcomes including 28 day and 6 month follow-up for organ dysfunction and death
- Flaws
  - No subgroup analyses with patients on physician driven adjunctive treatment.
    - Likely confounding with some adjunctive treatments such as steroids
  - Information regarding specific pathogens and appropriateness of antimicrobial therapy not collected
  - Information to ascertain presence of acute respiratory distress syndrome (ARDs) at baseline not collected

SOUNDCHECK!

- Risk of Bias

- Clinical Applicability

- Practical Applicability

CLINICAL PEARLS

- No benefit of utilizing vitamin C in patients with severe, refractory septic shock.
  - Strong signal of harm with vitamin C
- Benefit of adjunctive therapies to vasopressors for hemodynamic support for severe, refractory septic shock remains confounded and unsatisfying

PRIME CARE:
EFFECT OF PHARMACOGENOMIC TESTING FOR DRUG-GENE INTERACTIONS ON MEDICATION SELECTION AND REMISSION OF SYMPTOMS IN MAJOR DEPRESSIVE DISORDER

BACKGROUND

- Pharmacogenomic testing focuses on variation in genes that encode hepatic CYP 450 enzymes. In theory, this can help classify how a patient metabolizes medications (poor, normal, intermediate, rapid?)
- Pharmacogenomic testing may improve drug selection or dosing in patients with genetic variation that can alter drug PK/PD
- Theory is that pharmacogenomic testing may be helpful in treating patients with major depressive disorder (MDD).
    - Initial treatment response expected in only ~1/3 of patients with odds of remission and treatment engagement decreasing with each treatment trial (diminishing returns)

AUTHOR'S QUESTION

- "This study used a pragmatic study design to test 2 primary study hypotheses: (1) patients and clinicians would use pharmacogenomic test results to select fewer antidepressants with potential drug-gene interactions (treatment initiation) and (2) treatment in the pharmacogenomic-guided group would result in greater rates of remission."

METHODS

- Patients randomly assigned to receive pharmacogenomic test results when available (~2-3 days after randomization, pharmacogenomic-guided group) or 24 weeks later (usual care group)
- Eligible patients had a diagnosis of MDD, a history of at least 1 treatment episode, and a plan to start a new episode of antidepressant monotherapy (either switching from a prior treatment or starting a new treatment episode).
- Exclusion criteria were an active substance use disorder; bipolar illness; psychosis; borderline or antisocial personality disorder; treatment with an antipsychotic medication, methadone, buprenorphine, on naltrexone; augmentation treatment; and lack of a bank account for payments

METHODS

- Remission was measured for the primary outcome with the Patient Health Questionnaire-9 (PHQ-9, remission defined by a score less than/equal to 5.
  - Other assessments used included the Generalized Anxiety Disorder–7, Columbia-Suicide Severity Rating Scale, Veterans RAND 12-item Health Survey, current alcohol use, a modified version of the National Institute on Drug Abuse's Alcohol, Smoking, and Substance Involvement Screening, adverse drug reactions, and the PTSD Checklist for DSM-5
- Patients self reported history of treatment by reviewing list of psychotropic medications with doses representing an adequate trial
  - Treatment-refractory depression defined as history of 2 more medication treatments for at least 6 weeks with standard doses or treatment with ECT or TMS

PATIENT HEALTH QUESTIONNAIRE (PHQ-9)

ID #: _____ DATE: _____

Over the last *2 weeks*, how often have you been bothered by any of the following problems?
(use "✓" to indicate your answer)

	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself—or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed. Or the opposite — being so figety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead, or of hurting yourself	0	1	2	3
		add columns	+	+
		TOTAL:		

(Healthcare professional: For interpretation of TOTAL, please refer to accompanying scoring card).

10. If you checked off *any problems*, how *difficult* have these problems made it for you to do your work, take care of things at home, or get along with other people?

- Not difficult at all _____
- Somewhat difficult _____
- Very difficult _____
- Extremely difficult _____

Guide for Interpreting PHQ-9 Scores

Score	Depression Severity	Action
0 - 4	None-minimal	Patient may not need depression treatment.
5 - 9	Mild	Use clinical judgment about treatment, based on patient's duration of symptoms and functional impairment.
10 - 14	Moderate	Use clinical judgment about treatment, based on patient's duration of symptoms and functional impairment.
15 - 19	Moderately severe	Treat using antidepressants, psychotherapy or a combination of treatment.
20 - 27	Severe	Treat using antidepressants with or without psychotherapy.

Source material from:
J Gen Intern Med. 2001 Sep; 16(9): 606–613
Pictorial interpretation courtesy of the Government of BC Health Agency

Table 1. Participating Clinician Characteristics in Relationship to the Number of Their Patients Randomized in the Trial

Characteristic	No. (%)		
	Clinicians with 1-5 randomizations	Clinicians with 6-10 randomizations	Clinicians with ≥11 randomizations
No.	276	62	48
Age, y[a]			
<41	92 (33)	25 (40)	16 (33)
41-60	138 (50)	26 (42)	21 (44)
>60	42 (15)	10 (16)	11 (23)
Sex			
Female	162 (59)	42 (68)	39 (81)
Male	114 (41)	20 (32)	9 (19)
Race (self-report)			
African American/Black	15 (4)	2 (1)	3 (1)
American Indian/Alaskan	1 (0)	0	0
Asian	54 (14)	8 (2)	8 (2)
Pacific Islander or Native Hawaiian	1 (0)	0	0
White	176 (46)	45 (12)	34 (9)
Other[b]	4 (1)	2 (1)	0
Preferred not to answer	18 (5)	4 (1)	2 (1)
Selected >1 category	7 (2)	1 (<1)	1 (<1)
50% or more of current work time spent in clinical care	249 (90)	61 (98)	46 (96)
Professional degree			
Physician	216 (78)	45 (73)	22 (46)
Advanced practice nurse/ physician assistant	52 (19)	12 (19)	24 (50)
PharmD	8 (3)	5 (8)	2 (4)
Practice location			
Integrated care[c]	24 (9)	9 (15)	12 (25)
Primary care	74 (27)	5 (8)	3 (6)
Specialty mental health	178 (64)	48 (77)	33 (69)

JAMA. 2022;328(2):151-161

Table 2. Patient Baseline Demographics, Social, and Clinical Characteristics

Characteristic	Group, No. (%)	
	Pharmacogenomic guided	Usual care
No.	966	978
Patient characteristics		
Age, mean (SD), y	48 (15)	47 (15)
Sex		
Female	229 (24)	262 (27)
Male	737 (76)	716 (73)
Race		
African American/Black	185 (19)	167 (17)
Asian Pacific Islander	31 (3)	24 (3)
Native American/Alaskan	10 (1)	9 (1)
White	644 (67)	688 (70)
Other/mixed[a]	90 (9)	84 (9)
Refused	6 (1)	6 (1)
Hispanic ethnicity	113 (12)	104 (11)
Financial status		
Have just enough to get along	482 (50)	492 (50)
Are comfortable	338 (35)	352 (36)
Can't make ends meet	127 (13)	116 (12)
Clinical symptoms		
PHQ-9 score, inclusion criteria >9, mean (SD)[b]	17.5 (4.3)	17.5 (4.3)
Treatment refractory[c]	288 (30)	301 (31)
GAD-7 score, mean (SD)[d]	14.1 (4.8)	13.9 (5.0)
PTSD presence[e]	566 (59)	562 (58)
PCL-5 score in those with PTSD, mean (SD)[f]	51.5 (12.0)	51.8 (12.0)
Suicidal ideation (C-SSRS) (moderate or higher risk), No./total (%)[g]	187/597 (31)	190/596 (32)
Alcohol use		
Those with at-risk drinking[h]	219 (23)	230 (24)
Drinks per week, median (IQR)	0 (0-3)	0 (0-4)
Recent regular (last 3 mo) marijuana use[i]	227 (23)	238 (24)
Other recent regular (last 3 mo) drug use[i]	15 (2)	13 (1)
Current tobacco use[i]	256 (27)	250 (26)
VR-12 composite score, mean (SD)[j]		
Mental	23.8 (10.6)	24.9 (10.2)
Physical	37.9 (13.4)	36.4 (13.1)

JAMA. 2022;328(2):151-161

RESULTS

- Total of 1944 patients randomized, and 676 clinicians consented to participating in the study
- Estimated risks for receiving an antidepressant (pharmacogenomic guided group vs usual care group) at 24 weeks:
  - No drug-gene interactions (59.3% vs 25.7%, 0.289-0.384, p<0.001, **NNT 3, statistically significant difference**)
  - Moderate drug-gene interactions (30% vs 54.6%)
  - Substantial drug-gene interactions (10.7% vs 19.7%)
- Pharmacogenomic-guided group **more likely to receive**
  - medication with lower potential drug-gene interaction for no gene vs moderate/substantial interaction (OR 4.32, 3.47-5.39, p<0.00)
  - medication with no/moderate vs substantial interaction (OR 2.08,1.52-2.84, p<0.001)

RESULTS

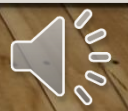
- Remission rates over 24 weeks were higher among patients guided by pharmacogenomic testing vs those in usual care (OR 1.28,1.05-1.57, p = 0.02), **NNT 36, statistically significant difference)**
- **Remission rates at week 24 not significantly different**
- Secondary Outcomes
  - Response to treatment and reduction in symptom severity favored pharmacogenomic group (OR 1.25,1.07-1.46, p = 0.005)
  - No significant difference in response rates at 24 weeks
- No identified harms to patients related to intervention

AUTHOR'S CONCLUSION

- "Among patients with MDD, provision of pharmacogenomic testing for drug-gene interactions reduced prescription of medications with predicted drug-gene interactions compared with usual care. Provision of test results had small nonpersistent effects on symptom remission."

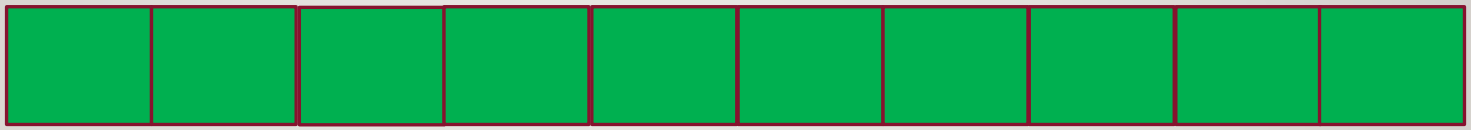
CRITICAL APPRAISAL

- Merits
  - Robust attempt to capture data on a complicated topic of relatively new importance in the pharmaceutical domain
  - Important attempt at randomization, which is often lacking in psychiatric treatment trials
- Flaws
  - Patients and clinicians not blinded, only outcome raters were blinded
  - Only 80% in each group completed assessment
  - Patients self-reported history of treatment including list of psychotropic meds – risk of recall bias
  - Unclear how authors analyzed groups to which they were randomized
  - A LOT of data collected, including clinician data. Detracts from focus of study
  - Active substance abuse and patients on antipsychotics excluded. Many patients had no or only moderate predicted drug gene interactions.
  - Trial not powered to evaluate outcomes such as the effect of changes in dosing, the presence of adverse drug reactions, the effect of medication adherence by patients, or the effect of antidepressant switches after randomization.



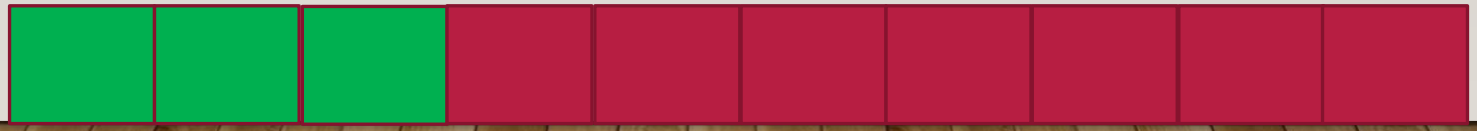
SOUNDCHECK!

- Risk of Bias



- Clinical Applicability

- Practical Applicability



CLINICAL PEARLS

- The use of pharmacogenomic testing seems to be a safe option to guide individualized treatment for MDD patients
  - Benefit seems to be found in refractory MDD patients with moderate-severe illness at baseline
  - Unclear effect of concomitant substance use
- The practical application of pharmacogenomic testing is in question, as pharmacogenomic testing is still not widely available
- If nothing else, the trial proves that individual variation is HUGE in developing psychiatric treatment plans and is largely based on completion of subjective assessments

MY TYPICAL RESPONSE TO QUESTIONS…

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