期刊報告

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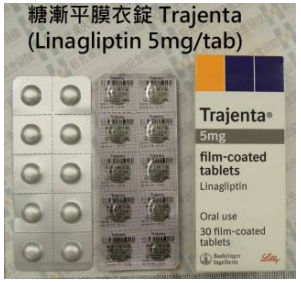
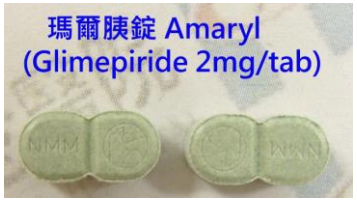
JAMA | Original Investigation

Effect of Linagliptin vs Glimepiride on Major Adverse Cardiovascular Outcomes in Patients With Type 2 Diabetes

The CAROLINA Randomized Clinical Trial

- Randomized, double-blind, noninferiority trial.
- From November 2010 to December 2012, Follow-up ended in August 2018, 43 countries.





N=6042

Type 2 diabetes, HbA1c: 6.5 to 8.5%, Elevated cardiovascular risk

Atherosclerotic CV disease, > 70 years, microvascular complications, multiple CV risk factors

n =3023 — **Linagliptin 5mg QD**

n =3010 — **Glimepiride 1-4 mg QD**

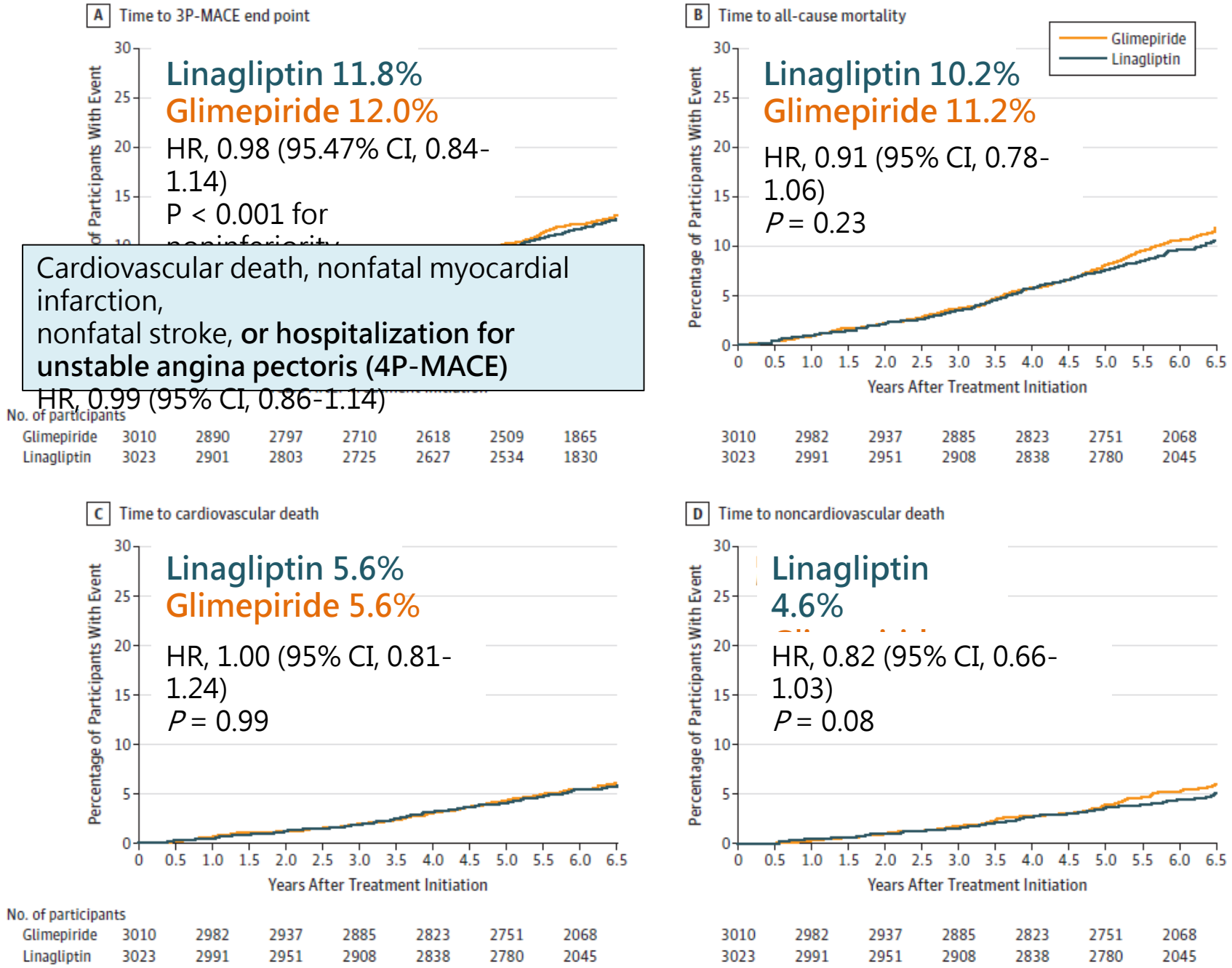
- Mean age, 64 years; mean HbA1c, 7.2%; median duration of diabetes, 6.3 years; 59% had undergone metformin monotherapy

MAIN OUTCOMES

- The primary outcome was time to first occurrence of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke.

RESULTS

Figure 2. Time to Occurrence of End Points Based on Cox Regression Analyses in Patients Treated With at Least 1 Dose of the Study Drug

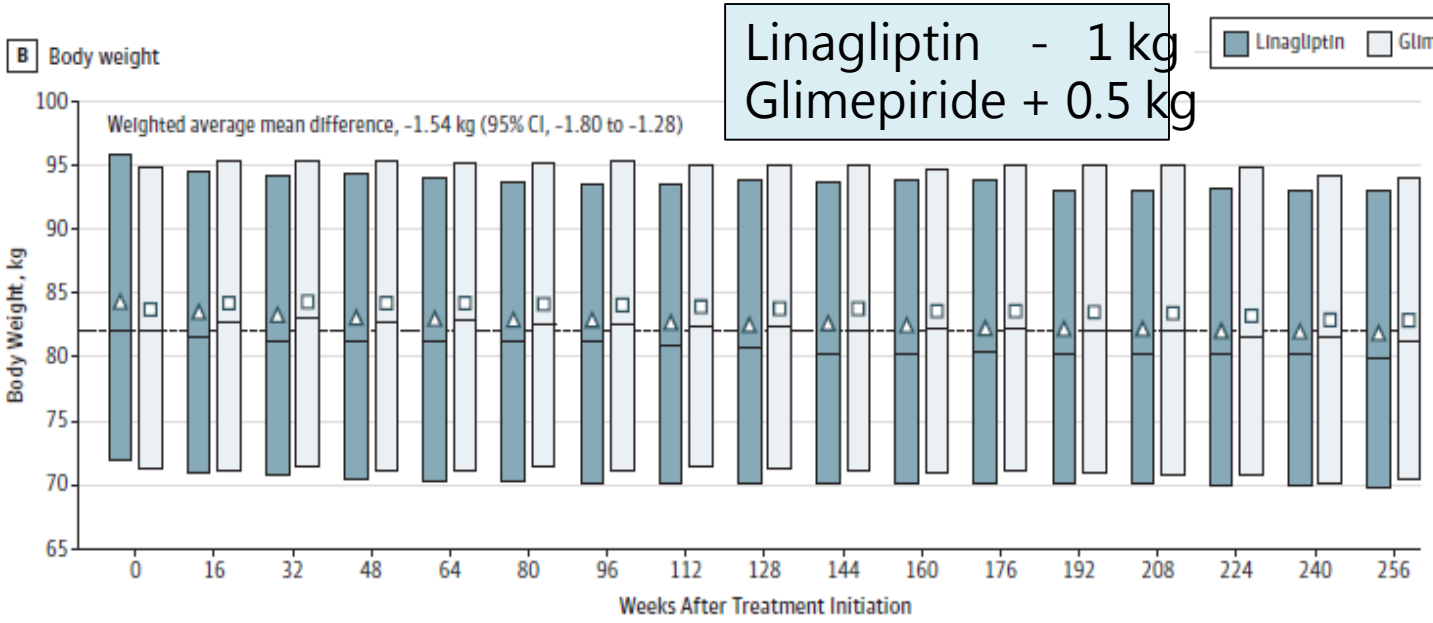


RESULTS

Figure 3. Glycated Hemoglobin (HbA_{1c}) and Weight Over Time by Treatment Groups

Weighted average mean difference, –1.54 kg (95% CI, –1.80 to –1.28

Linagliptin - 1 kg
Glimepiride + 0.5 kg



No. of participants																	
Glimepiride	2998	2933	2814	2740	2682	2621	2572	2534	2498	2434	2398	2341	2291	2257	2229	2193	2178
Linagliptin	3014	2936	2822	2741	2674	2620	2546	2522	2466	2433	2426	2378	2326	2280	2280	2236	2221
Total in follow-up analysis	6033	6021	5995	5979	5953	5929	5901	5879	5856	5826	5787	5752	5702	5662	5629	5592	5551

- **HbA1c**, Fasting plasma glucose, blood pressure, and lipid levels over time were **not significantly different between groups**

Safety

Table 3. Adverse Events of Participants in a Study of the Effect of Linagliptin vs Glimepiride on Cardiovascular Outcomes in Patients With Type 2 Diabetes

Adverse Events[a]	Linagliptin (n = 3023) No. (%)	Linagliptin (n = 3023) Rate/100 Patient-Years	Glimepiride (n = 3010) No. (%)	Glimepiride (n = 3010) Rate/100 Patient-Years
Any adverse events[b]	2821 (93.6)	121.9	2855 (95.2)	144.5
Serious adverse events	1403 (46.4)	12.8	1448 (48.1)	13.5
Adverse events leading to study medication discontinuation[b]	414 (13.7)	2.8	448 (14.9)	3.1
Any hospitalization	1245 (41.2)	9.2	1303 (43.3)	9.8
Adjudication-confirmed acute pancreatitis	15 (0.5)	0.1	16[e] (0.5)	0.1
Adjudication-confirmed chronic pancreatitis	3 (0.1)	<0.1	0 (0.0)	0.0
All cancers	280 (9.3)	1.6	303 (10.1)	1.7
Colorectal cancer	32 (1.1)	0.2	30 (1.0)	0.2
Adjudication-confirmed pancreatic cancer	16 (0.5)	0.1	24 (0.8)	0.1
Gastric cancer	9 (0.3)	0.1	5 (0.2)	<0.1
Thyroid cancer	1 (<0.1)	<0.1	3 (0.1)	<0.1
Hypoglycemic adverse events[b]				
≥1 Investigator-reported episode of hypoglycemia	320 (10.6)	2.3	1132 (37.7)	11.1
≥1 Investigator-reported episode of symptomatic hypoglycemia with plasma glucose ≤70 mg/dL or severe hypoglycemia	195 (6.5)	1.4	927 (30.9)	8.4
≥1 Investigator-reported episode of severe hypoglycemia[f]	10 (0.3)	0.1	65 (2.2)	0.5
≥1 Episode of hospitalized hypoglycemia	2 (0.1)	<0.1	27 (0.9)	0.2

HR, 0.23 [95%CI, 0.21-0.26]

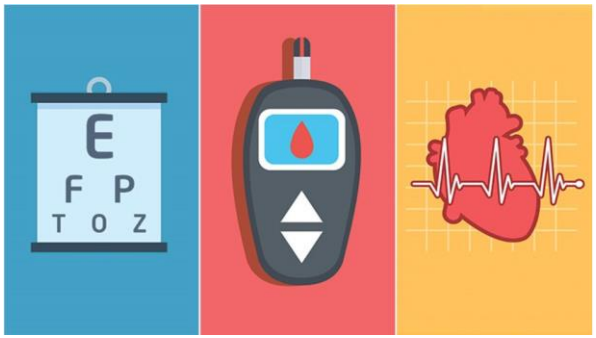
HR, 0.18 [95% CI, 0.15-0.21]

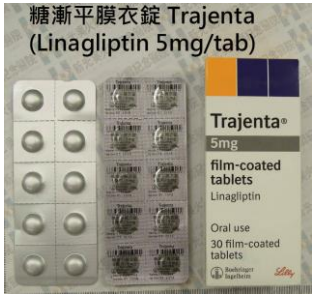
Limitations

- The trial recruited participants with relatively **early type 2 diabetes** and **insulin treatment was an exclusion criterion**.
- The results may not necessarily be applicable to patients with more advanced disease.

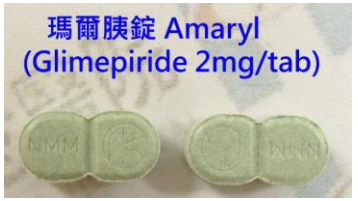
Conclusions

- Among adults with relatively early type 2 diabetes and elevated cardiovascular risk, the use of linagliptin compared with glimepiride over a median of 6.3 years resulted in a **noninferior risk of a composite cardiovascular outcome**.





Linagliptin 5mg QD



Glimepiride 1-4 mg QD

JAMA | Original Investigation

Association of Treatment With Metformin vs Sulfonylurea With Major Adverse Cardiovascular Events Among Patients With Diabetes and Reduced Kidney Function

- Retrospective cohort study of US veterans receiving care within the national Veterans Health Administration. From 2001 through 2016.

EXPOSURES

N= 96,725. New users of **metformin** or **sulfonylurea monotherapy** who continued treatment with their glucose-lowering medication after reaching reduced kidney function **(eGFR < 60 mL/min or Cr ≥ 1.4mg/dL (women) or ≥ 1.5mg/dL (men)).**

PATIENTS

- Median age, 70 years [IQR, 62.8-77.8]; median eGFR, 55.8 mL/min/1.73m2 [IQR, 51.6-58.2] and HbA1c, 6.6% [IQR, 6.1%-7.2%].
- During follow-up (median, 1.0 year for metformin vs 1.2 years for sulfonylurea).

MAIN OUTCOMES AND MEASURES

- **MACE** included hospitalization for acute myocardial infarction, stroke, transient ischemic attack, or cardiovascular death.

RESULTS

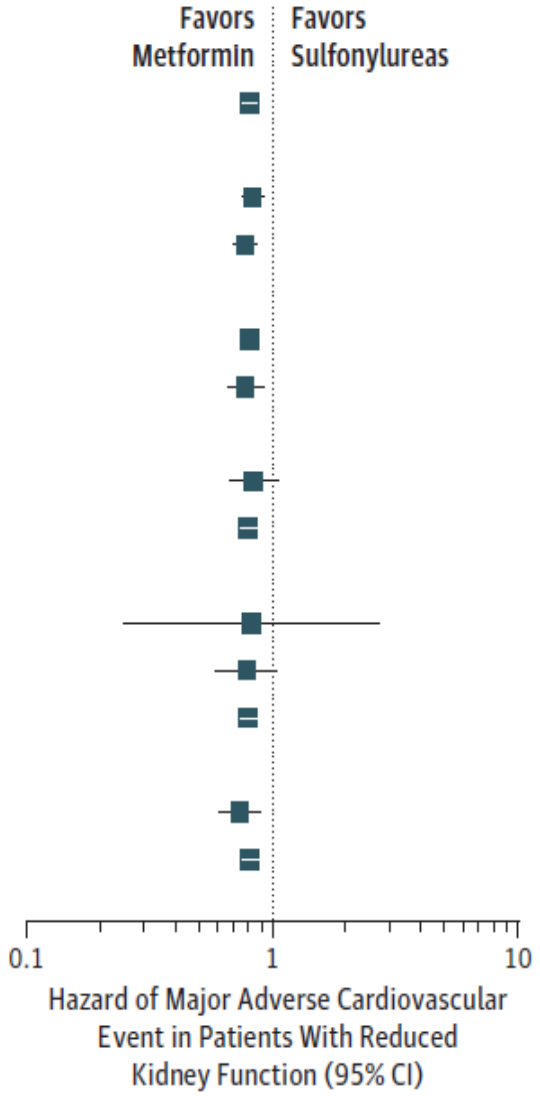
	Metformin	Sulfonylurea
Persistent Exposure Required		
Primary outcome: composite MACE		
Unadjusted rate/1000 person-years (95% CI)	23.0 (21.7-24.4)	29.2 (27.7-30.7)
Adjusted HR (95% CI)	**0.80 (0.75-0.86)**	1 [Reference]
Adjusted incident rate difference (95% CI)	**−5.8 (−7.3 to −4.1)**	
Component of primary outcome: cardiovascular hospitalization (AMI, stroke, or TIA)		
Unadjusted rate/1000 person-years (95% CI)	15.5 (14.4-16.7)	18.3 (17.1-19.5)
Adjusted HR (95% CI)	**0.87 (0.80-0.95)**	1 [Reference]
Adjusted incident rate difference (95% CI)	**−2.4 (−3.7 to −0.9)**	

- Component of primary outcome: **Cardiovascular death**: Adjusted hazard ratio (95% CI), **0.70 (0.63 to 0.78**)
- Secondary outcome: **AMI, stroke, or cardiovascular death**: Adjusted hazard ratio (95% CI), **0.78 (0.72 to 0.84**)

RESULTS

Figure 3. Adjusted Hazard Ratios for Major Adverse Cardiovascular Events by Subgroups

	Metformin	Sulfonylureas	
	No. of Events/ No. at Risk	No. of Events/ No. at Risk	Adjusted Hazard Ratio (95% CI)
Full matched-weighted cohort	1048/24679	1394/24799	0.80 (0.75-0.86)
Cardiovascular disease history			
Yes	511/7797	671/7868	0.83 (0.75-0.92)
No	537/16882	723/16931	0.78 (0.70-0.86)
Age, y			
≥65	870 /16796	136/16764	0.81 (0.75-0.88)
<65	178/7883	258/8034	0.78 (0.66-0.92)
Race			
Black	107/4035	154/4047	0.84 (0.67-1.06)
Nonblack	941/20644	1240/20752	0.80 (0.74-0.86)
Estimated glomerular filtration rate (eGFR)			
<30 mL/min/1.73 m^2	10/332	17/334	0.82 (0.25-2.72)
30-45 mL/min/1.73 m^2	65/1903	115/1886	0.79 (0.59-1.04)
>45 mL/min/1.73 m^2	973/22444	1262/22578	0.80 (0.74-0.86)
Cohort entry criteria			
Creatinine ≥ FDA threshold	125/5733	229/7779	0.74 (0.61-0.90)
eGFR <60 mL/min/1.73 m^2 + creatinine <FDA threshold	923/39809	1164/39983	0.81 (0.75-0.88)



① Patients with **DM and CKD**. The relative risk of all-cause mortality was lower in patients taking **metformin** than for patients not taking metformin (HR, 0.78 [95% CI, 0.63-0.96).

② Examined **heart failure** readmission in patients with **reduced kidney function**. Demonstrated lower readmission risk (n = 5859; HR, 0.91 [95% CI, 0.84-0.99]) for **metformin** compared with **sulfonylurea or insulin** use.

Limitations

- It is possible that for some patients this kidney threshold may represent an acute kidney injury event.
- Did not include a dose analysis.

CONCLUSIONS AND RELEVANCE Among patients with diabetes and reduced kidney function persisting with monotherapy, treatment with metformin, compared with a sulfonylurea, was associated with a lower risk of MACE.

JAMA | Original Investigation

Association of Change in N-Terminal Pro–B-Type Natriuretic Peptide Following Initiation of Sacubitril-Valsartan Treatment With Cardiac Structure and Function in Patients With Heart Failure With Reduced Ejection Fraction

- Prospective, 12-month, **single-group**, open-label study, United States.
- From October 25, 2016 through October 22, 2018.

Patients with HFrEF (N=794; Mean age: 65.1; NYHA II [70.3%])
Entresto (Sacubitril + Valsartan)
Whether NT-proBNP changes correlate with changes in measures of cardiac volume and function.

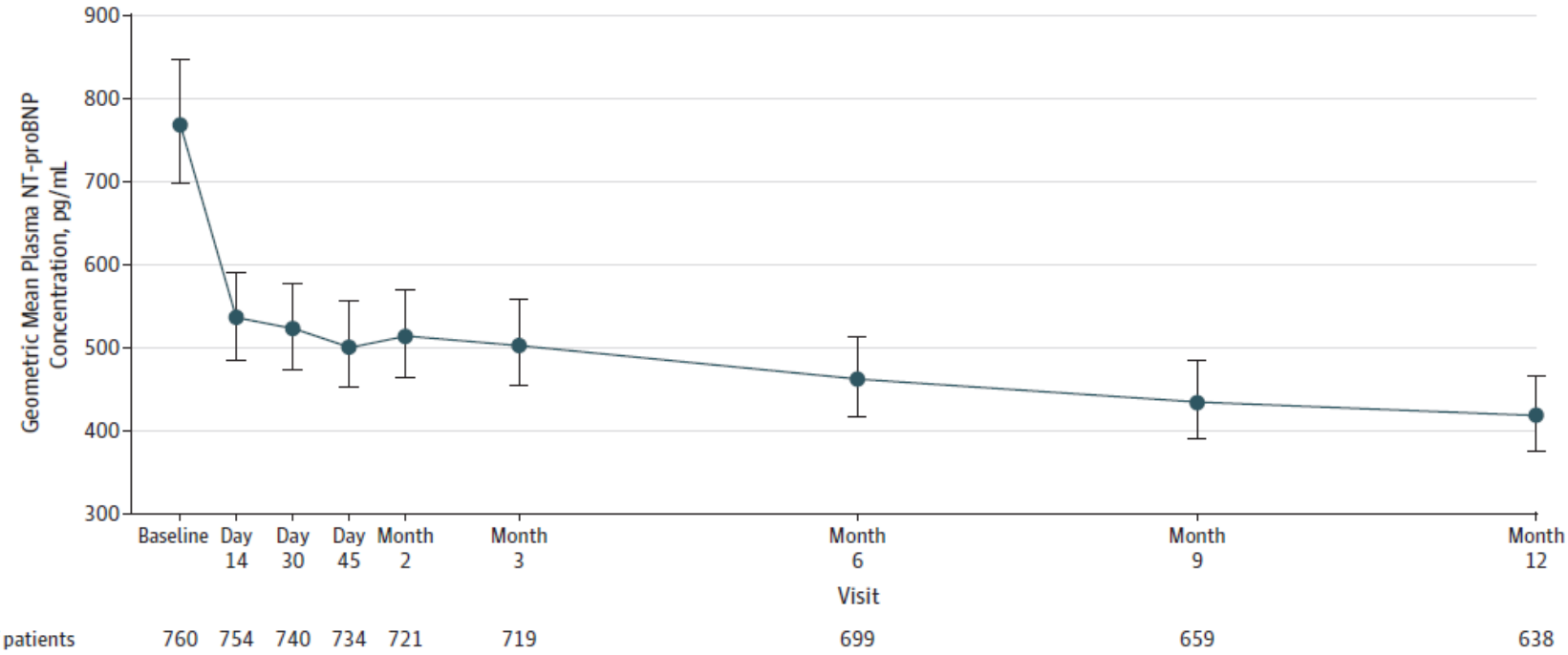
MAIN OUTCOMES AND MEASURES

- NT-proBNP concentrations
- LVEF: left ventricular ejection fraction
- LVEDVI: LV end-diastolic volume index
- LVESVI: LV end-systolic volume index
- LAVI: Left atrial volume index
- E/e´: Ratio of early transmitral Doppler velocity/early diastolic annular velocity

- HFrEF: Heart Failure With Reduced Ejection Fraction

RESULTS

Figure 1. Concentrations of N-Terminal Pro–B-Type Natriuretic Peptide (NT-proBNP) Across Study Visits



RESULTS

Figure 2. Scatterplots Detailing Correlations Between Baseline and 12-Month Concentrations of Log_2-Transformed N-Terminal Pro–B-Type Natriuretic Peptide (NT-proBNP) and Contemporaneous Change in LVEF, LVEDVI, LVESVI, LAVI, and E/e'

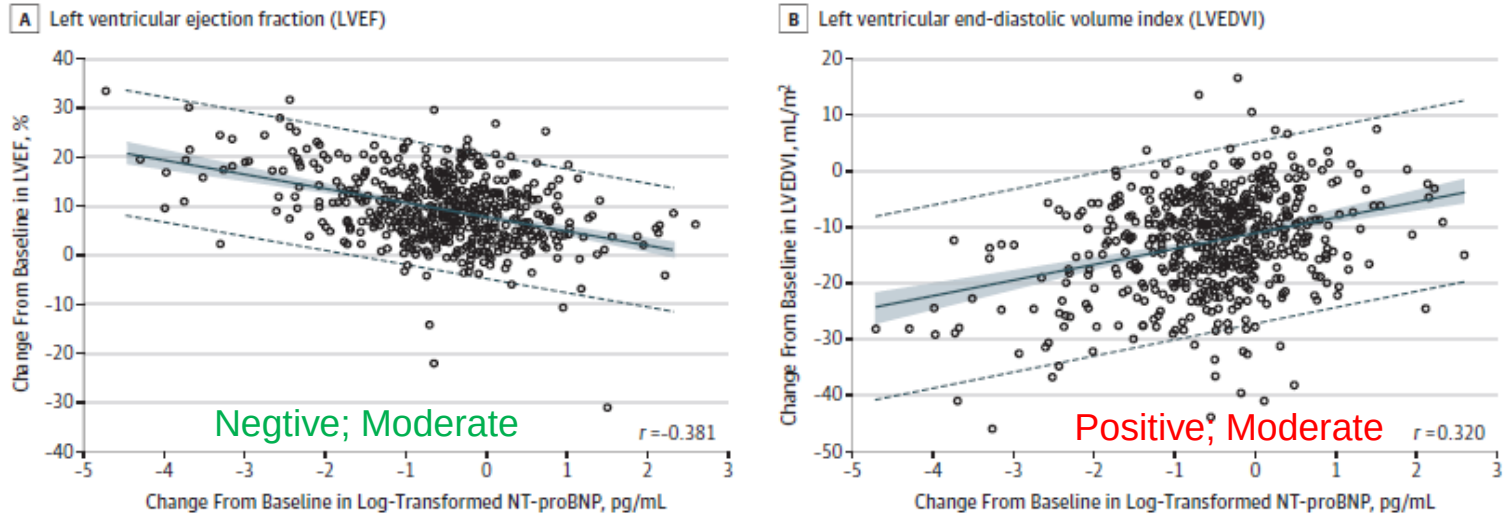
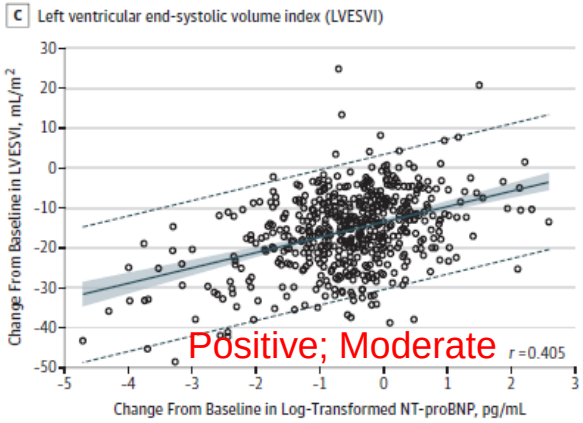
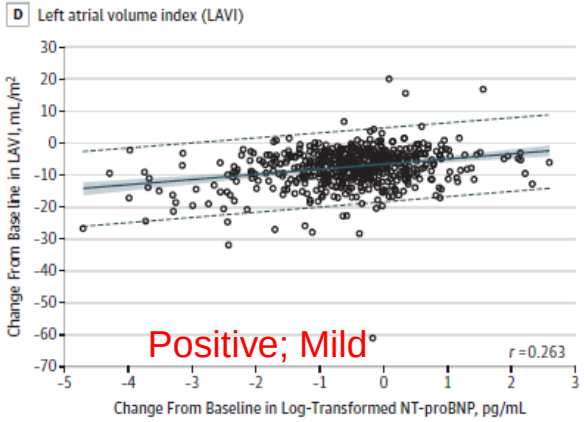


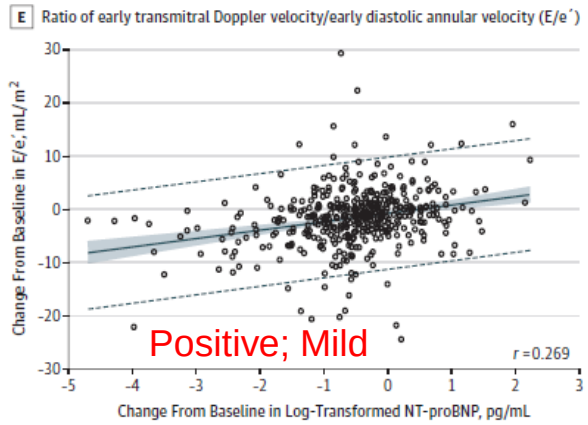
Table 3. Change in Cardiac Remodeling Measurements From Baseline to 6 and 12 Months After Initiation of Sacubitril-Valsartan Among Patients With New-Onset HF or Not Taking ACEI or ARB at Baseline

New-Onset HF or ACEI/ARB Naive	Baseline Value, Median (25th to 75th Percentile)	6-mo Value, Median (25th to 75th Percentile)	LS Mean Change From Baseline at 6 mo (95% CI)	*P* Value	12-mo Value, Median (25th to 75th Percentile)	LS Mean Change From Baseline at 12 mo (95% CI)	*P* Value
LVEF, %	n = 108	n = 102			n = 98	Preserved: >50%	
Yes	28.4 (25.2 to 33.9)	35.7 (30.7 to 42.1)	6.9 (5.7 to 8.0)	<.001	43.5 (35.4 to 50.5)	12.8 (11.05 to 14.5)	<.001
No	28.1 (24.3 to 32.6)	33.8 (28.7 to 39.1)	4.9 (4.5 to 5.3)	<.001	37.0 (31.8 to 44.4)	8.8 (8.3 to 9.3)	<.001
LVEDVI, No., mL/m²	n = 108	n = 102			n = 98	Preserved : <76 mL/m^2	
Yes	85.97 (70.13 to 95.47)	74.59 (62.70 to 85.90)	−7.21 (−8.50 to −5.93)	<.001	67.66 (57.77 to 79.39)	−13.81 (−15.78 to −11.83)	<.001
No	87.43 (76.89 to 101.38)	80.38 (70.46 to 93.89)	−6.56 (−7.05 to −6.07)	<.001	75.12 (64.11 to 86.83)	−12.00 (−12.71 to −11.29)	<.001

RESULTS







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LVESVI, No., mL/m²	n = 108	n = 102			n = 98	Preserved: <30 mL/m^2	
Yes	59.28 (48.64 to 71.29)	46.29 (36.44 to 58.94)	−10.01 (−11.45 to −8.58)	<.001	37.69 (28.97 to 51.16)	−17.88 (−20.07 to −15.68)	<.001
No	61.82 (52.70 to 75.91)	52.94 (43.28 to 66.42)	−8.46 (−9.01 to −7.90)	<.001	46.70 (36.47 to 58.1)	−14.86 (−15.64 to −14.09)	<.001
LAVI, No. mL/m²	n = 101	n = 101			n = 98	Preserved : ≤ 33 mL/m^2	
Yes	36.86 (31.53 to 45.02)	32.14 (25.24 to 38.78)	−4.83 (−5.84 to −3.83)	<.001	28.13 (23.32 to 35.53)	−8.44 (−9.73 to −7.15)	<.001
No	37.90 (31.63 to 46.25)	32.94 (27.90 to 40.65)	−4.28 (−4.68 to −3.88)	<.001	29.43 (25.04 to 35.90)	−7.42 (−7.85 to −6.99)	<.001
E/e', No.	n = 84	n = 88			n = 89	Preserved : ≤13	
Yes	11.85 (8.35 to 16.60)	9.70 (7.00 to 14.25)	−1.86 (−3.01 to −0.70)	.002	9.00 (6.80 to 12.70)	−2.60 (−3.83 to −1.37)	<.001
No	11.60 (8.80 to 16.00)	10.60 (7.80 to 14.80)	−1.13 (−1.56 to −0.70)	<.001	10.30 (7.80 to 14.40)	−1.10 (−1.57 to −0.63)	<.001

Adverse Events

- Hypotension (17.6%), Dizziness (16.8%), Hyperkalemia (13.2%), and Worsening kidney function (12.3%).
- The frequency of positively adjudicated angioedema was low, occurring in only 2 patients (0.3%), of which 1 was black (0.56%); both cases were mild, resolving with antihistamines or no therapy.

Conclusions

- This exploratory study of patients with HFrEF treated with sacubitril-valsartan, reduction in NT-proBNP concentration was weakly yet significantly correlated with improvements in markers of **cardiac volume and function** at 12 months.
- The observed **reverse cardiac remodeling** may provide a mechanistic explanation for the effects of sacubitril-valsartan in patients with HFrEF.

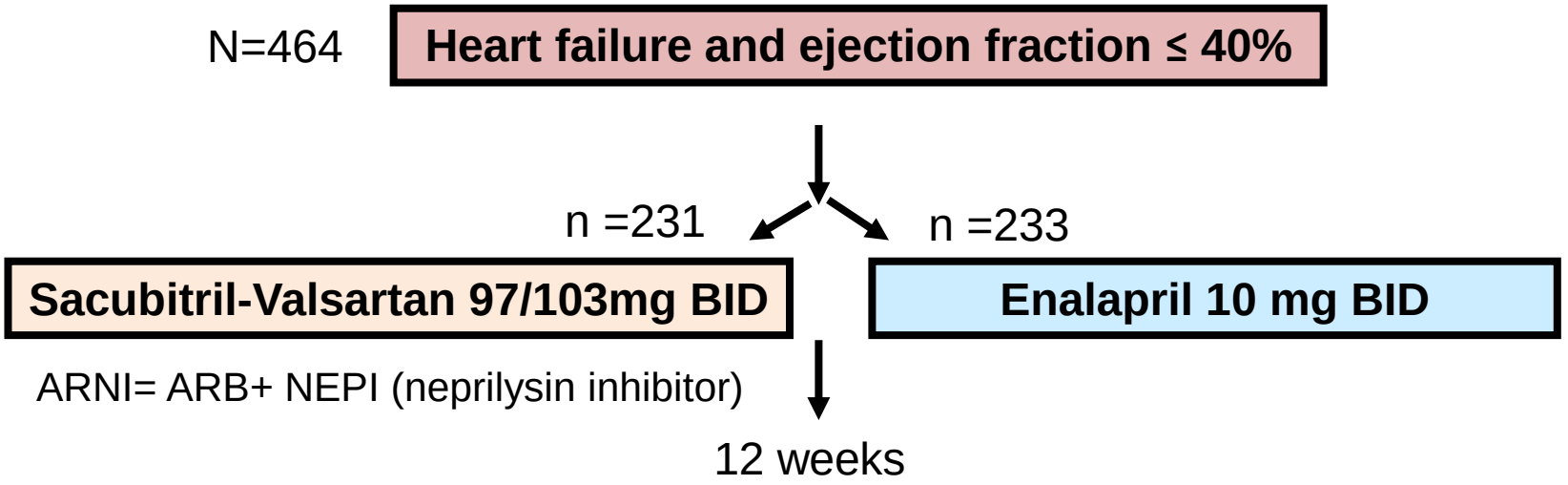
JAMA | Original Investigation

Effect of Sacubitril-Valsartan vs Enalapril on Aortic Stiffness in Patients With Heart Failure and Reduced Ejection Fraction

A Randomized Clinical Trial

Entresto 200mg/tab
(Sacubitril 97.2mg + Valsartan 102.8mg/tab)

- Randomized, double-blind clinical trial. Enrolled across 85 US sites between August 17, 2016, and June 28, 2018. Follow-up was completed on January 26, 2019.



MAIN OUTCOMES

The primary outcome was change from baseline to week 12 in aortic characteristic impedance (Zc).

RESULTS

Parameters	Sacubitril-Valsartan, Mean (SD)		Enalapril, Mean (SD)		Between-Group Difference (95% CI)	P value
	Baseline	12 wk	Baseline	12 wk		
Primary End Point						
Aortic Zc, dyne × s/cm^5	223.8 (112.7)	218.9 (112.7)	213.2 (102.6)	214.3 (95.2)	−2.2 (−17.6 to 13.2)	0.78
Secondary End Points						
LVEF, %	34 (10)	36 (10)	33 (10)	35 (10)	0.6 (−0.4 to 1.7)	0.24
LVEDVI, mL/m^2	75.1 (26.1)	70.3 (23.5)	79.1 (25.9)	75.6 (23.7)	−2.0 (−3.7 to −0.3)	0.02
LVESVI, mL/m^2	50.8 (22.6)	46.3 (20.5)	54.1 (22.6)	50.6 (20.0)	−1.6 (−3.1 to −0.03)	0.045
Left atrial volume index, mL/m^2	30.4 (9.5)	28.2 (9.0)	29.8 (8.7)	30.5 (9.1)	−2.8 (−4.0 to −1.6)	<0.001
Mitral E/e′ ratio	13.8 (7.6)	12.3 (5.6)	13.4 (6.8)	13.8 (7.4)	−1.8 (−2.8 to −0.8)	0.001
KCCQ overall summary score (1.7 to 7.3)	64.7 (23.1)	73.8 (21.3)	67.7 (20.8)	71.5 (21.0)	4.5	0.002

- LVEDVI, left ventricular end-diastolic volume index, LVESVI, left ventricular end-systolic volume index, KCCQ: Kansas City Cardiomyopathy Questionnaire

Adverse Events

	Sacubitril/Valsartan (N=231)	Enalapril (N=233)	RR* [95% CI]
Hyperkalemia (K>5.3 meq/L), n (%)	37 (16)	30 (12.9)	1.24 (0.80,1.94)
Worsening renal function, n (%)**	12 (5.2)	14 (6.0)	0.86 (0.41, 1.83)
Hypotension (SBP< 90 mm Hg), n (%)	9 (3.9)	4 (1.7)	2.27 (0.71, 7.27)
Angioedema, n (%)	0 (0.0)	1 (0.4)	--

Limitations

- Treatment exposure was limited to 12 weeks.
- Population reflects a mildly symptomatic HFrEF population without persistent atrial fibrillation.

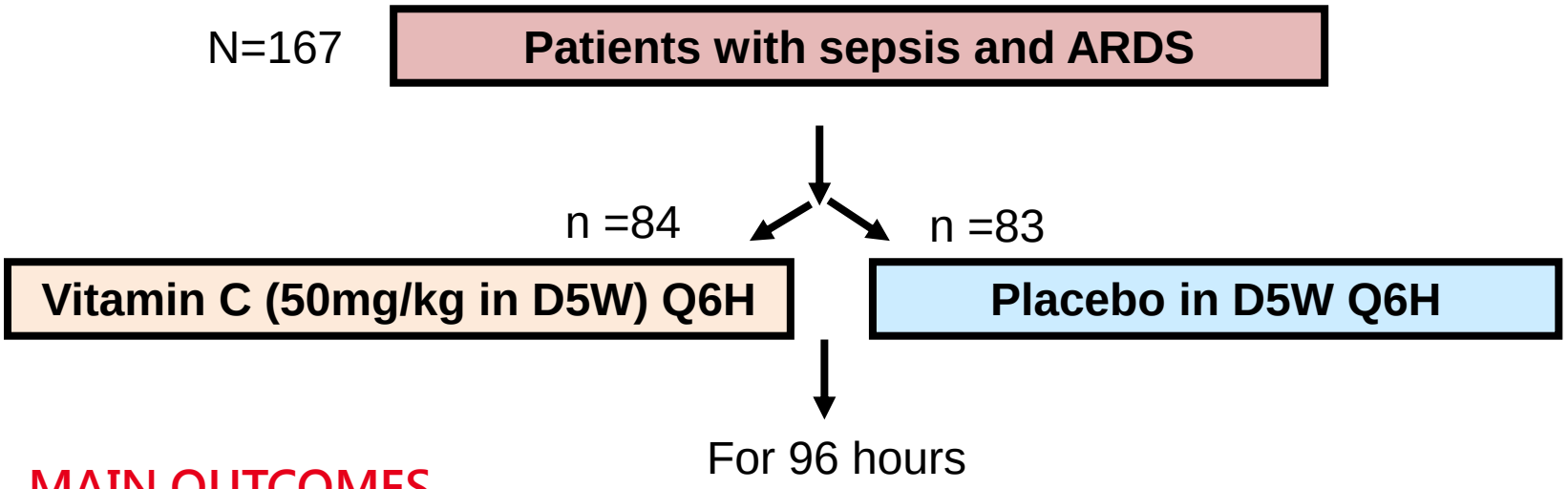
CONCLUSIONS AND RELEVANCE Treatment of HFrEF with sacubitril-valsartan, compared with enalapril, did not significantly reduce central aortic stiffness. The study findings may provide insight into mechanisms underlying the effects of sacubitril-valsartan in HFrEF.

JAMA | Preliminary Communication | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Vitamin C Infusion on Organ Failure and Biomarkers of Inflammation and Vascular Injury in Patients With Sepsis and Severe Acute Respiratory Failure

The CITRIS-ALI Randomized Clinical Trial

- Randomized, double-blind, placebo-controlled, multicenter trial in the United States.



MAIN OUTCOMES

- Modified Sequential Organ Failure Assessment (mSOFA) score.
- Plasma biomarkers of inflammation (C-reactive protein levels) and vascular injury (thrombomodulin levels)

Modified Sequential Organ Failure Assessment (mSOFA) score

TABLE 2

Modified Sequential Organ Failure Assessment (MSOFA) Score

Organ System	0	1	2	3	4
Respiratory SpO2/FiO2	>400	≤400	≤315	≤235	≤150
Liver	No scleral icterus or jaundice			Scleral icterus or jaundice	
Cardiovascular, hypotension	No hypo-tension	MAP <70 mm Hg	dopamine≤5 or dobutamine any dose	dopamine>5 epinephrine≤0.1 norepinephrine≤0.1	dopamine>15 epinephrine>0.1 norepinephrine>0.1
CNS, Glasgow Coma Score	15	13-14	10-12	6-9	<6
Renal, Creatinine mg/dL	<1.2	1.2-1.9	2.0-3.4	3.5-4.9	>5.0

MAP=mean arterial pressure

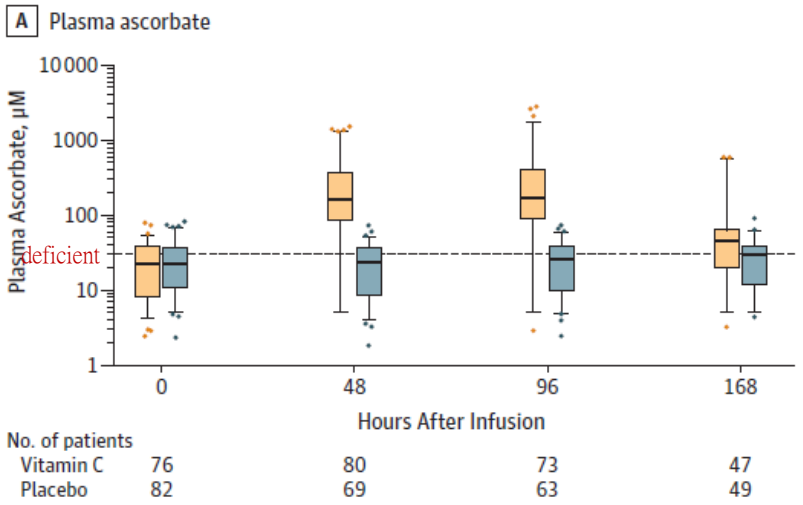
dopamine, dobutamine, epinephrine, and norepinephrine doses in micrograms per kilogram per minute

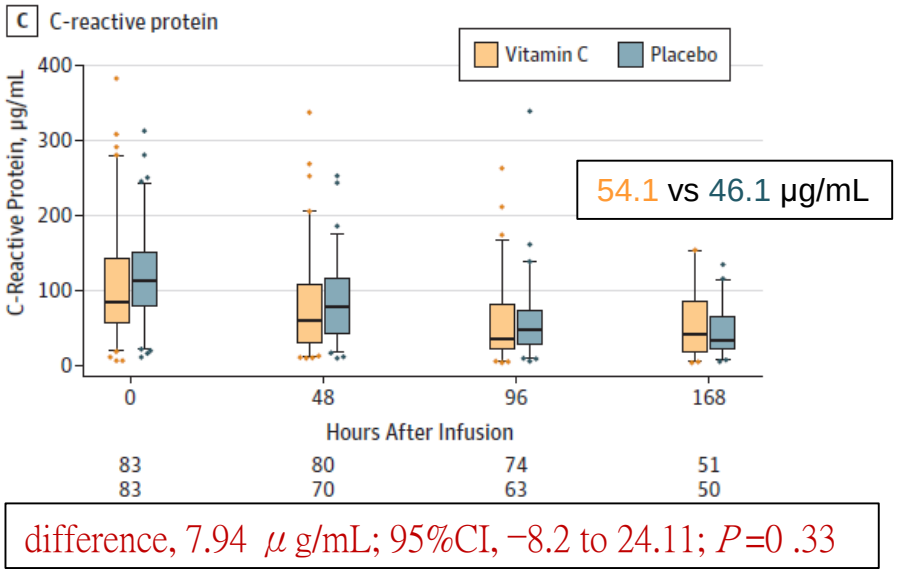
CNS=central nervous system

Ref: Disaster Med Public Health Prep. 2010 Dec; 4(4): 10.1001/dmp.2010.40. doi: 10.1001/dmp.2010.40

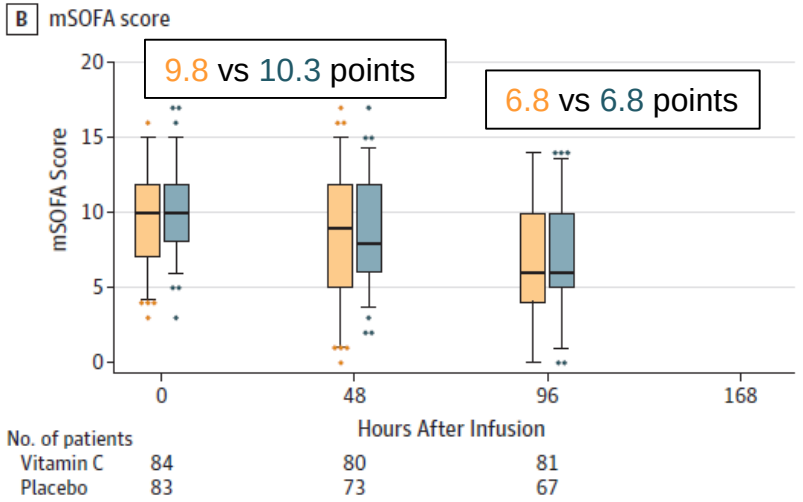
RESULTS

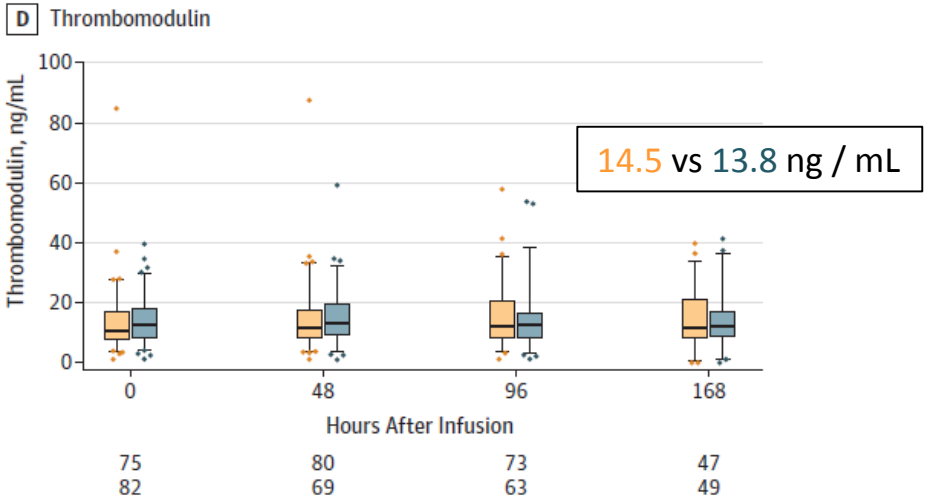
Figure 2. Plasma Ascorbate Concentrations, Modified Sequential Organ Failure Assessment Score, and Plasma Biomarkers





difference, 7.94 μg/mL; 95%CI, −8.2 to 24.11; P=0 .33



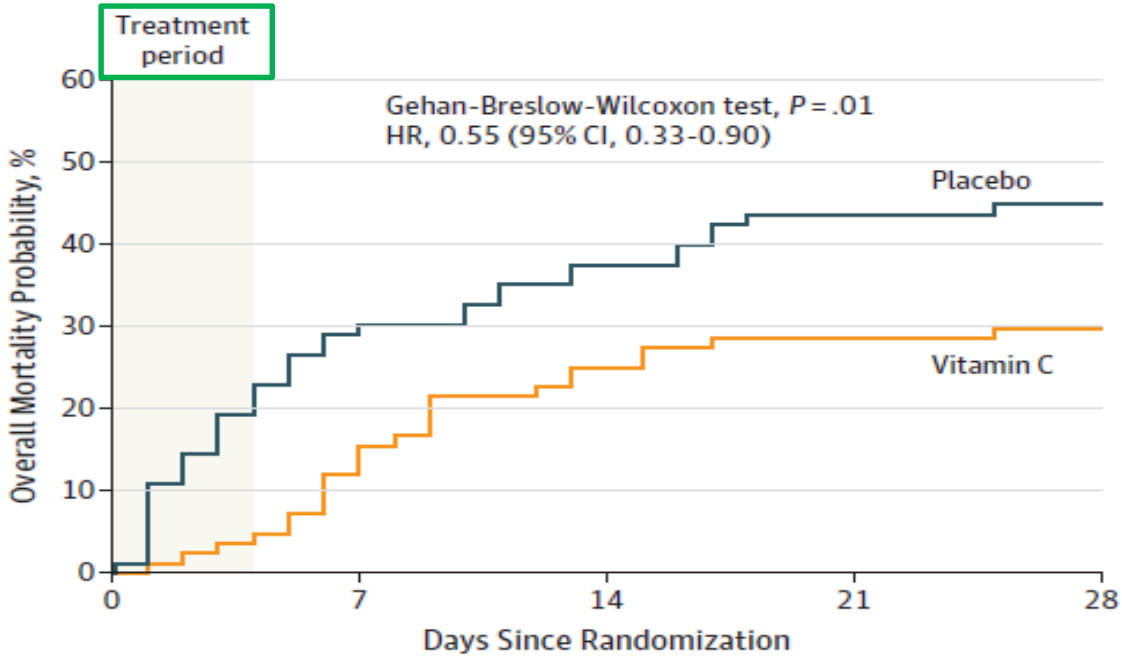


difference, −0.10; 95%CI, −1.23 to 1.03; P= 0.86

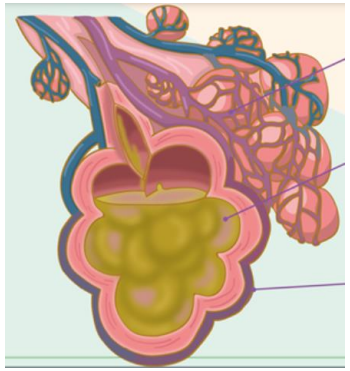
difference, 0.69 ng/mL; 95%CI, −2.8 to 4.2; P= 0.70

RESULTS

Figure 3. All-Cause Mortality From Randomization (Day 0) to Day 28 Among Patients With Sepsis-Associated Acute Respiratory Distress Syndrome



No. at risk					
Placebo	83	59	53	47	45
Vitamin C	84	74	65	61	59



Hydrocortisone, Vitamin C, and Thiamine for the Treatment of Severe Sepsis and Septic Shock

A Retrospective Before-After Study

Paul E. Marik, MD, FCCP; Vikramjit Khangoora, MD; Racquel Rivera, PharmD; Michael H. Hooper, MD; and John Catravas, PhD, FCCP

CHEST 2017; 151(6):1229-1238

The Effect of Vitamin C on Clinical Outcome in Critically Ill Patients: A Systematic Review With Meta-Analysis of Randomized Controlled Trials*

Alessandro Putzu, MD[1]; Anne-Marie Daems, MD[1]; Juan Carlos Lopez-Delgado, MD, PhD[2,3]; Vito Federico Giordano, MD[4]; Giovanni Landoni, MD[4,5]

Critical Care Medicine. 2019 Jun;47(6):774-783

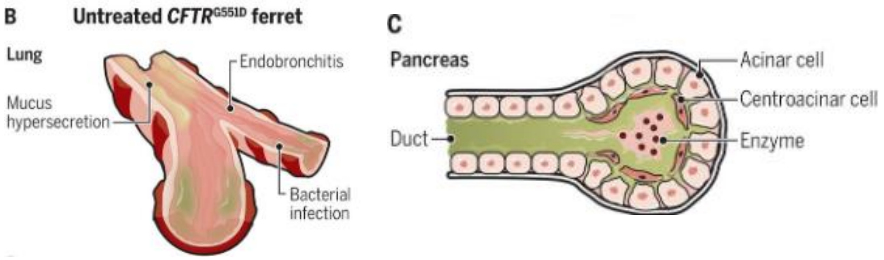
CONCLUSIONS AND RELEVANCE In this preliminary study of patients with sepsis and ARDS, a 96-hour infusion of vitamin C compared with placebo did not significantly improve organ dysfunction scores or alter markers of inflammation and vascular injury. Further research is needed to evaluate the potential role of vitamin C for other outcomes in sepsis and ARDS.

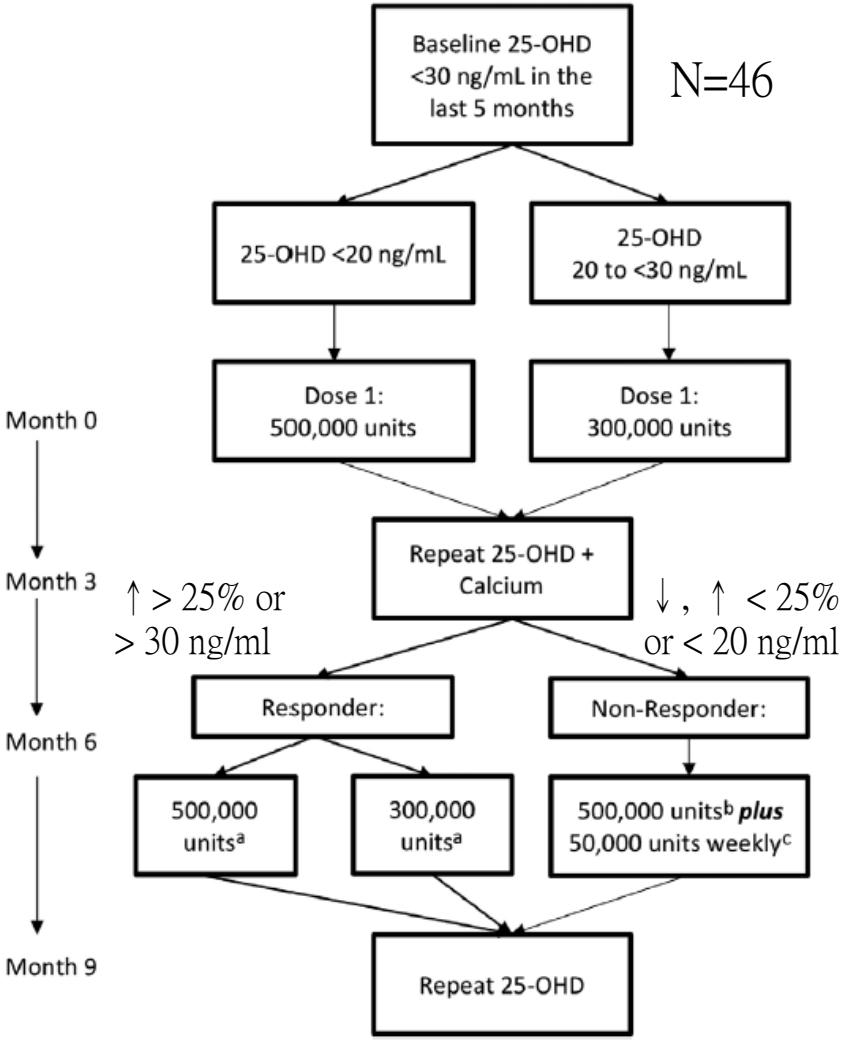
High-dose Cholecalciferol Supplementation in Adults with Cystic Fibrosis

囊狀纖維化

- Cystic fibrosis (CF) is caused by variants in a single, large gene on chromosome 7.
- Patients with CF have abnormal transport of chloride and sodium across secretory epithelia, resulting in thickened, viscous secretions in the:

a) Bronchi
b) Biliary tract
c) Pancreas
d) Intestines
e) Reproductive system



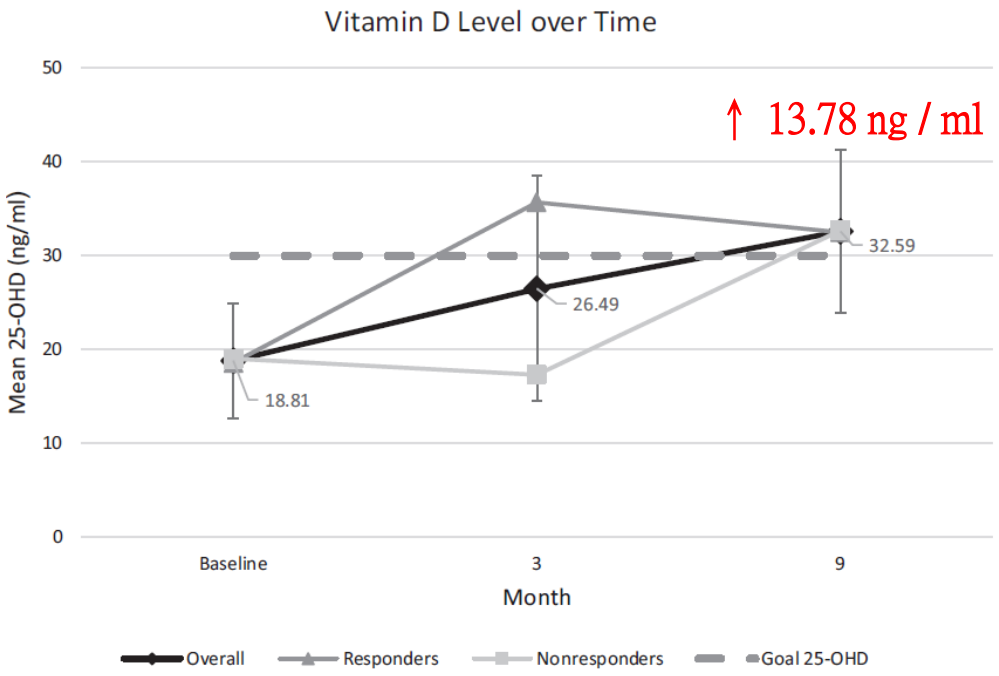


Results

Table 2. Characteristics of Responders vs Nonresponders

Characteristic	Responders (n=16)	Nonresponders (n=16)
Age, yrs	27.2 ± 7.8	24.1 ± 4.7
Male, n (%)	7 (44)	9 (56)
Genotype, n (%)		
F508del present	15 (94)	15 (94)
Heterozygous	8 (50)	4 (25)
Homozygous	6 (38)	11 (69)
G551 present	3 (19)	0
Weight, kg	58.9 ± 14.5	56.7 ± 11
BMI, kg/m^2	21.5 ± 3.8	21 ± 3.7
BMI < 18, n (%)	3 (19)	4 (25)
FEV_1 baseline, % predicted	52 ± 21	54 ± 17
CFTR modulator on enrollment, n (%)	4 (25)	3 (19)
Hospitalized on enrollment, n (%)	8 (50)	6 (38)
Baseline 25-OHD, ng/ml	18.6 ± 6	19 ± 6.4

25-OHD = 25-hydroxyvitamin D; BMI = body mass index; CFTR = cystic fibrosis transmembrane conductance regulator; FEV_1 = forced expiratory volume in 1 second.



- All patients achieved levels **above 20 ng/ml** by month 9.
- 18 patients (56%) had 25-OHD at goal of **30 ng/ml or above,** with 9 patients from both the responder and non-responder groups reaching this target.

- CFTR: cystic fibrosis transmembrane conductance regulator

Discussion

- Although we were initially concerned about elevated **25-OHD levels**, there were no levels at or above the laboratory standard upper limit of normal of 50 ng/ml. All **calcium levels** obtained were within or below normal limits, with mean serum calcium of 8.81 mg/dl and ionized calcium of 4.6 mg/dl.
- No adverse effects were reported during the study period.

Conclusion

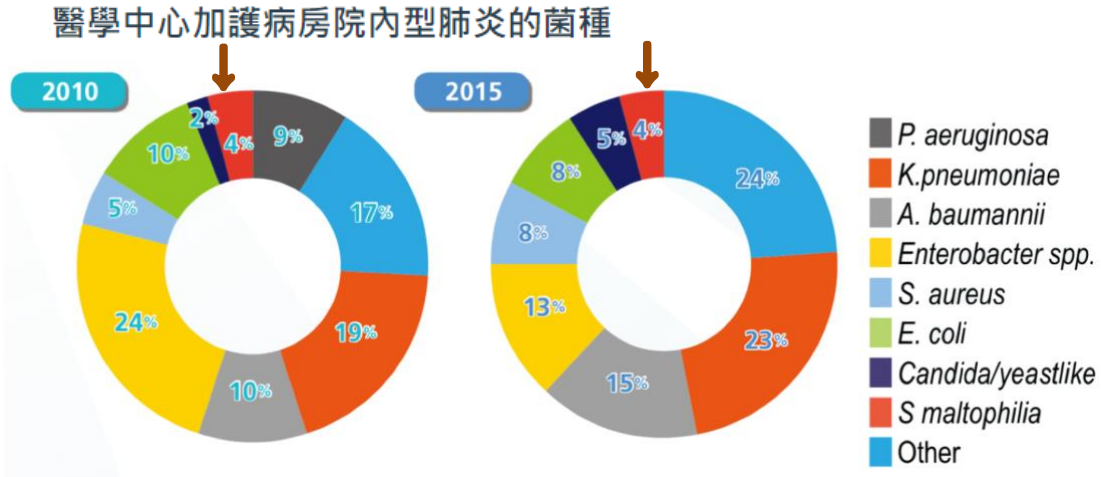
- A protocol using high-dose cholecalciferol or high-dose plus weekly cholecalciferol is safe and effective in increasing 25-OHD levels in adult patients with CF and pancreatic insufficiency.

CYSTIC FIBROSIS

Growing resistance in *Stenotrophomonas maltophilia*?

嗜麥芽窄食單胞菌

• *Stenotrophomonas maltophilia:* Aerobic, nonfermenting, gram-negative bacillus.
• This resistance is hypothesized to be due to low membrane permeability and the presence of efflux pumps that are characteristic for this organism.



First-line agents:

- Trimethoprim–sulfamethoxazole (Sevatrim)
- Levofloxacin (Cravit)

Others:

- Tigecycline (Tygacil)
- Ceftazidime (Tatumcef)
- Polymyxins (eg. Colistin)

Average susceptibility rates	**Reported**	**Inpatient isolates (2015-2017)**	**Reviewed susceptibility trends (2015-2018)**	**Taiwan (2016-2017)**
Trimethoprim-sulfamethoxazole	> 90%	78%	76%	85.5%
Levofloxacin	> 80%	80%	76%	84%

Several new antimicrobial agents have been approved, with in vitro data:

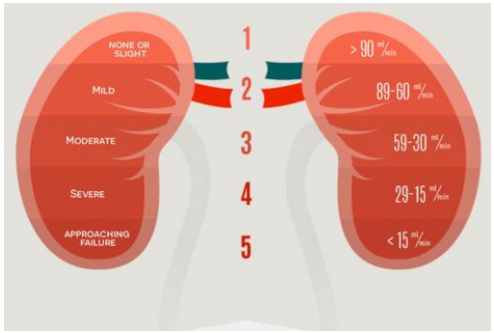
① **Eravacycline**: Fluorocycline (Intraabdominal infections)

② **Omadacycline**: Aminomethylcycline (Complicated acute bacterial skin and skin structure infections and community acquired bacterial pneumonia)

③ **Delafloxacin**: Newer fluoroquinolone (Acute bacterial skin and skin structure infections)

Chronic Kidney Disease Diagnosis and Management
A Review

Figure 2. Definition and Prognosis of Chronic Kidney Disease by GFR and Albuminuria Categories, KDIGO 2012



GFR categories, description, and range (mL/min/1.73 m²)				Persistent albuminuria categories, description, and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g	30-300 mg/g	>300 mg/g
	G1	Normal or high	≥90			
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

Green: low risk (if no other markers of kidney disease and no CKD)
Yellow: moderately increased risk
Orange: high risk
Red: very high risk.

KIDNEY FAILURE

RISK CALCULATION

If you don't have the information required below talk to your doctor.

Age (Yrs)

Sex

Select

Region

Select

GFR (Ml/Min/1.73M2)

Urine Albumin: Creatinine Ratio

Units

Select

The fields below are optional, but will get more accurate results.

Albumin

Phosphorous

Bicarbonate

Corrected Calcium

STAGE 3

MODERATE DECREASE IN FUNCTION

CKD STAGES

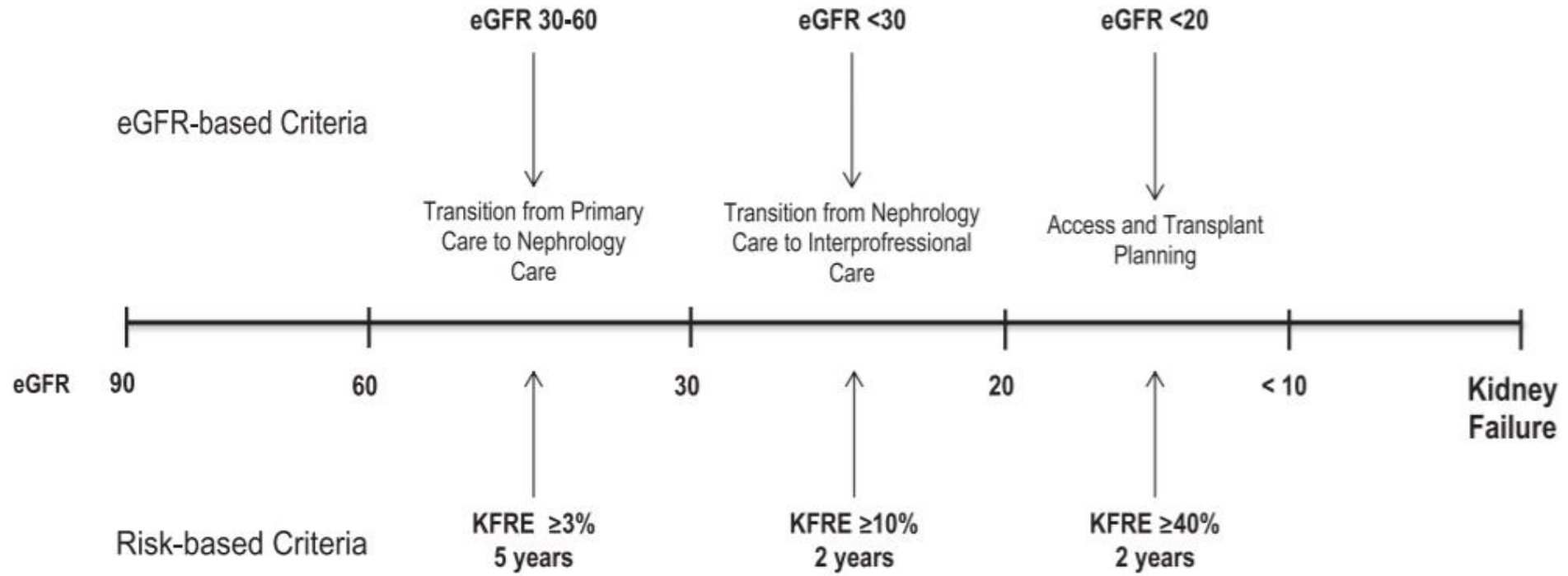
GLOMERULAR FILTRATION RATE

Patient risk of progression to kidney failure requiring dialysis or transplant:

AT 2 YEARS	AT 5 YEARS
1.51 %	4.64 %

0–5 % IS LOW RISK | 5–15 % IS INTERMEDIATE RISK | 15 % IS HIGH RISK

A risk-based versus eGFR-based approach to clinical decision-making in patients with CKD.



ABSTRACT

Bevacizumab Use and the Risk of Arterial and Venous Thromboembolism in Patients with High-Grade Gliomas: A Nested Case-Control Study

P	Patients with high-Grade Gliomas
I	Bevacizumab
C	Placebo
O	Risk of arterial thromboembolism (ATE) and venous thromboembolism (VTE)

Patients with ATE received bevacizumab compared with controls (28% vs 17%; adjusted OR 1.51, 95% CI 0.54–4.24), VTE (13% vs 9%; adjusted OR 1.40, 95% CI 0.71–2.75). Further research is needed to confirm the thromboembolic safety of bevacizumab in a larger sample of patients with high-grade gliomas.

Incidence of Rebound Hypertension after Discontinuation of Dexmedetomidine

P	ICU patients
I	Dexmedetomidine
C	Propofol or Midazolam
O	Incidence of Rebound Hypertension

Rebound hypertension occurred in patients with a history of HTN (71.1%) than in patients with no prior HTN (28.9%; p<0.001). There was no difference in incidence of rebound hypertension in the dexmedetomidine or propofol and midazolam arms (16.7% vs 17.9%, p=0.837). Patients with rebound hypertension (median duration, 4 hrs) compared with patients who did not have rebound hypertension (median duration, 17 hrs; p=0.011).

JAMA |

Effect of Fluoxetine on Obsessive-Compulsive Behaviors in Children and Adolescents With Autism Spectrum Disorders

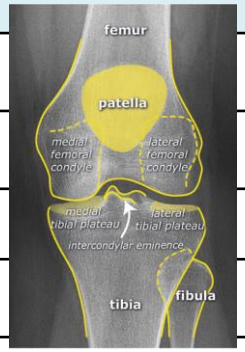
A Randomized Clinical Trial

P	Children and Adolescents With Autism Spectrum Disorders
I	Fluoxetine (first week: 4 or 8 mg/d; titrated to a MAX dose of 20 or 30 mg/d over 4 weeks)
C	Placebo
O	Reduce the frequency and severity of OCD behaviors

The mean CYBOCS-PDD score from baseline to 16 weeks decreased in the fluoxetine group from 12.80 to 9.02 points and in the placebo group from 13.13 to 10.89 points. The between-group mean difference at 16 weeks was −2.01 (95%CI, −3.77 to −0.25; P = 0.03).

Effect of Intra-Articular Sprifermin vs Placebo on Femorotibial Joint Cartilage Thickness in Patients With Osteoarthritis

The FORWARD Randomized Clinical Trial



P	Osteoarthritis
I	Sprifermin (rhFGF18) (Intra-Articular)
C	Placebo
O	Femorotibial Joint Cartilage Thickness

Compared with placebo, intra-articular administration of 100 μg of sprifermin every 6 or 12 months resulted in improvement in femorotibial joint cartilage thickness after 2 years that was statistically significant, but of uncertain clinical importance; the durability of response also was uncertain.

Peramivir for Influenza A and B Viral Infections: A Pharmacokinetic Case Series

Patients	Critically ill children treated for influenza A or B viral infections (N=11). The median age was 5 years (IQR 1.5-6.5 yrs) with a median weight of 16.4 kg (IQR14-24 kg).
Results	Larger volume of distribution (n=10), increase in clearance (n=11), shorter half-life estimate (n=11) → Q12H regimen (n=10), Q8H regimen (n=1).
Conclusion: The pharmacokinetics of PRV demonstrated in this PICU cohort **differs in comparison to healthy pediatric and adult patients**, and alterations to dosing regimens may be needed in PICU patients to achieve pharmacodynamic exposures. Additional investigations in the PICU population are needed to confirm these findings.	

Select topics in the management of critically ill children

- **Septic shock**: Rapid fluid administration of 20 mL/kg isotonic crystalloids (LR, N/S). **Epinephrine** is first-line for cold shock.
- **Rapid sequence intubation**: **Succinylcholine** should be avoided if possible. Nondepolarizing neuromuscular agent is the most common choice.
- **Trauma**: A bolus of 2–5 mL/kg **3% hypertonic saline** is the initial recommended hyperosmolar therapy for increased intracranial pressure in traumatic brain injury.
- **Status epilepticus**: First-line options for pediatric status epilepticus include i.v. **lorazepam or diazepam.**
- **Diabetic ketoacidosis**: Risk of cerebral edema can be mitigated by **avoiding insulin and sodium bicarbonate boluses** and using judicious fluid resuscitation.

Factors influencing rates of human papillomavirus vaccination (Utah)

- Poorly understood
- Personal and family preferences
- Missed opportunities to vaccinate
- Unsure if insurance will cover
- Patient does not tolerate vaccine

- HPV vaccine not discussed during sick-child visit
- Inaccurate health maintenance tab in medical record or tab not reviewed
- Follow-up visits for rest of series are not scheduled
- Vaccine out of stock

Conclusion

- Failure modes and effects analysis processes can help health systems identify workflow barriers and locally relevant opportunities for improvement.

2015/7→ New processes

2015/1	19%
2016/1	51.1%
2016/7	67.8%

Automated dispensing cabinet technology limitations compromise patient safety

- Provide different operational modes for ADC use such as patient order (profile mode) or emergency (non-profile mode) setting.

Non-Profile Mode: Nurse can choose any patient and choose any drug, could give drug prior to pharmacist approval of order

- Diazepam vs Diltiazem
- Versed (midazolam) vs Vecuronium

→ Diltiazem [Cardiac disturbance]

→ Midazolam [Sedation]

Restocking errors not caught due to over-confidence in system
Downtime
Removal of expired medications

Summary of Pharmacokinetic Differences in Pediatric versus Adult Patients

Age-Related Difference Compared With Adults	Pharmacokinetic Changes	Examples
Absorption		
Reduced gastrointestinal motility, higher intragastric pH	Higher oral bioavailability for acid labile drugs	Penicillin G, ampicillin
	Lower oral biovailability for weak acids	Phenytoin, phenobarbital
	Prolonged time to reach maximum concentration after oral administration in general	…[a]
Thinner stratum corneum, greater cutaneous perfusion, greater epidermal hydration	Increased percutaneous absorption, increased systemic exposure	Corticosteroids, lidocaine, povidone iodine
Less muscle mass, weaker muscle contraction, reduced muscle blood flow	Reduced i.m. bioavailability, erratic i.m. absorption in general	…
Distribution		
Reduced protein binding	Increased unbound plasma concentrations	Phenytoin
Increased water proportion in neonates	Increased volume of distribution of water-soluble drugs	Aminoglycosides
	Smaller volume of distributioin of lipid-soluble drugs	Diazepam
Metabolism		
Reduced metabolizing enzyme activity (phase I & II metabolism)	Lower clearance	Caffeine, chloramphenicol, morphine
Excretion		
Reduced renal function in neonates	Lower renal clearance	Aminoglycosides, vancomycin, digoxin
Elevated renal clearance per kg body weight in children older than 1 yr	Higher renal clearance	

Others

- Effect of Behavioral and Pelvic Floor Muscle Therapy Combined With Surgery vs Surgery Alone on Incontinence Symptoms Among Women With Mixed Urinary Incontinence

- Effect of Vaginal Mesh Hysteropexy vs Vaginal Hysterectomy With Uterosacral Ligament Suspension on Treatment Failure in Women With Uterovaginal Prolapse

- Association of Surgical Hematoma Evacuation vs Conservative Treatment With Functional Outcome in Patients With Cerebellar Intracerebral Hemorrhage

- Association of General Anesthesia vs Procedural Sedation With Functional Outcome Among Patients With Acute Ischemic Stroke Undergoing Thrombectomy

- Effect of Postextubation High-Flow Nasal Oxygen With Noninvasive Ventilation vs High-Flow Nasal Oxygen Alone on Reintubation Among Patients at High Risk of Extubation Failure


Thank You!