The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 14, 2020 VOL. 382 NO. 20

Vericiguat in Patients with Heart Failure and Reduced Ejection Fraction

Paul W. Armstrong, M.D., Burkert Pieske, M.D., Kevin J. Anstrom, Ph.D., Justin Ezekowitz, M.B., B.Ch., Adrian F. Hernandez, M.D., M.H.S., Javed Butler, M.D., M.P.H., M.B.A., Carolyn S.P. Lam, M.B., B.S., Ph.D., Piotr Ponikowski, M.D., Adriaan A. Voors, M.D., Ph.D., Gang Jia, Ph.D., Steven E. McNulty, M.S., Mahesh J. Patel, M.D., Lothar Roessig, M.D., Joerg Koglin, M.D., Ph.D., and Christopher M. O'Connor, M.D., for the VICTORIA Study Group*

TJC 2022/1/22 SR 永冨　旺

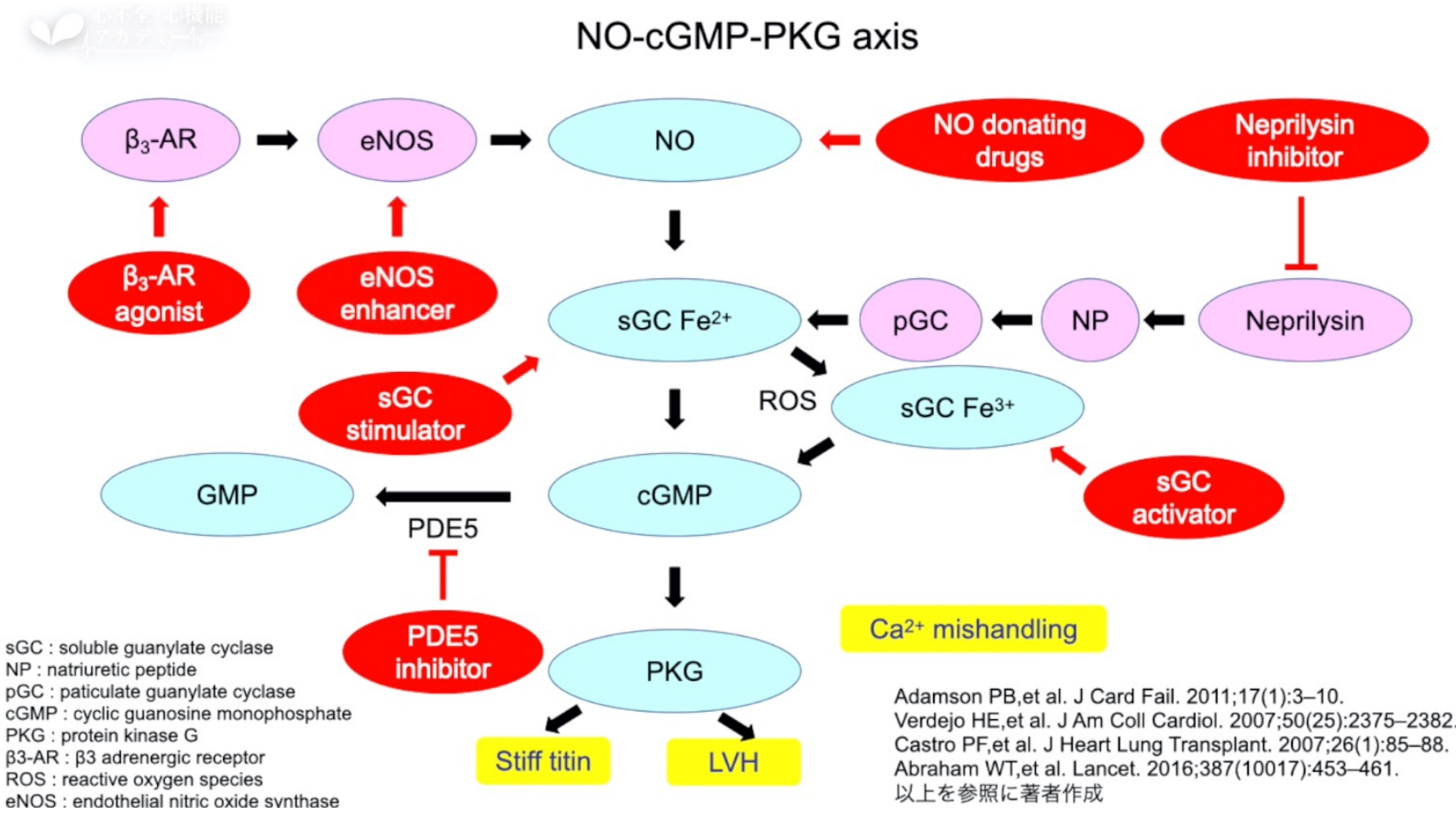
Background

・ガイドラインに基づいた治療をされていても、再入院や緊急での
受診が必要なHFrEF患者は医療的かなりの負担になっている

・1年以内に入院歴や緊急治療が必要ない患者と比べると
これらのハイリスク患者の予後は不良で追加の治療が望まれている

・ベルイシグアトは新規経口可溶性グアニル酸シクラーゼ刺激剤である

Background



Adamson PB,et al. J Card Fail. 2011;17(1):3–10.
Verdejo HE,et al. J Am Coll Cardiol. 2007;50(25):2375–2382.
Castro PF,et al. J Heart Lung Transplant. 2007;26(1):85–88.
Abraham WT,et al. Lancet. 2016;387(10017):453–461.
以上を参照に著者作成

Armstrong PW, et al. JACC: Heart Failure 2018;6:96– 104.

Background

・グアニル酸シクラーゼ(GC):GTPをcGMPに変換する作用がある

　　可溶性GC:細胞質に存在　リガンドがNO

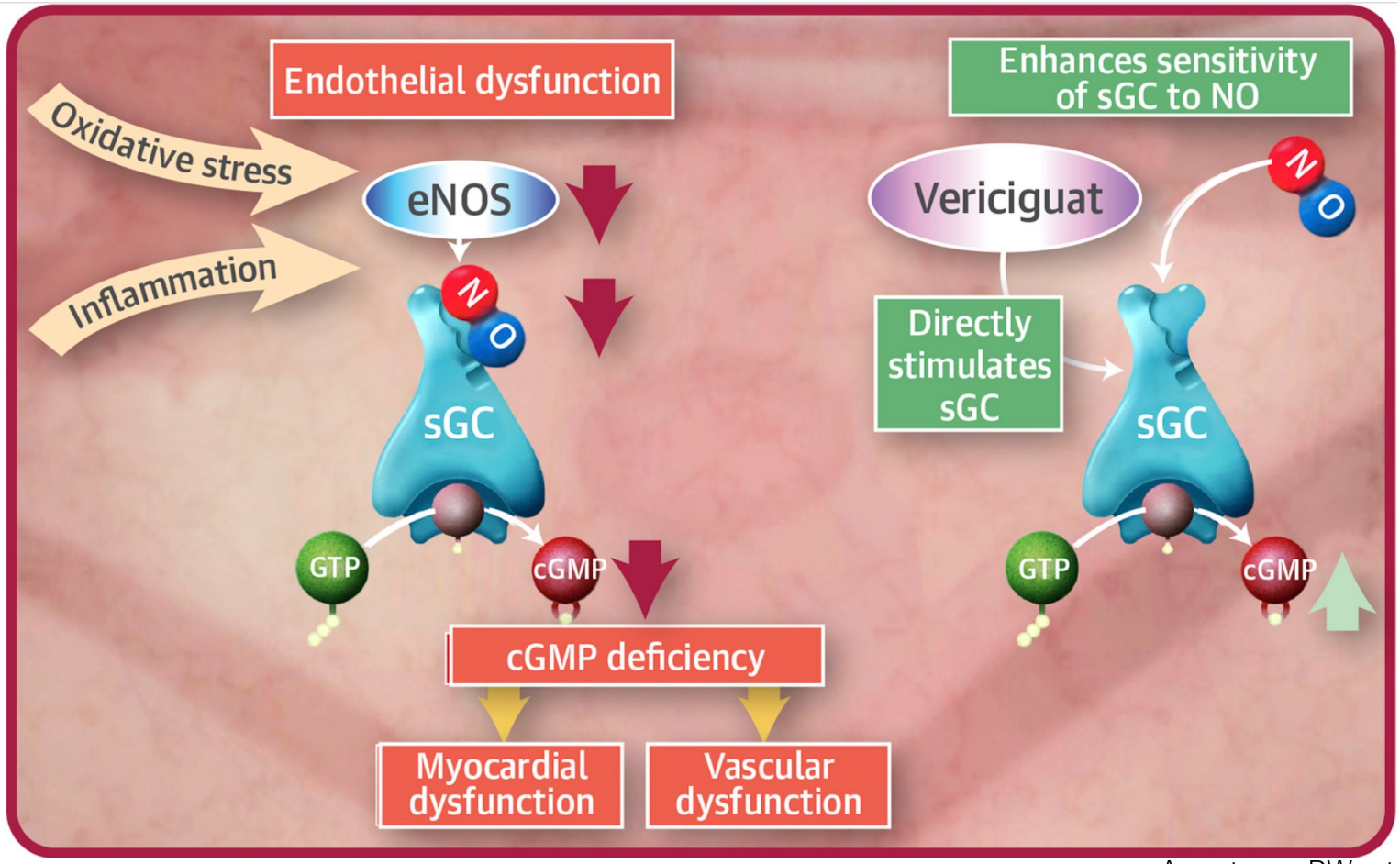
　　水溶性GC:細胞膜に貫通　リガンドがNa利尿ペプチド

・ベルイシグアトは2つの機序からcGMPを増加させる

　　NO非依存的にsCGを刺激する(直接的作用)

　　NOとsGCの結合を安定させる(間接的作用)

Background



Armstrong PW, et al. JACC: Heart Failure 2018;6:96– 104.

論文のPICO：　Patient

1884p 右段　"Patients”

参加基準

・18歳以上の慢性心不全で心不全の標準的治療を受けている患者
・NYHA Ⅱ～Ⅳの症状があるかつEF＜45%
・30日以内にNT-proBNP> 1000pg/ml or BNP > 300pg/ml
・心房細動ならNT-proBNP> 1600pg/ml or BNP > 500pg/ml
・6ヶ月以内に入院もしくは3ヶ月以内に静脈利尿剤使用歴がある

除外基準

・収縮期血圧＜100 mmHg もしくは症候性低血圧の場合
・長時間作用型の硝酸薬
・可溶性グアニル酸シクラーゼ刺激薬 or PDE5阻害薬の使用
・静脈投与の強心薬、埋め込み型左心室補助装置の使用

PATIENT ENROLLMENT

Eligible patients were at least 18 years of age and had chronic heart failure (New York Heart Association [NYHA] functional class II, III, or IV), a reduced left ventricular ejection fraction of less than 45% within 12 months before randomization, and an elevated natriuretic peptide level (determined at the trial sites) within 30 days before randomization. For patients in sinus rhythm, the criteria included a plasma B-type natriuretic peptide (BNP) level of at least 300 pg per milliliter or an NT-proBNP level of at least 1000 pg per milliliter. For patients in atrial fibrillation, the criteria included a BNP level of at least 500 pg per milliliter or an NT-proBNP level of at least 1600 pg per milliliter.

Patients also had to have evidence of worsening heart failure. They were categorized into three cohorts based on the timing of the deterioration: those hospitalized within 3 months before randomization, those hospitalized 3 to 6 months before randomization, and those receiving intravenous diuretic therapy, without hospitalization, within the previous 3 months.[4] The percentage of enrolled patients with an estimated glomerular filtration rate of 15 to 30 ml per minute per 1.73 m^2 of body-surface area was capped at 15%. All the patients received guideline-based medical therapy; the inclusion of patients who were receiving sacubitril–valsartan background therapy (in countries where it was available) was encouraged.

Exclusion criteria included a systolic blood pressure of less than 100 mm Hg; concurrent or anticipated use of long-acting nitrates, soluble guanylate cyclase stimulators, or phosphodiesterase type 5 inhibitors; and use of intravenous inotropes or implantable left ventricular assist devices. A full list of inclusion and exclusion cri-

論文のPICO　Intervention/Control

I ： Vericiguat
C ： Placebo

1885p 左段
Trial conduct

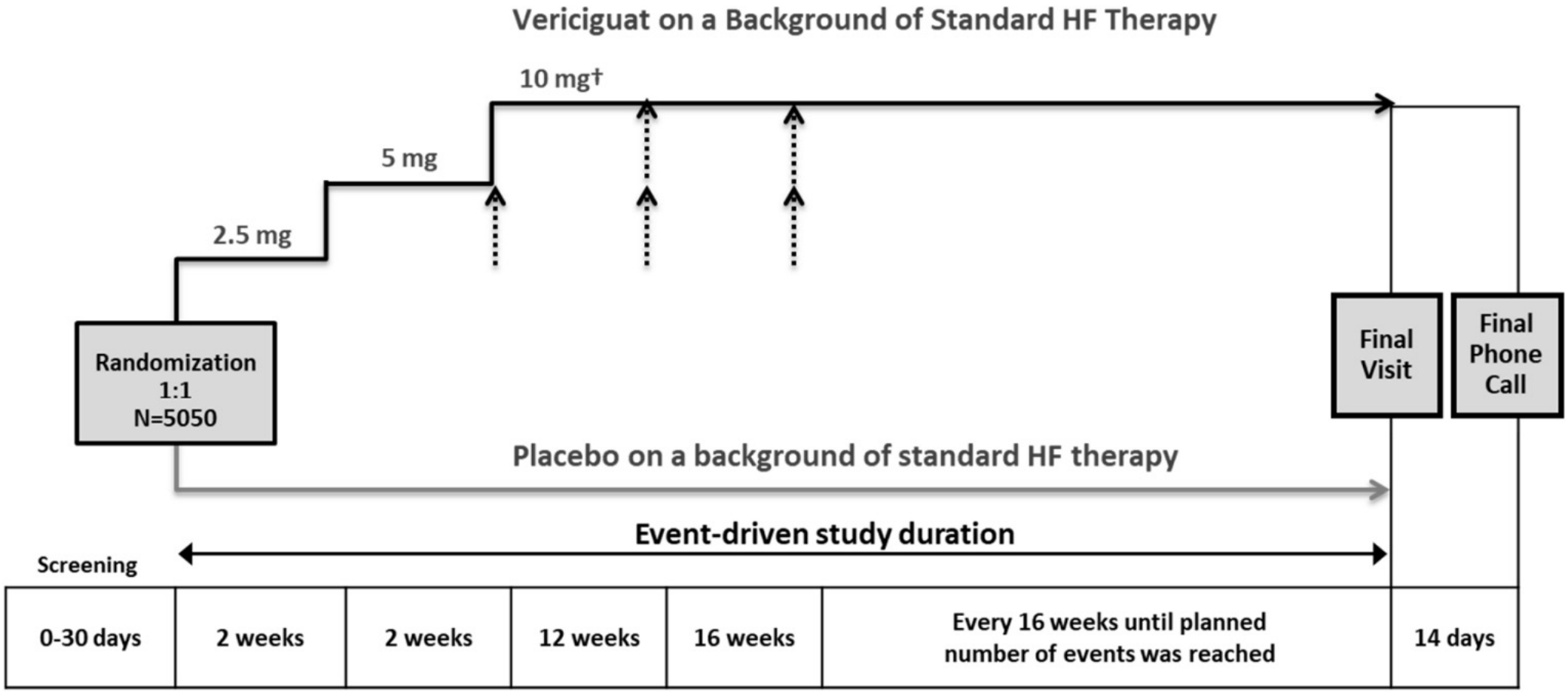
・vericiguatは初期量2.5mgから開始され、
血圧や臨床症状で5→10mgと増量された(placeboも)

・投与後の評価は2, 4およびその後4週ごとに実行された

TRIAL CONDUCT

All the patients provided informed consent and entered a screening period (0 to 30 days), without a run-in period, during which adherence to the entry criteria was confirmed. Patients were then randomly assigned, in a 1:1 ratio, to 2.5 mg of vericiguat or matching placebo, within six strata based on geographic region and, within North America, race. Doses were increased to 5 mg and ultimately to the target dose of 10 mg once daily in a blinded manner, as guided by evaluation of blood pressure and clinical symptoms (see the Supplementary Appendix).[4] Patients were evaluated at weeks 2 and 4, and every 4 months thereafter until the end of the trial. To enhance the likelihood of achieving and maintaining the target dose of 10 mg, investigators were encouraged to address dosing at each visit according to the patient's blood pressure and symptomatic status. The follow-up visit schedule is detailed in the protocol.[4]

論文のPICO　Intervention/Control



論文のPICO　Outcome

・Primary Outcome

心不全による初回入院

または心血管死の複合エンドポイント

・Secondary Outcome

1）心血管イベントでの死亡

2）初回心不全での入院

3）心不全での入院

4）全死亡 or 心不全入院

1885p 左段
Trial Outcomes

TRIAL OUTCOMES

The primary outcome was a composite of death from cardiovascular causes or first hospitalization for heart failure. The secondary outcomes were the components of the primary outcome, first and subsequent hospitalizations for heart failure, a composite of death from any cause or first hospitalization for heart failure, and death from any cause. Prespecified safety outcomes of clinical interest included symptomatic hypotension and syncope.[4] Members of an independent clinical-events committee who were unaware of the trial-group assignments adjudicated all deaths, hospitalizations for cardiovascular causes, and urgent visits for heart failure (definitions are provided in the Supplementary Appendix).

ランダム割付されているか

ランダム割付されているか？

■ランダム　□非ランダム

割付け方法

■中央割付け　□封筒法　□その他

ランダム割付けが隠蔽化concealmentされているか？

■隠蔽化　□隠蔽化なし　□不明

TRIAL DESIGN AND OVERSIGHT

VICTORIA was a multinational, randomized, double-blind, placebo-controlled trial; the trial methods have been described previously.[4] The executive committee designed the trial with national leaders from participating countries and regions and oversaw operations in collaboration with the Canadian VIGOUR Centre and the trial cosponsors, Merck and Bayer.[4] The trial protocol (available with the full text of this article at NEJM.org) was approved by regulatory agencies in the participating countries and institutional review boards or ethics committees at the participating sites. An independent data and safety monitoring committee evaluated patient safety.

The sponsors participated in the trial design, selection of participating centers, site monitoring, and data storage. Analyses were conducted by the sponsors and independently replicated at the Duke Clinical Research Institute (DCRI). The sponsors, the Canadian VIGOUR Centre and the DCRI, and the executive committee participated in the interpretation of the data. The first author had unrestricted access to the data and drafted the initial version of the manuscript, which was reviewed and edited by all the authors. All the authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

Baselineは同等か

Baselineは同等か？

■差がない　□差がある

結果に影響を与える可能性
のある因子は全て
検討されているか？

●検討されている
○不足しているものがある

（table1以外に、supplementary appendix
にも３ページにわたって両群データあり）

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Vericiguat (N=2526)	Placebo (N=2524)	Total (N=5050)
Mean age — yr	67.5±12.2	67.2±12.2	67.3±12.2
Sex — no. (%)			
Male	1921 (76.0)	1921 (76.1)	3842 (76.1)
Female	605 (24.0)	603 (23.9)	1208 (23.9)
Race — no. (%)†			
White	1621 (64.2)	1618 (64.1)	3239 (64.1)
Black	123 (4.9)	126 (5.0)	249 (4.9)
Asian	571 (22.6)	561 (22.2)	1132 (22.4)
Other	211 (8.4)	219 (8.7)	430 (8.5)
Geographic region — no. (%)			
Eastern Europe	848 (33.6)	846 (33.5)	1694 (33.5)
Western Europe	443 (17.5)	446 (17.7)	889 (17.6)
Asia–Pacific	592 (23.4)	591 (23.4)	1183 (23.4)
Latin America	362 (14.3)	362 (14.3)	724 (14.3)
North America	281 (11.1)	279 (11.1)	560 (11.1)
Index event — no. (%)			
Hospitalization for heart failure in previous 3 mo	1673 (66.2)	1705 (67.6)	3378 (66.9)
Hospitalization for heart failure in previous 3–6 mo	454 (18.0)	417 (16.5)	871 (17.2)
Intravenous diuretic for heart failure (without hospitalization) in previous 3 mo	399 (15.8)	402 (15.9)	801 (15.9)
Mean body-mass index‡	27.7±5.8	27.9±6.1	27.8±5.9
Mean ejection fraction at screening — %	29.0±8.3	28.8±8.3	28.9±8.3
Ejection fraction <40% — no. (%)	2158 (85.8)	2158 (85.6)	4316 (85.7)
NYHA class — no./total no. (%)			
I	0	2/2523 (0.1)	2/5046 (<0.1)
II	1478/2523 (58.6)	1497/2523 (59.3)	2975/5046 (59.0)
III	1010/2523 (40.0)	993/2523 (39.4)	2003/5046 (39.7)
IV	35/2523 (1.4)	31/2523 (1.2)	66/5046 (1.3)
Mean time from initial diagnosis of heart failure with reduced ejection fraction to randomization — yr	4.7±5.5	4.8±5.4	4.8±5.4

ちなみに、過去の心不全研究との患者背景比較

VICTORIA、DAPA-HF、PARADIGM-HFの患者背景

	ベルイシグアト（今回） VICTORIA[1]	ダパグリフロジン（SGLT2i） DAPA-HF[2,3]	サクビトリル/バルサルタン（ARNI） PARADIGM-HF[4-6]
6ヵ月以内の心不全による入院歴	84%	16%	31%
ベースラインのNYHAクラス II/IIIの割合	59/40%	68/32%	70/24%
NT-proBNPの中央値	2816 pg/ml	1437 pg/ml	1608 pg/ml#
	Vs. placebo	Vs. placebo	Vs. ACEI

全ての患者の転帰がOutcomeに反映されているか

・ITT解析か？

■ITT

□ITTでない

→結果をくつがえしうるか？

□くつがえしうる

□くつがえさない

・結果に影響を及ぼすほどの脱落があるか？

■ない□ある

追跡率＝Vericiguat：99.8%
placebo　：99.6%

□不明

除外理由：重大な臨床試験実施基準違反

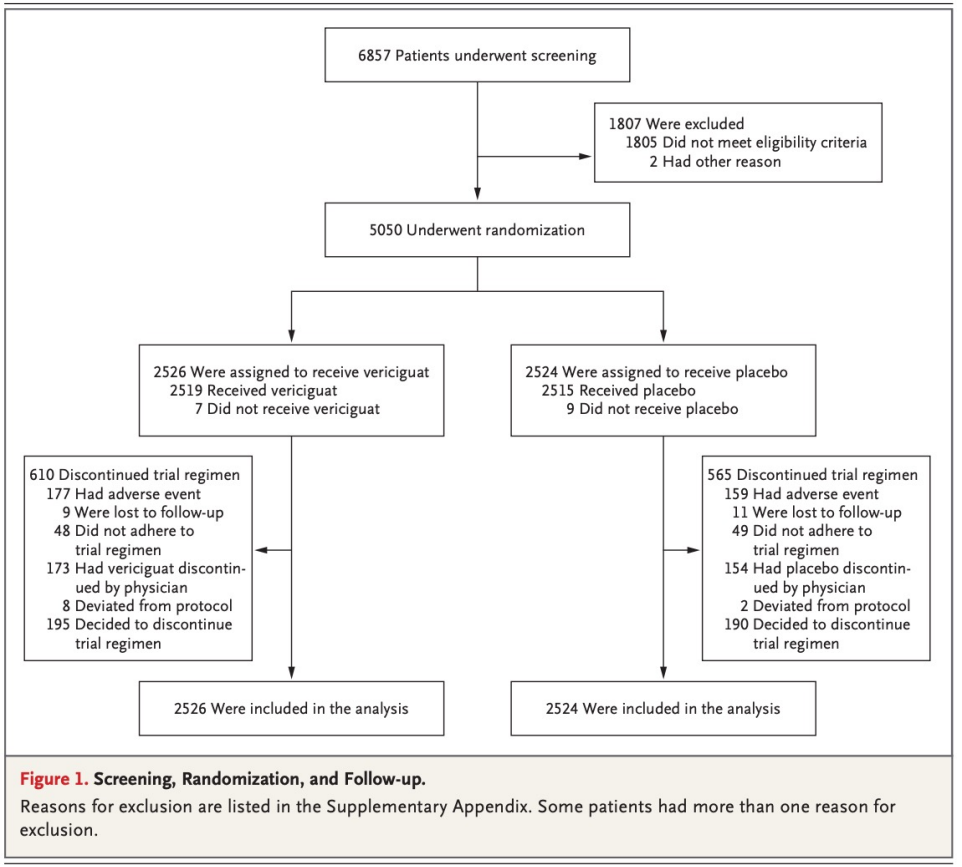


Figure 1. Screening, Randomization, and Follow-up.
Reasons for exclusion are listed in the Supplementary Appendix. Some patients had more than one reason for exclusion.

マスキングされているか

マスキング（盲検化）されているのは誰か？

●患者・参加者　○介入（治療）実施

● Outcome評価者　●データ解析者

□四重　■三重　□二重　□一重

□盲検なし　□盲検化不可能　□不明

TRIAL DESIGN AND OVERSIGHT

VICTORIA was a multinational, randomized, double-blind, placebo-controlled trial; the trial methods have been described previously.[4] The executive committee designed the trial with national leaders from participating countries and regions and oversaw operations in collaboration with the Canadian VIGOUR Centre and the trial cosponsors, Merck and Bayer.[4] The trial protocol (available with the full text of this article at NEJM.org) was approved by regulatory agencies in the participating countries and institutional review boards or ethics committees at the participating sites. An independent data and safety monitoring committee evaluated patient safety.

The sponsors participated in the trial design, selection of participating centers, site monitor-

症例数は十分か

症例数は十分か？

■結果に有意差がある　→症例数は十分

→サンプルサイズは？●計算されている　○計算されていない

□結果に有意差がない　→症例数は十分かどうか不明

→サンプルサイズは？

○計算されている

研究に参加した人数は計算されたサンプルサイズを？

○超えている　→症例数は十分

○超えていない　→症例数は不十分

○計算されていない

症例数（各群：　　合計：　　）

イベント発生率：　%　効果　　%　a：　power：%

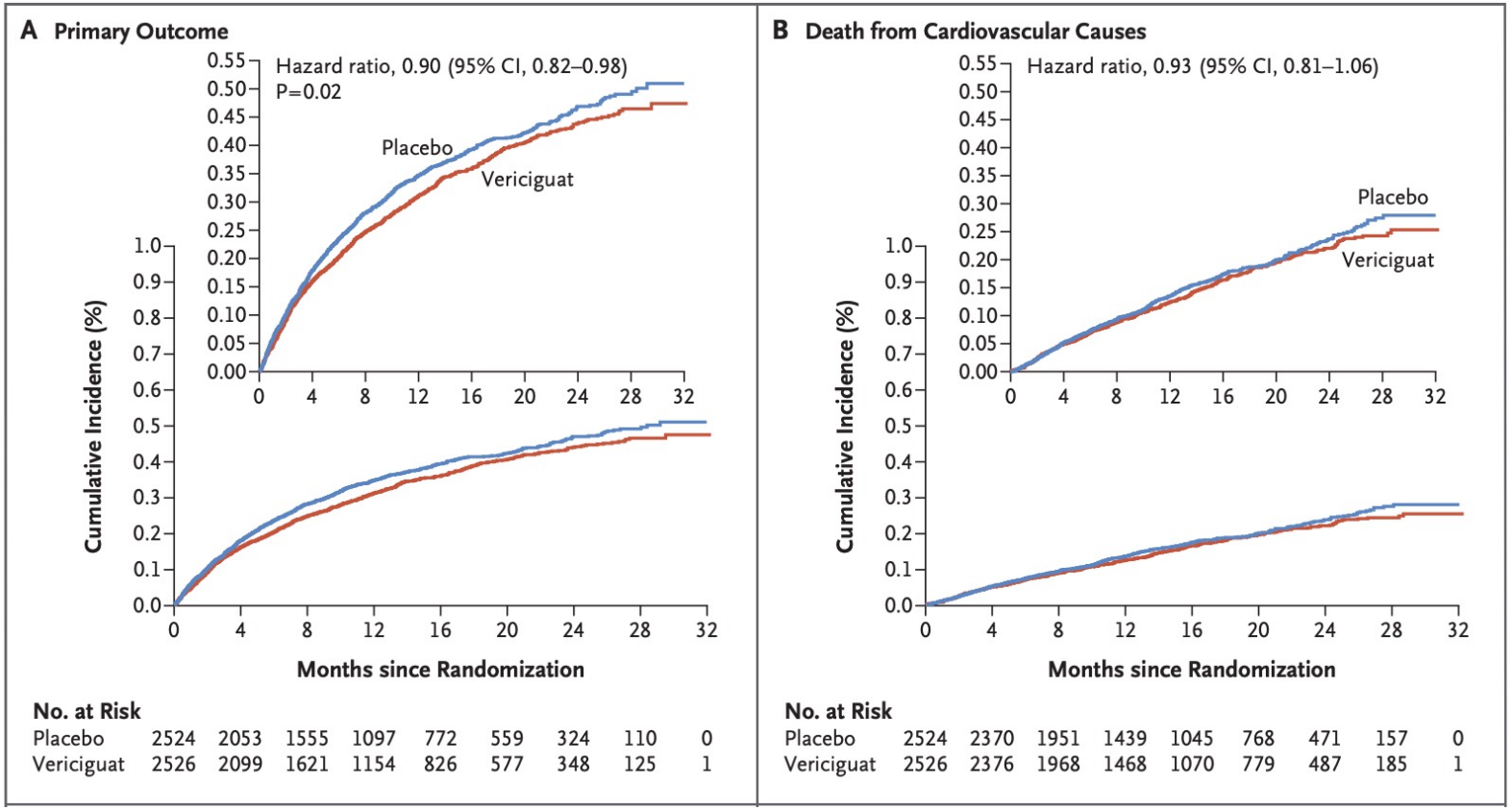
□不明

STATISTICAL ANALYSIS

The sample size was determined to provide adequate power for the assessment of the outcome of death from cardiovascular causes. The expected event rate among patients in the placebo group at 12 months was 11%. Assuming a hazard ratio of 0.80 for the outcome of death from cardiovascular causes, we estimated that a sample of 4872 patients, with an expected 782 events, would provide the trial with 80% power. A total of 1561 primary outcome events were expected. For the primary outcome, this sample size was expected to provide approximately 98% power. These calculations were performed with the use of the log-rank test and a one-sided type I error rate of 0.025. The data and safety monitoring committee reviewed the trial on a regular basis. Interim futility and efficacy analyses were planned but did not occur because of enrollment that was more rapid than expected and a higher than anticipated rate of death from cardiovascular causes.

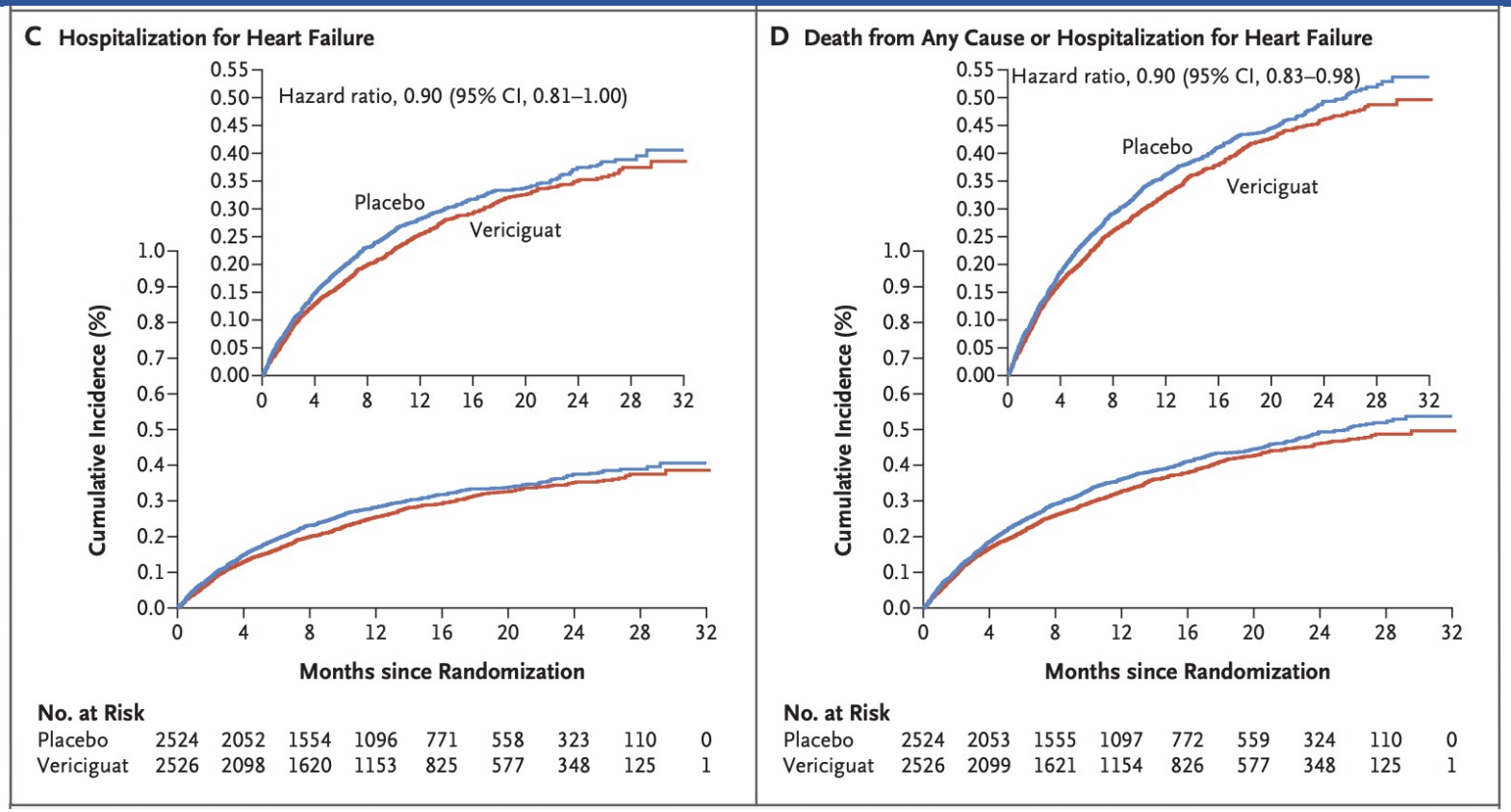
A hierarchical testing strategy was prespecified for the following secondary outcomes: total hospitalizations for heart failure, the composite of death from any cause or first hospitalization for heart failure, and death from any cause. P values are reported for the primary outcome and for subsequent secondary outcomes until the first outcome with a P value of greater than 0.05. P values are not reported for the components of the primary outcome because these analyses were not controlled for multiple comparisons.

結果の評価



primary endpoint（心不全初回入院 + 心血管死）HR 0.90（95%CI:0.82-0.98）
一方で、心血管イベント単独では有意差なし　　HR0.93（95%CI:0.81-1.06）

結果の評価



心不全初回入院　　HR0.90（95%CI:0.81-1.00）
総死亡＋心不全入院　HR0.90（95%CI:0.83-0.98）

入院は減ってるけど
死亡は減ってない？

結果の評価

Table 2. Primary and Secondary Outcomes.*

Outcome	Vericiguat (N=2526)		Placebo (N=2524)		Hazard Ratio (95% CI)†	P Value‡
	no. (%)	*events/100 patient-yr*	*no. (%)*	*events/100 patient-yr*		
Primary composite outcome and components						
Death from cardiovascular causes or first hospitalization for heart failure	897 (35.5)	33.6	972 (38.5)	37.8	0.90 (0.82–0.98)	0.02
Death from cardiovascular causes§	206 (8.2)		225 (8.9)			
Hospitalization for heart failure	691 (27.4)		747 (29.6)			
Secondary outcomes						
Death from cardiovascular causes	414 (16.4)	12.9	441 (17.5)	13.9	0.93 (0.81–1.06)	
Hospitalization for heart failure	691 (27.4)	25.9	747 (29.6)	29.1	0.90 (0.81–1.00)	
Total hospitalizations for heart failure¶	1223	38.3	1336	42.4	0.91 (0.84–0.99)	0.02
Secondary composite outcome and components						
Death from any cause or first hospitalization for heart failure	957 (37.9)	35.9	1032 (40.9)	40.1	0.90 (0.83–0.98)	0.02
Death from any cause§	266 (10.5)		285 (11.3)			
Hospitalization for heart failure	691 (27.4)		747 (29.6)			
Death from any cause	512 (20.3)	16.0	534 (21.2)	16.9	0.95 (0.84–1.07)	0.38

心不全入院は減ってるけど、やっぱり死亡は減ってない

結果の評価（adverse events）

Table S2. Patients with serious adverse events within a system organ class (incidence ≥2.0% in one or more groups): All patients as treated

	Vericiguat (n=2519)	Placebo (n=2515)	Total (n=5034)
One or more serious adverse events present	826 (32.8%)	876 (34.8%)	1702 (33.8%)
Blood and lymphatic system disorders	53 (2.1%)	29 (1.2%)	82 (1.6%)
Cardiac disorders	203 (8.1%)	269 (10.7%)	472 (9.4%)
Cardiac failure	80 (3.2%)	110 (4.4%)	190 (3.8%)
Gastrointestinal disorders	100 (4.0%)	92 (3.7%)	192 (3.8%)
Infections and infestations	269 (10.7%)	270 (10.7%)	539 (10.7%)
Pneumonia	101 (4.0%)	112 (4.5%)	213 (4.2%)
Injury, poisoning and procedural complications	65 (2.6%)	78 (3.1%)	143 (2.8%)
Metabolism and nutrition disorders	74 (2.9%)	89 (3.5%)	163 (3.2%)
Nervous system disorders	82 (3.3%)	83 (3.3%)	165 (3.3%)
Renal and urinary disorders	141 (5.6%)	133 (5.3%)	274 (5.4%)
Acute kidney injury	64 (2.5%)	51 (2.0%)	115 (2.3%)
Respiratory, thoracic and mediastinal disorders	88 (3.5%)	90 (3.6%)	178 (3.5%)
Vascular disorders	81 (3.2%)	86 (3.4%)	167 (3.3%)

Table S3. Patients with adverse events within a system organ class (incidence ≥2.0% in one or more groups): All patients as treated

	Vericiguat (n=2519)	Placebo (n=2515)	Total (n=5034)
One or more adverse events present	2027 (80.5%)	2036 (81.0%)	4063 (80.7%)
Blood and lymphatic system disorders	268 (10.6%)	212 (8.4%)	480 (9.5%)
Anaemia	192 (7.6%)	143 (5.7%)	335 (6.7%)

Table S4. Patients with adverse events of clinical interest: Symptomatic hypotension and syncope

	Vericiguat		Placebo		Difference in % vs. Placebo	
	No.	(%)	No.	(%)	Estimate (95% CI)*	P-Value
Patients in population	2519		2515			
Symptomatic hypotension	229	(9.1)	198	(7.9)	1.2 (-0.3 to 2.8)	0.121
Syncope	101	(4.0)	87	(3.5)	0.6 (-0.5 to 1.6)	0.303

*Based on the Miettinen & Nurminen method.
Note: Includes events/measurements from the day of first dose of study drug to 14 days after the last dose of study drug. Based on data up to the primary analysis cutoff date (18Jun2019).
CI indicates confidence interval.

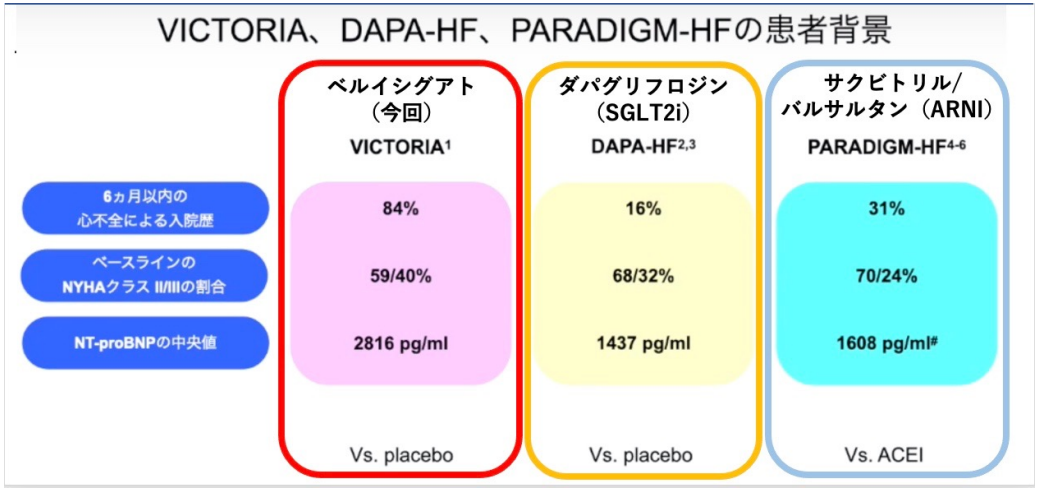
貧血、血圧低下、失神は実薬群で多いが有意差なし

結果の評価

今回の研究とPARADIGM-HF試験とDAPA-HF試験との比較

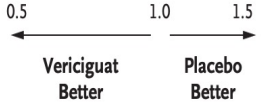
今回のVICTORIA試験では主要項目の年間発生率は33.6%で
上記2つの研究と比較すると2倍以上になっている

その理由としては、以下の要因が考えられている
・VICTORIA試験ではNYHA3-4の重症患者の割合が多い
(41% , 25% , 32%)
・NT-pro BNP値が高値
(2816pg/ml , 1608pg/ml, 1437pg/ml)



結果の評価（層別解析）

Subgroup	Vericiguat	Placebo	Hazard Ratio (95% CI)
	no. of events		
All patients	897	972	0.90 (0.82–0.98)
Sex			
Male	704	762	0.90 (0.81–1.00)
Female	193	210	0.88 (0.73–1.08)
Age			
<65 yr	290	348	0.81 (0.70–0.95)
≥65 yr	607	624	0.94 (0.84–1.06)
<75 yr	579	669	0.84 (0.75–0.94)
≥75 yr	318	303	1.04 (0.88–1.21)
Race			
White	593	635	0.91 (0.81–1.02)
Asian	199	207	0.91 (0.75–1.11)
Black	41	50	0.85 (0.56–1.28)
Other	64	80	0.80 (0.57–1.11)
Geographic region			
Eastern Europe	310	345	0.87 (0.75–1.01)
Western Europe	173	178	0.96 (0.78–1.18)
North America	103	117	0.85 (0.65–1.10)
Latin America	100	116	0.83 (0.63–1.08)
Asia–Pacific	211	216	0.96 (0.79–1.16)
Race in North America			
Black	26	29	0.93 (0.55–1.58)
Nonblack	77	88	0.82 (0.60–1.11)
Index event			
Intravenous diuretic in previous 3 mo	96	120	0.78 (0.60–1.02)
Hospitalization in previous 3 mo	660	701	0.93 (0.84–1.04)
Hospitalization in previous 3–6 mo	141	151	0.85 (0.67–1.07)
NYHA class			
I or II	445	484	0.91 (0.80–1.04)
III or IV	451	487	0.87 (0.77–0.99)
Use of sacubitril–valsartan			
Yes	134	153	0.88 (0.70–1.11)
No	760	818	0.90 (0.81–0.99)
Estimated GFR			
≤30 ml/min/1.73 m^2	143	128	1.06 (0.83–1.34)
>30 to ≤60 ml/min/1.73 m^2	392	455	0.84 (0.73–0.96)
>60 ml/min/1.73 m^2	346	372	0.92 (0.80–1.07)
NT-proBNP level			
Quartile 1 (≤1556.0 pg/ml)	128	161	0.78 (0.62–0.99)
Quartile 2 (>1556.0 to ≤2816.0 pg/ml)	165	201	0.73 (0.60–0.90)
Quartile 3 (>2816.0 to ≤5314.0 pg/ml)	213	257	0.82 (0.69–0.99)
Quartile 4 (>5314.0 pg/ml)	355	302	1.16 (0.99–1.35)
Ejection fraction			
<35%	637	703	0.88 (0.79–0.97)
≥35%	255	265	0.96 (0.81–1.14)
<40%	773	851	0.88 (0.80–0.97)
≥40%	119	117	1.05 (0.81–1.36)



65歳未満、NYHA≧III、
NT-proBNP≦5314pg/ml群で実薬群有利

この論文の利点・欠点

利点

・多国籍/多施設研究

・すでに心不全治療がされている
患者群での有用性が示唆された
特にARNIとは関係なく効果あり

・多くの患者で12ヶ月以上に渡って
内服継続できていること

欠点

・高齢者や腎機能が悪いと効果が乏しい

・SGLT2-i使用の割合が少ないこと

・入院は減っているが総死亡/心血管死亡
は減っていない

◯本薬剤の追加で入院頻度を減らしたい患者は適応かもしれない
◯けど他の心不全薬（特にSGLT2i, ARNI）との比較が欲しいところ
◯数多あるHFrEF治療薬の使い方の順序は、この研究では全く不明
◯ベリキューボⓇ10mg１錠403.8円.....高い、高すぎる！