How to Conquer Both Renal and Cardiovascular Diseases?
- Via AI-based Real World Data Analysis -

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COI Disclosure
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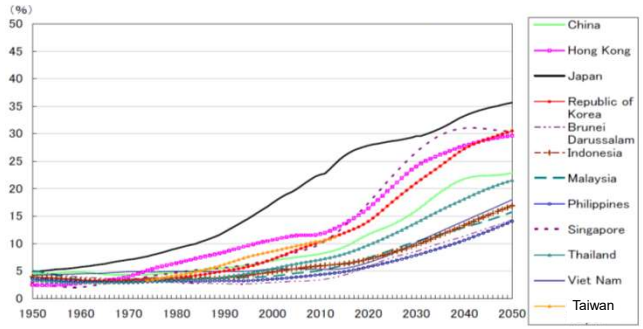
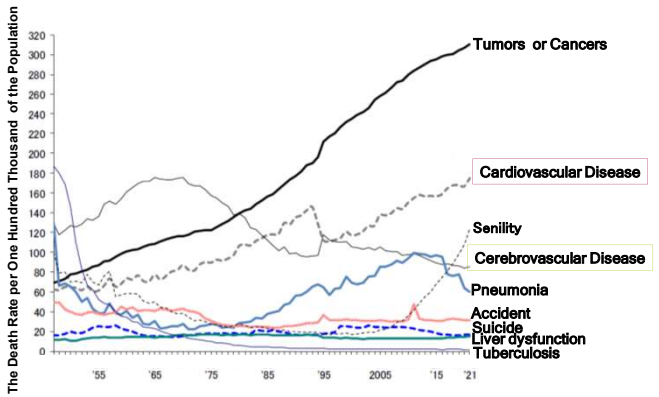
The Population Ratio of >65 Years Old in Asian Countries



https://www.mof.go.jp/policy/international_policy

Trends for The Causes of Death in Japan



Ministry of Health, Labor and Welfare of Japan , *Vital statistics*, 2021

The Medical Issues We Are Facing

We must urgently tackle the major disease burdens that dominate an aging society, i.e., malignant tumors, cardiovascular diseases, and frailty, including dementia.

But how should we approach this challenge?

There are two methodological strategies.

Kitakaze M

Two Major Methods of Science

Deductive Methods
Hypotheses come first, followed by the data and evidence

Inductive Methods
The data come first, followed by the analyses and evidence

Kitakaze M

Two Major Methods of Science

Deductive Methods
Hypotheses come first, followed by the data and evidence

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The data come first, followed by the analyses and evidence

Kitakaze M

Two Major Methods of Science

letters to nature

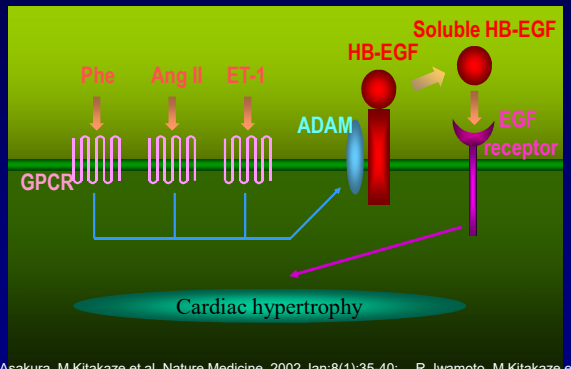
EGF receptor transactivation by G-protein-coupled receptors requires metalloproteinase cleavage of proHB-EGF

Norbert Prenzel*, Esther Zwick*, Henrik Daub†, Michael Leserer, Reimar Abraham, Christian Wallasch & Axel Ulrich

Department of Molecular Biology, Max-Planck-Institut für Biochemie, Am Klopferspitz 18A, 82152 Martinsried, Germany
** These authors contributed equally to this work*
† Present address: MRC Laboratory for Molecular and Cellular Biology, University College London, Gower Street, London WC1E 6BT, UK

(Nature. 1999;402(6764):884-8)

Shedding of HB-EGF via Metalloproteinase Activation as a Novel Pathway for Cardiac Hypertrophy



(M.Asakura, M.Kitakaze et al. Nature Medicine, 2002 Jan;8(1):35-40; R. Iwamoto, M.Kitakaze et al. Proc Natl Acad Sci U S A. 2003;100(6):3221-6; Y.Liao and M.Kitakaze et al. Biochem Biophys Res Commun. 2010;393(3):519-25; S.Tsuchida, M.Kitakaze et al. Int Heart J. 2018;59(6):1425-1431)

Two Major Methods of Science

Deductive Methods
Hypotheses come first, followed by the data and evidence

Inductive Methods
The data come first, followed by the analyses and evidence

Kitakaze M

Data-mining Analysis of the Patients with Heart Failure in NCVC

12,578 CHF patients of in NCVC

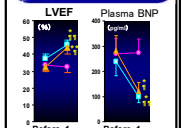
diseases	frequency	BNP
valvular heart disease	32%	254
Ischemic heart disease	28%	231
Primary cardiomyopathy	13%	282
Secondary cardiomyopathy	14%	246
Hypertensive heart	13%	324

Data-Mining

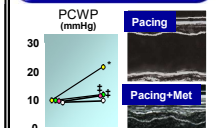
Proposal for the drugs of CHF

Known drugs	novel drugs
β Blockers	adenosine-related drugs
ACE inhibitors	Anti-DM drugs
ARB	H_2 antagonists
diuretics	aspirin
	statins

Adenosine-related drugs improves CHF in



Metformin improved CHF in dogs



H_2 blockers Improves the severity of CHF in humans

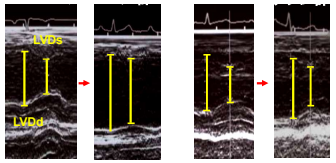
Kim J, et al. ***Cardiovasc Drug Ther*** 2004, Liao Y, et al. ***Cardiovasc Res*** 2006, Kim J. et al. ***J Am Coll Cardiol*** 2006, Asanuma H et al. ***J Mol Cell Cardiol*** 2006, Sanada S, et al. ***Hypertens Res*** 2007

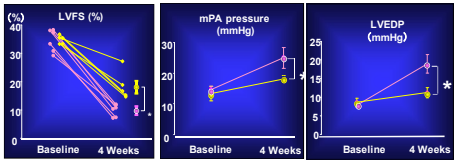
Cardioprotection due to Histamine H2 Receptors blockers in Canine Heart Failure Models

Mast cells in the heart

Echocardiogram

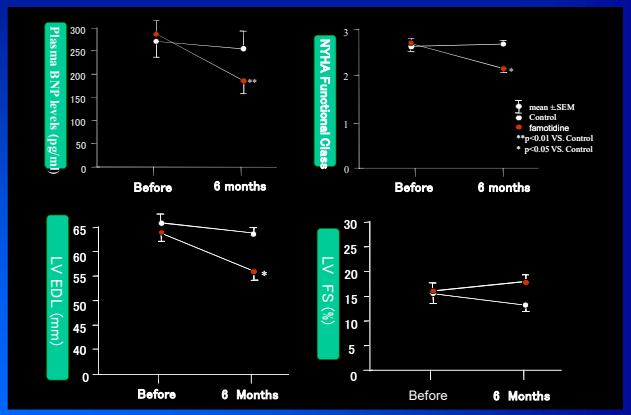
Baseline 4 Weeks rapid pacing Baseline4 Weeks rapid pacing



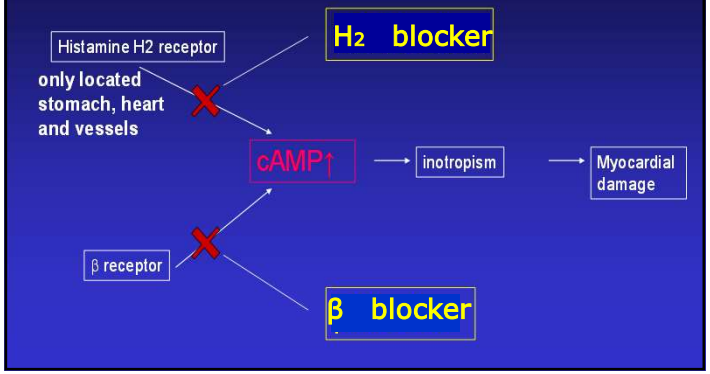


(H.Takahama, M Kitakaze et al. Basic Res Cardiol. 2010;105(6):787-94)

Famotidine Treatment for 6 Months Improved the Pathophysiology of Patients with Chronic Heart Failure



Cardio-protection Afforded by Blockade of H2 Receptors



Two Major Methods of Science

Deductive Methods

Merit: Acquisition of novel hypothesis

Demerit: Difficulties to acquire the novel hypothesis and how to prove the hypothesis and low success rate

Inductive Methods

Merit: Just accumulation of the big data and high success rate

Demerit: Difficulties to acquire big data and difficulty of mathematical analyses

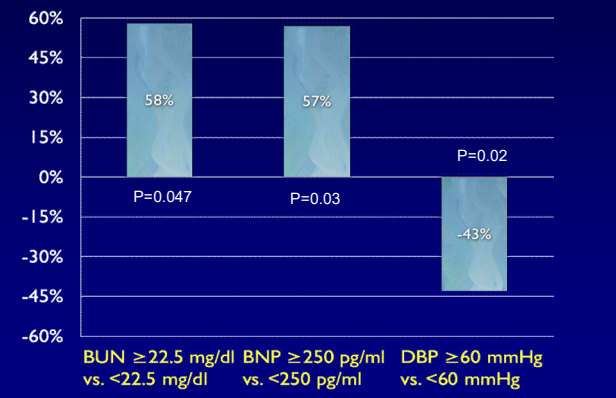
Kitakaze M

Two Major Methods of Science

Using a large set of clinical parameters, we applied data mining and machine learning as an inductive approach to uncover latent patterns in the data.

Kitakaze M

Biomarkers Associated With the High Incidence of Re-Hospitalization for Worsening of Heart Failure



(Chen CY, Kitakaze M, et al. Circ J. 2012;76(10):2372-9)

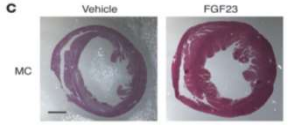
Three Important Biomarkers for Worsening of Heart Failure in the Patients with Heart Failure

1. ↑ Serum BUN levels
2. ↑ Plasma BNP levels
3. ↓ Diastolic blood pressure

Background

Fibroblast growth factor 23 (FGF23)

- Serum FGF23 levels increase as renal function decreases in CKD patients
  J Am Soc Nephrol 2010;21:1427-1435
- FGF23 is one of the hormones that control plasma Pi homeostasis
- In the basic studies, FGF23 is proved to cause cardiac hypertrophy

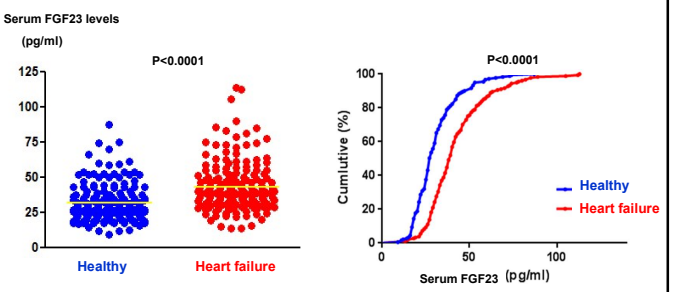


J Clin Invest 2011; 121: 4393-4408.

- In the clinical studies, the serum FGF23 levels are related to cardiac hypertrophy in progressed CKD patients *Circulation* 2009; 119: 2545-2552

We need to test whether the serum FGF23 levels, a biomarker of renal dysfunction, are linked the pathophysiology of heart failure.

The Serum FGF23 Levels in Patients with Heart Failure

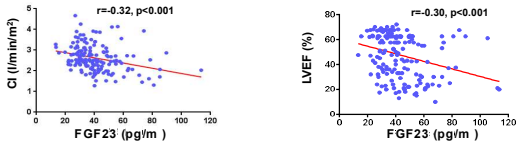


(M.Imazu, M.Kitakaze et al Am J Physiol. 2014;307:H1504-1511)

The Multivariate Analysis Reveals the Heart Failure-related Determinants of the Serum FGF23 Levels

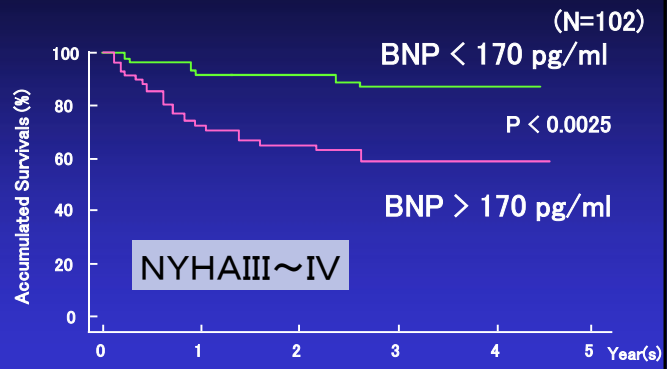
	Beta	SE	P 値
Cardiac index	-5.438	2.178	0.013
LVEF	-0.190	0.077	0.015
eGFR	-0.183	0.086	0.035
LAVi	0.024	0.040	0.547
Mean BP	-0.090	0.121	0.460
BMI	0.521	0.318	0.104

R^2=0.197



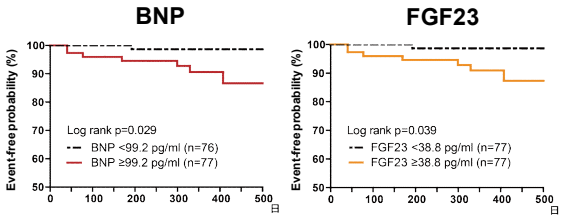
(M.Imazu, M.Kitakaze et al Am J Physiol. 2014;307:H1504-1511)

Survival Curves of the Patients with Heart Failure Stratified by Plasma BNP Levels



Maeda K et al. : J Am Coll Cardiol, 36, 1587-93 (2000)

Both BNP and FGF23 Levels in the Blood Were the Independent Predictors of Cardiovascular Outcomes

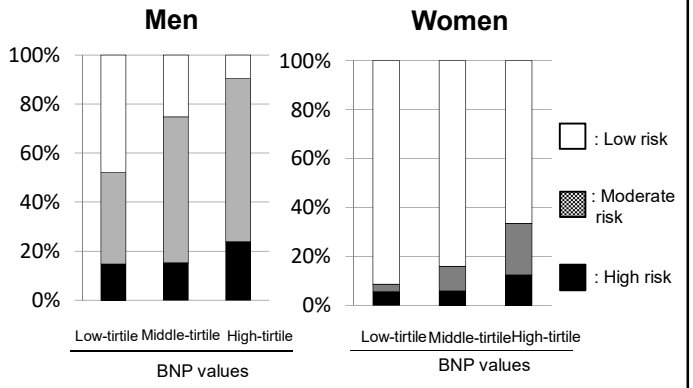


Cardiovascular events: cardiovascular death and/or hospitalization due to HF

(Hypertension Res 2017; 40:181-188)

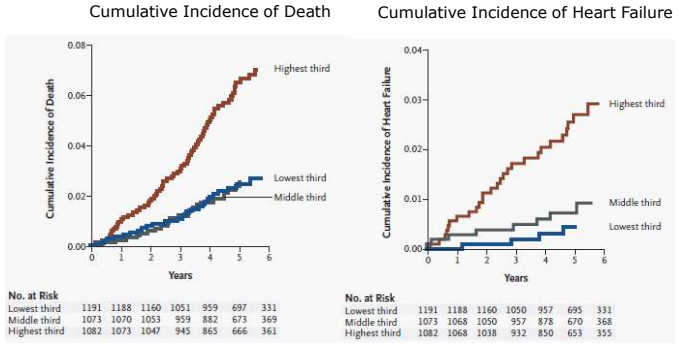
Do the plasma BNP levels predict the coronary events in addition to the heart failure-related events?

High Plasma BNP levels Link to High Risks for Coronary Heart Disease



(Hasegawa T and Kitakaze M et al. Hypertension Research 2015:38:74-79)

Elevated BNP Predicts CV events in a Community-based Population



Wang TJ et al. N Eng J Med 2004;350:655-663.

Three Important Biomarkers for Worsening of Heart Failure in the Patients with Heart Failure

1. Serum BUN levels
2. Plasma BNP levels
3. **Diastolic blood pressure**

We will focus on diastolic blood pressure diastolic blood pressure may reflect the aortic vascular function.

Worsening of the Pathophysiology of Heart Failure in the Patients with Heart Failure

TABLE 3. Proportional-Hazard Regression Coefficients Relating Incidence of CHD to Dual BP Indexes of SBP and DBP by Age Groups

Dual BP Components*	β†	SE†	Wald χ^2	HR (95% CI)†
Age <50 y				
SBP	−0.05	0.07	0.5	0.95 (0.83–1.09)
DBP	0.35	0.11	10.9	1.42 (1.15–1.74)‖
Age 50–59 y				
SBP	0.09	0.05	3.4	1.10 (0.99–1.21)
DBP	−0.03	0.09	0.1	0.97 (0.81–1.16)
Age ≥60 y				
SBP	0.21	0.04	33.7	1.24 (1.15–1.33)‖
DBP	−0.19	0.08	5.2	0.83 (0.71–0.98)§

*Both SBP and DBP appear in the same model, adjusted for age, sex, body mass index, cigarette smoking, diabetes mellitus, and ratio of total to HDL cholesterol.
†HR was associated with a 10 mm Hg increase in BP.
‡Wald $\chi^2 = (\beta/SE)^2$.
§$P<0.05$, ‖$P<0.001$.

(Circulation 2001;103(9):1245-1249)

The decreases in diastolic blood pressure reflect the severity of aortic atherosclerosis and the less arterial compliance via the increases in the speed of the reflection wave.

(Medical Hypothesis, 2020 Feb;135:109449)

Three Important Biomarkers for Worsening of Heart Failure in the Patients with Heart Failure

1. Serum BUN levels — Renal Function
2. Plasma BNP levels — Cardiac Function
3. Diastolic blood pressure — Vascular Function

The Medical Issues We Are Facing

We must address the rising morbidity and mortality of cardiovascular diseases driven by renal dysfunction in Viet Nam, Japan, and around the world.

Kitakaze M

What are New Trends for the Treatment of Heart Failure?

1. Nesiritide, Carperitide
2. ARNI
3. Vericiguat
4. SGLT2 inhibitors
5. Sarcomere Modulators

New Trends for the Treatment of Heart Failure

1. Nesiritide, Carperitide
2. ARNI
3. Vericiguat
4. SGLT2 inhibitors
5. Sarcomere Modulators

Large-Scale Trial Using Atrial Natriuretic Peptide or Nicorandil as an Adjunct to Percutaneous Coronary Intervention for ST-Segment Elevation Acute Myocardial Infarction

Masafumi Kitakaze*, M.D., Ph.D.
For the J-WIND Study Group
*National Cardiovascular Center, Osaka, Japan

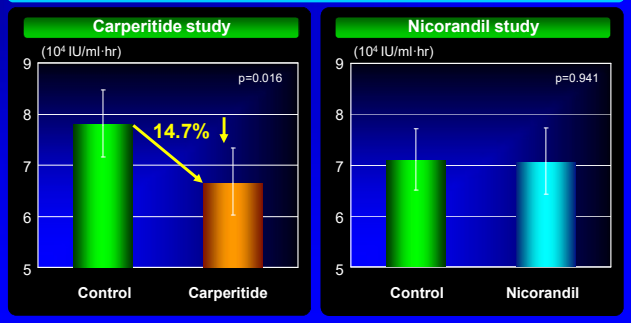
J-WIND: *Japan-Working Groups of Acute Myocardial Infarction for the Reduction of Necrotic Damage*

Study Design

Subjects:	Patients with first acute myocardial infarction
Treatment:	Carperitide (0.025μg/kg/min for 3days) vs. 5% glucose solution Nicorandil (0.067mg/kg bolus+1.67μg/kg/min for 24hrs) vs. saline
Design:	Prospective, randomized, blinded, controlled trial
Study period:	December 2001 to August 2006

Primary Endpoints

Area under curve of creatine kinase (ΣCK)

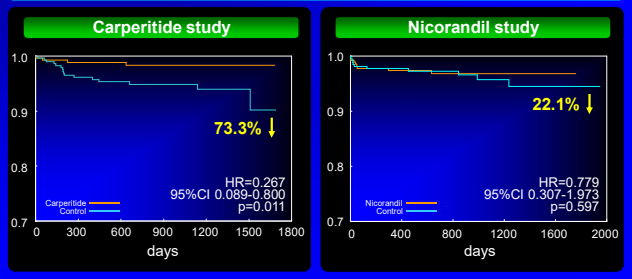


(Lancet 2007;27;370:1483-93)

Sub-analysis -1-

J-wind

Cardiac death & heart failure



(Lancet 2007;27;370:1483-93)

Articles

Human atrial natriuretic peptide and nicorandil as adjuncts to reperfusion treatment for acute myocardial infarction (J-WIND): two randomised trials

Summary

Background Patients with acute myocardial infarction remain at major risk of cardiovascular events. We aimed to assess the effects of either human atrial natriuretic peptide (ANP) or nicorandil on infarct size and cardiovascular outcome.

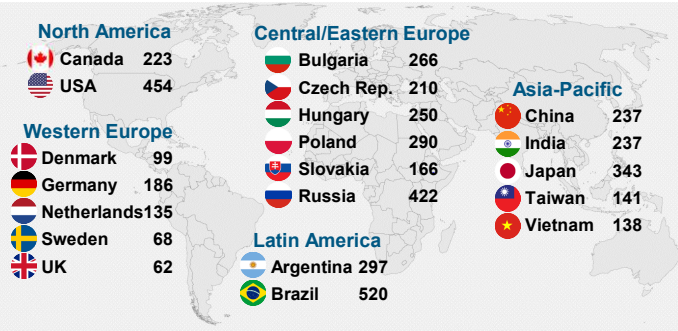
(LANCET, 2007 Oct 27;370(9597):1483-93)

New Trends for the Treatment of Heart Failure

1. Nesiritide, Carperitide
2. ARNI
3. Vericiguat
4. **SGLT2 inhibitors**
5. Sarcomere Modulators

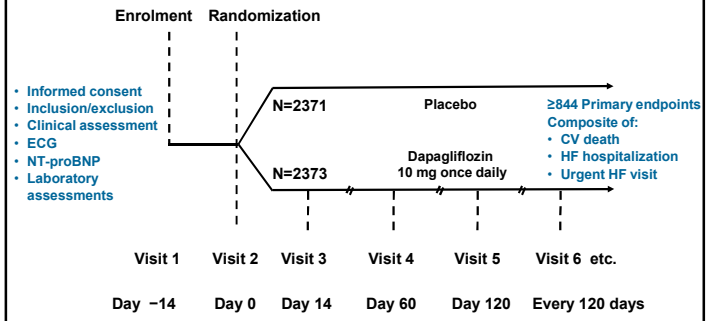
DAPA-HF - A global trial

4,744 patients 20 countries



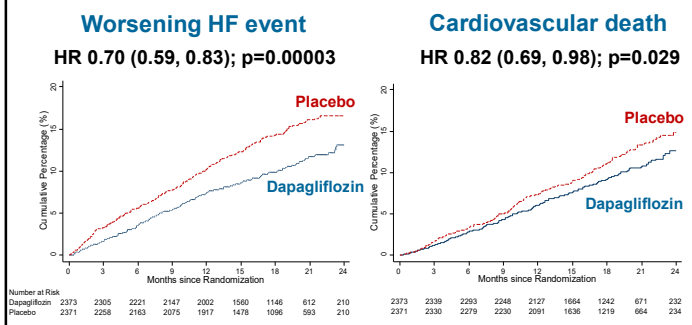
New England J Medicine 2019;381(21):1995-2008

DAPA-HF Design



New England J Medicine 2019;381(21):1995-2008

Components of primary outcome

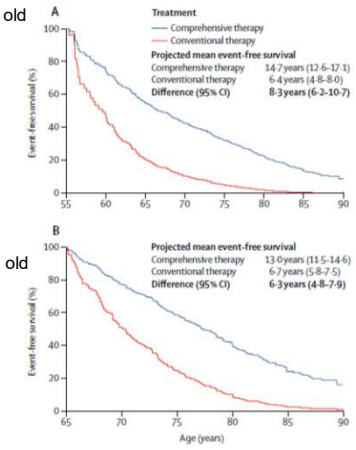


New England J Medicine 2019;381(21):1995-2008

Event-free survival in HFrEF Patients with Comprehensive Disease-modifying Therapy *vs* Conventional Therapy

Over 55 years old

Over 65 years old

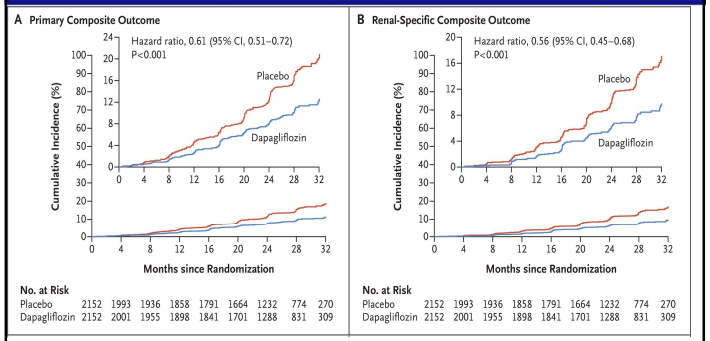


comprehensive disease-modifying pharmacological therapy (ARNI, β blocker, MRA, and SGLT2 inhibitor) versus conventional therapy (ACE inhibitor or ARB and β blocker)

Lancet 2020;396:121-128

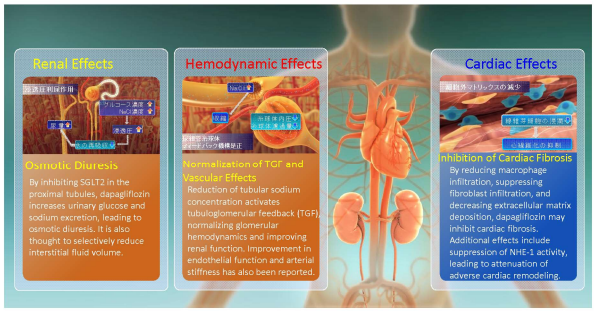
Primary Outcome of DAPA-CKD

Heerspink HJL. et al.: N Engl J Med. 383(15): 1436-1446, 2020



The primary composite outcomewas the first occurrence of any of the following: a decline of at least 50% in the estimated GFR (confirmed by a second serum creatinine measurement after ≥28 days), the onset of end-stage kidney disease (defined as maintenance dialysis for ≥28 days, kidney transplantation, or an estimated GFR of <15 ml per minute per 1.73 m^2 confirmed by a second measurement after ≥28 days), or death from renal or cardiovascular causes.

Main Mechanisms of Dapagliflozin in Chronic Heart Failure



Dapagliflozin improves glycemic control by inhibiting renal glucose reabsorption, leading to glycosuria. In addition to osmotic diuresis and hemodynamic effects via SGLT2 inhibition, dapagliflozin may exert cardioprotective effects through the inhibition of cardiac fibrosis.

†References
1) Verma S et al. Diabetologia. 61(10): 2108–2117, 2018
2) Solini A et al. Cardiovasc Diabetol. 16(1): 138, 2017
3) Lee T et al. Free Radic Biol Med. 104: 298–310, 2017
4) Uthman L et al. Diabetologia. 61: 722–726, 2018
5) Dapagliflozin Investigator's Brochure, 2020 (11th ed., Japanese translation)
6) Dapagliflozin Investigator's Brochure (Japanese)

New Trends for the Treatment of Heart Failure

1. **Nesiritide, Carperitide**
2. **ARNI**
3. **Vericiguat**
4. **SGLT2 inhibitors**
5. **Sarcomere Modulators**

New Trends for the Treatment of Heart Failure

The key and magic word to treat heart failure is "Cardio-vascular and Renal Protection"
via Protein Kinase G,
Because nesiritide/carperitide, ARNI, vericiguat, and SGLT2 inhibitors are known to active protein kinase G.

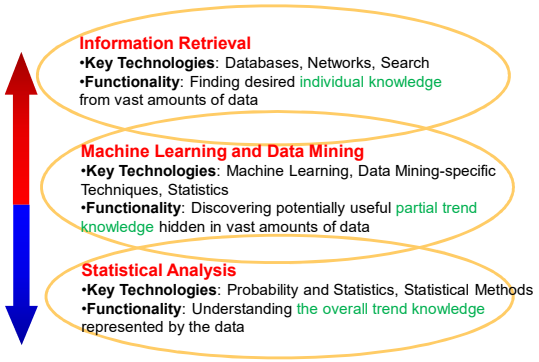
The Future Trends of Medical Science

It is critically important

1. to collect medical and genomic real-world data
2. to apply advanced mathematical approaches, including machine learning and data mining
3. to translate the results of such analyses into medical practice.

Kitakaze M

The Positioning of Data Mining and Machine Learning between Information Retrieval and Statistical Analysis



Made by Prof Takashi Washio at Osaka Univ.

The Problems of Big Population Data

1. Combinatorial explosion
2. Reduced statistical power due to a large number of variables
3. Difficulty in acquisition of statistical significance

Kitakaze M

Predicting Heart Failure Onset in the General Population using a Novel Data-mining Artificial Intelligence Method

Table 2 The combinations of clinical factors that predicted the occurrence of heart failure

The combinations of clinical parameters			Adjusted p-value
The plasma AST levels no greater than 40IU/L	The age less than 60 years old	The urinary glucose: Borderline levels	1.10E-26
The plasma ALT levels no greater than 40IU/L	The age less than 60 years old	The urinary glucose: Borderline levels	6.06E-26
The plasma AST levels no greater than 40IU/L	The age less than 60 years old		9.74E-26
The age less than 60 years old	The urinary glucose: Borderline levels		1.78E-25
The plasma ALT levels no greater than 40IU/L	The plasma AST levels no greater than 40IU/L	The age less than 60 years old	2.73E-25
The plasma ALT levels no greater than 40IU/L	The age less than 60 years old		5.03E-25
The age less than 60 years old			1.95E-24
The plasma HbA1c levels no greater than 6.2%	The plasma AST levels no greater than 40IU/L	The age less than 60 years old	6.60E-24
The plasma ALT levels no greater than 40IU/L	The age less than 60 years old	The plasma γ-GTP levels no greater than 71IU/L	8.82E-24
The age less than 60 years old	The urinary glucose: Borderline	The plasma γ-GTP levels no greater than 71IU/L	1.03E-23
The plasma ALT levels no greater than 40IU/L	The plasma HbA1c levels no greater than 6.2%	The age less than 60 years old	1.59E-23
The plasma AST levels no greater than 40IU/L	The age less than 60 years old	The plasma γ-GTP levels no greater than 71IU/L	1.99E-23
The plasma HbA1c levels no greater than 6.2%	The age less than 60 years old	The urinary glucose: Borderline levels	3.36E-23
The plasma HbA1c levels no greater than 6.2%	The age less than 60 years old		6.20E-23
The age less than 60 years old	The plasma γ-GTP levels no greater than 71IU/L		7.47E-23
The plasma HDL cholesterol levels more than 40mg/L	The plasma AST levels no greater than 40IU/L	The age less than 60 years old	3.11E-22
The plasma HDL cholesterol levels more than 40mg/L	The age less than 60 years old	The urinary glucose: Borderline levels	4.63E-22
The plasma ALT levels no greater than 40IU/L	The plasma HDL cholesterol levels more than 40mg/L	The age less than 60 years old	4.98E-22
The plasma HDL cholesterol levels more than 40mg/L	The age less than 60 years old		3.65E-21

(Scientific Reports 2023;13(1):4352)

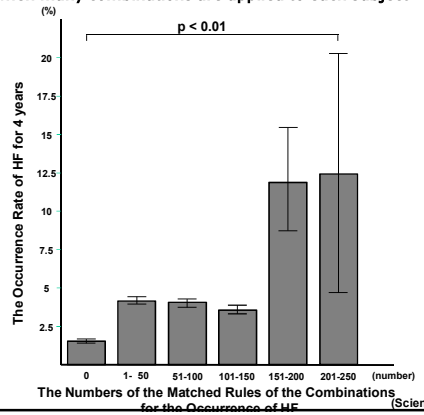
Cutting Edge of AI-derived Heart Failure Research

We identified 549 combinations of factors for the onset of HF. Then we classified 275,658 people into six groups who had 0, 1–50, 51–100, 101–150, 151–200 or 201–250 predictive combinations of factors for the onset of HF. We found that the probability of HF progressively increased as the number of predictive combinations of factors increased.

(Scientific Reports 2023;13(1):4352)

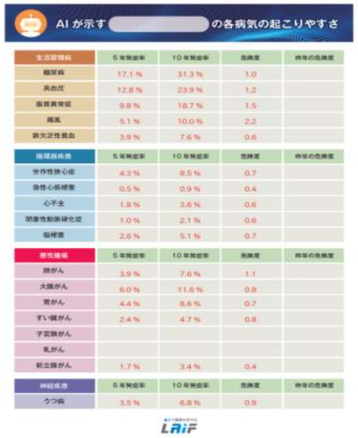
Predicting Heart Failure Onset in the General Population using a Novel Data-mining Artificial Intelligence Method

We have elucidated that the risks for the serious diseases increased in each subject when many combinations are applied to each subject



(Scientific Reports 2023;13(1):4352)

Data Sheets Analyzed by the AI Disease Onset Prediction System



Data Sheets Analyzed by the AI Disease Onset Prediction System

Summary of My Talk Today

- The world is entering an era of population aging, and the leading causes of death are malignant tumors, cardiovascular diseases, and senescence.
- To overcome these diseases, it is essential to apply both deductive and inductive scientific methods to medicine.
- Analyses using functional approaches based on real-world data (RWD) have revealed that chronic kidney disease plays a major role in cardiovascular disease.
- Furthermore, deductive analyses have led to the development of novel therapeutic agents for heart failure.
- In addition, analyses that combine RWD with advanced mathematical approaches have made it possible to predict the future onset of diseases.
- It is necessary to approach and solve the healthcare issues in Asian countries, including Vietnam and Japan.

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