Web 資料 1

1-1. SPRINT 試験のデータの矛盾　　その 1：アウトカムデータにおける矛盾

Table 2. Primary and Secondary Outcomes and Renal Outcomes.*

Outcome	Intensive Treatment		Standard Treatment		Hazard Ratio (95% CI)	P Value
	no. of patients (%)	*% per year*	*no. of patients (%)*	*% per year*		
All participants	**(N=4678)**		**(N=4683)**			
Primary outcome†	243 (5.2)	1.65	319 (6.8)	2.19	0.75 (0.64–0.89)	<0.001
Secondary outcomes						
Myocardial infarction	97 (2.1)	0.65	116 (2.5)	0.78	0.83 (0.64–1.09)	0.19
Acute coronary syndrome	40 (0.9)	0.27	40 (0.9)	0.27	1.00 (0.64–1.55)	0.99
Stroke	62 (1.3)	0.41	70 (1.5)	0.47	0.89 (0.63–1.25)	0.50
Heart failure	62 (1.3)	0.41	100 (2.1)	0.67	0.62 (0.45–0.84)	0.002
Death from cardiovascular causes	37 (0.8)	0.25	65 (1.4)	0.43	0.57 (0.38–0.85)	0.005
Death from any cause	155 (3.3)	1.03	210 (4.5)	1.40	0.73 (0.60–0.90)	0.003
Primary outcome or death	332 (7.1)	2.25	423 (9.0)	2.90	0.78 (0.67–0.90)	<0.001
Participants with CKD at baseline	**(N=1330)**		**(N=1316)**			
Composite renal outcome‡	14 (1.1)	0.33	15 (1.1)	0.36	0.89 (0.42–1.87)	0.76
≥50% reduction in estimated GFR§	10 (0.8)	0.23	11 (0.8)	0.26	0.87 (0.36–2.07)	0.75
Long-term dialysis	6 (0.5)	0.14	10 (0.8)	0.24	0.57 (0.19–1.54)	0.27
Kidney transplantation	0		0			
Incident albuminuria¶	49/526 (9.3)	3.02	59/500 (11.8)	3.90	0.72 (0.48–1.07)	0.11
Participants without CKD at baseline‖	**(N=3332)**		**(N=3345)**			
≥30% reduction in estimated GFR to <60 ml/min/1.73 m^2§	127 (3.8)	1.21	37 (1.1)	0.35	3.49 (2.44–5.10)	<0.001
Incident albuminuria¶	110/1769 (6.2)	2.00	135/1831 (7.4)	2.41	0.81 (0.63–1.04)	0.10

* CI denotes confidence interval, and CKD chronic kidney disease.
† The primary outcome was the first occurrence of myocardial infarction, acute coronary syndrome, stroke, heart failure, or death from cardiovascular causes.
‡ The composite renal outcome for participants with CKD at baseline was the first occurrence of a reduction in the estimated GFR of 50% or more, long-term dialysis, or kidney transplantation.
§ Reductions in the estimated GFR were confirmed by a second laboratory test at least 90 days later.
¶ Incident albuminuria was defined by a doubling of the ratio of urinary albumin (in milligrams) to creatinine (in grams) from less than 10 at baseline to greater than 10 during follow-up. The denominators for number of patients represent those without albuminuria at baseline.
‖ No long-term dialysis or kidney transplantation was reported among participants without CKD at baseline.

試験前に腎障害（CKD）のない人は、厳格群で圧倒的に腎障害を起こす人が多いのに、試験前に腎障害のある人は、両群で差がないか、むしろ厳格群に腎障害を起こすことが少ない傾向すらある。

矛盾する結果が起こるメカニズムについて、説明は困難である。

1-2. SPRINT 試験のデータの矛盾　その２：アウトカムデータと有害事象データの矛盾）

Table 3. Serious Adverse Events, Conditions of Interest, and Monitored Clinical Events.

Variable	Intensive Treatment (N=4678)	Standard Treatment (N=4683)	Hazard Ratio	P Value
	no. of patients (%)			
Serious adverse event*	1793 (38.3)	1736 (37.1)	1.04	0.25
Conditions of interest				
Serious adverse event only				
Hypotension	110 (2.4)	66 (1.4)	1.67	0.001
Syncope	107 (2.3)	80 (1.7)	1.33	0.05
Bradycardia	87 (1.9)	73 (1.6)	1.19	0.28
Electrolyte abnormality	144 (3.1)	107 (2.3)	1.35	0.02
Injurious fall†	105 (2.2)	110 (2.3)	0.95	0.71
Acute kidney injury or acute renal failure‡	193 (4.1)	117 (2.5)	1.66	<0.001
Emergency department visit or serious adverse event				
Hypotension	158 (3.4)	93 (2.0)	1.70	<0.001
Syncope	163 (3.5)	113 (2.4)	1.44	0.003
Bradycardia	104 (2.2)	83 (1.8)	1.25	0.13
Electrolyte abnormality	177 (3.8)	129 (2.8)	1.38	0.006
Injurious fall†	334 (7.1)	332 (7.1)	1.00	0.97
Acute kidney injury or acute renal failure‡	204 (4.4)	120 (2.6)	1.71	<0.001
Monitored clinical events				
Adverse laboratory measure§				
Serum sodium <130 mmol/liter	180 (3.8)	100 (2.1)	1.76	<0.001
Serum sodium >150 mmol/liter	6 (0.1)	0		0.02
Serum potassium <3.0 mmol/liter	114 (2.4)	74 (1.6)	1.50	0.006
Serum potassium >5.5 mmol/liter	176 (3.8)	171 (3.7)	1.00	0.97
Orthostatic hypotension¶				
Alone	777 (16.6)	857 (18.3)	0.88	0.01
With dizziness	62 (1.3)	71 (1.5)	0.85	0.35

* A serious adverse event was defined as an event that was fatal or life-threatening, that resulted in clinically significant or persistent disability, that required or prolonged a hospitalization, or that was judged by the investigator to represent a clinically significant hazard or harm to the participant that might require medical or surgical intervention to prevent one of the other events listed above.
† An injurious fall was defined as a fall that resulted in evaluation in an emergency department or that resulted in hospitalization.
‡ Acute kidney injury or acute renal failure were coded if the diagnosis was listed in the hospital discharge summary and was believed by the safety officer to be one of the top three reasons for admission or continued hospitalization. A few cases of acute kidney injury were noted in an emergency department if the participant presented for one of the other conditions of interest.
§ Adverse laboratory measures were detected on routine or unscheduled tests; routine laboratory tests were performed at 1 month, then quarterly during the first year, then every 6 months.
¶ Orthostatic hypertension was defined as a drop in systolic blood pressure of at least 20 mm Hg or in diastolic blood pressure of at least 10 mm Hg at 1 minute after the participant stood up, as compared with the value obtained when the participant was seated. Standing blood pressures were measured at screening, baseline, 1 month, 6 months, 12 months, and yearly thereafter. Participants were asked if they felt dizzy at the time the orthostatic measure was taken.

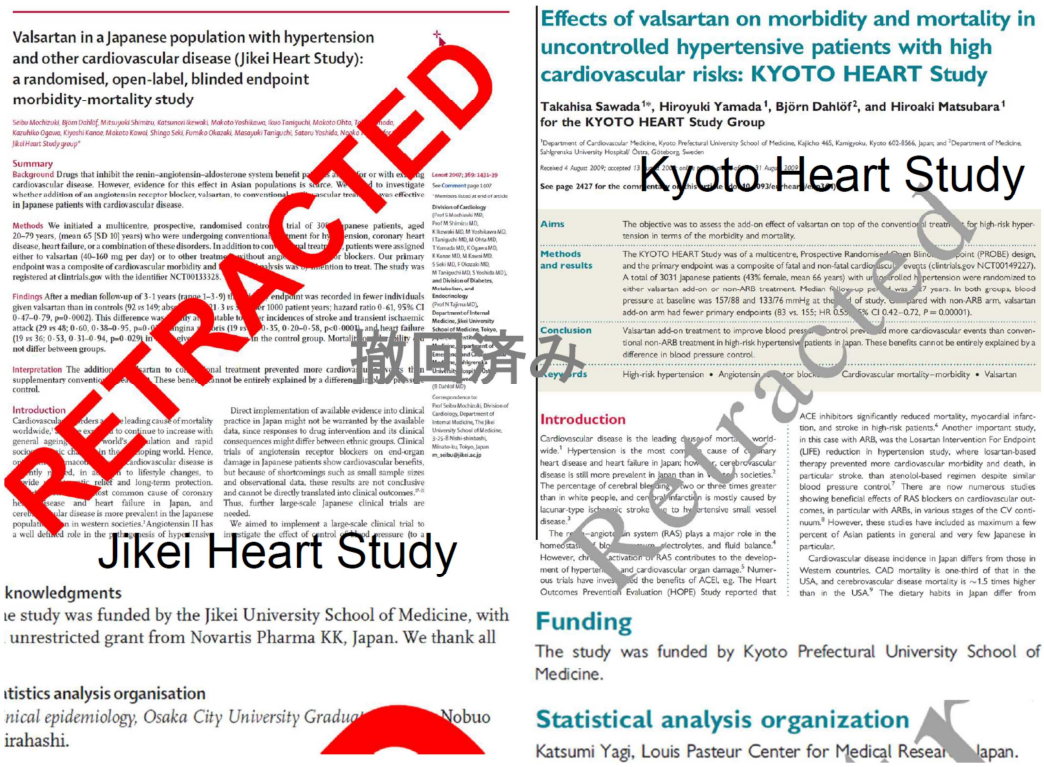
‡ 急性腎障害や急性腎不全は、退院サマリーに記載された病名情報に基づく（下線）。

前頁で示したアウトカム情報は、臨床試験を目的に収集される。一方、この有害事象における「急性腎障害など」情報は、退院サマリーに記載された病名情報であり、臨床試験用に収集されるデータとは独立して記載されていると考えられる。したがって、アウトカムデータよりも検出バイアス（detection bias）がかかり難い。すなわち、腎障害の出現に関しては、有害事象情報のほうが、アウトカム評価情報よりも信頼性が高いと考えられる。

急性腎障害や急性腎不全は、一過性で回復しうることが考えられ、すべてが慢性腎不全の悪化につながるものではないとしても、中には回復せずに慢性腎不全の永続する悪化につながる例もあるはずである。したがって、急性腎障害や急性腎不全の危険度が $p<0.0001$ で 1.7 倍（70%増し）であるのに、試験前に腎障害のある人で、厳格群と緩和群とで腎障害の悪化が同じというのは、医学的に説明が不可能である。

2．撤回された Kyoto Heart Study と Wei 論文

2-1．撤回された Jikei Heart Study と Kyoto Heart Study



Valsartan in a Japanese population with hypertension and other cardiovascular disease (Jikei Heart Study): a randomised, open-label, blinded endpoint morbidity-mortality study

RETRACTED

撤回済み

Jikei Heart Study

knowledgments

ıe study was funded by the Jikei University School of Medicine, with unrestricted grant from Novartis Pharma KK, Japan. We thank all

ıtistics analysis organisation

nical epidemiology, Osaka City University Graduat Nobuo irahashi.

Effects of valsartan on morbidity and mortality in uncontrolled hypertensive patients with high cardiovascular risks: KYOTO HEART Study

Takahisa Sawada[1*], Hiroyuki Yamada[1], Björn Dahlöf[2], and Hiroaki Matsubara[1] for the KYOTO HEART Study Group

Kyoto Heart Study

Aims

Methods and results

Conclusion

Keywords

Introduction

Funding

The study was funded by Kyoto Prefectural University School of Medicine.

Statistical analysis organization

Katsumi Yagi, Louis Pasteur Center for Medical Resear Japan.

Retracted

2-2. あまりにもよく似た背景因子をもつ Kyoto Heart Study

Table 1 Baseline characteristics

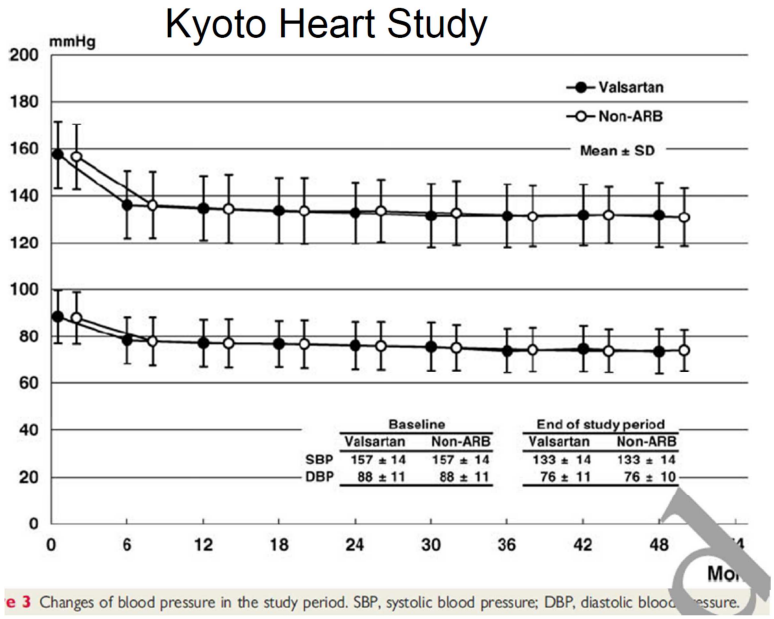
Kyoto Heart study

	Valsartan, n = 1517	Non-ARB, n = 1514
Age	66 (11)	66 (11)
Men/women	861/656 (57/43%)	867/647 (57/43%)
Current smoker	341 (22%)	332 (22%)
Obesity BMI ≥25	593 (39%)	584 (39%)
Coronary artery disease	355 (23%)	352 (23%)
Cerebrovascular disease	58 (4%)	65 (4%)
Heart failure	84 (6%)	109 (7%)
Diabetes	401 (26%)	406 (27%)
Dyslipidaemia	1065 (70%)	1079 (71%)
LVH by electrocardiogram	122 (8%)	129 (9%)
Systolic blood pressure (mmHg)	157 (14)	157 (14)
Diastolic blood pressure (mmHg)	88 (11)	88 (11)

背景因子があまりにも同じ

SDまで同じ

2-3. 達成された血圧も両群で一致



e 3 Changes of blood pressure in the study period. SBP, systolic blood pressure; DBP, diastolic blood pressure.

2-4. 同じ背景因子をもち、達成された血圧も全く同じであるのに
ディオバン群の結果が著しくよかった。なぜなのか？

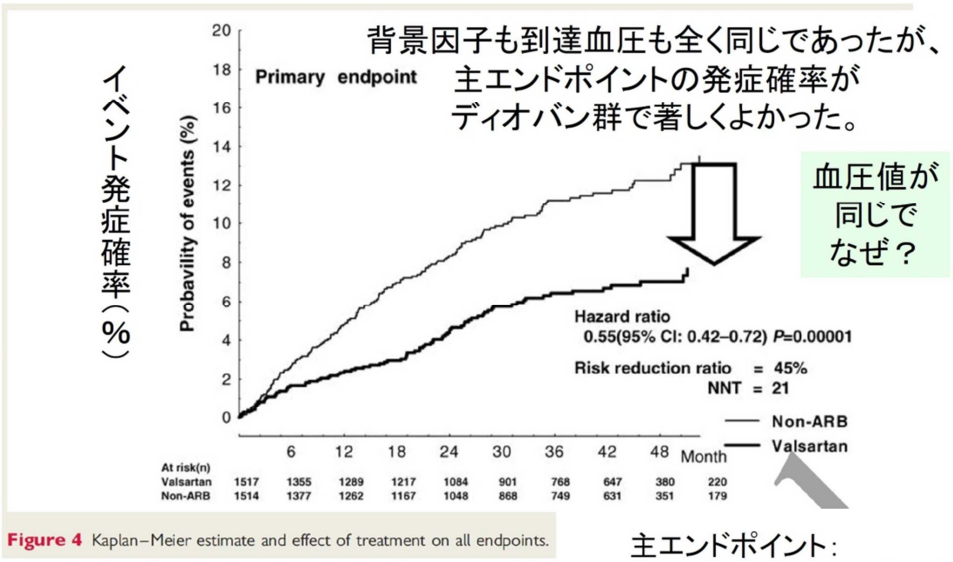


Figure 4 Kaplan–Meier estimate and effect of treatment on all endpoints.

主エンドポイント：
新発生の心血管疾患と脳血管疾患
＝心筋梗塞と脳卒中発症

Evaluation of outcomes

New onset and/or worsening of cardio- and cerebro-vascular events were assessed as the primary endpoints. They are the following

2-5. 研究者がデータ改ざんを認め謝罪

読賣新聞

高血圧薬 論文データ改ざん

製薬元社員関与か

「脳卒中に効果」偽る

京都府立医大

臨床研究 信頼揺る

2-6. 高血圧 2019 ガイドラインの根拠となった 19 論文中の 1 つ Wei 論文

ORIGINAL PAPER

Effects of Intensive Antihypertensive Treatment on Chinese Hypertensive Patients Older Than 70 Years

Yong Wei, PhD;[1] Zhimin Jin, MD;[1] Guoying Shen, MD;[1] Xiaowei Zhao, MD;[1] Wanhua Yang, MD;[1] Ye Zhong, MD;[1] Jiguang Wang, PhD[2]

From the Department of Cardiology, Songjiang Branch to Shanghai First People's Hospital, Shanghai Jiaotong University, Shanghai, China;[1] and Centre for Epidemiological Studies and Clinical Trials, Rujin Hospital, Shanghai Institute of Hypertension, Shanghai Jiao Tong University, Shanghai, China[2]

This study was performed to investigate whether intensive antihypertensive treatment with achieved blood pressure (BP) ≤140/90 mm Hg, as compared with standard treatment with achieved BP ≤150/90 mm Hg, could further improve cardiovascular outcomes in Chinese hypertensive patients older than 70 years. A total of 724 participants were randomly assigned to intensive or standard antihypertensive treatment. After a mean follow-up of 4 years, the mean achieved BP was 135.7/76.2 mm Hg in the intensive treatment group and 149.7/82.1 mm Hg in the standard treatment group. The visit-to-visit variability in systolic BP and diastolic BP was lower in the intensive group than that in the standard group. Intensive antihypertensive treatment, compared with the standard treatment, decreased total and cardiovascular mortality by 41.7% and 50.3%, respectively, and reduced fatal/nonfatal stroke by 42.0% and heart failure death by 62.7%. Cox regression analysis indicated that the mean systolic BP (*P*=.020; 95% confidence interval, 1.006–1.069) and the standard deviation of systolic BP (*P*=.033; 95% confidence interval, 1.006–1.151) were risk factors for cardiovascular endpoint events. Intensive antihypertensive treatment with achieved 136/76 mm Hg was beneficial for Chinese hypertensive patients older than 70 years. Long-term visit-to-visit variability in systolic BP was positively associated with the incidence of cardiovascular events. *J Clin Hypertens (Greenwich).* 2013;15:420–427. ©2013 Wiley Periodicals, Inc.

要約

70 歳超の中国人高血圧患者を対象として、達成血圧（BP）140/90 mmHg の厳格治療(厳格群）が、達成 BP150/90 mmHg の緩和治療（緩和群）と比較して心血管転帰をさらに改善できるかを調査するための研究を行った。合計 724 人の参加者が、厳格または緩和群にランダムに割りつけられた。平均 4 年間の追跡の後、平均達成血圧は、厳格群で 135.7/76.2 mm Hg、緩和群で 149.7/82.1 mmHg であった。収縮期血圧と拡張期血圧の来院時の変動は、緩和群よりも厳格群で低かった。厳格治療は、緩和治療に比較して、総死亡率と心血管死亡率をそれぞれ 41.7%と 50.3%減少させ、致死的/非致死的脳卒中を 42.0%、心不全死を 62.7%減少させた。COX 回帰分析で、平均収縮期血圧（P =.020; 95%信頼区間,1.006–1.069）および収縮期血圧の標準偏差(P=.033;95%信頼区間,1.006-1.151）がリスク因子であることが示された。136/76mmHg を達成した厳格治療は、70 歳以上の中国人高血圧患者に有益であった。長期追跡期間中に収縮期血圧が変動することは、心血管イベントの発生率と正の相関があった。

2-7. 対象者の背景因子の違い：全般的に厳格群に有利な傾向がある。

TABLE I. Baseline Characteristics of the Study Patients

	Intensive Group (n=363)	Standard Group (n=361)	*P* Value
Age, y	76.6±4.6	76.5±4.5	.826
Men, No. (%)	243 (66.9)	237 (65.7)	.753
Body mass index, kg/m^2	23.5±3.3	23.2±3.4	.352
Course of hypertension, y	13.1±7.5	12.9±7.1	.822
Baseline SBP, mm Hg	158.8±16.0	160.3±16.9	.201
Baseline DBP, mm Hg	83.7±9.6	84.8±9.5	.107
Serum creatinine, μmol/L	86.7±9.6	88.3±26.9	.410
Total cholesterol, mmol/L	4.59±1.10	4.45±1.11	.101
Triglyceride, mmol/L	1.62±1.01	1.48±0.98	.068
HDL-C, mmol/L	1.41±0.47	1.42±0.43	.927
LDL-C, mmol/L	2.89±0.86	2.81±0.98	.277
Uric acid, μmol/L	367.2±98.8	374.7±110.1	.339
Serum potassium, mmol/L	4.04±0.50	3.97±0.57	.077
Left ventricular mass index, g/m^2	128.7±34.8	130.3±38.4	.192
Smoking, No. (%)	93 (25.6)	87 (24.1)	.636
Diabetes mellitus, No. (%)	80 (22.0)	89 (24.7)	.406
History of stroke, No. (%)	25 (6.9)	23 (6.4)	.780

Abbreviations: DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure.

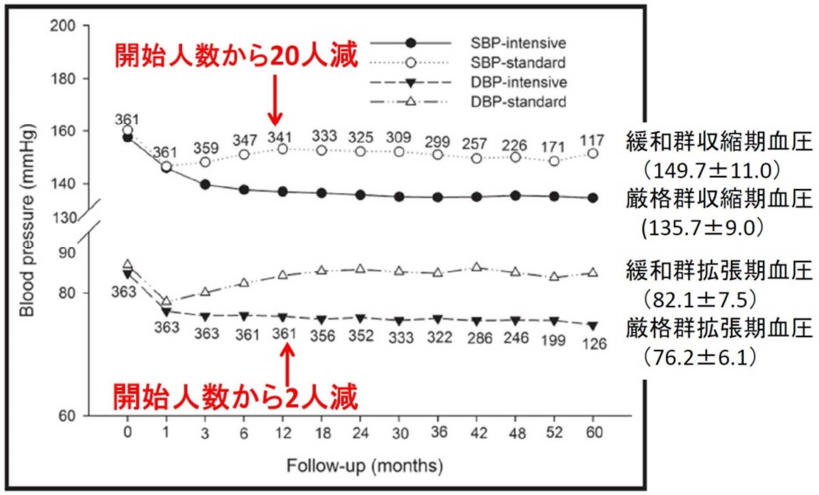
収縮期血圧：厳格群に有利
拡張期血圧：厳格群に有利

総コレステロール：厳格群に有利
中性脂肪：　　厳格群に有利

血清カリウム値：厳格群に有利
左室心筋重量係数（g/m^2）
：厳格群に有利

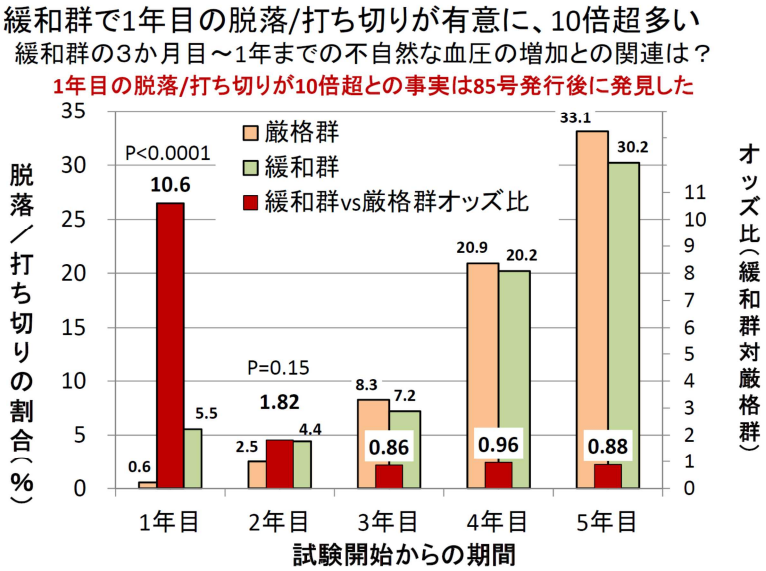
それぞれは、p>0.05 で統計学的には有意ではないが、ほぼすべての項目で厳格群に有利な背景の傾向があり、とくに重要な項目（拡張期血圧や血清カリウム値、中性脂肪、総コレステロール値などで有意に近かった。高齢者では特に、総コレステロールや LDL-コレステロール、中性脂肪も高い方が長生きである。

2-8. 厳格群と緩和群との血圧値の比較



試験開始１か月目は、収縮期血圧、拡張期血圧とも、厳格群も緩和群も同程度に血圧が低下していたが、３か月目以降は厳格群は血圧がさらに低下し、一方、緩和群は血圧が上昇しており、経過が不自然である。何らか人為的な操作がなされた可能性をうかがわせる。

2-9. Wei 試験における早期脱落/打ち切りの偏り



試験開始早期に容易に降圧した人は予後がよい可能性があり、そうした人を脱落させると、その後の平均血圧が高くなる。緩和群で予後が不良の原因と関連はないのか？　検証を要する。

2-10. Wei 論文の結果

Wei 論文における予後の比較
（厳格群　対　緩和群）

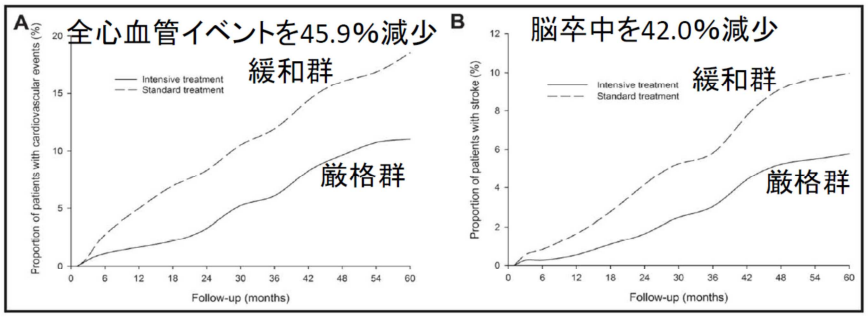


FIGURE 4. Kaplan-Meier estimates of cumulative rates of cardiovascular events (A) and stroke (B).

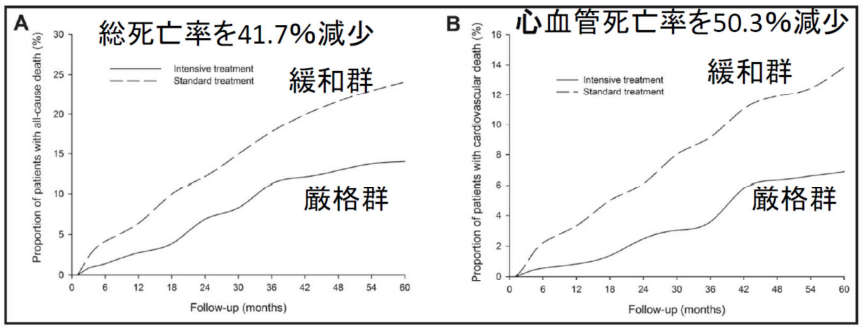


FIGURE 5. Kaplan-Meier estimates of cumulative rates of all-cause (A) and cardiovascular (B) death.

総死亡：51 人対 87 人（14.0%vs24.1%）、オッズ比 0.51（0.35-0.75、p=0.0006）
心血管死亡：25 人対 50 人（6.9%vs13.9%）、オッズ比 0.46（0.28-0.76、p=0.0021）
　わずか 360 ずつの試験で、これだけ大きな差が出るのは、撤回された Kyoto Heart Study を彷彿とさせるほどである。緩和群の予後不良は、予後良好例（容易降圧例）の早期脱落と関連はないのか？　検証を要する！！