

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) no. of patients (%)	Standard Treatment (N = 4683) no. of patients (%)	Hazard Ratio	P Value
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 hypotension 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

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Summary

Background Drugs that inhibit the renin-angiotensin-aldosterone system benefit people with hypertension or with existing cardiovascular disease. However, evidence for this effect in Asian populations is scarce. We aimed to investigate whether addition of an angiotensin receptor blocker, valsartan, to conventional cardiovascular treatment was effective in Japanese patients with cardiovascular disease.

Methods We initiated a multicentre, prospective, randomised controlled trial of 3031 Japanese patients, aged 20–79 years, (mean 65 (SD 10) years) who were undergoing conventional treatment for hypertension, coronary heart disease, heart failure, or a combination of these disorders. In addition to conventional treatment, patients were assigned either to valsartan (40–160 mg per day) or to other treatment (without angiotensin receptor blockers). Our primary endpoint was a composite of cardiovascular morbidity and mortality. Secondary endpoints were cardiovascular morbidity and mortality. The study was registered at ClinicalTrials.gov with the identifier NCT01333325.

Findings After a median follow-up of 3.1 years (range 1.0–5.0), a significant endpoint was recorded in fewer individuals given valsartan than in controls (92 vs 149 absolute events; 1000 patient years; hazard ratio 0.61, 95% CI 0.47–0.79, $p < 0.0002$). This difference was not statistically significant for the incidence of stroke and transient ischaemic attack (29 vs 48; 0.40, 0.23–0.70, $p = 0.0005$), myocardial infarction (19 vs 36; 0.53, 0.31–0.94, $p = 0.029$), or heart failure (19 vs 36; 0.53, 0.31–0.94, $p = 0.029$). Mortality was not significantly different between groups.

Interpretation The addition of valsartan to conventional treatment prevented more cardiovascular events than supplementary conventional treatment. These benefits cannot be entirely explained by a difference in blood pressure control.

Introduction Cardiovascular disease is the leading cause of mortality worldwide, and is expected to continue to increase with general ageing of the population and rapid socioeconomic changes in the developing world. Hence, cardiovascular disease is a major public health problem. Cardiovascular disease is caused by a combination of lifestyle changes, no lifestyle changes, and long-term protection. The most common cause of coronary heart disease and heart failure in Japan, and cerebrovascular disease is more prevalent in the Japanese population than in western societies. Angiotensin II has a well documented role in the pathogenesis of hypertension.

Direct implementation of available evidence into clinical practice in Japan might not be warranted by the available data, since responses to drug intervention and its clinical consequences might differ between ethnic groups. Clinical trials of angiotensin receptor blockers on end-organ damage in Japanese patients show cardiovascular benefits, but because of shortcomings such as small sample sizes and observational data, these results are not conclusive and cannot be directly translated into clinical outcomes.^{1–3} Thus, further large-scale Japanese clinical trials are needed.

We aimed to implement a large-scale clinical trial to

Jikei Heart Study

acknowledgments

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Statistics analysis organisation

Statistical epidemiology, Osaka City University Graduate School of Medicine, Nobuo Iwatahashi.

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

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See page 2427 for the complete text of this article online.

Kyoto Heart Study

Aims The objective was to assess the add-on effect of valsartan on top of the conventional treatment for high-risk hypertension in terms of the morbidity and mortality.

Methods and results The KYOTO HEART Study was of a multicentre, Prospective Randomised Open-Label Blinded Endpoint (PROBE) design, and the primary endpoint was a composite of fatal and non-fatal cardiovascular events (clinicaltrials.gov NCT00149227). A total of 3031 Japanese patients (43% female, mean 66 years) with uncontrolled hypertension were randomised to either valsartan add-on or non-ARB treatment. Median follow-up period was 3.1 years. In both groups, blood pressure at baseline was 157/88 and 133/76 mmHg at the end of study. Compared with non-ARB arm, valsartan add-on arm had fewer primary endpoints (92 vs. 149; HR 0.61, 95% CI 0.47–0.72, $P < 0.0001$).

Conclusion Valsartan add-on treatment to improve blood pressure control prevented more cardiovascular events than conventional non-ARB treatment in high-risk hypertensive patients in Japan. These benefits cannot be entirely explained by a difference in blood pressure control.

Keywords High-risk hypertension • Angiotensin receptor blockers • Cardiovascular mortality-morbidity • Valsartan

Introduction

Cardiovascular disease is the leading cause of mortality worldwide.¹ Hypertension is the most common cause of coronary heart disease and heart failure in Japan, however, cerebrovascular disease is still more prevalent in Japan than in Western societies.² The percentage of cerebral bleeding is two or three times greater than in white people, and cerebral infarction is mostly caused by lacunar-type ischaemic stroke due to hypertensive small vessel disease.³

The renin-angiotensin system (RAS) plays a major role in the homeostasis of blood pressure, electrolytes, and fluid balance.⁴ However, chronic activation of RAS contributes to the development of hypertension and cardiovascular organ damage.⁵ Numerous trials have investigated the benefits of ACEI, e.g. The Heart Outcomes Prevention Evaluation (HOPE) Study reported that

ACE inhibitors significantly reduced mortality, myocardial infarction, and stroke in high-risk patients.⁶ Another important study, in the case with ARB, was the Losartan Intervention For Endpoint (LIFE) reduction in hypertension study, where losartan-based therapy prevented more cardiovascular morbidity and death, in particular stroke, than atenolol-based regimen despite similar blood pressure control.⁷ There are now numerous studies showing beneficial effects of RAS blockers on cardiovascular outcomes, in particular with ARBs, in various stages of the CV continuum.⁸ However, these studies have included a maximum a few percent of Asian patients in general and very few Japanese in particular.

Cardiovascular disease incidence in Japan differs from those in Western countries. CVD mortality is one-third of that in the USA, and cerebrovascular disease mortality is ~1.5 times higher than in the USA.⁹ The dietary habits in Japan differ from

Funding

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Statistical analysis organization

Katsumi Yagi, Louis Pasteur Center for Medical Research, Japan.

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

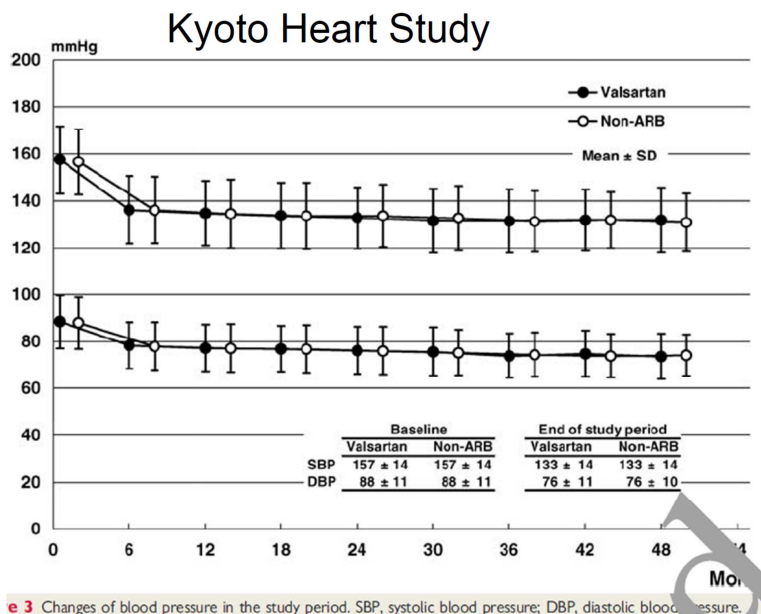
Table 1 Baseline characteristics

	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)

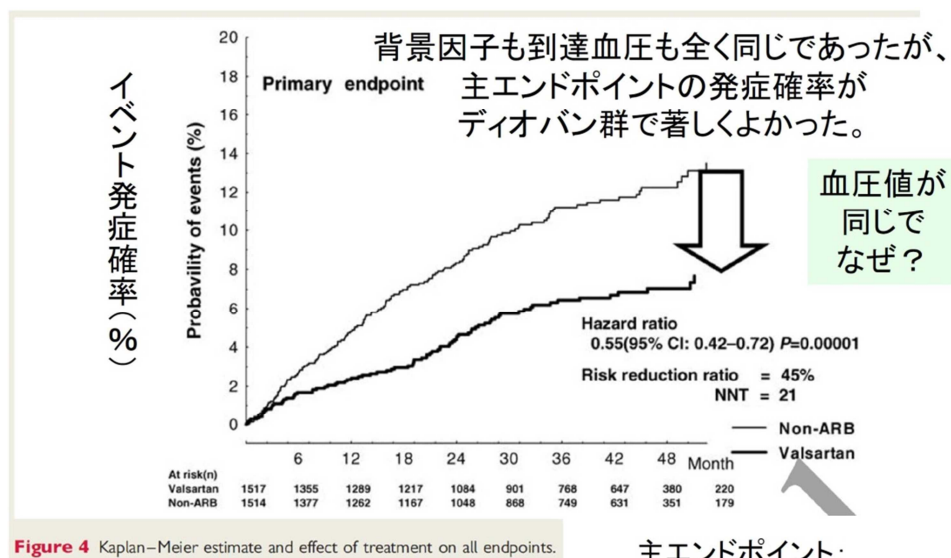
背景因子が
あまりにも
同じ

SDまで
同じ

2-3. 達成された血圧も両群で一致



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？



Evaluation of outcomes

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

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

2-5. 研究者がデータ改ざんを認め謝罪



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

ORIGINAL PAPER

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

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This study was performed to investigate whether intensive antihypertensive treatment with achieved blood pressure (BP) $\leq 140/90$ mm Hg, as compared with standard treatment with achieved BP $\leq 150/90$ 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、致死性/非致死性脳卒中を 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。

	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.

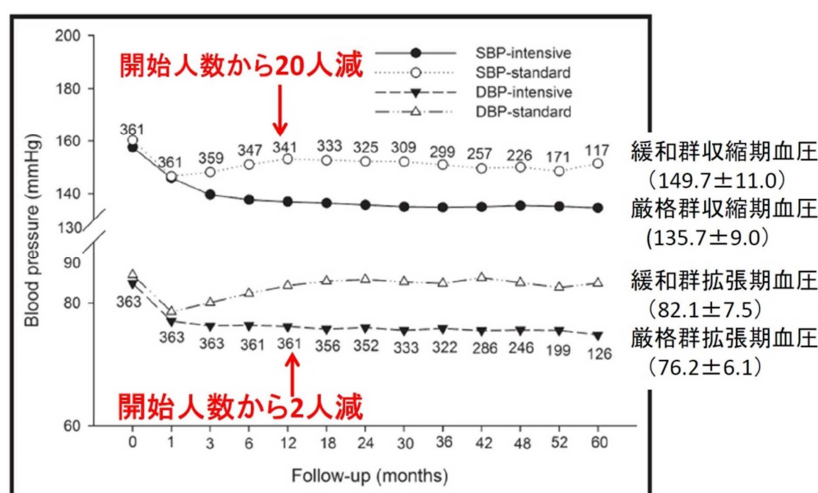
収縮期血圧：厳格群に有利
拡張期血圧：厳格群に有利

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/m²)：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。

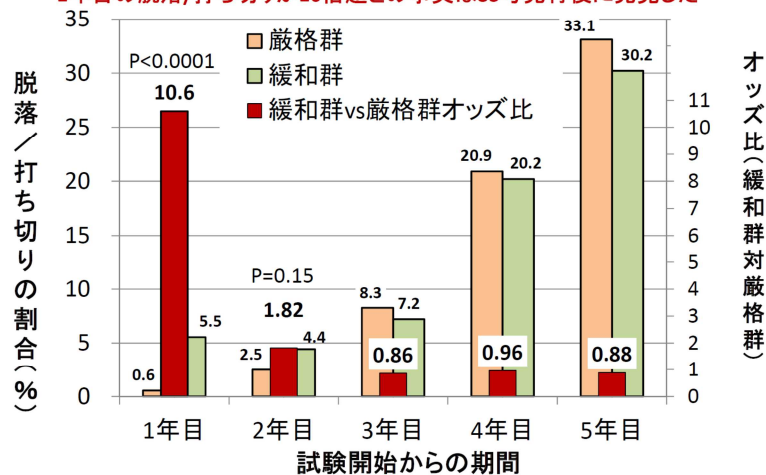
2-8. 厳格群と緩和群との血圧値の比較



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

緩和群で1年目の脱落/打ち切りが有意に、10倍超多い
 緩和群の3か月目～1年までの不自然な血圧の増加との関連は？
 1年目の脱落/打ち切りが10倍超との事実は85号発行後に発見した



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)

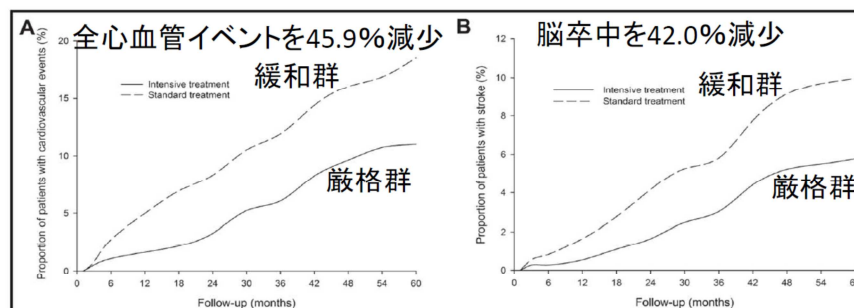


FIGURE 4. Kaplan-Meier estimates of cumulative rates of cardiovascular events (A) and stroke (B).

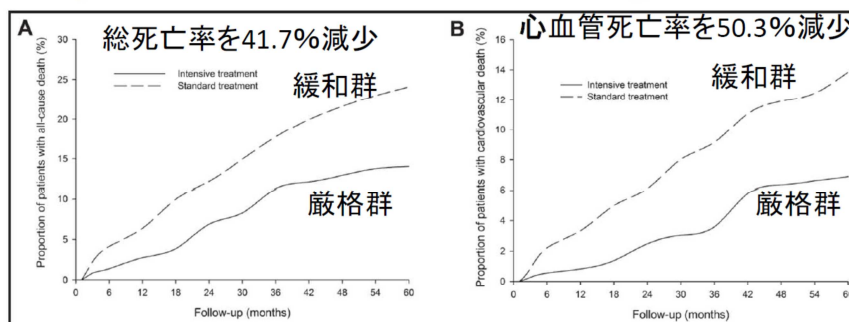


FIGURE 5. Kaplan-Meier estimates of cumulative rates of all-cause (A) and cardiovascular (B) death.

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！！