MED CHECK

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Problems in Selection of Members for Guidelines

Hypertension Guidelines Part 1, Part 2

Diovan Scandal

High Risk of Death from Tamiflu and Xofluza

CONTENTS （December 2019, Vol. 5, No. 15）

MED CHECK

Editorial

The Japanese Hypertension Guidelines 2019: Problem in Selection of Members

Translated from the Editorial in Med Check (in Japanese) Sep 2019 ; 19 (99)

Guidelines are recognized as highly reliable sources of medical information. They not only affect the prescribing behaviour of many doctors, but also are used as good evidence in medical litigation.

It would be a suicidal act to choose persons who would reduce its credibility as a committee member.

Two of the reviewers of the Guidelines for the Management of Hypertension 2019 by the Japanese Society of Hypertension (2019 GL) are the authors of the papers among 12 retracted valsaltan scandal papers which were revealed to have fabricated data **[1-4]**. This alone reduces the reliability of this guidelines significantly. Furthermore, it indicates that the Japanese Society of Hypertension, the parent body of this guidelines, did not learn any lessons from the valsaltan scandals.

In addition, there is a problem in the selection of committee members of the 2019 GL in terms of conflict of interest.

There is a database called Money Database (http://db.wasedachronicle.org/) jointly operated by Waseda Chronicle and Medical Governance Research Institute. This database is a tool that allows you to see how much money each pharmaceutical company has provided to individual doctors in Japan. Only the data of the year 2016 are available as of now.

Using this database, we investigated the amount of money paid by pharmaceutical companies in 2016 to the six board members of the 2019 GL. As a result, it was found that each of them has received 3,080,000 yen (860,000 to 6.1 million) or 28,000 US dollars (7,900 to 56,000 US dollars) from an average of 10.8 companies (5 to 17 companies) in the year of 2016 only. Can we expect these board members to make a fair decision regarding hypertension management or medication? Since the treatment descriptions in the hypertension guidelines are dominated by drug therapy, recommendations regarding the therapy should be made only by members with no or minimal funding from pharmaceutical companies.

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The 2019 annual theme: Criticism on treatment guidelines series (11) Part 1

The Scientific Evidence for the Hypertension Guidelines 2019 is Poor

The target blood pressure below 130/80 is dangerous

Synopsis from Med Check in Japanese September 2019 ;19 (85) : 104-109.

Med Check Editorial Team

Summary

- The Japanese Society of Hypertension changed the target blood pressure to less than 140/90 in the 2014 Guidelines (2014 GL) revision, assuming that the old target of less than 130/85, which had been used since 2000, was not based on evidence. However, in the guideline revised in April 2019 (2019 GL), it was lowered again to less than 130/80.
- The 2019 GL is based on the results from a meta-analysis of 19 randomized controlled trials (RCTs) comparing the intensive antihypertensive group (intensive group) and the milder antihypertensive group (milder group). Although the results indicated significant reduction in cardiovascular morbidity and mortality, there was no significant difference in total mortality.
- All studies included in the meta-analysis are open trials in which both investigators and participants know which group they were assigned to. Even if the outcomes are assessed blindly by PROBE method, it has fundamental limitations in ruling out bias.
- Among the 19 studies, many of them had favourable baseline characteristics for the intensive group, and there was a serious contradiction in the results of SPRINT, a pivotal study for the revision of 2019 GL.

Conclusion: The 2019 guidelines on hypertension are not based on scientific evidence. Do not follow the 2019 GL.

Keywords:

hypertension, guidelines, target blood pressure level, 2019 GL, SPRINT, SPS3

Introduction

In the second article (No.76) **[1]** of the Treatment Guidelines Criticism Series, we presented that general health check-up would find minor illnesses leading to unnecessary medical interventions which would conversely shorten life span especially of the elderly.

In the third article (No.77) **[2]** of the series, we showed that one out of every 3 to 4 adults and one out of two in the elderly takes anti-hypertensive drugs, due to the prevalence of general health check-up and hypertension guidelines 2000 that recommended drug therapy with a target of blood pressure below 130/85 mmHg (mmHg is omitted thereafter).

The Japanese Hypertension Society revised the 2014 guidelines (2014 GL) **[3]**. They stated that there was no evidence for the blood pressure target of less than 130/85, which had been used since 2000. They changed the target blood pressure to less than 140/90.

However, in the guidelines revised in April 2019 (2019GL) **[4]**, the target blood pressure was lowered to less than 130/80. What is the evidence for this revision?

The reason behind 2014 revision

In the 2014 GL, authors recognized that the target blood pressure below 130/85 in hypertension guidelines from 2000 to 2009 had no scientific evidence and changed the target to less than 140/90. The reason is as follows:

"The target blood pressure of less than 130/85, which has been set since 2000, is the same as the target recommended by the 1999 WHO guidelines. However, this target level is based on the results of the HOT study. In this study, three groups with different target diastolic blood pressure were compared: 90 mmHg or lower, 85 mmHg or lower and 80 mmHg or lower. The target blood pressure was set based on the findings that there was no increase in cardiovascular risk in the lowest blood pressure target group, although no significant difference was observed in cardiovascular prognosis among 3 groups."

The authors of the 2014 GL explained "There was a gap between the initiation criteria for treatment of hypertension and the blood pressure goal" and "We found that the results of intervention trials that supported target blood pressure lower than 140/90 mmHg were poor, so we set the antihypertensive goal at less than 140/90 mmHg. "

In the HOT study [5], which was the pivotal evidence for targeting "less than 130/85", achieved diastolic blood pressure 81 mmHg in the lowest blood pressure group, but the systolic blood pressure was barely less than 140 (139.7) **[6]**. Even so, the combined outcome including myocardial infarction, stroke and death did not significantly decrease, although only some tendency to decrease was observed. Moreover, all-cause mortality rate was 11% higher in the lowest target group than in the highest ($p = 0.32$) **[6]**. Again, the decrease in systolic blood pressure was only barely below 140, and the result did not justify lowering blood pressure to less than 130.

No difference in total mortality in the 2019 GL analysis

Japanese 2019 GL recommends to lower blood pressure to below 130/80, following the guidelines of US ACC/AHA **[7]** and European ESC/ESH **[8]**. The recommendation of the Japanese 2019 GL **[4]** is based on a meta-analysis **[9]** of 19 randomized controlled trials (RCT), including SPRINT study **[10]**. All these RCTs are comparison between the intensive antihypertensive group (intensive group) and the mild antihypertensive group (mild group) and are not placebo-controlled trials.

As a result, the intensive group had significantly fewer cardiovascular events (meta-analysis of 14 trials) and significantly fewer strokes (meta-analysis of 13 trials) than the mild group. However, it was also reported that there was no difference in all-cause mortality **[4,9]**.

If no improvement in total mortality, lowering blood pressure has no value

Med Check is a member of the International Society of Drug Bulletins (ISDB). ISDB and we believe that living long and healthy is an important goal when considering prevention of chronic illnesses **[11]**. This is because even if myocardial infarction or stroke, which is strongly related to high blood pressure, is reduced, there is no meaning if death from other diseases increases. In fact, ACE inhibitors reduce total mortality, but angiotensin receptor blocker (ARB) does not. The result of a meta-analysis has shown that ARB rather increases cancer [**12**], sepsis and death from sepsis **[13]**.

The 2019 GL **[4]** reported that according to the meta-analysis results of 19 studies, intensively lowering blood pressure did not reduce all-cause mortality.

If the blood pressure was very high, such as 115 or higher for diastolic blood pressure, hypotensive drug treatment reduced all-cause mortality compared to placebo **[14]**. However, the effect of hypotensive treatment on the people with mild high blood pressure (140-159/90-99) has been denied by the results of the Cochrane's systematic review and meta-analysis of placebo-controlled RCTs **[15]**. Treatment for 4 to 5 years with antihypertensive drugs as compared to placebo did not reduce total mortality (RR 0.85, 95% CI 0.63, 1.15). Treatment with antihypertensive drugs as compared to placebo did not reduce coronary heart disease (RR 1.12, 95% CI 0.80, 1.57), stroke (RR 0.51, 95% CI 0.24, 1.08), or total cardiovascular events (RR 0.97, 95% CI 0.72, 1.32). Withdrawals due to adverse effects were increased by drug therapy (RR 4.80, 95%CI 4.14, 5.57), absolute risk increase (ARI) 9%.

In their systematic review and meta-analysis using individual patients data of randomized controlled trials comparing lower targets for systolic/diastolic blood

pressure (<135/85 mmHg) and standard targets (<140-160 / 90-100 mmHg), Saiz et al [16] found no change in total mortality (risk ratio (RR) 1.06, 95%CI: 0.91-1.23) or cardiovascular mortality (RR 1.03, 95% CI: 0.82-1.29; moderate-quality evidence).

The trials, basis of 2019 GL, are not double blinded

Since all 19 RCTs are comparison of the intensive and mild antihypertensive treatment groups and it is impossible to conceal the allocation, not only the investigators, but also the subjects knew which group they were assigned to.

In such a non-blinded open trial, patients are at risk for being treated unfavourably or favourably by the investigator who know the allocation. For example, they might be removed from the trial (withdrawn) if serious events occurred in the participants assigned to the intensive group, or outcome events might be assessed favourably by the investigator.

In order to make fairer judgment, there is PROBE (prospective randomised open blinded end-point) method in which the result is judged by investigators who do not know the allocation. Of the 19 trials, PROBE method was used in 10 trials, but this method has fundamental flaws. Participants with unfavourable events or end-points in the intervention group can be withdrawn before the blinded end-point assessment. A typical example of such problem can be found in the Japanese MEGA study on cholesterol-lowering agents (pravastatin or brand name Mevalotin) [17]. Although the study reported that the all-cause mortality rate in the Mevalotin group showed tendency to decrease, the overall survival rate was significantly lower in the Mevalotin group than in the control group. This paradoxical results occurred because the Mevalotin group had significantly more withdrawals than non-Mevalotin control group [18].

Most subjects had complications

Out of 19 RCTs which 2019 GL is based on, 5 trials involved diabetic patients. The other 5 were for patients with renal disease, 2 trials were for hypertension patients with history of mild cerebral infarction (lacuna infarction) or those with cardiovascular diseases, and 3 trials were for elderly patients. There were only 4 trials involving people without specific illnesses or non-elderly adults.

Only 10 trials out of 14 trials achieved systolic blood pressure below 130

There were 14 trials in which the target systolic and diastolic blood pressure levels were below 130 and 80, respectively. (Among them, 5 trials aimed at lowering systolic blood pressure below 120 and diastolic blood pressure below 75.) In only 10 trials, these goals were actually achieved.

Trials which achieved less than 130/80 were full of flaws

One of the major problems is that in 7 trials out of 19 trials (almost 40% of the trials), the baseline characteristics may be more favourable for the intensive group than for the mild group, especially differences are remarkable for the important risk factors for total death or cardiovascular diseases.

In particular, in 5 trials out of the 10 trials in which the target of less than 130 was actually achieved, significant bias or tendency for bias was observed in favour of baseline characteristics of intensive group.

For example, in the SPS3 trial [19], which is considered as an important trial as SPRINT [10], baseline systolic pressures were 142 vs. 144 and diastolic pressures were 78 vs.79. These differences look minimal, but are not only statistically significant (0.004 and 0.009 respectively) but also may affect the outcomes favourably for intensive group (**Note**). Moreover, the paper does not mention if the differences are significant or not. In addition, the proportions of male patients were 61% vs. 65% (p = 0.0008). This difference was also favourable for the intensive group.

However, the primary outcome was not significantly different. Only cerebral hemorrhage was significantly decreased (HR = 0.37: 0.15-0.95, p = 0.03), but total death rather increased (intensive group 106/1501 vs. 101/1519, HR = 1.03: 0.79-1.35) [19].

Note: Statistical significance can be tested based on the number of subjects (1501 vs. 1519 persons), average blood pressure, and standard deviation (19 vs. 19). Difference in proportions of sex was tested by chi-square statistics.

Contradictions among SPRINT trial results

Although, we did not find clear bias among baseline characteristics in the SPRINT trial [10], which is considered as the pivotal evidence, we found major

contradictions in the results.

In the serious adverse event section, acute renal injury or acute renal failure listed in the medical record occurred overwhelmingly more frequently in the intensive group (193/4678) as compared with the mild group (117/4683) (p = 0.00001) (Figure 1).

On the other hand in the outcome section, no difference (composite renal outcome and ≧ 50 % reduction in e-GFR) or rather less renal impairment (long term dialysis) occurred in the intensive group than in the standard group in patients with chronic kidney diseases (CKD) at baseline. These findings in the outcome also contradict with the fact that 3.5 times more renal impairment (30% decrease in e-GFR) occurred in the intensive group (3.8%) than in the standard group (1.1%) in patients without CKD at baseline (Figure 2).

Data independent of trial show renal injury in intensive group

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

‡ Acute kidney injury or acute renal failure were coded if the diagnosis was listed in the hospital discharge summary

A hospital discharge summary is coded independent of the clinical trial, while data for GFRs are collected for the clinical trial (‡ and underlined). Hence hospital discharge summary data may be more reliable. Intensive treatment causes 1.7times more acute kidney injury and/or renal failure (→).

Major contradictions in outcomes and between adverse events

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 m²¶	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

Renal impairment occurs more in intensive group than standard group in patients without CKD at baseline, while no difference or rather less renal impairment in intensive group in patients with CKD at baseline. It is difficult to explain the reasons for such contradicting results.

These contradictions cannot be explained by medical common sense. However, a hospital discharge summary is coded independent of the clinical trial, while data for GFRs are collected for the clinical trial.

Because data coded independent of the clinical trial may be more reliable than the data collected as the clinical trial, increase of acute renal injury or acute renal failure based on the hospital discharge summary may be more reliable. Hence we consider that the overall results of SPRINT trial indicate that intensive treatment causes more kidney injury and/or renal failure.

A Chinese report by Wei et al. **[20]** showed impossible result. It reported that after the 4-year follow-up, the number of death from cardiovascular diseases in the intensive group is about half of that in the mild group (Figure 3). A similar type of result was reported in the trials of Diovan (valsartan) **[21,22]**, which were retracted after fabrication of data came to light in Japan (see page 48 in this issue).

Observational studies show intensive lowering increase mortality.

To date, long-term cohort studies conducted in Japan have shown that total mortality rate **[23,24]** and death from cancer **[24]** are higher in people who used antihypertensive drugs as compared with those without the medication. The risk is particularly high in people whose systolic blood pressure is below 120 **[25]**.

In a recent cohort study, JACC study that followed about 28,000 people without cardiovascular disease, cancer, or renal disorder, the risk of death may be higher by 30% in antihypertensive users with lowest

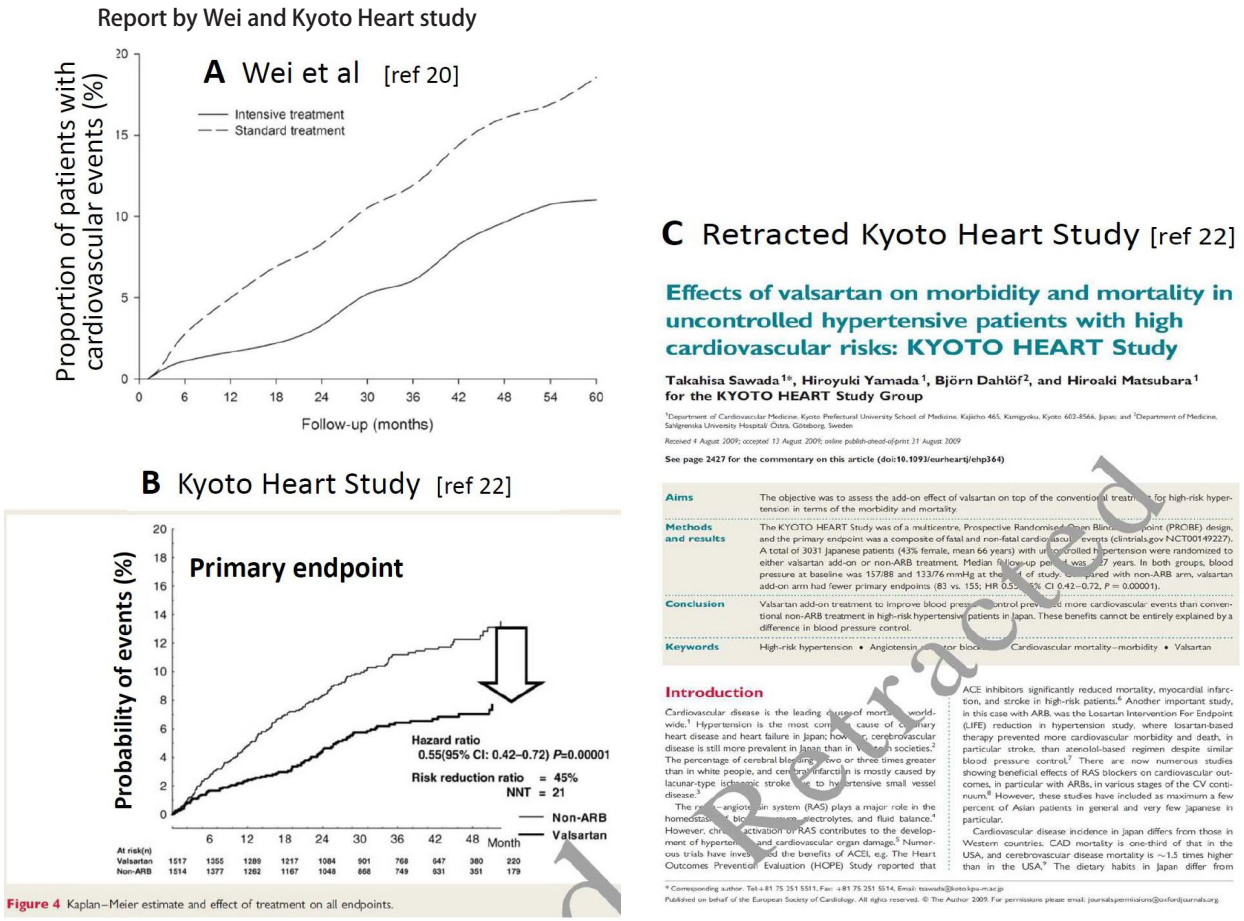


Figure 4 Kaplan–Meier estimate and effect of treatment on all endpoints.

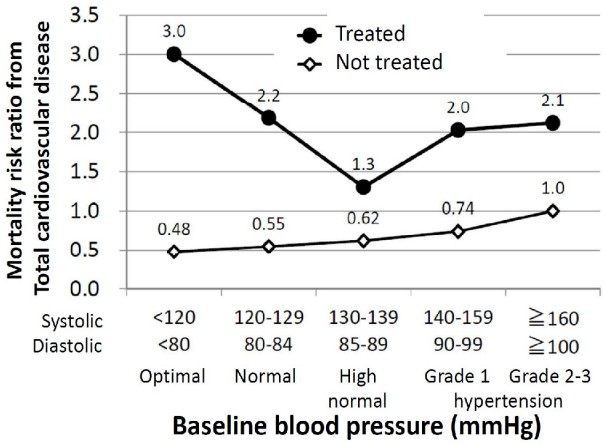
A: Intensive treatment compared with the standard treatment decreased cardiovascular (CV) mortality by 50.3% (p = 0.002) with 25 and 50 CV deaths respectively. It is extremely unnatural for a study with only 360 participants for each group to achieve such remarkable results of efficacy with high significance. However, it may be possible that such a result could be obtained if participants with good prognosis in the standard treatment group were withdrawn. The results recall that of Kyoto Heart Study [22] which was retracted due to manipulation and/or fabrication of data (**B** and **C**). Verification is required! !

risk (130-139/80-85) than in non-users with the highest blood pressure (above 160/100) **[26]**. The risk was 2.2 times and 3 times higher in antihypertensive users whose blood pressure was below 130/85 and 120/80, respectively, than in non-users whose blood pressure was above 160/100 (Figure 4).

Conclusion

Most of the trials which 2019 GL referred to as evidence for the target level of below 130/80 are flawed and unreliable. Therefore, the guidelines are not credible. It is dangerous to manage hypertension based on the guidelines. Do not follow them.

Comparison of mortality risk ratio by baseline blood pressure: treated vs not treated with anti-hypertensive agents



Reconstructed by MedCheck team from the data in ref [26].
The risks of death from cardiovascular disease in the untreated groups were calculated based on the hazard ratio adjusted for 7 risk factors including sex and age compared with that of 130-139/85-89 (reference) group by recalculating when hazard ratio of the highest blood pressure group is 1.0. The risks of the treated groups were calculated based on the hazard ratio adjusted for 7 risk factors including sex and age compared with that of reference group by multiplying the ratio (treated/untreated) of reference groups' crude mortality from cardiovascular disease.

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The 2019 annual theme: Criticism on treatment guidelines series (11) Part 2

NICE (UK) Recommends Treatment if Blood Pressure is 160/100 or over

The most appropriate guidelines revised in August, 2019

Synopsis from Med Check in Japanese November 2019 ; 19 (86):128-130

Med Check Editorial Team

Summary

●In the previous issue, we introduced that the guidelines in U.S. and Europe were revised to lower the target blood pressure below 130 mmHg (hereafter, mmHg is omitted). These guidelines were all created by medical associations which share the mutual interests with pharmaceutical companies.

●There are other guidelines for management of hypertension in the U.S. and Europe. As of now, the most appropriate standard is the guidance of National Institute for Health and Care Excellence (NICE) in the U.K., followed by the one created by the U.S. Eighth Joint National Committee (JNC-8). Unlike most medical associations, these two organizations have minimal conflict of interests with the industry.

●NICE recommends the use of antihypertensive drugs only when blood pressure remains 160/100 or over after lifestyle advises. Its basic standard is to lower blood pressure below 160/100. This is consistent with the results of two Cochrane reviews. The U.S. JNC-8 targets below 150/90 for people aged 60 years and older. For people aged under 60 years or those with diabetes and chronic kidney disorders, it basically recommends the target blood pressure below 140/90.

●The latest guidance on management of hypertension by NICE was revised on August 28th, 2019. Therefore, it has taken the result of SPRINT, which was published in 2015, into account as well.

Conclusion: No antihypertensive drug treatment is needed unless blood pressure is over 160/100.

Keywords:

hypertension, guideline, target blood pressure, NICE, JNC-8, Cochrane review, conflict of interest

Introduction

In our latest article [1] we criticised the Japanese guidelines for management of hypertension revised in 2019 (2019 GL) [2]. We explained that the 2019 GL followed the hypertension guidelines created by some medical associations in the U.S. [3] and Europe [4] which aim at lowering the target blood pressure below 130 mmHg in response to the result of SPRINT [5]. However, there are other guidelines which are more reliable than such strict guidelines [3,4].

As we referred in the latest article [1], one of the Cochrane's systematic reviews and meta-analysis of placebo-controlled RCTs [6] reported that the treatment by antihypertensive drugs in mild hypertension (140-150/90-99) does not reduce total death and cardiovascular diseases. Moreover it increases discontinuation of the treatment due to adverse events by almost 5 times as compared with placebo.

Another Cochrane review [7], which analyzed individual patient data from a study comparing intensive and mild lowering groups, showed no decrease in total death and cardiovascular diseases.

The hypertension guideline of NICE **[8,9]** is consistent with the findings of these reviews **[6,7]**.

The 8th guideline of the Joint National Committee **[10,11]** led by the U.S. National Institute of Health (NIH) also proposes a relatively appropriate standard. This article will examine them in detail.

U.K. NICE: Classification of hypertension, risk factors and target blood pressure

The latest guidance of NICE was published in 2011 **[8]**, and was renewed on August 28th, 2019 while no change was made in the main part.

Its target for antihypertensive treatment follows the principle of the treatment before 1999, which is to use antihypertensive drugs only when the blood pressure remains higher than 160/100 in the absence of particular risk factor after appropriate non-pharmacological interventions or lifestyle advises.

NICE classifies hypertension as follows

Stage 1 (mild hypertension): clinic blood pressure is 140/90 or higher and subsequent ambulatory blood pressure monitoring (ABPM) daytime average or home blood pressure monitoring (HBPM) average blood pressure is 135/85 or higher.

Stage 2 (moderate hypertension): clinic blood pressure is 160/100 or higher and subsequent ABPM daytime average or HBPM average blood pressure is 150/95 or higher.

Stage 3 (severe hypertension): clinic systolic blood pressure is 180 or higher or clinic diastolic blood pressure is 110 or higher.

The following organ damages are listed for determining whether to start antihypertensive medication or not.

Target Organs: damage to organs such as the heart, brain, kidneys and eyes. Examples are left ventricular hypertrophy, chronic kidney disease, hypertensive retinopathy, and increased urine albumin:creatinine ratio.

No advantage in using antihypertensives in mild hypertension

The NICE guidance recommends to start antihypertensive drug treatment with adults aged under 80 with mild hypertension (**Stage 1**) who has damage in the target organ (risk factor for cardiovascular disease). However, in those with mild hypertension who has no risk factor, there is no evidence to prove benefit of antihypertensive drug treatment.

The Cochrane review **[6]** evaluated 4 randomized controlled trials for antihypertensive drug treatment in patients with mild hypertension (systolic BP 140-159 or diastolic BP 90-99) who have no established cardiovascular disease at baseline. After 4-5 years of the treatment, comparison with placebo showed no significant difference in each endpoint: overall mortality rate (n=8912, RR = 0.85, 95%CI:0.63, 1.15.) , coronary artery disease（n = 7080, RR = 1.12, 95%CI:0.80, 1.57）, stroke (RR = 0.51, 95%CI:0.24, 1.08) and total cardiovascular event (RR = 0.97（95%CI: 0.72, 1.32）.

The data on those withdrawals due to adverse events were unknown in a subgroup of patients with mild hypertension. However, data are available for patients with mild and moderate hypertension combined (n = 17,354), and more withdrawals occurred in the treatment group (RR = 4.80, 95%CI:4.14,5.57, absolute risk increased by 8.9% over 5 years: **Note**) .

The conclusion of the Cochrane review is consistent with that of NICE CG127 which states that no evidence support the benefit of antihypertensive drug treatment in patients with mild hypertension who has no risk factor for cardiovascular disease.

> **Note:** The increase of absolute risk by 8.9% indicates that 1 out of 11 patients who used antihypertensive medication discontinued the treatment and dropped out due to adverse events.

The U.S. JNC-8 was created by committee members with no conflict of interest

The committee members of JNC-8 consist of 17 experts who specialize in hypertension, primary care including geriatrics, cardiology, nephrology, nursing, pharmacology, clinical trials, evidence-based medicine, epidemiology, informatics and the development and implementation of clinical guidelines in systems of care who were selected from more than 400 nominees. Unlike JNC-7 (2003), all the members are obliged to disclose their conflict of interest with pharmaceutical companies which are involved in development and marketing of

antihypertensive drugs. Among the 17 members, 4 (24%) had conflict of interest. Those with conflicts were allowed to participate in discussions as long as they declared their relationships, but they recused themselves from voting on evidence statements and recommendations relevant to their relationships or conflicts **[10]**.

Bakris told "JNC-8 is not just JNC-7 “Retooled” or “Repainted”, but Imploded and Reconstructed" **[11]**.

The main basis for NICE was the double blinded randomized placebo controlled trials and the meta-analysis of them. In addition, JNC-8 also referred to unblinded RCTs such as HOT which compared groups with different target blood pressure levels.

Target 150/90 for people aged 60 years and older

JNC-8 recommends as follows:

1) In the general population aged 60 years or older, initiate pharmacologic treatment to lower blood pressure (BP) at systolic blood pressure (SBP) of 150 mmHg or higher or diastolic blood pressure (DBP) of 90mmHg or higher and treat to a goal SBP lower than 150mmHg and goal DBP lower than 90mmHg. Strong Recommendation (Grade A).

2) Evidence for lowering diastolic blood pressure below 90 in general population aged 30-59 is available.

3) However, there is no sufficient evidence regarding the target systolic blood pressure for general population aged under 60 years or the target diastolic blood pressure for those aged under 30 years. Therefore, for those aged under 60 years, the committee recommends to maintain blood pressure below 140/90 (Expert opinion).

4) Likewise, the committee recommends below 140/90 for patients with diabetes or chronic kidney disease (Expert opinion).

American College of Physicians supports JNC-8

American College of Cardiology (ACC) and American Heart Association (AHA), which share mutual interest with pharmaceutical companies, do not support JNC-8 and have created their own guidelines, recommending to lower blood pressure below 130/80 **[3]**.

On the other hand, American College of Physician (ACP) and American Academy of Family Physicians (AAFP) have declared their support for JNC-8, but not for ACC/AHA guideline **[12,13]**.

Conclusion

As of now, among the guidelines published by public institutions, the British NICE offers the most appropriate guidance which recommends to start antihypertensive drug treatment for blood pressure over 160/100 (Table).

The guidelines created by medical associations in Japan, U.S. and Europe, which have major conflict of interest with the industry, recommend the target blood pressure of 130/80. However, this has not scientific basis, and thus should not be followed.

Guidelines Year of publication	Conflict of Interest	elderly	no risk factor	With organ impairment
		Blood pressure for initiation of drug treatment and target		
NICE Guidance 2019	minimal	elderly	no risk factor	With organ impairment
		If ≧160/100, to <160/100	If ≧160/100, to <160/100	If ≧140/90, to <140/90
JNC-8 2014 (endorced by ACP, AAFP)	minimal	age ≧60	age <60	With organ impairment
		If ≧150/90, to <150/90	If ≧140/90, to <140/90	If ≧140/90, to <140/90
Japanese Society of Hypertension 2019	Heavy	≧75	<75	With organ impairment
		If ≧140/90, to <140/90	If ≧130/80, to <130/80	If ≧130/80, to <130/80
US ACC/AHA 2017	Heavy	≧65	10 year risk of ASCVD <10%	10 year risk of ASCVD <10%
		If ≧130/80, to <130/80	If ≧130/80, to <130/80	If ≧130/80, to <130/80
Europe ESC/ESH 2018	Heavy	age: 65～80	all general population	age ≧65, With organ impairment
		If ≧140/90, to <140/90	If ≧140/90, most should be < 130/80	If ≧130/80, to <130/80

NICE：National Institute of Health and Care Excellence,
JNC: Joint National Committee.
ACP: American College of Physician,
AAFP: American Academy of Family Physicians,
ACC: American College of Cardiology,
AHA: American Heart Association,
ESC: European Society of Cardiology,
ESH: European Society of Hypertension
10 year risk of ASCVD: 10-year risk of atherosclerotic cardio vascular diseases

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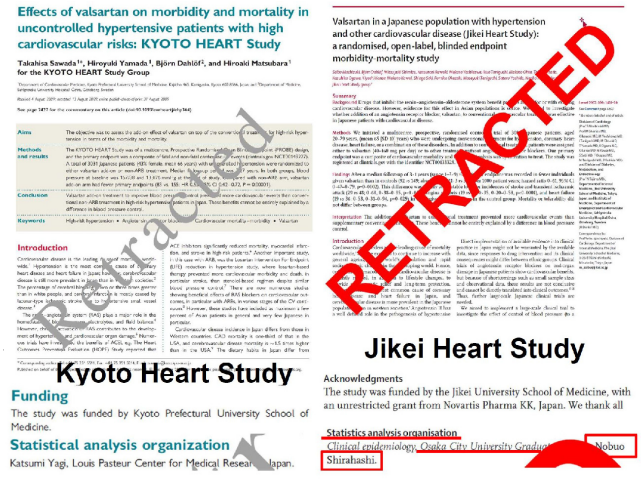
Neglect of Correcting Scientific Fraud: Ruling over Diovan Scandal

Med Check Editorial Team

On November 19, 2018, the Tokyo High Court made a ruling over a case of clinical trial involving an antihypertensive valsartan, the so-called Diovan case [1].

Diovan (generic name valsartan) is an antihypertensive agent classified as an angiotensin receptor blockage (ARB). Defendants, Nobuo Shirahashi (former Novartis Pharma employee, mentioned in the papers only as a statistician) and Novartis Pharma Co., Ltd. based in Japan, who played a key role in data manipulation and/or fabrication were acquitted [2,3]. The judgment clearly recognized that researchers from the Kyoto Prefectural University of Medicine, in addition to the above-mentioned defendants, were deeply involved in the manipulation and/or fabrication of data in a clinical trial called "Kyoto Heart Study" [4] (Figure 1-4).



Note that Mr. Shirahashi is described as an academic statistician in Jikei Heart Study.

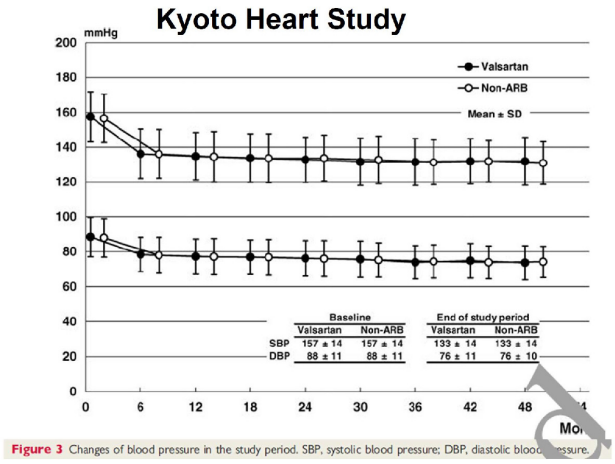


Figure 3 Changes of blood pressure in the study period. SBP, systolic blood pressure; DBP, diastolic blood pressure.

Blood pressures are exactly the same in both groups including the baseline and follow up period. Standard deviations are also exactly the same in both groups.

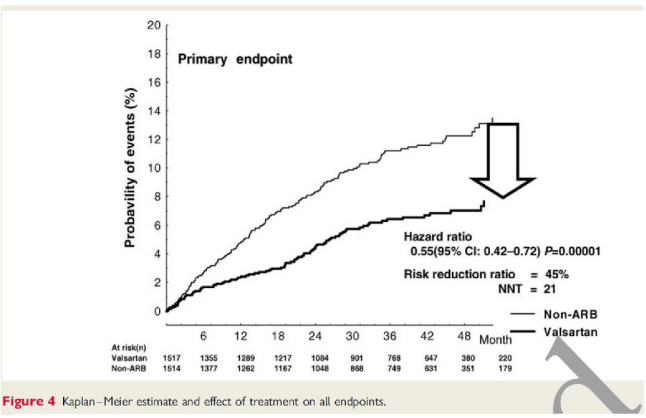


Figure 4 Kaplan–Meier estimate and effect of treatment on all endpoints.

Primary endpoint reduced nearly one half, although the baseline characteristics and the follow up blood pressures are exactly the same in both groups. Primary endpoint: mainly stroke, TIA, and angina pectoris.

However, the law at the time of 2009, when the "research paper" in question was published, did not stipulate any regulation to penalize researchers' scientific misconduct in medical research. The only legal basis is the prohibition on "false or exaggerated advertising". It is a law that prohibits advertising, describing, or disseminating false or exaggerated articles that may be misunderstood as guarantees of the efficacy and/or effectiveness of medicines.

In the judgment, "advertising" is defined by three criteria: **(1)** that it targets an unspecified large number of people, **(2)** on specific medicines, and **(3)** it is used as a means to attract customers.

The judgment included medical professionals such as doctors as customers. Based on the three criteria, the judgment concluded that the retracted articles were not "advertisement" and were not used as a means of attracting customers, because they were peer-reviewed academic papers although they included false description on a specific medicine, targeting an unspecified large number of people.

However, the fact that the articles were retracted from English peer-reviewed journals due to manipulated and/or fabricated data clearly shows that they were not scientific. Hence it should be concluded that they were merely advertisement with false statements, aiming at attracting customers. A peer-reviewed academic paper that shows efficacy and safety of a medicine has great advertising effects and influence doctors (customers for pharmaceutical companies). That's why the defendants created false documents as "academic" papers.

Defendants printed a large number of false documents as academic papers and distributed them to doctors. They used them to promote sales and prescriptions. The strategy worked well and contributed to maintaining annual sales of over 100 billion yen (nearly one billion U.S. dollars or one billion Euros) for many years. In other words, these documents are nothing but "advertising", and are exactly "false or exaggerated article" defined by the law. Therefore, even with the prohibition provision of "false or exaggerated advertisement" at that time, it was possible to make more just decision. However neither the district court nor the high court understood the actual situation, and the criminals were acquitted by a mere theory.

The subject of the trial was exclusively the Kyoto Heart Study [4] led by doctors at Kyoto Prefectural University of Medicine, but similar clinical trials were conducted at Jikei University [5], Chiba University, Shiga University of Medical Science, and Nagoya University. The data in these studies were forged and altered in the same way as those in the Kyoto Heart Study. As a result, total 12 documents were published in English peer-review journals as "academic papers", but all of them were later retracted due to the manipulated and/or fabricated data (Appendix).

If such scientific frauds are not judged as crimes, scientific misconducts by pharmaceutical companies and researchers will be out of control.

The penal provisions of the Clinical Research Law that was legislated after this scandal are extremely poor. They would not prevent scientific fraud and/or crime by pharmaceutical companies and academic researchers.

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Tamiflu: Deaths after Abnormal Behaviour among Teenagers Revisited:

Probably related to the removal of contraindications

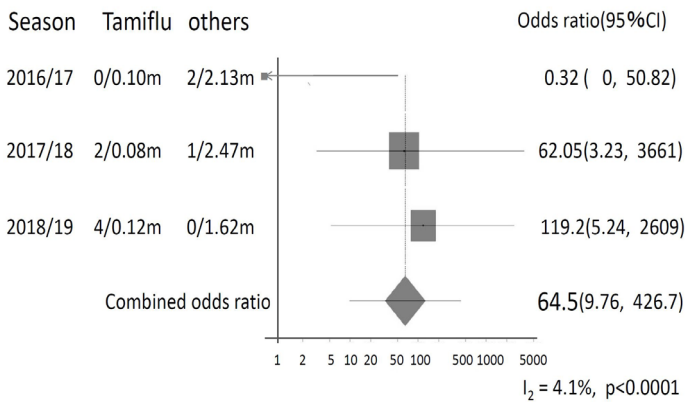
Translated from Med Check (in Japanese) Jan 2020 ; 20 (87) :12

Rokuro Hama

Keywords: oseltamivir, removal of contraindications, teenagers, abnormal behaviour, death, suicide

The Ministry of Health, Labor and Welfare (MHLW) has concluded that there is no causal relationship between Tamiflu use and abnormal behaviour **[1, 2]**, and revised the package insert in August 2018 to lift Red Box Warnings with relative contraindications of Tamiflu in children aged 10 to 19. A newspaper **[4]** reported that the MHLW's committee had reviewed 42 cases with serious abnormal behaviours such as running or jumping as adverse events during the winter season (2018/19) **[3]**.

The frequencies of serious abnormal behaviours or deaths after abnormal behaviour by kind of drug are unknown from the newspaper report. In addition, it was reported that a junior high school student died in the afternoon on December 10, 2019 after taking an anti-influenza drug for influenza. However, the name of the drug was not specified **[5]**. Isn't Tamiflu really related to abnormal behaviour? Let's examine it.



m: million prescriptions

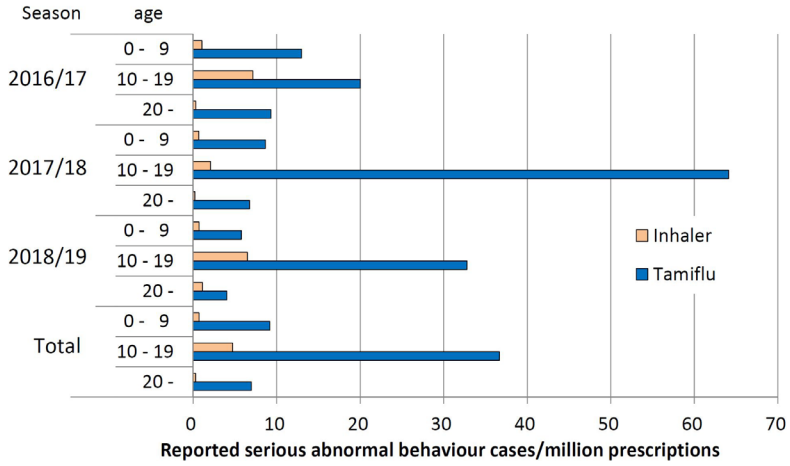
The risk of death after abnormal behaviour is 120 times higher with Tamiflu than with other drugs

According to the MHLW's data **[3]**, the numbers of anti-influenza prescriptions for children aged 10 to 19 in the 2018/19 season were 122,000 for Tamiflu, and 1.616 million for other drugs including Xofluza, Inavir, Relenza and Rapiacta. Among them, 4 fatal cases after abnormal behaviours or suicide were reported in patients prescribed with Tamiflu (1 in 30,000), while 0 in patients with other drugs. Statistically, the risk of Tamiflu is estimated to be about 120 times higher than that of other drugs (odds ratio 119.2, p <0.0001) (See 2018/19 in the Figure 1). When meta-analysis is performed for the last three years, the risk is about 65 times higher than that of other drugs (Figure 1).

Increased reports may be related to the removal of contraindication

The estimated number of prescriptions for Tamiflu for children aged 10 to 19 has remained similar in the last three seasons, at 100,000, 78,000 and 122,000, respectively. However, the number of deaths after abnormal behaviour has been increasing: 0, 2, and 4. It should be noted here that this is related to the move for lifting contraindications. .

Just before the 2017/18 season, the move rapidly became active. For example, the Japanese Society of Pediatrics published a guideline for the treatment of influenza in 2017/18, saying that it was necessary to



Proportions of reported serious abnormal behaviour cases per million prescriptions were higher among Tamiflu users than among inhaler users in all seasons and all age groups.
Inhaler antivirals: Relenza (zanamivir) and Inavir (laninamivir)

consider administration of Tamiflu by notifying the adverse event including abnormal behaviours, if the patient had respiratory diseases or milk allergy, and neither zanamivir nor laninamivir could be used. This is a sort of message, implying "Tamiflu can be prescribed for teens".

In addition, in 2018, the MHLW completely denied the causal relationship and contraindication was removed from the package insert, so the doctor was held liable even if a teenager who received prescription died after abnormal behaviour. It has become easier for doctors to report fatal cases.

Tamiflu induces 10 times more serious abnormal behaviours

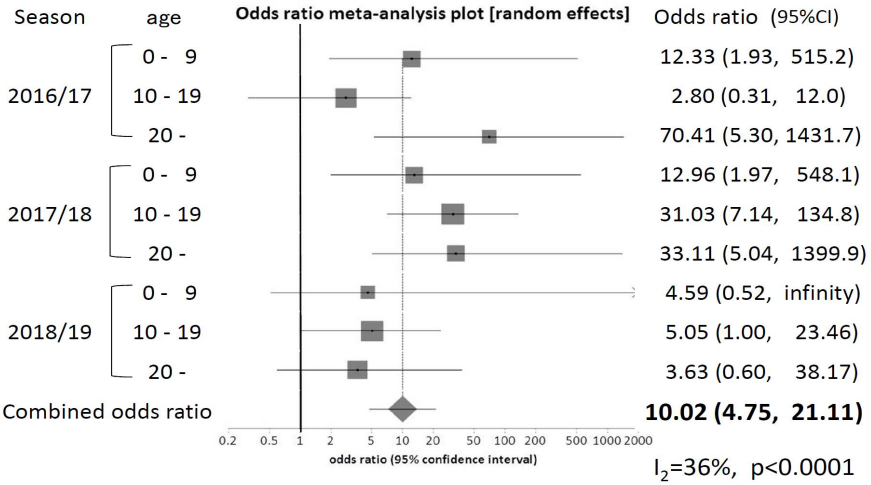
If you compare the proportion of serious abnormal behaviour reports per million prescriptions in the past three seasons by age (**0-9 years, 10-19 years , 20 years old and above**) between Tamiflu and inhalers (Relenza and Inavir), the risk of Tamiflu is always higher than that of the inhalers in all ages and all three seasons (Figure 2). Overall, the risk of Tamiflu is 10 times higher than that of the inhalers (odds ratio 10.02, p <0.0001) (Figure 3).

Epidemiological studies and animal experiments show causal relationships

As we have previously described in detail [7], Tamiflu use and abnormal behaviours or sudden deaths are firmly related based on evidence from various levels of studies including clinical case series, clinical study reports, epidemiological studies, animal toxicity studies and studies on mechanisms of action including receptor or enzyme levels.

Don't be misled by the MHLW's trick to cover up the truth. You should look at the data cautiously to avoid making wrong judgement.

References: see p54



Odds of reported serious abnormal behaviour were significantly higher among Tamiflu users than among inhaler users in 6 out of 9 strata. Combined odds ratio is 10.02 (p<0.0001).
Inhaler antivirals: Relenza (zanamivir) and Inavir (laninamivir)

High Risk of Death from Tamiflu and Xofluza

Serious toxicity necessitating suspension of its use

Translated from Med Check (in Japanese) Jan 2020 ; 20 (87) :13

Rokuro Hama

Keywords:
oseltamivir, baloxavir, sudden death, death from infection, diarrhea, melena, neuraminidase inhibition, endonuclease inhibition

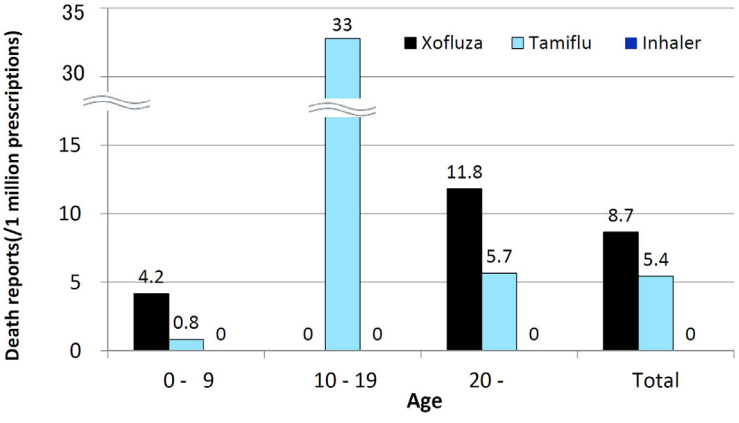
We have reported on the risk of bleeding **[8]**, resistance, bacterial pneumonia, melena, and serious arrhythmia **[9]** associated with Xofluza. In this article, we analyze the adverse reaction reports with fatal outcomes disclosed by MHLW **[3]**. We also present some typical fatal case reports after Xofluza use.

Case 1 (Sepsis with multiple organ failure): A healthy man in his 40s consulted 6 hours after onset of influenza symptoms. He was diagnosed with influenza due to typical symptoms such as high fever and chills, and took Xofluza 40mg. After resting in bed with fever for 2 days, he was transported to emergency room and hospitalized. Blood culture revealed pneumococcus. He was intubated and ventilated for multiple organ failure with septicemia and rhabdomyolysis, but he died three days later. The doctor reported "positive" for causality with Xofluza.

Case 2 (Sepsis with multiple organ failure): A woman in her 90s who had been prescribed with various medications, including an antihypertensive (losartan), donepezil, diuretics (furosemide and spironolactone), raloxifen and vitamin D, had a fever of 37.8°C and was prescribed with Xofluza 40 mg for a diagnosis of influenza A. Her temperature went down 2 days after taking Xofluza, but she revisited due to an increased respiratory rate at night. Pneumonia or heart failure was suspected and she was transferred to another hospital. She was hospitalized because pneumonia was suspected by chest X-rays. She had hepatic and renal insufficiency at the time of admission. Her condition worsened the next day, and she was complicated with DIC (disseminated intravascular coagulation) and died 9 days after taking the drug due to multiple organ failure. The doctor reported "positive" for causality with Xofluza.

Case 3 (Sudden death): A male in his 70s without heart disease consulted for sore throat, joint pain, cough and sputum. He was diagnosed with influenza A by rapid testing. He took Xofluza 40mg. On the next day, his fever continued and he was treated symptomatically. Three days later, his family member went to his room to check on him as he had not gotten up and found him dead, lying down beside his bed. He was diagnosed with "acute cardiac death" by the post-mortem examination. The doctor reported "positive" for causality with Xofluza.

High risk of death from Tamiflu and Xofluza use



Inhaler antivirals: Relenza (zanamivir) and Inavir (laninamivir)

In 2018/19 influenza season, no death case was reported among 2.94 million users of inhalers (Relenza and Inavir). On the other hand 14 death cases from adverse reaction were reported out of 2.57 million Tamiflu users and 37 death cases out of 4.27 million Xofluza users. One died out of 180,000 Tamiflu users and one died out of 120,000 Xofluza users. The number of death cases per million prescriptions in the age 10-19 group was 33 deaths for Tamiflu (all deaths occurred after abnormal behaviour). For patients aged over 20, 6 died out of 1 million Tamiflu users and 12 died out of 1 million Xofluza users. The risk of death for Tamiflu users and for Xofluza users were 33 times and 52 times higher than that for users of inhaler antivirals, respectively (Figure and see MedCheck Web No. 181 **[10]**).

Sudden death and sepsis due to Tamiflu and Xofluza use

During the three seasons since 2016/17, among 26 deaths reported as adverse reactions to Tamiflu, 8 died after abnormal behaviour, 6 died suddenly, and 4 died of sepsis.

Of the 39 deaths reported to date for Xofluza, 37 were aged over 20, and 25 were aged over 70. Among 33 death cases for which we could speculate the cause of death, 16 were sudden deaths including sudden loss of consciousness or respiratory arrest, and 14 had severe infections such as pneumonia, sepsis with multiple organ failure. In addition, although among 35 cases in which causal relationship was reported, physicians identified positive causality in 33 cases, the MHLW denied causality in all cases, explaining " causality cannot be assessed due to a lack of information etc."

Mechanisms of death are related to the action of the drug

Tamiflu itself enters into the brain and causes abnormal behaviour, suppresses respiration, leading to sudden death **[7]**. It inhibits not only neuraminidase of the influenza virus, but also human's endogenous neuraminidase, and reduces symptoms of influenza and simultaneously suppresses immunity, exacerbating infections, impairing renal function and inducing or worsening diabetes **[11]**.

On the other hand, possibility of inhibiting endogenous endonuclease in the human body cannot be ruled out although it is well-known that Xofluza inhibits cap-dependent endonuclease which is specific to influenza virus **[12]**.

Endonuclease activity is essential for cell division and cell proliferation to maintain normal tissues and tissue repair in case of injury **[13]**. Xofluza may inhibit these important processes for protection of human body.

In particular, in the intestinal tract where Xofluza may accumulate, it suppresses the function and regeneration of the intestinal epithelium, inhibits water absorption to cause diarrhea, damages the intestinal epithelium and induces melena. It may cause translocation of intestinal bacteria into blood stream and cause sepsis with bacteremia, multiple organ failure and septic shock.

In fact, a woman in her 20s who was diagnosed with influenza by testing without complication developed diarrhea every 30 minutes from the night after taking Xofluza 40 mg, Later, she found her stool mixed with blood and on the next day bloody stool was confirmed by a doctor. She recovered 6 days later **[14]**.

It is reported that secondary bacterial pneumonia occurred in 33.3% of Xofluza users, while it was observed in only 2% of Tamiflu users who visited an emergency facility **[15]**. The risk was 25 times greater for Xofluza than for Tamiflu ($P < 0.0001$) **[9]**.

The mechanism of sudden death in Xofluza users may also be related to the inhibition of endogenous endonucleases and impaired nerve and/or heart function.

In practice

Influenza is a self-limiting infection which is cured spontaneously. Antivirals are not required. Adequate rest and hydration are the best treatments. High-risk people, such as the elderly, diabetics and patients with impaired kidney function are at greater risk of death from harm of Xofluza or Tamiflu. Hence neither Xofluza nor Tamiflu should be used. Do not use these agents for influenza.

References: see p54

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