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# Anti-HCV agent LDV/SOF combination

8 week treatment may be better to reduce harm and costs with same efficacy

# Is Alteplase Beneficial for Treating Ischemic Stroke?

CONTENTS （December 2015,Vol. 1, No. 3）

# "Surrogate endpoint" qualify "real advance"?

Translated from the editorial in Med Check-TIP (in Japanese) 2015; 15 (Nov:#61) : 102.

Surrogate endpoints are overused.

The case of febuxostat (brand name: Feburic) provides a typical example. Although the primary purpose of the drug should be prevention of the severe pain that accompanies an acute gout attack, the endpoint used in clinical trials was reduction of the serum uric acid level to 6.0mg/dL. Febuxistat was approved because it achieved this surrogate endpoint, even though the incidence of acute gout attack was higher in the group treated with febuxostat than in either the placebo group or the group treated with the standard drug allopurinol.

Similarly, in clinical trials of the anti-HCV drug combination ledipasvir-sofosbuvir (brand name: Harvoni), a surrogate endpoint of " sustained virological response (SVR)" was used. In trials of the drug that used neither a placebo nor a standard drug as a control, 99% of participants achieved the surrogate endpoint. Since, in the natural state, the SVR rate is extremely low, a result of SVR12 (SVR for 12 weeks or more) indicates that a virus-negative state will likely continue for the long term, and strongly suggests that the drug prevents HCV-caused liver damage.

Nevertheless, a surrogate endpoint is still a surrogate endpoint. There is no guarantee that anti-HCV drugs can increase life expectancy.

One reason for uncertainty about the long-term efficacy and safety of the drug is that ledipasvir is strongly suspected to be more toxic than sofosbuvir. Toxicities that can be surmised to cause infection and/or general debilitation were observed with ledipasvir at the dose said to be safe by the manufacturer of the drug, and in clinical trials of ledipasvir in which the treatment period was extended, infections and bone fractures related to general debilitation were observed. Moreover, although the medication used clinically is a combination drug, no toxicity studies of the combination drug have been conducted.

For these reasons, even though the drug shows remarkable effectiveness as measured by the surrogate endpoint, there remain significant doubts as to whether it can improve long-term overall prognosis.

In addition, the drug is very expensive. If it were to be used to treat all HCV-infected persons in Japan, the total cost would be equivalent to the total amount of money spent annually on pharmaceuticals in Japan. Considering the uncertainty of long-term prognosis and its high cost, this drug can in no way be called " real advance" . In issue No. 60 of " Med Check TIP" , we prematurely used the phrase " real advance" in describing sofosbuvir. We now change our evaluation of sofosbuvir to " for severely restricted use" .

Among new drugs developed since 1990, anti-HIV drugs are truly " real therapeutic advance" . The decrease of CD4 positive lymphocytes (helper T-cells) was an excellent surrogate endpoint that correlated well with the development of AIDS or death due to AIDS. Even so, randomized control trials (RCTs) using placebos were conducted. In the first RCT, conducted on 282 patients with AIDS or AIDS-related complex (ARC, or " pre-AIDS state" ), 27 patients from the placebo group and 1 patient from the zidovudine group died over an 8- to 24-week period. The RCTs confirmed that the drugs were effective in suppressing the development of ARC into AIDS and in dramatically reducing the mortality rate.

As anti-HIV drugs have strong toxicities, additional RCTs were required to determine whether the drugs were appropriate for long-term use with mildly-ill patients.

In conclusion, in order to be able to say that the anti-HCV drug discussed above is truly " real advance" , RCTs that demonstrate improvement of long-term prognosis are needed.

# Anti-HCV agent LDV/SOF combination (brand name: Harvoni)

## Eight-week treatment may be better to reduce harm and costs with same efficacy

Translated synopsis based on Med Check TIP (in Japanese) 2015: 15 (Sep:#61): 103-108.

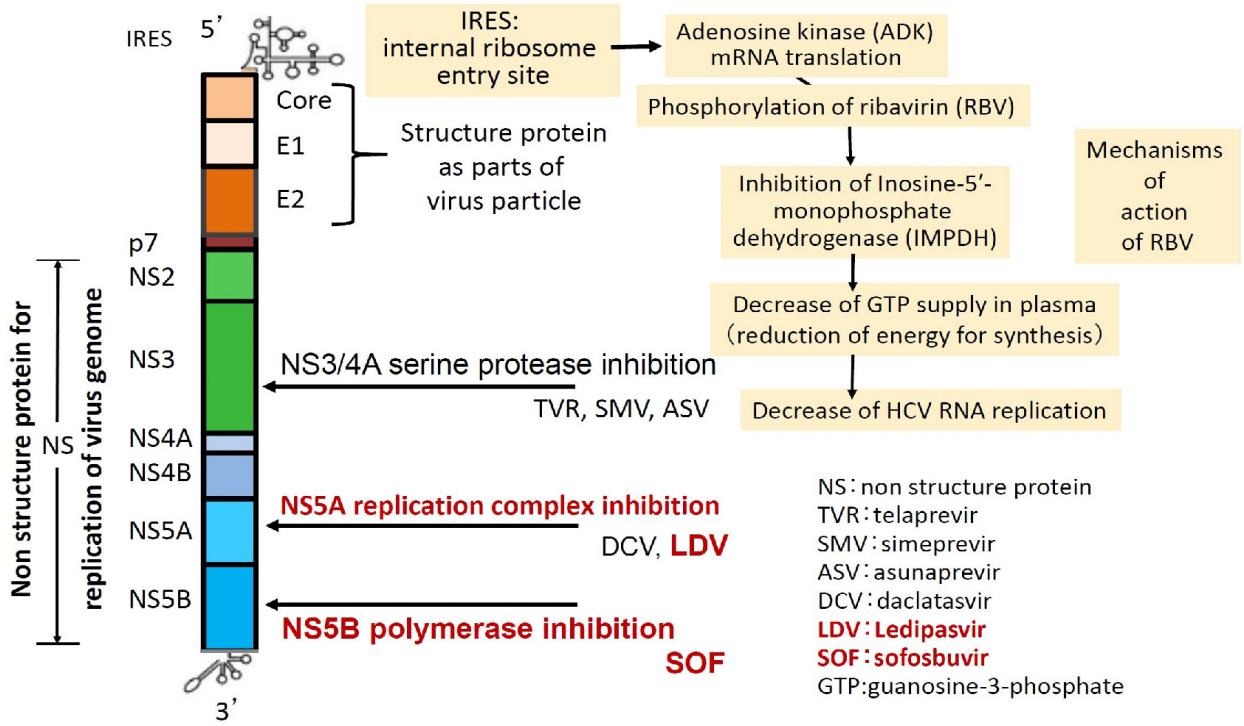
**General description:**

This anti-HCV combination drug containing ledipasvir (LDV) and sofosbuvir (SOF) (L/S combination: brand name "Harvoni") was approved for "improvement of viremia in chronic hepatitis or compensated cirrhosis induced by serotype (or genotype)-1 hepatitis C virus" in August 2015 in Japan. Type 1b hepatitis C is the major hepatitis C virus in Japan. Sofosbuvir is an NS5B polymerase inhibitor and ledipasvir is an NS5A replication complex inhibitor (**Figure 1**).

**Efficacy:**

The multivariate logistic regression analysis was conducted using the (non-controlled) clinical trials data from the Japanese regulatory documents. Predicted percentage of sustained virological response for 12 weeks or longer after the end of the treatment (SVR12) in Japanese trials was 99.1 % among the patients with hepatitis C serogroup 1 (genotype 1) (Table 1a and 1b). SVR12 in patients with genotype 1b tended to be higher than in those with genotype 1a (p=0.0758) in the US (**Table 1a**).

Figure 1: HCV genome and the mechanisms of action of anti-HCV agents




This figure was reconstituted from ref. [5] and [6], by the MedCheckTIP editorial team

**Efficacy and safety of different treatment durations:**

While treatment for 24 weeks gained significantly higher SVR12 than treatment for 12 weeks or 8 weeks, serious systemic adverse events such as infections and fractures were observed 7 to 25 times more frequently with 24 weeks treatment than 12 weeks treatment (**Table 2**). There was no additional beneficial effect in 12 weeks treatment when compared with 8 weeks treatment (**Table 1b**).

SVR12 observed in Japan tended to be apparently higher than that in the US. However, lower average body weight and higher proportion of patients with genotype 1b among Japanese may contribute to this difference. Hence data from the US for higher frequency of serious events in 24 weeks treatment and no difference in efficacy between 12 weeks and 8 weeks treatment could also be applied to Japanese cases.

Table 1: Results from the clinical trials in Japan:

| naïve /not | study agent *a | subjects N | SVR12 *b | % | predicted value *c | | |
|---|---|---|---|---|---|---|---|
| | | | | | % | 95%CI LL | 95%CI UL |
| naïve | **L/S** | **78** | **78** | **100** | 99.3 | 97.4 | 99.8 |
| | L/S+R | 81 | 78 | 96.3 | 99.2 | 97.3 | 99.8 |
| | total *d | 159 | 156 | 98.1 | 99.2 | 97.4 | 99.8 |
| history of treatment | **L/S** | **79** | **79** | **100** | 98.9 | 96.4 | 99.7 |
| | L/S+R | 80 | 80 | 100 | 98.8 | 96.2 | 99.7 |
| | total *d | 159 | 159 | 100 | 98.9 | 96.4 | 99.7 |
| Total *d | | 318 | 315 | 99.1 | 99.1 | 97.2 | 99.7 |
| US genotype | 1a | 1223 | 1168 | 95.5 | | | |
| | 1b | 358 | 350 | 97.8 | | | |

Proportion of patients with genotype 1b is 96 to 97 % among all genotype 1 hepatitis C patients.
All patients have chronic hepatitis C infection or compensated liver cirrhosis due to hepatitis C in Japan.
Duration of treatment is 12 weeks for all patients.
* **a:** L/S: ledipasvir/sofosbuvir combination, L/S+R: L/S + ribavirin
* **b:** SVR12: sustained virological response for 12 weeks or longer
* **c:** Predicted value: predicted value (%) and 95% confidence interval (95% CI) by exploring the results by the multivariate logistic-regression analysis including Japan and U.S. studies
* **d:** Predicted value for the "total" is a value using the data of the studies for 12 weeks and 8 weeks.

Table 1-b: SVR12 from various clinical trials of LDV/SOF combination

| country trial No | geno-type *a | CH / CH/LC *b | study agent *c | duration (w) | naïve /not *d | N *e | SVR12 *f | % | predicted value *g | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | % | 95%CI LL | 95%CI UL |
| Japan 0113 | 1b *a | CH/LC | **L/S** | **12** | naïve | **78** | **78** | **100** | 99.3 | 97.4 | 99.8 |
| | 1b *a | CH/LC | L/S+R | **12** | naïve | 81 | 78 | 96.3 | 99.2 | 97.3 | 99.8 |
| | 1b *a | CH/LC | **L/S** | **12** | not | **79** | **79** | **100** | 98.9 | 96.4 | 99.7 |
| | 1b *a | CH/LC | L/S+R | **12** | not | 80 | 80 | 100 | 98.8 | 96.2 | 99.7 |
| US 0102 | 1a | CH/LC | **L/S** | **12** | naïve | **144** | **139** | **96.5** | 96.9 | 94.3 | 98.3 |
| | 1a | CH/LC | L/S+R | **12** | naïve | 217 | 211 | 97.2 | 96.7 | 94.3 | 98.1 |
| | 1b | CH/LC | **L/S** | **12** | naïve | **66** | **66** | **100** | 98.4 | 96.2 | 99.3 |
| | 1b | CH/LC | L/S+R | **12** | naïve | 68 | 67 | 99 | 98.3 | 96.1 | 99.3 |
| | 1ab | CH/LC | **L/S** | **24** | naïve | **217** | **213** | **98.2** | | | |
| | 1ab | CH/LC | L/S+R | 24 | naïve | 217 | 215 | 99.1 | | | |
| US 0108 | 1a | CH | **L/S** | **8** | naïve | **171** | **159** | **93.0** | 93.0 | 89.1 | 95.5 |
| | 1a | CH | L/S+R | 8 | naïve | 172 | 159 | 92.4 | 92.6 | 88.7 | 95.3 |
| | 1a | CH | **L/S** | **12** | naïve | **172** | **163** | **94.8** | 94.9 | 90.7 | 97.2 |
| | 1b | CH | **L/S** | **8** | naïve | **43** | **42** | **97.7** | 96.3 | 92.1 | 98.3 |
| | 1b | CH | L/S+R | 8 | naïve | 44 | 42 | 95.5 | 96.1 | 91.7 | 98.2 |
| | 1b | CH | **L/S** | **12** | naïve | **44** | **43** | **97.7** | 97.3 | 93.6 | 98.9 |
| US 0109 | 1a | CH/LC | **L/S** | **12** | not | **86** | **82** | **95.3** | 95.5 | 91.2 | 97.7 |
| | 1a | CH/LC | L/S+R | **12** | not | 88 | 84 | 95.5 | 95.2 | 90.9 | 97.6 |
| | 1a | CH/LC | **L/S** | **24** | not | **85** | **84** | **98.8** | 99.0 | 96.0 | 99.8 |
| | 1a | CH/LC | L/S+R | 24 | not | 88 | 87 | 98.9 | 99.0 | 95.8 | 99.7 |
| | 1b | CH/LC | **L/S** | **12** | not | **23** | **20** | **87.0** | 97.7 | 94.1 | 99.1 |
| | 1b | CH/LC | L/S+R | **12** | not | 23 | 23 | 100 | 97.5 | 93.8 | 99.0 |
| | 1b | CH/LC | **L/S** | **24** | not | **24** | **24** | **100** | 99.5 | 97.6 | 99.9 |
| | 1b | CH/LC | L/S+R | 24 | not | 23 | 23 | 100 | 99.5 | 97.5 | 99.9 |

* **a:** Proportion of patients with genotype 1b is 96-97% among all genotype 1 hepatitis C patients in Japan. Hence all patients with gentype 1 in Japan were considered genotype 1b for multivariate logistic regression analysis.
* **b:** CH: chronic hepatitis, LC: compensated liver cirrhosis
CH/LC: chronic hepatitis or compensated liver cirrhosis
* **c:** L/S: ledipasvir/sofosbuvir combination, L/S+R: L/S + ribavirin
* **d:** naïve/not: first time treatment / history of treatment
* **e:** number of subjects
* **f:** SVR12: sustained virological response for 12 weeks or longer
* **g:** Predicted value: predicted value (%) and 95% confidence interval (95% CI) by exploring the results by the multivariate logistic-regression analysis including Japan and U.S. studies

## Resistance:

L31 and Y93H variants were mainly associated with no response. Table 3 shows that odds of resistant associated variants (RAV) among patients with no response was 30 to 54 times higher compared with baseline odds of RAV for genotype 1b ($p<0.001$) and 5 to 17 for genotype 1a ($p<0.01$).

## Toxicity:

We found serious flaw in the toxicity studies of the LDV/SOF combination. The dose-limiting toxicities and the target organ/tissue were not determined for ledipasvir alone. Moreover, the harmful dose in which death, infections and general deterioration that were also observed in the clinical trials (in 24 weeks treatment) were considered as non-observable adverse effect level (NOAEL) by the pharmaceutical company and regulator. Combination of LDV and SOF was not tested in the toxicity studies for approval, even though they are always used in combination in the clinical setting.

## Conclusions and recommendations:

LDV/SOF combination medication improves viremia remarkably but not by 100 %. We do not recommend the use of the drug to the patients with sustained normal level of ALT. Even in the case with abnormal ALT values, efficacy on SVR12 is not different with treatment duration (12 weeks vs 8 weeks).

Because the toxicities are duration-dependent and non-specific with infection or systemic debilitation, we recommend to use the least effective duration (8 weeks) unless patients have resistance associated variant. We recommend examination of RAV for L31 and Y93H which are related to no response. Twelve weeks treatment should be indicated in only those who have positive RAV. Eight weeks treatment may be preferable for the others.

Table 2: Comparison of serious adverse events by treatment duration

| Trial | 24 weeks | | | 12 weeks | | | 8 weeks | | |
|---|---|---|---|---|---|---|---|---|---|
| Country No | N | SAE | % | N | SAE | % | N | SAE | % |
| US 0102*a | 217 | 18 | 8.3 | 214 | 1 | 0.5 | | | |
| US 0109 | 109 | 6 | 5.5 | 109 | 0 | 0.0 | | | |
| US 0108 | | | | 216 | 5 | 2.3 | 215 | 4 | 1.9 |
| Total | 326 | 24 | 7.4 | 539 | 6 | 1.1 | | | |

SAE: serious adverse event

Odds ratio=25.5 (95% CI: 4.1, 1054, p<0.0001) (meta-analysis excluding trial 0108).

Odds ratio=7.1 (95% CI: 2.9, 17.5, p<0.0001) (using total).

Table 3: Resistance associated variants (RAV) related to "no response"

| genotype | RAV subtype | baseline | | non-responders | | OR | 95%CI | | P value |
|---|---|---|---|---|---|---|---|---|---|
| | | RAV | % | RAV | % | | LL | UL | |
| | | N=380 | | N=8 | | | | | |
| 1b | ≧1 | 60 | 16 | 7 | 87.5 | 37 | 3.5 | 309 | <0.001 |
| | Y93H | 35 | 9.2 | 6 | 75.0 | 30 | 5.7 | 152 | <0.001 |
| | L31I | 1 | 0.3 | 1 | 12.5 | 54 | 3.1 | 956 | <0.001 |
| | L31V | 1 | 0.3 | 1 | 12.5 | 54 | 3.1 | 956 | <0.001 |
| | | N=1,233 | | N=29 | | | | | |
| 1a | ≧1 | 192 | 16 | 22 | 75.9 | 17 | 7.2 | 40 | <0.001 |
| | Y93H | 29 | 2.4 | 6 | 20.7 | 11 | 4.1 | 29 | <0.001 |
| | L31M | 49 | 4.0 | 5 | 17.2 | 5.0 | 1.8 | 14 | <0.01 |
| | Y93N | 14 | 1.1 | 4 | 13.8 | 14 | 4.3 | 45 | <0.001 |

Denominators (N) at the baseline were all the patients tested.

For the non-responded cases, denominators (N) were also all non-responders.

"No RAV" was observed in one among 8 genotype 1b patients and 7 among 29 genotype 1a patients with no response.

Odds ratios (the odds of RAV among patients without response by the baseline odds) were calculated.

If it is significantly higher, the RAV may be related to ineffectiveness.

## Principles of Toxicity study by Zbinden G (F. Hoffmann-La Roche & Co)

***"In any toxicity experiment, animals are treated with drugs and observed for toxic manifestations. In order to increase the chances of recognizing possible toxic properties, the dose is raised above the therapeutically useful range, the duration of treatment is often lengthened, and the drug is administered not only to one individual animal but to animal groups. Thus, the toxicity experiment tries to imitate the clinical use of the drug and although bold exaggerations with respect to dose and duration of treatment are common and permissible, it is important that the future therapeutic applications in man guide the planning of a toxicity study."***

## Based on these principles, toxicity studies of the L/S combination have many flaws:

(1) Dose limiting toxicity and its target organ/tissues of LDV alone are not determined

(2) The major toxicity of LDV may be infections due to systemic debilitation?

(3) L/S combination was not tested for toxicity at all

(4) Other findings: hypoalubuminemia and high cholesterol level accompanied with increased body weight, and even death were not considered as toxicity findings.

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# Febuxostat (brand name: Febric)

## Too frequent cardiovascular events, gouty attacks, serious allergy: Inferior to allopurinol

Translated synopsis based on Med Check TIP (in Japanese) 2015; 15 (Sep:#61) : 109-113

### Synopsis

● For the management of hyperuricemia, the first choice is non-pharmacological intervention such as enough intake of water and alkalinisation of urine with least medicine. When it is failed or not indicated, pharmacotherapy is provided. The first-line medicine is allopurinol, but itself may induce gouty attack and serious allergic reactions relatively frequently.

● The primary aim of the pharmacotherapy for hyperuricaemia is "reduction and prevention of gouty attack and subsequent complications".

● However, febuxostat was approved only by surrogate endpoint namely "lowering plasma level of uric acid" and not by the achievement of the primary aim.

● Febuxostat use may induce gouty attack paradoxically more frequently than allopurinol **(Figure 1)**. It may induce serious allergic reactions (severe drug eruption, liver damage) more frequently than allopurinol. Therefore, we DO NOT recommend febuxostat.

● In addition, cardiovascular events were more reported in the febuxostat group than allopurinol group in the clinical trials conducted before approval **(Table 1)**.

● The analysis results of post-marketing adverse reaction reports that US Food and Drug Administration disclosed shows that reporting odds ratio (ROR) of cardiovascular reactions for febuxostat were 2-7 times higher than for allopurinol **(Table 2:Next pege)**.

● Similar efficacy in decreasing blood uric acid level was

**Figure 1 : Proportion of gouty attack**
**(whole period, classified by the drug at the time of gouty attack)**

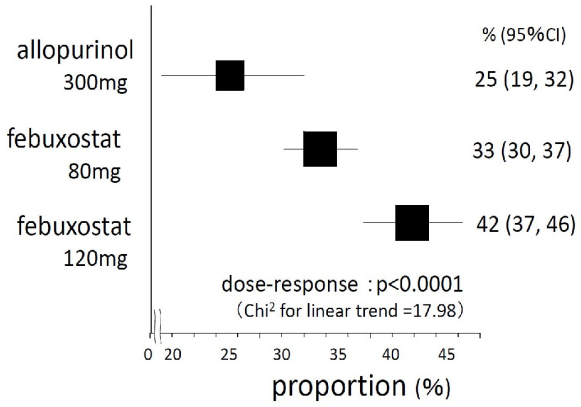



**Table1 : Proportion and incidence of cardiovascular events by febuxostat dose in the clinical trials *a**

| | | APEX C02-009 | | | FACT C02-010 | | | CONFIRMS FGT06-153 | | | Total | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | N | E | % | N | E | % | N | E | % | N | E | % | %/p-y |
| Placebo | | 134 | 1 | 0.7 | | | | | | | 134 | 1 | **0.75** | 1.67 |
| allopuriol | | 268 | 1 | 0.4 | 253 | 5 | 2.0 | 756 | 10 | 1.3 | 1277 | 16 | **1.25** | 2.38 |
| febuxostat | 40mg | | | | | | | 757 | 10 | 1.3 | 757 | 10 | **1.32** | 2.92 |
| | 80mg | 267 | 5 | 1.9 | 256 | 5 | 2.0 | 756 | 12 | 1.6 | 1279 | 22 | **1.72** | 3.41 |
| | 120mg | 269 | 4 | 1.5 | 251 | 7 | 2.8 | | | | 520 | 11 | 2.1 | 3.61 |
| | 240mg | 134 | 1 | 0.7 | | | | | | | 134 | 1 | 0.7 | 1.85 |
| | 120+240 | 403 | 5 | 1.2 | 251 | 7 | 2.8 | | | | 654 | 12 | **1.83** | 3.34 |
| | 合計 | 670 | 10 | 1.5 | 507 | 12 | 2.4 | 1513 | 22 | 1.5 | 2690 | 44 | 1.6 | 3.27 |

N : number of subjects 、E : events、% /p-y : % /person-year
***a** : cardiovascular adverse events according to the classification of APTC (Anti-Platelet Trialists' Collabolation (APTC) and non APTC events
Dose-response relation was not significant. This may be caused because the number allocated to placebo group was too few. If the subjects were 6 times more than the above, and the event occured at the same frequency, the dose response would be significant.

Table 2 Comparison of post-marketing spontaneous ADR reports (febuxostat vs allopurinol)

| ADR | febuxostat N=921 | | allopurinol N=6396 | | feb vs allop OR | 95% CI | |
|---|---|---|---|---|---|---|---|
| | reports | PRR | reports | PRR | | LL | UL |
| Acute myocardial infarction | 10 | 4.0 | 18 | 1.0 | **3.9** | **1.8** | 8.5 |
| Myocardial infarction | 22 | 1.1 | 34 | 0.2 | **4.6** | **2.7** | 7.9 |
| Myocardial ischemia | 3 | 1.9 | 3 | 0.3 | **7.0** | **1.4** | 34.6 |
| Myocarditis | 1 | | 13 | 4.8 | **0.5** | **0.07** | 4.1 |
| Cardiac failure | 31 | 6.3 | 96 | 2.8 | **2.3** | **1.5** | 3.4 |
| Cardiac failure acute | 6 | 19.3 | 15 | 7.0 | **2.8** | **1.1** | 7.2 |
| Cardiac failure congestive | 20 | 2.5 | 34 | 0.6 | **4.2** | **2.4** | 7.2 |
| cardio-respiratory arrest | 7 | 2.2 | 15 | 0.7 | **3.3** | **1.3** | 8.0 |

PRR (Proportional Reporting Ratio) and Reporting Odds Ratio (ROR)

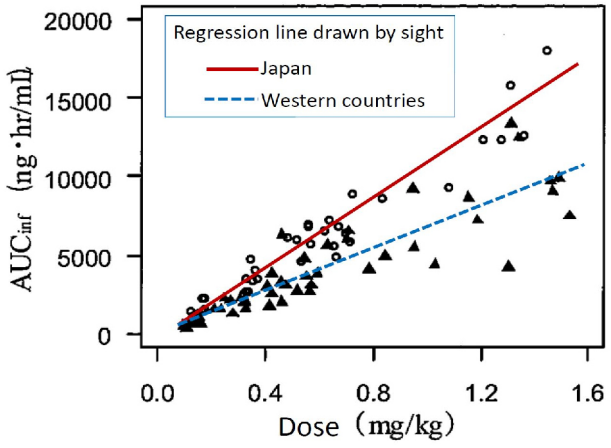
| | ADR (A) | Other ADRs | All ADRs |
|---|---|---|---|
| Drug (D) | a | b | a+b |
| Other drugs | c | d | c+d |
| All drugs | a+c | b+d | a+b+c+d |

PRR= (a/(a+b))／(c/(c+d)) ROR= (a/b)／(c/d)=(a*d)/(b*c)

achieved with lower dose in the Japanese clinical trials than in the Western countries. However, higher area under the curve (AUC) of the blood level seems achieved in Japanese than in the Western people if it is compared between those who were administered with the same dose per kg body weight **(Figure 2)**. Therefore, febuxostat may be more harmful for people in Japan than in the Western countries. .

● Febuxostat does not seem to have the cross sensitivity with allopurinol. Hence febuxostat may only be indicated as a second choice when allopurinol and probenecid cannot be used for an allergy. If indicated, it is essential to commence at lowest dose and very gradually and carefully to prevent gouty attack.

Figure 2：Relation of the body weight-adjusted-dose and AUC：
Difference between in Japan and in the Western countries




Relation of the body weight-adjusted-dose and AUCinf after single dose Healthy adult male ○：people in Japan（N=52）、 ▲：People in Western countries（N=48）

The slope of regression line by sight is sharp for Japan than for Western countries. The difference may be 1.7 times higher in Japanese than the Western countries. Body weight may be 1.4 times lower and the relative AUC per body may be 2 times or more in Japanese than in the Western people. 40mg/day for Japanese may be higher than 80 mg/day for the Western people.

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# Is Alteplase Beneficial for Treating Ischemic Stroke?

## No proven efficacy if it is given 1.5 hours after onset

Translated synopsis based on Med Check TIP (in Japanese) 2015; 15 (Sep:#60) : 85-88

**Abstract**

**Alteplase (rt-PA) is generally considered as a specific medicine for the treatment of acute-phase ischemic stroke. However, in the NINDS study, which justified the use of rt-PA within 3 hours of onset of stroke especially after 1.5 hours, an unacceptable, extreme bias in favor of the rt-PA group was detected. Therefore, it cannot be considered that benefit outweighs harm when the drug is given later than 1.5 hours after onset.**

**The editorial team examined the ECASS-III study, which provided the evidence for the use between 3 to 4.5 hours after onset. Again, we found an extreme bias in favor of the rt-PA group, thus it is hard to conclude that benefit outweighs harm. IST-3 study which is a randomized study but not double-blinded could have an extreme bias in favor of the rt-PA group. Consequently a meta-analysis published in 2014 that included IST-3 remains the same bias uncorrected. In NINDS, in patients treated within 1.5 hours of onset, bias in background variables was limited hence it is suggested that their symptoms improved and rt-PA may be effective. Except for them, no evidence has proven that rt-PA improved the outcome of ischemic stroke. Applying the idea of Dr. Archie Cochrane "One should, therefore (…) always assume that a treatment is ineffective unless there is evidence to the contrary" (see page XX), we must conclude that rt-PA is "not effective" for treating ischemic stroke when given later than 1.5 hours after onset of stroke.**

### Introduction:

Alteplase (genetic recombinant) (rt-PA) has been used as a thrombolytic agent for acute myocardial infarction. In 1996, it was approved for the treatment of ischemic stroke (cerebral infarction) by the FDA and subsequently in other countries in Europe and Asia[1]. In Japan, "the improvement of dysfunctions associated with acute-phase ischemic cerebrovascular disorders (administered within 3 hours of symptom onset)" was added to the indications in 2005.

The NINDS study [2, 3] is the randomized controlled trial (RCT) that provided pivotal evidence for the use of rt-PA within 3 hours of onset of stroke. The result of this study, however, is fundamentally questionable for the following reasons [4]: (1) None of the considerable bias in background variables was adjusted in the outcome analysis. (Although no bias was detected in patients treated within 1.5 hours of onset, an unacceptable bias was noted in the 1.5-3 hours group: Figure.1); (2) Almost no case of recanalization was reported; (3) No difference in 1-year mortality was observed, and the causes of death were unusual; (4) The effect of rt-PA was reversed by the use of antihypertensives.

Later, another RCT (ECASS-III [5]) reported that rt-PA was effective when given within 3 to 4.5 hours of symptom onset. On the basis of this single trial, the guidelines in Western countries recommended to use rt-PA within 4.5 hours of symptom onset in 2009. In 2011, regulatory agencies in Europe approved the use of rt-PA within 4.5 hours of onset. In Japan, in February 2013, a change to include a new time window of 4.5 hours was approved [1], followed by the revision of the guidelines (the second edition) [6].

Regarding the indications of rt-PA, this article summarizes the evidence for the validity of the conventional "use within 3 hours of onset". It also examines the evidence for the validity of the extended use within 3 to 4.5 hours of onset. In the NINDS and ECASS-III trials, the efficacy of rt-PA was assessed based on the proportion of patients with a favorable outcome (mRS 0-1) at 3 months (see **Table 1**).

Table 1: modified Rankin Scale (mRS) *

| score | Description |
|---|---|
| 0 | No symptoms at all |
| 1 | No significant disability despite symptoms; able to carry out all usual duties and activities |
| 2 | Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance |
| 3 | Moderate disability; requiring some help, but able to walk without assistance |
| 4 | Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance |
| 5 | Severe disability; bedridden, incontinent and requiring constant nursing care and attention |
| 6 | Dead |

## Changes from the conventional indications of rt-PA

Based on the Guidelines for Intravenous Application of rt-PA, the Second Edition published by the Subcommittee on Revision of the Guidelines for Intravenous Application, the Committee on Stroke Care Improvement and Social Insurance, the Japan Stroke Society (hereinafter referred to as "the revised guidelines"), the major differences in the indications of rt-PA between the old and revised guidelines are shown in a comparative table at the end of the reference[6]. The revised guidelines state "Intravenous alteplase is indicated in patients with ischemic cerebrovascular disorder that is treatable within 4.5 hours of symptom onset【Level of Evidence Ia, Grade of Recommendation A】." The biggest change is that intravenous rt-PA administered within 3 to 4.5 hours of symptom onset, which was previously the off-label use, was included in the revised indications.

Following this change, almost all conditions that used to be contraindicated in the old guidelines based on the package insert are simply listed as "off-label" in the revised guidelines even though they are still contraindicated in the current package insert. For instance, administration of rt-PA "within 3 months onset of ischemic stroke" or "in patients receiving warfarin with PT-INR > 1.7" are still "contraindicated" in the package insert. However, they are simply "off-label" in the revised guidelines. The use of rt-PA in patients with "seizure" or "cerebral aneurysm, intracranial tumor, cerebral arteriovenous malformation, Moyamoya disease (occlusive disease in circle Willis) are still contraindicated in the package insert, but are excluded from "contraindication" and included in "administer carefully" in the revised guidelines.

Moreover, the revised guidelines raised the age for "administer carefully" from 75-year and older to 81-year and older, and the NIHSS scores for "administer carefully" from 23 and above to 26 and above [6]. In any case, the revised guidelines allow wider use by listing many "contraindications" in the package insert under "administer carefully" and raising the upper age limit for the administration.

Note: The NIHSS is a scale to assess severity of stroke developed by National Institute of Health (NIH) in the US. Scores are given to 11 categories, and the scores from each category are summed up to assess severity. The total score of 0 indicates the least severe case while 42 indicates the severest. Assessment is made by classifying the scores into 0-4, 5-9, 10-14, 15-19, 20-24, and 25 (or 26) and above. The severest case is indicated as 25 (or 26) and above.

## Clinical Trials referred in the Guideline

Table 2 on page 4 of the guidelines [6] summarizes trial designs, the numbers of cases, onset-to-treatment time, doses, the primary endpoint, and the frequency of intracranial hemorrhage in the major clinical trials which the guidelines are based on. In addition, there is another trial, ATLANTIS-A [7], on the basis of which ATLANTIS-B was conducted, although it was not included as a reference in the guidelines. The ATLANTIS-A trial involved a population of patients treated within 6 hours of onset of stroke, but was discontinued due to safety concern regarding the use of rt-PA between 5 and 6 hours after onset [7].

NINDS [2, 3] is the only RCT that claimed the efficacy of rt-PA administered within 3 hours of symptom onset. Although the validity of its conclusion remains fundamentally questionable, many countries in the world recommend the administration of intravenous rt-PA within 3 hours of onset, based on the result of this study as important evidence.

However, as mentioned in the introduction, various problems are found in the study. The guidelines refer to the ECASS, ECASS-II, and ATLANTIS-A studies with patients treated within 6 hours of onset as well as ATLANTIS-B with patients treated within 3 to 5 hours and EPITHET with patients treated within 3 to 6 hours of onset. However, the efficacy of rt-PA has not been confirmed in these studies. Among the RCTs conducted after NINDS, ECASS-III [5, 8] is the only RCT that involved patients treated within 3 to 4.5 hours of onset and claimed the efficacy of rt-PA.

The guidelines refer to IST-3 [9] as important evidence for raising the standard age for "administer carefully" to 81-year and older. However, it is a large-scale open trial (non-placebo controlled randomized trial), thus the strength of its evidence is undermined. ECASS III, and the meta-analysis published in 2010 and in 2014 are mainly examined below.

## ECASS-III (the evidence for rt-PA within 3 to 4.5 hours) and its problems

(1) The frequency of hemorrhagic stroke is 10-fold higher, but rt-PA is effective?

ECASS-III is the only RCT that involved patients treated within 3 to 4.5 hours of onset. It was conducted with 821 ischemic stroke patients and compared an intravenous rt-PA (0.9 mg/kg) group (418 patients) and a placebo group (403 patients). The primary endpoint was the same as the other studies: "a proportion of a favorable outcome (a score of 0 or 1 on the modified Rankin scale) at 90 days" (hereinafter this is the primary endpoint unless especially mentioned). It was 52.4% in the rt-PA group and 45.2% in the placebo group, and the odds ratio (OR) was 1.34 (95% CI: 1.02-1.76), thus it was concluded that "rt-PA is effective" [5]. Regarding harm, the frequency of symptomatic intracranial hemorrhage was 2.4% in the rt-PA group and 0.2% in the placebo group (OR: 9.85, 95 % CI: 1.26-77.23). This indicates that the risk of bleeding was 10-fold higher in the rt-PA group, but the mortality at 90 days was 7.7% in the rt-PA group and 8.4% in the placebo group with no significant difference.

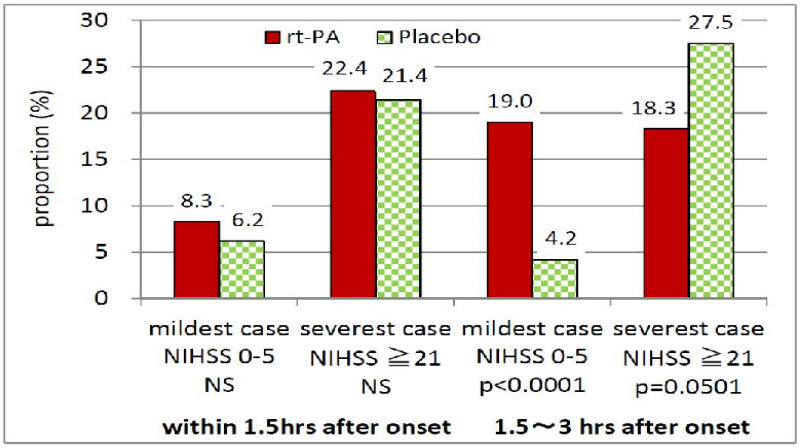
These findings led to the conclusion that intravenous rt-PA administered within 3 to 4.5 hours of onset increases the risk of bleeding, but improves an outcome with no significant difference in mortality between the two groups. Many countries in the world including Japan extended the time window in the indications to 4.5 hours, referring to this result as important evidence [6].

(2) The rt-PA group included less cases with a history of stroke and severe cases

Various problems in background variables were found in NINDS (**Figure.1**,[4]). The following figures 2 and Figure 3 summarize the case of ECASS-III.

The average NIHSS score at time of presentation was significantly lower in the rt-PA group (10.7 points vs 11.6 points, p=0.025). The proportion of severest cases (NIHSS ≧

Figure 1: Serious bias in the baseline severity of the cases treated during 1.5 to 3 hours after the onset of stroke (NINDS) [3]




Patients treated within 1.5 hours after onset were well randomly allocated to t-PA group or placebo group (baseline severity was not significantly different: NS). However, patients treated between 1.5 and 3 hours after onset were differently allocated significantly. Odds ratio of patients with least score in t-PA group compared with placebo group was 5.4（95 % CI：2.7, 12.6、p=0.00003)。OR in the severest cases =0.59（0.35,1.00、p=0.0501）

21) was 9.9% in the placebo group while it was 5.0% in the rt-PA group (OR=0.48: 95% CI: 0.28-0.82, p=0.007), roughly a half of that in the placebo group. Furthermore, even a greater difference was detected between the 2 groups when the proportions of patients with a history of stroke were compared (7.7 % in the rt-PA group, 14.1 % in the placebo group, OR=0.50: 95% CI: 0.32-0.79, p=0.003) (**Figure. 2**).

The reference [10], which describes the need to reexamine the efficacy of rt-PA, also criticizes this difference in background variables.

(3) More remarkable effect in patients with a history of stroke?

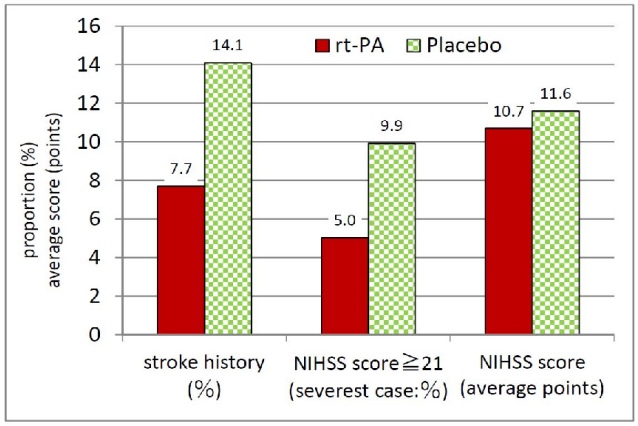
Figure. 3 shows the result of a subgroup analysis on the proportions of patients with a favorable outcome (mRS 0-1) at 3 months after the initiation of the trial by presence or absence of a history of stroke. When only the patients without a history of stroke were analyzed, the proportions were 52% in the rt-PA group and 47% in the placebo group, and the OR was 1.19 (95% CI: 0.89-1.59) with no significant difference. However, in the analysis of the patients with a history, the proportions were 63 % in the rt-PA group and 33 % in the placebo group, and OR was 3.33 (95 % CI: 1.35-8.22), indicating an unusually favorable outcome in the rt-PA group [8]. What conditions led to such an unusual phenomenon? (See Figure. 3 and think about it. Figure.4 and its footnote explain the idea of the editorial team.)

Given that the background variables are markedly biased (**Figure. 2**), and the significant difference, which cannot be simply explained as a coincidence, was found in the proportions of a favorable outcome (**Figure. 3**), it must be concluded that the patients were allocated deliberately to produce a positive result for rt-PA.

A comparison of outcomes adjusted by NIHSS scores has been reported, but that for per protocol population (PPP) adjusted by NIHSS scores has not. Unless the analysis were conducted adjusting the severity of prior stroke in the patients with a history, the result of ECASS-III cannot be reliable.

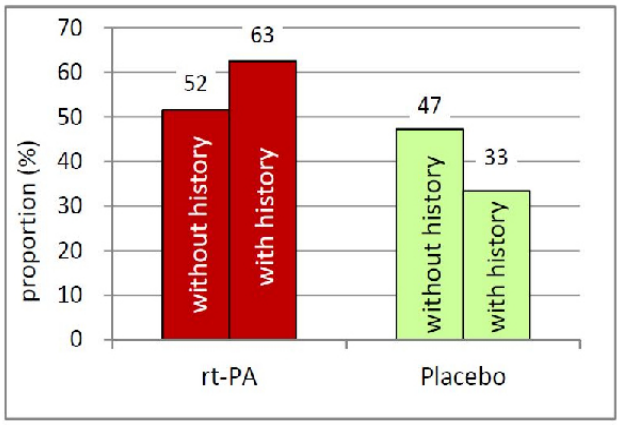
Similarly, as a result of a subgroup analysis, in patients aged 65-year and older, the OR of the proportions of patients with a favorable outcome (mRS 0-1) was 1.15 (95%CI: 0.80-1.64) and showed no significant difference. The total number of deaths (mRS 6) and severest cases (mRS 5) was greater

Figure. 2: Bias in baseline characteristics in ECASS-III




Odds ratio for patients with a history of stroke is 0.50 (p=0.003).
Difference in the average NIHSS score is not marked, but the odds ratio for the severest cases is marked with significant difference: OR=0.48 (p=0.007).

Figure 3: The proportion of cases with a favorable outcome by history of stroke




cases with a favorable outcome: 0-1 on the mRS

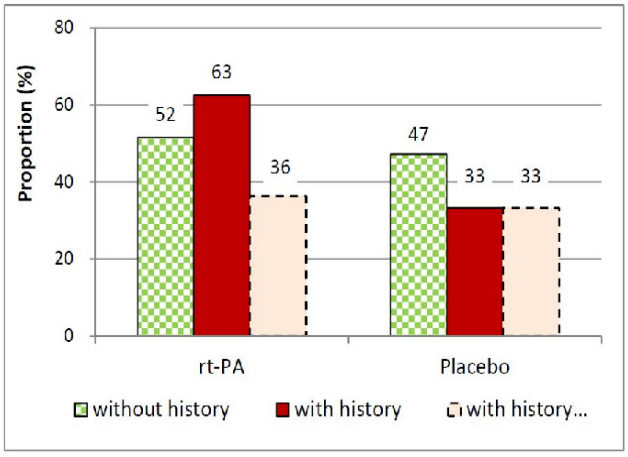
in the rt-PA group (14.8 % vs 13.4 % ) in the initial analysis [5] although it was not significantly different. This result is consistent with the finding that intracranial hemorrhage occurred 6 times more frequently in patients treated with rt-PA group.

ECASS-III involved patients aged 80-year and younger, and their NIHSS scores at baseline were low (average 10). It included milder cases than those in other trials. Nevertheless, even with such a condition, the proportion of patients with a history of stroke, one of the background variables, was lower in the rt-PA group, creating a more favorable condition for rt-PA. When patients with no history of stroke are analyzed, no significant difference is detected. Additionally, no significant difference was found in patients aged 65-year and older, the main age group of actual patients, with poor safety result. Based on these findings, we believe that the result of ECASS-III cannot provide evidence for approving a time window of 3 to 4.5 hours.

### The 2010 meta-analysis and its problems

As mentioned in the guidelines (second edition) [6], the efficacy of rt-PA was not confirmed in ECASS, ECASS-II and ATLANTIS-A for the use within 6 hours of onset, ATLANTIS-B for the use within 3 to 5 hours of onset, and EPITHET for the use within 3 to 6 hours of onset. However, in 2010, the meta-analysis of the 5 RCTs above as well as NINDS and ECASS-III demonstrated that the proportion of patients with the primary endpoint was significantly higher in the rt-PA group when rt-PA was administered within 3 to 4.5 hours of onset [11]. Indeed, it was higher in the rt-PA group (OR=1.34; 95% CI: 1.06-1.68). However, hemorrhage occurred certainly more frequently (OR=3.61; 95% CI: 1.76-7.38), and mortality was also slightly higher in the rt-PA group although it was not significantly different (11.0% vs 10.1% , OR=1.22; 95% CI: 0.87-1.71).

**Figure. 4: The proportion of cases with mRS (0-1) by history of stroke**




It can be inferred that patients with a history of stoke would have a less favorable outcome than those without a history. This natural outcome is shown in the placebo group. However, in the rt-PA group, patients with a history of stroke rather had a better outcome, and the OR was 1.57 (approximately 60% increase) although it was not significant. Such a phenomena would not easily occur unless the patients with a history of stroke in the rt-PA group included those with very mild stroke such as lacunar infarction.

Various problems, such as bias in background variables explained above, are found in the NINDS and ECASS-III studies. Taking these into account, it is difficult to conclude even with this combined analysis that rt-PA is more effective than placebo when administered within 3 to 4.5 hours of onset.

### The 2014 meta-analysis using IPD and its problems

In 2014, another meta-analysis was conducted by adding IST-3 study [9] to the 2010 analysis, using individual patients data (IPD) of 6756 patients [12]. The IST-3 study was an open trial that involved patients treated within 6 hours of onset, and patients aged 81-year and older accounted for a half of the enrolled patients. The primary endpoints included the proportion of patients with mRS (0-1) at 3 to 6 months, symptomatic intracranial hemorrhage, and fatal hemorrhage within 7 days, and 90-day mortality.

The analysis concluded "Irrespective of age or stroke severity, and despite an increased risk of fatal intracranial haemorrhage during the first few days after treatment, alteplase significantly improves the overall odds of a good stroke outcome when delivered within 4•5 h of stroke onset." The conclusion indicated that rt-PA is effective even if patients are older and their conditions are severer at baseline, and suggested to extend the coverage of the indications from that in the 2010 analysis.

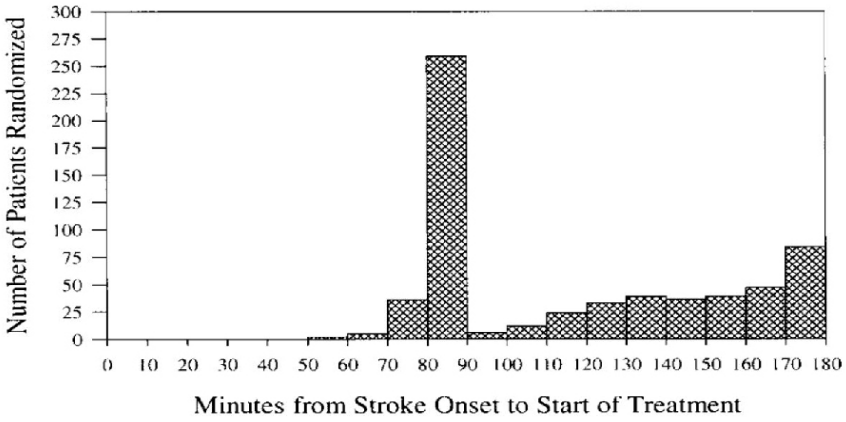
However, the 2014 combined analysis covered the same trials as the 2010 analysis except for IST-3, thus it inherited similar problems. The 2014 analysis reported that when the entire individual patient data were analyzed, no significant difference in background variables was found between the two groups. However, it can be suspected that the difference in background variables detected in NINDS and ECASS-III became less apparent in other trials which could not prove the efficacy of rt-PA. Additionally, the 2014 analysis included an open trial (IST-3), thus the conclusion above is inappropriate.

Among the patients treated within 3 to 4.5 hours of onset, in particular, 70% of them was also involved in ECASS-III [5] and IST-3 [9]. As discussed earlier, there are problems in the background variables, such as severity or presence of prior ischemic stroke, in ECASS-III. Moreover, in IST-3, in patients treated within 3 to 4.5 hours of onset, the proportion of patients with the primary endpoint is lower in the rt-PA group than in the placebo (OR=0.73: 95 % CI: 0.50-1.07). Mortality was higher in the rt-PA group at 7 days, 6 and 18 months when the treatment was given later than 3 hours after onset [13]. In all cases, mortality was also higher in the rt-PA group at 7 days (11% vs 7% , p=0.001), and mortality of the two groups became similar at 6 months.

### Efficacy is expected when rt-PA is given only within 1.5 hours of onset

The analysis [3]by onset-to-treatment time, which was published 5 years after NINDS [2], indicates that in patients treated with rt-PA within 1.5 hours of onset, almost no bias was found in background variables (**Figure. 1**). It suggests that many patients had a favorable outcome at 3 months, thus rt-PA may have been effective. The apparent efficacy observed in patients treated between 90 and 180 minutes after onset is highly likely to have been caused by substantial

Fig.ure 5: Distribution of Time from Onset to Start of Treatment among randomized patients




Most of the patients clustered close to the 90-minute limit. It raises suspicion that in prior to the initiation of the trial, rt-PA was predicted to be effective only in patients treated within 1.5 hours of onset. (The histogram was taken from the reference [3]. The comments are added by the editorial team.)

bias. In spite of the bias, efficacy of rt-PA administered later than 2.5 hours after onset was not demonstrated.

Moreover, in NINDS, most cases are concentrated in the 80-90 minutes stratum (**Figure. 5**). This raises strong suspicion that it was predicted at first place, before the initiation of the trial, that rt-PA would be effective only when delivered within 1.5 hours of onset.

## In Practice

No clear evidence is available to show that rt-PA use between 1.5 and 3 hours or 3 and 4.5 hours after onset of ischemic stroke would improve an outcome. When rt-PA is given within 1.5 hours of onset, evidence suggests the efficacy although it is not robust. In practice, the use of rt-PA should be restricted to patients treated within 1.5 hours of symptom onset.

In patients treated later than 1.5 hours up to 4.5 hours, the use of rt-PA should be avoided until the bias in background variables in the previous clinical trials is rigorously adjusted and the result of the adjustment is published.

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