MED CHECK

August 2019 Volume 5

№ 14

# Does the Japanese Regulator ignore science?

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# Does the Japanese Regulator ignore science?

Translated from the Editorial in Med Check (in Japanese) Jul 2019 : 19 (75)

Human bone marrow-derived mesenchymal stem cells (trade name: Stemirac) for spinal cord injury were listed in the Japan's National Health Insurance drug price list on February 26 through Preferential Designation System. One intravenous injection costs 14.95 million yen (140 thousand US dollars). In the case of anti-influenza drug, Xofluza, which was also listed through this system, at least a placebo-controlled randomized controlled trial (RCT) was conducted. However, in the case of Stemirac, only one open trial including 13 patients was conducted without untreated control.

The Nature advised the Ministry of Health, Labor and Welfare (MHLW) to "slow down" in its editorial in the January 31, 2019 issue, but the MHLW ignored it.

All of the following criteria must be fulfilled for the preliminary examination and designation; **(1)** the product should have a new mechanism of action, **(2)** the target medical condition is serious or life-threatening, **(3)** the product has extremely high efficacy and safety, and **(4)** the sponsor should develop the product rapidly and file an application in Japan ahead of the world. With regard to Stemirac, the criteria 1, 2 and 4 are indeed satisfied, but the criterion 3 has not been proven yet. The efficacy is ambiguous as what is believed to be the effect of Stemirac might simply be the natural recovery of spinal cord injury. Moreover, the risk of tumor development, which requires long-term follow-up, has not been ruled out.

The MHLW should reflect on the history of medications for spinal cord injury.

On March 31, 1990, the New York Times published an article introducing high-dose steroid therapy, stating "for the first time ever, a cure has been found to reduce the injury to spinal cord injury." It was also published as a dissertation in a prestigious medical journal (New Engl J Med 322: 1405, 1990), swaying over people's minds. However, a critical reanalysis revealed that the efficacy was doubtful. In addition, there are many harmful reactions, such as delayed wound healing and increased diabetes, and it is now believed that the therapy should not be used.

Before this high-dose steroid therapy was approved in Japan, "pseudo" RCT (an envelope method with no strict randomization) was conducted as a follow-up study (Otani K et al., Spine & Spinal Cord Journal 7: 633, 1994). There was no difference between treated and untreated (placebo) groups although "global improvement rating" was used to evaluate the result, a method which can be influenced by investigators' subjectivity. Then, an alternative endpoint "global efficacy rating" was used to create difference so that the therapy would be approved. However, compared to the process of Stemirac approval, it can be said that the MHLW was still decent at that time.

This time, the Japanese Society for Regenerative Medicine released a statement to support the MHLW that in the case of diseases with a small number of patients, it is difficult to arrange enough number of trial participants to confirm effectiveness statistically, and it would take enormous time to do so. However, considering the epidemiological fact that about 5,000 new spinal cord injuries occur each year in Japan, and the fact that Otani et al. have registered 158 persons in 15 months, this argument has no ground.

The MHLW should immediately withdraw the approval of Stemirac and call for the implementation of RCT. Japan's scientific decency is now questioned.

The 2019 annual theme: Criticism on treatment guidelines series (8)

# Guidelines for the Treatment of Dementia 2017

## No drug is needed for management of dementia, but appropriate ways to attend to and communicate with persons with dementia are essential.

Synopsis from MedCheck 2019 (82): 34-35.

MedCheck Editorial Team

**Summary**

- There are many drugs that may cause or worsen dementia, but there is no drug that prevents progression of dementia, reduces behavioral and psychological symptoms of dementia (BPSD), prevents progression of disability, or prevents institutionalization.
- There are currently four types of anti-dementia drugs approved in Japan and other countries, but in France, in August 2018, they were removed from health insurance coverage as they bring no benefit, but harm. As MedCheck pointed out in 2007, they are not effective, but indeed very harmful. Do not prescribe or take the medication for dementia.
- The symptoms of dementia are greatly affected by how caregivers attend to and communicate with the patients. Persons with dementia would feel comfortable and their various symptoms would be largely mitigated when Humanitude® is practiced. It is a multimodal comprehensive care methodology which incorporates eye contact, verbal communication, and touch as its elements. .
- Japan's Guidelines for the Treatment of Dementia 2017 (GL2017) does not mention about medications that cause delirium or dementia, and does not introduce appropriate treatment and preventive methods for people with dementia nor non-pharmacologic treatments. GL2017 focuses on classification of the disease and pharmacological treatment. Providing pharmacological treatments according to such guidelines should be avoided.

**Keywords:**
dementia, Alzheimer disease, dementia guidelines, dementia drugs, Aricept, exercise, cholesterol-lowering agent, statins, PPI, anticholinergics, Humanitude®

### After prescribing Aricept, nothing to do for dementia

This is a symbolic remark that represents Japanese "dementia guidelines" in simple words. It was tweeted by a veteran doctor who understands dementia fairly well [1].

We have addressed many times the issue of management or treatment of dementia [2-11], including in our special issue on Dementia and Delirium No. 27 [2]. Among the many articles, "France has delisted anti-dementia agents for reimbursement" [10] was really striking. Suppose doctors in France would follow the Japanese Guidelines, they would not have anything to do for dementia patients as no anti-dementia drugs are covered by insurance.

### 2017 GL: Only diagnosis and pharmacological treatment

The revised guidelines for dementia 2017 [12] focuses on early diagnosis,including BPSD, and pharmacological treatment. It recommends 4 drugs for dementia, such as donepezil, and easy prescription of antipsychotics for BPSD without explaining about the risk of drug-induced or drug-aggravated delirium and/or dementia.

## Drugs that cause or worsen delirium or dementia

**Statins:** In chapter 4 of GL2017, statins are described as a preventive factor for dementia. It is based solely on a large number of observational studies that have not been adjusted by initial cholesterol levels **[9]**.

The Cochrane Study **[13]** found that the statins do not prevent dementia as a result of randomized controlled trials (RCTs).

The US Food and Drug Administration (FDA) **[14]** revised the labels of statins in 2012 and warned of the risk of dementia, emphasizing the results of RCT that statins cause dementia **[15, 16]**. The fact that the FDA has revised the label should be taken seriously.

Nerve damage by statins is clearly observed in animal experiments, and it is certain that the drugs can cause dementia.

**Anticholinergics:** It has long been known that even short-term use of anticholinergics can cause memory loss, attention deficit, delirium, and loss of consciousness. In the epidemiological survey, the level of anticholinergic activity or the degree of clinical cognitive impairment, such as delirium, which the drugs may cause, is divided into three categories (note), and the association with the onset of dementia is reported **[17-20]**. The longer the use of potent anticholinergics is, the higher the incidence of Alzheimer disease and dementia of all types would become.

Gray et al. **[17]** converted rank 1 to 3 anticholinergics to standard daily dose (SDD) of rank 3 drugs to determine the total exposure dose (TSDD), and reported the association with the dementia risk.

We converted TSDD to exposure years and found the correlation coefficient with the onset of dementia was 0.988 ($p = 0.0001$) for Alzheimer disease and 0.952 ($p = 0.003$) for the dementia of all types (Figure). This means that it is possible to estimate that Alzheimer disease and all-type dementia would develop 4.2 times and 3.7 times more frequently, respectively, if rank 3 anticholinergics are used for 20 years. In addition, based on the data from other reports **[18]**, the correlation between rank 2 or rank 3 anticholinergic agents and total dementia was significant. The risk level is estimated to be 2.7 if it is continued for 20 years (see the web material for details).

**Note:** Note: There are many classification methods for anticholinergic activity **[17-19]**. The latest review found 18 classifications **[20]**.

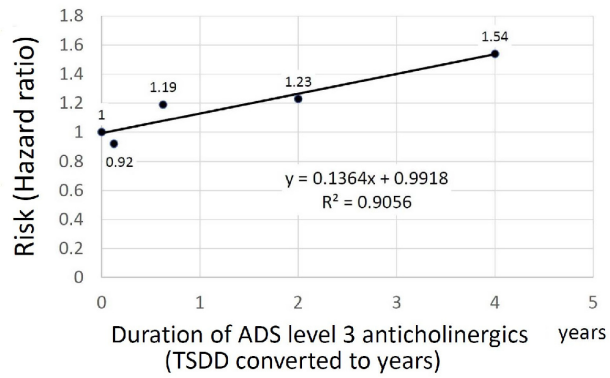
Animal studies also support the causal relationship between anticholinergics and the onset of dementia **[21-24]**.

**PPI (proton pump inhibitor):** PPI not only suppresses gastric acid by proton pump inhibition of the gastric mucosa, but also inhibits the proton pump (type V proton pump) of most cells in the body **[25]**. Therefore, it causes pneumonia and kidney disorder, and also interferes with the function of nerve cells to reduce cognitive function **[11]**.

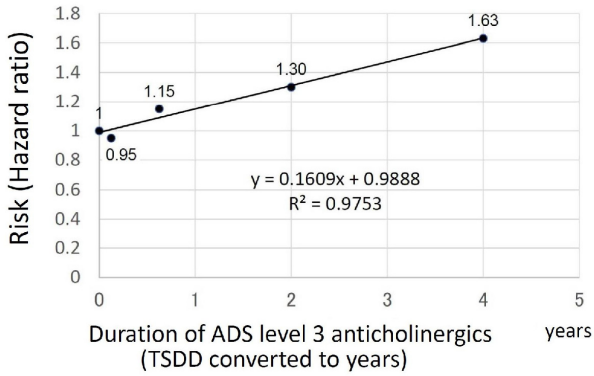
There are three appropriate studies **[26-28]** that followed people who had used PPI for a long time (6-9 years) to determine the risk (hazard ratio) of developing dementia. Overall, PPI increased dementia by 41%

**Figure: Anticholinergic prescription years and risk of developing dementia (from the data in ref [17])**

A. Dementia (any type)




B. Alzheimer disease



(p <0.0001). Persons who originally had depression developed dementia 2.3 times **[26]** or 2.7 times **[28]** more frequently.

Dementia Guidelines 2017 does not mention at all the risks of these agents that cause dementia.

## Antidementia agents do not prevent institutionalization

The methodology of a randomized controlled trial (RCT) conducted for donepezil was very complex **[29]**.

MMSE scores among people who could continue taking medication without stopping for 12 weeks of run-in period after the start of the trial was higher by 0.93 points in donepezil group than those in placebo group. However, proportions of people who discontinued was 12.8% (36/282) in the donepezil group, while 6.4% (18/283) in the placebo group (odds ratio=2.2, p=0.01). Cognitive function of people who were withdrawn was not examined. There were 19 people in the placebo group versus 40 people in the donepezil group who suffered from serious unwanted effects in the 12 weeks run-in period. This indicates that more people experienced harm than benefit in the donepezil group.

The relative risk of entering institutional care in the donepezil group compared with placebo was 0.97 (95% CI 0.72–1.30; p=0.8). The relative risk of reaching the disability endpoint was 1.02 (0.72–1.45; p=0.9).

The proportion of patients with fatal outcome or serious adverse events was significantly higher in the donepezil group (50.0%) compared with that in the placebo group (36.4%): odds ratio =1.75 (p = 0.001).

French regulators have warned of the risk of increased mortality with galantamine use (0.3% placebo vs. 1.4% galantamine) based on the results of two RCTs which were conducted for two years **[7]**. At the time of approval of galantamine in Japan, these two RCTs were not included in the examination report by the Japanese regulator **[7]**. The odds ratio was 4.7 (p = 0.008, NNTH = 93), which was calculated from the data of the published paper **[30]**.

In France, drugs for dementia have been delisted from reimbursement list because these data indicate no long-term benefit, but substantial harm.

## Appropriate and inappropriate ways for attending to or communicating with people with dementia

People with dementia have impaired memory, poor judgment ability or poor problem-solving ability, but they are very rich with emotions. However, their emotional control is diminishing, so they tend to be more anxious, be emotionally more vulnerable to trivial things, and get excited easily. If they are not properly attended, they might get hurt, excited and violent. Therefore, how to attend to them and communicate with them is very important. A specific example is introduced from a book "Do not Take Dementia Drugs" **[11]** (see the box on page 24).

The basics of inappropriate interaction that should be avoided are summarized in Kitwood's "Malignant Social Psychology" **[31]** (Table 1).

In addition, Humanitude ®, which was developed by Gineste and Marescotti **[32-35]**, is really important. It is a multimodal comprehensive care methodology, which involves eye contact, verbal communication, and touch as its elements **[33]**. Its 4 principles are summarized in Table 2 **[1]**. It is now widely practiced throughout the world, and Fukuoka City, Japan has incorporated it as a part of its project **[34]**.

**Table 1: Malignant Social Psychology by Kitwood [31]**

| | |
|---|---|
| · treachery | · objectification |
| · disempowerment | · ignoring |
| · infantffization | · imposition |
| · labeling | · withholding |
| · intimidation | · accusation |
| · stigmatization | · disruption |
| · outpacing | · mockery |
| · invalidation | · disparagement |
| · banishment | |

quoted from ref [1]

**Table 2: Principles of Humanitude ®**

| |
|---|
| 1. Do not look down, look from the front and meet the patient's gaze with same level. |
| 2. While caring, keep speaking calmly so that your patient feels comfortable. |
| 3. When moving your patient, do not hold his/her wrist but support him/her from below. |
| 4. Strive to let patient stand up to strengthen muscle, bones and respiratory function. |

quoted from ref [1]

**How we interact and communicate with people with dementia is particularly important**

Mr. X was 90 years old when he died. When he was first institutionalized, he had neither incontinence, hallucinations, delusions, nor violent behaviors. At night on day 68, as he was in bed with his glasses and hearing aid on, a care staff tried to take them off after telling him that he should. Then, he angrily said "what are you doing?" and he showed an action of attack with his belt. When the care worker lowered his posture and apologized, using gestures with eye-contact, Mr. X replied with a smile saying, "I do not want to fight. I am happy as you seem to understand me."

It is extremely important to understand the process in which the man got angry, but became calm and smiled after the care staff dealt with him in an appropriate manner.

In the morning on day 80, another care staff guided Mr. X to go outside for a walk, but he tried to get inside because it was too cold there. But the staff closed the door and he could not get inside. Mr. X hit the staff's abdomen with his fist. Other staff came in to assist, but failed to calm him down. In the afternoon, although his unrest continued, the staff took him out for a walk. However, during the walk, he did not follow the staff's advice and become violent against them. Mr. X was angry because he thought he was interfered by the staff when he felt cold outside and tried to get inside. If the staff had apologized then, he might not have gotten so angry.

His doctor considered the phenomena such as "anger" or "violence" seriously, prescribed 0.5 mg of risperidone (brand name Rispadar) to calm him and added memantine (brand name Memary) thereafter. However, his violence persisted when the staff did not understand his intention, while he thanked them when he was treated with respect and care. Parkinsonian symptoms, urinary and fecal incontinence emerged and continued as adverse reactions to risperidone. His body temperature decreased and finally hypothermia as low as 30 ° C developed, followed by convulsions. He died a half year after he entered the institution. Hypothermia is one of the typical adverse reactions to risperidone, which is described in the label.

The above is an excerpt from Ref [11]. Mr. X's greatest misery was that when he got angry and violent, the medical professionals did not review the possible causes nor reconsider seriously the way in which the care staff interacted and communicated. Instead, they erroneously relied on drugs, which offered no benefit but only harm.

Table 3 summarizes appropriate and inappropriate ways to attend to and communicate with people with dementia based on "No need to cure dementia" [1] by Ueda, "Dementia changes 100% depending on how you interact" [36] by Yoshida, and actual cases introduced in a book [11] and essays by Harumoto [2, 37].

## In Practice:No need to cure. Consider only how to interact

Dementia Guidelines 2017 gives little emphasis on such non-pharmacologic care methods and only focuses on disease classification and pharmacological treatment.

The prophylaxis methods of dementia are also important. Be careful with your daily diet, exercise properly, and ensure adequate sleeping time without relying on sleeping pills.

If you or one of your family members develop dementia, first of all, you should thoroughly check and avoid drugs that cause delirium and/or dementia.

We recommend non-pharmacological treatment including exercise. Some people may improve their cognitive function with drug therapy, but some may experience aggravation of behavioral and psychological symptoms such as overexcitement, which may be more difficult to care. Unfortunately, "dementia cannot be cured pharmacologically".

In contrast, because persons with dementia may feel relieved by the appropriate ways of interaction based on the three elements: eye contact, verbal communication, and touch.

We encourage you to review "what makes persons with dementia anxious or angry.

We recommend you to learn Humanitude® and improve eye contact, verbal communication, and touch. Through this methodology, you would surely find better strategy to improve the care for persons with dementia.

Table 3: Appropriate and inappropriate ways to interact and communicate with people with dementia

| Inappropriate | Appropriate |
|---|---|
| ① Talk suddenly, talk from behind or from side, talk fast, ask several questions at once. | ・ Start talking after confirming that it does not interfere the patien's thinking. |
| | ・ talk while looking at patients eyes at the same eye level. |
| | ・Speak slowly and at an understandable speed (If acceptable, while shaking patient's hands or touching their shoulders). |
| | ・Give easy-to-answer questions (ask only one question at one time). |
| | ・ Only after you get one answer to your previous qestion, then ask the next one. |
| ② Scold, scream, command, force, hurry, stop / restrain actions, condemn, threaten (frighten), label | ・ Do not blame the patients for their incapability. |
| | ・ Praise what the patient have succeeded. |
| | ・ Increase what the patient feels comfortable and smile. |
| | ・ Increase positive conversations as much as possible. |
| | ・ Support the patients not to fail. |
| | ・ Respect their preferences, pace and customs. |
| ③ When helping the patients move, grasp onto the wrist or the leg and pull them, etc. | ・ Touch the arms or legs as to support them from below.<br>・ Always consider not to feel fear. |
| ④ When patient show anxiety, excitement, anger, irritability, or violence, just say "calm down" or "do not do such a thing", without asking the reason. | ・ If the reason is clear, take appropriate measures. |
| | ・ If the reason is unknow, ask for a reason and take action accordingly. |
| ⑤ Even when you misunderstand the intention of the patient, you do not apologize for that. | ・ Apologize straightforward if you notice that you failed to understand the real intension of the patient and inappropriately responded to them. |
| ⑥ Take away roles from the patients. Do not allow them to do anyting. Ignore them, exclude them from a group, neglect them. | ・Let the patient take a role<br>・Show appreciation to the patients for being helpful for other people. |
| ⑦ Treat the patients like children or things. Tease or despise them. | ・ Do not hurt pride. Deal and contact the patient so that the patient could maintain the dignity as an elder who has lived for many years. |
| ⑧ Provide care or medical consultation without conversation. | ・ During nursing care, continue to talk calmly so that the patients would feel comfortable. |
| | ・ Let the patients talk about own history (especially what was fun when they were young). |
| ⑨ Prevent the patients from standing up or prevent to go outside because of possible danger. | ・Encourage the patients to stand up to strengthen muscles, bones and respiratory function. |
| ⑩ Try to follow the usual schedule even if the patients show unsual signs. Try to give medicines as prescribed even when there are signs of adverse reactions to (side effects of) the medicines. | ・ If you observe something different from usual in patients' behaviours, make an effort to find the cause. |
| | ・For example, check if prescribed drug is the cause. If this is the case, discontinue the drug. Anti-dementia drugs have no benefit, but only harm. Follow up the symptoms carefully after discontinuation. |

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The 2019 annual theme: Criticism on treatment guidelines series (9)

# Nocturia: non-drug therapy is the best treatment

## No drug can reduce sympoms

Synopsis from Med Check in Japanese March 2019 : 19 (83):60-64

MedCheck Editorial Team

**Summary**

- Nocturnal urinary frequency (nocturia) is a serious condition that lowers the quality of life (QOL), increases the risk of falling and fractures, and thus increases the mortality rate. It is one of the aging phenomena.
- In many cases, the cause of nighttime urinary frequency is nighttime polyuria, which is often caused by excessive water intake, lifestyle problems such as a lack of exercise, medical conditions such as diabetes, and medications. Fluid restriction and moderate exercise are more effective than drug therapy.
- The effects of anticholinergic agents and β3-agonists, which are used for treating so-called overactive bladder, are minimal in treating nocturia, but they rather decrease the blood flow in the brain and cause brain dysfunction, leading to dementia.
- Causal relations between nocturia and sleep disorders is an “eggs first or chickens first” issue. In either case, correct understanding of and non-pharmacological treatment for sleep disorders and nocturia are required. Sleeping agents are not recommended in principle because they cause various harms.

**Keywords:**
frequent nocturia, Guidelines for nocturia, nocturnal urine passing, nocturnal polyuria, anticholinergics, beta-3 agonists, antidiuretic hormone, sleep disorders, overactive bladder, prostatic hyperplasia

### Introduction

Japanese Guideline for nocturia is called "Guideline for frequent nocturia" [1]. However, International Continence Society defines nocturia as “waking to pass urine during the main sleep period" , without mentioning the frequency of nocturia [2,3].

No studies have shown that a single nocturia episode can be associated with an increase in all-cause mortality. There are several studies showing that two or more, especially three or more, nocturnal urinations are associated with an increase in all-cause mortality [4].

According to epidemiological surveys in Japan, the proportion of those who urinates at least once at night increases with age, and it is about 40% for men and women in their 40s and over 80% in their 80s [5]. Nocturnal urinary frequency with which a patient urinates twice or more during the main sleep period lowers the quality of life (QOL), as, for instance, it would cause fatigue during the day. In addition, an examination of the data used in the recent meta-analysis [4] showed that the total mortality rate for people who urinated twice or more at night was higher by 22% compared with people who urinated once or less at night. The total mortality rate for people who urinated three times or more was higher by 61% compared with that of all subjects. This is not only because nocturnal urination causes falls and fractures when patients get up to urinate at night, but also because it is associated with a decline in general brain functions and general physical functions.

### The bladder diary is the key to diagnosis

It is essential to have a detailed medical interview,

taking systemic diseases, such as diabetes, into consideration. In addition, doctors ask about the time to go to bed and wakeup (old people often stay in the bed for a long time), bedroom environment, the room temperature, access to the toilet etc. As for physical findings, it is necessary for diagnosis of fluid retention to check if there is edema in the lower legs. Urinalysis is essential to determine if there is urinary sugar, diluted urine, or urinary tract infections.

After that, patients should complete a bladder diary until their next hospital visit. A minimum of 24-hour consecutive record is required. A bladder diary contains not only the time and amount of urination, but also the intake of food, water and medicines. By doing this, the patient would be aware of the amount of fluid intake and output, and the amount of intake of salt, caffeine and alcohol. It will also motivate the patient to review his/her lifestyle, and will serve as a treatment.

## Three major causes

### 1. Nocturnal polyuria

According to epidemiological surveys in Japan, nocturnal polyuria is the most common cause of nocturia at night, accounting for 30 to 50% of all causes **[5]**.

Restrict fluid intake because it is often due to excessive fluid intake. Although excessive dehydration is a risk factor for ischemic stroke and myocardial infarction, the result of a systematic review shows that there is no evidence that excessive water intake leads to prevention of cerebral infarction and myocardial infarction **[6]**.

Japanese Guidelines mention the effectiveness of exercises for improving nocturia, such as walking, dumbbell exercise, and squat as they return the fluid stored in the stroma into the blood vessel by muscle pumping and also excrete it as sweat. But the guidelines downgrades the evidence level as they are not base on RCTs **[1]**. However there are some systematic reviews of many RCTs that showed moderate exercise reduces blood pressure **[7,8].** Moreover 46 year follow-up cohort study shows that it prolongs life-span **[9]**. Intensity of optimal exercise is indicated by Duzel et al **[10]** or Aoyagi et al **[11]** that were cited in Med Check **[12,13]**.

In young people, at night, antidiuretic hormone (vasopressin) is sufficiently secreted and nighttime urine volume decreases. Frequent urination with nighttime polyuria is a physiological phenomenon due to the disappearance of this rhythm with age. This type of nocturia can be prevented by restricting fluid intake in the evening. In addition, moderate daytime exercise is recommended as it increases brain blood flow and improves the secretion of antidiuretic hormone at night.

The use of the antidiuretic hormone preparation (desmopressin) as a drug therapy for this condition is not indicated and may cause hyponatremia.

### 2. Bladder storage disorder

Benign prostatic hyperplasia and/or overactive bladder cause nocturia. According to a recent review, none of the anticholinergic agents reduced the frequency of urination at night **[14]**, although Japanese Guidelines recommend them for frequent nocturia **[1]**.

### 3. Sleeping disorder

It is difficult to judge whether there is frequent urine at night because there is sleep disorder, or vice versa, but in many cases both are experienced. If there is little urine volume per urination during the daytime and frequent urination, the patient may be awake at night due to an urge to urinate. However, the frequency of urination is not high and urine volume per urination is sufficient at night, nocturnal polyuria may be the cause. If there is frequent urination in the daytime, urological consideration will be needed to determine if there is a bladder storage disorder as described above.

If polyuria is the cause, the cause of polyuria should be investigated and a non-drug therapy should be considered.

Japanese Guidelines warn against easy prescribing hypnotics but at the same time they describe the characteristics of the drugs as ultra-short acting or short acting suggesting that their blood concentrations decreases under the effective level by morning and they have no hangover effect **[1]**. These descriptions practically recommend prescribing ultra-short acting or short acting hypnotics. However hypnotics cause tolerance, dependence, fall, depression, dementia or impaired cognition, increase infection or even cancer and reduce life-span in total **[15]**.

Moderate exercise that is effective in reducing the frequency of nocturia is also effective in reducing

sleeping disorders. We recommend non-pharmacological intervention including moderate exercise also for sleeping disorders.

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The 2019 annual theme: Criticism on treatment guidelines series (10)

# Guidelines for Low-dose Pills (OC/LEP)

## Thromboembolism may occur in 1 out of 37 high risk women

Translated from Med Check in Japanese July 2019 : 19 (84):83-88

MedCheck Editorial Team

**Summary**

● Low-dose pill is a combination of two types of female hormones, namely estrogen (E) and progestin (P: luteinizing hormone) at low dose (L).

● It has been used as an oral contraceptive at users' own expense in Japan since 1998. In 2008, it was indicated for improving symptoms of primary dysmenorrhea. Since then, it has been widely used by women aged 40 and over, whose risk of thrombosis is higher than the yonger women. Four-fifths of serious thrombosis that occurs when taking low-dose pills is venous thrombosis.

● The use of low-dose pills particularly increases the risk of thrombosis by 12.6 times within 3 months after commencement compared with the risk of non-users. Then, the risk slowly decreases, but even after a year, it remains 5-fold higher over a long period of time (5 years, 10 years). More than a half of thromboembolism occurs 7 years after the initiation of treatment. Therefore, even if no harm occurs in a short-term, it is never safe.

● One thromboembolism may occur in 330-110 women who are on low-dose pills for 10 years. The risk becomes extremely high in women aged 40 or older. In women who initiated the medication at age 40 and continue the treatment for 10 years, the incidence rate would become as high as 1 out of 74 women.

●Estrogen increases coagulation in both arteries and veins. If blood clots in the small arteries, blood pressure would go up, and high blood pressure would promote blood clotting and the risk of venous thrombosis would be increased.

● If people with high blood pressure take low-dose pills, they are twice as likely to experience thrombosis as compared with people with normal blood pressure. As compared with those with normal blood pressure who are not on the medication, the risk would be 10-fold higher.

● The Guidelines of the Japan Obstetrics and Gynecology Association 2015, misrepresents "absolute contraindications" and "relative contraindications" in the WHO guideline as "relative contraindications" and "use with caution", respectively. It carelessly recommends the pills to people with high risk, such as those with high blood pressure, obesity and migraine, and smokers.

Conclusion: The low-dose pill guideline is dangerous as it promotes careless use of the medication among people with high risk.

**Keywords:**

low-dose pills, OC, LEP, deep vein thrombosis, pulmonary embolism, hypertension, contraception, dysmenorrhea, hypertension in pregnancy, Yaz, ethynyl estradiol, drospirenone

### Introduction

Low-dose contraceptive pill is a combination of an estrogenic agent (E), ethynyl estradiol (EE) (usually less than 40 μg, often 35 μg), and a progestin agent (P: synthetic luteinizing hormone) at low dose (L). E and P are both female hormones. Low-dose pills were launched in Japan in 1999 as oral contraceptives (OC).

In 2008, a product of similar components, a low-dose estrogen / progestin (LEP) combination, was approved for dysmenorrhea (Note 1), and is now widely used by women aged 40 years and older, who are more susceptible to thrombosis.

The Japanese Society of Obstetrics and Gynecology published guidelines on low-dose pills in 1999 [1], 2005 [2] and 2015 [3] (hereafter 1999 GL, 2005 GL, and 2015 GL, respectively).

In 2005 GL [2], warning was given quite carefully by accurately quoting the World Health Organization's (WHO) Medical Eligibility Criteria for Contraceptive Use (WHO-GL) [4] in order to prevent serious harm of low-dose pills that may lead to death. However, in 2015 GL [3], WHO-GL is quoted quite inaccurately, recommending the easy use of low-dose pills.

Let us see what have changed in the guideline and why it is dangerous.

Note1: Dysmenorrhea is uterine pain around the time of menses. Pain may occur with menses or precede menses by 1 to 3 days. Pain tends to peak 24 hours after onset of menses and subside after 2 to 3 days. It is usually sharp but may be cramping, throbbing, or a dull, constant ache; it may radiate to the legs [5].

## Meaning of terms 1:

### "Thrombosis" and "Thromboembolism"

Among many serious adverse reactions to low-dose pills, it is "thrombosis" that relatively frequently occurs and can lead to sudden death. It can occur in both veins and arteries. In Japan, about three-quarters to four-fifths of thrombosis due to low-dose pills is venous thrombosis (Note 2) [6], and pulmonary embolism (so-called "economy class syndrome"), which often leads to sudden death, accounts for 40% of all venous thrombosis [7].

Yaz combination tablet was approved for the treatment of dysmenorrhea in 2008. Its package insert "warns" in the beginning that "the drug might cause thrombosis which might follow a fatal course," in a red box [8] which is equivalent to to the black-box warnings in US. It explains that sudden development of pain/swelling in legs and/or shortness of breath are symptoms of thrombosis that requires urgent treatment. "Sudden development of pain/swelling in legs" suggests that a thrombus has formed or thrombophlebitis has developed in deep veins. In some cases, no pain is felt, but dyspnea is experienced as an initial symptom. In either case, thrombus that has formed in a leg brakes off, reach the heart, pass through the right ventricle and extensively obstructs the pulmonary artery. This may cause sudden shortness of breath or dyspnea as oxygen cannot be taken in, leading to loss of consciousness and sudden death.

US Food and Drug Administration (FDA) uses the term "thrombosis" referring mainly to venous thromboembolism in its guidance for industry (2004[9], 2017[10]).

We believe that the usage of this term is important. When oral contraceptives were first introduced in Japan, some obstetrician/gynecologists enthusiastically advocated the risk of thromboembolism caused by the drugs[11-13]. However, the same obstetrician/gynecologists recently changed their views and started claiming that "thrombosis mentioned in the package insert includes only arterial thrombosis, but not venous thrombosis" and "hypertension is not a risk factor for venous thrombosis" [14] . As a result, 2015 GL has incorporated their idea, and excluded hypertension as a risk factor for venous thromboembolism.

Note2: Venous thromboembolism does not refer to thromboembolism near the surface of the skin, but deep venous thrombosis and pulmonary embolism.

## Meaning of terms 2:

### Cases in which low-dose pills are contraindicated

In WHO-GL [4], categories 3 and 4 mean "A condition where the theoretical or proven risks usually outweigh the advantages of using the method: risk outweighs benefits" and "A condition which represents an unacceptable health risk if the contraceptive method is used: unacceptable health risk", respectively, in both of which "Do not use OC". Category 4 is absolute contraindications, meaning that the drug should not be used in any conditions. Category 3 is relative contraindications, meaning that "Use of method not usually recommended unless other more appropriate methods are not available or not acceptable" [4, 15, 16].

While 2005 GL followed the criteria of the WHO-GL, 2015 GL interpreted category 4, which originally means absolute contraindications in the WHO-GL, as "OC/LEP should not be prescribed in principle". Moreover,

2015GL interpreted category 3, which corresponds to relative contraindications in the WHO-GL, as "prescribe carefully". It explains as if the use of low-dose pills is the standard.

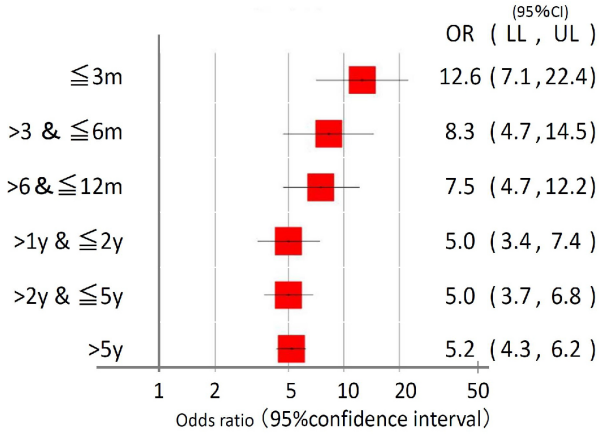
Regarding blood pressure, according to the WHO criteria, low-dose pills are contraindicated in patients whose systolic blood pressure is 140-159 mmHg or diastolic blood pressure is 90-99 mmHg when there are alternative treatment choices. In patients whose systolic blood pressure is over 160 mmHg or diastolic blood pressure is over 100 mmHg, low-dose pills are absolutely contraindicated.

## Means of contraception and treatment for dysmenorrhea other than low-dose pills

According to the WHO-GL, category 3 means that low-dose pills are "contraindicated" when other appropriate methods are available. Therefore, alternative means of contraception, and preventive methods and treatment for dysmenorrhea are important. While 2005 GL shows failure rates of various means of contraception in Table, 2015 GL does not, emphasizing that low-dose pills are more effective than other means. Indeed, the failure rate of contraceptive pills is low, and its persistency rate is moderate. It is the most effective method after sterilization among various choices of contraception. However, such a benefit would not outweigh the high risk of sudden death. If the drug is relatively contraindicated, it should be discontinued and other methods should be considered.

Non-drug therapies for prevention of dysmenorrhea are to take sufficient rest and secure adequate sleep time without depending on hypnotics as well as to have moderate exercise regularly **[16]**. Then, reduce intake of vegetable oils rich in linoleic acid, which turns into arachidonic acid that causes inflammation. Instead, use oils rich in omega-3 fatty acid (Note 3) **[5,17]**. This would help reduce the incidence of inflammation. As for drug therapy, non-steroidal anti-inflammatory drugs (NSAIDs) are effective **[5].** However, 2015 GL does not mention anything about non-drug therapies and simply recommends low-dose pills.

**Figure 1: Risk of venous thromboembolism by duration of use of low-dose pills**




Created by Med Check using data from Table 6 in ref [20], note high odds ratio continues after more than 5 years

**Table: Failure rates of various contraception methods within the first 1 year (conception rates)**

| Contraception methds | failure (%) | | continuous use through one year (%) |
|---|---|---|---|
| | ideal use * | general use ** | |
| Low-dose pill | 0.3 | 8 | 68 |
| condom | 2 | 15 | 53 |
| spermicide | 18 | 29 | 42 |
| pessary | 6 | 16 | 57 |
| IUD | 0.1-0.6 | 0.1-0.8 | 78-81 |
| rhythmic method | 1～9 | 25 | 51 |
| female sterilization | 0.5 | 0.5 | 100 |
| male sterilization | 0.1 | 0.15 | 100 |
| no contraception | 85 | 85 | |

*Ideal use: The chosen method is appropriately performed and continued.
**General use: The chosen method is generally performed, including occasionally skipping the drug.

**Note3:** Arachidonic acid is transformed to prostaglandin and leukotriene that are essential in inflammatory reaction. Therefore, when it exists excessively, inflammation may be induced. Oils rich in omega 3 fatty acid include EPA and DHA in fish oil, and perilla seed oils, Shiso oil and linseed oil among many vegetable oils [17].

## Risk of thromboembolism with low-dose pills

When 2015 GL **[3]** and its commentary **[18]** discuss the risk of thromboembolism with low-dose pills, they emphasize the absolute risk. For instance, the risk of venous thromboembolism among non-pregnant women is 1 to 5 persons in 10,000 person-years in non-low-dose pill users, 3 to 9 persons in 10,000 person-years in users of low-dose pills other than drospirenone containing ones, and 10 persons in 10,000 person-years in drospirenone containing low-dose pill users, such as Yaz. For pregnant women, thromboembolism may occur in 5 to 20 persons in 10,000 person-years. Within 12 weeks

after delivering a baby, it may occur in 40 to 65 persons in 10,000 person-years (announced by FDA **[19]**). Using these data, 2015 GL and its commentary emphasize that the risk of thromboembolism is lower in low-dose pill users than in pregnant women and women after delivery.

However, when the whole duration of pregnancy and 12 weeks after giving birth are counted as one pregnancy/delivery, the risk of thromboembolism can be calculated to be 13 to 30 per 10,000 pregnancy/delivery. In other words, 1 in 770-330 persons would develop thromboembolism during one pregnancy/delivery.

On the other hand, if low-dose pills are used for 4 years, thromboembolism may occur in 12-36 persons per 10,000 persons (1 in 830 to 280 persons). The average duration of low-dose pill use by women who developed thromboembolism is 8 years in Europe and the U.S. (This will be discussed more later).

In Japan, increasing number of women are expected to use the medication for a longer period. When low-dose pills are used for 8 years as is the case in Europe and the U.S., the risk of thromboembolism would become equivalent to the risk when experiencing pregnancy/delivery twice. When the medication is used for 10 years and 20 years, the incidence rate would be 30-90 persons in 10,000 persons (1 in 330-110 persons) and 60-180 persons in 10,000 persons (1 in 170-56 persons), respectively. This is an extremely high incidence; more frequent than that after experiencing pregnancy/delivery once.

Pregnancy and delivery carry some risks, but no matter how risky they are, there is no other means to have a child. In contrast, there are many alternative methods for contraception and treatments for dysmenorrhea. They are incomparable.

## The risk remains high after long-term use

The 2015 GL **[3]** and its commentary **[18]** emphasize that thromboembolism occurs most frequently within 3 months after initial treatment. This is indeed true. Furthermore, it is also true that the risk remains high after 5 years among low-dose pill users compared with non-users.

The problem in 2015 GL **[3]** and its commentary [18] is that they highlight reduction in the risk after 1 year, and this might create misunderstanding that the risk diminishes after that. Thromboembolism that occurs after 5 or 10 years might not be recognized as adverse reaction to low-dose pills, and thus might not be reported.

Van Hylckama Vlieg et al. **[20]** conducted a large-scale case control study on venous thrombosis and pulmonary embolism, involving non-pregnant, premenopausal women. Based on the Table 1 in their study **[20]** which shows odds ratio (OR) by duration of use. Odds ratio decreases over time; 12.6 within 3 months after initial treatment, 8.3 between 3 and 6 months, 7.5 between 6 months and 12 months, and 5.0 between 1 year and 2 years. However, after 1 year, OR remained arround 5.0 between 2 years and 5 years, and same level even after 5 years.

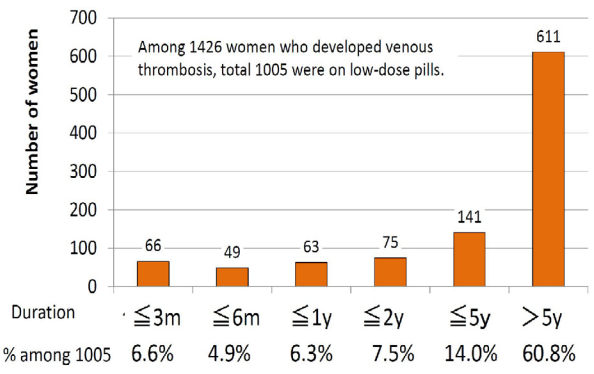
## Average duration of pill use was 8.3 years

Van Hylckama Vlieg et al. **[20]** reported that among persons who developed venous thrombosis while taking low-dose pills, duration of use was known in 1005 persons. Over 80% of them were on the medication for more than a year, and over 60% of them were on the medication for more than 5 years (**Figure 2**).

Suchon et al. **[21]** conducted a case control study, involving 968 venous thrombosis patients and 874 controls whose ages were matched. The study showed that the average duration of pill use of women who developed thromboembolism was 8.3 years (SD 7.4).

It is noteworthy that in the 2 large-scale case control studies involving around 1000 participants each, over

**Figure 2: Duration of pill use in women with thromboembolism**




Created by Med Check using data from Table 6 in ref [20].
More than 60 % among women who developed venous thrombosis used low-dose pills more than 5 years. Less than 20 % women used low-dose pills less than one year.

60 of the women who developed thrombosis with known duration of use were on the medication for more than 5 years. In addition, the average duration of use was 8 years, indicating the high risk even in the long-term users. In Japan, low-dose pills were approved in 1999, and almost 20 years have passed since then. This means that increasing number of women are on the medication for more than 5 years.

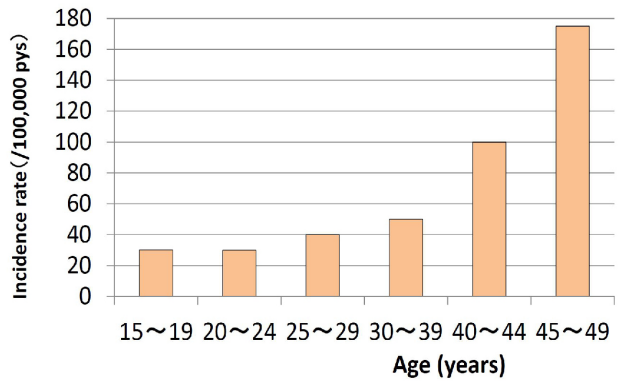
As mentioned above, when the duration exceeds 10 years, 1 in 330-110 persons would develop thromboembolism. The risk would become higher than that in women who experience 1 pregnancy/delivery (1 in 110-330 persons). This indicates that longer the medication period is, higher the risk would become.

## Risk sharply increases after age 40

Nightingale et al. **[22]** conducted a follow-up study on around 1 million person-years who were 15-49 years old and were on low-dose pills between 1992 and 1997. As a result, deep venous thrombosis was found in 395 women, and 43% of them was pulmonary embolism. They reported the risk by age group. **Figure 3** is reconstructed based on the data from the study.

The incidence rate was 30 persons/100,000 person-years in age group 15-19. It is 175 persons/100,000 person-years in age group 45-49; almost 6-fold increase. In age group 30-39, it is about 50 persons/100,000 person-years, but in age group 40-44, it sharply increases to 100 persons/100,000 person-years. Based on this rate, if the medication is initiated at age 40 and continued for 10 years, the cumulative incidence would be 1400 persons/100,000 person-years or 1 in 74 persons. In hypertension complicating cases, it would be doubled, and estimated 1 in 37 persons would develop thromboembolism. Another report **[23]** also points out that the risk of venous thrombosis sharply increases by aging. Including both low-dose pill treated and non-treated women, when the incidence rate in age group 15-19 is compared with that in age groups 35-39, 40-44 and 45-49, it increases by 4 times, 5.3 times and 6.6 times, respectively.

**Figure 3: Risk of venous thromboembolism in users of low-dose pills by age**




Created by Med Check using data from Figure and text in ref [22]. Note sharp increase in thrombosis risk after age 40 in low-dose pills users. While the incidence rate is about 50/100,000 person-years in age group 30-39, it is about 100/100,000 person-years in age group 40-44. In age group 45-49, it is 175/100,000 person-years. Based on this rate, if the medication is initiated at age 40 and continued for 10 years, the cumulative incidence would be 1400 persons/100,000 person-years or 1 in 74 persons. In case of persons with hypertension, the rate would be even doubled and would be as high as 1 in 37 persons.

## Low-dose pills double the incidence of hypertension

Hypertension caused by oral contraceptives has already been reported in 1967 **[24]**. It was a high-dose pill at that time. One woman with normal blood pressure experienced increase in blood pressure to 180/120 mmHg after taking an oral contraceptive. When the medication was discontinued, her blood pressure was normalized, but when it was resumed, it went up to 160/100 mmHg. Another woman originally had hypertension (150/90 mmHg), and her blood pressure rose to 230/140, but returned to normal after the medication was discontinued. Similar cases were reported later on. It was reported that among high-dose pill users, 15.5-18% of them had developed hypertension **[25]**. After that, another study reported that systolic blood pressure and diastolic blood pressure increased by average 6.4 mmHg and 2.7 mmHg in women who used low-dose contraceptives (ethynyl estradiol 30 μg), which is commonly used now, while no hypertension occurred in women who used progestin alone or IUD ($p<0.05$) **[26]**. Therefore, there is no doubt that hypertension is caused by oral contraceptives **[26]**.

According to the most recent meta-analysis **[27]**, oral contraceptives, including those used in the past, increased blood pressure by 1.5 times. Based on cohort studies alone, it doubled blood pressure. Moreover, the risk of hypertension increased as duration of use

became longer; 13% increase every 5 years.

## Low-dose pills promote coagulation and increases blood pressure

In order to investigate the cause of hypertension after administration of low-dose pills and pregnancy-induced hypertension, animal studies in which both estrogen and progestin are administered **[28-30]**. Since estrogen affects coagulation system and promote coagulation in peripheral arterioles, particularly arterioles in the glomerulus leading to reduction of renal blood flow and hypertension. In addition to this, sodium retention caused by synthetic progestin may contribute to development of hypertension. This is the likely mechanism (**Note 4**). It is reasonable that increased coagulation leads to not only artery thrombosis, but also deep venous thrombosis and pulmonary embolism.

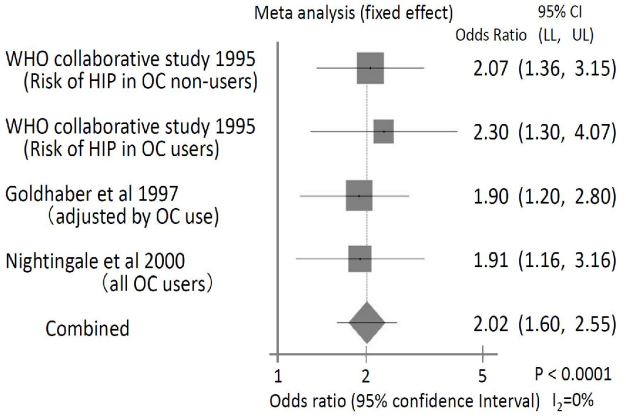
> **Note4:** Increased coagulation leads to vascular occlusion and hypertension. This coincides well with a study that showed that epsilon aminocaproic acid [28] and tranexamic acid [30] cause nephrosclerosis by promoting intravascular coagulation and occluding vessels in the kidneys, and increase blood pressure. Epsilon aminocaproic acid is a fibrinolysis inhibitor, which inhibits dissolving of clots. The study also demonstrated that antithrombin III, which suppresses formation of thrombus, inhibits this process [30]. Low-dose pills create hormonal condition similar to that during pregnancy. Therefore, women who are more likely to develop increased coagulation would develop a condition similar to pregnancy-induced hypertension. In other words, increased coagulation causes occlusion in peripheral arterioles, particularly vessels in the kidneys, leading to hypertension.

## Hypertension increases the risk of thromboembolism

The 2015 GL **[3]** states that hypertension is a risk factor for artery thrombosis, such as myocardial infarction and cerebral infarction, but does not mention at all that it is a risk factor for venous thrombosis. However, in the package insert, low-dose pills are contraindicated in “patients with hypertension” because “there is an increased risk of cardiovascular disorders including thrombosis”. The manufacturer clarified that “thrombosis” includes "venous thrombosis". This agrees with the US guidance for industry mentioned above.

Two large-scale cohort studies **[22, 32]** and one large scale case-control study with two comparison groups **[31]** which examined the risk of hypertension on occurrence of thromboembolism by use of low-dose pills (or adjusted by the use of low-dose pills) **[22,31,32]** were identified. According to a meta-analysis of the studies, hypertension would double the risk of thromboembolism (**Figure 4**).

**Figure 4: Risk of hypertension* on venous thromboembolism stratified or adjusted by OC use.**




Created by Med Check using data from ref [22,31,32].
*: Hypertension include HIP (history of hypertension in pregnancy).
OC: oral contraceptives or low-dose pills

Low-dose pills alone may increase the risk of thromboembolism by 5 times. Therefore, when persons with hypertension take the drugs, the risk increases by about 10 times as compared with that in non-hypertensive persons without the pills.

In fact, it was reported that when a woman who had hypertension during pregnancy took low-dose pills, the risk of thromboembolism increased by 9.2 times as compared with that in non-hypertensive persons without the medication **[31]**.

## Eighty percent were venous thromboembolism

Sugiura et al.**[5,6]** assessed the risk of thromboembolism (by venous or arterial) related to low-dose pill use using spontaneous reports recorded in the Japanese Adverse Reaction database of Pharmaceuticals and Medical Device Agency (PMDA) between April 2004 and December 2013. They assessed cases where Yaz, Lunabell or Jemina, which were approved for dysmenorrhea between 2005 and 2013, were used. They reported on 254 thromboembolism cases which could be classified as venous or artery. Among them, 20.9% (53 cases) was artery and about 80% was venous **[5]**. This represents how dominant venous thromboembolism

is in low-dose pill induced thromboembolism. Among the cases with venous thromboembolism, 40% had complicating pulmonary embolism.

Arterial thrombosis accounts for 0% in age group 10-19, 13% in age group 20-29, and over 20% in age group 30-39 and above, indicating increasing risk by aging (Figure 5).

## Yaz is particularly dangerous

Yaz is the first medicine introduced in Japan for treating "dysmenorrhea" in 2008. It is about 8 times likely to cause thromboembolism as compared with other low-dose pills [6] (Figure 6). At least 3 deaths were reported within 3 years after it was launched. Other reports also show that the risk increases by 1-3.3 times [34,35].

Drospirenone, a progestine in Yaz and Yaz Flex has an anti-androgenic potential[36]. It enhances estrogenic potential of these products, although they contain only 20 μg of ethynylestradiol. High incidence of thromboembolism by Yaz and Yaz Flex may be due to an anti-androgenic potential of drospirenone.

Yaz and Yaz Flex should not be used, and its approval should be withdrawn. The second generation oral contraceptives are relatively safer for dysmenorrhea among various generation of low-dose pills.

## Conclusion

**Low-dose pills are extremely dangerous agents as they may cause thromboembolism in 1/100 persons when they are used for 10 years. When the medication is initiated at age 40 and continued for 10 years, it might cause thromboembolism in 1/74 persons. In persons with hypertension, the incidence increases as high as 1/37 persons.**

**The guidelines of the Japan Obstetrics and Gynecology Association is misleading as it promotes the use of dangerous low-dose pills as if they are safe.**

**Low-dose pills should not be casually used for contraception nor dysmenorrhea.**

Figure 5: proportion of venous and arterial thrombosis in low-dose pills users by age

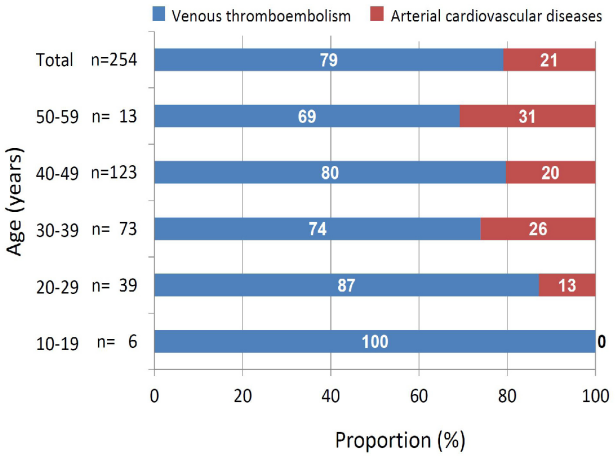
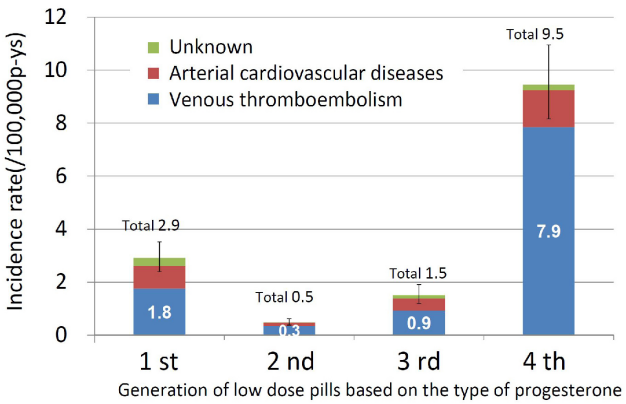



Figure 6: Incidence rate of thromboembolism by generation of low-dose pills (2009 ～ 2014 in Japan)




Generated by Med Check using the data in ref [6] p-ys: person-years
Vertical lines indicated 95% confidence interval of total incidence rate of thromboembolism. Note extremely high incidence rate in the users of 4th generation low-dose pill (Yaz) which contain drospirenone as progestin. High incidence of thromboembolism by Yaz may be due to anti-androgenic property of drospirenone which enhances estrogenisity of this product, although it contains only 20μg of ethynylestradiol.

**The 1st generation:** EE (ethynylestradiol) 35 μg + **norethisterone**
brand name: Synphase, Lunabell, Frewell

**The 2nd generation:** EE 30-40 μg + **levonorgestrel**
brand name: Ange, Triquilar, Jemina (EE 20 μg)

**The 3rd generation:** EE 30 μg + **desogestrel**
brand name: Favoir, Marvelon

**The 4th generation:** EE 20 μg + **droespirenone**
brand name: Yaz, Yaz Flex

Indication of underlined brand name is "dysmenorrhea".
Indication of Yax Flex is "improvement of pain complicated with endometriosis" in addition to "dysmenorrhea".

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