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# The incidence and prognosis of thromboembolism associated with oral contraceptives: Age-dependent difference in Japanese population

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## Abstract

***Aim:*** We analyzed the incidence and prognosis of thromboembolism associated with combined oral contraceptives (COCs) by age groups in Japan.

***Methods:*** A total of 581 events of venous thromboembolism (VTE) and arterial thromboembolism (ATE) associated with COCs were analyzed from the Pharmaceuticals and Medical Devices Agency database from 2004 to 2013. In a statistical analysis, a good-prognosis group included recovery cases and a poor-prognosis group involved unrecovered cases with some sequela and fatal cases. The significant difference between these two groups was calculated by Pearson's chi-square test, and the age-specific tendency and the trend of differences in prognosis according to different hormonal contraceptives were examined by Cochran–Armitage trend test.

***Results:*** A total of 543 events were analyzed except 38 events due to unknown age, in which DVT only was the most frequent, followed by cerebral infarction, PE with DVT, PE only, cerebral vein thromboses. ATE ratio for overall thromboembolism tended to increase with advancing age ($P = 0.0041$). Good-prognosis group was common (291 cases in VTE and 83 cases in ATE), followed by poor-prognosis group (46 cases in VTE and 34 cases in ATE). All ATE cases had a significantly poorer prognosis in comparison with all VTE cases ($P < 0.0001$). Types of progestin and age difference, however, showed no trend in the differences between good-prognosis group and poor-prognosis group ($P = 0.3548$ and $P = 0.6097$).

***Conclusion:*** Thromboembolic events were the most frequent in the 40s. The ATE ratio for overall thromboembolism tended to increase with advancing age. All ATE cases had a significantly poorer prognosis in comparison with all VTE cases.

**Key words:** age groups, arterial thromboembolism, oral contraceptive, prognosis, venous thromboembolism.

## Introduction

Thromboembolism is an unavoidable adverse event of combined oral contraceptives (COCs), and many studies have shown its increased risk associated with COC use worldwide.[1–22] We extracted thromboembolic events associated with COCs from the Pharmaceuticals and Medical Devices Agency (PMDA) database between 2004 and 2013 in Japan. The most common thromboembolic events associated with COCs were deep vein thrombosis (DVT), pulmonary embolism (PE) and their combination. The reported thromboembolic events increased year by year with an increase in the quantity of the prescription of low-dose estrogen progestin (LEP) after the approval of health insurance coverage for dysmenorrhea in 2008

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in Japan.[1–3] The incidence rates of both venous thromboembolism (VTE) and arterial thromboembolism (ATE) in Japanese COC users are estimated to be lower compared to those of people in the Western world. Our earlier study revealed,[1–3] however, the characteristics of thromboembolism associated with COC use in Japanese women were nearly similar to those of Western people in both VTE and ATE. Namely, the estimated incidence rates of VTE and ATE events per 10 000 person-years in users of LEP (35 μg ethinylestradiol combined with norethisterone, 20 μg ethinylestradiol combined with drospirenone) among women aged 10–59 years from 2009 to 2013 were 3.26 and 0.81.[2] However, the prognosis as well as age-specific incidence rates in the Japanese population are not yet known.

In this paper, we analyzed the incidence and prognosis of thromboembolism associated with COCs by age groups in Japan at present.

## Methods

We extracted adverse events including thromboembolism associated with the use of COCs from the PMDA database from April 2004 to December 2013. A total of 577 cases (581 events) of VTE, ATE and thrombosis of unspecified sites associated with the use of all contraceptives were analyzed. Contraceptives were categorized according to estrogen content and progestin content: 35 μg ethinylestradiol (EE) combined with norethisterone (the first-generation COCs), 30–40 μg EE combined with levonorgestrel or norgestrel (the second-generation COCs), 30 μg EE combined with desogestrel (the third-generation COCs), 20 μg EE combined with drospirenone (the fourth-generation COCs), 50–100 μg mestranol with norethisterone or 50 μg ethinylestradiol with norgestrel (other COCs), and progestin only (norethisterone, levonorgestrel, levonorgestrel releasing intrauterine device and dienogest). VTE included DVT, PE, cerebral vein thromboses (CVT) and other venous embolisms or thromboses. ATE included cerebral infarctions, coronary heart diseases and other arterial embolisms and thromboses. We defined it as one thromboembolic event of DVT when thrombosis of the pelvic vein, inferior vena cava or the right atrium was complicated by venous thrombosis of the lower extremities as a series of venous thromboses. In addition, we defined a case of PE complicated with DVT as one thromboembolic event for the same reason. Moreover, we counted it as one case when VTE was complicated with another thromboembolic event of ATE, or ATE was complicated with a different part of ATE at the same time.

The questionnaire about prognoses in the PMDA database was comprised of only four answers, that is, recovery, unrecovery with some sequela, fatal, and unknown. Therefore, in a statistical analysis, prognoses were divided into a good-prognosis group including recovery cases from thromboembolism, and a poor-prognosis group of unrecovered cases with some sequela or fatal cases definitely caused by thromboembolism.

The significant difference between these two groups was calculated by Pearson's chi-square test, and the age-specific tendency and the trend of differences in prognosis according to different hormonal contraceptives were examined by Cochran–Armitage trend test. Statistical analysis was done using SPSS version 20.

The study was approved by the Ethics Committee of Hamamatsu University, School of Medicine (approval number E 14–266/2014). It was performed in compliance with the Declaration of Helsinki. Consent was not obtained, but the presented data are anonymized and there is no risk of identification.

## Results

### Thromboembolic events according to age distribution every 10 years

The reported number of thromboembolic events according to age distribution between 2004 and 2013 is shown in Table 1. Among 543 events after excluding 38 events of unknown age, DVT only (150 events) was the most frequent, followed by cerebral infarction (108 events), PE with DVT (87 events), PE only (62 events), CVT (45 events), other venous thromboses (33 events), thrombosis of unspecified sites (26 events), coronary heart diseases (17 events) and other arterial thromboses (15 events), in that order. The thromboembolic events were the most frequent in the 40s (225 events), followed by the 30s (187 events), 20s (86 events), 50s (35 events) and teens (10 events). Judging from all of the VTE and ATE events in the different age groups by Cochran–Armitage trend test, the ATE ratio for overall thromboembolism tended to increase with advancing age, whereas the VTE ratio for them tended to decrease ($P = 0.0041$).

### Prognoses for each thromboembolism

The details of prognosis of each thromboembolism are shown in Table 2. In total cases of thromboembolism

**Table 1** Reported number of thromboembolic events according to age distribution between 2004 and 2013

| Age distinction | 10s (10–19) | 20s (20–29) | 30s (30–39) | 40s (40–49) | 50s (50–59) | Total |
|---|---|---|---|---|---|---|
| Thromboembolism | | | | | | |
| DVT only | 2 | 27 | 44 | 72 | 5 | 150 |
| PE only | 3 | 18 | 20 | 18 | 3 | 62 |
| DVT + PE | 2 | 15 | 24 | 39† | 7† | 87 |
| Cerebral vein thromboses | 1 | 5 | 10 | 24 | 5 | 45 |
| Other venous thromboses | 1 | 5 | 15 | 10 | 2 | 33 |
| **Total VTE** | **9** | **70** | **113** | **163** | **22** | **377** |
| Cerebral infarction | 1 | 7 | 45 | 45† | 10† | 108 |
| Coronary heart diseases | 0 | 2 | 12 | 2 | 1 | 17 |
| Other arterial thromboses | 0 | 3 | 5 | 7 | 0 | 15 |
| **Total ATE** | **1** | **12** | **62** | **54** | **11** | **140** |
| Thrombosis of unspecified sites | 0 | 4 | 12 | 8 | 2 | 26 |
| **Overall thromboembolism** | **10** | **86** | **187** | **225**† | **35**† | **543** |

DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism; ATE, arterial thromboembolism. and †Total number of cases are different from those in Table 4 because they include four complicated cases (three cases of VTE complicated with ATE, one case of ATE complicated with another part of ATE). Age unknown cases were 38.

except 105 with unknown outcomes, 387 cases were good-prognosis group and 85 cases were poor-prognosis group (71 unrecovered cases with some sequela and 14 fatal cases definitely caused by thromboembolism). In VTE cases except 54 with unknown outcomes, 291 cases were good-prognosis group and 46 cases were poor-prognosis group (34 unrecovered cases with some sequela and 12 fatal cases). Ten cases of PE and two cases of CVT were fatal. In ATE cases except 32 with unknown outcomes, 83 cases were good-prognosis group and 34 cases were poor-prognosis group (33 unrecovered cases with some sequela and one fatal case). Notably, three cases of ATE complicated by VTE resulted in poor prognoses including one fatal case. Thus, all ATE cases had a significantly poorer prognosis in comparison with all VTE cases, though fatal cases were frequent in VTE ($P < 0.0001$).

## Prognoses with different hormonal contraceptives

The details of prognosis with different hormonal contraceptives are shown in Table 3. Cases of overall thromboembolism were the most reported in the fourth-generation COC (176 cases), followed by the first-generation COC (125 cases), the second-generation COC (110 cases) and the third-generation COC (99 cases). The reported number in progestin only product was very small (nine cases). The rates of good prognosis calculated excluding unknown outcomes varied from 72.0% to 85.4%, and those of poor prognosis from 14.6% to 28.0%, whereas fatal cases of the third- and fourth-generation COC were more frequent than those of the first- and second-generation COC. As for the prognosis with different progestin types by Cochran–Armitage trend test, there was no trend in the difference between good-prognosis group and poor-prognosis group ($P = 0.3548$).

## Prognoses with age group

The details of prognosis with age group are shown in Table 4. Among good-prognosis group, 155 cases were the most frequent in the 40s, followed by the 30s (128 cases), 20 s (61 cases), 50s (24 cases) and teens (8 cases). Among poor-prognosis group, 35 cases were the most frequent in the 30s, followed by the 40s (29 cases), 20s (11 cases) and 50s (six cases). The fatal cases were mostly in their 20s and 30s (four cases for

**Table 2** Prognoses for each thromboembolism†

| Thromboembolism | VTE | ATE | Complicated cases | Thrombosis of unspecified sites | Total |
|---|---|---|---|---|---|
| Prognosis | | | | | |
| Good-prognosis group | 291 | 83 | 1 (ATE + ATE) | 12 | 387 |
| Poor-prognosis group | 46 | 34 | 3 (VTE + ATE) | 2 | 85 |
| Unknown outcomes | 54 | 32 | 0 | 19 | 105 |
| Total | 391 | 149 | 4 | 33 | 577 |

†Good-prognosis group includes recovery cases, and poor-prognosis group includes both unrecovered cases with some sequela and fatal cases. and ATE, arterial thromboembolism; VTE, venous thromboembolism.

 

**Table 3** Prognoses with different hormonal contraceptives

| Hormonal contraceptives / Prognosis | Progestin only | First-generation COC | Second-generation COC | Third-generation COC | Fourth-generation COC | Other COCs† | Total |
|---|---|---|---|---|---|---|---|
| Good-prognosis group (%)‡ | 7 (77.8) | 89 (84.0) | 73 (83.0) | 59 (78.7) | 123 (85.4) | 36 (72.0) | 387 (82.0) |
| Poor-prognosis group (%)‡ | 2 (22.2) | 17 (16.0) | 15 (17.0) | 16 (21.3) | 21 (14.6) | 14 (28.0) | 85 (18.0) |
| Unknown outcomes | 0 | 19 | 22 | 24 | 32 | 8 | 105 |
| Total | 9 | 125 | 110 | 99 | 176 | 58 | 577 |

†Other COCs include 50–100 μg mestranol with norethisterone, 50 μg ethinylestradiol with norgestrel. Good-prognosis group includes recovery cases, and poor-prognosis group includes both unrecovered cases with some sequela and fatal cases.; ‡The ratios (%) were calculated excluding unknown outcomes. and COC, combined oral contraceptive.

**Table 4** Prognoses with age group†

| Age group / Prognosis | 10s (10–19) | 20s (20–29) | 30s (30–39) | 40s (40–49) | 50s (50–59) | Unknown age | Total |
|---|---|---|---|---|---|---|---|
| Good-prognosis group | 8 | 61 | 128 | 155 | 24 | 11 | 387 |
| Poor-prognosis group | 1 | 11 | 35 | 29 | 6 | 3 | 85 |
| Unknown outcomes | 1 | 14 | 24 | 39 | 3 | 24 | 105 |
| Total | 10 | 86 | 187 | 223 | 33 | 38 | 577 |

†Good-prognosis group includes recovery cases, and poor-prognosis group includes both unrecovered cases with some sequela and fatal cases.

each), followed by 40s and 50s (two cases for each) and one in the teens. Therefore, there were many unrecovered cases with some sequela in the 30s and 40s and many fatal cases in the 20s and 30s. On the other hand, there were many recovery cases also in their 30s and 40s. As a result, there was no trend in the differences between the good-prognosis and poor-prognosis group in terms of age by Cochran–Armitage trend test ($P = 0.6097$).

## Discussion

In this study, we analyzed the incidence and prognosis of thromboembolism associated with COCs in different age groups in Japan. Our results revealed the following three findings: (i) Thromboembolic events were the most frequent in the 40s. Judging from whole VTE and ATE events in the different age groups, the ATE ratio for overall thromboembolism tended to increase with advancing age, whereas the VTE ratio for them tended to decrease ($P = 0.0041$). (ii) ATE cases had a significantly poorer prognosis in comparison with VTE cases ($P < 0.0001$). (iii) There was no trend in the differences in prognoses (good-prognosis versus poor-prognosis) either among different progestin types ($P = 0.3548$)) or different age groups ($P = 0.6097$).

COCs remain a widely used contraceptive method. Various types of pills are available worldwide, and many studies have shown an increased risk of thromboembolism associated with COC use.[1–22] This risk differs according to the type of progestin and decreases with shorter duration of use and less estrogen contents. However, there are few reports concerning the prognosis of thromboembolism associated with COC use by age groups. Roach *et al*. reported that COC use over 50 years of age was associated with the highest risk of VTE compared with non-hormone-use.[23] They also found that the absolute risk increased more in women over 50 than in younger COC users as the incidence of VTE increased exponentially with age.[24] From the rare published studies assessing predictive factors for fatal PE, mortality rates are often reported in subjects aged greater than 50 and are not stratified by age.[25,26] Schwingl *et al*. reported that the attributable risk of death from cardiovascular disease resulting from COC use was 0.06 and 3.0 per 100 000 in nonsmokers 15–34 years of age and 35–44 years of age, respectively.[27]

Mortality rates in the acute phase of cardiovascular events have decreased, but the disease burden remains high in the increasing number of survivors.[28] Maino *et al*. stated that young women who survived a cardiovascular event have a high long-term mortality and

morbidity when compared with the general population.[29] We revealed in this study that the thromboembolic events were the most frequent in the 40s, and the ATE ratio for overall thromboembolism tended to increase with advancing age ($P = 0.0041$). We understand that a ratio of ATE among overall thromboembolism tends to relatively increase with aging, though the incidence of VTE itself does not decrease with aging. Furthermore, we revealed that all ATE cases had a significantly poorer prognosis in comparison with all VTE cases ($P < 0.0001$). Though our former study[2] indicated that the age-specific estimated incidence rate of thromboembolic events was found to rise sharply after the age of 40, these data reveal the new aspect of prognosis concerning ATE and aging. Age-related vascular changes might affect these results.

COCs have long been attributed to development of CVT and have been reported in 54–71% of CVT patients.[30] In most cases, the outcome was good and the patients were functionally independent (83%). Very few patients remained dependent (10%). This finding contrasts with the outcome from arterial stroke types, in which the proportion of permanently dependent patients ranges between one third and two thirds of the survivors.[31] From their evaluation of 22 patients with CVT related to COC use, Özdemir *et al*. reported that 16 patients completely recovered, and six partially recovered with some neurological deficit.[32] The CVT mortality rate was 4.8% (2/42) in our study,[1] and Bousser *et al*. noted a mortality rate of 7.3% at the end of follow-up,[33] which was within the range reported in the literature (5.5–15%).[34–36] In our study, CVT was frequent, followed by DVT and/or PE among VTE, and 21.5% of CVT cases showed a poor prognosis regardless of age.

In France, more than 4 million women are daily exposed to COCs.[28] The mean annual number of premature deaths attributable to their use was 20. As compared to the use of first- and second-generation COCs, exposure to third- and fourth-generation COCs led to a mean annual excess of nine premature deaths. The mortality rate in this study was approximately 0.5 per 100 000 person-years, which is the same as our data published before.[1] In our study regarding the prognosis of thromboembolism, there was no significant difference according to progestin types ($P = 0.3548$), whereas fatal cases of the third- and fourth-generation COC outnumbered those of the first- and second-generation COC.

In conclusion, thromboembolic events were most frequent in the 40s. The ATE ratio for overall thromboembolism tended to increase with advancing age. All ATE cases had a significantly poorer prognosis in comparison with all VTE cases. It is important to explain sufficiently the benefits and the thromboembolic risk when prescribing COCs. Physicians should prescribe them carefully in women over 40, and particularly at over 50.

### Study limitation

The data of adverse events we used in the present study were based on a voluntary report to PMDA, and all events of COC-related thromboembolism may not be necessarily reported. Furthermore, the rate of unknown outcomes of 18.2% (105/577) posed a problem.

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## Disclosure

None declared.

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