ORAL CONTRACEPTIVES AND THE RISK OF MYOCARDIAL INFARCTION

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ABSTRACT

Background An association between the use of oral contraceptives and the risk of myocardial infarction has been found in some, but not all, studies. We investigated this association, according to the type of progestagen included in third-generation (i.e., desogestrel or gestodene) and second-generation (i.e., levonorgestrel) oral contraceptives, the dose of estrogen, and the presence or absence of prothrombotic mutations.

Methods In a nationwide, population-based, case–control study, we identified and enrolled 248 women 18 through 49 years of age who had had a first myocardial infarction between 1990 and 1995 and 925 control women who had not had a myocardial infarction and who were matched for age, calendar year of the index event, and area of residence. Subjects supplied information on oral-contraceptive use and major cardiovascular risk factors. An analysis for factor V Leiden and the G20210A mutation in the prothrombin gene was conducted in 217 patients and 763 controls.

Results The odds ratio for myocardial infarction among women who used any type of combined oral contraceptive, as compared with nonusers, was 2.0 (95 percent confidence interval, 1.5 to 2.8). The adjusted odds ratio was 2.5 (95 percent confidence interval, 1.5 to 4.1) among women who used second-generation oral contraceptives and 1.3 (95 percent confidence interval, 0.7 to 2.5) among those who used third-generation oral contraceptives. Among women who used oral contraceptives, the odds ratio was 2.1 (95 percent confidence interval, 1.5 to 3.0) for those without a prothrombotic mutation and 1.9 (95 percent confidence interval, 0.6 to 5.5) for those with a mutation.

Conclusions The risk of myocardial infarction was increased among women who used second-generation oral contraceptives. The results with respect to the use of third-generation oral contraceptives were inconclusive but suggested that the risk was lower than the risk associated with second-generation oral contraceptives. The risk of myocardial infarction was similar among women who used oral contraceptives whether or not they had a prothrombotic mutation. (N Engl J Med 2001;345:1787-93.)

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THE first report of coronary thrombosis associated with the use of oral contraceptives appeared in 1963.[1] Later studies established the use of oral contraceptives as a risk factor for venous as well as arterial thrombosis.[2-7] Various modifications were made in an attempt to lower these risks, including a reduction in the estrogen dose and changes in the progestagen compound. Oral contraceptives containing an estrogen and the progestagen desogestrel or gestodene, available since the 1980s, are associated with at least a doubling of the risk of venous thrombosis as compared with other combined oral contraceptives.[8-12] It has been suggested that these third-generation contraceptives protect against myocardial infarction by having a favorable effect on the lipid profile,[13-15] because studies showed that women who used these types had a slight increase in the level of high-density lipoprotein cholesterol.[15,16] Only a few studies of the association between oral contraceptives and myocardial infarction have included a direct comparison of third- and second-generation progestagens, and the results have been contradictory.[17-21] We investigated whether the use of low-dose combined oral contraceptives affects the risk of myocardial infarction. We assessed the effect of the type of progestagen included in the oral contraceptive (levonorgestrel as compared with gestodene or desogestrel), the dose of estrogen, and the presence of the G1691A mutation in the factor V gene (factor V Leiden) and the G20210A mutation in the prothrombin gene, which have been associated with myocardial infarction in young women[22,23] as well as with a particularly high

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risk of venous thrombosis in women who use oral contraceptives [24]

METHODS

Study Design

The Risk of Arterial Thrombosis in Relation to Oral Contraceptives (RATIO) study is a population based case–control study of the relation of arterial disease to the use of oral contraceptives among women 18 to 49 years of age in the Netherlands The study protocol was approved by the ethics committees of the participating hospitals (see the Appendix) Oral informed consent was obtained from all participants

Identification of Women with Myocardial Infarction

Eligible patients were women 18 to 49 years of age who were hospitalized for a first myocardial infarction between January 1990 and October 1995 Myocardial infarction was defined by the presence of symptoms, elevated cardiac enzyme levels, and electrocardiographic changes [25] The patients were identified through a search of computerized hospital data bases for *International Classification of Diseases, 9th Revision, Clinical Modification* codes for acute myocardial infarction Of the 321 women who were admitted to the 16 participating centers during this period, 29 (9 percent) were excluded 19 died during admission, 9 died between discharge and the start of the study, and 1 was unable to participate The medical records of all patients were reviewed by one investigator Of the 292 remaining patients, 21 could not be located and 23 declined to participate (response rate, 85 percent)

Control Women

The study was designed to investigate three types of arterial disease myocardial infarction, ischemic stroke, and peripheral arterial disease, the results for each type are reported separately We identified and recruited one large control group through random digit dialing [26] In this method, private telephone numbers randomly generated by a computer are dialed until someone answers or at least seven attempts have been made at various times of the day and the week, including the weekend We reached someone at 98 percent of the numbers after a total of 15,725 telephone calls Once it was ascertained that a household included a woman who was eligible for the study, she was asked to participate We recruited control women from the six geographic areas where the patients lived, and using questionnaires, we assigned each an index year corresponding to the one of the six years (1990 to 1995) in which the patients had had an index event Therefore, a control woman randomly received one of six questionnaires concerning one of the index years All questions elicited information about either the index date (in the case of questions about the body mass index, menopausal status, level of education, and family history), the year before the index date (in the case of questions about a history of hypertension, diabetes, hypercholesterolemia, alcohol use, and smoking), or the month before the index date (in the case of questions about the use of oral contraceptives) The index date was the date of the myocardial infarction in the patients and midyear in the controls To minimize age differences between the patients and the controls, control women in the older age groups were oversampled by increasing the age limit of eligibility criteria during recruitment The control group therefore was a population sample stratified according to age (in five year categories), area of residence, and calendar year

Eligible controls were women 18 to 49 years of age who had no history of coronary, cerebral, or peripheral arterial disease A total of 1259 eligible women were reached by random digit dialing, 925 of whom agreed to participate and returned the questionnaire (73 percent)

Data Collection

The standardized questionnaire that was mailed to patients and controls included questions about demographics, use of oral contraceptives, reproductive history, height and weight, and the presence or absence of a history of hypertension, diabetes, hypercholesterolemia, and cigarette smoking and a family history of cardiovascular disease Color photographs of all oral-contraceptive pills marketed in the Netherlands during the study period were included to help women recall the formulations they might have used Oral contraceptives were divided into four groups according to the type of progestagens included first-generation formulations containing lynestrenol or norethindrone, second-generation formulations containing levonorgestrel, third generation formulations containing desogestrel or gestodene, and oral contraceptives containing an estrogen and other progestagens (cyproterone or norgestimate) or a progestagen alone We also classified oral contraceptives according to the dose of estrogen Women were categorized according to their use of oral contraceptives (never, former, or current) The level of education was categorized as primary school or less, secondary school, or higher education or university Obesity was defined as a body mass index (the weight in kilograms divided by the square of the height in meters) of at least 27.3 [23] Women were classified as having hypertension, diabetes, or hypercholesterolemia when they reported that the condition had been diagnosed by a physician or that they had been taking medication for the condition before the index date Smoking status was categorized as never, former, or current Current smokers were those who reported smoking in the year before the index date Alcohol use was categorized as none, 1 to 15 drinks per week, and more than 15 drinks per week A family history of cardiovascular disease was defined as the occurrence of myocardial infarction, stroke, or peripheral arterial disease before the age of 60 years in one or more first degree relatives

Samples of venous blood or buccal swabs were obtained from 217 patients (88 percent) and 763 controls (82 percent) who consented to undergo DNA analysis for factor V Leiden and the G20210A mutation in the prothrombin gene The polymerase chain reaction was used for the analysis [27,28]

Statistical Analysis

We used unconditional logistic-regression analyses to calculate odds ratios for the relation between the use of oral contraceptives and myocardial infarction, and we derived confidence intervals from the model We adjusted for the three stratification factors — age (in five year categories), area of residence, and calendar year — and for putative confounding factors (smoking status, presence or absence of hypercholesterolemia, diabetes, hypertension, obesity, and a family history of cardiovascular disease, level of education, and alcohol intake) To exclude an effect of the dose of estrogen in the analyses that were focused on the type of progestagen included in the oral contraceptive, we excluded women who used formulations other than those containing 30 μg of ethinyl estradiol 28 women (13 patients and 15 controls) used second generation oral contraceptives containing 50 μg of ethinyl estradiol, 67 women (13 patients and 54 controls) used triphasic second generation oral contraceptives, 3 women (all controls) used triphasic third generation oral contraceptives, 18 women (2 patients and 16 controls) used third generation oral contraceptives containing 20 μg of ethinyl estradiol, and in 6 women (1 patient and 5 controls) the dose of ethinyl estradiol was unknown In a further effort to minimize the possibility of confounding, in particular by the presence of preexisting disease, we repeated the analysis after excluding women with major cardiovascular risk factors We also directly investigated whether confounding was present, in particular prescription bias, by analyzing risk factors and oral contraceptive use in the control women Analyses of the dose of ethinyl estradiol were restricted to women who used oral contraceptives containing 50 μg of ethinyl estradiol and 150 μg of levonorgestrel or 30 μg of ethinyl estradiol and 125 μg of levonorgestrel Finally, we assessed the effect of combinations of risk factors the use of oral contraceptives and conventional risk factors (current smoking, hypercholesterolemia, diabetes, and hypertension), as well as factor V Leiden and the G20210A mutation in the prothrombin gene

RESULTS

Table 1 shows the characteristics of the 248 women who had had a myocardial infarction and the 925 control women. Patients ranged in age from 24 to 49 years (mean, 43), and controls ranged in age from 18 to 49 years (mean, 38). Patients had a higher prevalence than controls of major risk factors for cardiovascular disease, such as hypertension (24 percent vs. 6 percent), hypercholesterolemia (11 percent vs. 3 percent), diabetes (6 percent vs. 1 percent), and current smoking (84 percent vs. 43 percent). Patients also had a lower level of education than controls (11 percent vs. 27 percent with post–secondary-school education).

The risk of myocardial infarction among users of any type of oral contraceptive was twice that of nonusers (95 percent confidence interval, 1.5 to 2.8), after adjustment for age, calendar year, and area of residence (Table 2). Additional adjustment for putative confounding factors increased the odds ratio in most age categories, and the overall risk remained doubled (Table 2). Women with no conventional risk factors (hypertension, hypercholesterolemia, diabetes, or smoking) who used oral contraceptives had a relative risk of myocardial infarction of 3.1 (95 percent confidence interval, 1.0 to 9.2). The duration of oral-contraceptive use did not differ significantly between patients and controls (median, 10 years).

Second-generation oral contraceptives containing levonorgestrel were used by 24 percent of the patients and 19 percent of the controls (Table 3). Third-generation oral contraceptives containing desogestrel or gestodene were used by 8 percent of the patients and 12 percent of the controls. The odds ratio for myocardial infarction was 2.8 (95 percent confidence interval, 1.3 to 6.3) for women who used first-generation contraceptives, as compared with those who had not used oral contraceptives; 2.4 (95 percent confidence interval, 1.6 to 3.6) for women who had used second-generation contraceptives; and 1.3 (95 percent confidence interval, 0.8 to 2.3) for women who had used third-generation contraceptives (Table 3). When we restricted this analysis to users of second-generation oral contraceptives (37 patients and 94 controls) and third-generation oral contraceptives (18 patients and 91 controls) that contained 30 μg of ethinyl estradiol, the odds ratios did not change substantially: 2.7 for users of second-generation oral contraceptives (95 percent confidence interval, 1.6 to 4.3) and 1.6 for users of third-generation oral contraceptives (95 percent confidence interval, 0.9 to 2.9). A direct comparison of oral contraceptives containing 30 μg of ethinyl estradiol and levonorgestrel, desogestrel, or gestodene revealed an odds ratio for myocardial infarction of 0.5 (95 percent confidence interval, 0.2 to 1.1) for third-generation as compared with second-generation oral contraceptives (after adjustment for stratification variables). The odds ratios were similar for third-generation brands containing desogestrel or gestodene. Further adjustment for confounding did not affect these estimates (Table 3).

TABLE 1. CHARACTERISTICS OF 248 WOMEN WITH A FIRST MYOCARDIAL INFARCTION AND 925 CONTROL WOMEN.*

CHARACTERISTIC	PATIENTS (N=248)	CONTROLS (N=925)
Age — yr	42 7±6 5	38 1±8 3
White race — no (%)	234 (94)	864 (93)
Level of education — no (%)		
Primary school or less	130 (53)	278 (30)
Secondary school	91 (37)	390 (42)
Higher education or university	26 (11)	252 (27)
History of hypertension — no (%)	59 (24)	56 (6)
History of hypercholesterolemia — no (%)	28 (11)	24 (3)
History of diabetes — no (%)	15 (6)	13 (1)
Body mass index	25 7±5 1	23 5±3 9
Smoking status — no (%)		
Never smoked	21 (8)	305 (33)
Former smoker	19 (8)	222 (24)
Current smoker	208 (84)	394 (43)
Family history of cardiovascular disease — no (%)	156 (65)	311 (36)
Premenopausal — no (%)	205 (83)	767 (83)

*Plus–minus values are means ±SD. Data on the level of education were missing for 1 patient and 5 controls, data on history of hypertension, history of diabetes, and smoking status were missing for 4 controls, data on history of hypercholesterolemia were missing for 5 controls, data on body-mass index (the weight in kilograms divided by the square of the height in meters) were missing for 30 controls, and data on family history of cardiovascular disease were missing for 9 patients and 54 controls.

In an analysis that was restricted to the 41 patients and 104 controls who had used contraceptives with a second-generation progestagen, as compared with those who had not used oral contraceptives, the risk of myocardial infarction was similar for oral contraceptives with different doses of estrogen. The odds ratio was 2.0 (95 percent confidence interval, 0.6 to 7.3) for brands containing 50 μg of ethinyl estradiol with levonorgestrel and 2.6 (95 percent confidence interval, 1.6 to 4.2) for brands containing 30 μg of ethinyl estradiol with levonorgestrel. A direct comparison of oral contraceptives containing levonorgestrel and ethinyl estradiol revealed an odds ratio of 1.7 (95 percent confidence interval, 0.4 to 7.9) for all brands that contained less than 50 μg of ethinyl estradiol as compared with brands that contained 50 μg of ethinyl estradiol or more.

We analyzed the effect of other cardiovascular risk factors in women who used oral contraceptives, as compared with the reference category of women who had not used oral contraceptives and who did not have the given risk factor (Table 4). The adjusted odds ratios for myocardial infarction among women who had not used oral contraceptives were 7.9 (95 percent con-

TABLE 2. ODDS RATIOS FOR MYOCARDIAL INFARCTION AMONG WOMEN WHO USED ANY TYPE OF ORAL CONTRACEPTIVE, ACCORDING TO AGE *

AGE	PATIENTS (N=248)		CONTROLS (N=925)		ODDS RATIO (95% CI)†	ODDS RATIO (95% CI)‡
	TOTAL NO	OC USE	TOTAL NO	OC USE		
	no (percent)					
18–24 yr	2	1 (50)	69	57 (83)	0.4 (0.01–10.0)	0.8 (0.1–10.9)
25–29 yr	8	6 (75)	118	88 (75)	1.2 (0.2–7.7)	3.8 (1.5–9.2)
30–34 yr	27	18 (67)	140	71 (51)	2.6 (0.9–7.1)	6.2 (1.1–35.7)
35–39 yr	31	12 (39)	167	52 (31)	1.6 (0.7–3.7)	5.7 (1.3–24.6)
40–44 yr	60	29 (48)	170	39 (23)	2.7 (1.4–5.3)	3.4 (1.3–8.7)
45–49 yr	117	33 (28)	252	41 (16)	2.0 (1.2–3.5)	1.7 (0.8–3.3)
Total	245	99 (40)	916	348 (38)	2.0 (1.5–2.8)	2.0 (1.4–3.0)

*For each age group, the women who had not used oral contraceptives served as the reference group. Twelve women (three patients and nine controls) were excluded from the analysis; it was not known whether seven controls had used oral contraceptives, and five women used hormone replacement therapy (three patients and two controls). OC denotes oral contraceptive, and CI confidence interval.

†Odds ratios were adjusted for the area of residence and calendar year.

‡Odds ratios were adjusted for the area of residence and calendar year, smoking status, presence or absence of hypertension, hypercholesterolemia, diabetes, obesity (a body mass index of at least 27.3), and a family history of cardiovascular disease, level of education, and alcohol intake.

TABLE 3. ODDS RATIOS FOR MYOCARDIAL INFARCTION IN RELATION TO THE TYPE OF PROGESTAGEN INCLUDED IN THE ORAL CONTRACEPTIVE *

TYPE OF ORAL CONTRACEPTIVE USED	PATIENTS (N=248)	CONTROLS (N=925)	ODDS RATIO (95% CI)†	ODDS RATIO (95% CI)‡
	no (%)			
Any type	99 (40)	348 (38)	2.0 (1.5–2.8)	2.1 (1.4–3.1)
First generation (lynestrenol or norethindrone)	11 (4)	31 (3)	2.8 (1.3–6.3)	2.7 (1.0–7.3)
Second generation (levonorgestrel)	59 (24)	173 (19)	2.4 (1.6–3.6)	2.5 (1.5–4.1)
Third generation (desogestrel or gestodene)	20 (8)	110 (12)	1.3 (0.8–2.3)	1.3 (0.7–2.5)
Other§	9 (4)	28 (3)	2.3 (0.9–5.6)	2.1 (0.7–6.4)

*For each comparison the group of women who had not used oral contraceptives (146 patients and 568 controls) served as the reference group. Twelve women (three patients and nine controls) were left out of the analysis; it was not known whether seven controls had used oral contraceptives, and five women used hormone replacement therapy (three patients and two controls). The type of oral contraceptive used was unknown in six controls. CI denotes confidence interval.

†Odds ratios were adjusted for age, area of residence, and calendar year.

‡Odds ratios were adjusted for age, area of residence, and calendar year, smoking status, presence or absence of hypertension, hypercholesterolemia, diabetes, obesity (a body mass index of at least 27.3), and a family history of cardiovascular disease, level of education, and alcohol intake.

§This category included oral contraceptives containing an estrogen and either cyproterone or norgestimate or containing a progestagen alone.

fidence interval, 4.9 to 12.9) for those who smoked, 5.1 (95 percent confidence interval, 2.9 to 8.8) for those with hypertension, 3.3 (95 percent confidence interval, 1.6 to 6.8) for those with hypercholesterolemia, 4.2 (95 percent confidence interval, 1.6 to 10.9) for those with diabetes, and 3.4 (95 percent confidence interval, 2.2 to 5.3) for those who were obese. Among women who had used oral contraceptives, the risk of myocardial infarction was highest among those who smoked (odds ratio, 13.6), those who had diabetes (odds ratio, 17.4), and those who had hypercholesterolemia (odds ratio, 24.7).

Factor V Leiden or a G20210A mutation in the prothrombin gene was present in 18 of 214 patients (8 percent) and 58 of 760 controls (8 percent). Two control women carried both mutations. The odds ratio for myocardial infarction among women with a prothrombotic mutation was 1.1 (95 percent confidence interval, 0.6 to 1.9), as compared with women without a mutation. In the subgroup of smokers the presence of one of these mutations increased the risk of myocardial infarction by 1.6 (95 percent confidence interval, 0.8 to 3.3). Among women younger than 35 years of age who had a prothrombotic mutation, the odds ratio was 1.6 (95 percent confidence interval, 0.4 to 5.8), and among those who were at least 35 years old it was 0.9 (95 percent confidence interval, 0.5 to 1.7). The use of oral contraceptives doubled the risk of myocardial infarction among women without a prothrombotic mutation (odds ratio, 2.1; 95 percent confidence interval, 1.5 to 3.0) and among women with a prothrombotic mutation (odds ratio, 1.9; 95 percent confidence interval, 0.6 to 5.5).

DISCUSSION

In this case–control study we found that the use of currently available combined oral contraceptives increased the overall risk of a first myocardial infarction. As compared with nonusers, women who used first- and second-generation oral contraceptives had a significantly increased risk, but the results were inconclusive for women who used third-generation oral contraceptives. The risk was increased in all age groups except for the small group of women who were 18 to 24 years old, and there were no significant differences in the odds ratios between the age categories

TABLE 4. ODDS RATIOS FOR MYOCARDIAL INFARCTION IN RELATION TO THE USE OF ORAL CONTRACEPTIVES AND TO THE PRESENCE OR ABSENCE OF CARDIOVASCULAR RISK FACTORS *

RISK FACTOR	NO USE OF ORAL CONTRACEPTIVES			USE OF ORAL CONTRACEPTIVES		
	PATIENTS (N=146)	CONTROLS (N=568)	ODDS RATIO (95% CI)	PATIENTS (N=99)	CONTROLS (N=348)	ODDS RATIO (95% CI)
	no. of women			no. of women		
Smoking						
No	25	338	1.0	15	183	2.0 (1.0–4.1)
Yes	121	228	7.9 (4.9–12.9)	84	165	13.6 (7.9–23.4)
Hypertension						
No	111	532	1.0	75	327	2.1 (1.5–3.1)
Yes	35	36	5.1 (2.9–8.8)	24	19	6.1 (3.1–12.1)
Hypercholesterolemia						
No	129	547	1.0	88	344	2.0 (1.4–2.8)
Yes	17	20	3.3 (1.6–6.8)	11	3	24.7 (5.6–108.5)
Diabetes						
No	136	556	1.0	94	345	2.1 (1.5–2.9)
Yes	10	11	4.2 (1.6–10.9)	5	2	17.4 (3.1–98.1)
Obesity (body mass index ≥27.3)						
No	95	476	1.0	75	300	2.4 (1.6–3.5)
Yes	51	76	3.4 (2.2–5.3)	24	37	5.1 (2.7–9.6)
Factor V Leiden or prothrombin G20210A mutation†						
No	116	446	1.0	80	258	2.1 (1.5–3.0)
Yes	13	36	1.4 (0.7–2.7)	5	20	1.9 (0.6–5.5)

*Twelve women (three patients and nine controls) were left out of the analysis: it was not known whether seven controls had used oral contraceptives, and five women used hormone replacement therapy (three patients and two controls). Data on smoking, hypertension, hypercholesterolemia, and diabetes were missing for 2 controls, and data on obesity were missing for 27 controls. Odds ratios were relative to those of the reference groups (nonusers without the given risk factor) and were adjusted for age, area of residence, and calendar year. CI denotes confidence interval.

†A total of 217 patients and 763 controls underwent DNA testing. DNA could not be analyzed in 3 patients and 3 controls.

or between the doses of estrogen. The risks were highest among users of oral contraceptives who smoked, who had diabetes mellitus, or who had hypercholesterolemia, but they were not affected by the presence of factor V Leiden or the G20210A mutation in the prothrombin gene.

The use of second-generation oral contraceptives increased the risk of myocardial infarction by a factor of 2.5. The use of third-generation oral contraceptives did not increase the risk significantly (odds ratio, 1.3). The direct comparison of second- and third-generation oral contraceptives suggested that the use of third-generation agents was associated with a lower risk of myocardial infarction, but the confidence interval was wide and therefore a definite conclusion could not be reached.

Five studies, including ours, have directly compared the effect of the use of second- and third-generation oral contraceptives on the risk of myocardial infarction,[17,21] with reported odds ratios that ranged from 0.3[18] to 1.8.[21] Only the study by Dunn et al.[21] and our study were designed to assess whether the use of third-generation oral contraceptives has a different effect on the risk of myocardial infarction than does the use of second-generation agents and included a sufficient number of women who used third-generation oral contraceptives to allow conclusions to be drawn. Dunn et al. suggested that the risk is higher with third-generation than with second-generation oral contraceptives (odds ratio, 1.8; 95 percent confidence interval, 0.7 to 4.8), whereas we found the reverse (odds ratio, 0.5; 95 percent confidence interval, 0.2 to 1.1). As can be seen from the confidence interval, the study by Dunn et al. also did not permit a definite conclusion to be reached.

Our study was designed as a nationwide, population-based, case–control study, with patients recruited from all eight academic centers in the Netherlands and eight surrounding hospitals. One of the strengths of our study is that the use of both second- and third-generation oral contraceptives is widespread in the Netherlands, thus providing a large population of potential study subjects. In the evaluation of our results, we also need to address the possibility of bias. Because all patients with known myocardial infarction were hospitalized and the patients were selected entirely on the basis of the discharge diagnosis, selection bias is improbable. The rate of nonresponse was fairly low and was unlikely to have been associated with the use of oral contraceptives or the type of agent used. Information bias was unlikely, because the women were not told about the primary objective of the study and the questionnaire elicited information about many issues. The subjects' recall was optimized by the inclusion in the questionnaire of color photographs of all available oral contraceptives.[29] However, the possibility of recall bias cannot be excluded. Patients who died after a myocardial infarction were not included in the study, but it is unlikely that the use of oral contraceptives would be a specific contributing factor to the case fatality rate.

Selective prescription following screening for risk factors may affect the risks associated with the use of oral contraceptives. We therefore investigated risk-factor status according to the use of oral contraceptives in the control women and found little difference in the prevalence of cardiovascular risk factors between those who used oral contraceptives and those who did not (Table 5). There were small differences in the incidence of hypercholesterolemia and diabetes and in body-mass index, which were in part explained by the younger age of oral-contraceptive users. To minimize the likelihood of confounding, we also conducted an analysis restricted to women with no cardiovascular risk factors and still found that women who used oral contraceptives had a risk of myocardial infarction that was three times the risk among nonusers.

Although the risk of myocardial infarction in users of oral contraceptives is small in absolute terms, it has an important effect on women's health, since 35 to

TABLE 5. PREVALENCE OF RISK FACTORS FOR CARDIOVASCULAR EVENTS IN CONTROL WOMEN, ACCORDING TO THEIR USE OF ORAL CONTRACEPTIVES.*

FACTOR	USE OF ORAL CONTRACEPTIVES (N=348)	NO USE OF ORAL CONTRACEPTIVES (N=568)
Age — yr	33 2±8 3	41 1±6 7
Level of education — no (%)		
Primary school or less	90 (26)	183 (32)
Secondary school	155 (45)	232 (41)
Higher education or university	100 (29)	152 (27)
History of hypertension — no (%)	19 (5)	36 (6)
History of hypercholesterolemia — no. (%)	3 (1)	20 (4)
History of diabetes — no (%)	2 (1)	11 (2)
Body mass index	22 9±4 0	23 8±3 6
Smoking status — no (%)		
Never smoked	114 (33)	187 (33)
Former smoker	69 (20)	150 (27)
Current smoker	165 (47)	228 (40)
Alcohol intake — no (%)		
None	129 (38)	188 (33)
0–15 drinks/wk	206 (60)	343 (61)
>15 drinks/wk	9 (3)	34 (6)
Family history of cardiovascular disease — no (%)	104 (32)	203 (38)

*Plus–minus values are means ±SD. Nine women were excluded from the analysis: it was not known whether seven women had used oral contraceptives, and two women used hormone replacement therapy. Data on the level of education were missing for 3 women who had used oral contraceptives and 1 woman who had not used them; data on smoking status were missing for 3 women who had not used oral contraceptives; data on alcohol intake were missing for 4 women who had used oral contraceptives and 3 women who had not used them; and data on family history of cardiovascular disease were missing for 22 women who had used oral contraceptives and 29 who had not used them.

45 percent of women of reproductive age use oral contraceptives.[30] Because all combined oral contraceptives are equally effective means of birth control, the issue of safety is paramount. Since the absolute risk of myocardial infarction is highly age-dependent, the risk associated with the use of oral contraceptives will have the greatest effect in older women. A large number of women who were 35 years of age or older still used oral contraceptives (26 percent). This finding, however, may be specific to the Netherlands (the rate is 24 percent in national statistics).[30] Before prescribing oral contraceptives, clinicians should screen women for conventional risk factors for cardiovascular events, and they should remember that the most important advice they can give these women remains to quit smoking.

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APPENDIX

The following investigators and centers in the Netherlands participated in the study Leiden University Medical Center, Leiden — E E van der Wall, Sint Antonius Hospital, Nieuwegein — N M van Hemel, Academic Medical Center, Amsterdam — R J G Peters, Rijnstate Hospital, Arnhem — H A Bosker, Medical Center Haaglanden, Westeinde Hospital, The Hague — J Kolf, University Medical Center, Nijmegen–St Radboud — F W A Verheugt, Leyenburg Hospital, The Hague — B J M Delemarre, University Medical Center, Rotterdam–Dijkzigt — F A M Jonkman, Academic Hospital, Maastricht — F Vermeer, Rijnland Hospital, Leiderdorp — C van Rees, Medical Center Free University, Amsterdam — O Kamp, University Medical Center, Utrecht — E O Robles de Medina (deceased), Academic Hospital, Groningen — M van den Berg, Bronovo Hospital, The Hague — P R M van Dijkman, Sint Franciscus Hospital, Rotterdam — A Schelling, and Diaconessenhuis Leiden — S A G J Witteveen

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