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Cardiovascular Events Associated With Different Combined Oral Contraceptives

A Review Of Current Data

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Abstract

Studies of combined oral contraceptive (COC) use and cardiovascular disease have been conducted against a background of low cardiovascular risk in young women, changing COC composition and changing user selection and monitoring. Studies of myocardial infarction have found inconsistent results, possibly because of differences in the prevalence of risk factors (particularly smoking and raised blood pressure) in the populations studied. In the absence of a history of smoking and other conventional risk factors, current users of modern COCs probably do not have an increased risk of myocardial infarction. Neither are former users at risk. Evidence for important differences in the risk of myocardial infarction between formulations is weak and contradictory.

Current users of low estrogen dose COCs have a small increased risk of ischaemic stroke although most of the risk occurs in women with other risk factors (notably smoking, hypertension and probably a history of migraine). Former users of COCs do not have an increased risk of ischaemic stroke. There is insufficient information to determine whether major differences in the risk of ischaemic stroke exist between products. Current users appear to have a modestly elevated risk of haemorrhagic stroke, mainly in women older than 35 years; former users do not. Data examining the risk of haemorrhagic stroke in current COC users with other risk factors are very sparse, as are those relating to the haemorrhagic stroke risk associated with particular COCs.

Numerous studies have found, with remarkable consistency, an elevated risk of venous thromboembolism among current users of low estrogen dose COCs. The

risk is substantially elevated among women with various inherited clotting factor defects. The effects in COC users with other risk factors for venous thrombosis tend to be less pronounced and more inconsistent. A number of studies have found higher relative risks among current users of low estrogen dose COCs containing desogestrel or gestodene, than among users of similar products containing levonorgestrel. A number of explanations, in terms of bias or confounding, have been proposed for these clinically small differences. At best, empirical evidence for these explanations, is weak.

The risk of cardiovascular disease of any description is low in COC users. Women can minimise, and possibly eliminate entirely, their arterial risks by not smoking and by having their blood pressure checked before using a COC (in order to avoid its use if raised blood pressure is discovered). Users may decrease their venous thromboembolic risk by their choice of COC preparation although the effects will be modest.

The first report suggesting a link between use of combined oral contraceptives (COCs) and pulmonary embolism appeared in 1961.[1] Since then, there have been more than 70 epidemiological studies investigating the relationship between COC use and myocardial infarction, stroke or venous thromboembolism.[2] This work has been conducted in an environment where the risk of cardiovascular disease in young women is very low, especially among nonsmokers (table I). Furthermore, since their introduction there have been many changes in the composition of available COCs, as well as in the selection and monitoring of women choosing to use this method of contraception. As a result, there has been limited opportunity to demonstrate with statistical robustness cardiovascular risks in subgroups of users, especially those using particular preparations.

The inability to recruit large numbers of women exposed to any particular formulation has caused epidemiologists to rely on less specific analyses when assessing the possible influence of the hormonal content of COCs on cardiovascular risk. For example, the estrogen component has often been evaluated by grouping preparations into those containing >50μg, 50μg, <50μg of estrogen. Such groupings ignore the pharmacological effects of the accompanying progestogen. Moreover, preparations containing lower doses of estrogen usually have lower doses of progestogen than those with a higher estrogen content; the progestogen may also be different. These changes cannot be compensated for by statistical adjustments. Analyses of high dose (≥50μg) versus low dose (<50μg) pills, therefore, are only crude comparisons between older and more recently available COCs. Although imprecise, such comparisons have been helpful when trying to assess whether the overall risk of cardiovascular disease associated with COC use has declined over time.

In recent years, a number of publications have suggested material differences in the cardiovascular risk profiles of particular COC formulations. Much of the evidence was reviewed in November 1997 by a World Health Organization (WHO) Scientific Group.[3,4] What influence should this information have on current clinical practice?

1. Myocardial Infarction

Studies which included data collected after 1980 (i.e. those likely to provide information about currently available COCs) and which have examined the relationship between myocardial infarction and current COC use have produced inconsistent results.[3] A number of recent studies have reported a significantly increased risk of myocardial infarction among all current users compared with non- or never-users of COCs. These studies include a large WHO-sponsored, case-control study conducted in 16 countries [relative risk in European countries: 5.0, 95% confidence interval (CI) 2.5 to 9.9, relative risk in developing countries 4.8, CI 2.5 to 9.1],[5] a

Table I. Estimated number of cardiovascular events at different ages in nonusers of combined oral contraceptives in developed countries, per million women (reproduced from the World Health Organization[3] with permission)

	Age (years)		
	20-24	30-34	40-44
Nonsmokers			
Acute myocardial infarction	0.135	1.697	21.28
Ischaemic stroke	6.030	9.837	16.05
Haemorrhagic stroke	12.73	24.28	46.30
Venous thromboembolism	32.23	45.75	59.28
Total	**51.12**	**81.56**	**142.9**
Smokers			
Acute myocardial infarction	1.083	13.58	170.2
Ischaemic stroke	12.06	19.67	32.09
Haemorrhagic stroke	25.46	48.55	138.9
Venous thromboembolism	32.23	45.75	59.28
Total	**70.83**	**127.6**	**400.5**

5-country Transnational case-control study (relative risk 2.4, CI 1.4 to 3.9)[6] and the Oxford/Family Planning Association cohort study (relative risk 4.9, CI 1.4 to 16.6).[7] On the other hand, no significantly increased risks were found in case-control studies conducted in California, US (relative risk 1.7, CI 0.5 to 5.9),[8] Washington State, US (relative risk 0.9, CI 0.4 to 2.2)[9] or England, Scotland and Wales (relative risk 1.4, CI 0.8 to 2.5).[10] The variation in risk estimates may be partly attributable to differences in study design, such as the use of hospital-based rather than community-based controls.[11] Perhaps more importantly, the variation may also be attributable to differences in the prevalence of risk factors such as smoking (especially heavy smoking) and the checking of blood pressure in the populations studied.

Several studies have found substantially higher relative risk among current COC users who also smoke.[5,7,12,13] For instance, in the Royal College of General Practitioners' Oral Contraception Study, current users who smoked ≥15 cigarettes per day had more than a 20-fold increase in risk of myocardial infarction than nonsmoking nonusers (relative risk 20.8, CI 5.2 to 83.1); the relative risk among nonsmoking users was 3.3 (CI 1.6 to 6.7).[13] The 2 studies which have examined the risk of myocardial infarction in current users with and without a history of high blood pressure found higher relative risks among those with such a history.[5,13] In both the WHO and the Transnational study, current users who reported not having had their blood pressure checked before the current episode of use had higher relative risks of myocardial infarction than current users who had had their blood pressure checked.[5,6] Little is known about the risk among COC users with other risk factors for heart disease, such as a history of diabetes mellitus or lipid abnormalities. The relative risk of myocardial infarction among current users does not appear to change with the age of the user.

These findings emphasise the importance of not exaggerating the risk of myocardial infarction in current users without known risk factors for heart disease. Indeed, evidence from the WHO study suggests that women who do not smoke and who do not have other cardiovascular risk factors (defined as no self-reported history of hypertension, diabetes mellitus, rheumatic heart disease or abnormal blood lipids) have no extra risk of myocardial infarction if they use a COC (relative risk 1.1, CI 0.1 to 9.7).[5] Thus, at the population level, oral contraceptives contribute little to the risk of myocardial infarction in young women. In the Myocardial Infarction and Oral Contraceptives (MICA) study, 87% of events occurred in women who were not taking oral contraceptives and 87% of women

experiencing a myocardial infarction had 1 or more cardiovascular risk factor.[10]

None of the studies observing an increased risk of myocardial infarction during current use found an increasing risk with longer periods of use. There is no substantive evidence of an increased risk of myocardial infarction among past users of COCs compared with never users. Curiously, the 2 recent US studies observed lower risks of myocardial infarction among past users of COCs, an effect which was not accounted for by use of hormone replacement therapy among past users.[8,9]

Currently, there is no strong evidence that lowering the estrogen content of COCs below 50μg reduces the risk of myocardial infarction.[3] A number of studies have compared the risk of myocardial infarction among users of COCs containing different progestogens, particularly levonorgestrel, desogestrel and gestodene.[5-10,14] Pooled results from 2 US case-control studies found similar relative risk among users of low dose COCs containing levonorgestrel and those containing norethisterone [0.9 (CI 0.2 to 6.6) and 1.0 (CI 0.4 to 2.9), respectively].[9] In the WHO study, the relative risk of myocardial infarction was 1.0 (CI 0.1 to 7.0) among current users of low dose COCs containing desogestrel or gestodene and 1.6 (CI 0.5 to 5.5) among users of preparations containing levonorgestrel, both compared with nonusers of COCs.[5] These risk estimates were not significantly different from each other. Interestingly, all of the users of COCs containing desogestrel or gestodene reported having their blood pressure checked prior to the episode of current use, compared with only 6 of the 13 cases and 11 of the 17 controls using levonorgestrel-containing products.

The Transnational study found a lower risk among users of low dose preparations containing desogestrel or gestodene (risk relative to nonusers: 0.8, CI 0.3 to 2.3) than among users of low dose formulations with levonorgestrel (risk relative to nonusers: 3.0, CI 1.5 to 6.1).[6] These risk estimates were significantly different from each other but were based on a small number of events. Thus, there were only 7 cases using desogestrel- or gestodene-containing COCs, and most of these came from recruiting centres in England or Scotland. Restriction of the analysis to cases from these 2 countries gave a relative risk for desogestrel- or gestodene-containing COCs of 0.8 (CI 0.3 to 2.2) and that for levonorgestrel-containing low dose COCs of 0.6 (CI 0.3 to 1.4). Very limited data from computerised general practice records from the UK failed to find evidence suggesting a particularly beneficial effect of low dose COCs containing desogestrel or gestodene.[14] No differences between 'second' generation COCs (low dose preparations containing levonorgestrel or norethisterone) and 'third' generation COCs (low dose products containing desogestrel or gestodene) were observed in the large MICA study (relative risk 1.8, CI 0.7 to 4.8).[10]

2. Ischaemic Stroke

A number of studies using data collected after 1980 have examined the risk of ischaemic stroke in current users of COCs.[3,15] In spite of a number of differences in study design, population studied and comparison group (i.e. never users alone or never users and past users combined) a fairly consistent pattern of increased risk was found among all current users. Most studies found the increased risk to be roughly 3- to 4-fold greater than that among nonusers; none had a relative risk of <1. The risk was not affected by duration of use. Past use of COC does not appear to be associated with a persisting elevated risk of ischaemic stroke. In several studies, past users had a lower risk of ischaemic stroke compared with never users[16,17] although it is unclear how COCs might exert any protective effect.

Higher relative risks in older users have been observed in several studies,[18,19] perhaps because of changes in the prevalence of hypertension among older women.[18] Greater relative risks have been observed among current users who smoke than users who do not smoke.[18,20,21] Thus, although smoking itself leads to a 1.5- to 2-fold increase in the risk of ischaemic stroke compared with that in nonsmokers, current use of a COC multiplies this risk by another 2- to 3-fold.[3] The rela-

tive risk of ischaemic stroke in current users with a history of hypertension appears to be at least 3-fold greater than that in current users without hypertension. Two studies have found smaller relative risks among women who reported having their blood pressure checked prior to the current episode of use, compared with current users who denied having this check.[18,22]

Current users of COCs with a history of migraine appear to be at higher risk of ischaemic stroke than users without this problem.[17,23,24] For instance, the WHO study observed a higher relative risk of ischaemic stroke in current users of low dose COCs with a history of migraine compared with users of similar preparations without such a history [6.6 (CI 0.8 to 54.8) and 1.2 (CI 0.3 to 4.3), respectively].[24]

As with myocardial infarction, it is important not to exaggerate the risk of ischaemic stroke in apparently healthy users of COCs. In women at low risk (nonsmokers without high blood pressure, and reportedly having had a blood pressure check prior to COC use) the risk of ischaemic stroke appears to be about 1.5-fold greater than that in non-users.[18,22] Studies in communities where highly organised medical services are likely to select out individuals at higher risk of stroke have tended to observe smaller relative risks among current users,[17] although it is impossible to be sure whether this is the full explanation for the findings.

Use of COCs containing 50μg of estrogen is associated with a greater risk of ischaemic stroke than use of COCs with a lower estrogen content.[3,16] There is, however, little information about the effects of 20μg preparations. In an interim analysis of a Danish case-control study of cerebral thromboembolism, low dose COCs containing desogestrel or gestodene had lower risk estimates (relative risk 1.3, CI 0.8 to 2.2) than those for preparations containing levonorgestrel or norgestimate (relative risk 2.4, CI 1.4 to 4.2).[25] However, the confidence intervals surrounding each estimate overlapped and in some instances were wide reflecting the small numbers upon which they were based. No statistically significant differences between COCs were observed in the WHO[18,26] or Transnational[22] studies although the data were too sparse to reliably demonstrate major differences that might exist.

3. Haemorrhagic Stroke

All of the relevant recent studies of haemorrhagic stroke have found relative risks for all current use of COCs of >1.0, although none were >2.0 and only 1 was statistically significant.[3] A relationship with duration of use does not appear to exist. There is no convincing evidence of an elevated risk of haemorrhagic stroke among past COC users.

Whereas smoking and hypertension have often been found to be independent risk factors for haemorrhagic stroke, most studies of the effects of COCs in women with these factors have been too small to provide useful risk estimates. In the WHO case-control study of cardiovascular disease, the risk of haemorrhagic stroke appeared to occur mostly in those aged 35 or more years.[27] Smoking increased the risk associated with COC use although the effect was modest; the relative risk increased from about 1.5 in nonsmoking COC users to 3.0 in smoking COC users. On the other hand, COC users with a history of hypertension had substantially greater relative risks of haemorrhagic stroke than users without this problem (perhaps a 10-fold increase).[3] Current users of COCs aged <35 years, who do not smoke and who do not have hypertension probably do not have an increased risk of haemorrhagic stroke.[27]

The limited available data do not suggest important differences between particular COC formulations in relation to their risk of haemorrhagic stroke.[3,26,28]

4. Venous Thromboembolism

Studies of the relationship between COC use and venous thromboembolism have been remarkably consistent in their finding of an increased risk.[3,29,30] None of the studies that included data collected after 1980 had relative risks among all current users of <2.0; most were close to 3.0 or above. The consistency and size of the observations across a large number of studies of different design conducted in a number of countries, and the

lack of plausible alternative explanations in terms of bias, confounding and chance, strongly suggest a causal relationship between venous thrombosis and COC use. The risk may be higher during the first year of use before falling to a smaller, albeit still elevated, risk while COCs are used.[31-36] The risk declines rapidly once COCs are stopped, perhaps within 3 months.

The relative risk of venous thrombosis among current users is not affected by age, smoking status or history of varicose veins. Evidence suggesting enhanced risks in obese current users is contradictory.[3] Women with inherited clotting factor defects, such as factor V Leiden mutation, protein C deficiency, protein S deficiency or antithrombin III defect, have a substantially elevated risk of venous thromboembolism if they use COCs,[37-40] including cerebral venous sinus thrombosis.[41,42] In 1 study, COC users with factor V Leiden mutation had a relative risk of deep vein thrombosis of 34.7 (CI 7.8 to 154.0) compared with nonusers without this defect; the relative risk in COCs users without the defect was 3.7 (CI 2.2 to 6.1).[38] The absolute risk of venous thromboembolism, however, remains low even among users with coagulation deficiencies; perhaps 3 extra cases of venous thrombosis per year per 1000 users with factor V Leiden mutation compared with users without this defect.[3]

Evidence to support the notion that the risk of venous thromboembolism has declined as the estrogen content of COCs has decreased is contradictory.[3] In late 1995/early 1996, a number of publications reported results that suggested a greater risk of venous thromboembolism among users of COCs containing desogestrel or gestodene than among users of preparations with other progestogens, principally levonorgestrel.[31,32,43-46] Another study found a similar pattern of different risk between preparations when they analysed their data in a cohort fashion, but not when they analysed it as a nested case-control study.[47] The risk of venous thrombosis among users of low dose COCs containing a fixed dose of desogestrel combined with 20 or 30μg of ethinylestradiol appeared to be higher for formulations containing lower doses of the estrogen.[32,43,47]

A number of studies have been published since. Some have found higher risk estimates between second and third generation COCs, although the differences were not always statistically significant possibly because many of the studies were small.[30,34,39,48,49] Others have not observed differences between products.[40,50,51] The largest new study reported interim results from a 5 year case-control of venous thromboembolism conducted in Denmark which compared information collected retrospectively 6 to 18 months after the event in 375 cases and contemporaneously in 1041 controls.[34] The control women were older than cases as they had originally been recruited as controls for a case-control study of stroke.[25] The older age distribution is likely to have increased the proportion of nonusers of COCs and, because age is related to type of COC used, increased the proportion of older COCs recorded in the control group. The effect will have been to diminish differences in risk between older and newer COCs, a problem that cannot be overcome by statistical adjustment. Low dose COCs containing desogestrel or gestodene were associated with higher risks of venous thromboembolism than low dose levonorgestrel-containing formulations, although the differences were not statistically significant.

Small studies of cerebral venous thrombosis have produced conflicting results regarding the effects of different COCs.[52,53]

Much scientific debate followed the reporting of the unexpected findings in 1995, with some observers attributing most or all of the difference to confounding or bias. In order to produce the observations the postulated problems (such as selective prescribing, diagnostic or referral bias, and depletion or attrition of susceptibles) would have to operate differentially among users of the various COCs.

The newer COCs have been marketed as being advantageous because they are associated with smaller changes in measured physiological variables than older preparations. The implication was that

these differences reduced the risk of cardiovascular disease. Clinicians may have responded to these marketing messages by preferentially prescribing newer COCs to women perceived to be at higher risk of cardiovascular disease. When doing so, clinicians are likely to have used selection criteria based on established cardiovascular risk factors such as age, smoking, hypertension and obesity; risk factors which relate mostly to arterial rather than venous disease. All of the studies excluded women with illnesses predisposing to venous thrombosis. Moreover, the 1 study to report in detail the characteristics of women using the different formulations found no suggestion that desogestrel- or gestodene-containing COCs were systematically prescribed to women at higher risk of venous or arterial disease.[44] None of the studies observed substantial confounding from age or any of the other measured potential confounders such as high body mass index.

In order for differential diagnostic or referral bias to account for the observed differences between products, clinicians would have had to have been particularly alert to possible thromboembolic problems in women using desogestrel- or gestodene-containing COCs, perhaps because they were aware they were prescribing these newer products to women at high risk of vascular problems. It is conceivable that clinicians might ask about COC use when considering the differential diagnosis in young women with leg or chest pain. It is also conceivable that clinicians referred such women for further investigation on the basis of the answer received. It seems highly unlikely, however, that clinicians would ask women what type of COC they were using, and then selectively decided to refer or investigate symptomatic women on the basis of brand of COC used. Further evidence against diagnostic and referral bias comes from 2 recent studies which compared women objectively diagnosed as having deep vein thrombosis with women referred to the same centres because of clinical suspicion of thrombosis which was not substantiated after full investigation.[29,30] Both studies found significantly elevated relative risks among current users of oral contraceptives.

Depletion or attrition of susceptibles is said to occur when women placed on a particular preparation experience an adverse effect, or symptom/sign related to future risk of venous thrombosis, and so are eliminated from the user group by changing to another brand or a different method of contraception.[45] Since long term users of a particular COC probably have good tolerance to adverse effects, this bias has also been termed the healthy user effect. It is argued that when a new preparation is first marketed, most users will be either new users (some of whom may be at increased risk of venous thrombosis because of the absence of previous exposure to any 'screening' effects of exogenous hormones) or women who have switched brands because they could not tolerate their previous COC. The latter group is said to constitute a higher risk group[45] although it is not clear why this should be the case given that most women change their COC because of 'minor' adverse effects such as nausea, bodyweight gain or menstrual upset; symptoms that are unlikely to be related to venous thrombosis.

Evidence to support the existence of attrition of susceptibles bias is weak and contradictory. In 1 analysis, the risk estimates for particular COCs used by women aged 25 to 44 years were ranked by the year in which the COC was first marketed and a positive trend of increasing risk with recency of introduction was observed.[45] This was interpreted as evidence for the presence of the bias. However, no such trend was observed among younger women, leading some commentators to question the conclusion.[54,55] Earlier studies of spontaneous adverse reaction reports from the late 1960s and early 1970s failed to find evidence of higher risk of venous thrombotic problems among users of lower estrogen dose preparations.[56-58] In these studies, the lower dose products represented the more recently introduced preparations and so presumably would have been used preferentially by first time users. The proportion of first time users in these earlier studies is likely to have been greater than in more recent studies since the earlier inves-

Table II. Estimated number of cardiovascular events and deaths attributed to combined oral contraceptive use in developed countries, per million woman-years[3]

	Age (years)		
	20-24	30-34	40-44
Events in nonsmoking users	67.58	97.34	183.5
Events in smoking users	83.77	132.4	312.2
Deaths in nonsmoking users	2.06	3.31	21.46
Deaths in smoking users	6.78	13.6	59.7

tigations took place at a time of both rapid increase in the size of the market and major change in the characteristics of the typical user (from older, married, parous women to younger, single nulliparous women). In the WHO study, differences between desogestrel- or gestodene-containing COCs and levonorgestrel-containing preparations were observed consistently among both first time and previous COC users.[59]

Inadequate statistical analysis has also been suggested as an explanation for the observed differences between products.[33,47,60] Similar analyses in different datasets, however, have produced opposite findings.[59,61,62]

All observational research, whether of case-control or cohort design, is prone to bias and confounding. Nevertheless, none of the proposed non-causal explanations for the venous thromboembolic differences between products have been supported by strong empirical evidence.[3,63]

5. Possible Biological Mechanisms for the Cardiovascular Effects

We do not currently understand how COCs exert their cardiovascular effects. Depending on their formulation, low dose COCs affect numerous aspects of haemostasis, lipoprotein metabolism, glucose and insulin metabolism.[64,65] Modern COCs are also associated with small changes in blood pressure.[66-69] Differences between preparations have been observed with respect to their effects on acquired resistance to activated protein C, with third generation COCs being more resistant than second generation COCs.[70-72] Although this has lead some observers to conclude that this is the biological mechanism by which the different COCs exert their thromboembolic effects,[73] this remains to be established.

6. Clinical Practice Implications

What messages should the clinician take from this evidence? First, the risk of cardiovascular disease, of whatever description, is low in COC users. Secondly, at all ages the effect of smoking on cardiovascular risk is greater than the effect of COC use (table II). The arterial risks can be minimised, and possibly removed entirely, by taking a careful personal and family history, and by checking the user's blood pressure.[74] Women who wish to use COCs and who smoke should be encouraged to stop smoking although in young women (perhaps aged <40 years) the additional risk from smoking is minimal.[3] Hypertension appears to be an important factor contributing to the arterial risks associated with COC use; wherever possible, blood pressure should be checked before and during COC use. Women with hypertension should probably use another method of contraception. Very little is known about the risk in COC users with other cardiovascular risk factors (such as diabetes mellitus). In the absence of smoking or hypertension women with other cardiovascular risk factors might use COCs with caution although this advice is not based upon a substantial body of evidence. The presence of multiple risk factors should lead to greater caution. There is no convincing evidence that women with cardiovascular risk factors will benefit from the use of low dose COCs containing desogestrel or gestodene in preference to other available COCs. The low prevalence of venous thromboembolism in young women results in a poor positive predictive value for tests screening for clotting abnormalities.[75] This and other considerations, such as fi-

nancial and social costs, argue against the screening of all women prior to COC use.[3,76]

Thirdly, the observed difference between desogestrel- or gestodene-containing COCs and other low dose preparations in venous thromboembolic risk is probably real. The difference, however, is of only marginal clinical significance in terms of absolute risk, particularly when mortality is considered. On the other hand, there is no suggestion that the newer preparations are associated with lower risks of venous thrombosis than the older low dose COCs. All other things being equal, therefore, prudent prescribers should probably use an older low dose formulation as first choice. This said, all of the currently available COCs are remarkably safe. Clinicians should not, therefore, feel that they are using an inferior preparation if other factors lead them to recommend the use of a desogestrel- or gestodene-containing COC.

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