Contraceptive Hormone Use and Cardiovascular Disease

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Contraceptive hormones, most commonly prescribed as oral contraceptives (OCs), are a widely utilized method to prevent ovulation, implantation, and, therefore, pregnancy. The Women’s Health Initiative demonstrated cardiovascular risk linked to menopausal hormone therapy among women without pre-existing cardiovascular disease, prompting a review of the safety, efficacy, and side effects of other forms of hormone therapy. A variety of basic science, animal, and human data suggests that contraceptive hormones have antiatheromatous effects; however, relatively less is known regarding the impact on atherosclerosis, thrombosis, vasomotion, and arrhythmogenesis. Newer generation OC formulations in use indicate no increased myocardial infarction risk for current users, but a persistent increased risk of venous thromboembolism. There are no cardiovascular data available for the newest generation contraceptive hormone formulations, including those that contain newer progestins that lower blood pressure, as well as the nonoral routes (transdermal and vaginal). Current guidelines indicate that, as with all medication, contraceptive hormones should be selected and initiated by weighing risks and benefits for the individual patient. Women 35 years and older should be assessed for cardiovascular risk factors including hypertension, smoking, diabetes, nephropathy, and other vascular diseases, including migraines, prior to use. Existing data are mixed with regard to possible protection from OCs for atherosclerosis and cardiovascular events; longer-term cardiovascular follow-up of menopausal women with regard to prior OC use, including subgroup information regarding adequacy of ovulatory cycling, the presence of hyperandrogenic conditions, and the presence of prothrombotic genetic disorders is needed to address this important issue.

In the U.S., hormone therapy delivered as oral contraceptives (OCs) is one of the most commonly prescribed birth control methods, used by 11.6 million or 19% of women (1). Since their introduction in the 1960s, OCs have been used by approximately 80% of U.S. women at some point in their life to block ovulation, implantation, and, therefore, pregnancy (2). The simplicity of the available regimens, low frequency of side effects, and relative safety compared with pregnancy (3) has resulted in widespread use.

Observational studies demonstrate that young women have a relatively lower age-adjusted risk of cardiovascular disease compared with men. Cardiovascular risk rises after menopause (4), suggesting that endogenous reproductive hormones may play a protective role. We and others have further demonstrated that disruption of ovulatory cycling, indicated by estrogen deficiency and hypothalamic dysfunction (5), or irregular menstrual cycling (6,7) in premenopausal women is associated with an increased risk of coronary atherosclerosis and adverse cardiovascular events, respectively. The concept that pre-menopausal contraceptive hormone use may be protective for atherosclerosis is appealing.

Conversely, recently published data on mortality from cardiovascular disease has shown that since the year 2000, mortality rates have increased in women between the ages of 35 and 44 years compared with decreases in all other age groups (4). Increased rates of obesity and smoking and declines in physical activity are prevalent in this group of midlife women (8). Also coincident in this age group was an increased OC use during the same decades, from 4% to 17% (1,2). In part because OCs are effective and safe for contraception, and because pre-menopausal women are at relatively lower cardiovascular risk than the general public, there has been relatively little specific study devoted to evaluating links between contraceptive hormone use and cardiovascular disease.

Data from the Women’s Health Initiative that demonstrated an increased cardiovascular risk with menopausal hormone therapy use among women without pre-existing cardiovascular disease (9–11) have prompted a review of risks and benefits of other forms of hormone therapy for women.
This review outlines the physiology and mechanisms of cardiovascular action of contraceptive hormones, particularly those found in OCs. It includes basic science, animal and human clinical studies that address contraceptive hormone use and cardiovascular disease. We also review the current guidelines for contraceptive hormone use in women with elevated cardiovascular risk.

Estrogen and Progesterone Physiology

Endogenous estrogen is produced by the ovaries in the form of 17β-estradiol, which acts at 2 estrogen receptors (ERs), ERα and ERβ, with equal binding affinity (12–14). There are 2 known pathways triggered by estrogen activation of these receptors, commonly referred to as the genomic and nongenomic pathways. The genomic pathway occurs through ligand binding, in which estrogen as a steroid passes through the lipid membrane and binds receptors located in the nucleus, which either activates or suppresses gene transcriptions. The nongenomic pathway is a rapid activation of the receptor located at the cell membrane and causes a release of intracellular messengers such as nitric oxide, calcium, or kinases. For example, the nongenomic pathway results in activation of nitric oxide synthase to cause acute arterial vasodilation (15,16).

Endogenous progesterone blood levels rise each month from the corpus luteum after ovulation, remain high during the luteal menstrual phase to inhibit ovulation, and eventually drop at the time of menstruation (17). Progestins are the synthetic form of the hormone progesterone derived from 19-nortestosterone, 17-OH progesterone derivatives, or 19-norprogesterone (18). Bioidentical progesterone is used for menopausal therapy but not for contraception. There are many types of progestins, each differing in its potency and affinity to the progesterone, estrogen, and androgen receptors. Levonorgestrel (LNG) and norethindrone directly bind to the receptor while desogestrel needs to be actively converted in the body before being bioavailable (17). The newer progestins, including gestodene, desogestrel, and norgestimate, are selective in that they have little androgenic effect while inhibiting ovulation and endometrial hypertrophy. The newest contraceptive and menopausal hormone formulations include combinations of estrogen and drospirenone, where the progestin is derived from spironolactone and has antiandrogenic and diuretic properties (19).

Contraceptive Hormones: Initiation and Evolution

Contraceptive hormones were first introduced in the 1960s as OCs that simulated a state of pregnancy by causing high hormonal blood levels that suppressed ovulation and implantation. The “pill” was developed to be cyclical, with a 28-day cycle of 3 weeks of continuous combined fixed-dose estrogen and progestin followed by 1 week of sham pills. This design induced hormonal withdrawal bleeding to simulate the monthly menses and reassure women of the absence of pregnancy.

There have been 3 main evolutions in OC development, including changes to: 1) the dose and types of hormones used; 2) the formulation timing and dosing; and 3) the delivery method. Doses of contraceptive hormones have decreased considerably since the 1960s, with initial OCs containing relatively high doses of both estrogen and progestin. While first-generation estrogen dosages started at 150 μg, second-generation dosages decreased to 50 μg, and current-generation doses are now even lower, ranging from 20 to 35 μg of ethinyl estradiol (EE) (20). Contemporary OCs remain at fairly high estrogen doses in contrast to menopausal hormone therapy, which typically contains one-tenth the dose or the equivalent of 2.5 to 5 μg of EE.

Contraceptive hormone formulation timing and dosing also varies. Table 1 outlines current hormonal contraceptive formulations available in the U.S. Monophasic dosing consists of doses that do not vary throughout the entire month, while in tricyclical dosing, the progestin portion of the contraceptive hormone increases each week to mimic the natural hormonal cycling in a woman. While many OCs are still taken for 21 days with a 7-day sham pill or no treatment phase, continuous dosing formulations of OCs that produce 4 menses/year and a continuous monophasic low-dose formulation that is taken 365 days/year with virtually absent menses have been approved (21).

OCs are classified into generations (first, second, and third), depending upon their introduction into the U.S. market, and vary according to their dose of estrogen and type of progestin used. The first-generation OCs used progestins called “estranes,” such as norethindrone, norethindrone-acetate, or ethynodiol diacetate. This generation of OCs contained 2 to 5 times the dose of estrogens and up to 10 times the dose of progestins compared with later generations (22). All subsequent-generation OCs contained ≤50 μg estrogen and varied by the type of progestin used. The second generation used progestins called “gonanes,” which are more potent and allowed the use of lower doses to produce an anovulatory effect. Examples include LNG or norgestimate. Third-generation OCs are also gonane progestins, such as desogestrol or gestodene, and have reduced androgenic and metabolic side effects. Most recently available are 2 nontestosterone-derived progestins, chloromadinone acetate and drospirenone, which may lead to a fourth-generation classification. Drospirenone is
an aldosterone antagonist with antiandrogenic and diuretic effects (19).

Contraceptive hormones also vary according to the method of delivery and now include nonoral routes such as the combined estrogen/progestin transdermal patch and vaginal ring. The transdermal patch or vaginal ring is worn continuously for 21 days and removed for 7 days and delivers a continuous estrogen and progestin formulation. Both of these methods avoid first-pass metabolism in the liver, provide continuous hormone dosing, and simplify compliance (23–25).

### Mechanisms of Estrogen and Progestin Action on the Cardiovascular System

ERs are found throughout the body in essentially all tissues in both women and men and play an important role in

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**Table 1** Overview of Hormonal Contraception Formulations Available in U.S. 2008

<table>
<thead>
<tr>
<th>Category</th>
<th>Dose</th>
<th>Brand/Trade Name</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oral Triphasic Formulation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estrogen/progestin*</td>
<td>25 µg/0.1, 0.125, 0.15 mg</td>
<td>Cyclessa</td>
</tr>
<tr>
<td>Ethinyl estradiol/levonorgestrel</td>
<td>30 µg/0.05 mg, 40 µg/0.075 mg, 30 µg/0.125 mg</td>
<td>Enpresse, Trivora</td>
</tr>
<tr>
<td>Ethinyl estradiol/norgestimate</td>
<td>25 µg/0.18, 0.215, 0.25 mg</td>
<td>Ortho Tri-Cyclen Lo</td>
</tr>
<tr>
<td>Ethinyl estradiol/norethindrone</td>
<td>35 µg/0.5, 0.75, 1 mg</td>
<td>Necon 7/7/7, Ortho-Novum 7/7/7</td>
</tr>
</tbody>
</table>

| **Oral Monophasic Formulation** |
| Estrogen/progestin‡ | 20 µg/0.09 mg | Lybrel |
| Estradiol/levonorgestrel | 20 µg/0.1 mg | Alesse, Aviane, Lutera |
| Estradiol/norgestimate | 30 µg/0.15 mg | Jolessa, Levora, Nordette, Portia, Quasense, Seasonale‡ |
| Estradiol/etynodiol | 50 µg/1 mg | Kelnor, Zovia 1/35 |

| **Nonoral Combined Formulations** |
| Transdermal estrogen/progestin | 20 µg/0.15 mg/day patch | Ortho Evra |
| Vaginal ring estrogen/progestin | 15 µg/0.12 mg/day vaginal ring | NuvaRing |

**Progestin Only**

| Oral progestin only |
| Norethindrone | 0.35 mg | Camilla, Errin, Jolivette, Nor-QD, OrthoMicronor, Ovrette |

| Progestin injection |
| Medroxyprogesterone acetate | 150 mg, intramuscular, every 3 months | Depo-Provera |
| | 104 mg, subcutaneous, every 3 months | Depo-SubQ Provera |

| Progestin-releasing IUD |
| Levonorgestrel | 52 mg IUD, daily release 20 µg | Mirena |

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For manufacturer information for all drugs, please see the Online Appendix. *21 active tablets and 7 placebo, active tablets divided into 7 tablet doses as indicated; †active pills are divided into 7 tablet doses, 9 tablet doses followed by 5 tablet doses; ‡21 active tablets and 7 placebo, active tablets are all same dose; §91-day extended formulation available with 84 consecutive active tablets and 7 placebo or 10 µg estradiol; ‡‡24 active tablets and 4 placebo.

IUD = intrauterine device.
health and disease. In animal models, estrogen administration directly prevents atherosclerosis (12). Specific pathways to the cardiovascular system include activation of the ERα receptor on endothelial and myocardial cells that have antioxidant effects and improved endothelial cell injury recovery (12). ERs in the cardiovascular system modulate a rapid vasodilatory response via nitric oxide and also have long-term effects via the genomic pathway by increasing endothelial cell growth and inhibiting smooth muscle cell proliferation. Estrogen reduces low-density lipoprotein cholesterol (LDL-C) oxidation and binding and platelet aggregation, and increases cyclooxygenase-2 activity (12). There is relatively less known regarding cardiovascular actions of progesterone and progestins.

**Lipoproteins.** Estrogen also affects the cardiovascular system indirectly through its impact on cardiovascular risk factors such as the lipid profile. OCs alter the lipid profile via the genomic pathway, in which ER alterations affect hepatic apolipoprotein up-regulation (12,26,27). Studies in pre-menopausal women using OCs have shown a dose-related response in the lipid profile. Women using a 20-µg EE/100-µg LNG OC demonstrated reductions in high-density lipoprotein cholesterol (HDLC) and small increases in LDL-C and triglycerides, in contrast to a 30-µg EE/150-µg LNG OC (28). The amount of lipid alteration also depends on the delivery route, where transdermal contraceptive hormone delivery is relatively less potent compared with oral (12,29). Barkfeldt et al. (30) conducted a randomized, double-blind study that evaluated the effects of lipid metabolism on 98 women who received 2 different types of progestin-only pills, desogestrel 75 µg/day or LNG 30 µg/day. There were minimal changes seen to the lipid profile except for decreasing trends with levels of HDL-C, its subfractions, and the apolipoproteins apolipoprotein-I and -II. No differences were observed between the 2 formulations despite the higher progesterin dose found in desogestrel, including no changes in LDL-C or apolipoprotein-B (30).

**Blood pressure.** Most studies on blood pressure in normotensive women have shown an increase in blood pressure associated with OC use (31). A review of 2 studies found an increase in systolic blood pressure by 7 to 8 mm Hg on average compared with systolic blood pressure in those not using OCs (32,33). The newer progestins such as drospirenone, with antiglucocorticoid diuretic effects, produce lower blood pressure. In a study of 120 women randomized to drospirenone/EE or LNG/EE, the drospirenone group demonstrated a mean decrease in the systolic blood pressure (from 107.4 to 103.5 mm Hg), and had a statistically significant lower group mean blood pressure compared with the LNG group (34). Another study of 80 healthy women randomized into groups of 3 mg of drospirenone combined with a 30-, 20-, or 15-µg dose of EE found that systolic blood pressure at 6 months fell by a range of 1 to 4 mm Hg across the groups, compared with an elevation of blood pressure of 4 mm Hg in the control group of LNG/EEs (35). Additionally, body weight fell by a range of 0.8 to 1.7 kg in the groups receiving the drospirenone compared with an increase in the LNG/EE group by 0.7 kg.

**Glucose tolerance and diabetes mellitus.** Contraceptive hormones can also impact glucose tolerance and diabetes mellitus. Oelkers et al. (35) studied glucose levels in 80 healthy women assigned to 4 equal groups who received 3 mg of drospirenone combined with 30-, 20-, and 15-µg doses of EE or LNG/30-µg EE. Each woman performed oral glucose tolerance tests at pre-treatment and at the end of the 6-month OC cycle. On treatment, fasting glucose was unchanged for all groups, but the area under the curve for the glucose tolerance increased for all formulations. Although not statistically significant between groups, the drospirenone/30-µg EE group had a 19% worsening of glucose tolerance (35). Available evidence with the earlier generation OCs demonstrates no apparent worsening of established diabetes (36,37).

**Novel risk factors.** Estrogen use in menopausal women elevates inflammatory markers such as C-reactive protein (38,39), although it is unclear if this is a specific adverse cardiovascular effect or a nonspecific up-regulation of hepatic protein synthesis. Elevations in high-sensitivity C-reactive protein have also been found in third-generation OC users containing desogestrel or gestodene. A case-control study of healthy women found high-risk levels of high-sensitivity C-reactive protein (3 to 10 mg/l) in 27% of OC users compared with 8.5% of non-OC users (odds ratio: 4.04, 95% confidence interval [CI]: 1.99 to 8.18) (40). There is little known regarding hormonal contraception use and other novel risk factors such as homocysteine, uric acid, and other inflammatory markers.

There are additional hormonal pathways that may impact cardiovascular disease. The dose of EE in OCs sustains relatively higher blood levels of estrogen than the ovaries in women with normal ovulatory cycling and ensures adequate estrogen levels in women with ovulatory dysfunction/estrogen deficiency. Prior work demonstrates that up to 33% of pre-menopausal women can have ovulatory dysfunction and estrogen deficiency and that this is associated with an increased osteoporosis risk (41). Recent work from the Nurses’ Health Study has documented a positive association between a history of irregular menstrual cycling and adverse cardiovascular events (6), suggesting that ovulatory dysfunction and relatively low estrogen levels may also elevate cardiovascular risk. Contraceptive hormones also suppress ovarian androgens and raise sex hormone binding globulin, thus reducing the free fraction of plasma testosterone. This is a useful mechanism of action of OCs in women with polycystic ovary syndrome and hyperandrogenemia, a condition that may be associated with elevated cardiovascular risk (42). Finally, contraceptive hormones appear to blunt the adverse adrenocortical stress response in primates, which might also offer indirect protection from atherosclerosis via neuroendocrine pathways (43).
Thrombosis. Estrogen has been known to have prothrombotic effects and elevates cardiovascular venous thromboembolism (VTE) risk by increasing prothrombin and decreasing antithrombin III (14). In a large, matched case-control study, Sidney et al. (44) found that OC use with <50-μg EE correlated with a 4 times higher risk of VTE compared with that seen in nonusers (95% CI: 2.77 to 4.00). Jick et al. (45) studied the risk of nonfatal VTE in a case-control study of low-dose estrogen <35 μg plus second-generation (LNG) or third-generation (desogestrel or gestodene) progestins and found that after adjusting for smoking and body mass index, third-generation progestins had a 2-fold higher risk ratio (RR) compared with second-generation progestins for nonfatal VTE. It was also noted that the increased risk associated with newer OC formulations was seen in the women who used OCs for <6 months compared with those who use OCs for longer periods of time, although the difference was not statistically significant.

Coronary vasomotion. Numerous clinical observations support the role of these reproductive hormones on regulation of vasomotor tone. Migraine headaches, Raynaud’s disease, and Prinzmetal’s angina are more common in women than men and can vary according to endogenous or exogenous reproductive hormones (46,47). While animal and human work demonstrates that low endogenous estrogen levels exacerbate endothelial dysfunction (48,49) and that estrogen replacement abolishes this effect (48,50,51), the data are mixed with regard to whether long-term estrogen therapy maintains or improves coronary or peripheral endothelial function in humans (51). Even less is known regarding progesterone, progestins, and androgens. Primate study has demonstrated a coronary vasoconstrictive effect with medroxyprogesterone that was not apparent with progesterone (52,53). More clinical work is needed.

Arrhythmogenesis. Women face a life-long higher risk of sudden cardiac death associated with electrocardiographic QT prolongation compared with men (54), and this is particularly apparent in the post-adolescence years. Androgens have been demonstrated to blunt QT prolongation in response to quinidine (55), in contrast to estrogens that modify the expression of potassium channels (56). Other investigators have demonstrated that the 9-month postpartum period has a significantly increased risk of cardiac events among women who are long QT genotype carriers (57). In healthy post-menopausal women, hormone replacement therapy with estrogen alone usually produces a prolongation of the QT interval, while estrogen plus progestrone had no significant effects on the QT interval but reduced QT dispersion; however, there are conflicting data reported (58,59). Further work is needed to understand the basis of gender differences in ventricular repolarization and arrhythmogenic etiologies of cardiac death. In particular, no study has been directed at the impact of contraceptive hormones and susceptibility to drug-induced QT interval prolongation and drug-induced arrhythmia that is relatively more prevalent in women. Figure 1 depicts the known mechanisms whereby contraceptive hormones impact the cardiovascular system including effects on atherosclerosis, thrombosis, vasomotion, and arrhythmogenesis (12,14,28–37,43,52,53,60,61).

Contraceptive Hormone Use and Cardiovascular Disease

Animal studies. Stress-induced interruption of the hypothalamic signaling of the ovary, resulting in anovulation and hypoestrogenemia in primates, produces pre-menopausal atherosclerosis in the primate model (47,62,63), and provision of hormone contraception has been demonstrated to block this atherosclerotic effect (63,64). The use of a primate model of pre-menopausal oophorectomy and menopausal hormone therapy demonstrates similar antiatherosclerotic effects (65).

Adams et al. (66) studied nonhuman primate models in cynomolgus macaques to determine the effect of OCs on lipoproteins and atherosclerosis. This design compared placebo with 2 different formulations of OCs over 24 months. Despite both OC preparations reducing plasma HDL-C, both had a 50% to 75% decrease in the extent of atherosclerosis compared with that seen in placebo. This study was further stratified by high-risk status, defined by total cholesterol/HDL-C ratio >4.5, and found a relatively greater decrease of atherosclerosis by 75% to 85% in the high-risk group (66).

A second study in cynomolgus macaques was designed to further assess the impact of separate or combined effects of estrogen and progestin in low-dose OC preparations on atherosclerosis progression. This study randomized the monkeys to receive triphasic combined EE/LNG, triphasic EE alone, LNG alone, or a placebo. All groups were treated for a 25-month period and continued on a pratherogenic diet. Results showed that among the animals treated with EE alone compared with untreated animals, atherosclerosis was reduced by 67% (p < 0.05), while the combination EE/LNG group had a 28% decrease in atherosclerosis, and the LNG alone group had no effect (67). Further lipid evaluation demonstrated LDL-C particles that were smaller and less esterified in the EE alone or EE/LNG groups.

Clinical Studies

Current and immediate past contraceptive hormone use in younger and midlife women. The Nurses’ Health Study, initiated in 1976, was an 8-year self-report prospective study that assessed the risk of myocardial infarction (MI) and OC use in midlife women (ages 30 to 55 years). This study found no increased risk among past users of OCs for cardiovascular disease, nonfatal MI, or fatal coronary disease when compared with those who had never used OCs (68). Additionally, there was no association between the duration of use and cardiovascular disease; women who had used OCs for more than 10 years had no alteration in risk. Among current OC users, however, there was a 2.5 relative
increased risk of adverse cardiovascular events, including cardiovascular death, nonfatal MI, and stroke (68). The increase in cardiovascular deaths and nonfatal MI and stroke in current users but not with past use was believed to be associated with the prothrombotic effects, and 7 of 10 of the adverse cardiovascular events occurred in current cigarette smokers (68). Stopping OCs was associated with a decline in the risk for adverse cardiovascular events, with an RR of 0.95 (95% CI: 0.81 to 1.11) among past users, suggestive of reversal of the OC prothrombotic effects with cessation of use; however, other mechanisms such as an antiatherosclerotic effect could also be contributory.

Other prospective studies consistently show an increased risk of acute MI among women who concomitantly use OCs and smoke, and extend the observation to past smokers on OCs (68–71). Notably, these studies evaluated OC predominantly with prior-generation OCs with the relatively higher estrogen doses compared with those currently used. No studies to date have specifically evaluated the newer fourth-generation as well as the non-OC hormone preparations with regard to current and immediate past use–associated adverse cardiovascular events.

Two separate case–control studies evaluated the association between OC use and MI, based on the second- and third-generation preparations with differing progestins and reached varying conclusions. Dunn et al. (72) performed a community–based case–control study of 2,176 women over a 2-year period and found a lower RR of 1.78 (95% CI: 0.66
to 4.83) for MI with third-generation OCs compared with second-generation OC use (Table 2). In this study, third-generation OCs were defined as the progestins gestodene or desogestrel combined with EE compared with second-generation OCs defined as LNG and norethisterone combined with <50 μg of EE. Tanis et al. (73) performed a case-control study of 1,173 women over 6 years and concluded that the use of second-generation OCs, containing LNG, increased the risk of MI by an RR of 2.3, while third-generation, containing desogestrel or gestodene, and other progestins such as cyproterone or norgestimate, did not significantly increase the risk (Table 2). Additionally, this latter study analyzed subjects for the presence of prothrombotic genetic mutations and concluded that there was a nonsignificant increased risk in subjects with a Factor V Leiden or prothrombin mutation who used third-generation OCs (RR: 1.9, 95% CI: 0.6 to 5.5).

A recent prospective study from Sweden followed 48,321 women age 30 to 49 years over an average of 11 years. The study, which ended in 2002, was conducted to determine the risk of MI associated with the use of OCs. During the follow-up period, there were 190 nonfatal MIs and 24 deaths due to MI. When adjusted for age as well as cardiac risk factors such as hypertension, smoking status, and diabetes, the study found no increased risk of MI in both former and current users of OCs (Table 2). Additionally, there was no increased risk of MI in women with duration of use of OCs stratified to over 15 years (RR: 0.7, 95% CI: 0.4 to 1.2) (2). Table 2 summarizes these cardiovascular risk data stratified according to first-, second-, and third-generation OC formulations (2,45,68,72–78).

**Longer-term prior contraceptive hormone use in post-menopausal women.** While it is clear that current OC use is associated with an increased risk of MI in women with pre-existing risk factors such as cigarette smoking (69,72,79), insufficient prior data have existed with regard to longer-term past OC use and subsequent cardiovascular disease in the post-menopausal period. There is a relative paucity of data due to: 1) the relatively short population exposure time (OCs have only been available since the 1960s); 2) the decades needed to perform clinical adverse event studies; and 3) the additional follow-up time needed due to the majority of cardiovascular disease events occurring later in life among older women. Given the animal and human data consistent with antiatherosclerotic effects of OC, it is reasonable to hypothesize that, compared with nonusers, women with a history of OC use in their pre-menopausal years may be relatively protected against atherosclerosis, resulting in a relatively lower cardiovascular disease burden during post-menopause.

Stampfer et al. (68) demonstrated a lower RR for adverse coronary disease events of 0.8 (95% CI: 0.6 to 1.0) among the past OC users compared with nonprior users in 119,061 women followed for 8 years. While these results were statistically significant, there were relatively few adverse coronary disease events in this population with an approximate mean age of 63 years, and this analysis has not been updated. Similar results suggestive of a protective OC effect have been found in smaller studies evaluating adverse cardiac events (80) and coronary angiography (81). A quantitative meta-analysis of 13 studies included in the Stampfer et al. (68) work provided an estimated RR associated with past OC use of 1.01 (95% CI: 0.91 to 1.13), resulting in their conclusion that past OC use had little or no impact on subsequent cardiovascular disease (82).

One study has directly assessed this question using quantitative measures of atherosclerosis. Past OC use and evidence of atherosclerotic coronary artery disease was assessed in 672 post-menopausal women with coronary risk factors and undergoing coronary angiography for suspected ischemia in the WISE (Women's Ischemia Syndrome Evaluation) study (83). Past OC hormone use was associated with a 2.4% reduced risk of atherosclerotic coronary artery disease measured by quantitative coronary analysis in a core laboratory despite adjustment for age and coronary risk factors (Fig. 2). There was no apparent relation between duration of past OC use and the coronary artery disease severity index score, however. Limitations of this observational study included a greater use of menopausal hormone therapy and a higher risk factor burden among the past users of OCs, although these factors may have mitigated more adverse cardiovascular events and atherosclerosis in this group, respectively.

**Current Hormonal Contraceptive Prescribing Guidelines for Women at Elevated Cardiovascular Risk**

The American College of Obstetrician and Gynecologists (ACOG) created guidelines for prescribing OCs in women with medical conditions, specifically addressing women with cardiovascular risk factors such as hypertension, dyslipidemia, diabetes, smoking, and obesity (60). In addition, ACOG addresses OC use in women older than 35 years of age. In women with pre-existing hypertension, who are otherwise healthy, OCs can be used if <35 years old and blood pressure is well-controlled and monitored. If blood pressure remains stable after a few months, then OC may be continued. Current ACOG guidelines recommend pre-treatment fasting lipid profiles in women who are dyslipidemic with monitoring once they have stabilized on an OC. Alternative nonhormonal contraceptive methods, such as an intrauterine device, should be used if the patient has an LDL-C >160 mg/dl or multiple cardiac risk factors. OC use in diabetic women, either type I or II, is only appropriate for use in otherwise healthy women younger than 35 years old. The ACOG cautions against prescribing OCs in women who smoke and are over the age of 35. Obesity is felt to be an independent risk factor for VTE; therefore, the guideline recommends alternate nonhormonal contraceptive methods. Finally, for women older than 35 years of age, OCs with <50 μg EE remain safer than pregnancy in
<table>
<thead>
<tr>
<th>Authors, Year (Ref. #)</th>
<th>OC Generation Definitions</th>
<th>n</th>
<th>CVD Definition</th>
<th>Follow-Up (yrs)</th>
<th>RR (Unless Stated, Compared With Nonusers)</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stampfer et al., 1988 (68)</td>
<td>No distinction made with OC generation</td>
<td>Total 62,718 Cases 485</td>
<td>All cardiovascular deaths, nonfatal MI, and CVAs</td>
<td>8</td>
<td>Past user 0.95 Current user 2.5</td>
<td>(0.81–1.11)* (1.3–4.9)*</td>
</tr>
<tr>
<td>Jick et al., 1995 (45)</td>
<td>Second generation: EE &lt;35 µg + LNG Third generation: &lt;35 µg + gestodene or desogestrel</td>
<td>Total 303,470 Cases 15</td>
<td>Death related to cardiovascular cause: MI, CVA, PE, cardiac arrest</td>
<td>3.8</td>
<td>Third-generation (desogestrel) users with second generation as baseline 0.4 Third-generation (gestodene) users 1.4</td>
<td>(0.1–2.1)* (0.5–4.5)*</td>
</tr>
<tr>
<td>WHO et al., 1996 (74)</td>
<td>No distinction made with OC generation</td>
<td>Total 1,309 Cases 368</td>
<td>Nonfatal first MI</td>
<td>5</td>
<td>Current users OR 5.01 in Europe Current users OR 4.78 in developing countries Past users &gt;10 yrs 1.61</td>
<td>(2.54–9.90)† (2.52–9.07)† (0.62–4.16)</td>
</tr>
<tr>
<td>Sidney et al., 1998 (77)</td>
<td>No distinction made with OC generation EE with 50 µg and &lt;50 µg Progestins with norethindrone and from gonane family</td>
<td>Total 1,264 Cases 271</td>
<td>MI</td>
<td>3.25</td>
<td>OR for current OC users 0.56 OR for past OC users 0.54</td>
<td>(0.21–1.49)† (0.31–0.95)†</td>
</tr>
<tr>
<td>Dunn et al., 1999 (72)</td>
<td>Second generation: EE &lt;50 µg + norethisterone or LNG Third generation: EE &lt;50 µg + gestodene or desogestrel</td>
<td>Total 2,176 Cases 448</td>
<td>MI</td>
<td>2</td>
<td>All combined OC users 1.4 Second-generation users 1.1 Third-generation users 1.96 Adjusted for third- versus second-generation users 1.78</td>
<td>(0.78–2.52)† (0.52–2.30)† (0.87–4.39)† (0.66–4.83)†</td>
</tr>
<tr>
<td>Dunn et al., 2001 (75)</td>
<td>Second generation: EE &lt;35 µg + norethisterone or LNG Third generation: EE &lt;35 µg + gestodene or desogestrel</td>
<td>Total 532 Cases 110</td>
<td>Fatal MI</td>
<td>2</td>
<td>Second-generation OC users 2.88 Third-generation OC users 0.83</td>
<td>(1.22–6.77)† (0.25–2.81)†</td>
</tr>
<tr>
<td>Rosenberg et al., 2001 (76)</td>
<td>No distinction made with OC generation EE with ≥50, 35–49, &lt;35 µg Progestins with norethindrone, LNG, desogestrel, and norgestimate</td>
<td>Total 6,574 Cases 627</td>
<td>Nonfatal first MI</td>
<td>14</td>
<td>OR for current OC use 1.3 Current user OC by type found NS OR around 1 except those with norethindrone (first generation) RR 2.5</td>
<td>(0.8–2.2) (1.1–5.5)</td>
</tr>
<tr>
<td>Tanis et al., 2001 (73)</td>
<td>First generation: EE 30 µg + lynestrenol Second generation: EE 30 µg + LNG Third generation: EE 30 µg + desogestrel or gestodene, and other progestins, cyproterone or norgestimate</td>
<td>Total 1,173 Cases 248</td>
<td>MI</td>
<td>6</td>
<td>Past second-generation users 2.4 Current-second-generation users 2.7 Past third-generation users 1.3 Current third-generation users 1.6</td>
<td>(1.6–3.6)* (1.6–4.3) (0.8–2.3) (0.9–2.9)</td>
</tr>
<tr>
<td>Spitzer et al., 2002 (78)</td>
<td>Second generation: EE &lt;35 µg + norgestrel or LNG Third generation: EE &lt;35 µg + desogestrel or gestodene</td>
<td>Total 6,464 Cases 214</td>
<td>MI</td>
<td>Meta-analysis 7 studies</td>
<td>OR for third-generation users 1.13 OR for second-generation users 2.18 OR for third- compared with second-generation users 0.62</td>
<td>(0.66–1.92) (1.62–2.94) (0.38–0.99)</td>
</tr>
<tr>
<td>Margolis et al., 2007 (2)</td>
<td>Second generation: EE &lt;35 µg + norgestrel or LNG Third generation: EE &lt;35 µg + desogestrel</td>
<td>Total 48,321 Cases 214</td>
<td>MI</td>
<td>11</td>
<td>Past users 1.0* Current users 0.7*</td>
<td>(0.7–1.4)† (0.4–1.4)</td>
</tr>
</tbody>
</table>

*Age-adjusted relative risk (RR); †adjusted for cardiac risk factors: age, body mass index, smoking status, alcohol intake, physical activity, hypertension, diabetes, menopausal status; see text for specific adjusted risk factors.

CVA = stroke; CVD = cardiovascular disease; EE = ethinyl estradiol; LNG = levonorgestrel; MI = myocardial infarction; NS = nonsignificant; OC = oral contraceptive; OR = odds ratio; PE = pulmonary embolism.
healthy, nonsmoking women, and can be continued until age 50 to 55 years or until menopause after reviewing risks and benefits. There are no guidelines for transitioning OCs to menopausal hormone therapy; however, after the age of 50 years, measurement of follicle-stimulating hormone after 6 days off OCs to determine menopausal status can provide guidance (84). There are no guidelines about the fourth-generation OCs to date; thus, prudent practice including these as well as the contraceptive transdermal patches is to consider them similar to the other available preparations and not as safer alternatives. Table 3 summarizes the prescribing guidelines for hormonal contraceptives in women with elevated cardiovascular risk.

**Discussion and Recommendations**

A variety of basic animal and human data suggest that contraceptive hormones have antiatherosclerotic effects; however, relatively less is known regarding the impact on thrombosis, vasomotion, and arrhythmogenesis, mechanistic pathways that also contribute to cardiovascular risk and benefit. No carefully controlled trials with cardiovascular follow-up of post-menopausal women with other vascular diseases, including migraines, before OC use. Current World Health Organization and ACOG guidelines for women age 35 years and older recommend against contraceptive methods such as progestin-only pills or IUD. Obesity is felt to be an independent risk factor for VTE.

Measurement of a fasting lipid panel is recommended in women with dyslipidemia before use of OCs, and alternative nonhormonal contraceptive should be sought if LDL-C is not below 160 mg/dl. Measurement and monitoring of blood pressure are also important to ensure that blood pressure control is not compromised. Women age 35 years and older should be assessed for cardiovascular risk including hypertension, smoking, diabetes, nephropathy, and other vascular diseases, including migraines, before OC use. Current World Health Organization and ACOG guidelines for women age 35 years and older recommend against the use of OCs in women with these risk factors (3). OCs may be used in the perimenopausal transition, where higher doses of estrogen are needed to suppress ovulation compared with doses needed to treat menopausal symptoms such as hot flashes.

There are no cardiovascular data available for the newest generation contraceptive hormone formulations, including the progestins that lower blood pressure and body weight, as well as the nonoral routes (transdermal and vaginal). While these newer formulations might be expected to have an overall lower risk, specific study is needed. Current guidelines indicate that, as with all medication, contraceptive hormones should be selected and initiated by weighing risks and benefits for the individual patient.

Existing data are mixed with regard to possible protection from early generation OCs for atherosclerosis; longer-term cardiovascular follow-up of post-menopausal women with regard to prior OC use, including subgroup information regarding adequacy of ovulatory cycling, the presence of hyperandrogenic conditions, and the presence of prothrombin.

**Table 3**

<table>
<thead>
<tr>
<th>Summary of Hormonal Contraceptive Prescribing Guidelines for Women With Elevated Cardiovascular Risk</th>
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<tbody>
<tr>
<td><strong>Hypertension</strong></td>
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<tr>
<td><strong>Dyslipidemia</strong></td>
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<td><strong>Diabetes</strong></td>
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<td><strong>Smoking</strong></td>
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<tr>
<td><strong>Obesity</strong></td>
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<tr>
<td><strong>Women older than 35 yrs of age</strong></td>
</tr>
</tbody>
</table>

BMI = body mass index; BP = blood pressure; IUD = intrauterine device; LDL-C = low-density lipoprotein cholesterol; VTE = venous thromboembolus; other abbreviations as in Table 2.
botic genetic disorders, is needed to address this important issue.

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Key Words: hormones | contraception | cardiovascular disease.

APPENDIX

For a list of manufacturers for the drugs included in Table 1, please see the online version of this article.