Cochrane for Clinicians

Putting Evidence into Practice

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The Risk of MI and Ischemic Stroke with Combined Oral Contraceptives

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Clinical Question

Do combined oral contraceptives increase the risk of myocardial infarction (MI) and ischemic stroke?

Evidence-Based Answer

The overall risk of MI and ischemic stroke is increased in women who use combined oral contraceptives. The relative risk of MI and ischemic stroke increases as estrogen dose rises, increasing by 60% with doses of 20 mcg and more than doubling when doses of 50 mcg or more are used. Risk of MI and ischemic stroke does not vary with the type or generation of progestin. Physicians should be cautious when prescribing combined oral contraceptives because of the increased risk of MI and ischemic stroke.[1] (Strength of Recommendation: B, based on limited-quality evidence from observational studies.)

Practice Pointers

Approximately one in six U.S. women of reproductive age uses combined oral contraceptives,[2] and all formulations are equally effective at preventing pregnancy. Although estrogen doses in combined oral contraceptive formulations have decreased over the past half-century to diminish the risk of thrombotic events, ensuring patient safety remains essential.

This Cochrane review included 24 observational studies in a meta-analysis comparing the risk of fatal or nonfatal MI or ischemic stroke between users and nonusers, 18 to 50 years of age, of combined oral contraceptives of varying generations, types, and doses. The generation and type varied according to the progestin included, and the dose varied according to the estrogen formulation. Studies with progestin-only contraceptives, non-oral contraceptives, and postmenopausal women using hormone therapy were excluded. Both previous combined oral contraceptive users and never-users were considered nonusers. No randomized trials that met inclusion criteria were found.

The overall combined risk of MI and ischemic stroke was increased for users of combined oral contraceptives when compared with nonusers (relative risk [RR] = 1.6; 95% confidence interval [CI], 1.3 to 1.9). The risks of MI alone and ischemic stroke alone were also similarly increased. Furthermore, data from seven studies demonstrated a dose-response for increased risk of MI and ischemic stroke with increasing estrogen dose. For estrogen doses of 20 mcg, the RR was 1.6 (95% CI, 1.4 to 1.8); for estrogen doses between 30 and 49 mcg, the RR was 2.0 (95% CI, 1.4 to 3.0); and for estrogen doses of 50 mcg or more, the RR was 2.4 (95% CI, 1.8 to 3.3). There were no differences in the risk of MI or ischemic stroke based on progestin type or generation. Because the analysis included mostly raw data, confounding by age, body mass index, smoking, and calendar time cannot be ruled out. However, all but one of the studies were case-control designs that employed matching to adjust for age and calendar time.

Previous systematic reviews have found an increased association with MI and ischemic stroke among combined oral contraceptive users. This Cochrane review complements and strengthens these findings with more stringent inclusion criteria. The U.S. Medical Eligibility Criteria for Contraceptive Use (US MEC) provides guidance on safe contraceptive use for women by underlying medical condition.[3] The US MEC limits its recommendations for combined oral contraceptive use to formulations containing no more than 35 mcg of ethinyl estradiol and states that combined oral contraceptive use in women with multiple major risk factors for cardiovascular disease may increase health risks to an unacceptable level.[3] These

guidelines also state that combined oral contraceptive use in patients with a personal history of ischemic heart disease or stroke is contraindicated. Given that unintended pregnancy itself increases the risk of adverse health events among women with these underlying medical conditions, clinicians must consider these risks and may want to offer alternative contraceptive methods for women who cannot take combined oral contraceptives.

The practice recommendations in this activity are available at http://summaries.cochrane.org/CD011054.

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Amiodarone for the Prevention of Sudden Cardiac Death

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Clinical Question

Is amiodarone effective for the prevention of sudden cardiac death in patients at increased risk?

Evidence-Based Answer

Although not a substitute for an implantable cardioverter-defibrillator (ICD), amiodarone is effective for the primary prevention of sudden cardiac death when compared with placebo (number needed to treat [NNT] = 47; 95% confidence interval [CI], 33 to 100), but it does not significantly lower all-cause mortality in those at high risk. Amiodarone increases the risk of all-cause mortality when used for secondary prevention (number needed to harm [NNH] = 15; 95% CI, 5 to 91) and should not be used in this setting. Adverse effects of therapy include thyroid and pulmonary toxicity.[1] (Strength of Recommendation: A, based on consistent, good-quality patient-oriented evidence.)

Practice Pointers

Sudden cardiac death causes approximately 25% of worldwide cardiac-related deaths each year.[2] ICDs are standard therapy for the prevention of sudden cardiac death in patients who have an expected survival of more than one to two years and have risk factors such as a history of cardiac arrest, sustained ventricular tachycardia with hemodynamic compromise, a familial cardiac condition with a high risk of sudden cardiac death, or heart failure with significant left ventricular dysfunction.[2-5] Despite this, high up-front costs limit the use of ICDs in resource-constrained areas, and some patients may not wish to have an ICD placed. The authors of this review sought to determine whether amiodarone, a class III antiarrhythmic, would be helpful for the prevention of sudden cardiac death in these settings.[1]

This Cochrane review included 24 randomized trials and 9,997 patients.[1] For primary prevention—that is, for patients at high risk of arrhythmia but no history of cardiac arrest or ventricular arrhythmia–associated syncope—amiodarone in a dosage of 200 to 400 mg daily (after a loading dose) decreased the risk of sudden cardiac death when compared with placebo (NNT over six months to five years = 47; 95% CI, 33 to 100). Amiodarone also decreased the risk of cardiac mortality (NNT over six months to five years = 46; 95% CI, 27 to 154), but not all-cause mortality when compared with placebo. Amiodarone did not decrease sudden cardiac death when compared with other antiarrhythmics, but it did reduce all-cause mortality vs. other pharmacologic agents (NNT over six months to five years =15; 95% CI, 12 to 42). Amiodarone was not directly compared with ICDs for primary prevention.

For secondary prevention—that is, in patients with a history of cardiac arrest or ventricular arrhythmia–associated syncope—amiodarone had no effect on sudden cardiac death when compared with placebo, but it did increase all-cause mortality (NNH over six months to five years = 15; 95% CI, 5 to 91). When compared with other antiarrhythmics, amiodarone had no significant effect on sudden cardiac death or all-cause mortality. Patients taking amiodarone for prevention were more likely to develop hyperthyroidism (NNH over six months to five years = 31; 95% CI, 8 to 344), hypothyroidism (NNH over six months to five years = 38; 95% CI, 29 to 274), or pulmonary effects (NNH over six months to five years = 91; 95% CI, 46 to 432).

Major guidelines from the United States and Europe recommend ICDs for patients at high risk of arrhythmia and with a life expectancy greater than one to two years.[2-5] Although amiodarone is mentioned as one of the few antiarrhythmics not to increase mortality in heart failure, it is not considered a substitute for ICD therapy, which is covered by insurance in the United States. In resource-constrained areas where ICDs are not available, or for patients who do not wish to receive an ICD, amiodarone may be helpful in the primary prevention of sudden cardiac death, but it has no role

in secondary prevention, including in patients who have an ICD.

The practice recommendations in this activity are available at http://summaries.cochrane.org/CD008093.

EDITOR'S NOTE: The numbers needed to treat and numbers needed to harm reported in this Cochrane for Clinicians were calculated by *AFP* medical editors based on raw data provided in the original Cochrane review.

The views expressed in this article are those of the author and do not reflect the official policy or position of the U.S. government, the Department of the Army, or the Department of Defense.

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