

# “Cardiovascular Risk Associated With the Use of an Etonogestrel-Containing Vaginal Ring” (2013), by Jürgen Dinger, Sabine Möhner, and Klaas Heinemann

In October 2013, Jürgen Dinger, Sabine Möhner, and Klaas Heinemann published the article “Cardiovascular Risk Associated With the Use of an Etonogestrel-Containing Vaginal Ring,” hereafter “Cardiovascular Risk,” in the journal *Obstetrics and Gynecology*. The authors enrolled patients in the study who were new users of either a vaginal contraceptive ring known as NuvaRing or a combined oral contraceptive pill. A combined oral contraceptive pill contains a formulation of the hormones progesterone and estrogen. They followed up with the patients for two to four years after they had started either hormonal contraceptive treatment to record the incidence of specific cardiovascular events. The authors found that the risks of cardiovascular events when starting use of either NuvaRing or a combined hormonal contraceptive pill were similar to each other in the patients they studied. The results of “Cardiovascular Risk” affirmed the results of similar studies and stated that the risk of cardiovascular events was similar in NuvaRing users to other contraceptive users.

The main cardiovascular events that the study authors found to be associated with the vaginal ring are venous and arterial thromboembolic events, which include the incidence of blood clots in blood vessels and other serious cardiovascular events like blood clots traveling to the lungs, heart attack, and stroke. Blood clots naturally form in the body to heal wounds and often will dissolve naturally after. However, if a blood clot forms in a vein or artery, it can block blood flow to tissues and can cause pain or malfunction of organs. Hormone treatments such as contraceptives contain estrogen and progesterone, which are hormones that regulate the menstrual cycle and development of the reproductive system and secondary sexual characteristics. Because the contraceptives contain those hormones, such treatments are associated with increased blood coagulability, which means that the blood is more likely to clot. Other risk factors for increased blood clotting include pregnancy, obesity, low physical activity, increased age, and surgery or injury.

At the time of publication, Dinger, Möhner, and Heinemann were affiliated with the Zentrum für Epidemiologie und Gesundheitsforschung Berlin (Berlin Center for Epidemiology and Health Research) in Berlin, Germany. Dinger and Heinemann have conducted many epidemiological studies for the research center relating to hormonal contraceptive use and female reproductive epidemiology. Dinger and Heinemann authored other studies about the efficacy of contraceptives and their relation to cardiovascular health.

“Cardiovascular Risk” is an article that describes the Transatlantic Active Surveillance on Cardiovascular Safety of NuvaRing, which was a prospective observational cohort study that Dinger and colleagues conducted of the United States and five European countries. An observational cohort study is a study in which researchers select a cohort, or group of patients who are similar in some way, and observe the effects of a treatment on the patients over a period of time. A prospective study involves observing how often a certain health problem develops within a cohort of people who do not already experience that health problem. Prospective studies are different from other observational studies in which researchers observe people who already experience a certain health problem.

“Cardiovascular Risk” is divided into four sections. In the unnamed introductory section, Dinger, Möhner, and Heinemann present their study, called the Transatlantic Active Surveillance on Cardiovascular Safety of NuvaRing study, or TASC. In “Materials and Methods,” they explain that their

objective is to understand short-term and long-term risks of arterial or venous thromboembolism in new NuvaRing users compared to other combined oral contraceptive pill users. The authors describe their recruitment of new NuvaRing and other combined oral contraceptive pill users and their process of following up with questionnaires for two to four years. They also discuss their comparisons of NuvaRing users to smaller cohorts of specific medication users. In "Results," the authors describe the demographic differences between the NuvaRing cohort and the combined oral contraceptive pill cohort. They then state that they found the NuvaRing cohort showed low incidence of arterial and venous thromboembolic events, which was similar to the incidence in the combined hormonal contraceptive pill cohort. In "Discussion," the authors discuss strengths and limitations of the study, and state that the results of their study are consistent with a similar 2013 study from the United States, but contradict the results of a 2012 Danish study. The authors conclude that NuvaRing and combined oral contraceptive pill users show similar risk of arterial or venous thromboembolism as the combined hormonal contraceptive pills.

In the introductory section, Dinger, Möhner, and Heinemann discuss the TASC study. They state that the efficacy of the NuvaRing in preventing pregnancy is similar to oral contraceptive pills. Both contraceptives are around ninety-eight percent effective with perfect use. The authors' study began in September 2007 and concluded in March 2012, and the authors claim that at the time that the study was planned, incidence of cardiovascular events with the NuvaRing was rare. However, because increased risk of arterial and venous thrombotic events is often associated with hormonal contraceptive use, they conducted a large study in order to observe the incidence of the events. The authors state that the outcomes they looked for in short-term and long-term follow ups with patients were venous thromboembolism and arterial thromboembolism.

In "Materials and Methods," the authors explain that they derived the methods for their study from the European Active Surveillance study of OCPs, which was another study researching the safety of oral contraceptives. They used that study's methods for their patient questionnaires and follow up procedures. The authors state that their objective is to evaluate and compare the risk of venous thromboembolism and arterial thromboembolism in new NuvaRing users to the risk in combined oral contraceptive pill users. The authors describe their recruitment process of patients for the study through a network of physicians who prescribe hormonal contraceptives. They included patients from the United States, Austria, Germany, Russia, Italy, and France. The authors included patients in the study if they were a new user of a combined hormonal contraceptive including NuvaRing. New users included starters, who were first time users of any hormonal contraceptives, switchers, who switched from one hormonal contraceptive to another, and restarters, who stopped and restarted a hormonal contraceptive after at least a four-week break.

The authors explain that they used a non-interference model for the study in which they observe the patients prescribed a medication with no other study treatments. That allowed the authors to include more participants in the study as well as avoid influencing the physicians who prescribed the contraceptives for the participants. Participants filled out a baseline health questionnaire to assess their current health and potential cardiovascular risks at the beginning of the study. The researchers scheduled follow up assessment with each participant six months and twelve months after beginning treatment, and then once a year for the next four years. A group of anonymous physicians who were unaffiliated with the study itself except as evaluators confirmed any thromboembolic event that occurred during the study. The physicians evaluated the patients' diagnostic test results to confirm that any reported thromboembolic event was legitimate. The authors explain that one of the research cohorts contained all combined oral contraceptive pill users excluding users of the hormones desogestrel or gestodene because the US was still carrying out safety testing of those hormones at the time, even though Europe had authorized use. 33,295 patients participated in the study.

In "Results," the authors state that neither the oral contraceptive cohort nor the vaginal ring cohort was more predisposed to have thromboembolic events. 16,864 patients in the study used the NuvaRing, and 16,431 patients used other combined oral contraceptive pills, with 13,811 using medications without desogestrel or gestodene. The authors explain that 2.9 percent of the 33,295 patients did not follow up for the full four years. The NuvaRing users had a slightly shorter exposure time to the treatment than the combined oral contraceptive users, meaning they were less likely to

experience cardiovascular events, and had a higher average body mass and age. There was a higher average body mass among patients in the US than patients in Europe. The authors evaluated the baseline health questionnaires of the participants and concluded that, among NuvaRing users and combined oral contraceptive users without desogestrel and gestodene, there were no significant differences in pre-existing risk for cardiovascular events.

Continuing in the "Results" section, the authors explain that they ultimately observed fifty-seven total venous thromboembolic events in the entire study cohort, nineteen in the NuvaRing cohort and twenty-six in the combined oral contraceptive pill cohort. Eleven of the events were in the no use cohort, who stopped use of contraceptives after the beginning of the study. The authors observed that incidence of venous thromboembolic events decreased after the first year of use, which demonstrates an established notion that early use of any hormonal contraceptive increases the risk of venous thromboembolisms. They also note that there were forty women in the study who had a personal history of venous thromboembolism before the study, and none of them experienced a venous thromboembolism during hormonal contraceptive use. The authors report seventeen arterial thromboembolic events in the study, with five cases in the NuvaRing cohort, nine cases in the combined oral contraceptive cohort, and three cases in the no use cohort.

In "Discussion," the authors state that the incidence for arterial and venous thromboembolism remained relatively the same for all cohorts in the study. The authors mention some potential biases of the study, including a diagnostic bias. They claim that the awareness of potential cardiovascular events could have contributed to increased detection and diagnosis of venous thromboembolisms that are mild or asymptomatic that physicians may not typically find. The authors do not believe the diagnosis bias affected the results of the study. The authors highlight the low number of patients that stopped follow ups among the cohort and their ability to keep track of most patients in the study even if their physician changed because patients in the study provided their personal addresses and phone numbers for contact. The authors state that their results are consistent with a 2013 US study by Stephen Sidney, who researches epidemiology, and colleagues, but contradict a 2012 Danish study that found that contraceptive ring users showed a twofold risk of cardiovascular events. Dinger and colleagues argue that although the Danish study was bigger, the methods they used left more room for bias or interfering variables, and therefore the researchers do not believe that the Danish results falsify their results. Finally, they conclude that the risk of venous and arterial thromboembolism is similar for NuvaRing and oral combined contraceptives with typical clinical use.

According to Google Scholar, "Cardiovascular Risk" has over fifty-five citations as of 2022. In 2013, NuvaRing included references to both Dinger and colleagues' and Sidney and colleagues' studies in the prescribing information available to a patient, and continues to reference them in the NuvaRing label as of 2022. The studies provided information for NuvaRing users or those considering NuvaRing about potential risks of thromboembolism.

## Sources

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