Hormonal contraception and venous thromboembolism.

Many myths are still being advanced.

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The question whether there is a difference in risk of venous thrombosis between users of combined oral contraceptives (COC) with drospirenone (DRSP) and users of 2nd generation pills with levonorgestrel is apparently still controversial. The aim of this survey was to test some of the most frequent claims against such a difference with the scientific evidence.

If we define a good study as a study with valid exposure data, valid outcomes, including relevant confounders, excluding women with a known predisposition for venous thrombosis, presenting all relevant data, and having a sufficient power to achieve precise estimates, it is not that difficult to evaluate the quality of different studies. In Table 1 the most important scientific properties of the two studies by Dinger et al.[1, 2] is compared with two recent studies by Lidegaard et al.[3, 4] because Dinger was the first and still is the most persistent critic of the Danish studies.

The first claim made initially by Dinger, but since repeated in several editorials and latest by Johannes Bitzer at the Congress of the European Society of Contraception and Reproductive Health in Lisbon, May 2014 is that "*The studies demonstrating no difference in risk of venous thrombosis according to progestin types are methodologically stronger than those finding a difference."*

The exposure information in Dingers EURAS and INAS studies was achieved retrospectively by questionnaires, therefore the term "retrospective cohort study" in Table 1. The women were followed on average 2.4 years. For comparison, the Danish study had daily updated exposure data on all Danish women through a 15-year period, transferred electronically by streak codes from each pharmacy at redemption of a prescription, and therefore the term "historical cohort study". The principal difference is that in the Danish cohort design we got information about the exposure before we knew about any end point. In the Dinger studies, the exposures were assessed retrospectively after the end points occurred.

In the Dinger studies, they relied on an increased D-dimer as a validation of a venous thrombosis, while in the Danish studies, the discharge diagnoses were be linked to succeeding anticoagulation therapy. In the Dinger studies, different experts voted about the validity of a diagnosis. If just one of the voters claimed a valid case, it was included despite declined by two other evaluators, while in the Danish studies a priori defined validation criteria were applied.

The number of included confounders was six in the Danish studies, two in the German studies. Thus the German studies did not control for education, estrogen dose, ovarian stimulation therapy, or major surgery, all included in the Danish analyses.

So methodologically, at all main points the Danish studies are stronger or much stronger than the German studies. In addition, the German studies included 118 (EURAS) and 162 (INAS) women with venous thrombosis. The Danish studies included 2,847 and 3.434 confirmed events, and had therefore a much higher statistical power.

Despite these methodological facts, the Danish group again and again experience successive commentaries, each just repeating the accusations originally made by Dinger and Shapiro, without checking the sweeping statements with the original document or with our published replies. Thus in the latest INAS publication Dinger write: "*In particular, the Danish cohort study is quite often used as the reference for an increased VTE risk of DRSP$_{21d}$ compared to second-generation OCs. This study linked several national registers in Denmark. Advantages and disadvantages of this methodological approach compared to the methodology used in EURAS-like studies (e.g., the INAS-OC study) have been discussed extensively [1,25–30]"*.

In point of fact, the references cited by Dinger et al. only include his own critique of the Danish studies, or authors supporting this critique. None of the published responses to that critique discussing the advantages of the Danish methodology are referenced.

Dinger et al continues: *"The Danish register studies are much larger than field studies like INAS-OC. However, the narrow CIs in large observational studies are misleading because their calculation "only takes into consideration random variation of data. It ignores the systematic errors, the biases and confounders, that will almost invariably overwhelm the statistical variation" [10]."*

No. A high statistical power with precise risk estimates does not imply a higher risk of bias. Let me repeat, that the Danish study included and adjusted for more confounders than any previous study on this matter. Instead of claiming the Danish studies to be biased and to have systematic errors, Dinger et al. should in accordance with good scientific practice indicate how and where our studies are biased. Dinger et al. continuous: *"In addition, specific limitations of the Danish register studies — such as sparse information on relevant prognostic factors (e.g., BMI and family history of VTE) and limited validity of information on exposure and clinical outcomes [31] —increase the impact of bias and confounding compared to the INAS-OC study"*.

Let us analyze this sweeping statement point by point.

Presumably what Dinger et al call "prognostic factors" are meant to be "risk factors". As mentioned, all of six studies with data on body mass index have found it not to be a confounder[1,2, 5-8]. Similarly, the new data by Dinger et al. confirm that family disposition has no confounding influence. Why then should the Danish study be invalidated for failing to include information which no study has found to have any effect on the results? Further, in the Danish database information is now available on body mass index for approximately one third of the fertile women. Analyses restricted to this one third reach quite the same results, demonstrating twice the risk of venous thrombosis with use of combined pills with DRSP compared to levonorgestrel. As long as body mass index is the same among users of different types of hormonal contraception (after adjustment for age), body mass index cannot by definition be a confounder.

Dinger and Shapiro never explains why our exposure data on all Danish women is biased. As compensation for not explaining how, they repeat this claim over and over again. Explain please, Dinger, how a prescription database covering a whole population with a daily update through a period of now 20 years is less valid than any other source of information, and especially than retrospective information from questionnaires where women have to recall their use months or years back as in the EURAS and the INAS study. Scientists from all over the world are now conducting pharmacoepidemiological research in Denmark due to this unique opportunity to achieve valid and precise exposure information from our national prescription database.

In regard to the allegation of "*limited validity of clinical end points*" in the Danish registry study we ensured that all women defined as having a confirmed diagnosis of venous thrombosis were anti-coagulated after the diagnosis. In comparison, Dinger at al considered an event as confirmed if a woman had an increased D-dimer. It is doubtful that any clinical expert would find the latter finding as proof of a diagnosis.

Dinger et al continue: *"It should be noted that the cohorts in the Danish register studies — unlike the cohorts in the INAS-OC study — were substantially different with regard to their age structure (and potentially with regard to a number of other important prognostic factors) and that, accordingly, crude and age-adjusted relative risks estimates were substantially different."*

The Danish study had an upper age limit of 49 years, whereas the INAS study included women until 65 years. The Danish study, however, included all 1.5 million Danish women in relevant age groups in the analysis and adjusted for age differences. Generally users of hormonal contraceptives are younger than non-users, not only in Denmark but worldwide. If Dinger et al. have not found such an age difference between users of non-users of hormonal contraception in their data, they have a biased selection of exposed and non-exposed women.

Dinger: *"Our analyses show, however, that the combination of risk factors (e.g., age 45, obesity and family history of VTE) results in overadditive risk increases that cannot be correctly adjusted for if information on one of these risk factors is missing."*

Nevertheless, adjustment for these confounders did not change the estimates in the INAS study at all. Secondly, Dinger over-interprets very tiny data, the confidence limits of which make any interpretation possible. And of course you can adjust for some confounders without adjusting for other non confounding risk factors.

Dinger: *"In addition, the recent findings from the Danish database that the levonorgestrel intrauterine system is associated with statistically significant protection against venous thrombosis [32] and thrombotic stroke [33] show the limitations of this database. This paradoxical protective effect is unprecedented in contraceptive research and devoid of biological plausibility. Hence, bias in the database is the most likely explanation. Therefore, the Danish register study does not invalidate our results on* $DRSP_{24d}$ *and* $DRSP_{21d}$*."*

It is true that the Danish study was the first to report a protecting effect of levonorgestrel-IUS for venous thrombosis, just as it was the first to demonstrate a higher risk with use of combined pills with $DRSP_{20ug}$ as compared with levonorgestrel combined pills.

However, the results for levonorgestrel-IUS are actually not that surprising and do have biologic plausibility. Sex hormone binding globulin (SHBG) is a surrogate marker for the risk of venous thrombosis in users of hormonal contraception[9, 10]. The magnitude with which combined hormonal contraceptives increase SHBG correlates roughly to the relative risk of venous thrombosis. Now two studies have demonstrated a *decreased* SHBG in users of levonorgestrel-IUS[9, 10]. A decreased risk of venous thrombosis in the presence of a decreased level of SHBG is consistent, and not an aberrant finding. This finding if anything supports the validity of the Danish results, and demonstrates a basic lack of endocrinological and coagulation knowledge among those who assume this finding should be an indicator of bad science.

An interesting question is what motivates Dinger et al. in their continued efforts to discredit the Danish studies, and thereby to "muddy the scientific waters".

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Table 1

Comparison of the EURAS / INAS Dinger studies[1,2] and the Lidegaard 2011[3] and 2012[4] studies, all assessing the risk of venous thromboembolism in users of hormonal contraception, according to recognized epidemiological quality indicators.

Quality indicator	Dinger et al.	Lidegaard et al.
Year of publication	2007[1] / 2014[2]	2011[3] / 2012[4]
Design	Retrospective cohort	Historical cohort
Exposure		
Exposure period assessed	Few years back	15 years / 10 (16) years
Update of exposure, time interval	6-12 months	Daily
Source of information	Questionnaire	Prescription registry
End point		
Case identification	Questionnaires	Hospital diagnosis
Confirmation	Woman and Doctor Increased D-dimer	Anti-coagulation therapy for at least 4 weeks
Predefined criteria for valid case	No / No	Yes / Yes
Exclusion of predisposed		
Pregnant women	No / No	Yes / Yes
Puerperal women	No / No	Yes / Yes
Previous venous thrombosis	No / No	Yes / Yes
Previous arterial thrombosis	No / No	Yes / Yes
Known thrombophilia	No / No	Yes / Yes
Previous cancer	No / No	Yes / Yes
Hysterectomy	No / No	Yes / Yes
Bilateral oophorectomy	No / No	Yes / Yes
Included confounders in analysis		
Age	Yes / Yes	Yes / Yes
Education	No / No	Yes / Yes
Length of use	Yes / Yes	Yes / Yes
Estrogen dose	No / No	Yes / Yes
Ovarian stimulation therapy	No /No	Yes / Yes
Major surgery	No / No	Yes / Yes
Included other risk factors		
BMI	Yes / Yes	No / No
Family disposition of VTE	No / Yes	No / No
Analysis		
Multiple regression analysis	Yes / Yes	Yes / Yes
Subanalysis on only new users	Yes / no	Yes / Yes
Statistical power		
Included women	58,674 / 85,109	1,296,120 / 1,626,158
Included womenyears in the analysis	142,475 / 206,296	7,937,565 / 9,429,128
Womenyears on 2nd generation OC	15,428 / 19,472	477,885 / 231,675
Womenyears on 3rd gen OC	Na / Na	1,781,704 / 50,334
Womenyears on 4rd generation OC	28,621 / 62,493	309,914 / na
Events on 2nd generation OC	25 / 19	242 / 144
Events on 3rd generation OC	Na / Na	1,229 / 55
Events on 4th generation OC	26 / 35	212 / na