Reply to Jürgen Dinger and Samuel Shapiro (Part 1) *(Link to online version BMJ)*

Jürgen Dinger (JD) and Samiel Shapiro (SS) have published in the Journal of Family Planning and Reproductive Health Care a critique (1) of our new study published in BMJ online on October 25, 2011, in which we described the risk of venous thromboembolism (VTE) in users of different types of oral contraceptives (OCs)(2). Permit us to go through each of the critique points raised by JD and SS roughly in the same order as they appear in their critique.

Background

The BMJ publication was not an abbreviated version of the report made for the European Medicines Agency (EMA). On the one hand, the EMA report was a priori restricted in its aim, e.g. we were limited to include results defined in the protocol and by the Steering Committee. Where the EMA report analysed six different product groups, the BMJ publication reported 16 different product groups. Thus results on low-dose (20 µg oestrogen) OCs with drospirenone (DRSP) first published in the BMJ paper, were not included in the EMA report. On the other hand, the EMA report included many supplementary tables, not included in the BMJ publication. The BMJ publication was based on analyses conducted by the author team, with no influence from parties other than the authors. The authors had the aim of reporting all relevant results on *all* types of oral contraceptives, to calculate relative risks with non-users as a reference, and to present rate ratios between different types of OCs according to oestrogen dose, progestogen types and duration of use. It is our opinion that all relevant results were presented in the paper and its appendices.

Relevance and presentation of different analyses

First JD & SS state that users of OCs with DRSP could only have commenced their OC use in 2001. This is wrong. While DRSP was introduced to the market in 2001, the majority of DRSP users had taken other OCs before 2001. Therefore, users of OCs with either LNG or DRSP could have used OCs long before 2001. Therefore the “attrition of susceptibles” would be in effect for users in either group.

Secondly, it was decided in the protocol to conduct sub-analyses stratified into starters, new-users (defined as users with at least 12 weeks of pause before the new use), re-starters (4-12 weeks of pause) and switchers (less than 4 weeks of pause). The results demonstrated significantly increased rate ratios of VTE between users of OCs with DRSP and levonorgestrel (LNG) ranging from 1.96 to 2.69 for the different user categories. These results were reported in appendix 4 (2).

Third, no studies on OCs and VTE (to our knowledge), including the studies by Dinger et al. have ever required exclusion of every woman who used any type of OCs before the beginning of the study period. The reason that no studies use this criteria is obvious; such a requirement would not provide a sufficient number of exposed women or a sufficient number of events to ensure reliable estimates. Further, the pharmacologic effect of OCs on coagulation disappears within days rather weeks after cessation. Therefore, no scientific reason exists to support such an exclusion criteria

Nevertheless, SS (not the Steering Committee) insisted upon seeing a sub-analysis in which all users were not only starters after 2001 but also women who had never used OCs at any time prior to 2001. As expected the rate ratio estimates between OCs with drospirenone versus OCs with LNG were unstable and ranged from 0.5 to 1.9 for different duration categories, with an overall

estimate of 1.0. We concluded this finding was due to chance as a result of the low number of events in users of OCs with LNG (n=11). This interpretation was confirmed by the rate ratio of 2.05 for all starters and new users as defined in the study.

Note that we conservatively required a pause of at least 12 weeks for a woman to be considered a new user in our study. No scientific evidence suggests that previous use before a pause of at least 12 weeks influences the risk of thrombosis with new use. Based upon the instability caused by the few cases contained in the sub-analysis of non-users before 2001, the lack of scientific basis for such an exclusion criteria and the inconsistency of these results when compared to our rationally designed comparison of starters and new users, we did not include the SS requested analysis in our BMJ paper. It simply did not add any reliable or relevant information to what already was included in Appendix 4. Further, as no previous study has adopted the requirement of no previous use of any OCs, all evidence suggests that the different results achieved in different studies have nothing to do with the speculations JD & SS have about this issue. We are confident that our inclusion of previous users of OCs before 2001 is a valid design decisions. It is also transparent as we do present in our paper rate ratios of the different user categories. As authors of a scientific paper it is our responsibility to present reliable data and not to report unsustainable results.

And fourth: If the speculations from JD & SS had the slightest relevance, you should expect a difference in risk between the older 3rd generation OCs with desogestrel or gestodene and the newer OCs with DRSP. However, the risk of VTE with use of OCs with DRSP was similar to the risk of VTE in users of 3rd generation pills. In addition, by allocating continuous users at start of study in the correct "duration category", the study gained power in rate ratio analysis for longer duration of use categories.

Fifth, in Dingers own study (3), he stressed that the risk by length of use was constant after the first year, which contradicts the proposal of "*attrition of susceptibles*" in their critique.

And finally sixth, if previous use of OCs was a relevant issue, you should expect a differential rate ratio in risk of VTE according to comparable length of use categories. However, even in the group of more than four years of use, the rate ratio DRSP versus LNG was 2.31.

So for at least six good reasons there is no evidence of any differential influence from previous use of OCs on the risk estimates of VTE achieved in our new study among users of OCs with DRSP versus LNG.

Part 2

Validity of data

It is important to realise, that determining a reliable risk estimate of a certain pill demands valid exposure as well as valid end point data. Every time an exposure is misclassified or an end point is wrong, we will underestimate the real risk of VTE in current users of OCs.

Concerning the exposure data, it is difficult to imagine a more precise data source than a prescription registry. Not only does a prescription registry give precise information about the date a woman receives package of pills, but it also provides valid information about which type of pill is prescribed. As compared with retrospective studies, in which women are asked about use of OCs

months or years back in time, or prospective studies, in which a certain exposure at a certain time is not up-dated, a prescription registry is by far the most reliable exposure data available.

The small uncertainty as to exactly which day a woman commences her use as compared with the date she buys the OC is minor as compared to misclassifications made from other data sources. And more important: Any such misclassification would underestimate both the risk of VTE with current use and the rate ratio between OCs with DRSP versus OCs with LNG.

Concerning the outcome data (VTE), the primary data source was discharge diagnoses from hospital wards. The fact that Denmark collects discharge diagnoses in a National registry does not make these diagnoses less reliable than diagnoses of VTE in other studies.

Moreover, we validated all 4,246 events by cross linking them with subsequent anticoagulation therapy, and restricted our analyses to these anticoagulation-confirmed events. This validation (not surprisingly) elevated the rate ratio estimates between users of OCs with DRSP versus LNG from 1.64 in our 2009 publication to 2.1 (1.6-2.8) in the new analysis (2).

Next, in a random sample of 200 women with a discharge diagnosis of VTE, through chart review we found a positive predictive value of confirmed VTE according to the registry data to be 99%. But again it is important to realise, that even when no record of anticoagulation therapy is present in the prescription registry, this is not the same as a false VTE diagnosis. First, about 10% of women get the anticoagulation therapy for free from the departments, and they are therefore not included in the prescription registry. In addition, 5-10 per cent are diagnosed based upon clinical symptomes of VTE despite lack of confirmation in the paraclinical investigations, possibly because the clot was too small, or alternatively, that the clot might have dissolved spontaneously. In both cases no treatment may have been warranted, but the woman was found and told to have probably had a VTE. If we add the 10% ward treated women and those with clinical symptoms but without treatment, we approach the 88% achieved in our 2002 study, which was based upon information from departments and from questionnaires, and in which the women themselves confirmed their diagnosis.

Also the fact that some real events were not included in the group of confirmed events will not change the rate ratio estimates, and only marginally affect the confidence intervals. The fact that the proportion of confirmed events among users of OCs with DRSP (73.7%) and in users of OCs with LNG (73.2% and 74.2% for combined and cyclic products, respectively) was similar, strongly contradict a differential referral or a differential diagnosis of VTE among these two groups of OC users. And the number of confirmed and non-confirmed events was the same in the EMA report as in the BMJ publication. But JD & SS compared figures from the period 2001-2005 in the EMA report with figures from another period 2001-2009 in the BMJ publication.

In conclusion our study had well defined validation criteria for VTE, applied to all groups of users of OCs. The rate ratio estimate for confirmed events; 2.1 (1.7-2.7) was slightly higher than for the non confirmed events; 1.8 (1.2-2.6), indicating that the more valid the diagnoses are, the larger rate ratio estimates of VTE we find between users of OCs with DRSP versus LNG-users.

And last but not least. If anything, the inclusion of uncertain events will tend to decrease the risk estimates as demonstrated by the rate ratios described above, and cannot provide a basis to discount positive findings in our study.

Considering how carefully JD & SS have evaluated the smallest methodological details in our studies, it is surprising that they never made any reflection as to which direction their many proposals of bias would move the risk estimates. In fact, any of the alleged biases suggested by JD & SS if anything all tend to underestimate the rate ratios between users of OCs with DRSP versus OCs with LNG.

Part 3

Risk according to length of use.

Most previous studies have demonstrated a decreasing risk of VTE with increasing length of use, so that the risk is elevated about 50% the first year, and thereafter is almost constant.

We were also able to demonstrate such an overall trend by time. When you stratify current users into 16 different user groups, each with confirmed and non-confirmed events, and thereafter further subdivide your exposure time into four categories according to length of use, you cannot expect to find an equal decrease for all sub-groups by time. We nevertheless found a small although significant decrease for users of OCs with DRSP when comparing use for less than a year with use for a year or longer (2). The difference in the relative risk estimates by time of use for OCs with DRSP between our 2009 and 2011 publications are probably a result of the different censoring rules applied in the two analyses. Actually we have found no other study demonstrating a decreasing trend by time for specifically OCs with drospirenone. On the contrary, the FDA study (4) and an Israeli study (5) did not find any consistent trend in risk of VTE by duration of use for OCs with DRSP. Surprisingly, Dinger did not report any risk estimates according to length of use in his EURAS publication or his German case-control study from 2010.

JD & SS write (page 3 second column) that "*...the investigators stipulated rules based on several assumptions, in order to minimise the impact of the lack of precise exposure information..*" This statement is wrong. The detailed set of allocation rules was a result of exceptionally precise exposure information. Therefore we had to decide how we would define e.g. continuous use, new use, re-started use and switched use, all made possible due to the very precise exposure information. These rules were not made on assumptions, but were established by the Steering Committee in order to ensure the highest possible validity of the risk estimates.

Confounding by BMI and family disposition.

Of nine existing studies examining the risk of VTE in users of OCs with DRSP, five had access to BMI. In none of these studies did confounder control for BMI change the risk estimates or rate ratios between OCs with DRSP versus LNG significantly, and in four of five not at all (5-9). Two of these studies were conducted by Dinger. The average BMI in his first study was 22.0 among users of OCs with LNG and 22.9 among users of OCs with DRSP (6). The proportion of women with BMI ≥30 was (read from Fig 1 in (6)) 5.3% in users of LNG OCs and 8.2% among users of DRSP OCs, but users of DRSP OCs were also slightly older than the users of LNG OCs. Dinger stated ""*..the differences were small, and the preferential prescribing pattern identified here could only slightly increase the incidence of VTE … for the DRSP cohort"* (6). As BMI did not influence the risk estimates materially in any of these five studies, it is difficult to understand why JD & SS continues to insist that our data should be invalid due the this missing information. The same studies have documented that users of DRSP are not selected according to BMI or other risk factors of VTE.

Similar arguments can be made concerning the postulated confounding influence from family disposition. Despite being a definite risk factor for VTE, in no study over the last 10 years was it found to be a confounder.

So despite being repeated by JD & SS again and again, there is no scientific evidence at all, suggesting that the lack of confounder control for BMI or family disposition distorted our results or rate ratios.

Audit

After we had delivered our EMA report, Bayer-Pharma asked us whether we were willing to participate in an external audit of our study. That request was not made by the Steering Committee. We accepted this audit on the condition that if it was used by Bayer-Pharma in any external connection, we should have the right to comment on the audit-report. With the statements about this audit made by JD & SS in their critique, Bayer-Pharma has violated this agreement. It should be noted, however, that the audit pertains to documentation of procedures, not the reliability of the results. Secondly we asked that the audit team not only analysed our scientific process but also our actual scientific results. This request was refused by Bayer-Pharma. The conclusion of the audit report was that certain formal recordkeeping procedures set forth in a set of accreditation rules, many of which are applicable in clinical trial settings rather than rules for use of a government national registry, were not followed, but that the auditors had no reason to doubt the qualifications of the investigator team or the validity of the results. We could add that no specific procedural rules were agreed to in advance of our study, and that we were working to meet specific time constraints making it difficult to fulfil some accreditation rules e.g. that two independent statisticians should have done all the analyses for comparison.

Several of the statements made by JD & SS concerning this audit are objectively wrong. E.g. there was a detailed signed protocol describing the statistical analysis strategy before the analysis was commenced. The audit team had access to all our data and all our analyses – so transparency was definitively present.

Concerning transparency, it is also important to be aware of the fact, that Danish registries are available for any (qualified) scientist who want to investigate a scientific issue. Thus any other researcher could get access to the same data as based our analyses, as these data belongs to the state and not to any particular scientist.

Finally the willingness to conduct a re-analysis of our 2009 study, and our agreement after the conclusion of the re-analysis to an external audit, prove more than anything else our scientific openness and wish to ensure transparency. Few researchers can claim to have accepted such oversight, nor have any of Bayer's company sponsored studies been subjected to such scrutiny.

On the authors behalf

Øjvind Lidegaard

Conflict of interests

The primary investigator received no salary for his work with this study, the EMA report or the manuscript. OLi has within the last three years received honorariums for speeches on pharmacoepidemiological issues, including fees from Bayer Pharma Denmark and Novo Nordisk, and will be an expert witness for plaintiffs in

a legal US case in 2011-2; FES received compensation for his work in the steering committee of the European Medicines Agency report. The other authors had nothing to declare.

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