

Protocol to assess risk of venous thromboembolism associated with use of hormone replacement therapy in real world settings: two nested case-control studies in primary care

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I. ABSTRACT

Hormone replacement therapy (HRT) is used to help women suffering from menopausal symptoms. Although effective, the therapy may have a rare but serious side effect – an increased risk of venous thromboembolism (VTE). Previous studies have not been powerful enough to investigate the risks associated with different types of HRT. The proposed nested case-control study aims to fill this gap. Women diagnosed with VTE between 1998 and 2017 will be matched to 5 controls by age, practice and calendar year. Exposure to each type of HRT will be defined as at least one prescription for that HRT in the year before the index date (date of diagnosis of VTE or equivalent date in matched controls). Conditional logistic regression will be used to assess the risks associated with the different types of oestrogen and progestogen. The effects of duration, length of any gap since last use and method of application will be analysed for the most common types of HRT.

Index Terms: hormone replacement therapy; venous thromboembolism; epidemiology

II. INTRODUCTION

A. *What is the problem being addressed?*

In November 2015, NICE published its first ever guidance on the menopause.¹ Menopause is when a woman stops having periods because she has reached the end of her natural reproductive life. The average onset age of menopause in the UK is 51. However, this varies widely and 1 in 100 women experience premature ovarian insufficiency (menopause occurring before the age of 40). Oestrogen depletion associated with menopause causes irregular periods, and has many other effects on the body such as hot flushes, night

sweats, mood changes, memory and concentration loss, vaginal dryness, a lack of interest in sex, headaches, and joint and muscle stiffness. Quality of life may be severely affected. Most women (8 out of 10) experience some symptoms, typically lasting about 4 years after the last period, but continuing for up to 12 years in about 10% of women. Prolonged lack of oestrogen may affect the bones and cardiovascular system and postmenopausal women may be at increased risk of several long-term conditions, such as osteoporosis.

A central theme to the new NICE guideline is the need to provide patients with information on the short and longer term benefits and risks of hormone replacement therapy (HRT), and so help women make an informed choice about which treatment, if any, to choose for menopausal symptoms. The guidance distinguishes different age groups such as those under the age of 40 who have had a premature menopause due to premature ovarian insufficiency; those undergoing the menopause resulting from medical or surgical treatment (including women with cancer) as well as older women experiencing the menopause naturally. The use of HRT halved following the publication of two large studies (the Women's Health Initiative of 2002² and the Million Women study of 2003³), which both raised concerns about the safety profile of the therapy. Conversely, the new NICE guidance may result in a renewed interest among women in the use of HRT. Media reports about the effectiveness, side effects and safety of HRT have not always been accurate, so providing healthcare professionals and women with up-to-date robust sources of information is vital.

One issue specifically highlighted as a research question in the NICE guidance is how the specific preparation of HRT affects risks of venous thromboembolism (VTE). This is the problem which our study will address.

B. *Why is the research important in terms of improving health?*

Each year over 13,000 women in England die from VTE, accounting for the immediate cause of death in 10% of all hospitalised patients.⁴ This is more than the combined total of deaths from breast cancer and traffic accidents.⁴ VTE is an important and preventable cause of morbidity and

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mortality⁵ with almost a third of survivors experiencing long-term effects.^{6,7} To improve survival and to prevent complications, the occurrence of venous thromboembolism needs to be reduced.⁸ Studies that have evaluated the association between HRT and VTE have suggested some types of HRT may double the risk of VTE⁹, with the greatest effects occurring in the first year of treatment.¹⁰

There are, however, significant gaps in our knowledge regarding the risk of VTE with different types of HRT and different methods of administration. Such safety profile information is essential given the number of women who may now consider or be considered for HRT treatment under the new NICE guidelines.

Fortunately, there are now very large electronic research databases of primary care records (QResearch and CPRD), which have detailed anonymised information on diagnoses, prescriptions and clinical values, also linked to serious diagnoses recorded in hospital and mortality records. Since these databases have very detailed prescription data from over 20 years linked to hard outcomes, they can provide an efficient way to quantify the risks associated with different types of HRT.

C. How does the existing literature support this study?

1) VTE risk and type of progestogen

There are two main groups of progestogen used in HRT – progesterone and its analogues (dydrogesterone and medroxyprogesterone acetate), and testosterone analogues (norethisterone and norgestrel derivatives). All of the large randomised controlled trials of HRT used medroxyprogesterone acetate (MPA) so no direct comparison can be made between these different components based on clinical trial data.^{2, 11-13} There have been several observational studies examining risk of VTE with different types of progestogen but these have been small, with limited numbers of exposed VTE cases, and the results have been conflicting.

The UK Million Women Cohort study identified 542 cases of VTE among current users of combined HRT of which 155 were exposed to MPA, 145 to norethisterone and 232 to norgestrel.¹⁴ The study reported that the risk of VTE was significantly greater for MPA (relative risk 2.67, 95% confidence interval 2.25 to 3.17) than either norethisterone (1.82, 95% CI 1.52 to 2.17) or norgestrel (1.98, 95% CI 1.71 to 2.17).

Conversely, Canonico et al¹⁵ found an almost four-fold increased risk for other types of progesterone (odds ratio 3.9 (95% CI 1.5 to 10) but no increased risk of VTE for MPA

(0.9 (95% CI 0.4 to 2.3). However, this was a very small case control study with only 39 of cases exposed to MPA.

Renoux et al¹⁶ reported similar risks among women prescribed MPA (rate ratio 1.72, 95% CI 1.52 to 1.94) to those taking a norethisterone derivatives (1.48, 95% CI 1.37 to 1.60). However, this case control study of 23,505 cases, primarily focused on VTE risk associated with transdermal preparations and did not present detailed data on VTE risks associated with other types of progesterone or methods of application.

2) VTE risk and types of oestrogen

There are two main groups of oestrogen used in HRT – conjugated equine oestrogen (CEE) derived from the urine of pregnant horses and the natural oestrogens estradiol, estrone or estriol. Risk of VTE may vary both by the type of oestrogen used as well as the route by which it is administered (oral; transdermal patches; subcutaneous).

The large randomised clinical trials of HRT which included VTE as an endpoint have largely been based on equine oestrogen^{2, 11, 17} and few, if any have directly compared equine with non-equine preparations.¹² Several observational studies have suggested that VTE risk may be greater with oral than transdermal HRT.^{15, 16, 18}

Canonico et al undertook a case control study with 271 cases of VTE matched to 610 controls.¹⁵ Oral HRT was associated with a four-fold increase risk of VTE (odds ratio 4.2, 95% CI 1.5 to 11.6) compared with nonusers, despite adjustment for potential confounding factors. There was no increased risk with transdermal HRT (0.9, 95% CI 0.4 to 2.1).¹⁵ Limitations of this industry-funded study included its small size and potential for selection, survival and recall bias, since the study involved questionnaires to patients still alive following hospital admission for VTE.

Two studies^{16, 18} used the General Practice Research Database to study risk of VTE associated with transdermal hormonal therapy compared with oral use, and found increased risk associated with oral use but not with the transdermal route. Only one of these studies reported risk of VTE by type of oestrogen although this compared oral conjugated equine oestrogen in 20 patients with transdermal oestradiol in only 7 patients.¹⁸

3) VTE risk among patient subgroups

Few studies have examined the relationship between HRT and VTE risk in relation to body mass index (BMI) and those that did have reported conflicting results. Sweetland et al found that VTE risk decreased with increasing body mass index among women using oral oestrogen¹⁴ whereas Canonico showed the opposite (higher BMI values were associated with

greater VTE risk).¹⁰ We have also found no studies examining the relationship between HRT and VTE risk by ethnic group.

A large-scale robust observational study, comparing VTE risk for different patient subgroups as well as by different HRT preparations and different application methods is required.¹⁹

D. 1.4 What is the research question?

The study aim is to quantify how different preparations of HRT affect the risk of VTE in order to determine which preparations have the best safety profile for women. Our objectives are to:

- quantify the risks of VTE associated with hormone replacement therapy (HRT), by regimen of HRT (unopposed oestrogen; combined cyclical; combined continuous); type of oestrogen (conjugated equine oestrogen vs. oestradiol) or progestogen (MPA vs. norethisterone/norgestrel); dose and duration of treatment; and route of delivery (oral vs. transdermal);
- determine whether these risks vary by patient characteristics such as age; body mass index; ethnicity; pre-existing co-morbidity and concurrent medication, to identify those women most likely to suffer from VTE.

III. METHODS

A. Design

We will undertake two nested case control studies with cases of VTE and matched controls using the QResearch database and CPRD. QResearch is a large validated database including the records of 23 million patients registered with approximately 1300 practices linked at patient level to hospital and mortality data. CPRD also consists of data routinely collected from GP computer systems. It currently includes 711 practices of which 405 have data linked to ONS and hospital episode statistics.

B. Population and selection of cases and controls

For each database, we will identify an open cohort of women aged from 40 to 79 years registered during the study observation period from 1st January 1998 to 28th February 2017 (or latest available for QResearch). Practices will be included if they have been using the relevant clinical system for at least 12 months. Women will be eligible for inclusion in the cohort if they have been registered with the practice at least a year.

Cases will be women in the cohort who have a first diagnosis of VTE during the observation period recorded on either the GP record, hospital or mortality record. We will match each

case diagnosed with VTE to 5 controls who are alive and registered with the same practice at the time of the VTE diagnosis of the case (index date). Controls will be matched with cases by practice, age, and calendar time using incidence density sampling. Each control will be allocated an index date, which will be the date of first diagnosis for the matched case. Women with an existing diagnosis of VTE prior to study entry will be excluded.

C. Outcome measure

The outcome is an incident diagnosis of VTE. VTE will include deep vein thrombosis or pulmonary embolus. VTE cases will be identified based on diagnoses recorded on the GP record or the linked hospital or mortality records using code lists validated for use in previous studies of VTE.¹⁹

D. Exposure

We will extract all prescriptions for HRT in cases and controls since the early 1990s. This will allow us to look at long term exposure as well as medium and short term effects. Using definitions from similar studies using electronic records, we will categorise HRT by any use, type of drug prescribed; type of oestrogen and progesterone; regimen of use; route of delivery; duration; dose; recency.¹⁴
¹⁸

Two types of oestrogen (CEE and natural oestrogens) and two types of progestogen (progesterone-and-analogues and testosterone-analogues) will be considered. Three types of progesterone (MPA, dydrogesterone and drospirenone) and two types of testosterone (norethisterone acetate; norgestrel/levonorgestrel) are prescribed in the UK. Oral and transdermal (patches, subcutaneous and gels) preparations will be analysed separately.

For oestrogen, the dose will be categorised into low dose ($\leq 0.625\text{mg}$ for oral equine oestrogen, $\leq 1\text{mg}$ for oral oestradiol, ≤ 50 micrograms for transdermal oestradiol) and high dose ($> 0.625\text{mg}$ for equine oestrogen, $> 1\text{mg}$ for oestradiol, > 50 micrograms for transdermal oestrogen).¹⁴

We will investigate recency of use by calculating the gap in days between the estimated date for last use of HRT and the index date, categorising it as follows: used at index date or last use 1 to 90 days before the index date (current use);¹⁸ ²⁰ last use 91 to 365 days before the index date (past use); no use in the last year before the index date.

Duration of use will be assessed by calculating the number of days of exposure. If the gap between the end of one prescription and the start of next is 90 days or less, we will consider exposure as continuous²¹ ²² and combine the duration of the prescriptions. We will classify duration as short-term (up to 84 days) and long-term (85 to 365 days).

We will combine duration with recency of use into the following categories: short-term current users (new users and restarters); long-term current use (prevalent users); past use; no use in the previous year.

We will concentrate on recent exposure because it has been shown that past exposure is not associated with increased risk of VTE.^{14 20} We will include past exposure into the analysis because the exact date of starting a medication is not known. No use in the previous year will be the reference category for all exposures.

E. Confounders

Potential confounders will be variables which are risk factors for VTE²³⁻²⁵ or indications for HRT. Patient characteristics will include: ethnicity; body mass index (BMI); Townsend deprivation score; smoking status; alcohol consumption; family history of venous thromboembolism; premature menopause; and oophorectomy or hysterectomy. Chronic conditions will include: varicose veins; congestive cardiac failure; cardiovascular disease (stroke, transient ischaemic attack or coronary heart disease); rheumatoid arthritis; atrial fibrillation; systemic lupus erythematosus; Crohns or ulcerative colitis; chronic kidney disease; asthma; chronic obstructive pulmonary disease; cancer. Acute conditions will include: recent hospital admission in the preceding 2 to 6 months; recent hip fracture and/or hip surgery in the preceding 6 months. Other medications will include current (up to 90 days before the index date) or recent (91 to 365 days before the index date) use of: antipsychotics; antidepressants; tamoxifen; combined oral contraceptive; aspirin.

F. Statistical analysis

The two studies using QResearch and CPRD will be conducted in exactly the same way, selecting the same confounders and running the same procedures. All observations will be from general practices in the UK, from the same time period, with similar exposures and using similar methods for recording outcomes.

Conditional logistic regression will be used to estimate odds ratios with 95% confidence intervals for the HRT exposure variables. Unadjusted odds ratios and odds ratios adjusted for all confounders listed above will be reported. Adjusted odds ratios from the conditional regression analyses of the two datasets will be pooled using a fixed effect model with inverse variance weights.²⁶ We will also run a sensitivity analysis using a random effect model to allow for any heterogeneity. For statistically significant findings, numbers needed to harm will be calculated.

As BMI, smoking status and alcohol consumption may be important confounders but have non-negligible numbers of missing data, multiple imputation will be used to impute

missing values.²⁷⁻³⁰ Ten imputed datasets will be created. Index year, case/control status, age, years of records, potential confounders, and exposure to hormonal replacement therapy and other drugs, will be included in the imputation model. The distribution for BMI will be tested and, if not normal, a transformation will be carried out prior to inclusion in the imputation model. Characteristics of women with missing values and with complete data will be compared to assess whether it is plausible that data are missing at random.

G. Sub-group and sensitivity analyses

Subgroup analyses will be run by age group (40 to 54, 55 to 64, 65 to 79) and by BMI (normal up to 25kg/m², overweight more than 25kg/m² and up to 30kg/m² and obese 30kg/m² or more). For the BMI analysis, only women with valid BMI will be included. A test will be run for interactions between HRT, age and concurrent medication.

Sensitivity analyses will be run addressing different assumptions. In QResearch, all patients are linked to HES and ONS data and have a valid patient-level Townsend deprivation score. In CPRD, only 60% of practices are linked and have a valid patient-level Townsend score. For CPRD, we will run the analyses based on all available practices, but the analyses will be repeated on the subgroup of patients linked to HES and ONS data. Cases and controls with VTE previously diagnosed and recorded in HES will be excluded from the analyses. We will also use patient-level Townsend deprivation index as a confounder for these analyses. If the results of these sensitivity analyses are different from the main analyses we will publish them as the main findings and use them in the meta-analysis described above.

It is possible that a small number of patients experienced VTE in the past, which was not recorded but followed by anticoagulant prescriptions. In our previous research for combine oral contraceptives we excluded such patients.¹⁹ In this study, patients are older and may have been prescribed anticoagulants for other reasons such as atrial fibrillation or VTE prevention after hip replacement operation. A sensitivity analysis will be run where cases with anticoagulant prescriptions six or more weeks before the index date and controls with all such prescriptions at any time before the index date will be excluded.

Regarding the multiple imputation assumption of missing at random, a sensitivity analysis will be run, restricted to women without missing data for BMI, smoking status or alcohol consumption. Regarding the assumption of being white for missing values for ethnicity, a sensitivity analysis with an extra category of unrecorded ethnicity will be included.

An additional analysis will be run on the sub-group of linked cases and their matched linked controls where the case diagnosis is supported either by thrombolytic prescriptions in the 6 weeks before or after the VTE diagnosis, or by a diagnosis made on hospital or mortality records.

Another additional analysis will be run on idiopathic cases and their controls (identified from GP records), excluding from the analysis all cases and controls with medical conditions and recent events established as VTE risk factors described in the Potential Confounders sub-section.

A 1% level of statistical significance will be used to allow for multiple comparisons. Stata v 15 will be used for all the analyses.

H. Sample size calculations

For an individual drug with exposure of 0.8%, 29,495 cases will be needed to detect a clinically important odds ratio of 1.3. For rarer exposure of 0.3%, it will be possible to detect an odds ratio of 1.5 with a sample of 30,206 cases. All calculations are done for a significance level of 1%, 90% power and correlation of exposure between cases and controls of 0.1.

IV. STRENGTHS AND LIMITATIONS

The main strength of the study is its generalisability and the large scale. Designing a two-database study will not only allow us to provide more precise estimates but will also increase the statistical power, facilitating investigation of less common exposures.

The limitations of the study will include possible uncertainty about VTE diagnoses because the results of diagnostic tests needed to confirm VTE are not usually available from the primary care dataset. There might be some false positives for cases and some false negatives for controls. The likelihood of misclassification is much higher for cases than for controls because of the low incidence of VTE in the general population. Such errors, if non-differential, would tend to shift odds ratios towards unity. To address this limitation, we plan to run an additional analysis restricted to cases with thrombolytic prescriptions or with a diagnosis taken from hospital or mortality records.

Another limitation is the potential misclassification of exposure to HRT. We do not know with certainty whether a woman has filled a prescription or whether/when she started taking a prescribed medication. We do not see, however, any reason why this should differ between cases and controls. These two potential misclassifications are likely to be small but might also shift odds ratios towards unity.

V. SUMMARY OF PATIENT ENGAGEMENT PLANS

The research questions have been identified by the NICE guideline group on HRT, which was published in 2015 and as such have been subject to public consultation at all stages of the development and publication of the guideline in accordance with NICE's policy and procedures. In addition, the lead applicant author has discussed the proposal informally with a number of peri-menopausal and postmenopausal women, including several general practitioners.

As part of our research we will involve a group of women who have used hormone replacement therapy, in order to discuss their experiences of the treatments, any problems they experienced, whether this affected their ability or willingness to maintain treatment and their concerns about risks. We will describe to them our proposed research and ensure that any issues they might raise are considered and appropriately incorporated. We also intend to disseminate our findings through general practices and in community settings.

A. Lay summary

At a certain age or after some health problems women stop having periods and enter the biological stage called menopause. This is characterised by low levels of particular hormones and during this period many women experience unpleasant symptoms, such as hot flushes, sweats or depression. They are also at increased risk of developing bone fragility, heart disease and urinary problems. Hormone replacement therapy (HRT) was introduced to relieve unpleasant symptoms and reduce the risks of chronic health problems. There are different therapy types, which depend on the symptoms experienced by an individual. Some women require a therapy based only on the oestrogen hormone, others may need a combination of oestrogen and another hormone called progestogen. These therapies can also be administered in different ways – as tablets, patches or a cream.

Although all these treatments are effective in managing menopausal symptoms, they have a rare, but serious side effect – an increased risk of blood clots. A recently issued guideline from the National Institute for Health and Care Excellence (NICE) has stressed that research findings from studies trying to estimate the risk of developing blood clots as a result of taking HRT are still not clear, and not a good basis for decision-making by doctors or patients. In particular, the studies so far have not been able to identify different levels of risk for different treatment types, regimens or application methods. This is because they only included a relatively small number of patients for each treatment type, making comparisons of outcomes unreliable.

This study will, for a 18-year period from 1998 to 2016, investigate risks of blood clots from all types of hormone replacement therapy. We shall use two large databases containing records from over 1700 English general practices and their associated hospital patient records. Patient confidentiality will be absolute because the information in these databases has been anonymised. We will compare the HRT treatment prescription records of all women who developed blood clots with those of women who did not. We will take into account other health conditions and patient characteristics which might affect the risk of blood clots to ensure that our results properly demonstrate the effects of the different therapies rather than other factors.

For single hormone and for hormone combination therapies we will investigate which specific types of treatment have the lowest risks of blood clots and will investigate outcomes related to different ways of administering the drugs (tablets, patches or creams).

The findings will provide much clearer and more detailed information for doctors and patients about blood clot risks related to different types of HRT to help them in their decisions.

VI. OTHER INFORMATION

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B. Approvals

The project has been reviewed in accordance with the QResearch® agreement with NRES Committee East Midlands – Derby [reference 03/4/021]. The protocol for CPRD has been approved by The Independent Scientific Advisory Committee for MHRA Database Research (N 16_275R).

C. Competing Interests

JHC is professor of clinical epidemiology at the University of Nottingham and co-director of QResearch® – a not-for-profit organisation which is a joint partnership between the University of Nottingham and Egton Medical Information Systems (the leading commercial supplier of IT for 60% of general practices in the UK). JHC is also a paid director of ClinRisk Ltd which produces open and closed source software to ensure the reliable and updatable implementation of clinical risk equations within clinical computer systems to help improve patient care. CC is Professor of Medical Statistics at the University of Nottingham and a paid consultant statistician for ClinRisk Ltd. This work and any views expressed within it are solely those of the co-authors, and not of any affiliated bodies or organisations.

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