Economic evaluation of a novel genetic screening test for risk of venous thromboembolism compared with standard of care in women considering combined hormonal contraception in Switzerland

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ABSTRACT

Aim The aim of this study was to assess the cost effectiveness of the Pill Protect (PP) genetic screening test for venous thromboembolism (VTE) risk compared with standard of care (SoC), for women considering combined hormonal contraceptives (CHCs) in Switzerland.

Methods A two-part microsimulation model was developed to estimate VTE events, costs and quality-adjusted life years (QALYs) associated with the PP and SoC strategies. In the first portion of the model, a cohort of 1 million Swiss first-time seekers of a CHC were simulated. It was determined whether each woman would receive a CHC or non-CHC by using prescribing patterns elicited from a modified Delphi study. These results formed the basis of the SoC strategy. For the PP strategy, a PP test was included and the results considered in addition to SoC practice. Each woman then entered a Markov model that captured morbidity and mortality over a lifetime. The risk of having a VTE was derived from the risk algorithm that underpins the PP test. The remaining model inputs relating to population characteristics, costs, health resource use, mortality and utilities were derived from published studies or national sources. The model was validated and calibrated to align with population-based studies. Extensive uncertainty analyses were conducted.

Results From a Swiss health system perspective, the PP strategy in comparison with the SoC strategy generated an additional CHF 231, and gained 0.003 QALYs per woman, leading to an incremental cost-effectiveness ratio of CHF 76 610 per QALY gained. Assuming a threshold of CHF 100 000 per QALY gained, the PP strategy is likely to be cost effective. Our results were generally robust to variations in the parameter values.

Conclusions The PP test may be cost effective in Switzerland for screening women seeking CHCs for their risk of VTE based on the current evidence.

Strengths and limitations of this study

- We used advanced quantitative methods to appropriately model the long-term costs and effects of the strategies compared.
- In addition, we undertook primary qualitative research through a modified Delphi study to inform the pathway of SoC patients through the model.
- The model was calibrated and validated to accurately predict estimates of venous thromboembolism using published data from European cohort studies.
- Extensive sensitivity and scenario analyses were undertaken to test the robustness of the results.
- Limitations are that our clinical and cost-effectiveness results are dependent on the accuracy of Pill Protect to predict the occurrence of venous thromboembolism events (which has been validated retrospectively but not yet prospectively or externally), and the hypothesis that all Swiss clinicians behave as assessed by our modified Delphi study.

INTRODUCTION

The development of the contraceptive ‘pill’ began in the 20th century and gained popularity due to its benefits in controlling menstrual bleeding and as a simple and effective family planning mechanism. The combination of ethinyl estradiol (EE) and various progestins has become the basis for combined (hormonal) oral contraceptives. Combined hormonal contraceptives (CHCs) comprise oral pills and other contraceptive devices (ie, rings or patches) that contain oestrogen in combination with a progestogen. Venous thrombosis is a serious medical condition that occurs when a blood clot...
(thrombus) forms in one or more veins of the body. One particular form of venous thrombosis is called deep vein thrombosis (DVT). Here, the blood clot occurs in deep veins, typically of the legs. Such blood clots may travel through the bloodstream and lodge in lungs, where they can block blood flow, causing pulmonary embolism (PE). The term, venous thromboembolism (VTE), incorporates both conditions of DVT and PE. The incidence of VTE increases with age from 1:100,000 in children per year to 1:10,000 for individuals per year in the reproductive age, and finally to 1:1000 individuals per year at the age of 50–60. All ages included, the disease occurs in 1–2 per 1000 individuals per year. The association between dosage of EE in CHCs and VTE has been known since 1970, and recent studies show that VTE risk in CHC users is 3–18 times higher than for non-users according to the hormonal combination underlying the CHC.

Genetic studies have identified many variations associated with the development of VTE. Among them are variations in Factor V Leiden and Factor II G20210 (also known as prothrombin) or deficiencies in C and S proteins. In addition, VTE is a multifactorial disease influenced by genetic factors but also by behavioural and environmental factors such as smoking status and hormonal treatment. Several studies have developed algorithms to estimate thrombosis risk according to an individual’s clinical and/or genetic profile, but few have estimated this for CHC users specifically. The field of personalised medicine tailored to people’s genetic profiles by using specific algorithms is expected to expand in the next decades following recent initiation into Swiss clinical practice. Personalised approaches could be used to inform patients about their risk of VTE. For many first-time seekers of CHCs, genetic testing may flag up an increased VTE risk associated with a CHC prescription which exceeds the benefits and for which alternative contraceptive methods exist.

The Swiss Society of Gynaecology and Obstetrics (SSGO) guidelines and published recommendations suggest that clinicians assess thrombosis risk in patients and only prescribe CHCs for those with low or no apparent thrombogenic risk. However, women often do not know their medical or family history and clinicians make qualitative judgements of when the combined risks of CHCs exceed the benefits.

The Pill Protect (PP) algorithm was developed and validated using published PILI Genetic Risk Monitoring and Cohort Lausanne cohorts. The algorithm quantifies a CHC user’s VTE risk according to her genetic and behavioural characteristics. Retrospective validation results showed the algorithm successfully predicted thromboembolic events for oral contraceptive users (area under the receiver operator characteristic curve=0.71, 95% CI 0.69 to 0.74). The algorithm underlies the PP genetic test currently reimbursed in Swiss clinical practice under certain conditions for health providers. Although several alternative tests evaluating clinical and genetic thrombosis risk exist, only PP assesses VTE risk related directly to CHC use.

Recent reviews of the literature have found scarcity of economic evaluations for screening genetic risk of VTE in first-time CHC users. Furthermore, most of the studies were based on short-term decision tree models, although a personalised microsimulation model may be a more appropriate specification. This is the first study to assess clinical, quality of life, cost outcomes and cost-effectiveness of the PP test when screening first-time seekers of CHCs at risk of VTE in comparison to the Swiss standard of care (SoC).

METHODS

We developed an individual sampling model simulating VTE and other clinical events occurring over the lifetime of each woman based on her personal characteristics (using Swiss and European prevalence data) and the contraceptive method recommended to her. One million women were simulated, and the model was populated with inputs derived from literature searches, national databases, local pharmacies and expert opinion from a modified Delphi study that we conducted. The model calculated annual outcomes for costs, VTEs, life years gained and quality-adjusted life years (QALYs) gained. Perspectives of cost assessed included a Swiss health system perspective considering direct medical costs irrespective of payer (base-case analysis), a health insurer perspective only considering reimbursement by insurers within the framework of the Swiss statutory health insurance (45% of inpatient services, 100% of drug treatment and PP test costs, 50% of laboratory fees and 0% of contraceptive interventions) and a societal perspective including all direct costs and productivity costs.

A lifetime time horizon (maximum of 85 years since model entry) was used for the model and considered appropriate as single and recurrent VTE events often occur in the longer term and may have long-term consequences. However, the model does not take into consideration that early detection of genetic risk for thrombosis might lead to prophylactic treatments later in life, except for the choice of contraception method. A discount rate of 3% for costs and outcomes was applied as is typical for Swiss economic evaluation.

Population, intervention, comparator, outcomes and setting

Our analysis targeted Swiss women aged 15–29 years, as this was the age range of potential first-time users seeking CHCs elicited from the modified Delphi study described in the ‘strategy description’. The comparator was the Swiss SoC also described in strategy description, while the intervention incorporated the PP test into SoC. The setting was Switzerland, and the following outcomes were reported: VTEs, mortality, life years gained, QALYs, costs and cost per QALY gained.

Strategy description

Schematic diagrams of the SoC and PP clinical pathways are illustrated in figure 1. For both SoC (figure 1A) and
PP (figure 1B), the first step for the clinician is to review the woman’s medical history and subsequently recommend an alternative to CHCs (such as progestin-only pills, condoms, diaphragms or sponges), or prescribe a CHC. However, for the PP strategy, the first step also includes the completion of the PP test (refer to figure 1B), and if the test indicates high relative risk (RR) of VTE, a non-combined contraceptive is recommended. Otherwise, patients are automatically prescribed a CHC unless they have a positive family history of thrombosis in which case additional thrombophilia testing takes place and the result of this determines prescription of either a CHC or non-combined contraceptive. A threshold of 18 was established for a high RR of VTE; it was chosen because it is very close the highest naturally occurring risk in a woman’s lifetime (during the postpartum period).

We determined characteristics of SoC in practices of Swiss clinicians recommending CHCs, by undertaking a modified Delphi study between 2017 and 2018. We asked questions to clinicians related to how general practice for recommending CHCs in Switzerland is carried out. Nineteen gynaecologists completed the first round, six the second round (97% agreement) and three participated in a final round used to clarify a few questions where second round consensus was not reached. The results of the Delphi study indicated that clinicians’ prescription processes in Switzerland are broadly aligned with SSGO recommendations (refer to online supplementary appendix table A1). Clinicians are cautious in prescribing CHCs to women with apparently high VTE risk, and often seek further biochemical (ie, Protein C, S, lupus anticoagulants, etc.) and genetic tests (ie, Factors II and V) if positive family history of VTE is present. In addition, they do not prescribe CHCs to women with a confirmed genetic risk (ie, Factor II or V Leiden), and at times avoid CHC prescription in the presence of multiple clinical risk factors (ie, body mass index (BMI), smoking, age), even when genetic testing has confirmed the absence of Factor II G20210A and Factor V Leiden mutations which are known to be contributing to thrombosis risk.

Modelling

We developed a microsimulation model in StataMP V.15 (College Station, TX, USA). Within the model, events occur at an individual level. The simulation of 1 million women seeking prescription of contraception for the first time was generated based on characteristics of age, BMI, smoking status, family history and nine genetic factors.

The first step in the model simulates each patient through a clinical decision pathway, determined by the strategy (PP or SoC), to establish whether or not a CHC is prescribed based on the patient’s baseline characteristics. Once the contraceptive intervention is determined for each individual (CHC or non-combined contraceptive), each woman enters the Markov part of the model for her lifetime. This is done separately for the SoC and PP strategies. The model contains five main health states: no VTE, first VTE, second VTE, post-VTE and death (figure 2). Through this state-transition modelling, costs and utilities associated with each health state are calculated and accrued over the lifetime. Details on the different health states are provided next.
Each woman begins the model without previous VTE event (‘no VTE’) but is at risk of death or having a first VTE (‘first VTE’). If a VTE occurs, the model determines whether it is DVT only or also PE. A patient who survives the VTE then remains in the post-VTE health state for her remaining life (until ‘death’) or until another VTE event occurs (‘second VTE event’). Options for transitions after second VTE mirror those after first VTE, however the event probabilities may differ.

The post-VTE health state comprises women after one or two VTE events. Here, additional morbidity associated with living after VTE is incorporated (Table 1). It is assumed CHC use is stopped after a VTE, and contraception switched to a non-combined variety. Costs of contraception continue to incur for the period each woman is estimated to use contraception, determined at baseline in the model. The model is run for each woman up until the point she reaches the ‘death’ state.

Modelling assumptions

Key modelling assumptions include: the estimates derived from PP algorithm accurately predict relative VTE risk of women with different risk factors. The data obtained from the modified Delphi panel accurately represent actual clinical practice related to contraceptives prescription in Switzerland. Also, we assumed the PP algorithm in combination with appropriate calibration allowed appropriate modelling of real-life occurrence and distribution of VTE events. We also assumed that risks from CHCs were only present while women take CHCs (ie, no spill-over effects) and additional surgery and life events that possibly increase VTE risk did not occur during one’s lifetime. We limited the number of recurring VTE events to ‘two’ at most, and due to lack of evidence, did not incorporate further risk reduction of VTE for those given anti-coagulant prophylaxis (ACP) after VTE.

Validation and calibration

Several modelling calibration and validation exercises were undertaken. Primarily, the model was first designed in Microsoft Excel 2016 and then duplicated in StataMP V.15. Both models produced alike results demonstrating internal validity. In addition, parameters relating to absolute incidence of VTE were calibrated against a Danish cohort study for women aged 15–50 years20 and a Swedish cohort study for women aged over 50.21 In order that entry age into our model was 21 years; hence, the incidence estimate is similar to those of the same age in the Danish cohort study (ie, ages 20–24; VTE incidence 2.1 per 10 000 women years). The median life expectancy simulated by the model was 87 years, which indicates validity as it is close to actual life expectancy of Swiss women (85 years).

Model input parameters

Clinical efficacy, event and population characteristics

Table 1 summarises population, clinical efficacy and event parameters used for the analysis. Parameters relating to population characteristics, BMI and expected duration of CHC use according to age are detailed in online supplementary appendix table A2–A4. The probability that a woman has a first VTE event was calculated using the PP algorithm derived from a study by McDaid et al.13 (for additional calibration to real world data, see above). One of the algorithm components is the RR of having a VTE related to a CHC according to its generation or formulation (ie, second, third, fourth, cyproterone acetate, etc.). This RR of VTE for CHC users compared with non-users was derived from pooled estimates of cohort studies reported by Martinez et al.22 RR of VTE for the progestogen-only pill and non-hormonal contraception was estimated to be 1.03 (95% CI 0.76 to 1.39) and 1, respectively.

The proportion of VTE events that were DVT and PE were 41.0% and 59.0%, respectively, derived from a USA population study.23 A Danish database was used to determine that onset of DVT resulted in 1.5% cardiovascular events (myocardial infarction (MI) or stroke) and onset of PE resulted in 1.7% cardiovascular events in the first year.24 Probability of death related to PE and DVT was derived from Italian hospital records.25 To understand recurrence of VTE, a study by Laczkovics et al in 2007 was used.26 Mortality for recurrent VTE was assumed to be the same as for first VTE.

Underlying probability of death from general causes is based on Swiss Federal Statistical Office (SFSO) lifetables.

Health-related quality of life (HRQoL)

Table 1 summarises HRQoL values for the model. Utility (preference-based HRQoL) in the female Swiss population is based on a Swiss-specific valuation algorithm.27 Using this algorithm, the microsimulation model calculates age-related utility on an annual basis, and when a VTE event occurs, or a woman remains in post-VTE, the weighted disutility of PE and DVT is applied.

Disutility values after DVT28 and PE29 were derived from Norwegian data. This disutility was applied long term in the post-VTE state as the studies that the values were taken from estimated disutility resulting from DVT/PE for at least 10 years following the event. Disutilities for stroke and MI events were derived from an external study.29
| Table 1 | Key model inputs |
|---------|-----------------|
| **Inputs** | **Mean estimate (95% CI)** | **Source** |
| **Clinical efficacy and event inputs** | | |
| RR of contraceptives | | |
| Second generation: levonorgestrel | 3.48 (2.26 to 5.09) | Martinez et al 2012\(^{22}\) |
| Third generation: gestodene, desogestrel | 5.65 (3.67 to 8.28) | |
| Fourth generation: drospirenone, dienogestrel | 5.78 (3.05 to 10.61) | |
| Cyproterone acetate | 5.74 (3.74 to 8.39) | |
| Other (ie, Qlaira) | 3.48 (2.26 to 5.09) | |
| Progestogen only: desogestrel | 1.03 (0.76 to 1.39) | Mantha et al 2012\(^{23}\) |
| Non-combined: that is, of condoms, IUD, and so on | 1 | Assumption |
| **Proportion of CHCs** | | |
| Second generation: levonorgestrel | 47.7% (45% to 50.4%) | Modified Delphi study |
| Third generation: gestodene, desogestrel | 27.0% (24.6% to 29.4%) | |
| Fourth generation: drospirenone, dienogestrel | 17.5% (15.4% to 19.5%) | |
| Cyproterone acetate | 7.1% (6.1% to 8.1%) | |
| Other (estradiol valerate/dienogest, etonogestrel, chlormadinone acetate) | 0.8% (0.5% to 1.1%) | |
| **Proportion of non-CHCs** | | |
| Non-CHCs: desogestrel | 42.3% (39.4 to 45.2) | Modified Delphi study |
| Non-CHCs: that is, condoms, contraceptive sponge, and so on | 57.7% (49.1 to 66.3) | |
| **VTE-related events** | | |
| Proportion of VTE that is DVT alone | 41% | Silverstein et al, 1998\(^{23}\) |
| Proportion of VTE that is DVT and PE | 59% | |
| **Probability** | | |
| DVT leads to MI or stroke | 0.015 | Sørensen et al, 2007\(^{24}\) |
| PE leads to MI or stroke | 0.017 | |
| Mortality for PE | 0.045 (0.031 to 0.065) | Compagni et al, 2013\(^{25}\) |
| Mortality for DVT | 0.007 (0.0033 to 0.0128) | |
| Probability of recurrent VTE | 0.0429 | Laczkovics et al, 2007\(^{26}\) |
| **Utility inputs** | | |
| Constant | 0.84822 | Perneger et al, 2010\(^{27}\) |
| Age coefficient | 0.00208 | |
| Age coefficient\(^2\) | 0.00002 | |
| Gender coefficient*NOTE=1, since female | 0.02090 | |
| VTE PE disutility | −0.09 | Tavoly et al, 2016\(^{28}\) |
| VTE DVT disutility | −0.08 | Utne et al, 2016\(^{28}\) |
| Disutility stroke | −0.2547 | Sullivan et al 2011\(^{29}\) |
| Disutility MI (acute) | −0.1690 | |
| Death | 0.00 | Assumption |
| **Cost inputs** | | |
| Consultation with clinician for CHC: first visit | CHF 91 | TARMED Tarifbrowser 1.08 (22.001)\(^{32}\) |
| Consultation with clinician for CHC: second visit | CHF 91 | Modified Delphi study |
| Third visit (if labs required) | CHF 91 | TARMED Tarifbrowser 1.08 (22.001)\(^{32}\) |

Continued
Table 1 Continued

| Inputs | Mean estimate (95% CI) | Source |
|--------|------------------------|--------|
| PP test | CHF 270 | Gene Predictis (oral communication, 21 March 2017) |
| Laboratory testing | | |
| Laboratory testing for *FV Leiden/FII* (including administrative and extraction fees) | CHF 616 (553 to 679) | Viollier Switzerland, SFOPH, Analysenliste (AL) 2021, 4700, Modified Delphi study |
| Laboratory testing for Protein C, S and Lupus anticoagulant only (including administrative fees) | CHF 185 (241 to 252) | Viollier Switzerland, SFOPH, AL, SFOPH, 4700, Modified Delphi study |
| Extraction cost for DNA testing (*FV Leiden/FII*) | CHF 61 | SFOPH, AL 2021 |
| Administrative costs for any laboratory testing (added tax) | CHF 24 | SFOPH, AL 4700 |
| Hospitalisation costs, VTE | | |
| DVT | CHF 6813 (6501 to 7194) | SFOS, DRG F63 |
| PE | CHF 8722 (8499 to 9033) | SFOS, DRG E64 |
| Cardiovascular events related to VTE | | |
| MI | CHF 9141 (8974 to 9401) | SFOS, DRGs F41, F60 |
| Stroke | CHF 13940 (13262 to 13 744) | SFOS, DRGs B04B, B39, B70 |
| Haematologists consultations and visits | | |
| Cost per one outpatient visit (patients require two visits in the first year to manage VTE) | CHF 132 | TARMED Tarifbrowser 1.08, 22.002 |
| Anticoagulant prophylaxis (3 months) | CHF 238 | SFOPH, Spezialitaetenliste |
| CHC generation: progestin contained | Annual costs | |
| Second generation: levonorgestrel | CHF 143 (128 to 157) | TopPharm Pharmacies (toppharm Apotheke) |
| Third generation: gestodene, desogestrel | CHF 169 (152 to 186) | |
| Fourth generation: drospirenone, dienogestrel | CHF 226 (20 to 249) | |
| Cyproterone acetate | CHF 170 (153 to 187) | |
| Other | CHF 302 (263 to 340) | |
| Non-combined contraceptives | | |
| Progestogen only: desogestrel | CHF 228 (205 to 251) | TopPharm Pharmacies (toppharm Apotheke) |
| Non-combined alternatives | CHF 177 (159 to 195) | Apotheke HERSBERGER BASEL |
| Indirect costs | | |
| Productivity loss per disability claim DVT (short term) | CHF 4286 (CHF 2857 to 9183) | SFOS data and expert opinion |
| Productivity loss per disability claim PE (short term) | CHF 6122 (CHF 2857 to 9183) | SFOS data and expert opinion |

CHCs, combined hormonal contraceptives; CHF, Swiss Franc; DRG, diagnosis-related group; DVT, deep venous thrombosis; FII, Factor II; FV, Factor V; IUD, intrauterine device; MI, myocardial infarction; PE, pulmonary embolism; PP, Pill Protect; RR, relative risk; SFOPH, Swiss Faculty of Public Health; SFOS, Swiss Federal Statistical Office; VTE, venous thromboembolism event.

Health resource use and direct costs

Table 1 details cost and resource use values for the model. We selected unit costs in Swiss francs (CHF) and 2016 prices. Costs derived from older sources were inflated to 2016 values using the Swiss Consumer Price Index provided by the SFOS. Direct costs related to recommending contraception in Switzerland included gynaecologist visits and, where applicable, the PP test, thrombophilia tests and further biochemical tests for women with low PP RR scores but positive family history of VTE.

Hospitalisation costs related to a VTE event, stroke or MI were derived from the Swiss diagnosis-related group (DRG) reimbursement database. Where more than one
DRG was relevant, the weighted average was calculated. Unit costs for haematologist visits for women with a VTE were derived from TARMED, and we assumed visit duration of 30 min. Unit costs for drugs with relevant Anatomical Therapeutic Chemical Classification System codes were obtained from the Swiss Federal Office of Public Health Specialty List. Market share data and costs of CHCs were provided by TopPharm Pharmacies in Basel, Switzerland. The annual cost for non-combined contraceptives was taken from a weighted average of the costs of condoms, diaphragms, contraceptive sponges and contraceptive pills that only include desogestrel from a Swiss pharmacy (personal communication, Prof. Hersberger).

Indirect costs related to productivity losses based on SFSO data and expert opinion were included in the societal perspective. Additional details regarding these calculations are provided in the online supplementary appendix.

One-way sensitivity analysis
We varied all key model input parameters (refer to table 1) individually using the 95% CI when available or otherwise ±25% of the base-case value.

Probabilistic sensitivity analysis (PSA)
In accordance with Consolidated Health Economic Evaluation Reporting Standards guidelines, we included analysis of joint parameter uncertainty through a PSA by running the model using parameter distributions instead of mean values, to generate 1000 simulations. The inputs in the PP algorithm calculating the VTE and the PP RR score, and characteristics related to the population of 1 million women remained fixed, except for the mean estimate of protein C/S prevalence which was assigned a beta distribution. Proportions derived from our modified Delphi study were also assigned beta distributions. Log normal distributions were assigned to RR parameters with the SE of the ln(RR) calculated from the 95% CI derived from the original studies. For parameters with no available 95% CI, the SE was assumed to be 10% of the mean estimate. Beta distributions were assigned to transition probabilities, and gamma distributions to cost inputs and utility decrements.

Scenario analyses
We investigated 12 scenarios varying key model parameters by running analyses where:

1. Only high-risk individuals, based on the assessment by SGGO questionnaire (having a family history with two or more clinical risk factors), proceeded through the PP algorithm within the PP strategy.
2. Only low-risk individuals, based on the assessment by SGGO questionnaire, proceeded through the PP algorithm within the PP strategy.
3. The age of first-time users varied (15–49 years old).
4. The proportion of clinicians who review a woman’s medical history was varied. In scenario 4a, it was assumed that 100% of clinicians considered medical history in the SoC and PP strategies, while scenario 4b assumed 100% of clinicians, in the PP strategy only, considered medical history.
5. We assumed that if more than one clinical risk factor was present, all clinicians did not recommend CHCs.
6. Discount rates varied to 2% and to 5%.
7. Shortened time horizons of 15, 30 and 50 years were evaluated.
8. The PP RR threshold of 18 in the base case varied from 5 to 40.
9. The clinical decision algorithm of ‘SoC’ was adjusted. For 9a, we assumed that no clinical decision algorithm was applied in the SoC strategy and 100% of SoC women received CHCs, for 9b assumed only second generation CHCs were prescribed if a CHC was recommended; and for 9c assumed no clinical decision algorithm was applied in SoC and 100% of SoC women received a progesterone-only pill.
10. Variations in the market share were applied. For 10a, we based the distribution of CHCs prescribed on Swiss market share data (31% second generation, 38% third generation, 22% fourth generation, 9% cyproterone acetate CHCs). For 10b, 100% of SoC women were given contraception according to a random sampling distribution of Swiss market proportions (17% given non-combined contraception, 26% second generation CHC, 32% third generation, 19% fourth generation, 7.5% cyproterone acetate CHC).
11. We assessed the impact of using the PP test instead of a Factor II or a Factor V test.
12. The CHC duration in 15–19 years old women was assumed to be the maximum possible duration (until 50 years old or occurrence of a VTE).

Patient and public involvement (PPI)
There was no PPI for this study.

RESULTS
Base-case results analysis showed the PP strategy is associated with 21 fewer VTE-related deaths and 669 fewer first VTEs (table 2) for a population of 1 million women over their lifetime horizon. The PP strategy was also associated with higher costs relative to SoC mostly attributable to the addition of the PP test itself, and more CHC prescriptions (table 3). These higher costs were to a small part offset by reductions in unneeded thrombophilia laboratory testing, VTE-related hospitalisations and treatments, and prescriptions of non-combined contraceptives which cost more than CHCs in Switzerland. For the PP strategy in comparison with the SoC strategy, base-case cost-effectiveness results indicated slightly higher discounted health system costs of CHF 251 per woman and a gain of approximately 0.003 QALYs per woman, generating an incremental cost-effectiveness ratio (ICER) of CHF 76 610 per QALY gained (table 4). When the PP strategy
was assessed from the societal and health insurer perspectives, ICERs of CHF 75,229 and 84,624 per QALY gained were generated, respectively.

The key input parameters in the model were varied individually in one-way sensitivity analyses (online supplementary appendix figure A1). None of these variations resulted in an ICER over CHF 100,000 per QALY. Assessment of the parameters with the biggest impact on cost effectiveness show that reducing the proportion of clinicians who conduct a medical history assessment before prescribing a CHC had the biggest impact (online supplementary appendix figure A1).

We conducted 12 scenario analyses (table 5). Scenario 1 indicated that PP was cost effective when targeting only high-risk individuals. On the other hand, PP generated an ICER of CHF 53,708 per QALY gained where high-risk women (with two combined clinical risk factors and/or positive family history of VTE) received a non-combined contraceptive in any case, and women with no apparent risk were assessed using PP (scenario 2b).

We tested scenarios that were less likely to occur. In scenario 10b, PP was associated with an ICER of CHF 31,138 per QALY gained. Here, clinicians were assumed to prescribe CHCs according to the market share in Switzerland (without considering medical history). Under scenario 12, where women who were first prescribed CHCs during their adolescent years remained on CHCs until 50 years old (unless VTE occurs sooner), PP was associated with an ICER of CHF 28,911 per QALY gained. Under scenario 8 where the PP RR threshold which determines whether the patient undergoes further thrombophilia testing or not was reduced, ICERs close to CHF 50,000 per QALY gained were produced.

In the PSA, we found the probability of PP being cost effective assuming a CHF 100,000 per QALY gained threshold exceeded 99% (figures 3 and 4).

### DISCUSSION

We developed an individual sampling model to assess the cost effectiveness of a PP strategy where the PP test is used to inform the prescription of CHCs, with the purpose of reducing overall risks of contraceptive users experiencing VTEs. The PP strategy (PP test combined with SoC) was compared with SoC alone in terms of costs and QALYs accruing over the lifetime of Swiss women aged 15–29 years who are potential first-time users seeking CHCs. The economic evaluation was conducted from the Swiss health system, health insurer and societal perspectives. In the base case, PP generated ICERs of CHF 76,610, 75,229 and 84,624 per QALY gained for the health system, societal and health insurer perspectives, respectively. The results were quite robust across a wide range of sensitivity and scenario analyses. Considering a cost-effectiveness threshold in Switzerland of CHF 100,000 per QALY gained (tentatively assumed in other Swiss analyses), and if our

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**Table 2** Results: clinical outcomes without discounting, base-case scenario

|                | SoC       | PP        | Incremental* |
|----------------|-----------|-----------|--------------|
| Average LYGs   | 64.038    | 64.041    | 0.002        |
| Average age at death | 84.410    | 84.412    | 0.002        |
| Persons with CHCs prescribed | 733,361   | 763,705   | 30,344       |
| Number of first VTEs† | 108,026   | 107,357   | −669         |
| VTE-related deaths | 3,418     | 3,397     | −21          |

*Incremental calculations based on Pill Protect (PP) standard of care (SoC).
†This was estimated over a lifetime (since model entry) and not only during the lifespan when combined hormonal contraceptives (CHCs) are taken.
LYG, life years gained; VTE, venous thromboembolism event.

**Table 3** Results for costs per women (CHF), health system perspective

|                | Undiscounted | Discounted |
|----------------|--------------|------------|
|                | SoC          | PP         | Incremental* | SoC          | PP         | Incremental* |
| PP             | 0            | 270        | 270          | 0            | 270        | 270          |
| Consultation   | 182          | 182        | 0            | 182          | 182        | 0            |
| Laboratory testing | 34        | 11         | −22          | 34           | 11         | −22          |
| CHCs           | 1314         | 1372       | 57           | 1085         | 1132       | 47           |
| Non-CHCs       | 579          | 511        | −68          | 476          | 421        | −55          |
| VTE inpatient  | 906          | 900        | −6           | 243          | 235        | −8           |
| VTE treatment (ACP) | 26.70      | 26.53      | −0.17        | 7.16         | 6.93       | −0.23        |
| VTE (MI/stroke)| 20.97        | 20.83      | −0.14        | 5.63         | 5.44       | −0.19        |
| Total costs    | 3,062.67     | 3,293.36   | 230.69       | 2,032.79     | 2,263.37   | 231.58       |

*Incremental calculations based on Pill Protect (PP) standard of care (SoC).
ACP, anticoagulant prophylaxis; CHCs, combined hormonal contraceptives; MI, myocardial infarction; VTE, venous thromboembolism event.
main assumptions hold true, the PP strategy may be cost effective for the studied population.

Our results show that many apparently low-risk individuals are in fact at substantial risk, with young women especially affected. The latter is further supported by real-world data that show that substantial number of DVTs related to CHC occur every year in Switzerland despite the clinical screening indicated by the modified Delphi study. Furthermore, other publications already indicated that the limited number of genetic tests included in the standard trombophilia testing (Factor II G20210A variant and Factor V Leiden), as well as the clinical information assessed, are insufficient to reliably estimate risk of DVT by health insurance in 50% of cases. Also, few clinicians participated in the second and third rounds of the Delphi study. Finally, it was beyond the model scope to capture certain risk factors for VTE including pregnancies, surgeries and more than two occurrences of VTE in one’s lifetime. Nevertheless, it would be interesting to assess the potential benefits that could appear if all women with high genetic risk of thrombosis would be identified early enough and preventatively treated during pregnancy and post partum.

Study limitations include assuming PP realistically predicts VTE events and adequately reflects proportional risks from genetic and clinical risk factors, and assuming the SoC pathway in the model realistically represents real clinical practice in Switzerland. The PP algorithm has been developed and validated retrospectively in a cohort comprising about 800 women who developed VTE while using CHCs and a similar number of controls who were also CHC users, using state-of-the-art split-sample methods. While it has been shown to perform better than other published models and is the first model specific to CHC use, external validation has not yet occurred. Modelling also assumed that BMI remained constant throughout the lifetime and that laboratory testing costs were covered by health insurance in 50% of cases. Also, few clinicians participated in the second and third rounds of the Delphi study. Finally, it was beyond the model scope to capture certain risk factors for VTE including pregnancies, surgeries and more than two occurrences of VTE in one’s lifetime. Nevertheless, it would be interesting to assess the potential benefits that could appear if all women with high genetic risk of thrombosis would be identified early enough and preventatively treated during pregnancy and post partum.

### Table 4 Results, cost effectiveness, base-case scenario

| SoC | PP | Incremental* | ICER (CHF per QALY) | Discounted |
|-----|----|--------------|----------------------|------------|
|     |     | Discounted |                      |            |
| Average QALYs per woman | 51.803 | 51.810 | 0.007 | 23.901 | 23.904 | 0.003 |
| **Average costs per woman (CHF)** | | | | | | |
| Health system | 3063 | 3294 | 231 | 32642 | 2033 | 2264 | 231 | 76610 |
| Societal | 3471 | 3699 | 228 | 32169 | 2148 | 2374 | 227 | 75229 |
| Health insurer | 543 | 799 | 256 | 36147 | 218 | 473 | 255 | 84624 |

*Incremental calculations based on Pill Protect (PP) standard of care (SoC).
CHF, Swiss francs; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.
### Table 5  Scenario analyses from a health system perspective (with discounting)

| Input parameter(s) | Base-case value | Scenario value | SoC | Average costs (CHF) | Average QALYs | PP | Average costs (CHF) | Average QALYs | Incremental costs (CHF) | Incremental QALYs | ICER CHF per QALY |
|---------------------|-----------------|----------------|-----|---------------------|---------------|----|---------------------|---------------|------------------------|----------------|------------------|
| Base case           | All             | NA             |     | 2033                | 23.901        |    | 2264                | 23.904        | 231                   | 0.0030         | 76610            |
| 1. PP targets only ‘high-risk’ groups | Only PP for persons at high risk, while low-risk individuals go through SoC clinical pathway | 2033 | 23.901 | 2276 | 23.902 | 243 | 0.0009 | 257926 |
| 2. Low-risk groups | a) Only PP for persons at low risk clinical risk factors, while high-risk individuals go through SoC clinical pathway | 2033 | 23.901 | 2269 | 23.904 | 236 | 0.0021 | 113759 |
|                     | b) Only PP for persons at low risk clinical risk factors, while high-risk individuals receive non-CHC | 2033 | 23.901 | 2284 | 23.906 | 251 | 0.0047 | 53708 |
| 3. Age of first-time user | 15–29 | 15–19 | 2239 | 24.557 | 2470 | 24.560 | 231 | 0.0029 | 78840 |
|                     | 20–24 | 2010 | 23.730 | 2240 | 23.733 | 230 | 0.0031 | 74170 |
|                     | 25–29 | 1573 | 22.806 | 1808 | 22.809 | 235 | 0.0023 | 101908 |
|                     | 30–34 | 1287 | 21.771 | 1525 | 21.773 | 238 | 0.0018 | 134312 |
|                     | 35–39 | 1201 | 20.625 | 1369 | 20.624 | 218 | −0.0012 | SoC dominant |
|                     | 40–44 | 1174 | 19.371 | 1347 | 19.370 | 173 | −0.0016 | SoC dominant |
|                     | 45–49 | 1040 | 18.013 | 1223 | 18.012 | 183 | −0.0012 | SoC dominant |
|                     | 20–29 (uniform) | 1792 | 23.267 | 2024 | 23.270 | 232 | 0.0026 | 88146 |
|                     | 20–29 (weighted) | 1884 | 23.462 | 2115 | 23.465 | 231 | 0.0029 | 79164 |
| 4. Proportion of clinicians who review a woman’s medical history during the recommendation of a CHC | 84% | a. SoC and PP—100% medical history | 2021 | 23.901 | 2247 | 23.904 | 226 | 0.0031 | 73616 |
|                     | b. SoC 84% (same), PP 100% medical history | 2033 | 23.901 | 2247 | 23.904 | 214 | 0.0022 | 96178 |
| 5. Combined clinical risk factors | Delphi R3 | a) assuming that 100% of clinicians would not recommend CHCs if more than one clinical risk factor is present | 2034 | 23.902 | 2264 | 23.904 | 230 | 0.0026 | 87601 |
| 6. Discount rates | 3% | 5% | 1751 | 16.698 | 1983 | 16.700 | 232 | 0.0019 | 120207 |
|                     | 2% | 2253 | 29.834 | 2483 | 29.838 | 230 | 0.0039 | 59020 |
| 7. Time horizon | 85 years | 15 years | 1707 | 10.591 | 1938 | 10.592 | 231 | 0.0009 | 270492 |
|                     | 30 years | 1867 | 17.139 | 2097 | 17.141 | 230 | 0.0020 | 116633 |
|                     | 50 years | 1939 | 21.903 | 2169 | 21.906 | 230 | 0.0028 | 82973 |

Continued
### Table 5 Continued

| Input parameter(s) | Base-case value | Scenario value | SoC | PP |
|--------------------|-----------------|----------------|-----|-----|
| 8. PP thresholds (5–40) | 18 | Threshold buffer (±10%) | 2033 | 23.901 | 2264 | 23.904 | 231 | 0.0030 | 77299 |
| 5 | 2033 | 23.901 | 2362 | 23.911 | 329 | 0.0093 | 35337 |
| 10 | 2033 | 23.901 | 2295 | 23.908 | 262 | 0.0063 | 41279 |
| 11 | 2033 | 23.901 | 2288 | 23.907 | 255 | 0.0057 | 44390 |
| 12 | 2033 | 23.901 | 2282 | 23.907 | 249 | 0.0052 | 47572 |
| 13 | 2033 | 23.901 | 2277 | 23.906 | 244 | 0.0048 | 50878 |
| 14 | 2033 | 23.901 | 2274 | 23.906 | 241 | 0.0043 | 55539 |
| 15 | 2033 | 23.901 | 2270 | 23.905 | 237 | 0.0039 | 60385 |
| 16 | 2033 | 23.901 | 2268 | 23.905 | 235 | 0.0036 | 66041 |
| 17 | 2033 | 23.901 | 2266 | 23.905 | 233 | 0.0033 | 70518 |
| 19 | 2033 | 23.901 | 2263 | 23.904 | 230 | 0.0028 | 83379 |
| 20 | 2033 | 23.901 | 2261 | 23.904 | 228 | 0.0025 | 91892 |
| 25 | 2033 | 23.901 | 2257 | 23.903 | 224 | 0.0016 | 138605 |
| 40 | 2033 | 23.901 | 2254 | 23.901 | 221 | −0.0002 | SoC dominant |

9. Changes to comparator strategy (‘standard of care’ (SoC))

| Clinical pathway based on Delphi study | Do nothing (assign 100% CHC in SoC) | 1982 | 23.894 | 2264 | 23.904 | 282 | 0.0105 | 26925 |
| SoC and PP—prescribe all second generation CHCs (RR and cost second generation only for CHC prescriptions) | 2022 | 23.905 | 2256 | 23.907 | 234 | 0.0021 | 112446 |
| SoC only—no screening, prescribe progestogen only | 1926 | 23.913 | 2264 | 23.904 | 338 | −0.0088 | SoC dominant |

10. Market share

| a | b |
| 2037 | 23.900 | 2267 | 23.904 | 230 | 0.0033 | 70101 |
| 2023 | 23.896 | 2267 | 23.904 | 244 | 0.0078 | 31138 |

11. PP instead of Factor II G20210A and Factor V Leiden tests

| Lab testing | PP |
| 2033 | 23.901 | 2034 | 23.902 | 1 | 0.0009 | 751 |

12. CHC duration in ages 15–19

| CHC duration based on distribution | 35 years CHC duration (maximum) | 4249 | 24.539 | 4456 | 24.546 | 207 | 0.0072 | 28911 |

CHC, combined hormonal contraceptive; CHF, Swiss franc; ICER, incremental cost-effectiveness ratio; NA, not applicable; PP, Pill Protect; QALY, quality-adjusted life year; RR, relative risk.
Our literature review found that PP is currently the only algorithm available for screening for VTE risk related to CHCs, although other algorithms potentially marketable as products for future practice exist, such as ThromboInCode. Although this algorithm is not yet available in Switzerland and not specifically indicated for use in CHC prescribing, it potentially may be used in this way and considered a competitive alternative test. However, the PP test assesses more genetic variants linked to VTE risk in the context of CHC use than ThromboInCode. Nevertheless, future comparison of ThromboInCode with PP might be informative.

Overall, this study has indicated an opportunity for PP to provide accurate diagnosis and cost-effective benefits when used during the first recommendation of contraceptives for young women in Switzerland.

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Figure 3 Cost-effectiveness planes for the health system, health insurer and societal perspectives; CHF, Swiss francs; QALYs, quality-adjusted life years.

Figure 4 Cost-effectiveness acceptability curves; CHF, Swiss francs; QALYs, quality-adjusted life years.

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