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# Pharmaceutical thrombosis prophylaxis, bleeding complications and thromboembolism in a national cohort of hysterectomy for benign disease

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**BACKGROUND:** Pharmaceutical thrombosis prophylaxis (PTP) with low-molecular-weight heparin (LMWH) is highly effective in preventing venous thromboembolic events (VTEs) and fatal pulmonary embolism. Important risk factors for VTEs are surgery and immobilization, along with malignancy. Many studies involving gynaecological malignancies show no increased risk for bleeding complications with PTP. Little is known about the PTP-associated risk for bleeding complications with hysterectomy for benign disease, or about current VTE incidence in the less-invasive hysterectomy methods.

**METHODS:** Our observational prospective national 1-year cohort from 1 January to 31 December 2006 in 53 hospitals represented 79.4% (5297 of 6645) of hysterectomies performed for benign cause in Finland in 2006. We evaluated PTP use and VTE incidence. Operative and post-operative bleeding complications were analysed with logistic regression adjusted for confounders: age, BMI, experience of the gynaecological surgeon, hospital type, indication for hysterectomy, uterine weight, operative haemorrhage, concomitant surgery, adhesiolysis and antibiotic prophylaxis.

**RESULTS:** Hysterectomies were performed by three main approaches: 2345 vaginal hysterectomies (VHs, 44%), of which 1433 were for uterine prolapse and 912 for other indications, 1679 laparoscopic hysterectomies (LHs, 32%) and 1255 abdominal hysterectomies (AHs, 24%). PTP was given to 64.8% of patients (3420 of 5279) and was identified as LMWH in 3313 patients (97%); 107 left unidentified. By type of hysterectomy, PTP was given in VH for uterine prolapse to 73.2% of patients, VH for other indication to 51.6%, in LH to 59.4% and in AH to 71.9%. For all hysterectomies analysed together, PTP doubled the odds for post-operative haemorrhage or haematoma. By type of hysterectomy, PTP associated with post-operative haemorrhage or haematoma in VH for prolapse [2.7% of PTP given, versus 0.8% of no PTP; odds ratio (OR): 4.82, 95% confidence interval (CI): 1.38–16.83]; and in AH (3.1% versus 1.4%; OR: 2.87, 95% CI: 1.03–7.98), and in AH also with post-operative transfusion (3.1% versus 1.4%; OR: 3.34, 95% CI: 1.41–7.88). For LH and VH for indications other than prolapse, the effect of PTP on post-operative haemorrhage was non-significant. For VH, the risk for post-operative haemorrhage fell with age. Operative mean haemorrhage with all hysterectomy types, and operative bleeding complications in AH and VH also fell with age. Obesity increased haemorrhage and operative bleeding complications for LH and VH, whereas post-operative bleeding complications were less for the obese in AH. VTEs were 6 of 5279 (0.1%): two PEs each occurred after AH and VH, and two deep venous thromboses after LH.

**CONCLUSIONS:** With a relatively wide PTP coverage (64.8%), VTEs were rare (0.1%). All affected had received PTP. Analysis of efficacy, meaning interpretation of how many VTEs or deaths were prevented, cannot be done from our observational study but related to safety in hysterectomy for benign disease, PTP associated with post-operative bleeding complications with AH and with VH for prolapse.

**Trial registration number:** ClinicalTrials.gov protocol (NCT00744172).

**Key words:** pharmaceutical thrombosis prophylaxis / venous thromboembolic events / hysterectomy / low-molecular-weight heparin / benign disease

# Introduction

Almost four decades have passed since the landmark study on heparin as pharmaceutical thromboprophylaxis (PTP; Kakkar *et al.*, 1975). PTP is highly effective in the prevention of venous thromboembolic events (VTEs) and fatal pulmonary embolism (PE), and the prevention of deep venous thrombosis (DVT) prevents PE (Geerts *et al.*, 2008). About 10% of PEs are rapidly fatal (Kearon, 2003). In patients diagnosed with DVT, the rate for asymptomatic PE detected radiologically is nearly 40% (Moser *et al.*, 2004). Important risk factors for VTEs are surgery, immobilization, increasing age and obesity and also malignancy. A recent meta-analysis on VTEs in gynaecologic malignancy showed no increased risk for bleeding complications with PTP (Einstein *et al.*, 2007). Recommendations regarding the surgery state that most patients undergoing hysterectomy are by definition at least at moderate risk for VTEs (ACOG, 2007; Geerts *et al.*, 2008). Little is known about the PTP-associated risk for bleeding complications with hysterectomy for benign disease, or about the current VTE incidence in the less invasive hysterectomy methods.

As a quality assessment, the frequency of PTP is analysed in this national FINHYST cohort. The aim was to evaluate the incidence of VTE with the current use of PTP, and further to study whether any association with bleeding complications exists, in a large prospective national 1-year setting, including abdominal (AH), laparoscopic (LH) and vaginal hysterectomy (VH).

# Materials and Methods

Data of the FINHYST study were prospectively collected from 1 January to 31 December 2006 in 53 hospitals in Finland. The study plan was approved by the Ministry of Social Affairs and Health in Finland and by the ethics committees at the hospitals and was included in the ClinicalTrials.gov protocol. Each patient provided a written consent.

VTEs were collected separately, as deep vein thromboses of the lower extremity (DVT) and PEs, by the operating gynaecological surgeons. A FINHYST study form comprising surgical data and complications was completed for each patient at discharge. Another form was completed at any possible readmission. The patients also received at discharge a questionnaire with a request to return it after 2 months post-operatively; 3924 of them replied (75%). Information directly from the patients allowed a subsequent tracing of VTEs. The Patient Insurance Centre register, to which patients report complications when seeking economic compensation, was another source of data on VTEs in the context of hysterectomies for benign disease in 2006. In addition, verifications were permitted retrospectively from the Hospital Discharge Register (HDR) provided by the National Institute for Health and Welfare in Finland for all hysterectomies performed in 2006. All discharge diagnoses of various events of thromboses (ICD-10 codes I80, I82, I26), within a post-operative range of 3 months were requested. From the administrative register data, search for matches in FINHYST were performed by date of operation, age, ICD-10 code and type of hysterectomy. Cohort coverage of FINHYST was 79.4% (5279/6645) of hysterectomies performed for benign cause in Finland in 2006. We verified VTE cases from hospital files of FINHYST; diagnostics always involved spiral computed tomography for PEs and Doppler ultrasonography for DVTs. For cases outside FINHYST, hospital file verification was unavailable.

Operative haemorrhage (ml) was estimated by standard local operating room routines: suction and surgical sponges. Analysis of the risk associated with PTP was performed separately for operative and post-operative bleeding complications occurring at the index hospitalisation. All use of PTP, irrespective of product or dosage, was analysed together. Frequency of mechanical thrombosis prophylaxis and initiation of PTP (pre- or post-operative) is unknown. Severe operative haemorrhage was defined as haemorrhage $\geq$1000 ml. Post-operative haemorrhage or haematoma comprises both minor and major cases, the latter defined as the need for intervention in the operating room. The need for transfusion was collected as preoperative, intraoperative and/or post-operative. We analysed the risk for intra- and post-operative transfusions for those receiving PTP.

Analysis of the effect of PTP on the occurrence of bleeding complications was performed with a logistic regression model adjusted for hospital type (university, central, local or private hospital) and experience of the gynaecological surgeon (30 operations or fewer ever performed), characteristics of the patient (age and BMI, both linear), indication for hysterectomy (myomas, menorrhagia, dysmenorrhoea, endometriosis, uterine prolapse, adnexal mass or other), haemorrhage (linear, ml), concomitant surgery (any), adhesiolysis and uterine size (post-operative weight, linear, g). In the analysis of operative bleeding complications, haemorrhage was not a covariate, for the obvious reason of its application as the dependent variable. In addition, the model was always adjusted for type of hysterectomy when all 5279 hysterectomies were analysed together.

For descriptive purposes, patient age was categorized as the pre-, peri- and post-menopausal age groups of under 45, 45–54 and 55 years or over, and BMI (kg/m$^2$) defined as normal weight (under 24.9), overweight (25.0–29.9), obese (30.0–34.9) and extremely obese (35.0 or over). Of the 5279 cases, BMI was unknown for 166 (3.1%) and operative haemorrhage unknown for 113 cases (2.1%).

Differences in means were analysed with Student's *t*-test or with analysis of variance, and categorical data comparisons performed by $\chi^2$ or by Fisher's exact test if needed. Multivariate logistic regression, adjusted as explained above, was applied to analyse the associations for complications. Univariate data analysis preceded the adjustments; the choice of covariates was guided by clinical interest and prior research. $P < 0.05$ was considered statistically significant. Analyses were performed with the Statistical Package for the Social Sciences 17.0.

## Results

The FINHYST study is described in detail elsewhere (Brummer *et al.*, 2009, 2011). Briefly, the hysterectomies were performed by three main approaches, 1255 AH (24%), 1679 LH (32%) and 2345 VH (44%); overall, 1.7% of hysterectomies were subtotal. Conversions from LH (5.2%) and VH (0.6%) are analysed as intention-to-treat, as the type of hysterectomy initially chosen. Uterine prolapse was the most common indication for VH, with 61% (1433); most required concomitant anterior, and/or posterior colpoperineoplasty and/or enterocele repair (82%, 1177/1433).

PTP was given in 64.8% of hysterectomies in FINHYST (3420 of 5279); PTP by type of hysterectomy is presented in Table I. PTP was identified as low-molecular-weight heparin (LMWH) in 3313 patients (97%), with 107 left unidentified. With LMWH, the exact drug and dosage were indicated for 1792 patients (54%). The use of enoxaparine (1097, 61%) was somewhat more common than of dalteparine (695, 39%). Duration was reported for 1445 (44%).

**Table I PTP by type of hysterectomy, in relation to bleeding.**

| Type of hysterectomy | Abdominal | Laparoscopic | Vaginal | Vaginal main indication | |
|---|---|---|---|---|---|
| | | | | Prolapse | Other than prolapse |
| *N* | 1255 | 1679 | 2345 | 1433 | 912 |
| Thrombosis prophylaxis given, *n* (%) | 902 (71.9) | 998 (59.4) | 1520 (64.8) | 1049 (73.2) | 471 (51.6) |
| % indicated as LMWH | 96.5 | 96.7 | 97.2 | 98.0 | 96.2 |
| Post-operative hospital stay when PTP given, days (mean [SD], maximum) | 4.0 [1.6], 18 | 2.2 [1.7], 31 | 2.6 [1.5], 17 | 2.7 [1.6], 17 | 1.8 [1.1], 9 |
| Duration of PTP, days (mean [SD], maximum) | 4.3 [2.8], 30 | 3.0 [2.8], 35 | 3.2 [2.9], 30 | 3.3 [2.7], 30 | 2.9 [3.2], 30 |
| % indicated prolonged PTP after discharge | 5.2 | 5.0 | 4.9 | 4.9 | 5.1 |
| Mean operative haemorrhage, ml (SD) | 355 (360) | 255 (273)[a] | 203 (269) | 183 (238) | 235 (308) |
| Mean haemorrhage, ml (SD) with PTP | 345 (343) | 265 (290)[a] | 201 (218) | 182 (197) | 243 (255) |
| Mean haemorrhage, ml (SD) with no PTP | 377 (398) | 240 (246) | 218 (342) | 186 (327) | 227 (355) |
| *P* | 0.182 | 0.067[a] | 0.546 | 0.777 | 0.431 |
| Logistic regression for bleeding complications | | | | | |
| Operative haemorrhage ≥1000 ml, *n* (%) | 72 (5.7) | 50 (3.0) | 37 (1.6) | 16 (1.1) | 21 (2.3) |
| With PTP, n/*N* (%) | 48/902 (5.3) | 34/998 (3.4) | 24/1520 (1.6) | 12/1049 (1.1) | 12/471 (2.5) |
| With no PTP, n/*N* (%) | 24/353 (6.8) | 16/681 (2.3) | 13/825 (1.6) | 4/384 (1.0) | 9/441 (2.0) |
| Adjusted OR (95% CI) | 1.01 (0.56–1.82) | 1.41 (0.71–2.83) | 1.66 (0.77–3.57) | 1.97 (0.58–6.69) | 1.34 (0.50–3.61) |
| *P* | 0.977 | 0.328 | 0.193 | 0.276 | 0.564 |
| Transfusion in operating room, *n* (%) | 37 (2.9) | 23 (1.4) | 27 (1.2) | 11 (0.8) | 16 (1.8) |
| Transfusions with PTP, *n/N* (%) | 26/902 (2.9) | 18/998 (1.8) | 18/1520 (1.2) | 9/1049 (0.9) | 9/471 (1.9) |
| Transfusions with no PTP, *n/N* (%) | 11/353 (3.1) | 5/681 (0.7) | 9/825 (1.1) | 2/348 (0.5) | 7/441 (1.6) |
| Adjusted OR (95% CI) | 1.52 (0.69–3.36) | 2.03 (0.65–6.36) | 1.22 (0.90–5.46) | 2.79 (0.56–14.00) | 1.92 (0.64–5.78) |
| *P* | 0.298 | 0.224 | 0.082 | 0.213 | 0.246 |
| Post-operative haemorrhage or haematoma, *n* (%) | 33 (2.6) | 45 (2.7) | 65 (2.8) | 31 (2.2) | 34 (3.7) |
| With PTP, *n/N* (%) | 28/902 (3.1) | 30/998 (3.0) | 45/1520 (3.0) | 28/1049 (2.7) | 17/471 (3.6) |
| With no PTP, *n/N* (%) | 5/353 (1.4) | 15/681 (2.2) | 20/825 (2.4) | 3/384 (0.8) | 17/441 (3.9) |
| Adjusted OR (95% CI) | 2.87 (1.03–7.98) | 1.67 (0.82–3.40) | 1.81 (0.99–3.29) | 4.82 (1.38–16.83) | 1.11 (0.50–2.46) |
| *P* | 0.043 | 0.157 | 0.053 | 0.014 | 0.798 |
| Transfusion post-operatively given, *n* (%) | 56 (4.5) | 59 (3.5) | 53 (2.3) | 29 (1.9) | 26 (2.9) |
| Transfusions with PTP, *n/N* (%) | 46/902 (5.1) | 39/998 (3.9) | 34/1520 (2.2) | 21/1049 (2.0) | 13/471 (2.8) |
| Transfusions with no PTP, *n/N* (%) | 10/353 (2.8) | 20/681 (2.9) | 19/825 (2.3) | 6/384 (1.6) | 13/441 (2.9%) |
| Adjusted OR (95% CI) | 3.34 (1.41–7.88) | 1.16 (0.59–2.26) | 1.38 (0.70–2.74) | 2.16 (0.73–6.38) | 1.07 (0.41–2.80) |
| *P* | 0.006 | 0.666 | 0.354 | 0.162 | 0.889 |

Timing of PTP unknown. OR, odds ratio. CI, confidence interval; LMWH, low-molecular-weight heparin. Each of the logistic regression analyses are adjusted for uterine weight, experience of the gynaecological surgeon, hospital type, age, BMI, indication for hysterectomy (except with a single indication, prolapse), concomitant surgery, adhesiolysis, antibiotic prophylaxis and haemorrhage (except when analyzing the operative bleeding complications as dependent variables).

[a]If a single disrupting case of 25 000 ml was included, the overall LH mean (SD) was 270 ml (669), for those with PTP 290 ml (841), $P = 0.134$.

Higher dose equivalents for enoxaparine and dalteparine are daily 40 mg and 5000 IU, and lower doses of 20 mg and 2500 IU, respectively. A lower daily dose was given to 1023 patients (57%), and a higher dose to 742 patients (41%); even higher doses or combinations of varying daily doses were reported for only 27 patients.

Bleeding complications are presented in Table I. No difference appeared in the mean operative haemorrhage, risk for operative haemorrhage ≥1000 ml or intraoperative transfusions between cases receiving or not receiving PTP (Table I), but the timing of PTP was not recorded. For post-operative bleeding complications, in the logistic regression analysis with all hysterectomies together, PTP was an independent risk factor for post-operative haemorrhage or haematoma (OR: 2.00, 95% CI: 1.34–3.00, $P < 0.001$) and for post-operative transfusion (OR: 1.74, 95% CI: 1.16–2.59, $P = 0.007$). By type of hysterectomy, PTP was a risk factor for post-operative haemorrhage in AH, but not in LH. In VH, the overall result was close to significance (Table I). Investigated separately for the most common indication for VH, uterine prolapse, PTP raised significantly the odds for post-operative haemorrhage. The risk for post-operative transfusions with PTP was significantly increased with AH only (Table I).The exact LMWH dose for those with post-operative haemorrhage or haematoma in AH was known for 50% (14 of 28), and in VH for prolapse for 42.9% (12 of 28); differences between frequencies of high- and low-dose LMWH were non-significant for both hysterectomy types.

The use of PTP increased with age (Fig. 1), whereas operative haemorrhage fell with age (Fig. 2, Table II). Age had no effect on any bleeding complications of LH. In VH, the risk for operative haemorrhage ≥1000 ml decreased by age (Table II), in addition the risk for intraoperative transfusion for indications other than prolapse was reduced by an average of 12.7% per year (3.2–21.3%, $P = 0.010$). In AH, the trend was towards a decrease in age for operative haemorrhage ≥1000 ml (Table II), and in the adjusted logistic regression analysis, the risk was reduced for intraoperative transfusions: 7.6% per year (2.3–12.6%, $P = 0.006$). Post-operative bleeding complications were also affected: in VH, the risk for post-operative haemorrhage or haematoma fell with age, independent of PTP (Table II).

The use of PTP became more frequent with increasing BMI (Fig. 1). Increasing BMI promoted operative haemorrhage (Table II). In VH and LH, the more overweight the women, the higher the incidence of operative haemorrhage ≥1000 ml, and a significant effect of increasing BMI appeared also irrespective of PTP (Table II). Such an effect was strongest in VH for prolapse, with one unit of BMI raising the risk for operative haemorrhage ≥1000 ml on an average by 14.6% (3.1–27.4%, $P = 0.012$; Table II). For AH, the appearance of operative bleeding complications was high also for those of normal weight, whereas for the post-operative haemorrhage or haematoma, those overweight and obese had fewer complications; the extremely obese had none (Table II). A one-unit rise in BMI reduced the risk for post-operative haemorrhage or haematoma on an average by 17.0% (8.3–25.0%, $P < 0.001$).

The incidence of VTEs was 0.1% in total: for AH 0.16%, for LH 0.12% and for VH 0.09%. All six VTE cases had received PTP (Table III). No deaths occurred. In the FINHYST study, two PEs only were reported by the gynaecological surgeons (Cases 1 and 2 in Table III; Brummer *et al.*, 2011). The vascular injury itself described in Table III (Case 6) was reported but the DVT on the injured side was traced from the register of the Patient Insurance Centre. The rest of the cases were traced from patient questionnaires (3924, 75% response), and from the HDR; all were verified from hospital files.

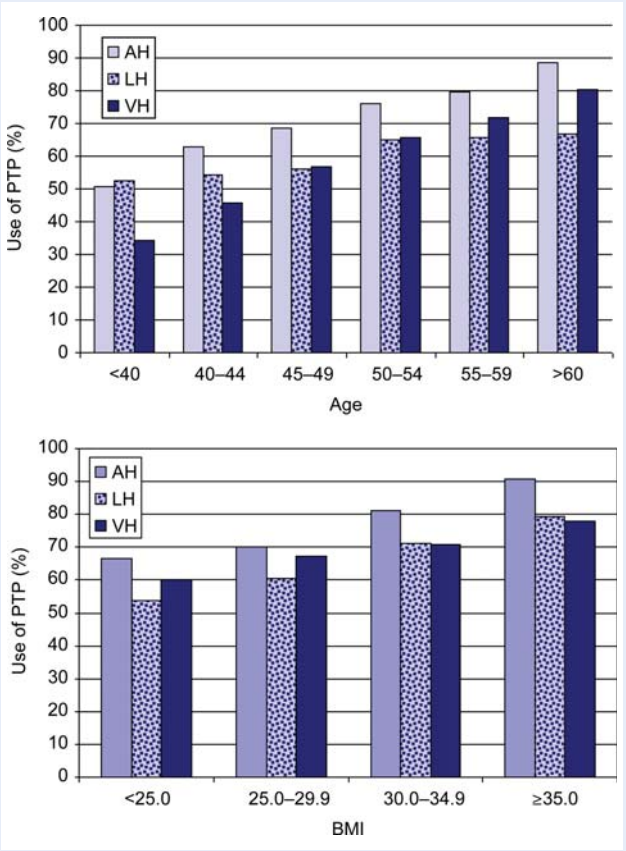


**Figure 1** PTP by category of age (years) and BMI (kg/m$^2$). AH, abdominal hysterectomy; LH, laparoscopic hysterectomy; VH, vaginal hysterectomy.

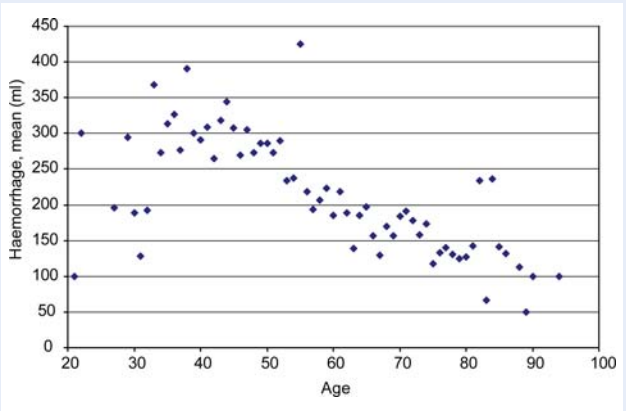


**Figure 2** Mean operative haemorrhage (ml) by age. Haemorrhage data were available for 5166 hysterectomies. The median for number of hysterectomies was 45 per age (year). For ages 32 or younger and 82 or older, hysterectomies were 10 or fewer; otherwise ranging between 12 and 275 operations per age (year).

**Table II** Mean haemorrhage and bleeding complications, operative and post-operative, by age and BMI.

| | Age (years) | | | *P* | Logistic regression for bleeding complications | | | |
|---|---|---|---|---|---|---|---|---|
| | Under 45 | 45–54 | 55 or over | | Adjusted OR | 95% CI | | *P* |
| Mean operative haemorrhage (ml) | | | | | | | | |
| AH | 409 | 352 | 304 | 0.003 | | | | |
| LH | 266 | 271 | 200[a] | <0.001 | | | | |
| VH | 288 | 225 | 148 | <0.001 | | | | |
| VH for uterine prolapse | 349 | 227 | 145 | <0.001 | | | | |
| VH for other than prolapse | 264 | 224 | 183 | 0.041 | | | | |
| Operative haemorrhage ≥1000 ml, *n/N* (%) | | | | | | | | |
| AH | 30/289 (10.4) | 31/682 (4.5) | 11/284 (3.9) | 0.001 | 0.96 | 0.92 | 1.00 | 0.058 |
| LH | 11/470 (2.3) | 30/850 (3.5) | 9/359 (2.5) | 0.400 | 0.99 | 0.95 | 1.04 | 0.830 |
| VH | 20/471 (4.2) | 14/810 (1.7) | 3/1064 (0.3) | <0.001 | 0.90 | 0.86 | 0.95 | <0.001 |
| VH for uterine prolapse | 6/130 (4.6) | 7/337 (2.1) | 3/966 (0.3) | <0.001 | 0.92 | 0.86 | 0.97 | 0.005 |
| VH for other than prolapse | 14/341 (4.1) | 7/473 (1.5) | 0/98 (0) | 0.013 | 0.88 | 0.80 | 0.97 | 0.007 |
| Post-operative haemorrhage or haematoma, *n/N* (%) | | | | | | | | |
| AH | 3/289 (1.0) | 24/682(3.5) | 6/284 (2.1) | 0.072 | 1.00 | 0.95 | 1.05 | 0.919 |
| LH | 17/470 (3.6) | 21/850 (2.5) | 7/359 (1.9) | 0.292 | 0.97 | 0.92 | 1.01 | 0.180 |
| VH | 22/471 (4.7) | 27/810 (3.3) | 16/1064 (1.5) | 0.001 | 0.97 | 0.94 | 1.00 | 0.044 |
| VH for uterine prolapse | 3/130 (2.3) | 13/337 (3.9) | 15/966 (1.6) | 0.043 | 0.99 | 0.95 | 1.03 | 0.544 |
| VH for other than prolapse | 19/341 (5.6) | 14/473 (3.0) | 1/98 (1.0) | 0.050 | 0.91 | 0.85 | 0.98 | 0.012 |
| | **BMI (kg/m$^2$)** | | | | | | | |
| | **Normal weight <25.0** | **Overweight 25.0–29.9** | **Obese 30.0–34.9** | **Extremely obese ≥35** | | | | |
| Mean operative haemorrhage (ml) | | | | | | | | |
| AH | 311 | 356 | 394 | 435 | 0.006 | | | |
| LH | 235 | 254 | 296[a] | 319 | 0.006 | | | |
| VH | 180 | 201 | 239 | 344 | <0.001 | | | |
| VH for uterine prolapse | 161 | 190 | 204 | 333 | <0.001 | | | |
| VH for other than prolapse | 206 | 224 | 310 | 351 | <0.001 | | | |
| Operative haemorrhage ≥1000 ml, *n/N* (%) | | | | | | | | |
| AH | 23/476 (4.8) | 25/427 (5.9) | 12/203 (5.9) | 6/108 (5.6) | 0.998 | 1.02 | 0.97 | 1.07 | 0.408 |
| LH | 20/737 (2.7) | 11/569 (1.9) | 13/247 (5.3) | 4/68 (5.9) | 0.033 | 1.06 | 1.00 | 1.13 | 0.038 |
| VH | 11/983 (1.1) | 12/865 (1.4) | 8/339 (2.4) | 6/91 (6.6) | <0.001 | 1.09 | 1.03 | 1.16 | 0.003 |
| VH for uterine prolapse | 3/557 (0.5) | 7/578 (1.2) | 4/224 (1.8) | 2/35 (5.7) | 0.021 | 1.15 | 1.03 | 1.27 | 0.012 |
| VH for other than prolapse | 8/426 (1.9) | 5/287 (1.7) | 4/115 (3.5) | 4/56 (7.1) | 0.057 | 1.08 | 1.00 | 1.17 | 0.051 |
| Post-operative haemorrhage or haematoma, *n/N* (%) | | | | | | | | |
| AH | 23/476 (4.8) | 8/427 (1.9) | 2/203 (1.0) | 0/108 (0) | 0.005 | 0.83 | 0.75 | 0.92 | <0.001 |
| LH | 26/737 (3.5) | 13/569 (2.3) | 2/247 (0.8) | 2/68 (2.9) | 0.120 | 0.95 | 0.88 | 1.02 | 0.161 |
| VH | 36/983 (3.7) | 18/865 (2.1) | 8/339 (2.4) | 3/91 (3.3) | 0.318 | 0.97 | 0.91 | 1.03 | 0.256 |
| VH for uterine prolapse | 15/557 (2.7) | 9/578 (1.6) | 6/224 (2.7) | 1/35 (2.9) | 0.688 | 0.98 | 0.89 | 1.08 | 0.707 |
| VH for other than prolapse | 21/426 (4.9) | 9/287 (3.1) | 2/115 (1.7) | 2/56 (3.6) | 0.463 | 0.96 | 0.88 | 1.04 | 0.286 |

Logistic regression analyses presented for increasing age (per one year) and BMI (per one unit) are adjusted for thrombosis prophylaxis, uterine weight, experience of the gynaecological surgeon, hospital type, indication for hysterectomy (except with a single indication, prolapse), concomittant surgery, adhesiolysis, antibiotic prophylaxis and haemorrhage (except when analyzing operative haemorrhage ≥1000 ml).

[a]If a single disrupting case of 25 000 ml was included, the mean haemorrhage for age >55 equals 271 ml and for the obese 397 ml (analysis of variance, $P = 0.990$ and $P = 0.010$).

Both DVT cases with LH had had extreme predisposing factors (Table III). Case 5 even was receiving ongoing therapy; clopidogrel and enoxaparine were halted for 3 and 1 days preoperatively; and in addition for 1 day owing to vaginal bleeding occurring on the 11th post-operative day.

FINHYST covered 79.4% of national hysterectomies for benign disease (5279 of 6645). As the VTE data from the HDR was requested as verification on FINHYST, subsequently we evaluated the number of all post-operative VTEs associated with any hysterectomy nationally, during the calendar year of our study. VTEs requiring hospital ward treatment within the post-operative range of 3 months were 24: 16 PEs and 8 DVTs. Excluding malignant disease, there were six PEs: four with AHs and two with VHs; matches emerged for the four cases in FINHYST (Table III). DVTs were three: one with VH, and the two previously described LH cases in FINHYST (Table III). In addition, the ICD-codes for VTE registered only in the emergency room, with no hospital inpatient care for VTEs, were 15 in total. Seven of the 15 were operated on for benign disease, and 6 of the 7 were FINHYST recruits. Verification from hospital files of the FINHYST listed showed that in reality all six, five DVTs and one PE had been at the level of suspicion only, with negative ultrasonography and spiral CT examinations. Thus including VTEs involving hospital inpatient care only, the national HDR 1-year incidence of VTEs after hysterectomy for malignant disease equalled 1.3% (15 of 1112) and for benign disease 0.1% (9 of 6645, $P < 0.001$). This verification demonstrates that the VTE incidence of our prospective FINHYST study is applicable on a national level.

## Discussion

Our national evaluation showed that PTP was frequent, and VTEs were rare. No cases emerged among those not receiving PTP—suggesting that those at risk were generally well recognized. With all hysterectomies analysed together, PTP doubled the odds for post-operative haemorrhage or haematoma. Further, by type of hysterectomy, with PTP, the risk for post-operative haemorrhage or haematoma increased in AH, whereas no adverse effects occurred in LH, or in VH for the non-prolapsed uterus. In VH for uterine prolapse, however, PTP associated strongly with post-operative haemorrhage. In addition, for AH only, the risk for post-operative transfusion was also increased, possibly reflecting the severity of the complication. Simultaneously, the risk for post-operative haemorrhage or haematoma fell with older age in VH, and with obesity in AH.

This was an observational study, and lack of randomization may be considered a limitation. Analyses of bleeding complications were therefore adjusted for various confounders. Other limitations were the timing of PTP not being recorded and no information being available on other medications affecting coagulation. Nor were adjustments possible for co-morbidity, such as coronary heart disease, calling for treatment with acetylsalicylic acid. No VTE occurred in those without PTP but one flaw is that we have no information on how many received mechanical thrombosis prophylaxis. In one evaluation of prophylaxis in 13 Finnish hospitals, the use of intermittent pneumatic calf compression was sporadic only. In addition, only 33% of patients who were undergoing gastrointestinal, orthopaedic or gynaecological surgery wore compression stockings. Nor did all of those at risk for VTE receive prophylaxis: 72% were given LMWH, during which the concomitant use of compression stockings was 47% (Virtanen *et al.*, 2010): that study was done 2 years later in hospitals that also took part in our study. Such results imply that our low VTE incidence might not be a result of a wide implementation of mechanical prophylaxis.

We obtained verification of VTEs from all possible sources, so our incidence (0.1%) is reliable. Evidence from Denmark shows retrospective hospital discharge data on VTE to be overestimated (Severinsen *et al.*, 2010). We verified register data within the hospital files of FINHYST; DVTs (ICD-codes) recorded from visits to the emergency room only, without any need for re-admittance to a hospital ward, were all confirmed as false—remaining at the level of suspicion only. Moreover, VTEs are not primarily treated by gynaecologists, which is probably the reason why cases diagnosed after discharge had remained unreported by the gynaecologists. Of the 6 cases, only 2 (33%) were originally reported to FINHYST (Brummer *et al.*, 2011). Nevertheless, owing to the observational design of our study, interpretation of how many VTEs or deaths were prevented is impossible. Combining rates of fatal PE in prospective studies of over 7000 gynaecologic surgeries including for malignant disease, with prophylaxis a 75% risk reduction can be demonstrated (from 0.4 to 0.1%; Geerts *et al.*, 2001); for general surgery, the clinical PE risk reduction is identical (Mismetti *et al.*, 2001). In our study involving benign disease, we may presume that the incidence was low also related to the current wider PTP coverage (65%). A decade earlier in Finland, with a 35% PTP coverage in 10 110 hysterectomies, the incidence was doubled (0.2%; Mäkinen *et al.*, 2001). In fact, based on our current verifications showing late-onset VTEs as being unknown to the gynaecologists, the true incidence most probably was much higher in the earlier national hysterectomy study population.

In routine screening of untreated controls, DVTs in major gynaecological surgery without PTP occurred in 16% (Geerts *et al.*, 2001) but including only cases operated on for benign disease, 11% (69 of 612; Bonnar *et al.*, 1972; Ballard *et al.*, 1973; Walsh *et al.*, 1974; Taberner *et al.*, 1978; Turner *et al.*, 1984; Clarke-Pearson *et al.*, 1987). In contrast to routine screening, a register of 1.6 million operations and over 13 000 thromboses showed an overall incidence of symptomatic VTE of 0.8%; for AH, 0.3% if performed for benign and 1.2% if for malignant disease (White *et al.*, 2003). Importantly, VTEs were usually diagnosed after discharge (56%), and their occurrence as PE was high (39%). Similar to FINHYST, in other hysterectomy studies most VTEs have occurred as PEs (Garry *et al.*, 2004; Hansen *et al.*, 2008).

A recent study enrolling 266 gynaecological laparoscopies with routine DVT screening found none (Ageno *et al.*, 2007). In contrast to minor laparoscopy, hysterectomy is of longer duration with more bleeding, theoretically requiring a more efficient coagulation response. In the earlier national evaluation, 7 (0.3%) VTEs occurred with 2434 LHs, with 22% receiving PTP (Mäkinen *et al.*, 2001). One register study on 60 013 LHs, with the majority for benign disease (96.2%), observed PEs rarely (0.07%) but DVTs relatively often (0.9%). PTP was used less frequently (11.9%) than in FINHYST (59.4%; Ritch *et al.*, 2011).

LMWH, versus placebo or no treatment, more than doubled the risk for haemorrhage in general surgery (Mismetti *et al.*, 2001) but in a gynaecologic oncology study with daily high-dose LMWH, no increase occurred versus intermittent calf compression (Maxwell *et al.*, 2001). Risk for bleeding complications is affected by risk for

**Table III** VTEs occurring with 5279 hysterectomies for benign indication.

| Case | Hysterectomy | VTE | Age (years) | BMI (kg/m$^2$) | Duration of surgery | Predisposing other factors | LMWH | Dose, duration | First dose post-operatively | Post-operative day of diagnosis |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | AH | PE | 60 | 31.2 | 3 h 33 min | Bedrest (hypertension, ileus) | Enoxaparine | 40 mg initiated 12 h preop., then 20 mg once | 12 h | 12 |
| 2 | VH | PE | 60 | 27.7 | 1 h 15 min, 1 h 55 min | Reoperation (laparotomy) | Dalteparine | 2500 IU first dose, then 5000 IU × 1[a] | 24 h | 6 |
| 3 | AH | PE | 46 | 38.9 | 2 h 55 min | | Dalteparine | 5000 IU × 1, for 2 days | 6 h | 17[b] |
| 4 | VH | PE | 43 | 32.0 | 1 h 9 min | Previous stroke, APS | Enoxaparine | 20 mg × 1, for 4 days | 12 h | 17[b] |
| 5 | LH | DVT, bilateral | 34 | 22.5 | 45 min | Previous 18 DVTs and 1 PE | Dalteparine | 2500 × 1 first dose, then 5000 IU × 2[a] | 6 h | 13 and 15[b] |
| 6 | LH, conversion | DVT | 54 | 30.4 | 8 h 10 min | Injured iliac vein obliterated | Enoxaparine | 20 mg × 1 day 1, 40 mg × 1 day 2, then 40 mg × 2[a] | 24 h | 3, verified on 7 |

All affected had received PTP. PE, pulmonary embolism; DVT, deep venous thrombosis, APS, antiphopholipid syndrome.
[a]Until diagnosed
[b]After discharge

thrombosis. For high-dose dalteparin compared with low, the risk for bleeding was higher particularly for those without a single risk factor for thrombosis (Flordal *et al.*, 1996). In another general surgery study, the risk for bleeding complications with a high dose was 5-fold for those operated on for benign disease; with malignancies, however, no dose-dependent difference occurred (Bergqvist *et al.*, 1995).

Considering the timing of PTP, in orthopedics, preoperative initiation was not required for prophylactic efficacy. Begun, however, within 2 h of surgery, PTP caused increased major bleeding also at a low dose; thus early post-operative administration is suggested at 6 h (Raskob *et al.*, 2003). As the timing of PTP was not recorded in our study, findings that operative bleeding complications remained unaffected must be interpreted with great caution. Typically, patients arrive in the hospital on the morning of the operation. Thus, presumably the initiation of PTP was more commonly post-operative. Besides our study, only a single large national evaluation focusing on benign disease has appeared: For that cohort of over 9000 hysterectomies, the study claimed post-operative heparin initiation to be safer than preoperative, but operative and post-operative bleeding complications were analysed together, with neither type nor dose of heparin stated. Post-operative bleeding occurred in 7% (Hansen *et al.*, 2008). In FINHYST, post-operative bleeding in PTP users (2.7–3.6%) was similar to the rate (3.7%) described in a review of abdominal and pelvic surgery involving mostly malignant disease (Rasmussen *et al.*, 2009). In that study, extended LMWH for up to a month did not lead to increased bleeding. With malignant disease, no risk may occur (Einstein *et al.*, 2007) but our results showed an increased risk for post-operative bleeding with LMWH in women at a generally lower risk for thrombosis. This reflected their coagulability overall. The risk seemed also to be related to the extent of surgery: with AH where heavy tissue manipulation and large incisions are combined, and with VH for prolapse, where concomitant vaginal repair was performed for the majority (82%).

The evidence that hysterectomy complications are fewer for the elderly has remained unexplained. The reason may be the reduced bleeding. Severe operative complications continuously decrease with age, a trend evident also for haemorrhage and visceral damage (McPherson *et al.*, 2004). Younger women are more likely readmitted with haemorrhage (Spisbury *et al.*, 2006) and are at risk for infections (Shapiro *et al.*, 1982; Löfgren *et al.*, 2004; Spilsbury *et al.*, 2006; Brummer *et al.*, 2011). Blood collections and burned necrotic tissue are ideal sites for infection. Hormonal status affects both size and vascularization of the target organ. Arteriosclerosis accelerates and blood coagulation capacity undergoes changes as plasma concentrations of several coagulation factors in healthy individuals increase with age (Hamilton *et al.*, 1974; Hager *et al.*, 1989; Mari *et al.*, 2008). Although the pathophysiologic significance of such modest increases may be uncertain, as a consequence, combined with endothelial damage, thrombosis taking place in the elderly is well known (Geerts *et al.*, 2008).

The thickened abdominal wall may bleed more, and sufficient visibility of the vault closure vaginally may be difficult in obese patients. Evidence of excessive operative bleeding being related to obesity has occurred in LH (Heinberg *et al.*, 2004), in VH (Rasmussen *et al.*, 2004), and in analysing all hysterectomies together (Osler *et al.*, 2011). Rasmussen *et al.* (2004), however, found no significant increase

in excessive bleeding (>500 ml) in the obese in AH, corresponding to our results: haemorrhage ≥1000 ml was similarly frequent to figures for those of normal weight. Analysing post-operative complications, Rasmussen *et al.* (2004) were surprised to find a higher risk for wound haematoma in those of normal weight, suspecting that diagnostics for haematoma in the obese are more difficult. For post-operative bleeding, we also observed a decline; and no cases appeared in the extremely obese. The possibility of a true benefit from obesity exists. Adipose tissue is not very well vascularised. Thrombosis associates to a lesser degree with laparoscopic surgery (Geerts *et al.*, 2008) than with open surgery, where the larger tissue damage activates the coagulation system. The outsized tissues of the obese patient are exposed to even greater damage, accelerated by blunt trauma caused by wound retractors. This may call for further physiological coagulation efficacy, consequently being protective against post-operative bleeding.

## Conclusions

In Finland, as surgery has become less invasive, simultaneously awareness of PTP has increased and VTEs have reduced. With hysterectomy for benign disease, an association between PTP and post-operative bleeding has occurred, dependent upon the extent of surgery. Yet, the current development with increasing popularity of minimally invasive hysterectomy methods reduces this risk, and by allowing quick mobilization, is also beneficial in VTE prevention.

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## Authors' roles

The conception of the study was by T.B., A.H., J.J., J.F., J.M., E.T., J.S. and P.H., who all also participated in the acquisition of the data. Advice on the statistical design and analysis was provided by T.S., and the analyses conducted by T.B. and T.S. All authors contributed to the critical revision of the paper drafted by T.B. The final version was approved by all authors.

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## Conflict of interest

None declared.

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