

## **Venous thromboembolic complications to hysterectomy for benign disease**

*a nationwide cohort study*

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# **Venous thromboembolic complications to hysterectomy for benign disease. A nationwide cohort study.**

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## **Source of the study**

A nationwide cohort study using The Danish National Patient Register.

## **Disclosure statements**

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## **Prior Presentation**

This work has not been presented before.

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2,809 (Title page, abstract, précis and references not included)

## **Short title**

Venous thromboembolism after hysterectomy

## **Précis**

The risk of venous thromboembolism after hysterectomy for benign disease is generally low, highest with an abdominal procedure, and particularly low after laparoscopic and vaginal procedures.

## 46 **Abstract**

47 Study Objective: To estimate the risk of venous thromboembolic complications following  
48 abdominal, laparoscopic and vaginal hysterectomy when performed for benign disorders.

49 Design: Nationwide cohort study (Canadian Task Force Classification II-2).

50 Setting: Data from Danish national registers on all women undergoing hysterectomy for benign  
51 conditions in the period 1996-2015.

52 Patients: Women aged 18 and above who underwent hysterectomy for benign disease were  
53 stratified into 3 groups according to hysterectomy approach: abdominal, laparoscopic or vaginal.

54 Intervention: Hysterectomy.

55 Measurements and Main Results: 89,931 women met the inclusion criteria. Venous  
56 thromboembolism (VTE) as a diagnosis or cause of death was identified. Risk of postoperative  
57 VTE was examined with Cox proportional hazard models adjusting for age, surgical approach and  
58 relevant comorbidities. Mean age was 49.9, 47.9 and 54.3 years for women with abdominal,  
59 laparoscopic and vaginal hysterectomy, respectively. Crude incidences of VTE within 30 days after  
60 hysterectomy were 0.24% (n=142), 0.13% (n=12) and 0.10% (n=21). The most important  
61 predictors of VTE were approach to hysterectomy and a history of thromboembolic disease. In the  
62 multivariable analysis risk of VTE was significantly reduced with laparoscopic hysterectomy (HR  
63 0.51; 95% CI 0.28-0.92,  $P=.03$ ) and vaginal hysterectomy (HR 0.39; 95% CI 0.24-0.63,  $P<.001$ )  
64 when compared to the abdominal procedure. Data on postoperative heparin thromboprophylaxis  
65 were available in 53,566 patients and adjusted HR was 0.63 (95 % CI 0.42-0.96,  $P=.03$ ) in patients  
66 receiving heparin thromboprophylaxis.

67 Conclusions: The 30-day cumulative incidence of VTE after hysterectomy for benign conditions  
68 was low overall (0.19%). Laparoscopic and vaginal hysterectomy carry a lower risk than the

abdominal procedure. Postoperative heparin thromboprophylaxis significantly reduces risk of VTE and should be considered especially if risk factors are present.

**Keywords:** Deep venous thrombosis; hysterectomy; pulmonary embolism; thromboprophylaxis.

## 96 Introduction

97 Postoperative venous thromboembolism (VTE) is the second-most common medical complication  
98 to general surgery and results in excess morbidity and mortality[1]. The most feared consequence,  
99 pulmonary embolism (PE), is the most common preventable cause of hospital death[1]. Deep vein  
100 thrombosis (DVT) and PE are preventable with proper thromboprophylaxis as demonstrated in  
101 clinical trials[2].

102 One of the most common gynecologic procedures is hysterectomy with 400- 600,000 procedures  
103 per year in the United States[3,4]. Few studies have focused on the incidence of VTE in women  
104 undergoing hysterectomy for benign conditions. There are three different approaches to  
105 hysterectomy: abdominal, laparoscopic and vaginal. In 2015, 20 % were performed as abdominal,  
106 64 % as laparoscopic assisted (including robotic-assisted surgery) and 16 % as vaginal  
107 hysterectomies in Denmark[5]. The risk of postoperative DVT and PE, in patients undergoing  
108 surgery for benign conditions, is presumed to be low in general[6,7], and in particular when  
109 performed laparoscopically[8]. This is probably the reason, why pharmacologic VTE prophylaxis  
110 has not been used systematically. Despite being the recommendation in most clinical guidelines,  
111 the proportion of patients actually receiving thromboprophylaxis after hysterectomy may be as low  
112 as 11.9%[6]. Danish guidelines recommend postoperative venous thromboprophylaxis with low  
113 molecular weight heparin administered 4-12 hours following hysterectomy in prophylactic dose  
114 once daily until discharge from hospital, this can optionally be supplemented with graduated elastic  
115 compression stockings[9]. Few studies have focused on VTE in benign gynecologic surgery and  
116 recommendations on thromboprophylaxis have mostly been based on the experience from  
117 abdominal surgery and study populations with a broad variation of risk factors[10]. The striking  
118 difference between clinical practice and guidelines calls for a more precise estimation of risk of  
119 VTE after hysterectomy for benign conditions.

120

121

122

## 123 **Materials and Methods**

### 124 **Data-sources**

125 This study is based on data from national Danish administrative registries.

126 In Denmark, every resident is at the time of birth or immigration assigned a unique and permanent  
127 civil registration number, which enables linkage between nationwide administrative registers on the  
128 individual level. The Danish National Patient Register (DNPR) was established in 1977 and holds  
129 data on all hospitalizations in Denmark[11]. Each admission is registered at discharge with one  
130 primary and if appropriate one or more secondary diagnoses according to the International  
131 Classification of Diseases, the 10<sup>th</sup> revision (ICD-10). Surgical procedures are registered according  
132 to the Nordic Medico-statistical Committee's Classification of Surgical Procedures[12], together  
133 with the indication for the procedure. There could be multiple indications for hysterectomy.

134 We retrieved information on hormone substitution and anticoagulant treatment from The Danish  
135 Register of Medicinal Product Statistics where all prescription based pharmacy dispensings are  
136 stored. The National Population Register and the National Causes of Death Register hold  
137 information on vital status, date of birth and death including cause of death.

### 138 **Study population**

139 All patients who underwent hysterectomy from January 1<sup>st</sup> 1996 until December 31<sup>st</sup> 2015 were  
140 identified. The patients were separated into three groups according to the surgical approach:  
141 abdominal (subtotal or total abdominal hysterectomy comprised the codes KLCD00, KLCD96,  
142 KLCC10), laparoscopic (total, subtotal, vaginal and robotic assisted laparoscopic hysterectomy  
143 comprised the codes KLCD01, KLCD04, KLCC11, KLCD11, KLCD97) or vaginal (total or subtotal  
144 comprised the codes KLCD10, KLCC20, colpoperineoplasty and vaginal hysterectomy KLEF13).  
145 Patients diagnosed with any type of cancer within 1 month prior to surgery or two months following  
146 the surgical procedure were excluded (ICD10 codes DC00-96). Radical hysterectomies (KLCD30,  
147 KLCD31, KLCD40) were excluded because these procedures are only performed in the case of  
148 gynecologic malignancy. We did not include hysterectomies performed at the same time as  
149 cesarean section or hysterectomy performed at the same time as cystectomy in the case of urine

150 bladder malignancy.

151 Patients were excluded if the specific date of surgery was not defined.

## 152 **Outcome**

153 VTE comprised the following ICD-10 codes: I80.1 (phlebitis or thrombophlebitis in the femoral  
154 vein), I80.2 (deep phlebitis or thrombophlebitis in other veins in lower extremities), I80.3 (deep  
155 phlebitis or thrombophlebitis in other veins in lower extremities without specification), I80.8  
156 (phlebitis or thrombophlebitis at other locations), I80.9 (phlebitis or thrombophlebitis without  
157 specification) and I26 (pulmonary embolism). If one of these codes occurred prior to the date of  
158 hysterectomy it was registered as a previous VTE. If the code was assigned to a patient within one  
159 month after hysterectomy it was registered as a postoperative VTE.

## 160 **Confounders**

161 Use of hormones or antithrombotic agents prior to surgery was defined as at least one claimed  
162 prescription within 180 days before surgery of the following agents: oral contraceptives with  
163 estrogen in combination with progesterone (Anatomical Therapeutic Chemical Classification G03A,  
164 G03HB01) or hormone therapy (estrogen as monotherapy or in combination with progesterone,  
165 both orally and transdermal administrated G03F, G03CX, G03CA and G03CB; low dose estrogen  
166 vagitories were excluded by product number). Antithrombotic agents were defined including  
167 antiplatelet drugs (B01AC) and anticoagulant drugs (B01 except B01AC).

168 Co-morbidities were defined as one of the following ICD-10 codes if the code was used at  
169 discharge within 365 days prior to the hysterectomy date: ischemic heart disease (I20, I23, I24,  
170 I25), cerebral vascular disease (I60-69), acute myocardial infarction (I21), varices of the lower  
171 extremities (I83), thrombophilia (D68), heart failure (I50), chronic obstructive lung disease (J44).

172 Two time periods were compared as the Danish Board of Health in 2003 published a national  
173 guideline for benign hysterectomy including recommendations on postoperative VTE prophylaxis  
174 with heparin injections and graduated elastic compression stockings during hospitalization[13]. A  
175 Danish national hysterectomy database was established in October 2003 and one of the clinical



indicators is the use of VTE prophylaxis which is registered in the DNPR by the clinicians (BOHA03C).

Information on Body Mass Index (BMI) was obtained from the Danish Anesthesia Database (DAD). This information was not available for all patients since the database was established in 2004 and it does not cover all departments in Denmark.

Data are reported in accordance with the STROBE statement[14].

## Statistics

Cumulative incidence was calculated for the competing risks VTE and death after abdominal, laparoscopic and vaginal hysterectomy respectively. Time to event was calculated from the date of surgery, follow-up time was 30 days and data were analyzed using univariable and multivariable Cox proportional hazard regression. Hazard ratios (HRs) of VTE after abdominal, laparoscopic and vaginal hysterectomy were hence estimated and presented with 95% confidence intervals (95% CI). A *P*-value less than 0.05 was considered statistically significant. Plots of Schoenfeld Residuals were used to examine the proportional hazard assumption. Linearity between the continuous variable age and outcome was tested. Interaction between approach to hysterectomy and presence of uterine fibroids was tested using analysis of variance.

Calculations were performed using SAS V.9.4 (SAS Institute, Cary, North Carolina, USA) and R version 3.1.0 (R Core Team (2014))[15].

## Ethics

The study was approved by The Danish Data Protection Agency (Re: 2007-58-0015, int.ref: GEH-2010-001). Permission from the ethics committee is not required for retrospective register studies in Denmark.

## Results

202 We identified 89,931 patients who underwent hysterectomy for benign conditions in the period  
 203 January 1<sup>st</sup> 1996 until December 31<sup>st</sup> 2015. Patients were divided into three groups according to  
 204 the route of hysterectomy: Abdominal (n=59,231), laparoscopic (n=9,198) and vaginal (n=21,502)  
 205 (figure 1). Table 1 shows the demographic data of the cohort according to age at surgery, length of  
 206 stay, body mass index (BMI), concomitant disease, use of medicine before surgery, the indication  
 207 for hysterectomy and postoperative pharmacologic VTE prophylaxis. Women undergoing vaginal  
 208 hysterectomy were older and more likely to have comorbidities, although the general incidence of  
 209 comorbidity was low in the total cohort. The indication for hysterectomy was uterine prolapse in  
 210 more than 50 % of cases within the vaginal hysterectomy group. In the abdominal and  
 211 laparoscopic hysterectomy groups, uterine fibroids and abnormal uterine bleeding were the  
 212 dominant causes.

213 Comparing the two time periods before and after January 1<sup>st</sup>, 2004 showed that the proportion of  
 214 minimally invasive hysterectomy was increasing during the study period with 29,060 abdominal  
 215 approaches in 36,365 hysterectomies before 2004 ~80 %. After January 1<sup>st</sup>, 2004 44 % of  
 216 hysterectomies were performed as laparoscopic and vaginal procedures.

217 During 30-day follow up after surgery we observed 175 cases of VTE with 100 cases of PE. There  
 218 were 109 deaths in the abdominal hysterectomy group compared to one in the laparoscopic and  
 219 12 in the vaginal hysterectomy group.

220 Competing risk analysis of the cumulative incidence of VTE showed higher incidence with open  
 221 surgery compared to the two minimally invasive methods. Cumulative incidence of mortality  
 222 showed the highest incidence with open surgery compared to the two minimally invasive methods.  
 223 (Figures S1 and S2 are provided in supplemental material).

224 Unadjusted HRs in different exposure groups are provided in table 2. The indication for  
 225 hysterectomy could be strongly correlated to the choice of surgery approach as surgeons might  
 226 prefer to perform abdominal hysterectomy in the presence of uterine and ovarian neoplasms.  
 227 Statistical testing showed no evidence of interaction between hysterectomy approach and uterine  
 228 fibroids ( $P=0.35$ ).

Length of stay was associated with surgical approach (table 1) with median value highest in the abdominal hysterectomy group and univariable analysis (table 2) shows that it is significantly associated with HR of VTE.

Adjusting for age, time period, ovarian and uterine neoplasms, relevant drugs and concomitant disease, the laparoscopic (HR 0.51; 95% CI 0.28-0.92,  $P=.03$ ) and vaginal (HR 0.39; 95% CI 0.24-0.63,  $P<.001$ ) procedures are correlated with a significantly reduced HR of VTE when compared to abdominal hysterectomy (figure 2).

The use of oral hormonal contraceptives or hormone therapy did not influence on the HR of VTE in women undergoing hysterectomy (figure 2 and 3). In contrast, anticoagulant drugs, previous acute myocardial infarction (AMI) and previous VTE significantly increase the HR of VTE (figure 2 and 3). Usage of postoperative heparin as VTE prophylaxis has been registered in the DNPR since 2004. There is no change in the impact of the different factors included in the first model (figure 2) when performing the same multivariable analysis on hysterectomies performed after 2003 including VTE prophylaxis instead of time period (figure 3). This subgroup analysis shows a reduced HR (0.63; 95% CI 0.42-0.96,  $P=.03$ ) for VTE in patients receiving pharmacologic VTE prophylaxis.

Data on BMI were available in 11,177 patients with overall mean BMI 26.1 (SD  $\pm 5.0$ ) and 19 VTE events (table 1). We found no difference in risk of VTE between BMI groups in a univariable Cox proportional hazard regression analysis. Because of the smaller number of events we did not attempt of multivariable analysis including BMI.

## Discussion

This study demonstrates that the 30-day incidence of postoperative VTE after hysterectomy for any benign condition is low. The rate of VTE was lowest in patients treated with laparoscopic and vaginal hysterectomy compared to the abdominal approach.

A Cochrane review (2009) comparing the complication rates between different procedures concluded that vaginal hysterectomy was superior to abdominal on almost all outcome measures

and recommended laparoscopic surgery in cases where vaginal hysterectomy could not be performed[17]. However, there was no apparent difference in the VTE incidence according to surgical approach, probably due to limited power.

Barber et al (2014) found an overall incidence of VTE at 0.35 % in 44,167 women undergoing hysterectomy for benign conditions and showed abdominal hysterectomy to be associated with higher risk of VTE compared to minimally invasive surgery (OR 2.45; CI 1.77-3.40)[18]. Swenson et al (2015) registered 110 VTE events (0.5%) during 30 days of follow-up in 20,496 women with hysterectomy for benign, malignant and obstetric indications. Prominent risk factors were abdominal approach, cancer, BMI>35 and increased surgical time[19].

The frequency of VTE in these studies is consistent with our findings. The association between BMI and VTE is debated and experience from bariatric surgery suggests that it has been overestimated[20]. We found no association between BMI and VTE in a subgroup of the cohort; due to missing data, we could not include BMI in the multivariable analysis.

White et al (2003) showed, that the incidence of first-time VTE increases exponentially with age with a dramatically increase after the age of 60[21]. Ritch et al (2011) identified age as a significant risk factor of VTE after hysterectomy[6].

In accordance with these studies we found the crude HR of VTE increasing with age in the unadjusted model. This association could not be reproduced in the multivariable models, indicating a stronger association between VTE and approach to hysterectomy.

Several studies have reported an increased risk of VTE with hormone therapy (HT) [22]. In the present study we found no difference in HR between women on HT or oral contraceptives containing estrogen compared to women not exposed.

A benign pelvic mass might compress the iliac veins leading to venous stasis and subsequent thrombosis. Fletcher et al. (2009) found an increased risk of VTE (OR 3.75; CI 2.92-4.78,  $P<.001$ ) among women with uterine fibroids with and without surgery when compared to the expected rate in hospitalized women[23]. Shiota et al. (2011) found an overall incidence of preoperative asymptomatic DVT at 3.7 % (31/843) in patients with benign ovarian tumors[24]. Our analysis

282 indicated no correlation between any benign indication for hysterectomy and risk of postoperative  
 283 symptomatic VTE. Our dataset did not contain neoplastic size, therefore, the possible impact of  
 284 large tumors on VTE risk cannot be assessed.

285 It must be emphasized that we can only report cases of symptomatic VTE's. The incidence would  
 286 probably be higher with more sensitive methods as demonstrated in randomized controlled  
 287 trials[2].

288 In Denmark, thromboprophylaxis is administered by the hospital and was not registered in the  
 289 DNPR before 2004. Hansen et al. (2008) reported an increase in heparin thromboprophylaxis  
 290 administered following hysterectomy from 20 % in 2004 to more than 90 % of patients undergoing  
 291 hysterectomy for benign disease in 2006[25]. Surgeons were probably paying more attention to  
 292 VTE prophylaxis after the establishment of the Danish Hysterectomy and Hysteroscopy Database  
 293 and implementation of recommendations on postoperative VTE prophylaxis. Our results indicate a  
 294 significant reduction in risk of VTE following hysterectomy for benign conditions when  
 295 pharmacologic VTE prophylaxis was administered during hospital stay after surgery. The ACOG  
 296 Practice Bulletin (2007) recommends initiation of venous thromboprophylaxis with graduated  
 297 compression stockings or pneumatic compression devices before surgery as VTE begins in the  
 298 perioperative period[10]. Our results show a decrease in HR of VTE in patients receiving  
 299 postoperative heparin which is supported by Hansen et al. (2008) who found preoperative  
 300 administration associated with higher risk of bleeding complications compared to postoperative  
 301 administration and no apparent difference in risk of VTE.[26] From our study we cannot draw any  
 302 conclusions on the timing of VTE prophylaxis. Not all patients received prophylaxis, it is likely that  
 303 patients within a fast track regimen undergoing MIS are discharged before heparin administration.  
 304 Increasing length of stay increased the HR of VTE in a univariable analysis (table 2), despite this  
 305 finding we did not include it in the multivariable analysis as we believe the variable is not a  
 306 confounder because it is on the causal pathway between main exposure and outcome[27]. Talec  
 307 et al (2016) suggest individual evaluation of thromboprophylaxis in each patient based on patient-

308 related risk factors, type of surgery including length of operation and duration to mobilization[28].  
 309 Our results support this approach to the planning of VTE prophylaxis.  
 310 The strength of epidemiologic research using national registries is the availability of a large patient  
 311 cohort. Through our study, we found an important association between the risk of VTE and the  
 312 approaches to hysterectomy. Groups were considered highly comparable according to baseline  
 313 characteristics. The vaginal approach was used more often in case of pelvic organ prolapse and  
 314 the abdominal approach in the presence of benign neoplasms, consistent with available  
 315 gynecologic guidelines[29,30]. Bias could arise from misclassification of diseases and treatments.  
 316 We calculated cumulative incidence of VTE considering mortality as a competing risk to illustrate  
 317 how mortality affect the probability of a VTE event to occur. As mortality was highest in the  
 318 abdominal hysterectomy group we found no reason to think mortality precluded the occurrence of  
 319 VTE in the laparoscopic and vaginal hysterectomy groups.  
 320 The coding of co-morbidity and coexisting diseases in DNPR is validated by Thygesen et al.  
 321 (2011), with a positive predictive value ranging from 82 to 100 %.[31]. The validity of VTE  
 322 discharge diagnoses in DNPR was investigated by Severinsen et al. (2010) who found a positive  
 323 predictive value of 75% for diagnoses coded at wards[32].  
 324 Confounding by indication could arise if the indication for hysterectomy carries a risk of developing  
 325 VTE. Most other studies included patients with both benign and malignant diseases[6,19]. We  
 326 chose to exclude patients with malignant disease and also obstetric patients, as these conditions  
 327 are recognized risk factors for VTE[33,34].

328

### 329 **Conclusion:**

330 The risk of postoperative VTE in the first 30 days after hysterectomy is low (0.19 %). Laparoscopic  
 331 and vaginal approach to hysterectomy significantly reduce the risk of VTE when compared to  
 332 abdominal approach and adjusted for age and relevant risk factors. Our results indicate that  
 333 postsurgical use of pharmacologic thromboprophylaxis reduce the risk of VTE. If heparin  
 334 prophylaxis is not routinely used we suggest individual evaluation in each patient considering

335 approach to surgery, concomitant disease and previous thromboembolic events.

336

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339

340

### 341 **References**

- 342 1 Geerts William H, Bergqvist David, Pineo Graham F, et al. Prevention of venous  
 343 thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice  
 344 Guidelines (8th Edition). *Chest*. 2008;133(6 Suppl):381S–453S.
- 345 2 Gould Michael K, Garcia David a, Wren Sherry M, et al. Prevention of VTE in nonorthopedic  
 346 surgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American  
 347 College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*.  
 348 2012;141(2 Suppl):e227S–77S.
- 349 3 Clarke-Pearson Daniel L, Geller Elizabeth J. Complications of hysterectomy. *Obstet*  
 350 *Gynecol*. 2013;121(3):654–73.
- 351 4 Wallace Sumer K, Fazzari Melissa J, Chen Hui, Cliby William A, Chalas Eva. Outcomes and  
 352 Postoperative Complications After Hysterectomies Performed for Benign Compared With  
 353 Malignant Indications. *Obstet Gynecol*. 2016;128(3):467–75.
- 354 5 Settnes Annette. Dansk Hysterektomi og Hysteroskopi Database National Årsrapport 2015  
 355 2016:1–159.
- 356 6 Ritch Jessica MB, Kim Jin Hee, Lewin Sharyn N, et al. Venous thromboembolism and use of  
 357 prophylaxis among women undergoing laparoscopic hysterectomy. *Obstet Gynecol*.  
 358 2011;117(6):1367–74.
- 359 7 Ageno W, Manfredi E, Dentali F, et al. The incidence of venous thromboembolism following  
 360 gynecologic laparoscopy: a multicenter, prospective cohort study. *J Thromb Haemost*.  
 361 2007;5(3):503–6.

- 362 8 Nguyen Ninh T, Hinojosa Marcelo W, Fayad Christine, et al. Laparoscopic surgery is  
 363 associated with a lower incidence of venous thromboembolism compared with open surgery.  
 364 *Ann Surg.* 2007;246(6):1021–7.
- 365 9 Dansk Hysterektomi og Hysteroskopi Database 2011.
- 366 10 ACOG practice bulletin no 84. Prevention of Deep Vein Thrombosis and Pulmonary  
 367 Embolism. *Obstetrics Gynecol.* 2007;110(2):429–40.
- 368 11 <http://www.ssi.dk/Sundhedsdataogit/Registre/Landspatientregisteret.aspx> n.d.
- 369 12 *Nordic Medico-statistical Committee. NOMESCO Classification of Surgical Procedures.*  
 370 2009. n.d.
- 371 13 Knudsen UB. Referenceprogram for Hysterektomi på benign indikation. [Reference  
 372 programme for hysterectomy for benign disease] 2003.
- 373 14 von Elm Erik, Altman Douglas G, Egger Matthias, Pocock Stuart J, Gøtzsche Peter C,  
 374 Vandembroucke Jan P. The Strengthening the Reporting of Observational Studies in  
 375 Epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin*  
 376 *Epidemiol.* 2008;61(4):344–9.
- 377 15 R Core Team (2014). R: A language and environment for statistical computing. R  
 378 Foundation for Statistical Computing, Vienna, Austria 2004.
- 379 16 Heit John A, Spencer Frederick A, White Richard H. The epidemiology of venous  
 380 thromboembolism. *J Thromb Thrombolysis.* 2016;41(1):3–14.
- 381 17 Nieboer TE, Johnson N, Lethaby A, et al. Surgical approach to hysterectomy for benign  
 382 gynaecological disease ( Review ). *Cochrane Database Syst Rev.* 2009;(3).
- 383 18 Barber Emma L, Neubauer Nikki L, Gossett Dana R. Risk of venous thromboembolism in  
 384 abdominal versus minimally invasive hysterectomy for benign conditions. *Am J Obstet*  
 385 *Gynecol.* 2014:1–7.
- 386 19 Swenson Carolyn W, Berger Mitchell B, Kamdar Neil S, Campbell Darrell a, Morgan Daniel  
 387 M. Risk Factors for Venous Thromboembolism After Hysterectomy. *Obstet Gynecol.*  
 388 2015;125(5):1139–44.



- 389 20 Westling Agneta, Bergqvist David, Boström Annika, Karacagil Sadettin, Gustavsson Sven.  
390 Incidence of deep venous thrombosis in patients undergoing obesity surgery. *World J Surg*.  
391 2002;26(4):470–3.
- 392 21 White Richard H. The epidemiology of venous thromboembolism. *Circulation*. 2003;107(23  
393 Suppl 1):I4-8.
- 394 22 Rossouw JE, Anderson GL, Prentice RL. Risks and Benefits of Estrogen Plus Progestin in  
395 Healthy Postmenopausal Women. *JAMA*. 2002;288(3):321–33.
- 396 23 Fletcher H, Wharfe G, Williams NP, Gordon-Strachan G, Pedican M, Brooks A. Venous  
397 thromboembolism as a complication of uterine fibroids: a retrospective descriptive study. *J*  
398 *Obstet Gynaecol*. 2009;29(8):732–6.
- 399 24 M Shiota, Y Kotani M Umemoto. Risk Factors for Deep-Vein Thrombosis and Pulmonary  
400 Thromboembolism in Benign Ovarian Tumor. *Tohoku J Exp Med*. 2011;225:1–3.
- 401 25 Hansen Charlotte T, Møller Charlotte, Daugbjerg Signe, Utzon Jan, Kehlet Henrik, Ottesen  
402 Bent. Establishment of a national Danish hysterectomy database: preliminary report on the  
403 first 13,425 hysterectomies. *Acta Obstet Gynecol Scand*. 2008;87(5):546–57.
- 404 26 Hansen Charlotte T, Kehlet Henrik, Møller Charlotte, Mørch Lina, Utzon Jan, Ottesen Bent.  
405 Timing of heparin prophylaxis and bleeding complications in hysterectomy a nationwide  
406 prospective cohort study of 9,949 Danish women. *Acta Obstet Gynecol Scand*.  
407 2008;87(10):1039–47.
- 408 27 Greenland Sander, Pearl Judea, Robins James M. Causal Diagrams for Epidemiologic  
409 Research. *Epidemiology*. 1999;10(1):37–48.
- 410 28 Talec P, Gaujoux S, Samama CM. Early ambulation and prevention of post-operative  
411 thrombo-embolic risk. *J Visc Surg*. 2016;153:S11–4.
- 412 29 Sundhedsstyrelsen. *Referenceprogram for hysterectomi på benign indikation*. 2006.
- 413 30 American College of Obstetricians and Gynecologists Committee on Gynecologic Practice.  
414 Choosing the Route of Hysterectomy for Benign Disease. *Committee Opin ACOG*.  
415 2009;114(5):1156–8.

- 416 31 Thygesen Sandra K, Christiansen Christian F, Christensen Steffen, Lash Timothy L,  
417 Sørensen Henrik T. The predictive value of ICD-10 diagnostic coding used to assess  
418 Charlson comorbidity index conditions in the population-based Danish National Registry of  
419 Patients. *BMC Med Res Methodol.* 2011;11(1):83.
- 420 32 Severinsen Marianne Tang, Kristensen Søren Risom, Overvad Kim, Dethlefsen Claus,  
421 Tjønneland Anne, Johnsen Søren Paaske. Venous thromboembolism discharge diagnoses  
422 in the Danish National Patient Registry should be used with caution. *J Clin Epidemiol.*  
423 2010;63(2):223–8.
- 424 33 Wun Ted, White Richard H. Epidemiology of cancer-related venous thromboembolism. *Best*  
425 *Pract Res Clin Haematol.* 2009;22(1):9–23.
- 426 34 Greer Ian A. Epidemiology, risk factors and prophylaxis of venous thrombo-embolism in  
427 obstetrics and gynaecology. *Baillieres Clin Obstet Gynaecol.* 1997;11:403–30.

430 **Figure 1.** Flowchart presenting the patient selection using Danish National Registries.

432 **Figure 2.** Multivariable Cox proportional Hazards Regression analysis presenting hazard ratios of  
433 venous thromboembolism associated with the approach to hysterectomy, adjusted for age, time  
434 period, ovarian and uterine neoplasm, use of sex hormones, a history of acute myocardial  
435 infarction (AMI) and previous venous thromboembolism (VTE).

436 Abdominal hysterectomy is used as reference in the main exposure group, among categorical  
437 variables in the confounder group exposed individuals are compared to non-exposed.

439 **Figure 3.** Multivariable Cox proportional Hazards Regression analysis presenting hazard ratios of  
440 venous thromboembolism associated with the approach to hysterectomy, adjusted for age, use of  
441 postoperative thromboprophylaxis, ovarian and uterine neoplasm, use of sex hormones and a  
442 history of acute myocardial infarction (AMI) and previous venous thromboembolism (VTE).

443 Stratified for period, showing results after 2003. Abdominal hysterectomy is used as reference in  
444 the main exposure group, among categorical variables in the confounder group exposed  
445 individuals are compared to non-exposed.

446

447 **Figure S1.** Cumulative incidence of venous thromboembolism 30 days following hysterectomy.

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449 **Figure S2.** Cumulative incidence of death 30 days following hysterectomy.

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453 **Table 1. Baseline characteristics and variables related to treatment**

<b>Variable*</b>	<b>Abdominal hysterectomy N=59,231</b>	<b>Laparoscopic hysterectomy N=9,198</b>	<b>Vaginal hysterectomy N=21,502</b>	<b>Totals N=89,931</b>
Mean age, years	49.9 ±10.4	47.9 ±10.5	54.3 ±13.2	50.7 ±11.3
Median length of stay, days (interquartile range)	3 (2,5)	1 (1,2)	2 (1,2)	3 (2,4)
Length of stay data missing	4	1	10	15
Body Mass Index (BMI)	26.2±5.2	25.7±5.3	25.9±4.7	26.1±5.0
BMI missing	52,706	8,394	17,654	78,754
Anticoagulant drugs	631 (1.1)	110 (1.2)	177 (0.8)	918 (1.0)
Antiplatelet drugs	2,243 (3.8)	359 (3.9)	1,633 (7.6)	4,235 (4.7)
Hormonal contraception	4,422 (7.5)	894 (9.7)	1,280 (6.0)	6,596 (7.3)
Hormone therapy	7,183 (12.1)	927 (10.1)	4,821 (22.4)	12,931 (14.4)
Hysterectomy before 2004	29,060 (49.1)	2,166 (23.5)	5,139 (23.9)	36,363 (40.4)
Hysterectomy after 2003	30,171 (50.9)	7,032 (76.5)	16,363 (76.1)	53,566 (59.6)
<b>Indication for hysterectomy<sup>†</sup></b>				
Abnormal uterine bleeding	21,187 (35.8)	4,389 (47.7)	7,806 (36.3)	33,382 (37.1)
Benign ovarian neoplasm	4,910 (8.3)	292 (3.2)	189 (0.9)	5,391 (6.0)
Uterine fibroids	34,849 (58.8)	3,314 (36.0)	4,888 (22.7)	43,051 (47.9)
Pelvic organ prolapse	1,209 (2.0)	319 (3.5)	10,935 (50.9)	12,463 (13.9)
Pelvic pain	8,536 (14.4)	2,061 (22.4)	3,115 (14.5)	13,712 (15.2)
Endometriosis	5,161 (8.7)	1,192 (13.0)	1,191 (5.5)	7,544 (8.4)
Cervical intraepithelial neoplasia	1,958 (3.3)	624 (6.8)	872 (4.1)	3,454 (3.8)
Endometrial hyperplasia	485 (0.8)	123 (1.3)	184 (0.9)	792 (0.9)
Urinary incontinence	628 (1.1)	66 (0.7)	588 (2.7)	1,282 (1.4)
Cancer predisposition	100 (0.2)	91 (1.0)	8 (0.04)	199 (0.2)
<b>Concomitant diseases</b>				
Ischemic heart disease	1,498 (2.5)	329 (3.6)	902 (4.2)	2,729 (3.0)
Cardiovascular disease	873 (1.5)	176 (1.9)	419 (1.9)	1,468 (1.6)
History of acute myocardial infarction	320 (0.5)	67 (0.7)	186 (0.9)	573 (0.6)
Thrombophilia	266 (0.4)	68 (0.7)	120 (0.6)	454 (0.5)
Varicose disease	1,838 (3.1)	350 (3.8)	1,166 (5.4)	3,354 (3.7)
Heart failure	345 (0.6)	53 (0.6)	158 (0.7)	556 (0.6)
Chronic obstructive lung disease	720 (1.2)	136 (1.5)	337 (1.6)	1,193

Venous thromboembolism after hysterectomy

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				(1.3)
				1,540
Previous VTE	1,026 (1.7)	182 (2.0)	332 (1.5)	(1.7)
				N=53,56
<b>Postoperative VTE prophylaxis<sup>‡</sup></b>	<b>N=30,171</b>	<b>N=7,032</b>	<b>N=16,363</b>	<b>6</b>
				22,175
No prophylaxis	13,755 (45.6)	2,797 (39.8)	5,623 (34.4)	(41.4)
				31,391
VTE prophylaxis	16,416 (54.4)	4,235 (60.2)	10,740 (65.6)	(58.6)

\* Data are expressed as N (column %), mean  $\pm$  SD.

<sup>†</sup>There could be more than one indication for hysterectomy.

<sup>‡</sup> Only registered in patients undergoing surgery after 2003.

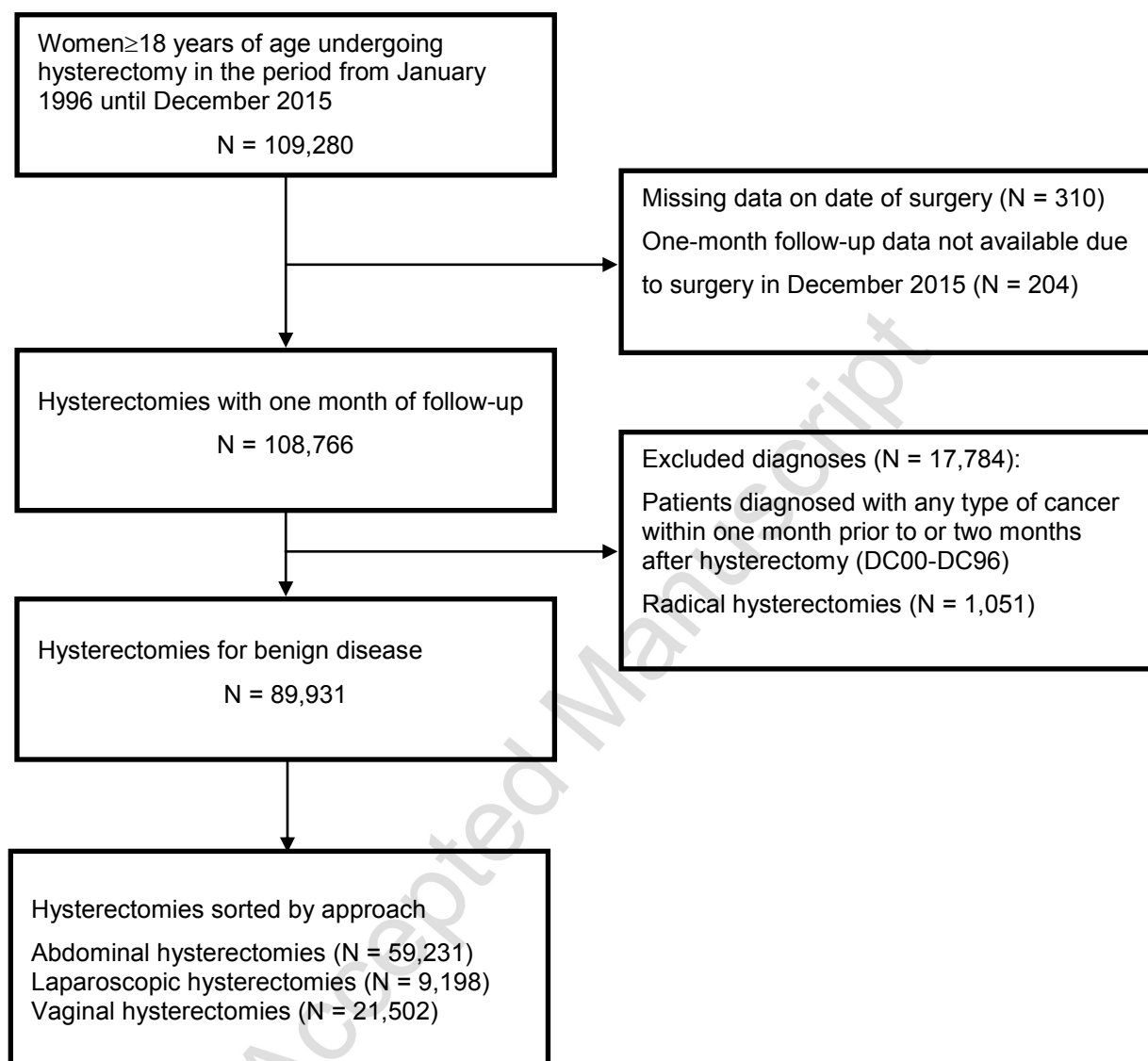
**Table 2. Unadjusted hazard ratios (HRs) of venous thromboembolism (VTE) in different exposure groups**

	VTE events/N total	HR	95 % CI	P value
Age (by decade)	175/89,931	1.16	1.02-1.31	.019
Age<60 years	129/72,847	1.0 (reference)		
Age≥60 years	46/17,084	1.53	1.09-2.14	.013
Length of stay (LOS), days*	175/89,577	1.09	1.05-1.13	<.001
Abdominal hysterectomy	142/59,231	1.0 (reference)		
Laparoscopic hysterectomy	12/9,198	0.54	0.30-0.98	.042
Vaginal hysterectomy	21/21,502	0.41	0.26-0.64	<.001
Previous VTE	67/1,540	36.7	27.1-49.8	<.001
Previous acute myocardial infarction	6/573	5.7	2.5-12.8	<.001
Benign ovarian neoplasm	11/5,391	1.05	0.57-1.94	.867
Uterine fibroids	76/43,051	0.83	0.62-1.13	.834
Abnormal uterine bleeding	55/33,318	0.78	0.56-1.07	.117
Hormone therapy	24/12,931	0.95	0.62-1.46	.804
Contraceptives	13/6,596	1.01	0.58-1.78	.965
Anticoagulant drugs	31/918	21.5	14.6-31.7	<.001
<b>Surgery after 2003</b>				
After implementation of VTE prophylaxis	105/53,566	1.02	0.75-1.38	.907
VTE prophylaxis registered	43/31,391	0.49	0.33-0.72	<.001

\*354 patients with missing data on LOS or LOS exceeding follow-up time of 30 days were excluded from the analysis. There were no cases of VTE within this group.

467 Figure 1.

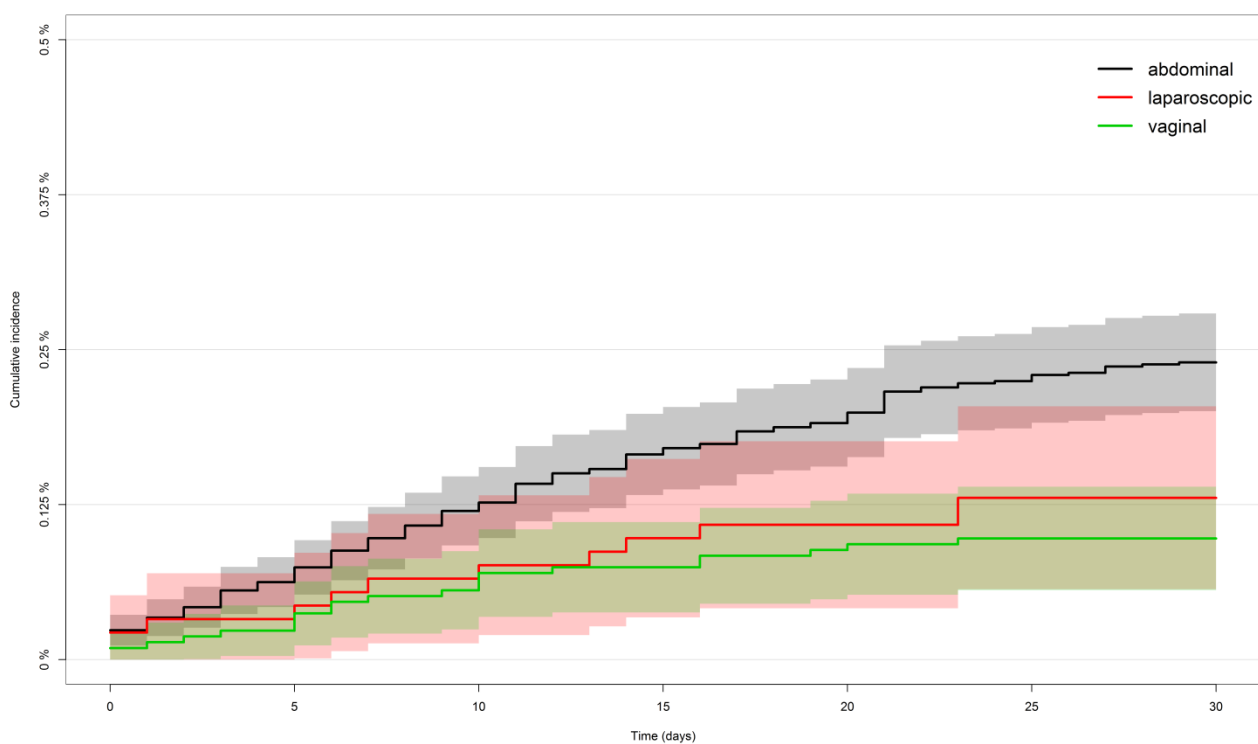
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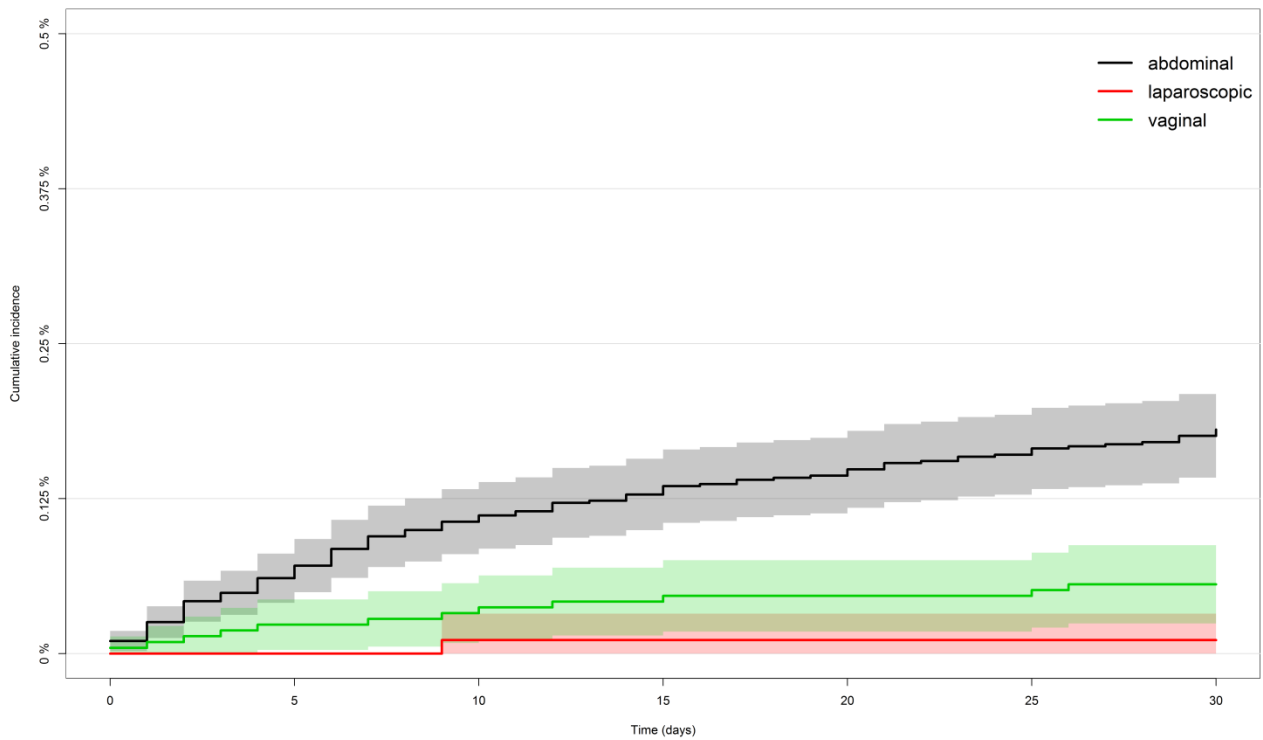


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