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# Pre- vs. postoperative initiation of thromboprophylaxis in liver surgery

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## Abstract

**Background:** Thromboprophylaxis protocols in liver surgery vary greatly worldwide. Due to limited research, there is no consensus whether the administration of thromboprophylaxis should be initiated pre- or postoperatively.

**Methods:** Patients undergoing liver resection in Helsinki University Hospital between 2014 and 2017 were reviewed retrospectively. Initiation of thromboprophylaxis was changed in the institution in the beginning of 2016 from postoperative to preoperative. Patients were classified into two groups for analyses: thromboprophylaxis initiated preoperatively (Preop-group) or postoperatively (Postop-group). The incidences of VTE and haemorrhage within 30 days of surgery were compared between these groups. Patients with permanent anticoagulation were excluded.

**Results:** A total of 512 patients were included to the study (Preop, n = 253, Postop, n = 259). The incidence of VTE was significantly lower in the Preop-group compared to the Postop-group (3 (1.2%) vs. 25 (9.7%), $P = <.0001$), mainly due to a lower incidence of pulmonary embolisms in the Preop-group (3 (1.2%) vs. 24 (9.3%), $P < .0001$). The rates of posthepatectomy haemorrhage within 30 days of surgery were similar (Preop 38 (15.0%) vs. Postop 36 (13.9%), p = .719).

**Conclusion:** Initiating thromboprophylaxis preoperatively may reduce the incidence of postoperative VTE without affecting the incidence of posthepatectomy haemorrhage in patients undergoing liver resection.

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## Introduction

Liver resection is a relatively common procedure for primary and metastatic liver tumours. Liver surgery is associated with a simultaneous risk of venous thromboembolism (VTE) and haemorrhage. VTE is a major potentially preventable cause of prolonged hospitalization, morbidity, and even mortality of patients undergoing liver resection. Thromboprophylaxis is the primary mean to mitigate the risk of VTE, but it may increase the risk of postoperative bleeding.[1] The timing of thromboprophylaxis could influence the risk balance between thrombosis and bleeding.[2]

Although international guidelines widely recommend thromboprophylaxis in liver surgery, there is no consensus when the administration of thromboprophylaxis should be started, because of limited data.[3,4] Notably, Dutch guidelines recommend postoperative thromboprophylaxis, and in many centres thromboprophylaxis is administered only postoperatively.[3,5] However, some centres initiate thromboprophylaxis preoperatively.[4,6] Intuitively, starting thromboprophylaxis preoperatively might reduce the incidence of VTE, but could increase the risk of haemorrhage. However, this remains to be proven. Because of lack of evidence, there is considerable variation regarding thromboprophylaxis among liver surgeons, even inside the same institution.[6]

This study was presented at the 13th congress of the European–African Hepato-Pancreato-Biliary Association (E-AHPBA), 05/June/2019, Amsterdam.

 

In our institution, patients undergoing liver resection received thromboprophylaxis only postoperatively before 2016. In January 2016, the protocol was changed to include additional preoperative prophylaxis. The aim of this study is to examine how preoperatively initiated administration of thromboprophylaxis affects the incidence of posthepatectomy VTE and haemorrhage by comparing the incidences of thromboembolic and bleeding complications before and after the change of protocol.

## Methods

### Study design, patients and data collection

Electronic patient records of patients undergoing liver resection in Helsinki University Hospital during January 2014 to December 2017 were reviewed retrospectively. Patients undergoing liver resection were identified from an electronic operating theatre database (Centricity Opera, GE Healthcare, Chicago, United States) using liver resection -specific Nordic Medico-Statistical Committee (NOMESCO) Classification of Surgical Procedures -operation codes (JJB00 – 96). Emergency operations and patients on anticoagulation medication (warfarin, low-molecular-weight heparin (LMWH), or novel oral anticoagulant) were excluded. Demographic, operative, and postoperative data and tumour characteristics were collected from electronic patient records (Uranus Miranda Desktop, CGI Suomi, Helsinki, Finland). Anaesthesiologic details were collected from an electronic perioperative and intensive care database (Critical Care Manager, CareSuite, Picis Inc., Wakefield, United States). The institutional review board of Helsinki University Hospital approved the study.

### Study groups and procedures

Patients were classified into two groups for analyses: patients receiving postoperative (the Postop-group) or pre- and postoperative (i.e. preoperative initiation of) thromboprophylaxis (the Preop-group). The Postop-group consisted mainly of patients from years 2014–2015 (before protocol change), whereas the patients in the Preop-group were mainly from years 2016–2017 (after protocol change). The Preop-group was instructed to receive a single 40 mg enoxaparin injection given subcutaneously the evening before surgery between 7:00 and 9:00 p.m. Most patients were instructed to self-administer the preoperative LMWH at home, while a minority of patients (e.g. patients who live far away from the hospital) were admitted to the hospital the evening before the operation, and the LMWH was administered at the hospital. Both groups received the first postoperative dose of 20–80 mg of enoxaparin (depending on patient's weight) 4–6 h after surgery, and thereafter once daily between 6:00 and 8:00 p.m. Enoxaparin was continued for 3 weeks after discharge in both groups. Other LMWH drugs (tinzaparin, dalteparin) were used instead of enoxaparin when clinically needed, but enoxaparin was the preferred LMWH. The dose and LMWH given were recorded.

All patients were treated according to our Enhanced Recovery Protocol, and no changes in the operative techniques or perioperative care protocols were made during the study period.[7] According to the practice of the centre, all the liver resections were performed without Pringle's manoeuvre and liver dissections were performed using ultrasound devices. Compression stockings were used with all patients. The anaesthesia group was in agreement with the timing and dosage of the preoperative thromboprophylaxis, and the preoperative administration of chemoprophylaxis did not limit the use of neuraxial (epidural, spinal) anaesthesia.

### Outcomes

VTE was defined as a postoperative pulmonary embolism (PE), deep vein thrombosis (DVT), or portal vein/mesenteric venous thrombosis. All PEs and portal vein/mesenteric venous thromboses were diagnosed using CT, and DVTs with ultrasonography. Diagnostic imaging tests were ordered in cases of clinical suspicion, and no routine screening for asymptomatic VTE took place. Scanning protocols for VTE remained the same during the entire study period. Lower extremity ultrasound to diagnose DVT in patients diagnosed with PE was not routinely performed. Posthepatectomy haemorrhage was classified using the International Study Group of Liver Surgery (ISGLS) definition.[8] Grade A is defined as a postoperative haemorrhage requiring up to 2 units of packed red blood cells (PRBC), grade B as requiring more than 2 units of PRBC, and grade C as requiring an invasive intervention (angioradiologic or surgical). In this study, grade B and C haemorrhages were considered clinically significant.

The primary outcome was the incidence of VTE within 30 days of surgery. As no routine screening for VTE was implemented, primary outcome consists of mostly symptomatic VTE.

Secondary outcomes included VTE within 6 months, posthepatectomy haemorrhage (within 30 days and 6 months), postoperative complications (Clavien-Dindo classification, within 30 days), length of hospital stay (LOS), 30- and 90-day mortality, posthepatectomy liver failure (ISGLS-classification, within 30 days), bile leak (ISGLS classification, within 30 days), and epidural complications (within 30 days).[9–11]

### Statistical analyses

Continuous variables with normal distribution are presented as mean (SD) and compared using two-tailed t-test. Continuous variables with non-normal distribution are presented as median (IQR) and compared using Mann–Whitney U test. Categorical variables are presented as absolute numbers (percentage) and compared using $\chi^2$ or Fischer exact tests. Adjusted analyses were performed using logistic regression multivariable analysis using primary outcome (any VTE) as the outcome variable and reported as an odds ratio with 95% confidence intervals. Two-tailed $p$-values under 0.05 were considered statistically significant. Statistical analyses were performed using SPSS (version 24) software (IBM, Armonk, NY).

 

## Results

A total of 613 patients underwent liver resection between 2014 and 2017. One hundred one patients were excluded from analyses, leaving 512 patients in the final study cohort (259 patients in the Postop-group and 253 in the Preop-group) (Fig. 1). Basic demographics (e.g. age, sex, body mass index, comorbidities, liver disease, previous venous thromboembolisms, antithrombotic medications, and extent of malignancy) were similar between the Postop- and Preop-groups, except that in the Preop-group there were more patients with Child-Pugh class A cirrhosis and more patients with lung and liver metastases only (Table 1). Tumour characteristics (e.g. type, number, and size of tumours) and earlier treatments were similar between the Postop- and Preop-groups (Table 2). Operative details (such as operative time, rate of major resection, and rate of extrahepatic biliary resection) were similar between the two groups, except that laparoscopic hepatectomy was more common and operation duration was shorter in the Preop-group (Table 3). Anaesthesiologic details (e.g. ASA-class, intraoperative fluid balance and intraoperative bleeding and transfusions) were similar between the Postop- and Preop-groups, except for ASA class, use of epidural anaesthesia, perioperative IV fluids and albumin (Table 3). There were more ASA class 3 patients in the Postop-group and more ASA class 2 patients in the Preop-group. Epidural anaesthesia was used more in the Preop-group, and patients in the Preop-group received less IV fluids and more albumin perioperatively.

Enoxaparin was used in 256 patients (98.5%) in the Postop-group and in 253 patients (98.4%) in the Preop-group ($P = 0.875$). Dalteparin was used in two and one patients, and tinzaparin in one and three patients in the Preop- and Postop-groups, respectively. Two patients (0.8%) from years 2014–2015 received preoperative thromboprophylaxis and are included in the Preop-group. Fifteen patients (5.6%) from years 2016–2017 received only postoperative prophylaxis and are included in the Postop-group. Two hundred and forty-three patients (95%) in the Preop-group received 40 mg of enoxaparin preoperatively as per protocol. Nine patients (3.5%) in the Preop-group received 20 mg of enoxaparin preoperatively, one (0.4%) received 60 mg of enoxaparin, two (0.8%) received 2500 IU of dalteparin, and one (0.4%) received 3500 IU of tinzaparin preoperatively.

The primary outcome, VTE within 30 days, occurred in 3 (1.2%) patients in the Preop-group and in 25 (9.7%) patients in the Postop-group (OR 0.1123 (95% CI 0.0335–0.3769), $P < .0001$) (Table 4). The lower rate of VTE within 30 days in the

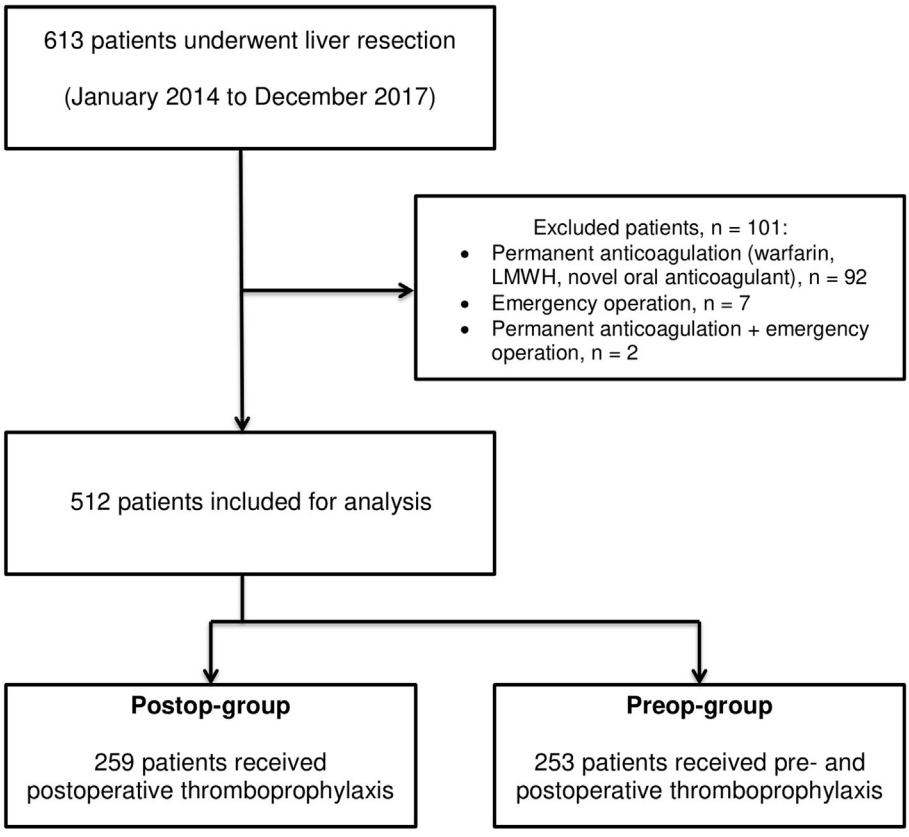


**Figure 1** Study population. LMWH – low-molecular-weight heparin

 

**Table 1** Basic demographics

| | Postop ($n$ = 259) | Preop ($n$ = 253) | $P$-value |
|---|---|---|---|
| Age - mean (SD), years | 63.2 (13.1) | 62.9 (12.8) | .8425 |
| Female sex - No. (%) | 105 (40.5) | 121 (47.8) | .0969 |
| BMI - mean (SD) | 26.1 (4.58) | 26.3 (5.12) | .6140 |
| Charlson Comorbidity Index - mean (SD) | 6.79 (2.70) | 6.85 (2.65) | .8058 |
| MELD score - mean (SD) | 7.5 (3.87) | 7.2 (1.99) | .1934 |
| Child-Pugh class - No. (%) | | | |
| A (5–6 points) | 3 (1.2%) | 12 (4.7%) | **.0162** |
| B (7–9 points) | 0 | 1 (0.4%) | .4941 |
| C (>10 points) | 0 | 0 | 1.000 |
| No cirrhosis | 256 (99.0%) | 240 (94.9%) | **.0097** |
| Earlier liver resection - No. (%) | | | |
| 1 | 22 (8.5%) | 23 (9.1%) | .8116 |
| 2 | 5 (1.9%) | 2 (0.8%) | .4501 |
| 3 | 0 | 1 (0.4%) | .4941 |
| Earlier VTE - No. (%) | | | |
| DVT without PE | 8 (3.1%) | 4 (1.6%) | .2595 |
| PE without DVT | 4 (1.5%) | 4 (1.6%) | 1.0000 |
| DVT + PE | 0 | 1 (0.4%) | .4941 |
| MVT/PVT | 1 (0.4%) | 0 | .5059 |
| Antithrombotic medication - No. (%) | | | |
| ASA | 32 (12.4%) | 42 (16.6%) | .1720 |
| Clopidogrel | 2 (0.8%) | 1 (0.4%) | .5088 |
| Ticagrelor | 1 (0.4%) | 1 (0.4%) | .7446 |
| Dipyridamole | 1 (0.4%) | 2 (0.8%) | .6200 |
| Extent of malignancy - No. (%) | | | |
| No malignancy | 32 (12.4%) | 32 (12.6%) | .9202 |
| Only liver primary | 41 (15.8%) | 44 (17.4%) | .6350 |
| Only liver metastases | 138 (53.3%) | 145 (57.3%) | .3591 |
| Primary + liver metastases | 14 (5.4%) | 6 (2.4%) | .0765 |
| Primary + liver + lung metastases | 4 (1.5%) | 2 (0.8%) | .6858 |
| Liver and lung metastases only | 21 (8.1%) | 10 (4.0%) | **.0487** |
| Other | 9 (3.5%) | 14 (5.5%) | .2608 |
| Comorbidities - No. (%) | | | |
| Myocardial infarction | 9 (3.5%) | 4 (1.6%) | .1732 |
| Congestive heart disease | 0 | 4 (1.6%) | .0589 |
| Coronary disease (no infarction) | 11 (%) | 13 (5.1%) | .6334 |
| Atrial fibrillation | 3 (1.2%) | 6 (2.4%) | .3343 |
| Peripheral vascular disease | 5 (1.9%) | 8 (3.2%) | .3758 |
| CVA or TIA | 7 (2.7%) | 11 (4.3%) | .3122 |
| Hemiplegia | 2 (0.8%) | 0 | .4991 |
| Dementia | 2 (0.8%) | 1 (0.4%) | .5088 |
| COPD | 4 (1.5%) | 7 (2.8%) | .3402 |
| Connective tissue disease | 4 (1.5%) | 5 (2.0%) | .7491 |
| Liver disease | | | |
| Mild | 1 (0.4%) | 10 (4.0%) | .0054 |

(*continued on next page*)

 

**Table 1** (*continued*)

| | Postop ($n$ = 259) | Preop ($n$ = 253) | $P$-value |
|---|---|---|---|
| Moderate/severe | 2 (0.8%) | 3 (1.2%) | .6827 |
| Peptic ulcer disease | 4 (1.5%) | 2 (0.8%) | .6858 |
| Diabetes mellitus | | | |
| Type 1 | 2 (0.8%) | 3 (1.2%) | .6827 |
| Type 2, tablet-treated | 25 (97%) | 24 (9.5%) | .9490 |
| Type 2, insulin-treated | 12 (4.6%) | 7 (2.8%) | .2640 |
| Uncomplicated | 39 (15.0%) | 31 (12.3%) | .3557 |
| End-organ damage | 0 | 3 (1.2%) | .1199 |
| Chronic kidney disease (moderate/severe) | 4 (1.5%) | 5 (2.0%) | .7491 |
| Malignancy | | | |
| Local | 62 (23.9%) | 58 (22.9%) | .7867 |
| Metastatic | 172 (66.4%) | 171 (67.6%) | .7767 |
| Leukemia | 0 | 1 (0.4%) | .4941 |
| Lymphoma | 4 (1.5%) | 2 (0.8%) | .4281 |
| AIDS | 0 | 0 | 1.000 |
| No comorbidity | 18 (6.9%) | 20 (7.9%) | .6801 |

Abbreviations: MELD – model for end-stage liver disease; VTE – venous thromboembolism; DVT – deep vein thrombosis; PE – pulmonary embolism; MVT – mesenteric venous thrombosis; PVT – portal vein thrombosis.
Bold means $p$ <0.05.

**Table 2** Tumour characteristics

| | Postop ($n$ = 259) | Preop ($n$ = 253) | $P$-value |
|---|---|---|---|
| Tumour type - No. (%) | | | |
| CRLM | 144 (55.7%) | 141 (55.7%) | .9759 |
| CCA | 18 (6.9%) | 29 (11.5%) | .0770 |
| HCC | 25 (9.7%) | 21 (8.3%) | .5927 |
| NET metastasis | 8 (3.1%) | 8 (3.2%) | .9620 |
| Other malignant | 29 (11.2%) | 22 (8.7%) | .3447 |
| Hepatocellular adenoma | 8 (3.1%) | 5 (2.0%) | .4237 |
| Other benign[a] | 27 (10.4%) | 27 (10.7%) | .9274 |
| Number of tumours - median (range) | 1 (0–9) | 1 (0–14) | .5022 |
| Size of (biggest) tumour - mm, mean (SD) | 31.6 (31.5) | 28.9 (32.4) | .3557 |
| Chemotherapy prior to surgery - No. (%) | 148 (57.1%) | 132 (52.2%) | .2796 |
| Earlier TACE - No. (%) | 5 (1.9%) | 4 (1.6%) | 1.0000 |
| Earlier RFA - No. (%) | 2 (0.8%) | 5 (2.0%) | .2805 |
| Earlier portal vein embolization - No. (%) | | | |
| Angioradiologic | 3 (1.2%) | 7 (2.8%) | .2172 |
| Ligated during earlier operation | 2 (0.8%%) | 1 (0.4%) | 1.0000 |
| Earlier liver radiation therapy - No. (%) | 1 (0.4%) | 0 | 1.0000 |

Abbreviations: CRLM – colorectal carcinoma liver metastasis; CCA – cholangiocarcinoma; HCC – hepatocellular carcinoma; NET – neuroendocrine tumour; TACE – trans-arterial chemoembolization; RFA – radiofrequency ablation.
[a] Other benign lesions include (Postop, Preop): focal nodular hyperplasia (2, 4), cyst (4, 1), haemangioma (3, 0), cystadenoma (2, 2), primary sclerosing cholangitis (1, 1), cystic neoplasia (0, 2), granulocellular tumour (0, 1), hamartoma (0, 1), dysplastic nodulus (1, 1), ciliated hepatic foregut cyst (0, 1), epithelioid angiomyolipoma (1, 1), IPN (2, 1), echinococcosis (2, 2), fibrosis (1, 0), steatosis (0, 1), suspicion of gallbladder cancer with concurrent gallbladder bed resection, no malignancy in resecate (4, 4), hepatic abscess (1, 0), lymphatic infiltrate/foreign body reaction (0, 1), reoperation due to suspicion of residive, but no residive in resecate (1 CRLM suspect, 1 HCC suspect), cholangitis (0, 1), suspicion of CCA, dysplasia levis of the biliary tract (1, 0), suspicion of CCA, dysplasia gravis of the biliary tract (0, 1), secondary sclerosing cholangitis due to cholecystolithiasis (1, 0).

 

**Table 3** Operative and anaesthesiologic details

| | Postop ($n$ = 259) | Preop ($n$ = 253) | $P$-value |
|---|---|---|---|
| Length of operation - mean (SD), min | 226 (90) | 206 (95) | **.0198** |
| Hemihepatectomy/resection of ≥3 segments - No. (%) | 89 (34.4%) | 95 (37.5%) | .4525 |
| Operational approach - No. (%) | | | |
| Laparoscopy | 25 (9.7%) | 59 (23.3%) | <**.0001**[a] |
| Laparotomy | 227 (87.6%) | 182 (71.9%) | |
| Laparoscopy converted to laparotomy | 7 (2.7%) | 12 (4.7%) | |
| Extrahepatic biliary tract resection - No. (%) | 10 (3.9%) | 10 (4.0%) | .9642 |
| Hepatic artery resection and reconstruction - No. (%) | 0 | 1 (0.4%) | .4951 |
| Portal vein resection and reconstruction - No. (%) | 1 (0.4%) | 3 (1.2%) | .3687 |
| Hepaticojejunostomy - No. (%) | | | |
| x 1 | 4 (1.5%) | 7 (2.8%) | .3434 |
| x 2 | 7 (2.7%) | 6 (2.4%) | .8064 |
| Epidural anaesthesia - No. (%) | 64[b] (24.7%) | 84 (32.8%) | **.0341** |
| ASA class - No. (%) | | | |
| 1 | 14 (5.4%) | 13 (5.1%) | .1292 |
| 2 | 76 (29.3%) | 95 (37.5%) | |
| 3 | 160 (61.8%) | 131 (51.8%) | |
| 4 | 9 (3.5%) | 14 (5.5%) | |
| Mean CVP during operation - mean (SD) | 4.3 (2.70) | 4.1 (2.16) | .5413 |
| IV fluids given during operation - mean (SD), ml | 2229 (1092) | 2037 (937) | **.0333** |
| Albumin given during operation - mean (SD), mg | 12.15 (21.5) | 18.68 (27.1) | **.0027** |
| Intraoperative bleeding - mean (SD), ml | 749 (1079) | 633 (777) | .1643 |
| Intraoperative red blood cell transfusions | | | .7582 |
| No. of receiving patients | 25 (9.7%) | 23 (9.1%) | |
| Units per receiving patient, median (IQR) | 2 (1–4) | 1 (1–3) | |

Bold means $p$ <0.05.
[a] $P$-value was calculated using per protocol analysis: laparoscopy converted to laparotomy = laparotomy.
[b] Included 1 spinal anaesthesia.

Preop-group was mostly due to a significantly lower incidence of pulmonary embolism in the Preop-group (3 (1.2%) vs. 24 (9.3%), respectively, $P$ < .0001) (Table 4). One patient in both the Postop- and Preop-groups had an asymptomatic, incidentally diagnosed pulmonary embolism, which were included in the primary outcome (Table 4). Excluding these asymptomatic patients from analyses did not affect the significance of the primary outcome ($P$ < .0001). All other patients who had a pulmonary embolism were symptomatic (i.e. dyspnoea and $SpO_2$ < 85–90). Most pulmonary embolisms were diagnosed before discharge (3 out of 5 in the Preop-group and 20 out of 30 in the Postop-group). Posthepatectomy haemorrhage was detected in 38 patients (15.0%) in the Preop-group and 36 patients (13.9%) in the Postop-group ($P$ = 0.7186). Grade B/C haemorrhage was seen in 7 (2.8%) and 8 (3.5%) patients ($P$ = 0.651) (Table 4). Overall complications, clinically significant complications (Clavien-Dindo grade 2 or over), and major complications (Clavien-Dindo grade 3 or over) occurred similarly in both groups (Table 4). The rates of posthepatectomy liver failure and bile leakage were similar in both groups (Table 4). There were no epidural complications in either of the two groups. The median length of stay was clinically similar in both groups, although statistically significantly shorter in the Preop-group (Table 4). Thirty and 90-day mortalities were similar in both groups (Table 4).

The four deaths were not associated with VTE or haemorrhage. One patient died of myocardial infarction in the Postop-group, and a CT pulmonary angiography taken on the 1st postoperative day did not show signs of pulmonary embolism. Three patients died in the Preop-group, two due to pneumonia and one due to peritonitis caused by colon perforation. A CT pulmonary angiography was taken of the two patients who died of pneumonia, and no signs of pulmonary embolism were found.

Sensitivity analysis by excluding patients receiving antithrombotic medication (ASA, clopidogrel, ticagrelor or dipyridamole; 42 in the Preop-group and 32 in the Postop-group) did

 

**Table 4** Primary and secondary outcomes

| | Postop ($n$ = 259) | Preop ($n$ = 253) | $P$-value |
|---|---|---|---|
| **Primary outcome** | | | |
| VTE, any, within 30 days from operation - No. (%) | 25[a] (9.7%) | 3 (1.2%) | **<.0001** |
| **Secondary outcomes** | | | |
| VTE, any, within 6 months from operation - No. (%) | 33 (12.7%) | 12 (4.7%) | **.0014** |
| DVT - No. (%) | | | |
| Within 30 days from operation | 1 (0.4%) | 0 | .5059 |
| Within 6 months from operation | 2 (0.8%) | 2 (0.8%) | .6794 |
| PE - No. (%) | | | |
| Within 30 days from operation | 24 (9.3%) | 3 (1.2%) | **<.0001** |
| Within 6 months from operation | 30 (11.6%) | 5 (2.0%) | **<.0001** |
| Portal vein/mesenteric venous thrombosis - No. (%) | | | |
| Within 30 days from operation | 1 (0.4%) | 0 | .5059 |
| Within 6 months from operation | 3 (1.2%) | 5 (2.0%) | .3494 |
| Posthepatectomy haemorrhage - ISGLS grade, No. (%) | | | |
| Any | 36 (13.9%) | 38 (15.0%) | .7186 |
| A | 28 (10.8%) | 31 (12.3%) | .6094 |
| B | 8 (3.1%) | 3 (1.2%) | .1376 |
| C | 0 | 4 (1.6%) | .0589 |
| Clavien-Dindo classification - grade, No. (%) | | | |
| Any | 82 (31.7%) | 80 (31.6%) | .9834 |
| 2 or over | 72 (27.8%) | 59 (23.3%) | .2562 |
| 3 or over | 19 (7.3%) | 18 (7.1%) | .9329 |
| Length of stay - median (IQR) | 6 (5–7) | 6 (5–7) | **.0308** |
| 30-day mortality - No. (%) | 0 | 0 | 1.0000 |
| 90-day mortality - No. (%) | 1 (0.4%) | 3 (1.2%) | .4912 |
| Posthepatectomy liver failure - ISGLS grade, No. (%) | | | |
| A | 7 (2.7%) | 4 (1.6%) | .3815 |
| B | 4 (1.5%) | 2 (0.8%) | .6858 |
| C | 1 (0.4%) | 0 | 1.0000 |
| Bile leakage - ISGLS grade, No. (%) | | | |
| A | 3 (1.2%) | 0 | .2486 |
| B | 4 (1.5%) | 4 (1.6%) | 1.0000 |
| C | 2 (0.8%) | 1 (0.4%) | 1.0000 |
| Epidural complication - No. | 0 | 0 | 1.0000 |

Abbreviations: VTE – venous thromboembolism; DVT – deep vein thrombosis; PE – pulmonary embolism.
Bold means $p$ <0.05.
[a] One patient in the Postop-group had both a DVT and a PE within 30 days of surgery.

not affect the significance of the primary outcome (3 (1.5%) patients in the Preop-group vs. 24 (10.6%) patients the Postop-group; $P$ = .0001). Excluding all laparoscopically operated patients (59 in the Preop-group and 25 in the Postop-group) did not affect the significance of the primary outcome either (3 (1.5%) patients in the Preop-group vs. 25 (10.7%) patients the Postop-group; $P$ = .0001).

In multivariable analysis, preoperative initiation of thromboprophylaxis remained associated with a reduction in the rate of primary outcome (any VTE) (OR 0.0950 (95% CI 0.0217–0.4165), $P$ = .0018) when adjusted for age, extent of liver resection (major vs. minor), approach (laparotomy vs. laparoscopy), body mass index, sex, history of VTE, Charlson comorbidity index, tumour type (malign vs. benign), model for end-

stage liver disease (MELD) score, ASA class and duration of surgery (Supplementary Table).

## Discussion

In this retrospective analysis of consecutive patients undergoing liver resection in two eras of different strategies for thromboprophylaxis, we found significant reduction in VTE rates, and especially in pulmonary embolisms, in patients with preoperatively initiated thromboprophylaxis compared to patients with postoperative thromboprophylaxis. Sensitivity analyses or adjusted analyses for potential confounders did not change this finding. Notably, we did not find elevated risk of intra- or postoperative bleeding in patients with preoperatively initiated thromboprophylaxis.

At the moment, the ideal timing of thromboprophylaxis in liver surgery has been scarcely investigated. The international guidelines recommend pharmacological thromboprophylaxis but are unable to recommend the timing of its commencement due to lack of evidence.[1,2]

Because of unique, liver-related haemostatic changes, thromboprophylaxis in liver surgery is not readily comparable to that of other major oncological (abdominal) surgery. Liver resection results in a biochemical phenotype (thrombocytopenia, prolonged prothrombin time), which normally would appear to increase susceptibility to bleeding. However, viscoelastic tests and thrombin generation parameters reveal that, following liver resection, patients actually are in a hypercoagulable state, which deepens with the extent of resection.[12,13] Historically, because of this belief of elevated bleeding risk, thromboprophylaxis has been withheld with patients who underwent liver resection.[14,15] Large published series have, however, revealed that postoperative VTE risk appears to outweigh the risk of haemorrhage.[14,15] It has therefore been suggested that thromboprophylaxis should be augmented in liver surgery. One way of augmenting thromboprophylaxis is to initiate it preoperatively.

Some earlier studies have tried to assess the timing of thromboprophylaxis in liver surgery. Melloul et al. assessed the effect of preoperative prophylaxis on the incidence of pulmonary embolism, but the study didn't include a control group with postoperative prophylaxis.[16] Doughtie et al. compared the incidence of VTE and haemorrhage between patients receiving preoperative and postoperative prophylaxis in hepato-pancreatico-biliary (HPB) surgery.[4] In this study, preoperative prophylaxis reduced the incidence of VTE, but increased the incidence of postoperative bleeding requiring intervention. This retrospective analysis, however, included patients undergoing other HPB operations (e.g. pancreaticoduodenectomy) in addition to liver resections, and the results of liver resections were not separately analysed, limiting the interpretation of the results. A recent meta-analysis reported the efficacy and safety of thromboprophylaxis in liver surgery.[17] Five retrospective studies were included in the analyses, and of these studies only one had patients in whom thromboprophylaxis was commenced preoperatively. In this study Ejaz et al. analysed risk factors for postoperative VTE on a retrospective cohort in patients undergoing liver resection during 1990–2012, but did not identify preoperative initiation of thromboprophylaxis as a factor.[18] However, the reason why some patients had received preoperatively administered thromboprophylaxis was unknown and could introduce a significant bias in the results.

Our study has its limitations. The study was a single centre retrospective study with inherent limitations. In addition, the two patient groups (the Pre- and the Postop-group) were from two separate periods of time: the Postop-group from years 2014–2015 and the Preop-group from years 2016–2017. Although no other changes were made in the care protocol during the study period (except for the change in the thromboprophylaxis), there might be some other unknown improvements in patient care that might be a source of bias. The incidence of postoperative VTE in the Postop-group was 9.7%, which is higher compared to other published reports.[17–19] In other reports, the incidence ranges from 2.6% to 4.7%, which is still higher than in the Preop-group in our study. Although there were two asymptomatic VTE in our cohort, it is likely that some asymptomatic VTE were not diagnosed since no routine screening for VTE took place. The exclusion of the asymptomatic VTE did not affect the significance of the primary outcome. On the other hand, this study has several strengths. The study cohort is relatively large. The study is comparing patients in two different eras and is thus less prone to patient selection bias (i.e. the thromboprophylaxis protocol was applied in a standardized fashion and not tailored individually per patient or surgeon). This led to highly similar patient cohorts in both groups. Furthermore, we tried to minimize the potential known confounders by sensitivity and adjusted analyses, which did not change our findings.

Even though our results present the best current evidence on the timing of thromboprophylaxis in liver surgery, considering the retrospective nature of the study, the results should be confirmed in a randomized controlled study.

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### Conflicts of interest

None to declared.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.hpb.2020.10.018.

 