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JOHNS HOPKINS MEDICINE

Effect of Pharmacologic Prophylaxis on Venous Thromboembolism after Radical Prostatectomy:

The PREVENTER Randomized Clinical Trial

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Disclosures

- None

Background

- 192,000 cases of prostate cancer in 2020
  - 50% of low- and intermediate-risk men receive radical prostatectomy (RP)
- Post-surgical venous thromboembolism (VTE)
  - Death, recurrent VTE, venous stasis syndrome, venous ulcer, chronic thromboembolic pulmonary hypertension
  - Early ambulation, intermittent pneumatic compression devices (IPCs), pharmacologic prophylaxis (PP)
- Most guidelines: RP by any approach classifies a patient as high-risk
  - ACCP, NICE, NCCN Guidelines for Cancer-Associated VTE Disease
  - Caprini risk score ≥5

Violette PD, Cartwright R, Briel M, Tikkinen KA, Guyatt GH. Guideline of guidelines: thromboprophylaxis for urological surgery. BJU Int. 2016 Sep;118(3):351-8.
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Gould MK, Garcia DA, Wren SM, et al. Prevention of VTE in nonorthopedic surgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Feb;141(2 Suppl):e227S-e277S.

ACCP Guidelines by VTE Risk

- Very low (< 0.5%): **early ambulation**
- Low (~1.5%): **mechanical** prophylaxis with IPCs
- Moderate (~3%): **heparin (HSQ or LMWH) or mechanical** prophylaxis
- High (~6%): **heparin (HSQ or LMWH) plus mechanical** prophylaxis
- High & for cancer: **extended-duration LMWH** (4 weeks)

Gould MK, Garcia DA, Wren SM, et al. Prevention of VTE in nonorthopedic surgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Feb;141(2 Suppl):e227S-e277S.

Where does RP fit in?

- Lack of VTE data with symptom assessment, reporting of prophylaxis used, and consistent follow-up
- No high quality RCTs for RP or minimally-invasive abdominopelvic surgery of any kind (for in-hospital prevention)
- No accepted standard practice for VTE prophylaxis after RP
  - 98% receive PP in the UK (61% post-discharge) vs. 17.8% in US (30% none)
- Rate of symptomatic VTE
  - Without PP: estimated to be 4-6% based on validated Caprini risk score
  - With PP: estimated to be 1-2% with greater risk with PLND or open approach

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Pannucci CJ, Swistun L, MacDonald JK, Henke PK, Brooke BS. Individualized Venous Thromboembolism Risk Stratification Using the 2005 Caprini Score to Identify the Benefits and Harms of Chemoprophylaxis in Surgical Patients: A Meta-analysis. Ann Surg. 2017 Jun;265(6):1094-1103.
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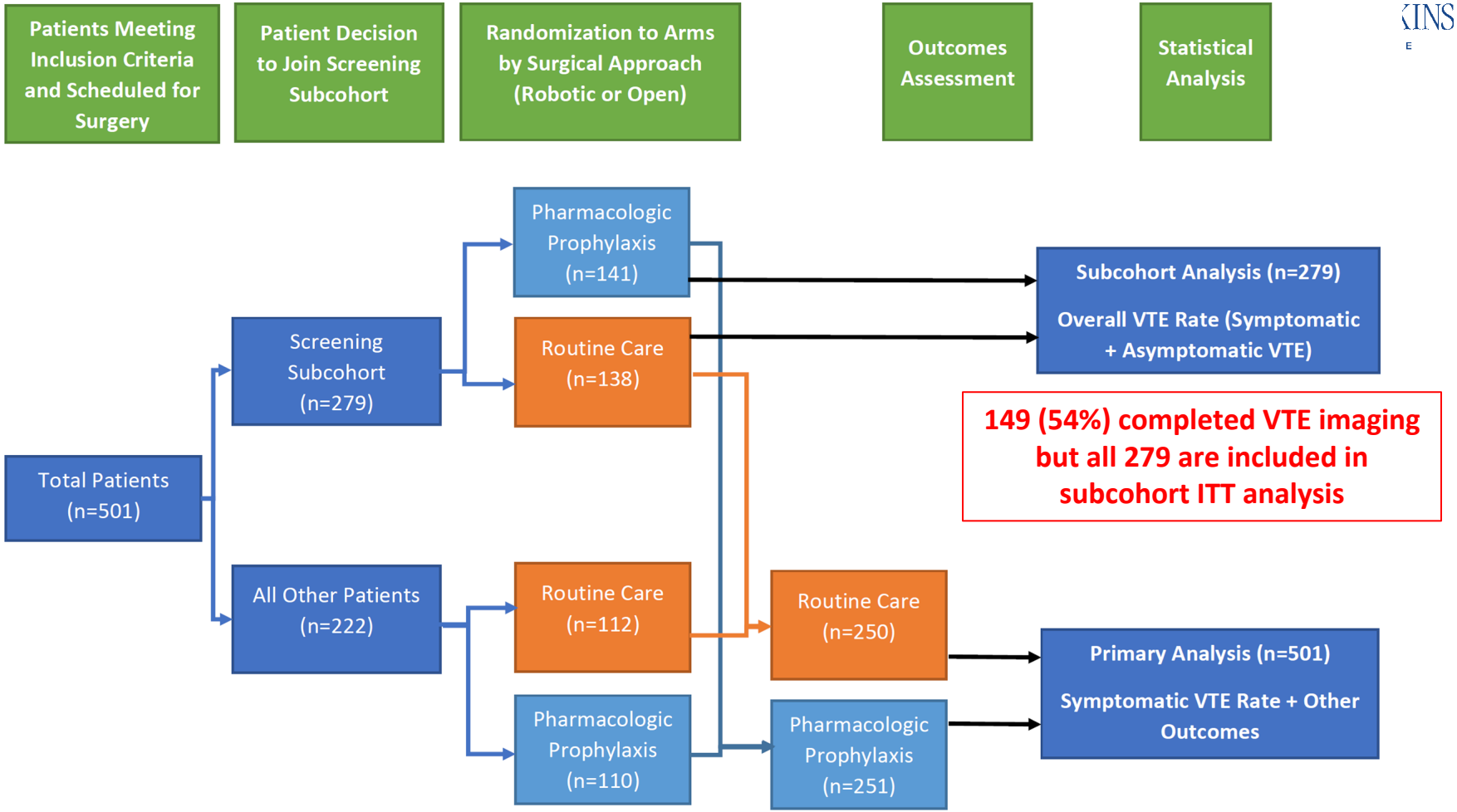
Methods

- PREvention of VENous ThromboEmbolism Following Radical Prostatectomy
  - Prospective, phase 4, single-center, randomized trial (NCT03006562; PREVENTER)
- **Objective**: Evaluate effect of perioperative in-hospital PP + IPCs (**intervention**) vs. IPCs alone (**routine care**) on risk of VTE after RP
  - PP = HSQ 5,000 units 2 hours prior and every 8 hours after RP
- **Primary efficacy outcome**: symptomatic VTE at 30-days
  - Primary safety outcomes: symptomatic lymphocele, symptomatic hematoma, or bleeding after RP
  - Optional screening subcohort to assess secondary outcome of overall VTE
- Block randomization, assigned 1:1, patients not blinded
  - Power: 5% vs. 1.5% with **2 interim analyses** → N=666 (333 per arm)

Results

- July 2017 to November 2018 at JHH and JHBMC
- N=445
  - 2nd interim analysis: **futility endpoint reached → early stopping**
- N=501
  - **Final included randomized sample** for analysis; 500/501 completed follow-up
  - 548 assessed → 22 declined, 25 not eligible → 501
- Analyses performed for both 2nd interim analysis and final enrolled population


Patients Meeting Inclusion Criteria and Scheduled for Surgery
Patient Decision to Join Screening Subcohort
Randomization to Arms by Surgical Approach (Robotic or Open)
Outcomes Assessment
Statistical Analysis
Pharmacologic Prophylaxis (n=141)
Screening Subcohort (n=279)
Routine Care (n=138)
Subcohort Analysis (n=279)
Overall VTE Rate (Symptomatic + Asymptomatic VTE)
149 (54%) completed VTE imaging but all 279 are included in subcohort ITT analysis
Total Patients (n=501)
All Other Patients (n=222)
Routine Care (n=112)
Routine Care (n=250)
Primary Analysis (n=501)
Symptomatic VTE Rate + Other Outcomes
Pharmacologic Prophylaxis (n=110)
Pharmacologic Prophylaxis (n=251)

Results

- Arms well-balanced at baseline
- Pathologic outcomes comparable
  - Stage, Grade, LNs
  - 83.6% PLND
  - 79.2% ≥GG2
- Median 4 (IQR 3-4) HSQ doses

Variable		Routine Care Arm	Pharmacologic Prophylaxis Arm
		All Enrolled Patients (n=501)	
N		**250**	**251**
Preoperative Characteristics			
Age, *median (IQR)*		61 (56-67)	63 (57-67)
BMI, *median (IQR)*		27.5 (25.1-30.4)	27.3 (25.0-30.3)
PSA, *median (IQR)*		6.3 (4.8-8.8)	5.9 (4.5-9.1)
SHIM, *median (IQR)*		20 (14-24)	21 (13-25)
AUA-SI, *median (IQR)*		6 (3-11.5)	7 (3-13)
Caprini Score, *median (IQR)*		6 (6-7)	6 (6-7)
NCCN Clinical Risk, *n(%)*	**Low**	55 (22.0)	52 (20.7)
	Intermediate	159 (59.6)	138 (55.0)
	High	46 (18.4)	61 (24.3)
Surgical Approach, *n (%)*	**Open**	63 (25.2)	61 (24.3)
	Robotic	187 (74.8)	190 (75.7)

Results

- Symptomatic VTE Events: 5 for Routine Care, 2 for PP
- 2nd interim analysis (N=445)
  - **2.3% (0.7-5.2) vs. 0.9% (0.1-3.2)**
  - RR 0.40 (95%CI 0.08-2.03), p=0.3
- Final trial population (N=501)
  - **2.0% (0.7-4.6) vs. 0.8% (0.1-2.9)**

Patient	Study Arm	Days from Surgery	PE Location	DVT Location	Treatment	Treatment Duration
1	Pharmacologic Prophylaxis	5	None	L posterior tibial, L soleal	Xarelto (rivaroxaban)	3 months
2	Routine Care	6	RUL, LUL; Segmental	L posterior tibial	Xarelto (rivaroxaban)	6 months
3	Pharmacologic Prophylaxis	9	RUL, RLL, LUL, LLL; Submassive	R peroneal	Eliquis (apixiban)	6 months
4	Routine Care	9	RUL, RML, RLL, LUL, LLL; Segmental and Subsegmental	L peroneal	Eliquis (apixiban)	Home medication[1]
5	Routine Care	13	RLL, LLL; Not Further Specified	R common femoral, R peroneal, L peroneal	Eliquis (apixiban)	6 months
6	Routine Care	15	None	R popliteal	Eliquis (apixiban)	3 months
7	Routine Care	30	RUL, RML, RLL, LUL, LLL; Extensive with Saddle Embolus and RV strain	L femoral, L popliteal	Eliquis (apixiban)	6 months

PE = pulmonary embolus; DVT = deep venous thrombosis; RUL = right upper lobe, RML = right middle lobe, RLL = right lower lobe, LUL = left upper lobe, LLL = left lower lobe

[1]Patient taking apixiban prior to surgery for atrial fibrillation (restarted and continued indefinitely)

Outcomes		Routine Care Arm	Pharmacologic Prophylaxis Arm	p-value[3]
		All Enrolled Patients (n=501)		
N	Measure	250	251	
Primary Efficacy Outcome				
Symptomatic VTE	*% (95% CI)*	2.0 (0.7-4.6)	0.8 (0.1-2.9)	0.284
Secondary Efficacy Outcome				
Overall VTE[1]	*% (95% CI)*	2.9 (0.1-7.3)	2.8 (0.1-7.1)	1.00
Primary Safety Outcomes				
Symptomatic Lymphocele	*% (95% CI)*	2.4 (0.9-5.2)	3.2 (1.4-6.2)	0.788
Symptomatic Hematoma	*% (95% CI)*	1.2 (0.3-3.5)	1.6 (0.4-4.0)	1.00
Bleeding	*% (95% CI)*	0.8 (0.1-2.9)	1.6 (0.4-4.0)	0.686
Secondary Safety Outcomes				
EBL (mL)	*median (IQR)*	200 (100-300)	150 (100-300)	0.520
Drain Output (mL)[2]	*median (IQR)*	100 (54-150)	95 (60-180)	0.456
Clavien ≥1 Complication	*% (95% CI)*	15.7 (11.4-20.8)	17.1 (12.7-22.4)	0.718
Claiven ≥3 Complication	*% (95% CI)*	3.6 (1.7-6.8)	3.6 (1.7-6.7)	1.00
Unplanned VTE Imaging	*% (95% CI)*	5.2 (2.8-8.8)	3.6 (1.7-6.7)	0.393
Any Unplanned Imaging	*% (95% CI)*	12.5 (8.6-17.2)	10.0 (6.6-14.4)	0.355

Subgroup Analyses

- No statistically significant differences
  - **PLND**: all VTE events occurred among patients receiving PLND (1.7% vs. 0%)
  - **Caprini**: ≤6 (1.5%) vs. ≥7 (1.3%)
    - Only 11% had Caprini ≥8
  - **Approach**: Open (2.4%) vs. Robotic (1.1%)

- Exploratory analysis for confounders
  - Pathologic stage (**pT3** vs. pT2) associated with symptomatic VTE
  - RR 8.79 (95% CI 1.07-72.3, p=0.043)
  - Adjustment did not impact association with PP

PREVENTER: Limitations

- Single-institution with 75% robotic cases
- Underpowered for event rate observed
  - Based on 2nd interim analysis, would require sample size >2000
  - It is probable PP reduces symptomatic VTE by a less than powered amount (e.g. 2.3% vs. 0.9%)
- Patients not blinded
- Few patients with Caprini scores ≥8
- Did not require screening ultrasonography of all patients

PREVENTER: Summary & Implications

- PP not associated with a significant reduction in symptomatic VTE nor overall VTE by 30 days after RP when added to routine care (IPCs).
- No increase in development of symptomatic lymphoceles, hematoma, bleeding, or other adverse events with PP.
- Patients with Caprini scores ≥8 deserve further evaluation to determine relative benefit of in-hospital (and potentially extended PP).
- The results of PREVENTER may be applicable to other surgeries that may be performed in a minimally-invasive (laparoscopic or robotic) fashion with low morbidity and short hospital length of stay (<48 hours).

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