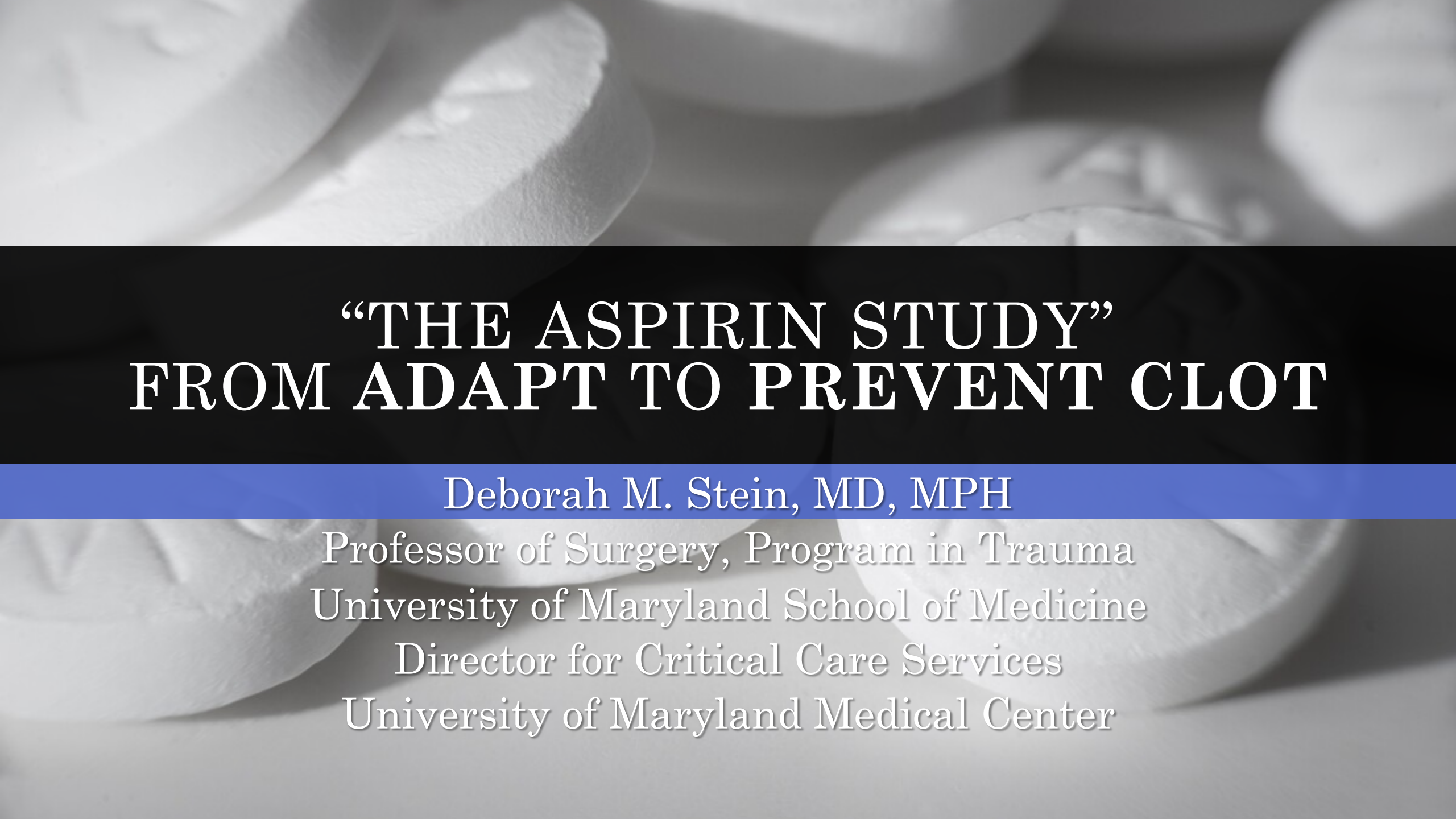

"THE ASPIRIN STUDY" FROM **ADAPT** TO **PREVENT** CLOT

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Director for Critical Care Services
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DISCLOSURE

Funded by PCORI for the Randomized Pragmatic Trial Comparing the Complications and Safety of Blood Clot Prevention Medicines Used in Orthopaedic Trauma Patients

IT STARTED WITH A "DISCUSSION"

LMWH CAUSES INCREASED COMPLICATION RATES?

- Observational study

- The rate of wound-related complications, SWI, DWI and wound drainage was
  - 0.45, 0.27, 0 and 0.18%, respectively, for patients who received aspirin
  - 3.5, 2.6, 0.2 and 0.7 %, respectively, for patients who received Coumadin

Vulcano E, et al. Aspirin for elective hip and knee arthroplasty: a multimodalthromboprophylaxis protocol.. International Orthopaedics (SICOT) (2012) 36:1995–2002

LMWH CAUSES INCREASED COMPLICATION RATES?

- A total of 290 consecutive patients who underwent total hip and total knee arthroplasty were prospectively entered into a clinical anticoagulation trial using a 10-day course of Lovenox with the ACCP -1A guidelines

- Major complications occurred in 9% of patients
  - symptomatic deep vein thrombosis occurred in 9 (3.8%) patients
  - nonfatal pulmonary embolism in 3 (1.3%) patients

- Complications included
  - 4.7% readmissions
  - 3.4% return to the operating room for wound incision and drainage
  - 5.1% prolonged hospitalization (wound drainage)
  - 3.4% injection site complications

- Return to the operating room for wound complications occurred **3× more frequently** with the use of Lovenox than previous study using warfarin.

Burnett RS, et al. Failure of the American College of Chest Physicians Guidelines. A protocol for lovenox in clinical outcomes for thromboembolic prophylaxis. J Arthroplasty. 2007 Apr;22(3):317-24.

ANTIPLATELET AGENTS FOR VTE PREVENTION?

- Antiplatelet therapy had previously not generally been accepted to DVT or PE
- All trials had been small

Antiplatelet agents such as aspirin or hydroxychloroquine show limited efficacy in preventing deep vein thrombosis (table III)[15 17 19]; their effects on pulmonary embolism and mortality are not yet published.

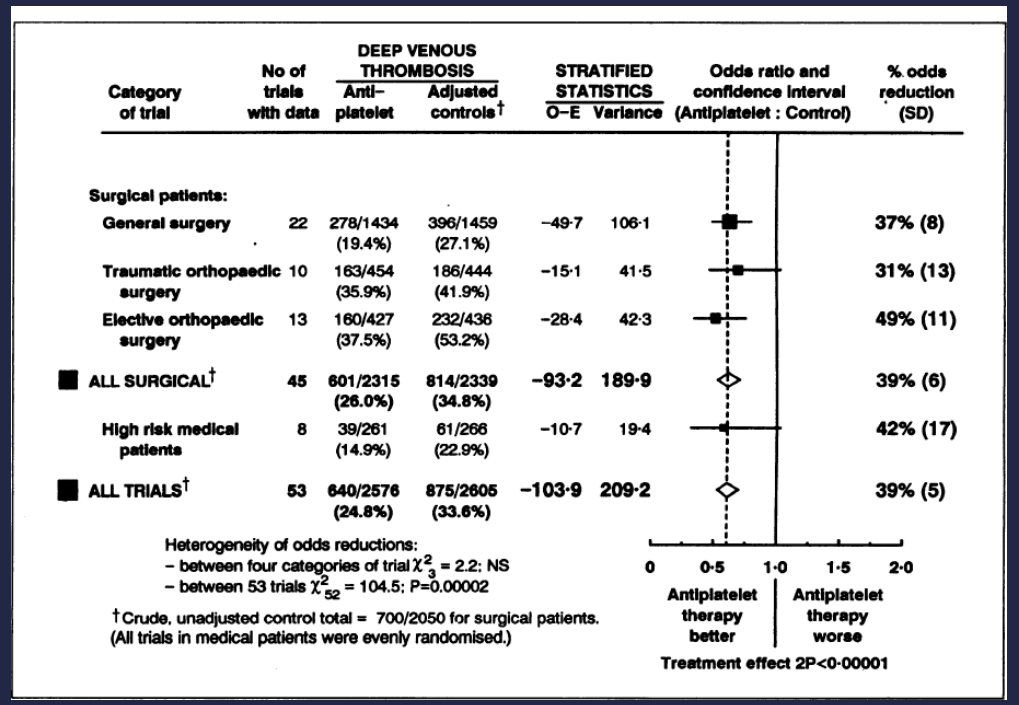
TABLE III—*Meta-analysis of incidence of deep vein thrombosis after major general surgery (defined by ^{125}I fibrinogen scanning)*[17]

	Mean incidence (%) (95% confidence interval)
No prophylaxis	25·1 (23·9 to 26·5)
Low dose heparin	8·7 (7·8 to 9·7)
Graduated elastic compression stockings	9·3 (6·4 to 13·3)
Intermittent pneumatic compression	9·9 (6·9 to 13·9)
Dextran	16·6 (13·1 to 18·4)
Aspirin	20·4 (16·5 to 25·0)

Thromboembolic Risk Factors (THRIFT) Consensus Group. Risk of and prophylaxis for venous thromboembolism in hospital patients. BMJ. 1992;305:567-74.

ANTIPLATELET AGENTS FOR VTE PREVENTION?

- 25% of patients allocated antiplatelet therapy versus 34% of appropriately adjusted controls had DVT
- Representing prevention in about 90 patients per 1000 allocated to antiplatelet therapy.



Category of trial	No of trials with data	DEEP VENOUS THROMBOSIS: Anti-platelet	DEEP VENOUS THROMBOSIS: Adjusted controls†	STRATIFIED STATISTICS: O−E	STRATIFIED STATISTICS: Variance	% odds reduction (SD)
Surgical patients:						
General surgery	22	278/1434 (19.4%)	396/1459 (27.1%)	−49·7	106·1	37% (8)
Traumatic orthopaedic surgery	10	163/454 (35.9%)	186/444 (41.9%)	−15·1	41·5	31% (13)
Elective orthopaedic surgery	13	160/427 (37.5%)	232/436 (53.2%)	−28·4	42·3	49% (11)
ALL SURGICAL†	45	601/2315 (26.0%)	814/2339 (34.8%)	−93·2	189·9	39% (6)
High risk medical patients	8	39/261 (14.9%)	61/266 (22.9%)	−10·7	19·4	42% (17)
ALL TRIALS†	53	640/2576 (24.8%)	875/2605 (33.6%)	−103·9	209·2	39% (5)

Odds ratio and confidence interval (Antiplatelet : Control)

Heterogeneity of odds reductions:
– between four categories of trial $\chi^2_3 = 2.2$; NS
– between 53 trials $\chi^2_{52} = 104.5$; P=0.00002

†Crude, unadjusted control total = 700/2050 for surgical patients.
(All trials in medical patients were evenly randomised.)

0 0·5 1·0 1·5 2·0
Antiplatelet therapy better | Antiplatelet therapy worse
Treatment effect 2P<0·00001

Collaborative overview of randomised trials of antiplatelet therapy—III: Reduction in venous thrombosis and pulmonary embolism by antiplatelet prophylaxis among surgical and medical patients

Antiplatelet Trialists' Collaboration

Collaborative overview of randomised trials of antiplatelet therapy--III: Reduction in venous thrombosis and pulmonary embolism by antiplatelet prophylaxis among surgical and medical patients. Antiplatelet Trialists' Collaboration. BMJ. 1994 Jan 22;308(6923):235-46.

ANTIPLATELET AGENTS FOR VTE PREVENTION?

Articles

Prevention of pulmonary embolism and deep vein thrombosis with low dose aspirin: Pulmonary Embolism Prevention (PEP) trial

- Aspirin reduced the risk of PE and DVT by at least a third throughout a period of increased risk.
- "Hence, there is now good evidence for considering aspirin routinely in a wide range of surgical and medical groups at high risk of venous thromboembolism."

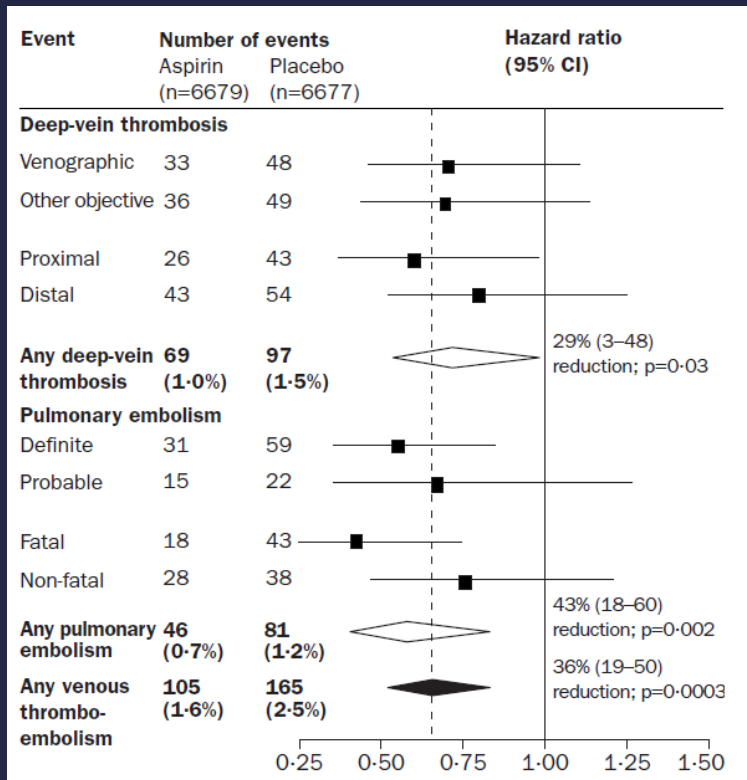


Figure 2: **Proportional effects of aspirin on pulmonary embolism and symptomatic deep-vein thrombosis after hip fracture**

Pulmonary Embolism Prevention (PEP) Trial Collaborative Group. Prevention of pulmonary embolism and deep vein thrombosis with low dose aspirin: Pulmonary Embolism Prevention (PEP). Lancet 2000; 355: 1295–302

ANTIPLATELET AGENTS FOR VTE PREVENTION?

- Since those original studies, many changes have occurred the perioperative management, including
  - multi-disciplinary clinical care pathways
  - multi-modal pain management protocols
  - increased use of regional anesthesia
  - modifications in surgical technique
  - aggressive early ambulation and physical therapy
  - early discharge to home

Seon JK, et al. Comput Aided Surg. 2007; 12(3):189–93.
Nuelle DG, Mann K. J Arthroplasty. 2007; 22(1):20–5.
Laskin RS. Surg Technol Int. 2004; 13:231–8.
Vendittoli PA, et al. J Bone Joint Surg Am. 2006; 88(2):282–9.
Turjanica MA. Medsurg Nurs. 2007; 16(3):151–4. quiz 155.
Long WT, et al. J Knee Surg. 2006; 19(2):137–43.
Scuderi GR. Am J Orthop. 2006; 35(7 Suppl):4–6.
Lombardi AV Jr. Viacava AJ, Berend KR. Clin Orthop Relat Res. 2006; 452:117–22.
Jones CA, et al. Rheum Dis Clin North Am. 2007; 33(1):71–86.
Pandit H, et al. J Surg Orthop Adv. 2006; 15(2):79–85.

ANTIPLATELET AGENTS FOR VTE PREVENTION?

- Analyzed clinical and administrative data from 93,840 patients who underwent primary TKA at 307 U.S. hospitals over a 24 month period.
- 51,923 (55%) patients received warfarin, 37,198 (40%) received injectable agents, and 4,719 (5%) received aspirin.
- After adjustment for patient and hospital factors, patients who received aspirin had lower odds for thromboembolism compared to warfarin patients, but similar odds compared to injectable VTEP
- There were no differences in risk of bleeding, infection or mortality after adjustment.

"Our results suggest that aspirin, when used in conjunction with other clinical care protocols, may be effective VTEP for certain TKA patients."

Unadjusted rates of postoperative adverse events

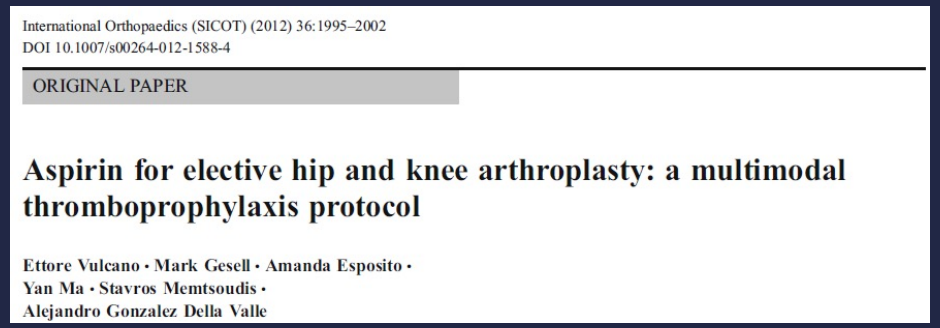
Outcome	Aspirin (n=4719)	Injectable VTEP (n=37198)	Warfarin (n=51923)
Any thromboembolism	110* (2.3%)	1152 (3.1%)	2009 (4%)
Proximal deep vein thrombosis or pulmonary embolism	77* (1.6%)	901 (2.4%)	1632 (3%)
Wound Infection	559 (12%)	4366 (12%)	6349 (12%)
Bleeding related to surgical site	30* (0.6%)	459 (1%)	548 (1%)
Mortality	9 (0.2%)	46 (0.1%)	54 (0.1%)

Bozic KJ, et al. Does Aspirin Have a Role in Venous Thromboembolism Prophylaxis in Total Knee Arthroplasty Patients? J Arthroplasty. 2010 October ; 25(7): 1053–1060.

ANTIPLATELET AGENTS FOR VTE PREVENTION?

- A total of 1,568 consecutive patients undergoing hip and knee replacement surgery received multimodal thromboprophylaxis
  - 1,115 received aspirin
  - 426 received Coumadin
  - 27 patients received LMWH and Coumadin with or without an IVC filter

- The rate of VTE, PE, proximal DVT, and distal DVT was
  - 1.2, 0.36, 0.45 and 0.36%, respectively, in patients who received aspirin.
  - 1.4, 0.9, 0.47 and 0.47%, respectively, in patients who received coumadin


International Orthopaedics (SICOT) (2012) 36:1995–2002
DOI 10.1007/s00264-012-1588-4

ORIGINAL PAPER

Aspirin for elective hip and knee arthroplasty: a multimodal thromboprophylaxis protocol

Ettore Vulcano · Mark Gesell · Amanda Esposito · Yan Ma · Stavros Memtsoudis · Alejandro Gonzalez Della Valle

Vulcano E, et al. Aspirin for elective hip and knee arthroplasty: a multimodal thromboprophylaxis protocol.. International Orthopaedics (SICOT) (2012) 36:1995–2002

ANTIPLATELET AGENTS FOR VTE PREVENTION?

Multicenter randomized, controlled trial

Noninferiority design

12 tertiary care orthopedic referral centers in Canada

778 patients who had elective unilateral THA between 2007 and 2010

28 days of dalteparin (*n* 400) or aspirin (*n* 386)

Anderson DR, et al. Aspirin Versus Low-Molecular-Weight Heparin for Extended Venous Thromboembolism Prophylaxis After Total Hip Arthroplasty. Ann Intern Med. 2013;158:800-806.

ANTIPLATELET AGENTS FOR VTE PREVENTION?

- The study was halted prematurely because of difficulty with patient recruitment.
- Extended prophylaxis for 28 days with aspirin was *noninferior to and as safe as dalteparin* for the prevention of VTE after THA (in patients who initially received dalteparin for 10 days).

Table 2. **Primary Outcome Results***

Outcome	LMWH Recipients (n = 398)	Aspirin Recipients (n = 380)	P Value	Difference (95% CI), *percentage points*
Total	5 (1.3)	1 (0.3)	0.22†	1.0 (−0.5 to 2.5)
Pulmonary embolism	3 (0.8)	0	–	–
Proximal DVT	2 (0.5)	1 (0.3)	–	–

DVT = deep venous thrombosis; LWMH = low-molecular-weight heparin.
* Values reported are numbers (percentages).
† Aspirin was noninferior ($P < 0.001$) but not superior to dalteparin.

Table 4. **Secondary Outcomes***

Outcome	LMWH Recipients (n = 400)	Aspirin Recipients (n = 385)	P Value
Wound infection	10 (2.5)	12 (3.1)	0.67
Deep incisional	3 (0.8)	3 (0.8)	–
Superficial	6 (1.5)	7 (1.8)	–
Deep incisional >30 d from procedure	0	1 (0.3)	1.00
Superficial >30 d from procedure	1 (0.3)	1 (0.3)	–
Myocardial infarction	1 (0.3)	0	1.00
Death	1 (0.3)	0	1.00
Stroke or transient ischemic attack	0	0	1.00
Thrombocytopenia	1 (0.3)	0	1.00

LMWH = low-molecular-weight heparin.
* Values reported are numbers (percentages).

Table 3. **Bleeding Results***

Outcome	LMWH Recipients (n = 400)	Aspirin Recipients (n = 385)	P Value	Difference (95% CI), *percentage points*
Major bleeding†	1 (0.3)	0	1.00	0.25 (−4.9 to 1.0)
Clinically significant nonmajor bleeding†	4 (1.0)	2 (0.5)	0.68	0.48 (−1.0 to 2.0)
Minor bleeding	18 (4.5)	8 (2.1)	0.164	2.40 (−0.3 to 5.2)
Bleeding at operative site	5 (1.3)	4 (1.0)	–	–
Gastrointestinal	2 (0.5)	0	–	–
Epistaxis	3 (0.8)	2 (0.5)	–	–
Hematuria	1 (0.3)	1 (0.3)	–	–
Ecchymosis	4 (1.0)	1 (0.3)	–	–
Hemoptysis	1 (0.3)	0	–	–
Conjunctival	2 (0.5)	0	–	–

LMWH = low-molecular-weight heparin.
* Values reported are numbers (percentages).
† All events were wound hematomas.

Anderson DR, et al. Aspirin Versus Low-Molecular-Weight Heparin for Extended Venous Thromboembolism Prophylaxis After Total Hip Arthroplasty. Ann Intern Med. 2013;158:800-806.

ANTIPLATELET AGENTS FOR VTE PREVENTION?

- Single institution
- 28,923 patients underwent TJA
- Multivariate analysis and 3:1 and 5:1 propensity score matching for comorbid and demographic variables.

Aspirin

An Alternative for Pulmonary Embolism Prophylaxis After Arthroplasty?

Ibrahim J. Raphael MD, Eric H. Tischler BA, Ronald Huang MD, Richard H. Rothman MD, PhD, William J. Hozack MD, Javad Parvizi MD, FRCS

Table 5. Ninety-day complication rates of the 5:1-matched aspirin and warfarin groups

Complication	Number of patients		Odds ratio (95% CI)	p value
	Warfarin (n = 9450)	Aspirin (n = 1980)		
Pulmonary embolism	96 (1.02%)	2 (0.11%)	9.69 (2.61–81.21)	< 0.001
Deep vein thrombosis	76 (0.80%)	2 (0.11%)	7.65 (2.04–64.46)	< 0.001
Acute infection	55 (0.58%)	4 (0.21%)	2.76 (1.02–10.50)	0.051
Hematoma/bleeding	14 (0.15%)	0 (0%)		0.147
Wound drainage	27 (0.29%)	0 (0%)		0.016
90-day mortality	2 (0.02%)	0 (0%)		1.000

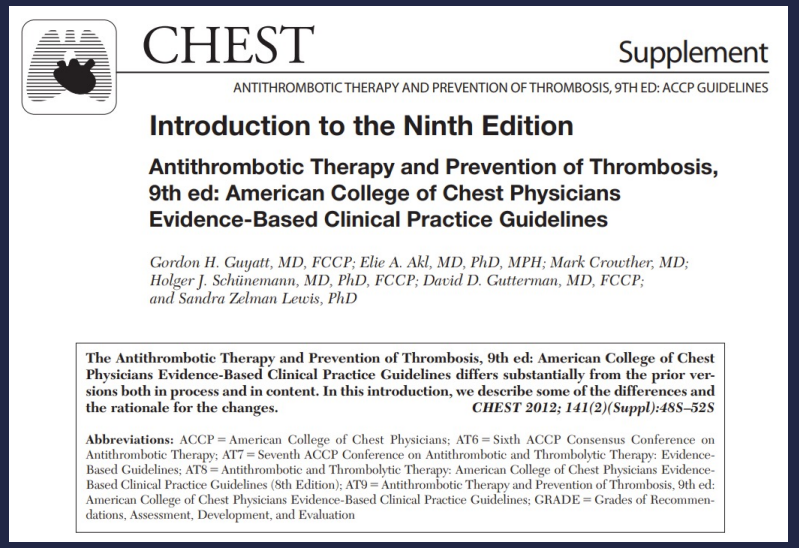
- "Aspirin offers suitable prophylaxis against symptomatic PE in selected patients"

Raphael, IJ, et al. Aspirin. An Alternative for Pulmonary Embolism Prophylaxis After Arthroplasty? Clin Orthop Relat Res (2014) 472:482–488

ANTIPLATELET AGENTS FOR VTE PREVENTION?

- The American Academy of Orthopaedic Surgeons (AAOS) has endorsed aspirin for VTE prevention after TJA

- In 2012, the American College of Chest Physician (ACCP) evidence-based clinical practice guidelines (9th edition), for the first time, acknowledged the use of aspirin as a means of PE chemoprophylaxis after TJA (Grade IB recommandation)



CHEST Supplement

ANTITHROMBOTIC THERAPY AND PREVENTION OF THROMBOSIS, 9TH ED: ACCP GUIDELINES

Introduction to the Ninth Edition

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

Gordon H. Guyatt, MD, FCCP; Elie A. Akl, MD, PhD, MPH; Mark Crowther, MD; Holger J. Schünemann, MD, PhD, FCCP; David D. Gutterman, MD, FCCP; and Sandra Zelman Lewis, PhD

The Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines differs substantially from the prior versions both in process and in content. In this introduction, we describe some of the differences and the rationale for the changes. ***CHEST 2012; 141(2)(Suppl):48S–52S***

Abbreviations: ACCP = American College of Chest Physicians; AT6 = Sixth ACCP Consensus Conference on Antithrombotic Therapy; AT7 = Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy: Evidence-Based Guidelines; AT8 = Antithrombotic and Thrombolytic Therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition); AT9 = Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines; GRADE = Grades of Recommendations, Assessment, Development, and Evaluation

Johanson NA, et al, American academy of orthopaedic surgeons clinical practice guideline on. Prevention of symptomatic pulmonary embolism in patients undergoing total hip or knee arthroplasty. J Bone Joint Surg Am. 2009 Jul;91(7):1756-7.

Falck-Ytter Y, et a;; American College of Chest Physicians. Prevention of VTE in Orthopedic Surgery Patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141 (2 suppl):e278S–e325S.

Geerts WH, et al; American College of Chest Physicians. Prevention of Venous thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest. 2008;133(6 suppl):381S–453S.

WHICH TURNED INTO A COLLABORATION

SO…WE DECIDED TO DO AN RCT

- First order of business…cute acronym
- A Different Approach to Preventing Thrombosis = ADAPT
- Second order of business…establishing our primary outcome metric and methodology
- Discrete choice experiment

PATIENT PREFERENCES

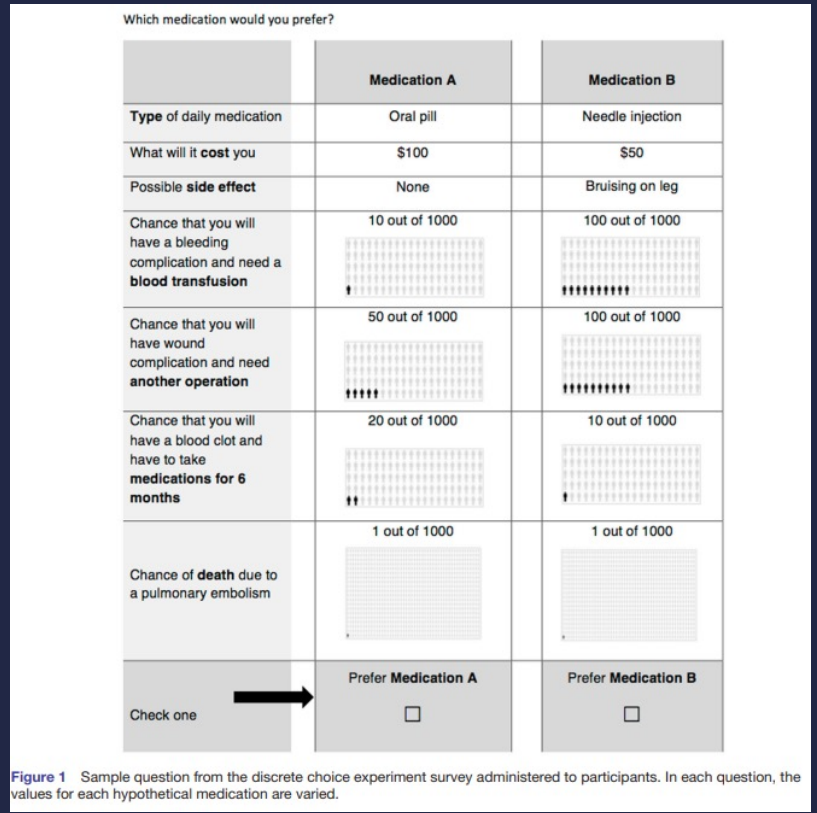
Open Access Research

BMJ Open

Patient preferences for venous thromboembolism prophylaxis after injury: a discrete choice experiment

Bryce E Haac,[1] Nathan N O'Hara,[1] C Daniel Mullins,[2] Deborah M Stein,[1] Theodore T Manson,[1] Herman Johal,[3] Renan Castillo,[4] Robert V O'Toole,[1] Gerald P Slobogean[1]

- Discrete choice experiments (DCE) are a quantitative technique used to measure individual preferences in a variety of healthcare settings by administering surveys that ask individuals to choose the best option between two or more hypothetical scenarios or choice sets.
- Options are described with a fixed set of attributes levels that vary in each scenario.
- The data collected can be used to assess the relative importance of each



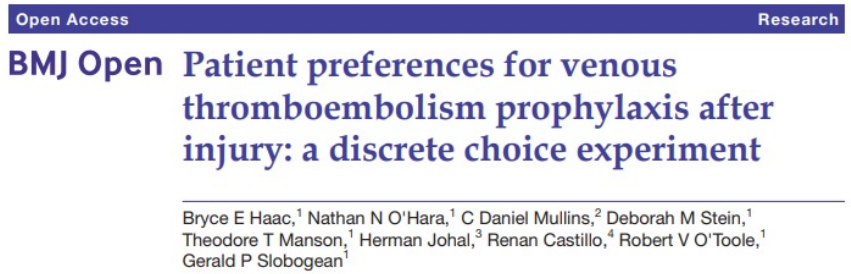
Which medication would you prefer?

	Medication A	Medication B
Type of daily medication	Oral pill	Needle injection
What will it **cost** you	$100	$50
Possible **side effect**	None	Bruising on leg
Chance that you will have a bleeding complication and need a **blood transfusion**	10 out of 1000	100 out of 1000
Chance that you will have wound complication and need **another operation**	50 out of 1000	100 out of 1000
Chance that you will have a blood clot and have to take **medications for 6 months**	20 out of 1000	10 out of 1000
Chance of **death** due to a pulmonary embolism	1 out of 1000	1 out of 1000
Check one	Prefer **Medication A** ☐	Prefer **Medication B** ☐

Figure 1 Sample question from the discrete choice experiment survey administered to participants. In each question, the values for each hypothetical medication are varied.

Haac B, et al. Patient preferences for venous thromboembolism prophylaxis after injury: a discrete choice experiment. BMJ Open 2017;7:e016676

PATIENT PREFERENCES



- A DCE was prospectively administered to orthopaedic trauma patients at a level 1 trauma center.

- 232 adult trauma patients with pelvic or acetabular fractures or operative extremity fractures.

- Primary and secondary outcome measures
  - Relative preferences and trade-off estimates for a 1% reduction in complications were estimated using multinomial logit modelling.
  - Interaction terms were added to the model to assess heterogeneity in preferences.

Haac B, et al. Patient preferences for venous thromboembolism prophylaxis after injury: a discrete choice experiment. BMJ Open 2017;7:e016676

PATIENT PREFERENCES

Open Access Research

BMJ Open

Patient preferences for venous thromboembolism prophylaxis after injury: a discrete choice experiment

Bryce E Haac,[1] Nathan N O'Hara,[1] C Daniel Mullins,[2] Deborah M Stein,[1] Theodore T Manson,[1] Herman Johal,[3] Renan Castillo,[4] Robert V O'Toole,[1] Gerald P Slobogean[1]

- Patients preferred oral tablets over subcutaneous injections (marginal utility, 0.16; 95% CI: 0.11 - 0.21, P<0.0001)

- Preferences changed in favor of subcutaneous injections with an absolute risk reduction of
  - 6.98% in bleeding
  - 4.53% in wound complications
  - 1.27% in VTE
  - 0.07% in death from PE

Table 2 Patient preferences and valuation of venous thromboembolism prophylaxis attributes

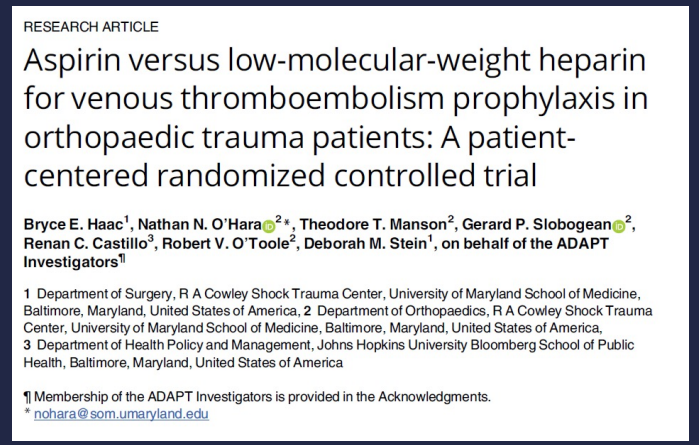
Attribute	Level	Marginal utility	95% CI	WTP	p Value
Route	Oral tablet	0.16	0.11 to 0.21	$117.45	<0.0001
	Subcutaneous injection	−0.16	−0.21 to −0.11	–	–
Side effects	Bruising on leg	−0.04	−0.11 to 0.02	-$45.94	0.11
	Stomach pain	−0.04	−0.12 to 0.04	-$44.08	–
	No side effects	0.08	0.003 to 0.16	$45.08	–
Bleeding complications requiring transfusion	Reduce risk by 1%	0.05	0.04 to 0.05	$16.83	<0.0001
Wound complications requiring another surgery	Reduce risk by 1%	0.07	0.06 to 0.08	$25.91	<0.0001
Blood clot requiring long-term medication	Reduce risk by 1%	0.25	0.15 to 0.36	$92.29	<0.0001
Death due to PE	Reduce risk by 1%	4.57	3.26 to 5.89	$1686.90	<0.0001
Cost	$10 increase	−0.03	−0.04 to −0.02	Reference	<0.0001

Marginal utility quantifies the additional satisfaction gained by the patient for each described attribute/level. Negative marginal utility values signify an aversion to or dissatisfaction with the described attribute/level. All risk reductions are absolute. Willingness to pay for the route and side effect category is based on the full treatment course, not per dose. Willingness to pay for all other attributes is based on the incremental change in level.
PE , pulmonary embolism; WTP, willingness to pay.

Haac B, et al. Patient preferences for venous thromboembolism prophylaxis after injury: a discrete choice experiment. BMJ Open 2017;7:e016676

ADAPT STUDY

- We conducted an open-label randomized clinical trial of adult patients admitted to an academic trauma center with an operative extremity fracture, or a pelvis or acetabular fracture.
- Patients were randomized to receive LMWH (enoxaparin 30-mg) twice daily (n = 164) or aspirin 81-mg twice daily (n = 165).
- The primary outcome was a composite endpoint of
  - bleeding complications
  - dSSI
  - DVT
  - PE
  - death within 90 days of injury



RESEARCH ARTICLE

Aspirin versus low-molecular-weight heparin for venous thromboembolism prophylaxis in orthopaedic trauma patients: A patient-centered randomized controlled trial

Bryce E. Haac[1], Nathan N. O'Hara[2]*, Theodore T. Manson[2], Gerard P. Slobogean[2], Renan C. Castillo[3], Robert V. O'Toole[2], Deborah M. Stein[1], on behalf of the ADAPT Investigators[¶]

1 Department of Surgery, R A Cowley Shock Trauma Center, University of Maryland School of Medicine, Baltimore, Maryland, United States of America, 2 Department of Orthopaedics, R A Cowley Shock Trauma Center, University of Maryland School of Medicine, Baltimore, Maryland, United States of America, 3 Department of Health Policy and Management, Johns Hopkins University Bloomberg School of Public Health, Baltimore, Maryland, United States of America

¶ Membership of the ADAPT Investigators is provided in the Acknowledgments.
* nohara@som.umaryland.edu

Haac BE, et al. Aspirin versus low-molecular-weight heparin for venous thromboembolism prophylaxis in orthopaedic trauma patients: A patient centered randomized controlled trial. (2020) PLoS ONE 15(8):e0235628.

ADAPT STUDY

- Weighting of study outcomes
  - Outcome weights were derived for the study outcomes based on the results of the DCE
  - The relative importance of the component outcomes was used to calculate the outcome weights and determined a hierarchy of severity for the observed combination of events experienced during the first 90 days from injury

Table 1. Weights for component outcomes derived from previously published data.

Component Outcome	Weight
Death	1.000
VTE Event (Pulmonary Embolism or Deep Vein Thrombosis)	0.055
Deep Surgical Site Infection	0.015
Bleeding Complication	0.010

Haac BE, et al. Aspirin versus low-molecular-weight heparin for venous thromboembolism prophylaxis in orthopaedic trauma patients: A patient centered randomized controlled trial. (2020) PLoS ONE 15(8):e0235628.

ADAPT STUDY

- Overall, 18 different combinations of outcomes were experienced by patients in the study.
- 99 patients in the aspirin group (59.9%) and 98 patients in the LMWH group (59.4%) were event-free within 90 days of injury.
- Using a Global Rank test, the LMWH had a 50.4% (95% CI, 47.7–53.2%, p = 0.73) probability of treatment superiority over aspirin.

Table 3. Outcomes experienced by patients in the study and their assigned weight.

Rank	Weight	Overall N (%)	ASA N (%)	LMWH	Event Description
1	0	197 (59.9)	99 (60.3)	98 (59.4)	Event free
2	0.0099	61 (18.5)	32 (19.5)	29 (17.6)	Bleeding event
3	0.0153	16 (4.9)	7 (4.3)	9 (5.5)	Deep SSI
4	0.0198	21 (6.4)	10 (6.1)	11 (6.7)	Two bleeding events
5	0.0252	7 (2.1)	3 (1.8)	4 (2.4)	Deep SSI, bleeding event
6	0.0351	3 (0.9)	2 (1.2)	1 (0.6)	Deep SSI, two bleeding events
7	0.0398	1 (0.3)	0 (0.0)	1 (0.6)	Four bleeding events
8	0.0548	7 (2.1)	5 (3.1)	2 (1.2)	VTE
9	0.0647	5 (1.5)	1 (0.6)	4 (2.4)	VTE, bleeding event
10	0.0746	1 (0.3)	1 (0.6)	0 (0.0)	VTE, two bleeding events
11	0.0845	2 (0.6)	2 (1.2)	0 (0.0)	VTE, three bleeding events
12	0.0899	1 (0.3)	0 (0.0)	1 (0.6)	VTE, deep SSI, two bleeding events
13	0.1096	1 (0.3)	0 (0.0)	1 (0.6)	Two VTEs
14	0.1393	1 (0.3)	0 (0.0)	1 (0.6)	Two VTEs, three bleeding events
15	0.1644	1 (0.3)	1 (0.6)	0 (0.0)	Three VTEs
16	0.1842	1 (0.3)	0 (0.0)	1 (0.6)	Three VTEs, two bleeding events
17	1.000	2 (0.6)	0 (0.0)	2 (1.2)	Death
18	1.0198	1 (0.3)	1 (0.0)	0 (0.0)	Death, two bleeding events

https://doi.org/10.1371/journal.pone.0235628.t003

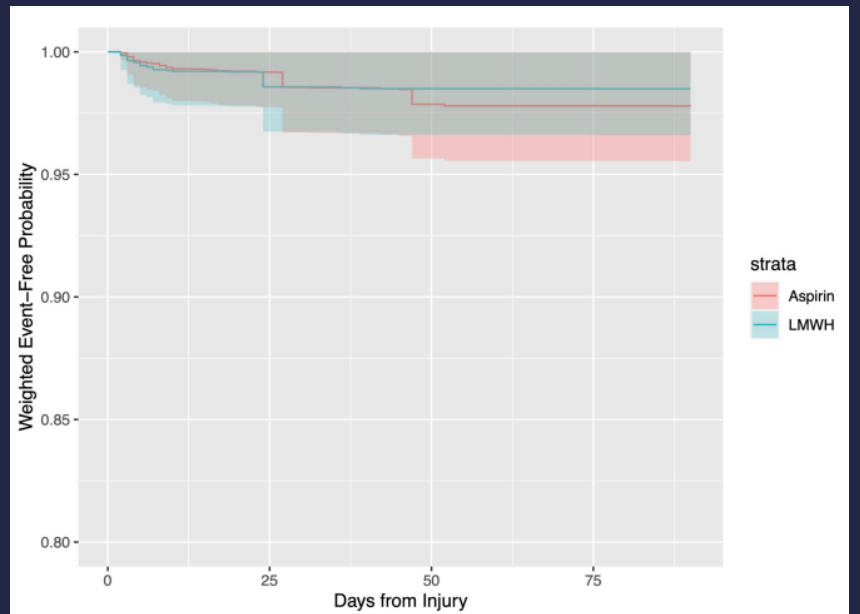


Fig 4. Weighted time to event analysis comparing the probability of being event-free within 90 days of injury. This analysis allows for multiple events for a given patient.

Haac BE, et al. Aspirin versus low-molecular-weight heparin for venous thromboembolism prophylaxis in orthopaedic trauma patients: A patient centered randomized controlled trial. (2020) PLoS ONE 15(8):e0235628.

ADAPT STUDY

Inpatient compliance with venous thromboembolism prophylaxis after orthopaedic trauma: results from a randomized controlled trial of aspirin versus low molecular weight heparin

Bryce E. Haac, MD[a], Nathan N. O'Hara, MHA[b,*], Theodore T. Manson, MD[b], Gerard P. Slobogean, MD, MPH[b], Renan C. Castillo, PhD[c], Robert V. O'Toole, MD[b], Deborah M. Stein, MD, MPH[a], on behalf of the ADAPT Investigators

- A secondary analysis of patients enrolled in the ADAPT RCT.
- To compare inpatient compliance with venous thromboembolism prophylaxis regimens.
- The primary outcome measure was the number of doses missed compared with prescribed number of doses.
- Results
  - A total of 329 patients were randomized to receive either LMWH 30mg BID (164 patients) or aspirin 81mg BID (165 patients).
  - No differences observed in % of patients who missed a dose (aspirin: 41.2% vs LMWH: 43.3%, P=0.7) or mean number of missed doses (0.6 vs 0.7 doses, P=0.4).
  - The majority of patients (57.8%, n=190) did not miss any doses.
- Concluded
  - "These data should reassure clinicians that inpatient compliance is similar for low molecular weight heparin and aspirin regimens."

Haac BE, et al. Inpatient compliance with venous thromboembolism prophylaxis after orthopaedic trauma: results from a randomized controlled trial of aspirin versus low molecular weight heparin. OTAI (2021) e150

ADAPT STUDY

Post-discharge adherence with venous thromboembolism prophylaxis after orthopedic trauma: Results from a randomized controlled trial of aspirin versus low molecular weight heparin

Bryce E. Haac, MD, Richard Van Besien, Nathan N. O'Hara, MHA, Gerard P. Slobogean, MD, MPH, Theodore T. Manson, MD, Robert V. O'Toole, MD, Herman Johal, MD, MPH, Peter Z. Berger, George B. Reahl, Dimitrius Marinos, Yasmin Degani, MPH, Daniel Mascarenhas, Daniel Connelly, Thomas M. Scalea, MD, *and* Deborah M. Stein, MD, MPH

- Patients prescribed outpatient prophylaxis were contacted between 10 - 21 days after discharge to assess adherence measured by the Morisky Medication Adherence Scale (MMAS-8).
- Adherence scores were compared between the two treatment arms with similar results for intention-to-treat and as-treated analyses.
- As-treated multivariable logistic regression was performed to determine factors associated with low-medium adherence scores.

©Morisky Medication Adherence Scale (MMAS-8-Item).

You indicated that you are taking medication(s) for your **(name of health condition)**. Individuals have identified several issues regarding their medication-taking behavior, and we are interested in your experiences. There is no right or wrong answer. Please answer each question based on your personal experience with your atrial **(name of health condition) medication(s).**

(Please mark your response below)

	No	Yes
1. Do you sometimes forget to take your **(name of health condition)**-related medication(s)?		
2. People sometimes miss taking their medication(s) for reasons other than forgetting. Thinking over the past two weeks, were there any days when you did not take your **(name of health condition)**-related medication(s)?		
3. Have you ever cut back or stopped taking your medication(s) without telling your doctor, because you felt worse when you took it?		
4. When you travel or leave home, do you sometimes forget to bring along your **(name of health condition)**-related medication(s)?		
5. Did you take your **(name of health condition)**-related medication(s) yesterday?		
6. When you feel like your **(name of health condition)**-related condition is under control, do you sometimes stop taking your medication(s)?		
7. Taking medication(s) every day is a real inconvenience for some people. Do you ever feel hassled about sticking to your **(name of health condition)**-related condition treatment plan?		

8. How often do you have difficulty remembering to take all your medication(s)?

(Please circle your answer below)

Never/Rarely

Once in a while

Sometimes

Usually

All the time

Haac BE, et al. Post-discharge adherence with venous thromboembolism prophylaxis after orthopedic trauma: Results from a randomized controlled trial of aspirin versus low molecular weight heparin. J Trauma Acute Care Surg. 2018;84: 564–574.

ADAPT STUDY

Post-discharge adherence with venous thromboembolism prophylaxis after orthopedic trauma: Results from a randomized controlled trial of aspirin versus low molecular weight heparin

Bryce E. Haac, MD, Richard Van Besien, Nathan N. O'Hara, MHA, Gerard P. Slobogean, MD, MPH, Theodore T. Manson, MD, Robert V. O'Toole, MD, Herman Johal, MD, MPH, Peter Z. Berger, George B. Reahl, Dimitrius Marinos, Yasmin Degani, MPH, Daniel Mascarenhas, Daniel Connelly, Thomas M. Scalea, MD, *and* Deborah M. Stein, MD, MPH

- 150 patients (64 on LMWH, 86 on aspirin) on chemoprophylaxis at time of follow-up completed the questionnaire.
- As-treated analysis showed that adherence was high overall (mean MMAS 7.2 out of 8, SD 1.5) and similar for the two regimens (LMWH: 7.4 vs. aspirin: 7.0, $p = 0.13$).
- Patients on LMWH were more likely to feel hassled by their regimen (23% vs. 9%, $p = 0.02$).
- In a multivariable model, low-medium adherence was associated with
  - taking LMWH as the prophylaxis medication (aOR 2.34, CI 1.06–5.18, $p = 0.04$)
  - having to self-administer the prophylaxis (aOR 4.44, CI 1.45–13.61, $p < 0.01$)
  - male sex (aOR 2.46, CI 1.10–5.49, $p = 0.03$)
  - younger age (aOR 0.72 per additional 10 years of age, CI 0.57–0.91, $p < 0.01$).

Haac BE, et al. Post-discharge adherence with venous thromboembolism prophylaxis after orthopedic trauma: Results from a randomized controlled trial of aspirin versus low molecular weight heparin. J Trauma Acute Care Surg. 2018;84: 564–574.

SO…WE DECIDED TO DO A MULTICENTER RCT

- First order of business…cute acronym
- PREVENTion of CLot in Orthopaedic Trauma study = PREVENT CLOT
- Second order of business…secure funding

PREVENT CLOT

Open access Protocol

BMJ Open PREVENTion of CLots in Orthopaedic Trauma (PREVENT CLOT): a randomised pragmatic trial protocol comparing aspirin versus low-molecular-weight heparin for blood clot prevention in orthopaedic trauma patients

Robert V O'Toole ,[1] Deborah M Stein,[2] Katherine P Frey,[3] Nathan N O'Hara ,[1] Daniel O Scharfstein,[4] Gerard P Slobogean,[1] Tara J Taylor,[3] Bryce E Haac,[5] Anthony R Carlini,[3] Theodore T Manson,[1] Kuladeep Sudini,[3] C Daniel Mullins,[6] Stephen T Wegener,[7] Reza Firoozabadi,[8] Elliott R Haut,[9] Michael J Bosse,[10] Rachel B Seymour,[10] Martha B Holden,[11] Ida Leah Gitajn,[12] Samuel Z Goldhaber,[13] Alexander L Eastman,[14] Gregory J Jurkovich,[15] Heather A Vallier,[16] Joshua L Gary,[17] Conor P Kleweno,[8] Joseph Cuschieri,[18] Debra Marvel,[19] Renan C Castillo,[3] METRC

- The trial was funded by the Patient-Centered Outcomes Research Institute

- PREVENT CLOT was co-led by
  - University of Maryland School of Medicine's Department of Orthopaedics
  - Major Extremity Trauma and Rehabilitation Consortium (METRC) Coordinating Center (MCC) at the Johns Hopkins Bloomberg School of Public Health.

Table 1 Recruiting sites for PREVENT CLOT

Hospital	City, State
Allegheny General Hospital	Pittsburgh, Pennsylvania
Atrium Health – Carolinas Medical Center	Charlotte, New Carolina
Brooke Army Medical Center	San Antonio, Texas
Dartmouth-Hitchcock Medical Center	Lebanon, New Hampshire
Harborview Medical Center	Seattle, Washington
Indiana University – Methodist Hospital	Indianapolis, Indiana
Inova Fairfax Hospital	Falls Church, Virginia
Massachusetts General Hospital	Boston, Massachusetts
McGovern Medical School at UTHealth Houston	Houston, Texas
McMaster University – Hamilton General Hospital	Hamilton, Ontario
MetroHealth Medical Center	Cleveland, Ohio
Rhode Island Hospital – Brown University	Providence, Rhode Island
University of Arizona	Tucson, Arizona
University of Calgary Foothills Medical Centre	Calgary, Alberta
University of Maryland – R Adams Cowley Shock Trauma Center	Baltimore, Maryland
University of Miami – Ryder Trauma Center	Miami, Florida
University of Mississippi Medical Center	Jackson, Mississippi
University of Tennessee – Regional One Medical Center	Memphis, Tennessee
University of Wisconsin Health University Hospital	Madison, Wisconsin
Vanderbilt Medical Center	Nashville, Tennessee
Wake Forest University Baptist Medical Center	Winston-Salem, North Carolina

PREVENT CLOT, PREVENTion of Clot in Orthopaedic Trauma study.

O'Toole RV, et al. PREVENTion of CLots in Orthopaedic Trauma (PREVENT CLOT): a randomised pragmatic trial protocol comparing aspirin versus low-molecularweight heparin for blood clot prevention in orthopaedic trauma patients. BMJ Open 2021;11:e041845.

PREVENT CLOT

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- A multicenter, randomized, pragmatic trial
- Enrolled ~12,200 adult patients admitted to 1 of 21 participating centers
- Inclusion criteria
  1. Must be 18 years of age or older.
  2. Have a planned operative or non-operative pelvis or acetabular fracture, or any operative extremity fracture proximal to the metatarsals or carpals.
  3. Will receive a VTE prophylactic regimen per standard of care at the treating center.

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Brooke Army Medical Center	San Antonio, Texas
Dartmouth-Hitchcock Medical Center	Lebanon, New Hampshire
Harborview Medical Center	Seattle, Washington
Indiana University – Methodist Hospital	Indianapolis, Indiana
Inova Fairfax Hospital	Falls Church, Virginia
Massachusetts General Hospital	Boston, Massachusetts
McGovern Medical School at UTHealth Houston	Houston, Texas
McMaster University – Hamilton General Hospital	Hamilton, Ontario
MetroHealth Medical Center	Cleveland, Ohio
Rhode Island Hospital – Brown University	Providence, Rhode Island
University of Arizona	Tucson, Arizona
University of Calgary Foothills Medical Centre	Calgary, Alberta
University of Maryland – R Adams Cowley Shock Trauma Center	Baltimore, Maryland
University of Miami – Ryder Trauma Center	Miami, Florida
University of Mississippi Medical Center	Jackson, Mississippi
University of Tennessee – Regional One Medical Center	Memphis, Tennessee
University of Wisconsin Health University Hospital	Madison, Wisconsin
Vanderbilt Medical Center	Nashville, Tennessee
Wake Forest University Baptist Medical Center	Winston-Salem, North Carolina

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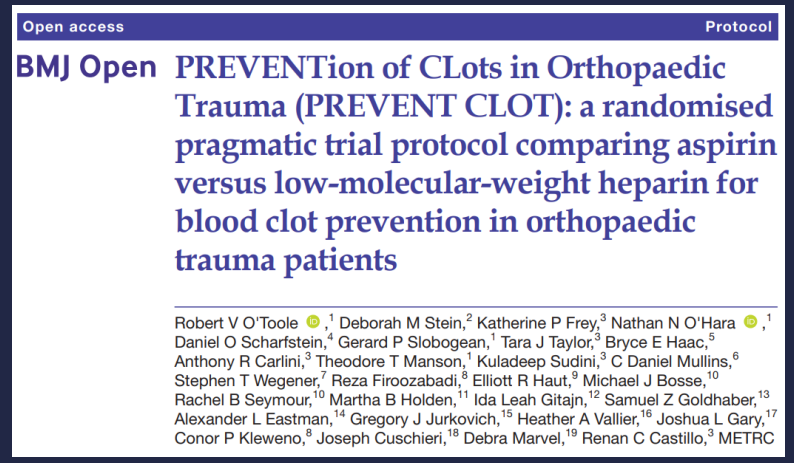
PREVENT CLOT

- The primary outcome is all-cause mortality.
- Secondary efficacy outcomes include
  - cause-specific mortality
  - non-fatal PE
  - DVT
- Safety outcomes include
  - bleeding complications
  - wound complications
  - deep surgical site infections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I'M SO EXCITED! AND
I JUST CAN'T HIDE IT...

THANK YOU!

Questions?