



ADOPT

Apixaban Dosing To Optimize Protection From Thrombosis (ADOPT) Trial

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On behalf of the ADOPT Executive Committee
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Sponsored by Bristol-Myers Squibb and Pfizer

Disclosures

- Research support
 - Bristol-Myers Squibb/Pfizer Inc; Boehringer-Ingelheim; Eisai; EKOS; Johnson & Johnson, sanofi-aventis
- Consultant
 - Boehringer-Ingelheim; Bristol-Myers Squibb; Daiichi; Eisai; EKOS; Merck; Pfizer; Portola; sanofi-aventis

Background

- The efficacy and safety of prolonging VTE prophylaxis beyond hospital discharge in medically ill patients remains uncertain.
- We hypothesized that extended use of apixaban would be more effective than short-term use of enoxaparin.
- Apixaban is an orally active direct inhibitor of factor Xa, with established efficacy and safety for VTE prevention after THR/TKR and for SPAF.

Inclusions and Exclusions



• Inclusions

- Hospitalized with congestive heart failure or acute respiratory failure
- Infection, acute rheumatic disorder, or IBD, plus at least one of the following VTE risk factors:
 - Age ≥ 75 years, prior VTE, BMI ≥ 30 , estrogen therapy
 - Mobility restricted to walking in room

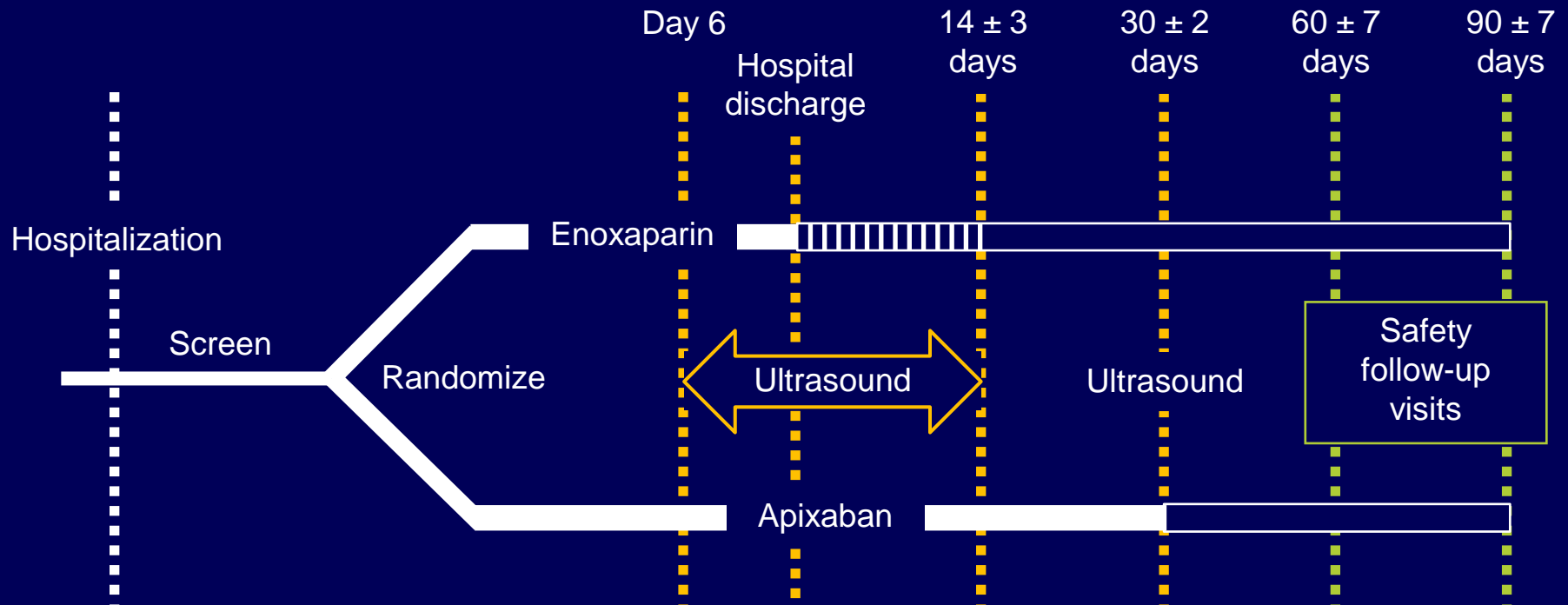
• Exclusions

- Confirmed VTE
- Requires anticoagulation
- Dual antiplatelet therapy
- CrCl ≤ 30 mL/min
- ALT $\geq 2x$ ULN
- Active or high risk of bleeding

Study Design



- Randomization in a 1:1 ratio to double-blind, double-dummy oral apixaban 2.5 mg BID for 30 days versus subcutaneous enoxaparin 40 mg QD for 6–14 days



Primary Efficacy Endpoint and Efficacy Objectives



- Primary efficacy endpoint
 - Composite of total VTE/ VTE-related death
 - Fatal PE or sudden death where PE cannot be excluded as a cause
 - Non-fatal PE
 - Symptomatic DVT
 - Asymptomatic proximal DVT (ultrasound)
- Efficacy objectives
 - Primary objective: Demonstrate that apixaban 2.5 mg BID reduces the rate of total VTE/ VTE-related death, compared with enoxaparin 40 mg QD during the study treatment period
 - Key secondary objective: Demonstrate that apixaban 2.5 mg BID is non-inferior to enoxaparin 40 mg QD, for the total VTE/ VTE-related death endpoint during the parenteral treatment period

Safety Objectives and Endpoints



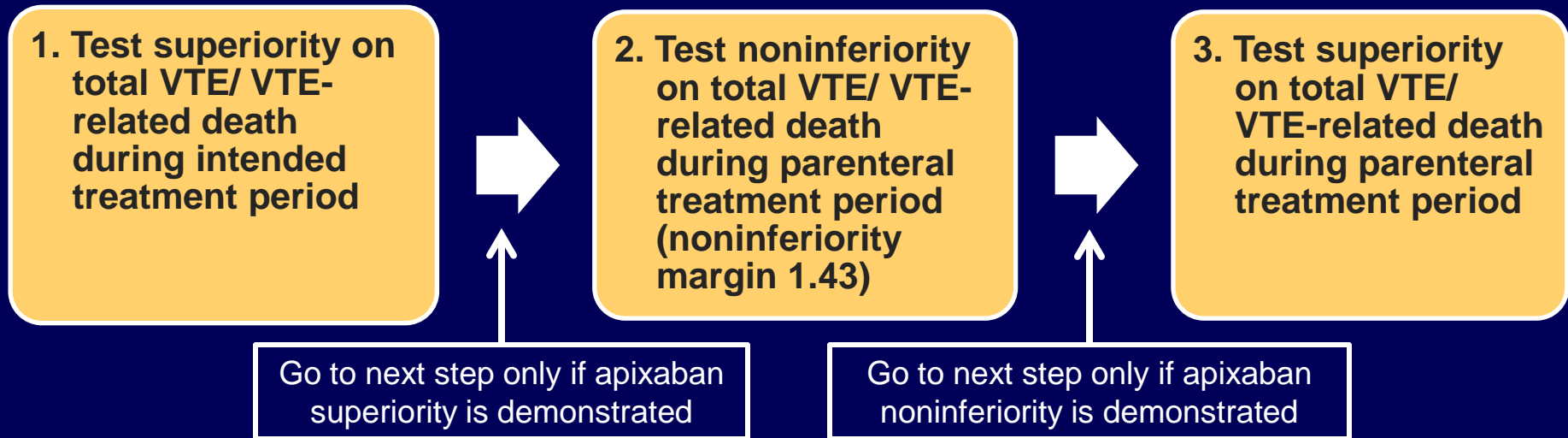
- Assess the effect of apixaban 2.5 mg BID versus enoxaparin 40 mg QD on major (ISTH guidelines*) and CRNM bleeding
- Inclusion in safety analysis required receiving at least one dose of study medication

*Fatal bleeding, and/or symptomatic bleeding in a critical area or organ, or bleeding causing a fall in hemoglobin level of ≥ 20 g/L or leading to transfusion of ≥ 2 units of blood

Sequential Testing Strategy and Sample Size Determination



- Sequential testing strategy



- Sample size

- 6,524 patients would be needed for 90% power to demonstrate superiority (1-sided $\alpha=0.025$) if there were 2.5% and 4% event rates in the apixaban and enoxaparin groups, respectively.
- Assumed 10% of follow-up ultrasounds would not be obtained or would not meet quality/protocol criteria for analysis. (Will return to this point later in the presentation)

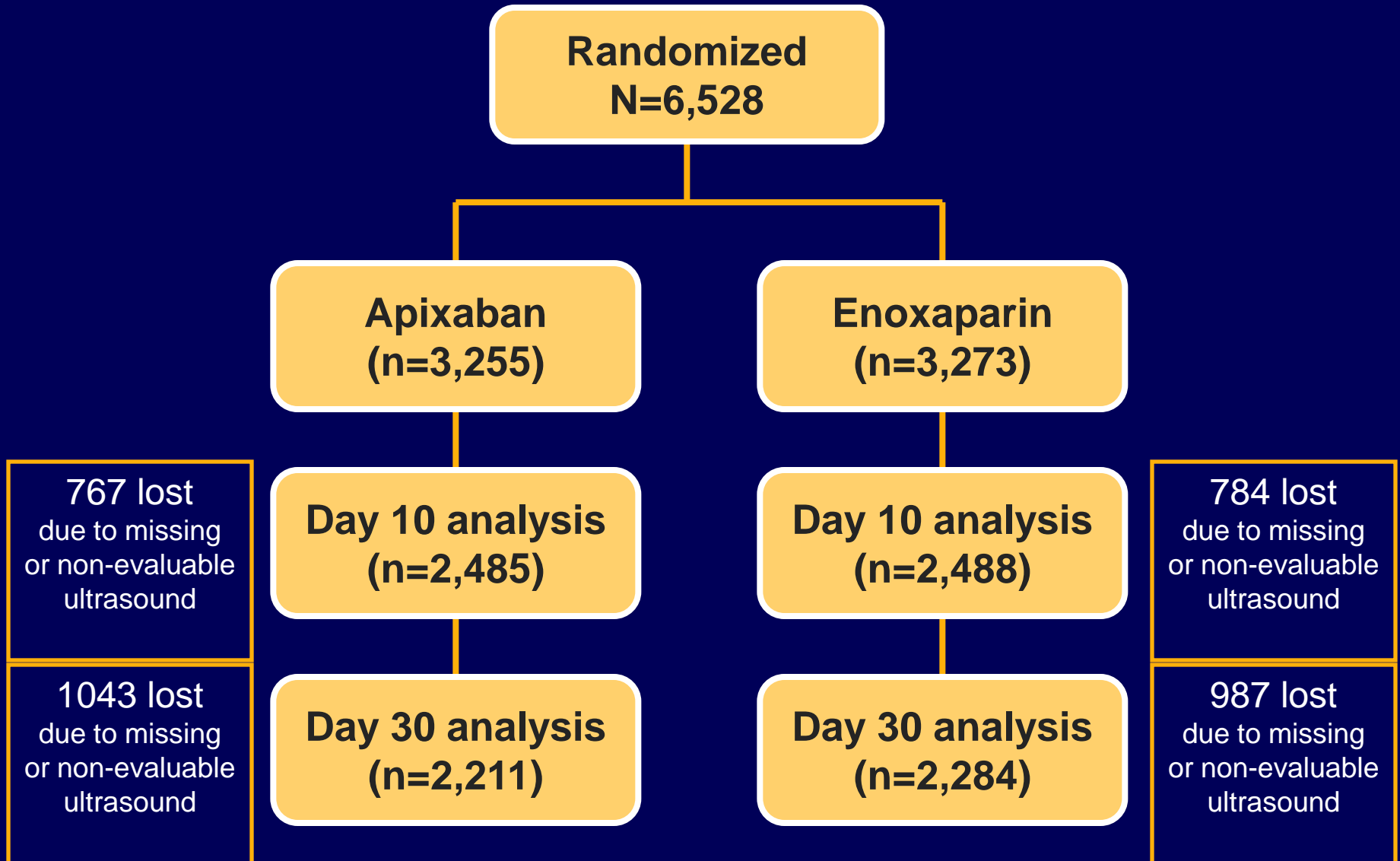
Study Enrollment



6528 patients, 302 centers, 35 countries



Patient Disposition



Demographics



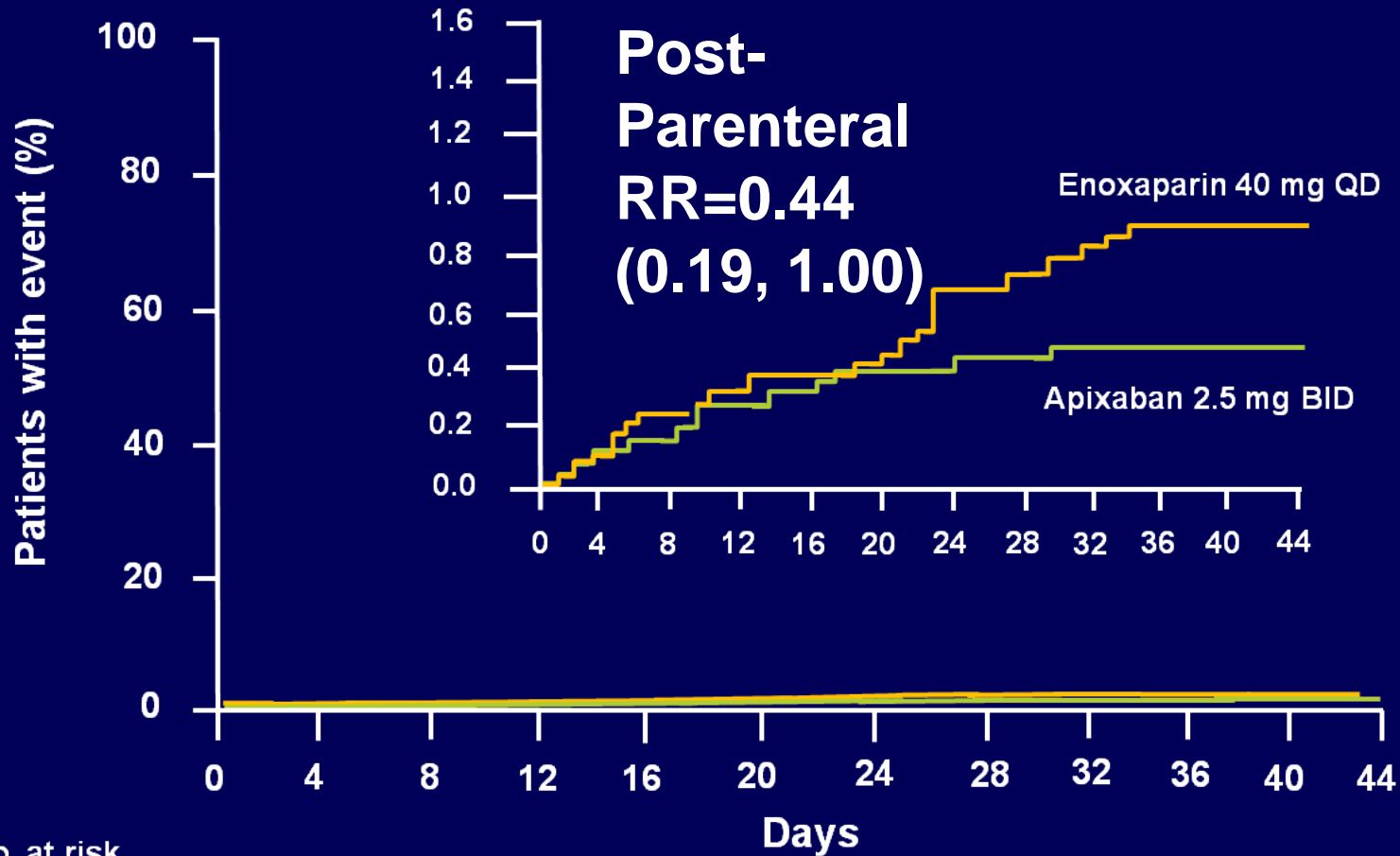
Variable	Apixaban	Enoxaparin
Mean age (SD), years	66.8 (12.0)	66.7 (12.0)
Gender, n (%)		
Male	1626 (50)	1577 (48)
Female	1629 (50)	1696 (52)
White, n (%)	2474 (76)	2476 (76)
Congestive heart failure, n (%)	1270 (39)	1246 (38)
Acute respiratory failure, n (%)	1208 (37)	1213 (37)
Body mass index ≥ 30 , n (%)	1448 (44)	1451 (44)
Mobility, n (%)		
Moderately restricted	2388 (73)	2323 (71)
Severely restricted	846 (26)	929 (28)

Efficacy



Variable	Apixaban n/N (%)	Enoxaparin n/N (%)	Relative risk (95% CI)
Day 30: Primary efficacy outcome (Total VTE/ VTE-related death)	60/2211 (2.71)	70/2284 (3.06)	0.87 (0.62, 1.23)
Day 0 to end of parenteral period: Key secondary outcome	43/2485 (1.73)	40/2488 (1.61)	1.06 (0.69, 1.63)
<u>Post-parenteral:</u> Total VTE/ VTE-related death	18/1959 (0.92)	31/2002 (1.55)	0.59 (0.33, 1.05)
<u>Post-parenteral:</u> Symptomatic VTE/ VTE-related death	8/3175 (0.25)	18/3205 (0.56)	0.44 (0.19, 1.00)

Symptomatic VTE/ VTE-related Death (Randomized Patients)



No. at risk

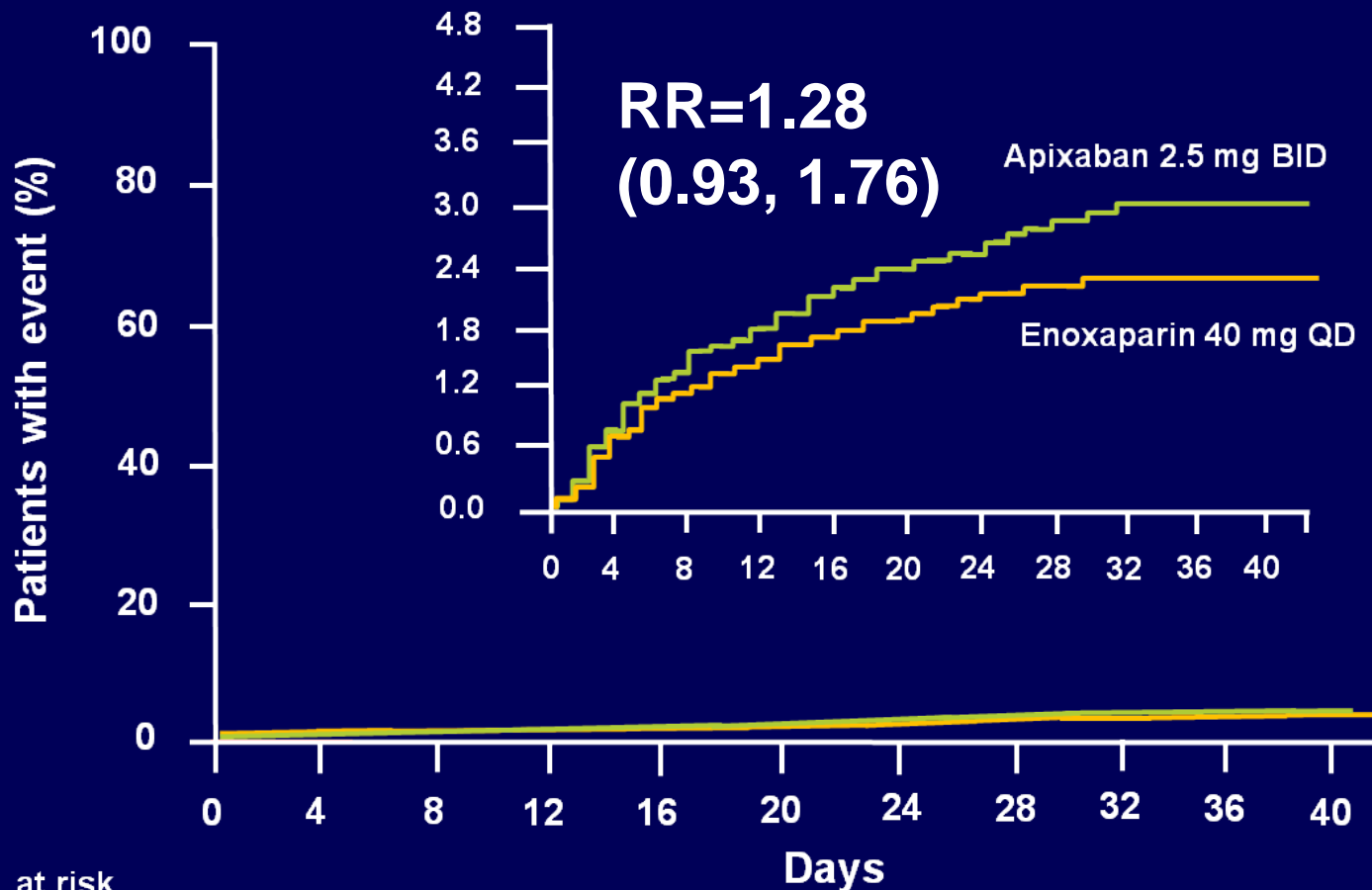
Apixaban	3251	3098	2998	2935	2889	2850	2830	2810	2736	157	10	2
Enoxaparin	3266	3136	3049	2993	2946	2925	2892	2865	2783	195	12	1

Bleeding



Variable	Apixaban n/N (%)	Enoxaparin n/N (%)	Relative risk (95% CI)
Major bleeding	15/3184 (0.47)	6/3217 (0.19)	2.58 (1.02, 7.24) P=0.04
Major and clinically relevant non-major bleeding	85/3184 (2.67)	67/3217 (2.08)	1.28 (0.93, 1.76) P=0.12

ISTH Major or CRNM Bleeding (Treated Patients)



No. at risk

Apixaban	3184	3042	2840	2664	2569	2493	2447	2392	1559	154	10
Enoxaparin	3217	3078	2885	2705	2627	2562	2513	2457	1640	192	12

Limitations of ADOPT

- Underpowered, primarily because one-third of ultrasounds were not evaluable or obtained
- Enoxaparin administered ≥ 6 days, even if patients were discharged sooner –not standard of care—favored better efficacy with enoxaparin than would be expected with ordinary care.
- Day 10 ultrasound (not standard of care) altered the natural history of VTE because “silent DVTs” were identified and treated.

Conclusions

- The risk of VTE increases after hospital discharge.
- Despite a nonsignificant trend after the parenteral period in favor of extended prophylaxis, ADOPT does not provide evidence to justify such a policy in a broad population of medically ill patients.
- We need to identify high-risk subgroups who might benefit from extended VTE prophylaxis.

Study Personnel



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ORIGINAL ARTICLE

Apixaban versus Enoxaparin for Thromboprophylaxis in Medically Ill Patients

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ABSTRACT

BACKGROUND

The efficacy and safety of prolonging prophylaxis for venous thromboembolism in medically ill patients beyond hospital discharge remain uncertain. We hypothesized that extended prophylaxis with apixaban would be safe and more effective than short-term prophylaxis with enoxaparin.