

Full-Dose Betrixaban Reduces Venous Thromboembolism-Related Mortality: An APEX Trial Substudy

Background

- ▶ Approximately **0.5M** VTE occur annually in the United States, with **50%** related to recent or current hospitalization.

Estimates of thrombotic conditions per 100,000 population:

Measure	Ischemic Heart Disease	Venous Thromboembolism	Ischemic Stroke	Atrial Fibrillation
Incidence	1518.7	115–269	114.3	59.5–77.5
Mortality	105.5	9.4–32.3	42.3	1.7

Study Design & Endpoints

- ▶ APEX randomized 7,513 acutely ill hospitalized medical patients to:
 - ▶ **Betrixaban for 35–42 days (extended prophylaxis)**
 - OR
 - ▶ **Enoxaparin for 6–14 days (standard prophylaxis)**
- ▶ Analysis was performed on an “as-treated” basis in the prespecified populations:
 - ▶ **Modified intention-to-treat (mITT) population:**
 - ▶ All randomized subjects who received ≥ 1 dose of the study medication
 - ▶ **Full-dose stratum (betrixaban 80 mg daily vs. enoxaparin 40 mg daily):**
 - ▶ Subjects with CrCl ≥ 30 mL/min and without use of strong P-gp inhibitors

Study Design & Endpoints

- ▶ Study endpoints:
 - ▶ **VTE-related mortality** at the end of extended prophylaxis (day 42)
 - ▶ **VTE-related mortality** at the end of study (day 77)

- ▶ **VTE-related mortality** (as opposed to all-cause mortality):
 - ▶ This outcome is selected as this will best illustrate the effect of the primary drug mechanism of action on the disease process.
 - ▶ Although all-cause mortality is preferable in many indications, it is impractical in acutely ill patients as the death rate due to the primary illness is much higher and would obscure the treatment effect.

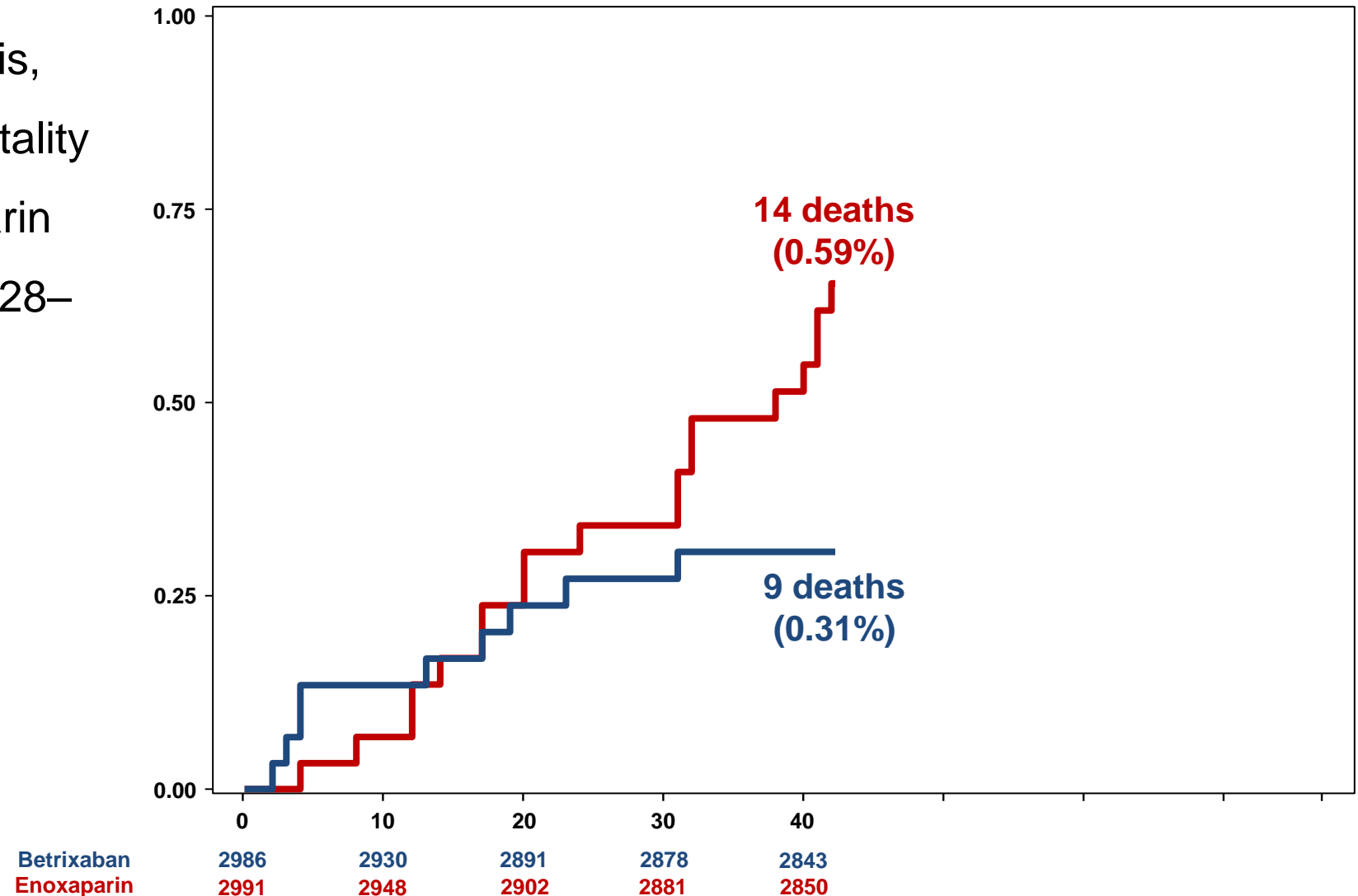
Study Design & Endpoints

- ▶ Study endpoints:
 - ▶ VTE-related mortality at **the end of extended prophylaxis** (day 42)
 - ▶ VTE-related mortality at **the end of study** (day 77)

- ▶ **“Legacy effect”** of antithrombotics (as opposed to catch-up phenomenon):
 - ▶ Difference in the cumulative incidence sustains after discontinuation of study drug
 - ▶ RE-SONATE trial: the benefit of extended treatment with dabigatran was maintained up to 12 months after the cessation of treatment.

End of Extended Prophylaxis (Day 42)

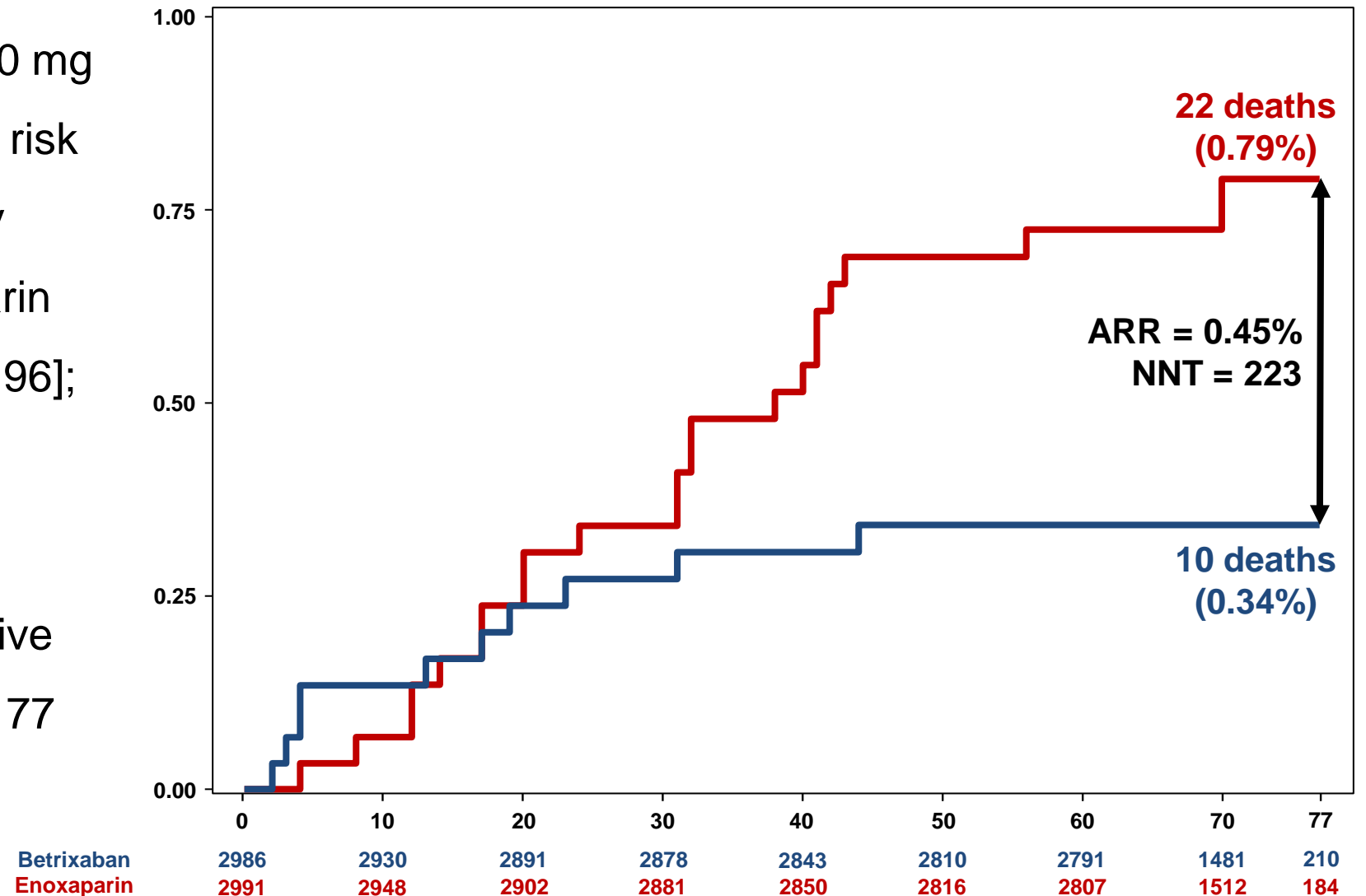
At the end of extended prophylaxis, the difference in VTE-related mortality between betrixaban and enoxaparin was not significant (HR = 0.65 [0.28–1.49]; P = 0.30).



End of Study (Day 77)

At the end of study, betrixaban (80 mg daily) was associated with a **54%** risk reduction in VTE-related mortality compared with standard enoxaparin (40 mg daily) (HR = 0.46 [0.22–0.96]; P = 0.0349).

A sustained difference in cumulative incidence was observed for up to 77 days.



Conclusions

- ▶ Betrixaban (80 mg daily for 35 to 42 days) halved the risk of VTE-related mortality at 77 days compared with enoxaparin.
- ▶ One death from VTE could be prevented with betrixaban for every 223 acutely ill hospitalized patients treated.
- ▶ Treatment effect of betrixaban was sustained up to 1 month after discontinuation of therapy.