

Safety

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Safety Presentation Agenda

- ◆ Pooling strategy
- ◆ Surgical and nonsurgical safety
 - Adverse events
 - Adjudicated bleeding events
- ◆ Topics of interest
 - Myocardial ischemic events
 - Hepatic profile
- ◆ Mortality
- ◆ Conclusions

Pooling Strategy

3 Safety Populations

Phase I

- ◆ Healthy volunteers
- ◆ Dosed 1 to 8 days
- ◆ No safety signals

Surgical safety population

- ◆ Evaluates safety postsurgery
- ◆ Bleeding risk is increased with surgery
- ◆ Dosed up to 12 days

Nonsurgical safety population

- ◆ Evaluates safety with chronic dosing
- ◆ Dosed > 35 days and up to 4 yr

Surgical Pool

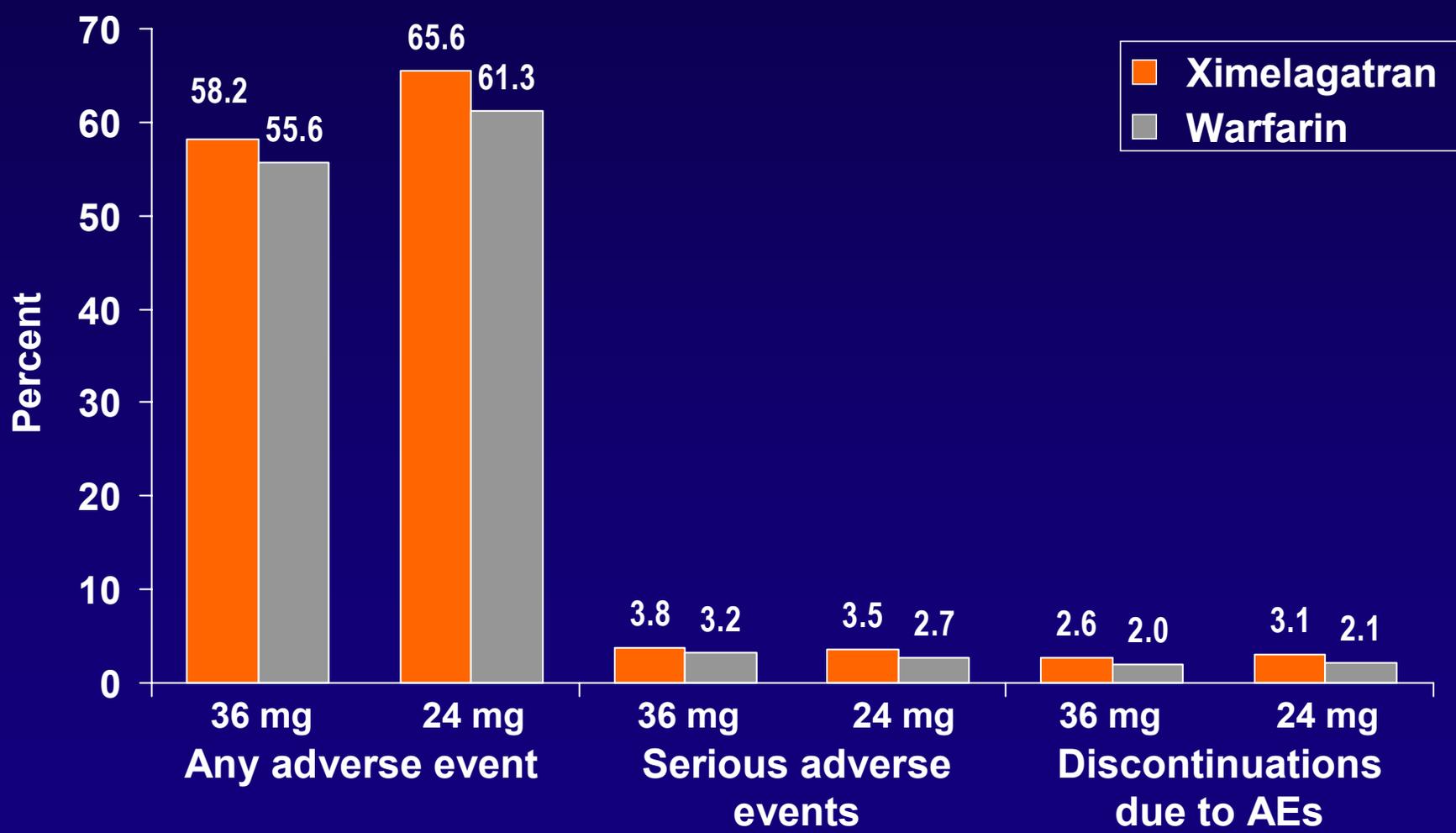
Surgical Safety Population

- ◆ **Warfarin-comparison pool** **n = 5236**
 - **Postoperative, total knee replacement**
 - **Oral ximelagatran or warfarin**
 - **Ximelagatran 36 mg** **n = 1913**
 - **Warfarin†** **n = 1897**
 - **Ximelagatran 24 mg** **n = 1097**
 - **Warfarin†** **n = 1081**

† 752 patients are used in both comparisons.

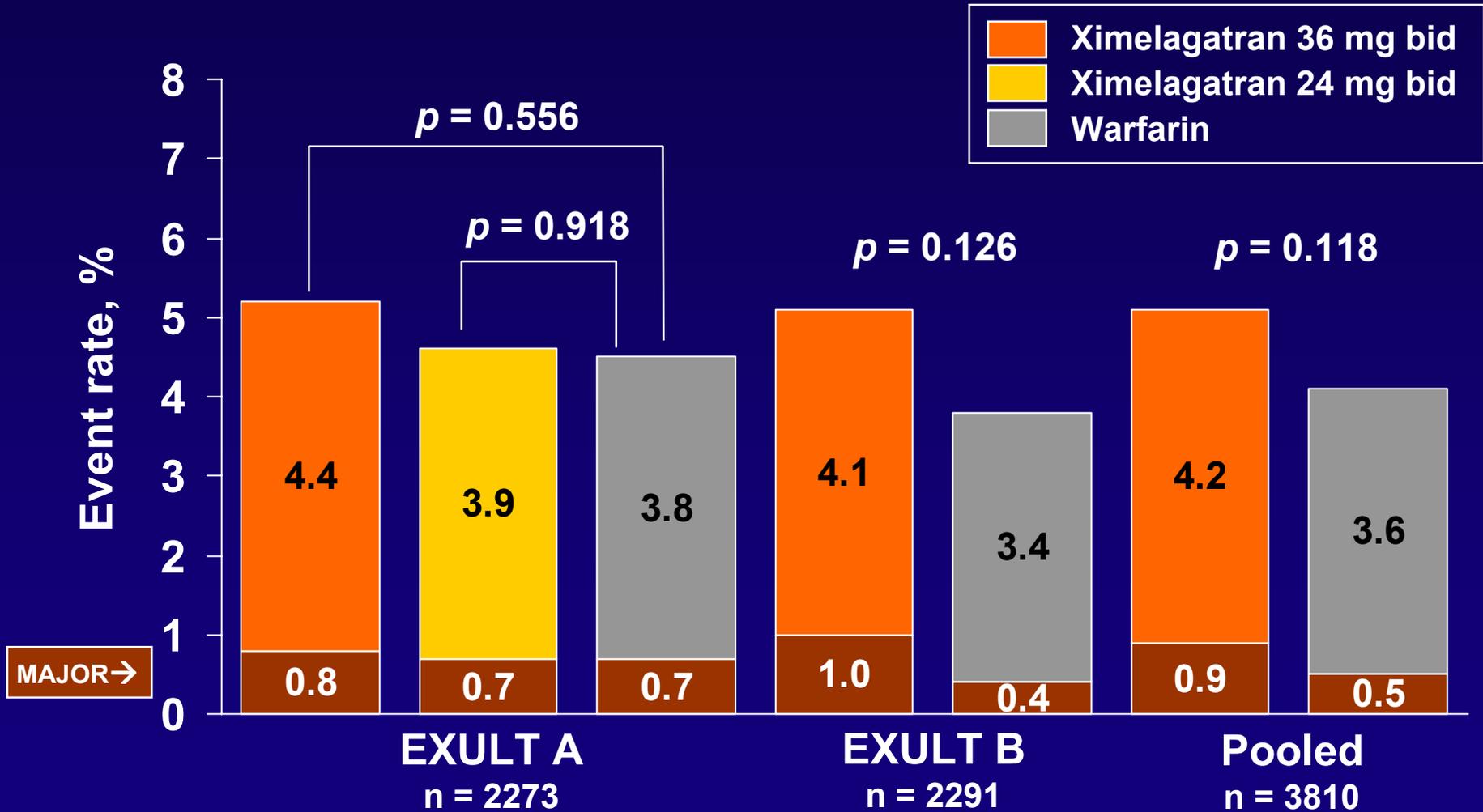
Similar Incidence of Adverse Events (AE) Between Groups

Surgical Safety—Warfarin-Comparison Pool (n = 5236)



Patients can appear in more than 1 category.

Major and/or Minor Bleeding EXULT (On-Treatment)



Other Bleeding Indicators

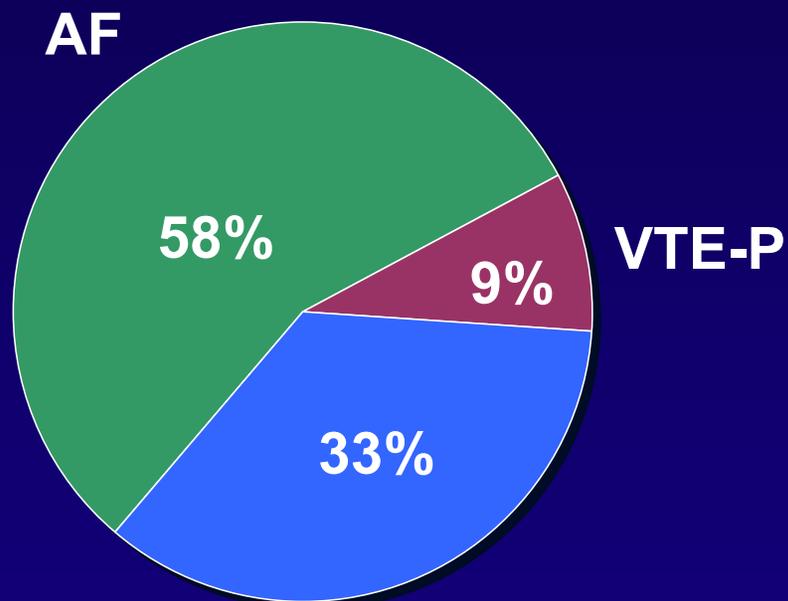
Surgical Safety—Warfarin-Comparison Pool

	Ximelagatran 36 mg	Warfarin
Wound bleeding		
Wound hematoma or bruising	4.9%	4.6%
Intra-articular bleeding	3.4%	2.9%
Transfusions		
Patients transfused	33.5%	33.6%
Volume transfused	630 mL	606 mL

Long-term Exposure Pool (LTE)

Nonsurgical Safety Population

% of patients in LTE pool



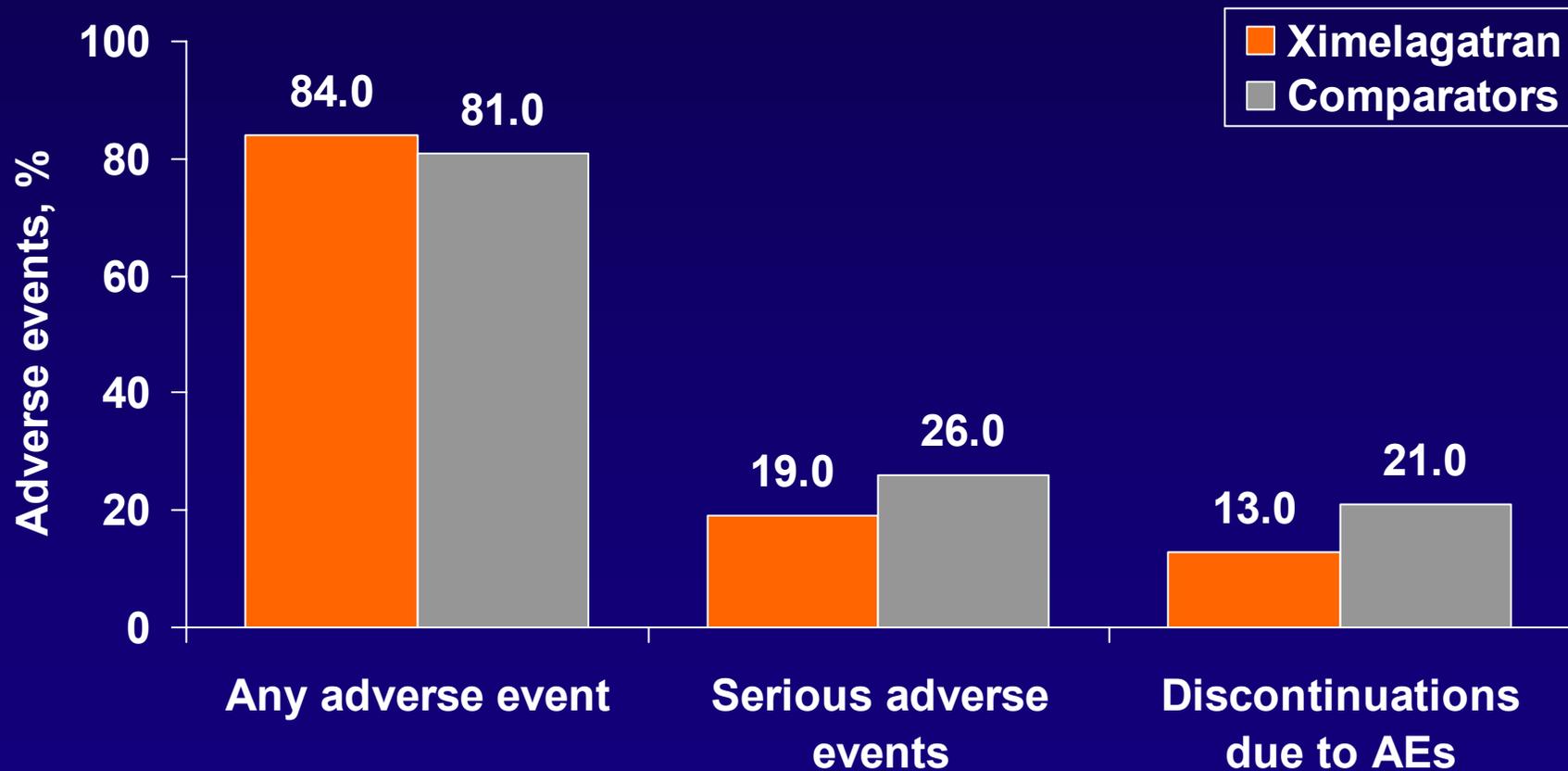
Other:
VTE-T, post ACS

Long-term exposure (LTE) pool
n = 13,147

- ◆ Ximelagatran exposure
 - 6768 patient-yr
 - Median 370 days
- ◆ Disease-based patient populations: AF, VTE-P, VTE-T and post ACS
- ◆ Ximelagatran dose
 - 36 mg bid (range 20 to 60)
- ◆ Comparators
 - Warfarin
 - Placebo

Adverse Events in the VTE-P Pool

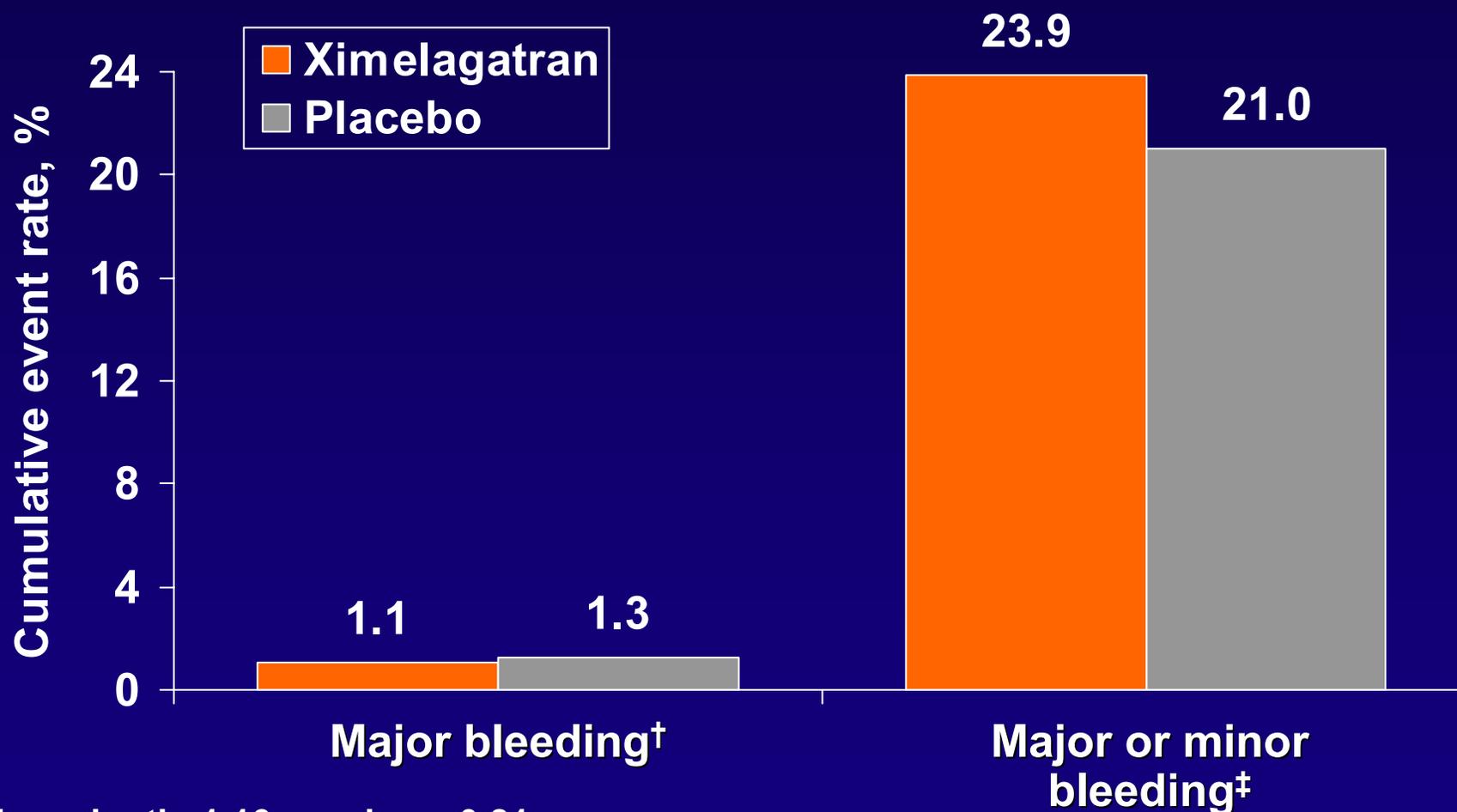
Nonsurgical Safety—VTE-P Pool (n = 1223)



Patients can appear in more than 1 category.

Adjudicated Major and/or Minor Bleeding

THRIVE III

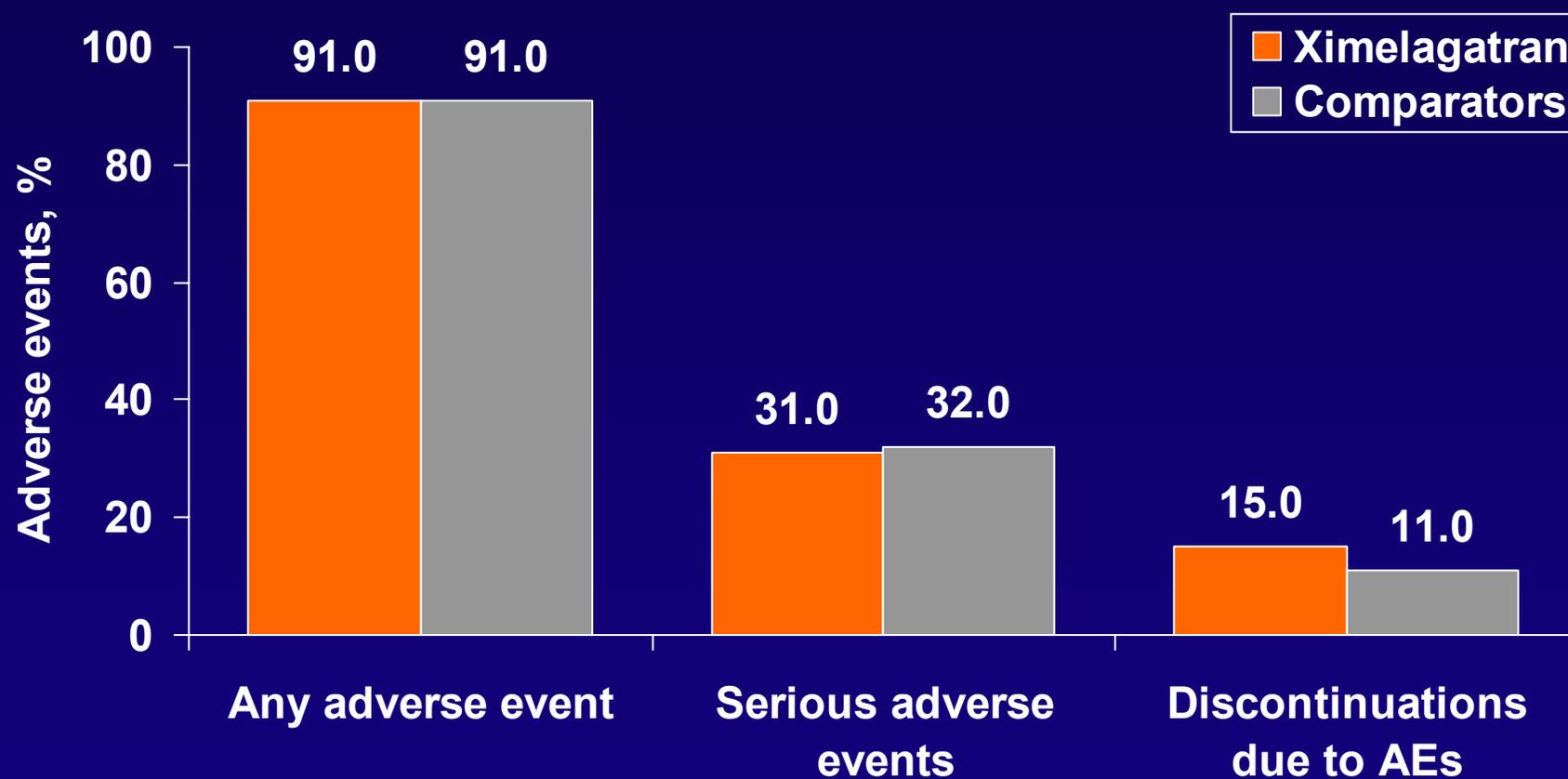


[†] Hazard ratio 1.16, *p* value = 0.81.

[‡] Hazard ratio 1.19, *p* value = 0.17.

Adverse Events in the AF Pool

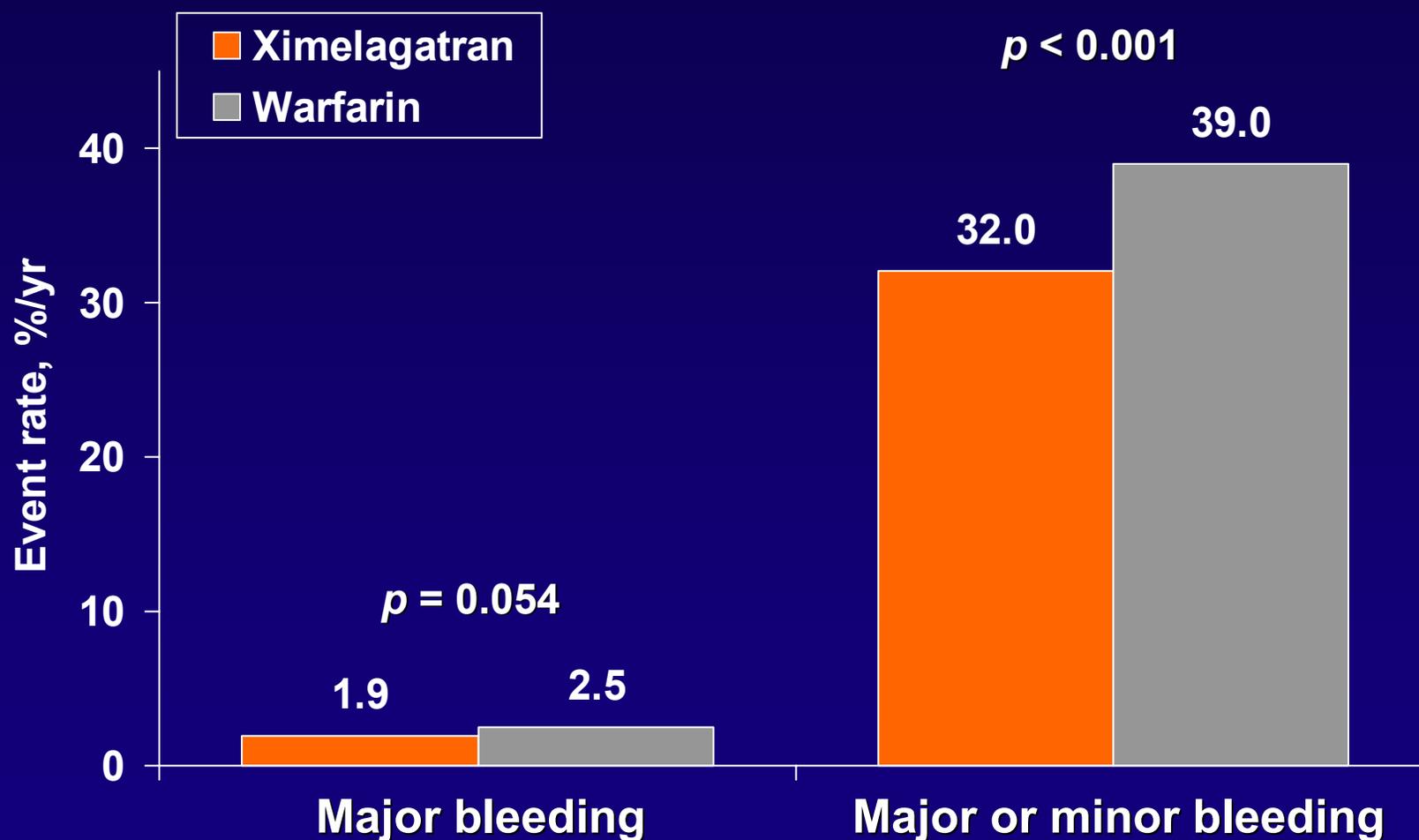
Nonsurgical Safety—AF Pool (n = 7557)



Patients can appear in more than 1 category.

Adjudicated Major and/or Minor Bleeding

SPORTIF III, SPORTIF V Pooled Data (OT Analysis)



Adverse Event and Bleeding Profile Supports Benefit/Risk

- ◆ **Ximelagatran compared to warfarin after TKR, placebo in extended secondary prophylaxis of VTE and warfarin in patients with atrial fibrillation demonstrated no important differences in**
 - **Adverse events**
 - **Bleeding profile**
 - **Safety between the 24-mg and 36-mg doses of ximelagatran**
- ◆ **Subgroup analysis for bleeding supports a fixed dose for all patients**

Table 12. Summary of CAD Adverse Events Following Short-term Use of Ximelagatran

Event, n (%)	EXULT A		EXULT B		EXULT A and B	
	Ximelagatran n = 1526	Warfarin n = 759	Ximelagatran n = 1151	Warfarin n = 1148	Ximelagatran n = 2677	Warfarin n = 1907
Myocardial infarction	11 (0.72)	1 (0.13)	5 (0.43)	3 (0.26)	16* (0.60)	4* (0.21)
Other CAD (angina/ischemia)	3 (0.2)	0	1 (0.17)	1 (0.09)	4 (0.15)	1 (0.05)
Total	14 (0.92)	1 (0.13)	6 (0.7)	4 (0.35)	20** (0.75)	5** (0.26)

* $p = 0.04951$; ** $p = 0.02800$

Table 40. Incidence of Investigator-Reported Coronary Events Nonsurgical Safety Population

Population		Patients, n (%)		p value
		Ximelagatran (AF, n = 3836) (VTE-T, n = 1236) (VTE-P n = 612)	Warfarin (AF, n = 3719) (VTE-T, n = 1248) (VTE-P n = 611)	
AF	Total CAD	268 (7.0)	248 (6.7)	0.584
	MI	62 (1.6)	52 (1.4)	0.437
VTE-T	Total CAD	16 (1.3)	1 (0.1)	0.0002
	MI	3 (0.2)	0	0.082
VTE-P	Total CAD	16 (2.6)	12 (2.0)	0.447
	MI	10 (1.6)	3 (0.5)	0.051
VTE	Total CAD	32 (1.7)	13 (0.7)	0.00411
	MI	13 (0.7)	3 (0.16)	0.01183
Total	Total CAD	300 (5.3)	261 (4.7)	0.1441
	MI	75 (1.3)	55 (1.0)	0.0976

Adjudicated Myocardial Infarction

OT Analysis

Trial	Events (%/yr)	
	Ximelagatran	Warfarin
SPORTIF pooled	50 (1.0)	50 (1.0)
SPORTIF III	24 (1.1)	13 (0.6)
SPORTIF V	26 (1.0)	37 (1.4)

Trial	Events (%)	
	Ximelagatran + ASA n = 1245	Placebo + ASA n = 638
ESTEEM	50 (4.0)	33 (5.2)

History of Hepatic Findings

Nonsurgical Safety—LTE Pool

- ◆ **Preclinical toxicology and the phase I studies**
 - **No hepatic safety issues**
- ◆ **Surgical program**
 - **No hepatic signal**
- ◆ **Phase II long-term dosing study in atrial fibrillation patients**
 - **Asymptomatic increase in ALT $> 3 \times$ ULN noted**
 - **Testing was increased in phase III studies**

Hepatic Lab Testing

- ◆ Liver function testing panel
 - ALT, AST, alkaline phosphatase, bilirubin
- ◆ Regular testing
 - Monthly × 6 mo, every 2 mo × 6 mo, quarterly

Algorithm 1

Algorithm 2

Weekly testing ALT > 3 → ALT > 2

Discontinuation ALT > 7 → ALT > 5

ALT Elevations With Short-term Use

Surgical Safety Warfarin-Comparison Pool (n = 5236)

- ◆ **Incidence of ALT > 3 × ULN low and similar between groups on treatment**
- ◆ **8 patients on ximelagatran and 3 patients on warfarin with ALT > 3 × ULN after treatment discontinuation**
 - **2/8 on ximelagatran received LMWH in follow-up**
- ◆ **Documented resolution of ALT elevation**
 - **7/8 Ximelagatran**
 - **2/3 Warfarin**

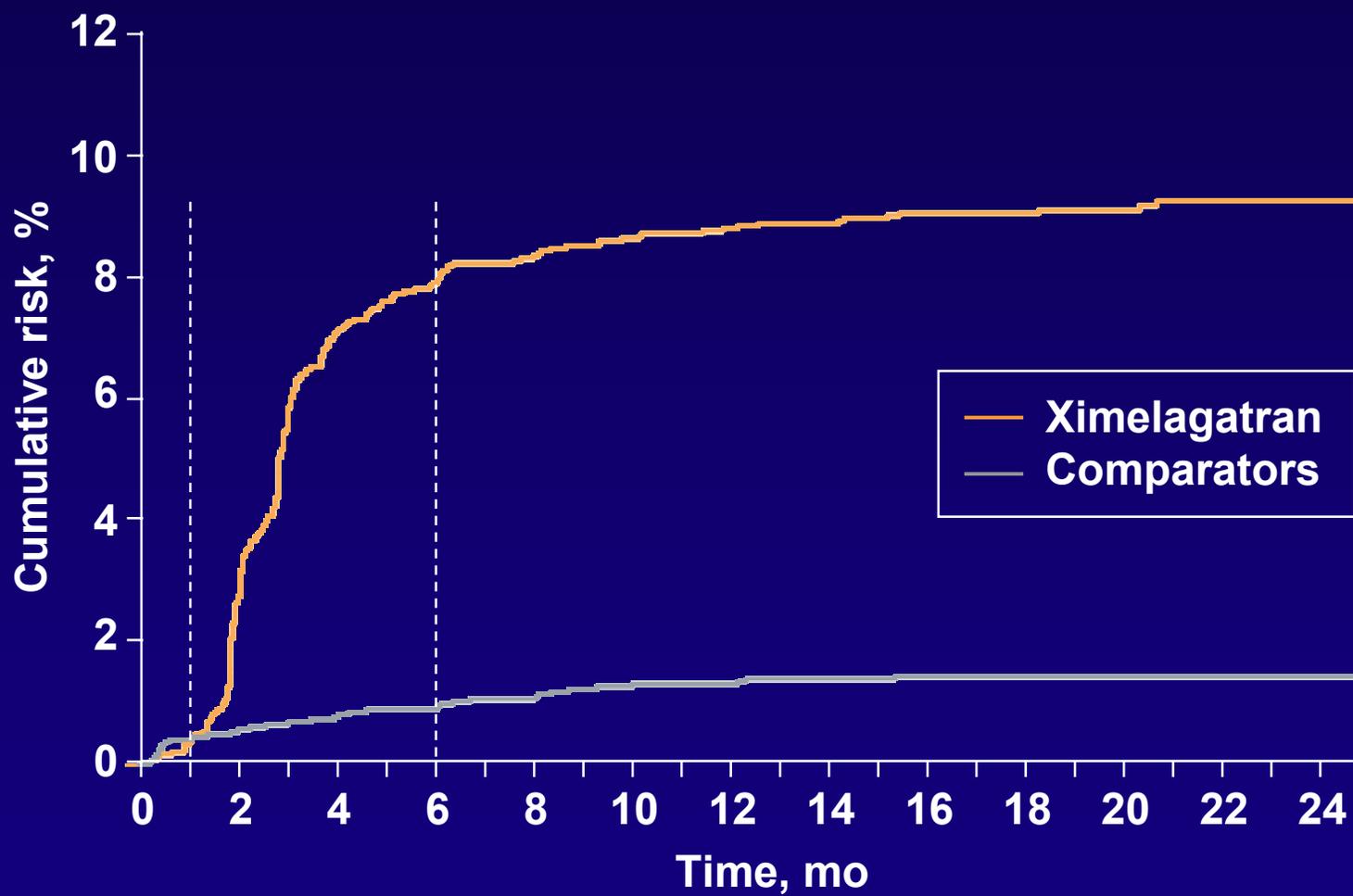
Incidence of Hepatic Test Elevations

Nonsurgical Safety—LTE Pool

	Patients, n (%)	
	Ximelagatran n = 6948	Comparators n = 6230
ALT > 3 × ULN	546 (7.9)	74 (1.2)
Bilirubin > 2 × ULN	86 (1.2)	66 (1.1)

Cumulative Risk of ALT > 3 × ULN vs Time After Randomization†

Nonsurgical Safety—LTE Pool



† Central and local laboratory data.

Recovery of ALT With Continuation or Discontinuation Nonsurgical Safety—LTE Pool

Patients

Ximelagatran Comparators

n = 546

n = 74

Continued treatment

46%

31%

Discontinued treatment

54%

69%

Total recovered

96%

93%

Recovery of ALT (Ximelagatran Group) With Continuation or Discontinuation Nonsurgical Safety—LTE Pool

- ◆ Median time to recovery
 - Continued drug ~28 days
 - Discontinued drug ~40 days
- ◆ 18 patients rechallenged. Only 2 had a repeat ALT elevation
- ◆ No evidence in any patient of an immunoallergic reaction

Incidence of Combined ALT and Bilirubin Elevations Nonsurgical Safety—LTE Pool

	Patients, n (%)	
	Ximelagatran n = 6948	Comparators n = 6230
ALT > 3 × ULN	546 (7.9)	74 (1.2)
Bilirubin > 2 × ULN	86 (1.2)	66 (1.1)
<u>Combined</u>		
ALT > 3 × ULN/ Bilirubin > 2 × ULN	37 (0.53)	5 (0.08)

Outcome in Patients With ALT > 3 × ULN and Bilirubin > 2 × ULN CS-25

Nonsurgical Safety—LTE Pool

- ◆ **37 ximelagatran patients**
 - **25 with confounding diagnoses**
 - 7 died (3 metastatic cancer, 3 heart failure, 1 reactivation hepatitis)
 - 18 recovered
 - **12 without alternative diagnosis**
 - 2 died (GI bleed)
 - 10 recovered

- ◆ **5 comparators patients**
 - **4 alternative diagnosis**
 - 2 died (pancreatic cancer)
 - 2 recovered
 - **1 without alternative diagnosis**
 - 1 recovered

Mechanism of Action of ALT Increase

- ◆ Pathogenesis of ALT increase is unknown
 - No evidence for reactive metabolites, mitochondrial dysfunction, protein binding
 - No evidence for P450 involvement
- ◆ Similar pattern of asymptomatic, reversible or nonprogressive ALT increases seen with other drugs (tacrine ~50%, amiodarone 25%, diclofenac 15%, INH 10%, methyldopa 5% to 35%, statins ~5%, etc)

Analysis of Potential Prognostic Factors for ALT > 3 × ULN

CS-27

Nonsurgical Safety—LTE Pool

- ◆ Treatment is the most significant factor
 - OR 6.8 (5.3 - 8.7)
- ◆ Other factors have an OR < 2
 - Post ACS patients 1.8 (1.5 - 2.2)
 - VTE-T patients 1.7 (1.4 - 2.1)
 - BMI < 25 kg/m² 1.4 (1.2 - 1.7)
 - Female gender 1.3 (1.1 - 1.6)
- ◆ Statins, creatinine clearance were not significant

Patients With Hepatobiliary Adverse Events

Nonsurgical Safety Population—LTE Pool

Preferred term	Patients, %	
	Ximelagatran n = 6931	Comparators n = 6216
Cholelithiasis	0.8	0.9
Bilirubinemia	0.6	0.6
Cholecystitis	0.4	0.3
Hepatomegaly	0.3	0.2
Jaundice	0.1	0.1
Biliary pain	0.1	0.1
Hepatic cyst	0.1	0.1
Hepatitis	0.1	0.1
Hepatocellular damage	0.1	< 0.1
Hepatitis cholestatic	< 0.1	0.1

Selected Cases With Hepatic Injury and Death

Nonsurgical Safety Population—LTE Pool

Case #	Days to ALT > 3 × ULN	Max ALT × ULN	Max bilirubin × ULN	Comment	Cause of death
7259 Male 80 yr	100	34	8	<ul style="list-style-type: none"> ◆ Hepatic Bx-Hepatic necrosis ◆ Prednisone ◆ Autopsy 	Perforated Duodenal ulcer
7859 Male 77 yr	63	11	9.4 (50% indirect)	<ul style="list-style-type: none"> ◆ PMH: duodenal ulcer, Bilioth II anastomosis (site of bleed) ◆ Admission: INR 3.4, APTT 69 seconds, Bili 1.4 × ULN ◆ Massive transfusions ◆ At death: ALT 1.9 × ULN, bilirubin 7.3 × ULN ◆ No autopsy 	GI bleed
5442 Male 73 yr	12	14.8	3.64	<ul style="list-style-type: none"> ◆ PMH: lupus ◆ Prednisone and azathioprine ◆ Baseline ALT 1.96 × ULN 	Fulminant Hepatitis B

Summary of Hepatic Findings

- ◆ **ALT elevations**
 - **> 3 × ULN (7.9%), primarily first 6 mos**
- ◆ **Typically asymptomatic and reversible**
- ◆ **No evidence of immunoallergic reaction**
- ◆ **Concomitant elevation of ALT > 3 × ULN and bilirubin > 2 × ULN (0.5%)**
- ◆ **Exposure not predictive of individual risk of transaminase elevation**
- ◆ **No patient subset identified at higher risk of developing severe liver toxicity**

Actions Based on Hepatic Data

- ◆ **Recommend ALT testing in the label**
- ◆ **Implement a comprehensive Risk Minimization Action Plan (Risk MAP)**
- ◆ **Meeting scheduled to agree to specifics of Risk MAP with FDA**

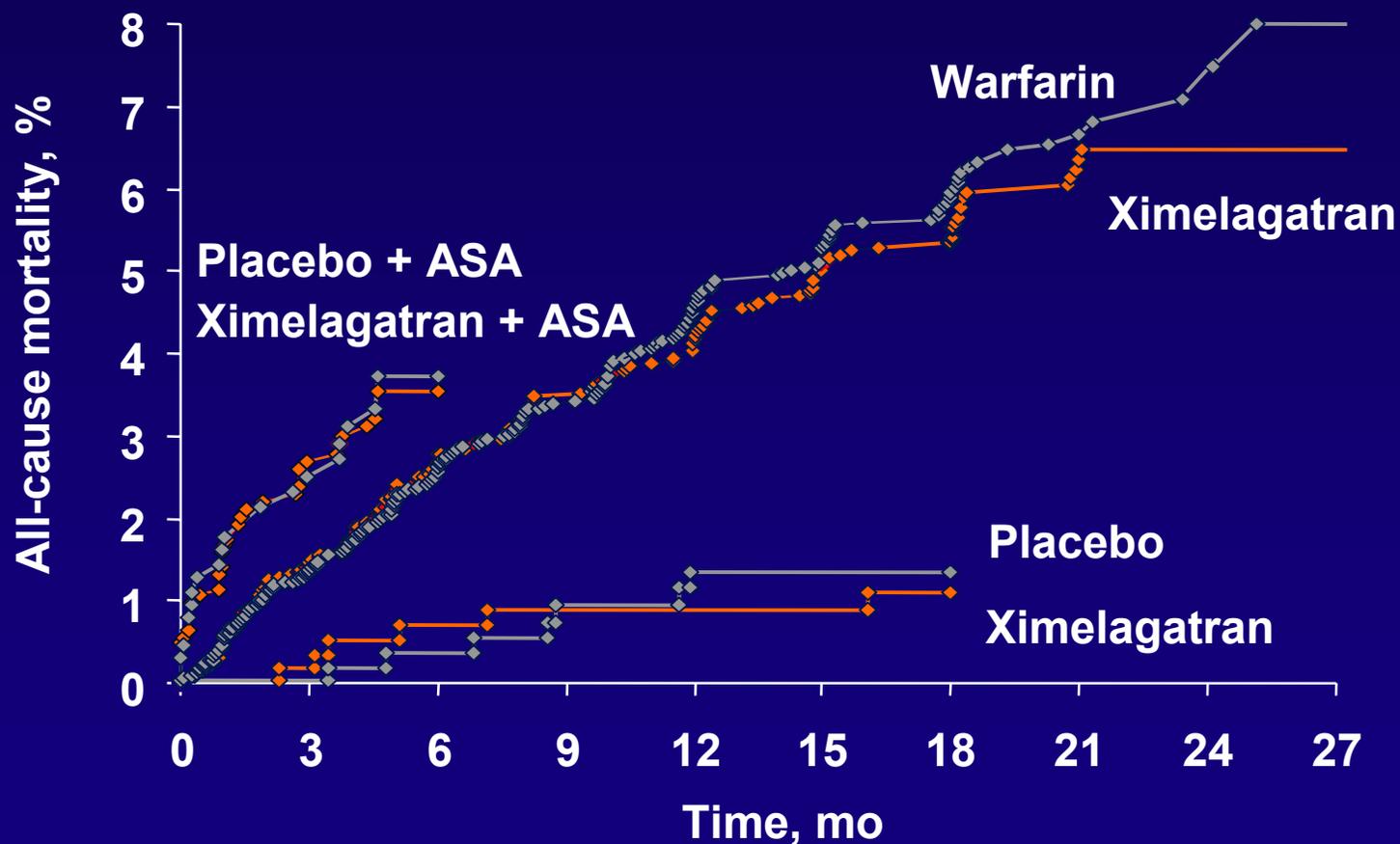
Risk Minimization Action Plan

- ◆ **Goal: prevent any hepatic failure caused by treatment with ximelagatran**
- ◆ **Objective: help ensure compliance with labeled ALT testing recommendations**
- ◆ **Program elements**
 - **Targets patients, physicians, pharmacists**
 - **Strong educational focus, special packaging**
 - **Enhancements to be incorporated to help ensure ALT testing as recommended in label**
 - **Continuous evaluation of program effectiveness**

All-Cause Mortality Similar Between Groups

Nonsurgical Safety—LTE Pool (n = 13,147)

- ◆ 3.9% ximelagatran vs 4.4% comparators



Conclusions—TKR

- ◆ **Prevention of VTE in patients undergoing knee replacement surgery**
- ◆ **36 mg bid vs warfarin**
 - **Benefit**
 - **NNT 12 to prevent VTE and all-cause mortality**
 - **Risk**
 - **No difference in bleeding**

Conclusions—VTE-P

- ◆ Long-term secondary prevention of VTE after standard treatment
- ◆ 24 mg bid vs placebo
 - Benefit
 - NNT 10 to prevent DVT and PE
 - Risk
 - Bleeding similar to placebo
 - Severe liver injury
 - ALT testing recommended in label
 - Risk MAP to be implemented

Conclusions—AF

- ◆ **Prevention of stroke and other thromboembolic complications associated with atrial fibrillation**
- ◆ **36 mg bid vs warfarin**
 - **Benefit**
 - **Noninferior to warfarin**
 - **Risk**
 - **Less bleeding than warfarin**
 - **Severe liver injury**
 - **ALT testing recommended in label**
 - **Risk MAP to be implemented**