Engage AF
TIMI 48

Efficacy and Safety Outcomes in 8040 Women Compared with 13065 Men with Atrial Fibrillation Treated with Edoxaban vs Warfarin for an Average 2.8 Years

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ENGAGE AF-TIMI 48 Investigators

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VE RI TAS

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MY CONFLICTS OF INTEREST ARE:

Research Grants:

Daiichi Sankyo, Merck

Honoraria/Consulting:

Bristol-Myers Squibb, Daiichi-Sankyo, Janssen, Merck, Pfizer, Portola, Sanofi

Background: Women, Oral Anticoagulation (OAC) and AF

- Study-level metanalysis of 6 trials* of OAC in patients with AF found:
  - Women treated with *warfarin*
    - ↑ risk of thromboembolism (HR 1.3) c/w men
    - Similar risk of bleeding (HR 0.93) as men
  - Women treated with *DOAC*
    - Similar risk of thromboembolism (HR 1.1) as men
    - ↓ risk of bleeding (HR 0.84) c/w men
- Limitations: unadjusted, study-level data

* 6 RCTs: BAFTA, SPORTIF III/IV, RE-LY, ROCKET-AF, ARISTOTLE, AVERROES

Pancholly SB et al, Am J Card 2014;113:485-90

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Study Design

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21,105 PATIENTS
AF documented within last 12 m
$CHADS_2$ ≥2

RANDOMIZATION 1:1:1

Double-blind, Double-dummy

Warfarin (N=7036)
(INR 2.0–3.0)
Median TTR 68.4%

Higher-dose Edoxaban
60* mg QD
(N=7035)

Lower-dose Edoxaban
30* mg QD
(N=7034)

Median follow-up 2.8 yrs
(~60,000 patient-years)

*Edoxaban dose reduced by 50% if:
- CrCl 30–50 mL/min
- weight ≤60 kg
- strong P-gp inhibitor

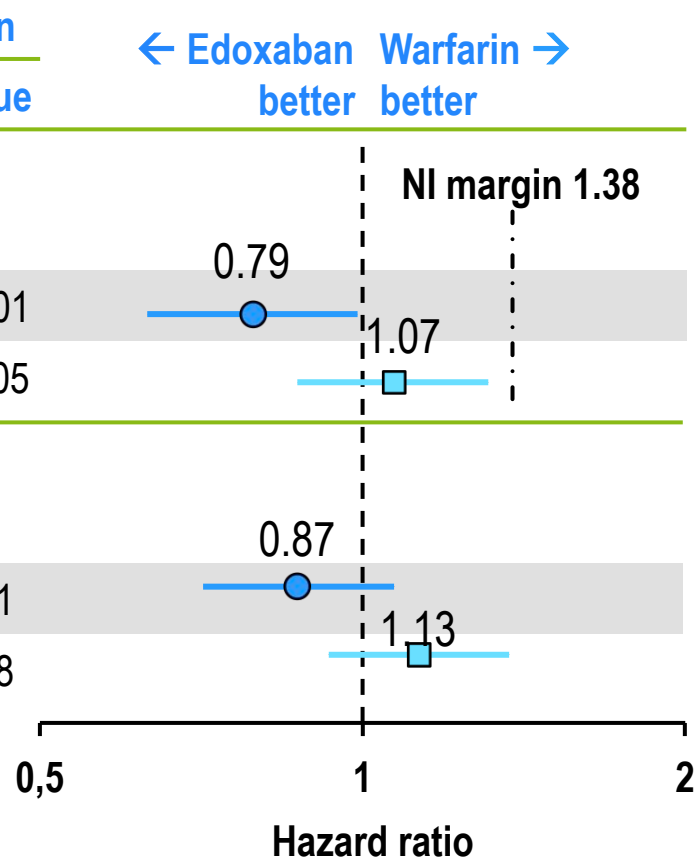
1º Efficacy EP = Stroke or SEE
1º Safety EP = Major Bleeding (ISTH criteria)

CrCl, creatinine clearance; ISTH, International Society on Thrombosis and Haemostasis; P-gp, P-glycoprotein; SEE, systemic embolic event

Ruff CR et al. Am Heart J 2010; 160:635-41
Giugliano RP. NEJM 2013; 369:2093-2104

Primary Efficacy Endpoint: Stroke or SEE

Treatment	n	Event rate, %/yr	Edoxaban vs warfarin HR (97.5% CI)	P value
Noninferiority (mITT on-treatment)				
Warfarin	232	1.50	—	—
Edoxaban 60/30 mg QD	182	1.18	0.79 (0.63, 0.99)	< 0.001
Edoxaban 30/15 mg QD	253	1.61	1.07 (0.87, 1.31)	0.005
Superiority (ITT overall)			HR (99% CI)	
Warfarin	337	1.80	—	—
Edoxaban 60/30 mg QD	296	1.57	0.87 (0.71, 1.07)	0.081
Edoxaban 30/15 mg QD	383	2.04	1.13 (0.93, 1.37)	0.098



Giugliano RP. NEJM 2013; 369:2093-2104

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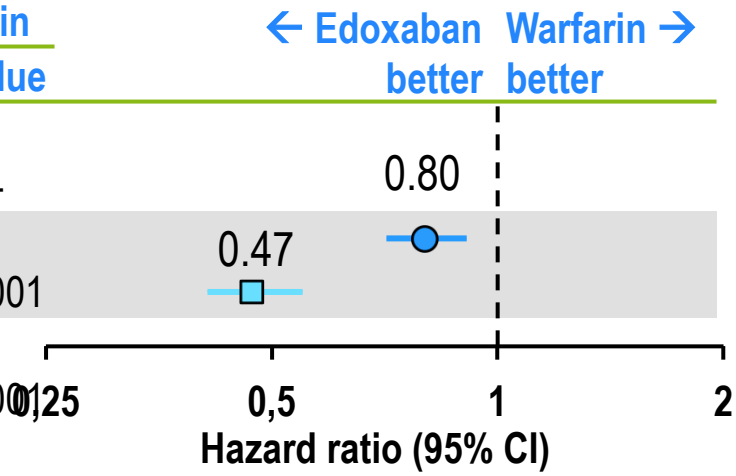
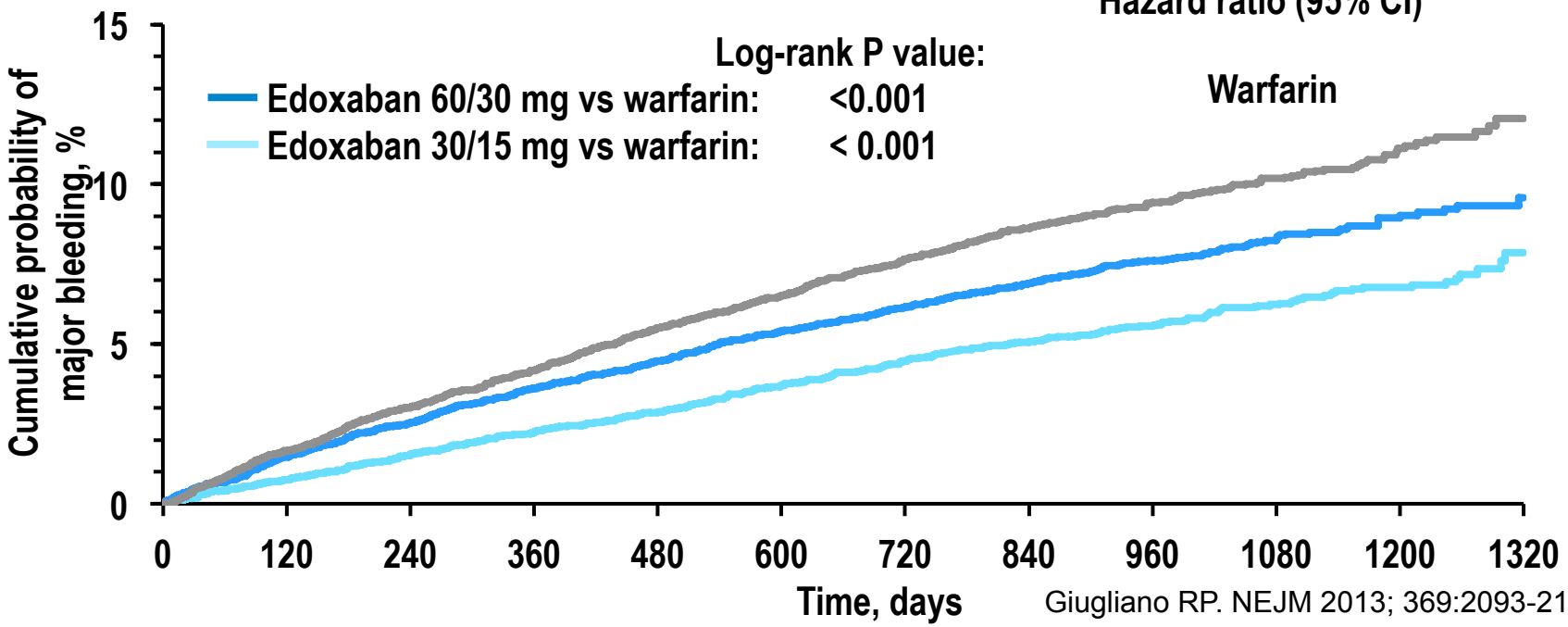
Principal Safety Outcome—Major Bleeding

Safety On-Treatment

Outcome Treatment	n	Event rate, %/yr	Edoxaban vs warfarin HR (95% CI)	P value
Major bleed				
Warfarin	524	3.43	—	—
Edoxaban 60/30 mg	418	2.75	0.80 (0.71, 0.91)	< 0.001
Edoxaban 30/15 mg	254	1.61	0.47 (0.41, 0.55)	< 0.001





Giugliano RP. NEJM 2013; 369:2093-2104

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Summary: Main Trial

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- Compared to well-managed warfarin (TTR 68.4%) once-daily edoxaban:
  - Non-inferior for stroke/SEE (both regimens)
    - High dose ↓stroke/SEE on Rx (trend ITT)
  - Both regimens *significantly* reduced:
    - Major bleeding (20%/53%)
    - ICH (53%/70%)
    - Hemorrhagic stroke (46%/67%)
    - CV death (14%/15%)
  - *Superior* net clinical outcomes
  - No excess in stroke or bleeding during transition → oral anticoagulant at end of trial

Giugliano RP. NEJM 2013; 369:2093-2104

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Baseline Characteristics by Gender

	Women 8040 (38%)	Men 13065 (62%)
Median Age (years)	74 [67–79]	71 [63–77]
Region		
Western Europe	15%	15%
Eastern Europe	37%	32%
North America	20%	24%
Latin America	13%	12%
Asia / Australia / S Africa	14%	17%
Paroxysmal AF	30%	23%
Median Weight (kg)	74 [64–86]	86 [75–99]
CrCl ≤50 ml/min	28%	14%
Dose reduction	36%	19%

P<0.001 for all comparisons

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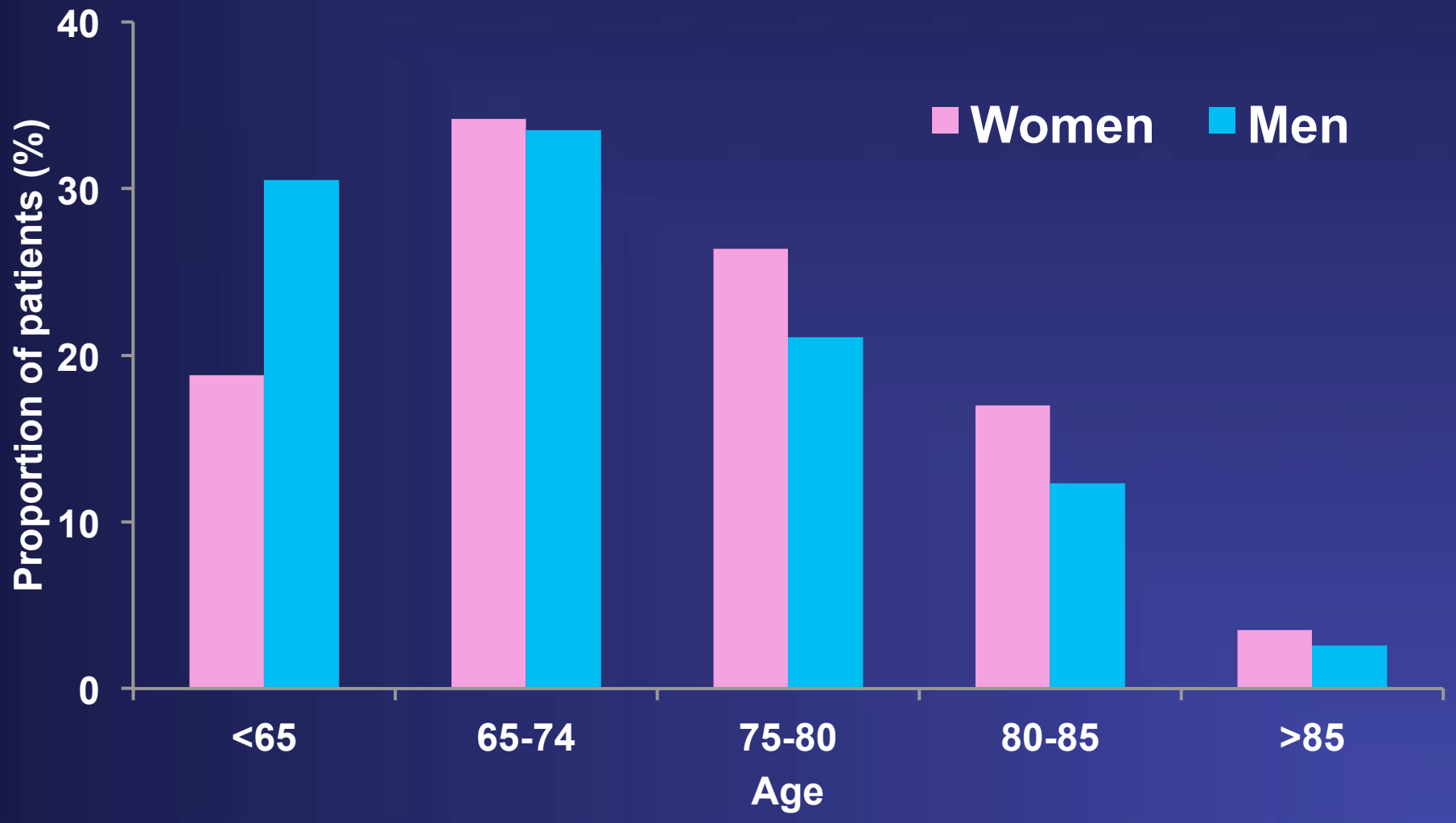
Age Distribution by Gender



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Risk Factors by Gender

	Women 8040 (38%)	Men 13065 (62%)
Congestive heart failure	57%	58%
Hypertension	**95%**	**93%**
Diabetes	**35%**	**37%**
Prior stroke/TIA	28%	28%
$CHADS_2$ ≥4	**25%**	**21%**
Mean $CHADS_2$ score	**2.9 (1.0)**	**2.8 (1.0)**
CHA_2DS_2-VASc ≥4	**92%**	**58%**
Mean CHA_2DS_2-VASc score	**5.0 (1.3)**	**3.9 (1.3)**
HAS-BLED ≥3	**43%**	**49%**
Median TTR (warfarin)	**67% (55-76)**	**69% (58-78)**

P<0.001 for all comparisons, except CHF (p=0.22), prior stroke/TIA (p=0.91)

CHF, chronic heart failure; TIA, transient ischemic attack; TTR, time in therapeutic range

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Annualized Rate of Stroke/SEE by Gender and Age (Warfarin)

	Women (N=2641)	Men (N=4395)	Adjusted HR* (95% CI)	Adj P*
All Ages	2.00%	1.68%	1.22 (0.95, 1.57)	0.125

*Adjusted for Age, BMI, creatinine, race, region, increased risk of falling, smoking status, pattern of afib, alcohol use, cardiac medications; and prior history of hypertension, dyslipidemia, diabetes, stroke or TIA, CHF, neuropsychiatric disease, CAD, hepatic disease, non-ICH Bleed

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Annualized Rate of Major Bleed by Gender and Age (Warfarin)

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	Women (N=2629)	Men (N=4383)	Adjusted HR* (95% CI)	Adj P*
All Ages	3.35%	3.47%	0.91 (0.74, 1.13)	0.41

*Adjusted for Age, BMI, creatinine, race, region, increased risk of falling, smoking status, pattern of afib, alcohol use, cardiac medications; and prior history of hypertension, dyslipidemia, diabetes, stroke or TIA, CHF, neuropsychiatric disease, CAD, hepatic disease, non-ICH Bleed

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Secondary Efficacy Outcomes Women vs Men (Warfarin)

Endpoint	Women	Men	Adj HR*	Adj P*
CV death, stroke, SEE	4.15%	4.60%	0.98	0.79
MACE†	4.66%	5.18%	0.98	0.76
All cause mortality	3.77%	4.70%	0.86	0.08
CV death	2.73%	3.43%	0.87	0.18
Hemorrhagic stroke	0.50%	0.46%	1.17	0.53
Ischemic stroke	1.41%	1.15%	1.18	0.27
Myocardial infarction	0.62%	0.83%	0.88	0.54

*Adjusted for Age, BMI, creatinine, race, region, increased risk of falling, smoking status, pattern of afib, alcohol use, cardiac medications; and prior history of hypertension, dyslipidemia, diabetes, stroke or TIA, CHF, neuropsychiatric disease, CAD, hepatic disease, non-ICH Bleed

CV, cardiovascular; † MACE, major adverse cardiac event; SEE, systolic embolic event;

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Secondary Safety Outcomes Women vs Men (Warfarin)

Endpoint	Women	Men	Adj HR*	Adj P*
Fatal bleeding	0.33%	0.40%	1.04	0.90
Intracranial bleeding	0.89%	0.82%	1.06	0.80
Death or ICH	4.34%	5.21%	0.88	0.13
Major GI bleeding	1.08%	1.31%	0.92	0.66
Major or clinically-relevant non-major bleed	13.6%	12.7%	1.13	0.037
Any bleeding	17.1%	16.0%	1.15	0.009

*Adjusted for Age, BMI, creatinine, race, region, increased risk of falling, smoking status, pattern of afib, alcohol use, cardiac medications; and prior history of hypertension, dyslipidemia, diabetes, stroke or TIA, CHF, neuropsychiatric disease, CAD, hepatic disease, non-ICH Bleed

GI, gastrointestinal; ICH, intracranial hemorrhage

Primary Efficacy Outcome by Gender

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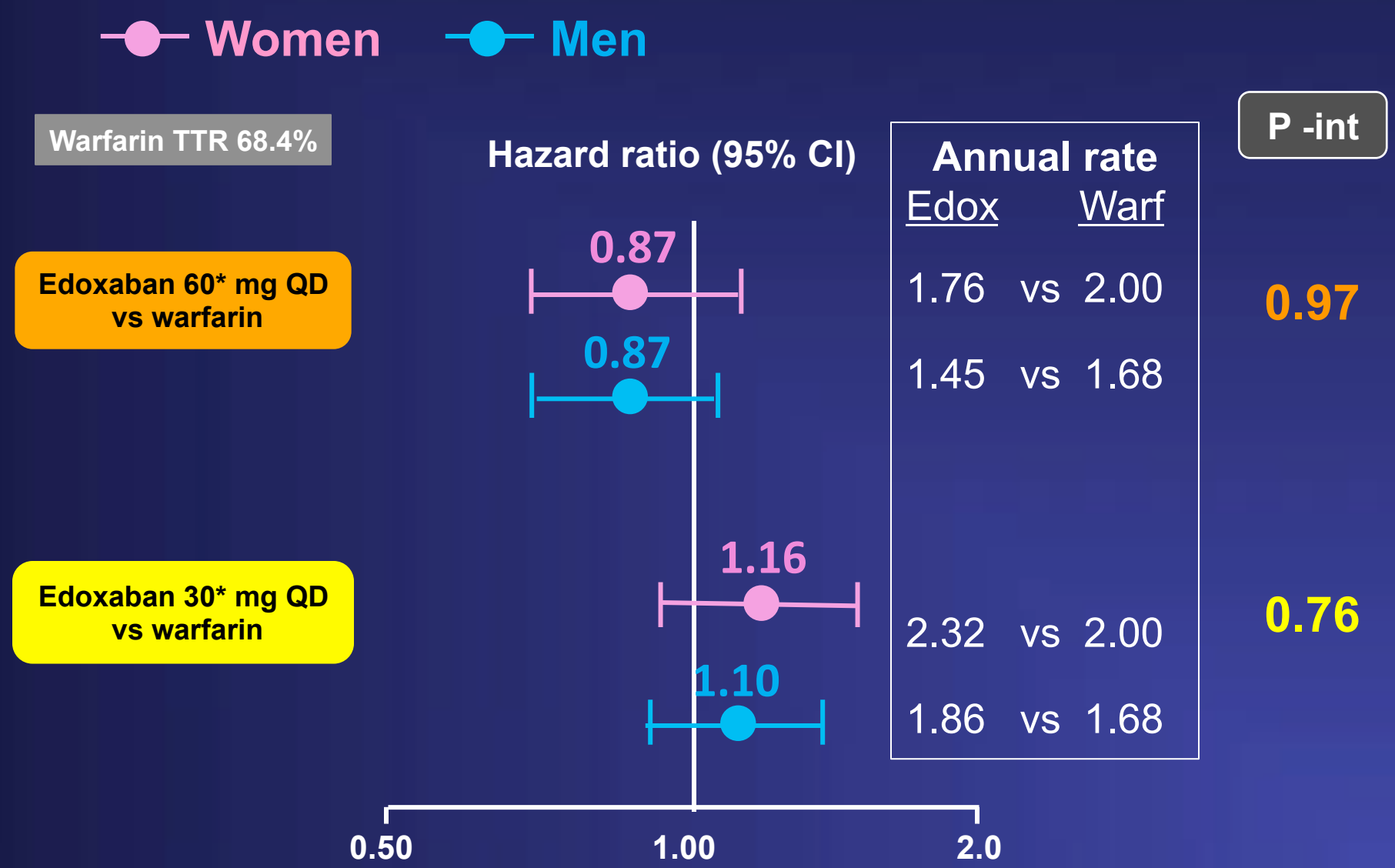
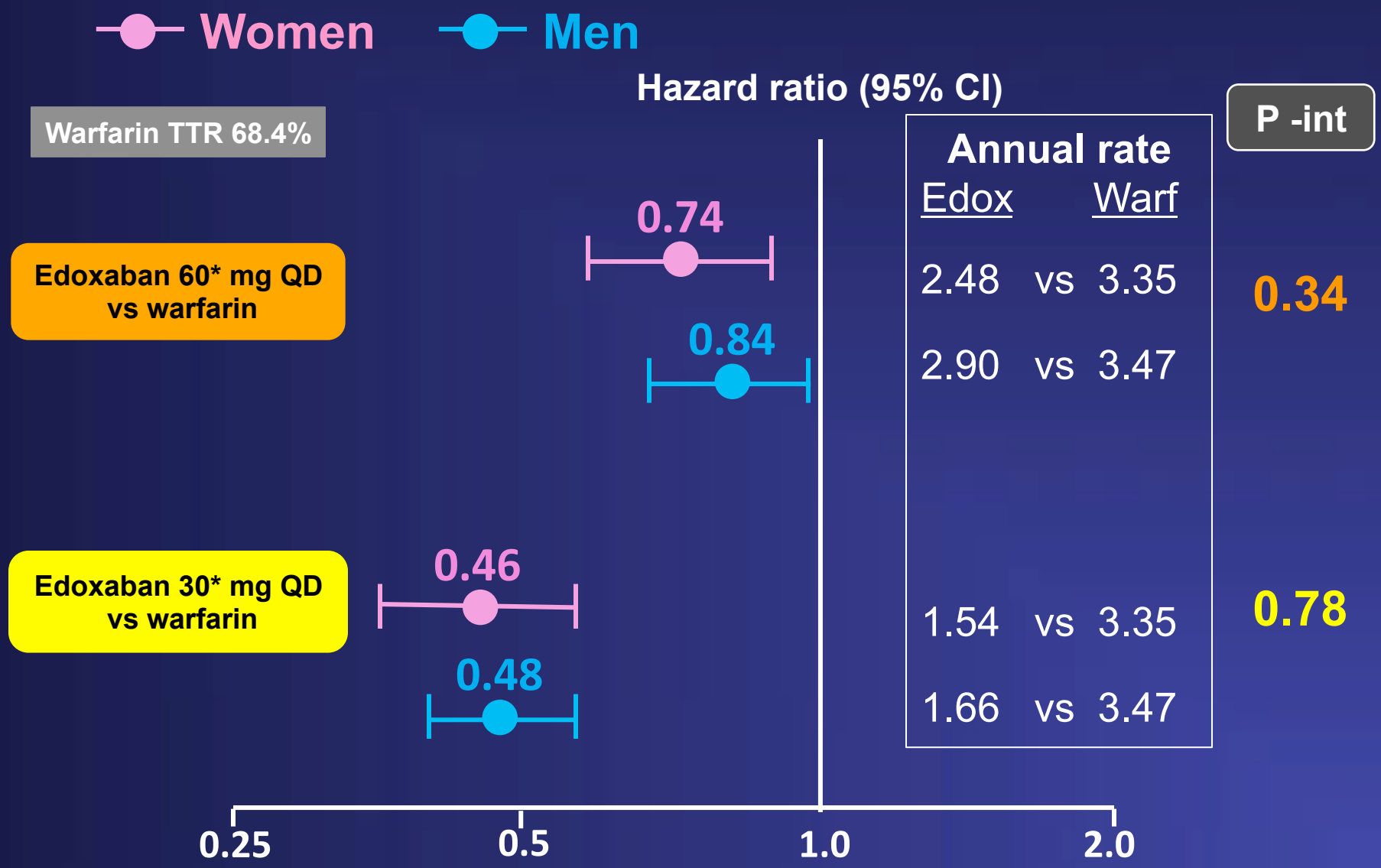
Stroke/SEE: ITT cohort, Overall time period



Primary Safety Outcome by Gender

Major Bleeding: Safety cohort, On Treatment



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Secondary Efficacy Outcomes Higher Dose Edox vs Warfarin

	Hazard Ratios (HDE vs W)		
Endpoint	Women	Men	P-int
CV death, stroke, SEE	0.87	0.87	0.95
MACE*	0.89	0.88	0.99
All cause mortality	0.93	0.91	0.88
CV death	0.87	0.86	0.97
Hemorrhagic stroke	0.30	0.70	0.037
Ischemic stroke	1.08	0.94	0.44
Myocardial infarction	0.99	0.91	0.75

CV, cardiovascular; HDE, high dose edoxaban; MACE, major adverse cardiac event; SEE, systolic embolic event; W, warfarin

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Secondary Safety Outcomes Higher Dose Edox vs Warfarin

	Hazard Ratios (HDE vs W)		
Endpoint	Women	Men	P-int
Fatal bleeding	0.38	0.63	0.32
Intracranial bleeding	0.20	0.63	0.003
Death or ICH	0.80	0.69	0.42
Major GI bleeding	1.34	1.19	0.59
Major or clinically-relevant non-major bleeding	0.76	0.92	0.011
Any bleeding	0.78	0.92	0.010

CV, cardiovascular; GI, gastrointestinal; HDE, high dose edoxaban; ICH, intracranial hemorrhage; W, warfarin

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Net Clinical Outcomes Higher Dose Edox vs Warfarin

	Hazard Ratios (HDE vs W)		
Endpoint	Women	Men	P-int
Death, Stroke, Systemic embolism, or Major Bleeding	0.89	0.89	0.99
Death, disabling stroke or life-threatening bleeding	0.85	0.91	0.49
Death, Stroke, SEE or life-threatening bleeding	0.85	0.89	0.62

HDE, high dose edoxaban, SEE, systolic embolic event; W, warfarin

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Summary

In the ENGAGE AF-TIMI 48 Trial, warfarin arm

- Women and men have similar risk of ischemic events, death, major bleeding *after adjustment*
- Non-major bleeding more frequent women

Comparison of Edoxaban vs Warfarin

- Efficacy of high-dose edoxaban is comparable in women and men
- The superior safety profile of edoxaban overall in the main trial was *enhanced* in women as compared to men

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MILLE GRAZIE !!!

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N. Babilonia

THAILAND (115)
P. Sritara

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A. Oto

FRANCE (110)
J.J. Blanc

AUSTRALIA (102)
P. Aylward

GREECE (51)
D. Alexopoulos

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M. Nieminen

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SWITZERLAND (5)
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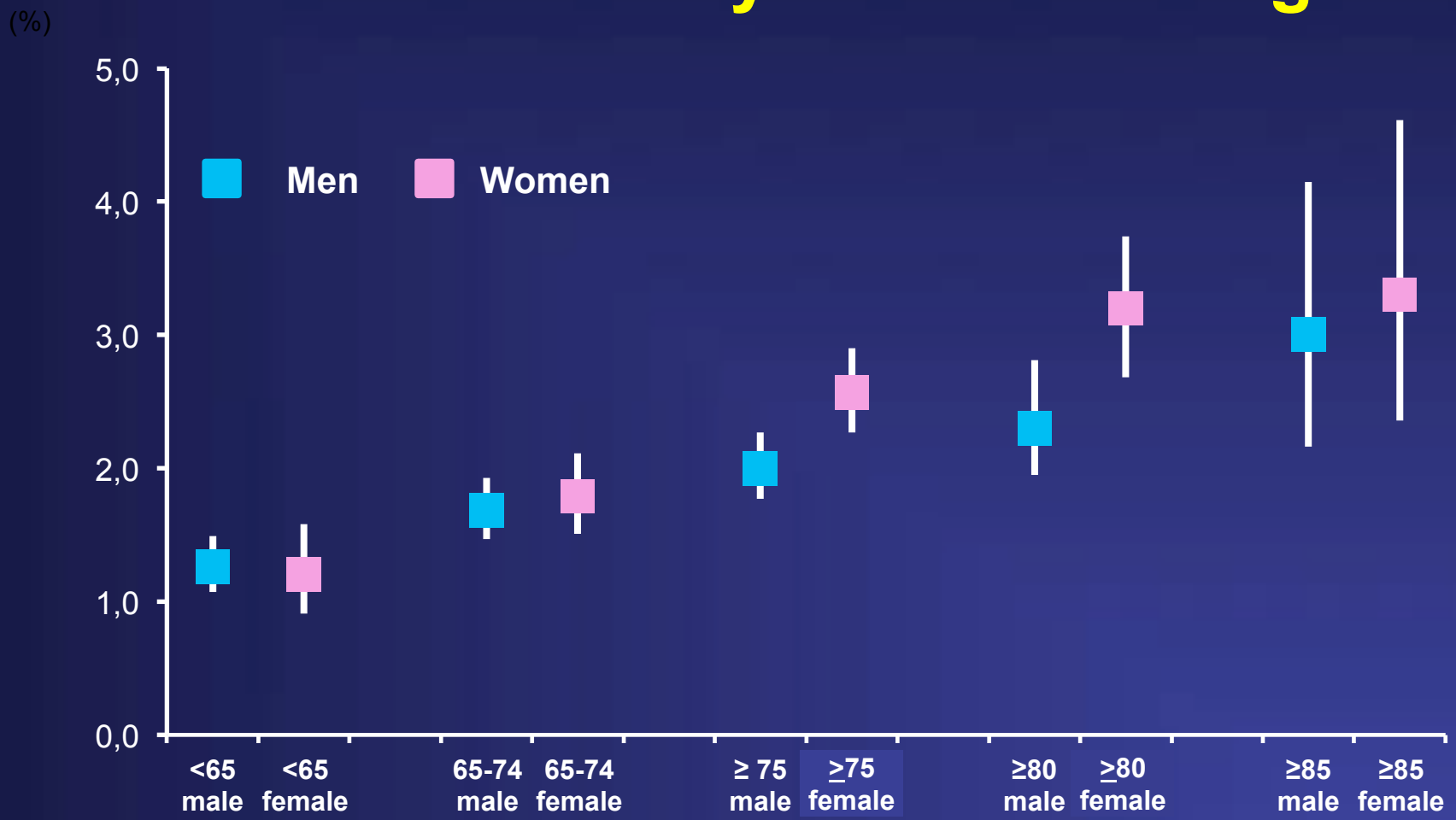
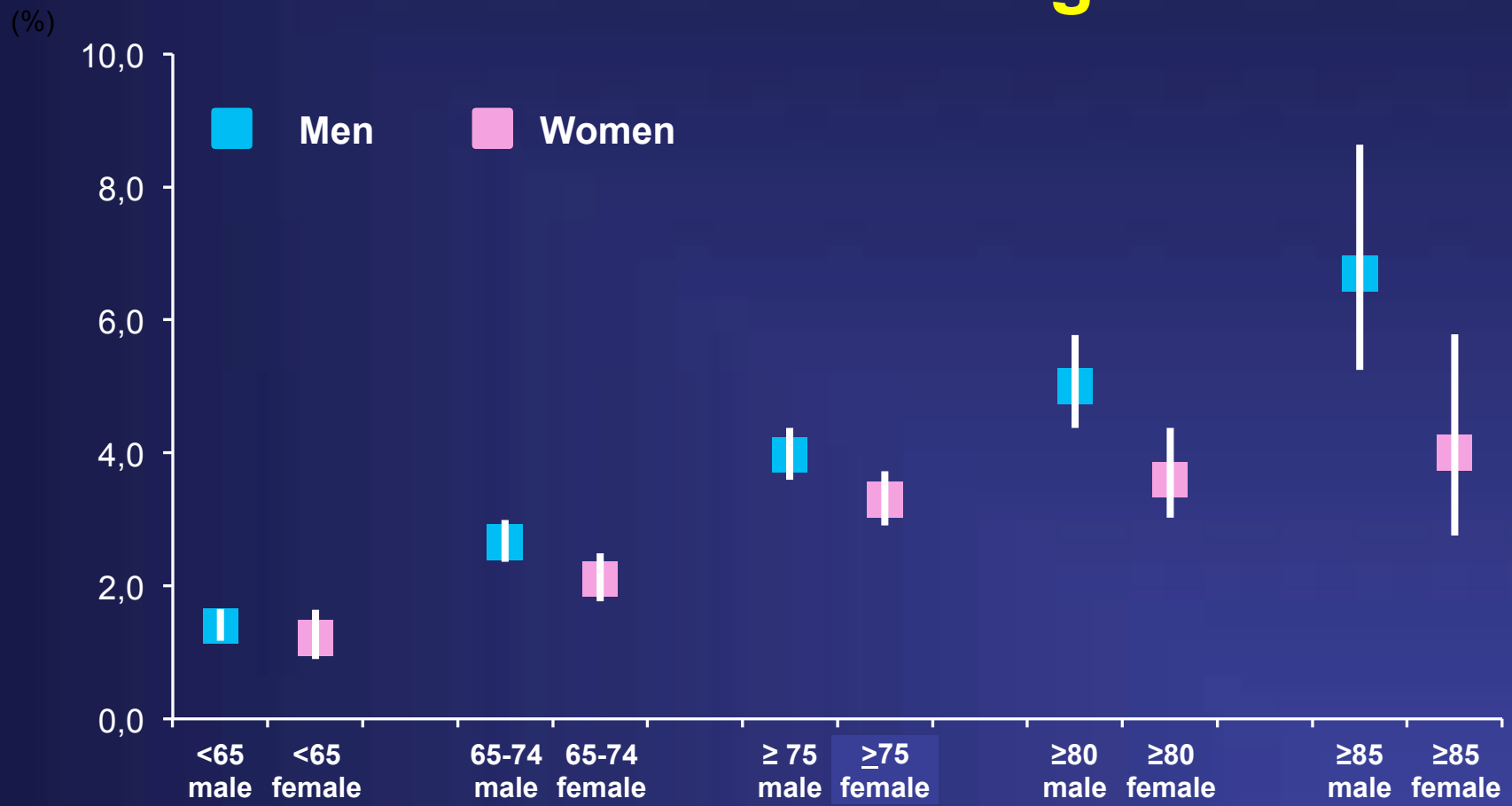
Stroke/SEE by Gender and Age



	<65 male	<65 female	65-74 male	65-74 female	≥ 75 male	≥75 female	≥80 male	≥80 female	≥85 male	≥85 female
n	138	50	198	133	244	253	114	133	35	33
N	3987	1510	4381	2753	4697	3777	1937	1654	493	406

Kato ET, AHA 2014 Chicago, IL

Major Bleeding by Gender and Age



	<65 male	<65 female	65-74 male	65-74 female	≥ 75 male	≥75 female	≥80 male	≥80 female	≥85 male	≥85 female
n	133	43	264	129	383	244	187	109	58	27
N	6486	2524	7376	4531	8205	6235	3425	2690	848	636

Kato ET, AHA 2014 Chicago, IL