ADVANCES IN CARDIAC ARRHYTHMIAS
and
GREAT INNOVATIONS IN CARDIOLOGY

XXVI Giornate Cardiologiche Torinesi

Torino, 23 – 25 ottobre2014

THE ITALIAN EXPERIENCE WITH DABIGATRAN

Pasquale Perrone Filardi
Università Federico II di Napoli

STUDIO OSSERVAZIONALE

La gestione del rischio tromboembolico nei pazienti con fibrillazione atriale in Italia: dati al basale del Registro Europeo PREFER in AF

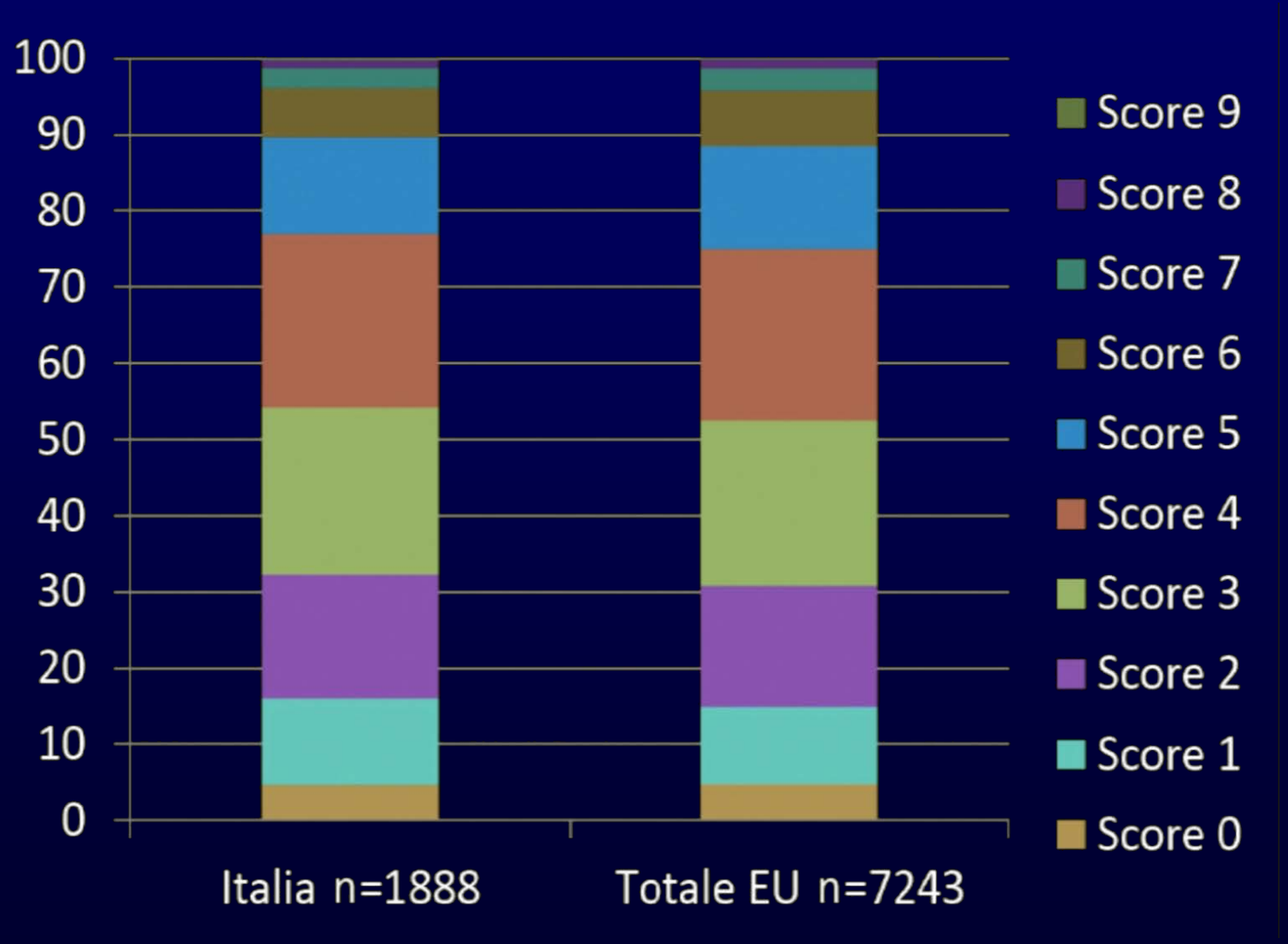
Raffaele De Caterina[1], Giulia Renda[1], Raffaele Sangiuolo[2], Emilio Attena[2], Livio Di Lecce[3], Fabio Romeo[3], a nome dello Steering Committee del Registro Europeo PREFER in AF (vedi Appendice 1)

Suddivisione dei pazienti in base al tipo di fibrillazione atriale (FA) nei singoli paesi europei

Tipo di FA	Francia (n=1532)	Germania (n=1771)	Italia (n=1888)	Spagna (n=858)	UK (n=1194)	Totale (n=7243)
Parossistica	35.5%	30.8%	26.9%	29.3%	27.4%	30.0%
Persistente	23.4%	11.0%	31.7%	20.6%	34.4%	24.0%
Persistente da lungo tempo	8.6%	4.7%	5.9%	7.0%	11.2%	7.2%
Permanente	32.5%	53.5%	35.5%	43.1%	27.0%	38.8%

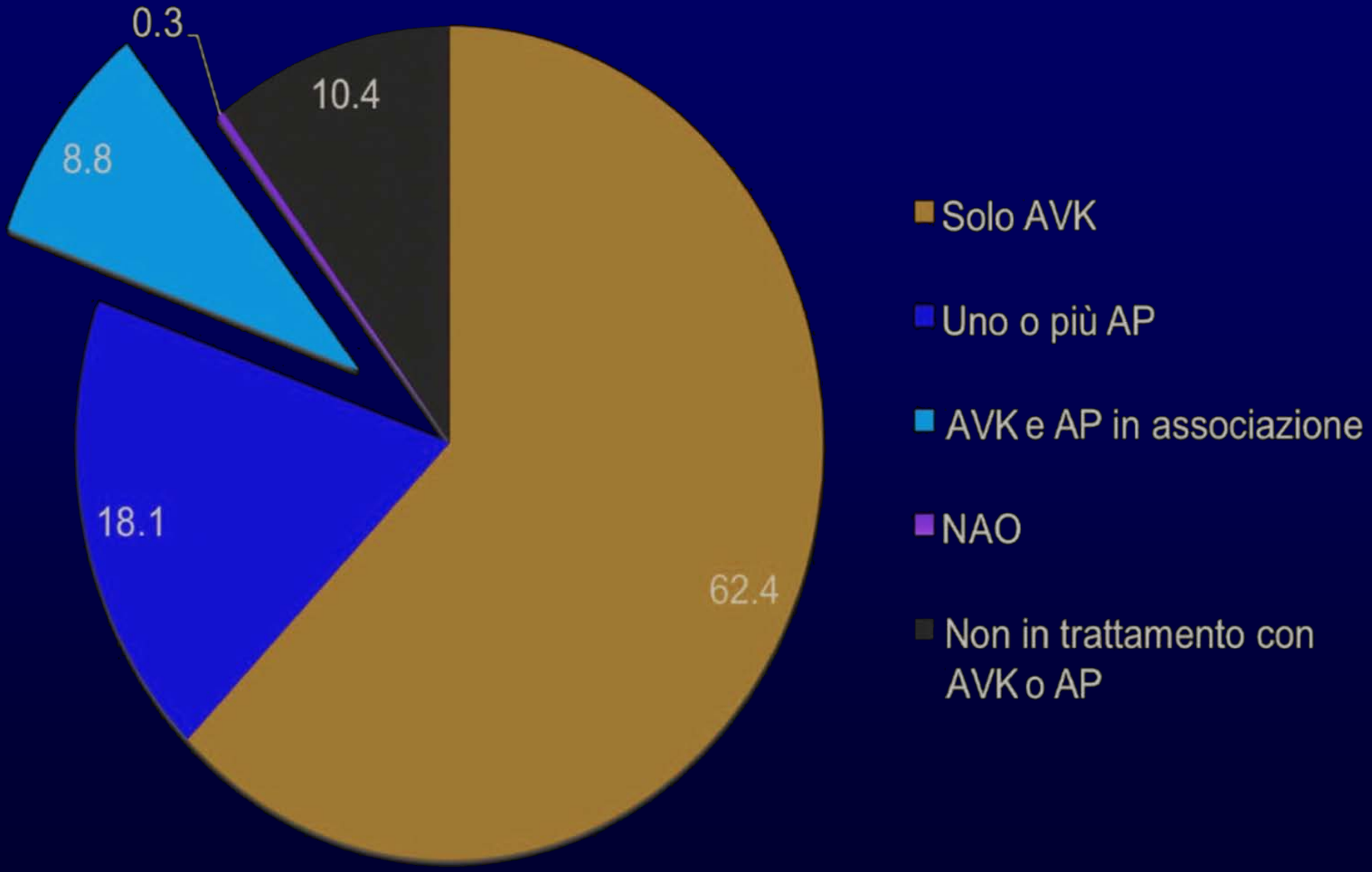
G Ital Cardiol 2014;15(2):99-109

Distribuzione dei pazienti in base al punteggio CHA2DS2-VASc: raffronto tra dati italiani ed europei (EU)



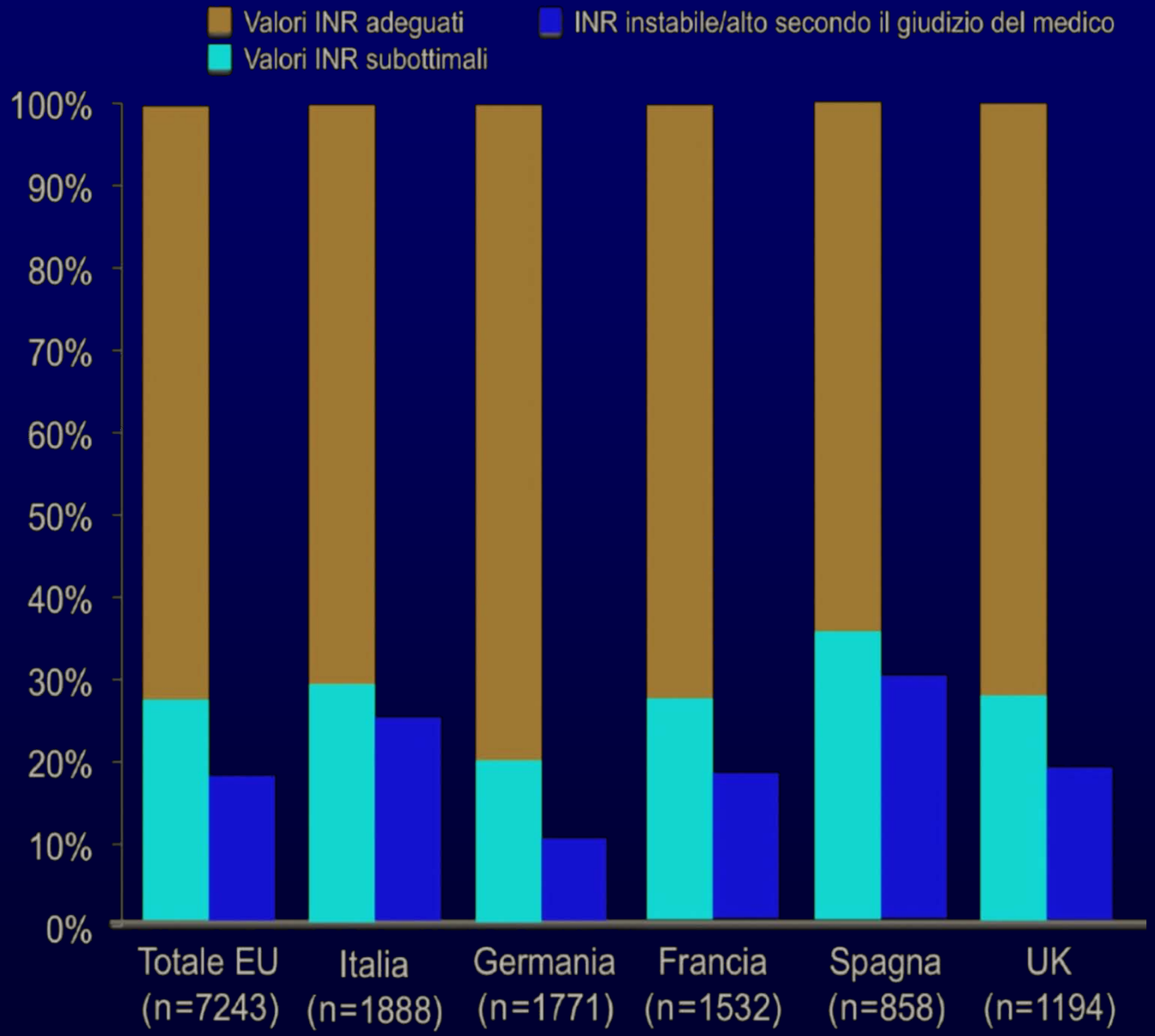
G Ital Cardiol 2014;15(2):99-109

Distribuzione delle classi di trattamento nei pazienti italiani



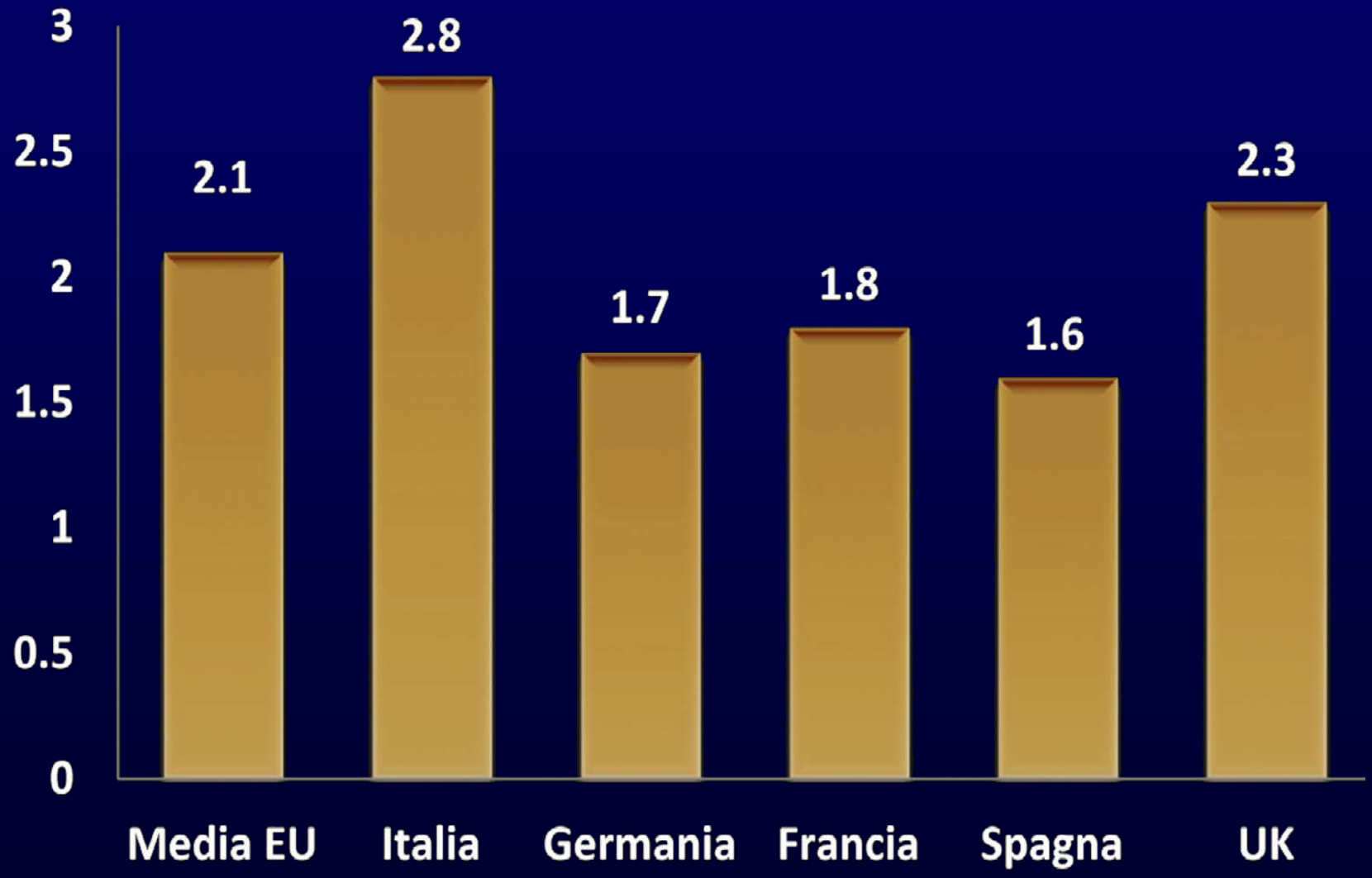
G Ital Cardiol 2014;15(2):99-109

Percentuale di pazienti con valori di INR adeguati, subottimali o instabili/alti



G Ital Cardiol 2014;15(2):99-109

Numero medio di monitoraggi dell'INR nell'ultimo mese nei paesi europei (EU) partecipanti allo studio



G Ital Cardiol 2014;15(2):99-109

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http://dx.doi.org/10.1016/j.jacc.2013.03.020

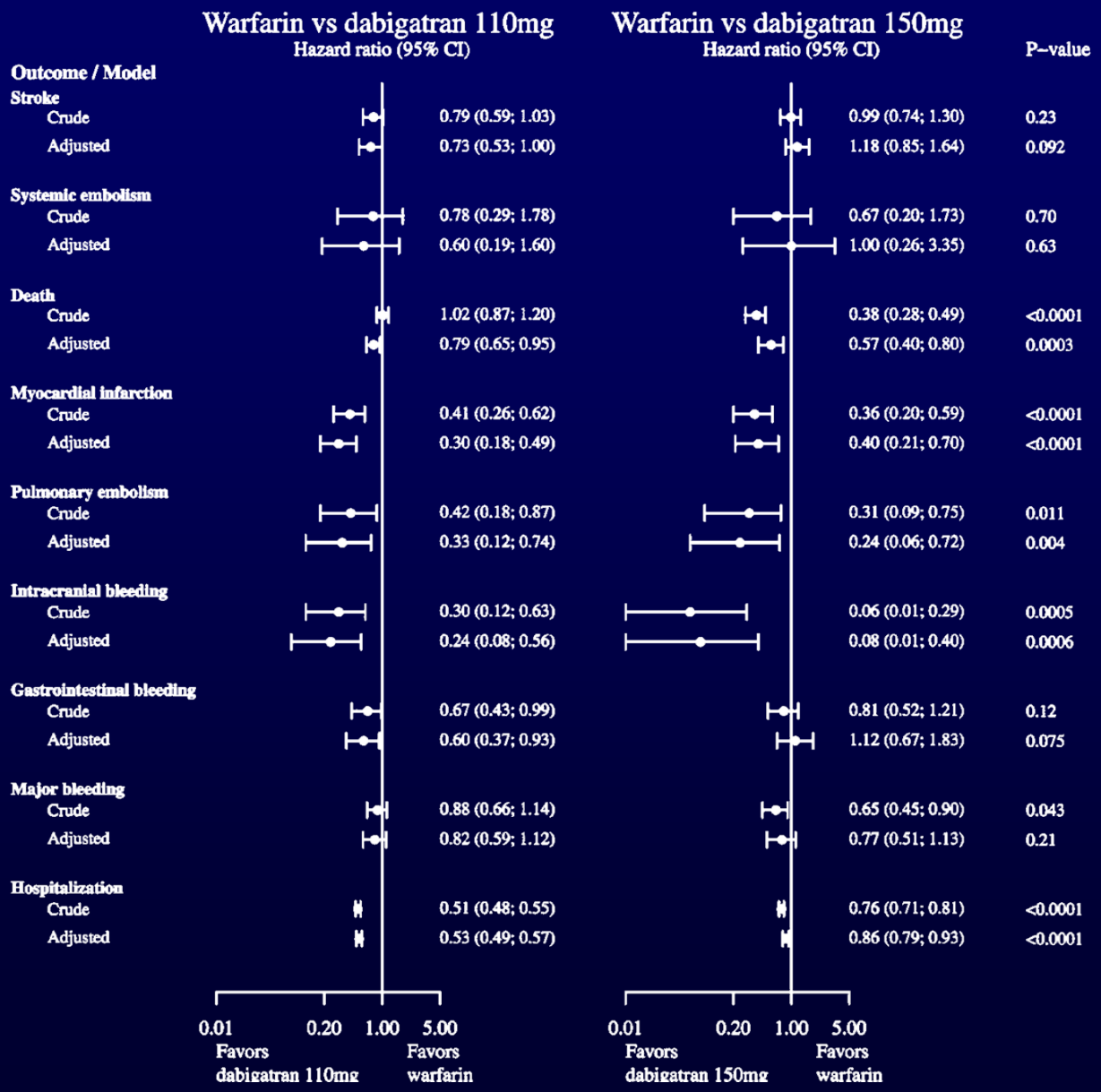
Efficacy and Safety of Dabigatran Etexilate and Warfarin in "Real-World" Patients With Atrial Fibrillation

A Prospective Nationwide Cohort Study

Torben Bjerregaard Larsen, MD, PhD,*† Lars Hvilsted Rasmussen, MD, PhD,†
Flemming Skjøth, MSc, PhD,* Karen Margrete Due, MSc,* Torbjörn Callréus, MD, PhD,‡
Mary Rosenzweig, MSc,‡ Gregory Y. H. Lip, MD†§

Aalborg and Copenhagen, Denmark; and Birmingham, United Kingdom

Main Outcome Measures

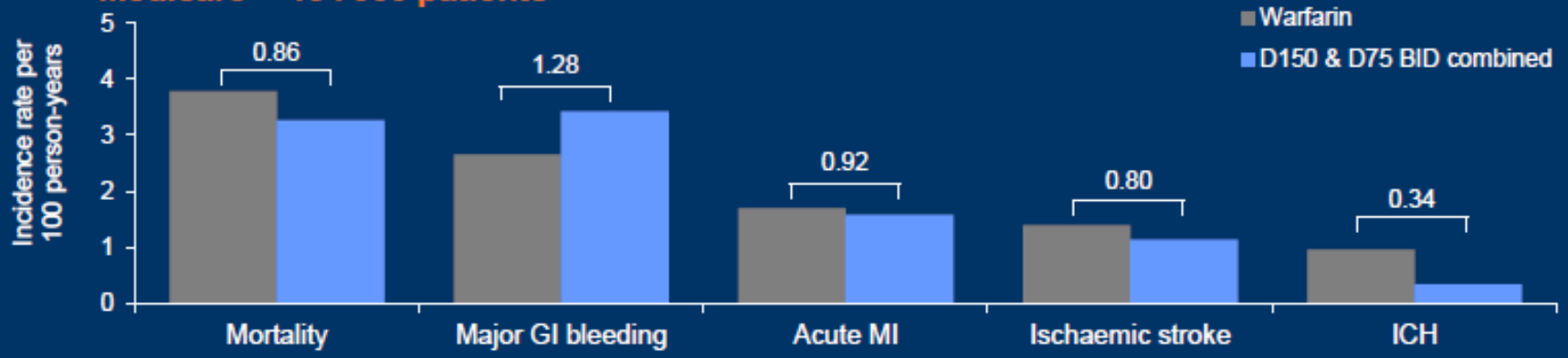


Larsen et al. JACC 2013;61:2264–73

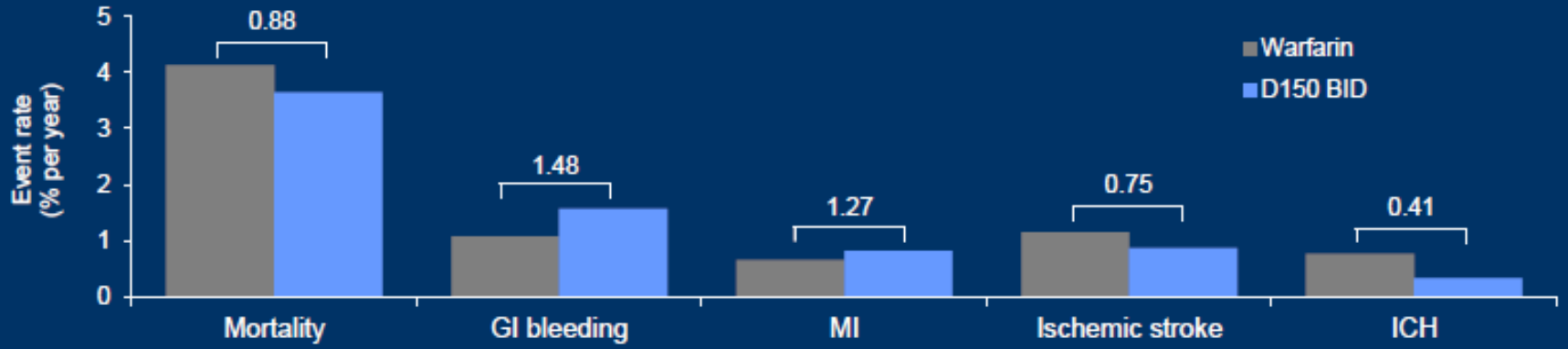
2014

Independent FDA analysis confirmed the positive safety and efficacy of dabigatran in clinical practice

Medicare[1] >134 000 patients



RE-LY®[2–4] >18 000 patients



In the USA, the licensed doses for dabigatran etexilate are 150 mg BID and 75 mg BID for the prevention of stroke and systemic embolism in adult patients with nonvalvular AF

Numbers on bars denote hazard ratios vs warfarin; MI = myocardial infarction

1. http://www.fda.gov/Drugs/DrugSafety/ucm396470.htm. Accessed on August 2014; 2. Connolly SJ et al. N Engl J Med 2009;361:1139–51; 3. Connolly SJ et al. N Engl J Med. 2010;363:1875–6; 4. Pradaxa®: EU SPC 2014

Bleeding events among new starters and switchers to dabigatran compared with warfarin: an observational study among patients with atrial fibrillation

Larsen TB et al.

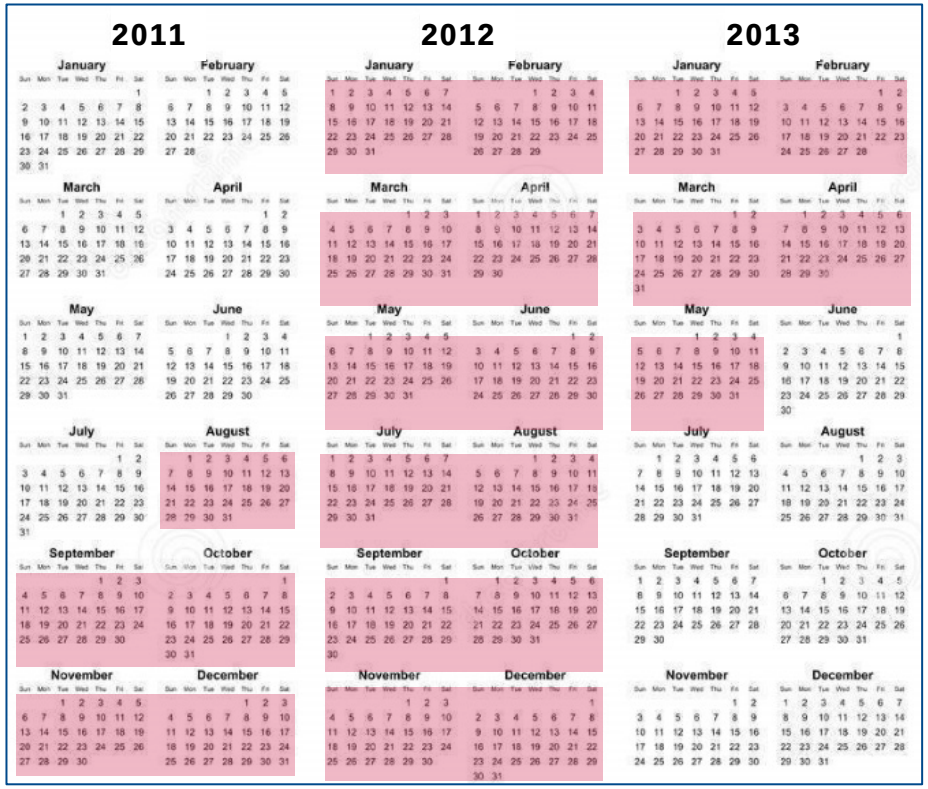
Am J Med 2014;127:650–6.e5
doi: 10.1016/j.amjmed.2014.01.031

Observational study of bleeding risk in patients with AF

- Observational cohort study
- Nationwide Danish registries

- Patients with AF, stratified by prior VKA use
- 11 315 first-time dabigatran users (7063 VKA-naïve)
- 22 630 matched warfarin users
- VKA-naïve = ≥2 years since last warfarin purchase

Study period



13 months of follow-up (mean)

Larsen TB et al. Am J Med 2014;127:650–6.e5. doi: 10.1016/j.amjmed.2014.01.031

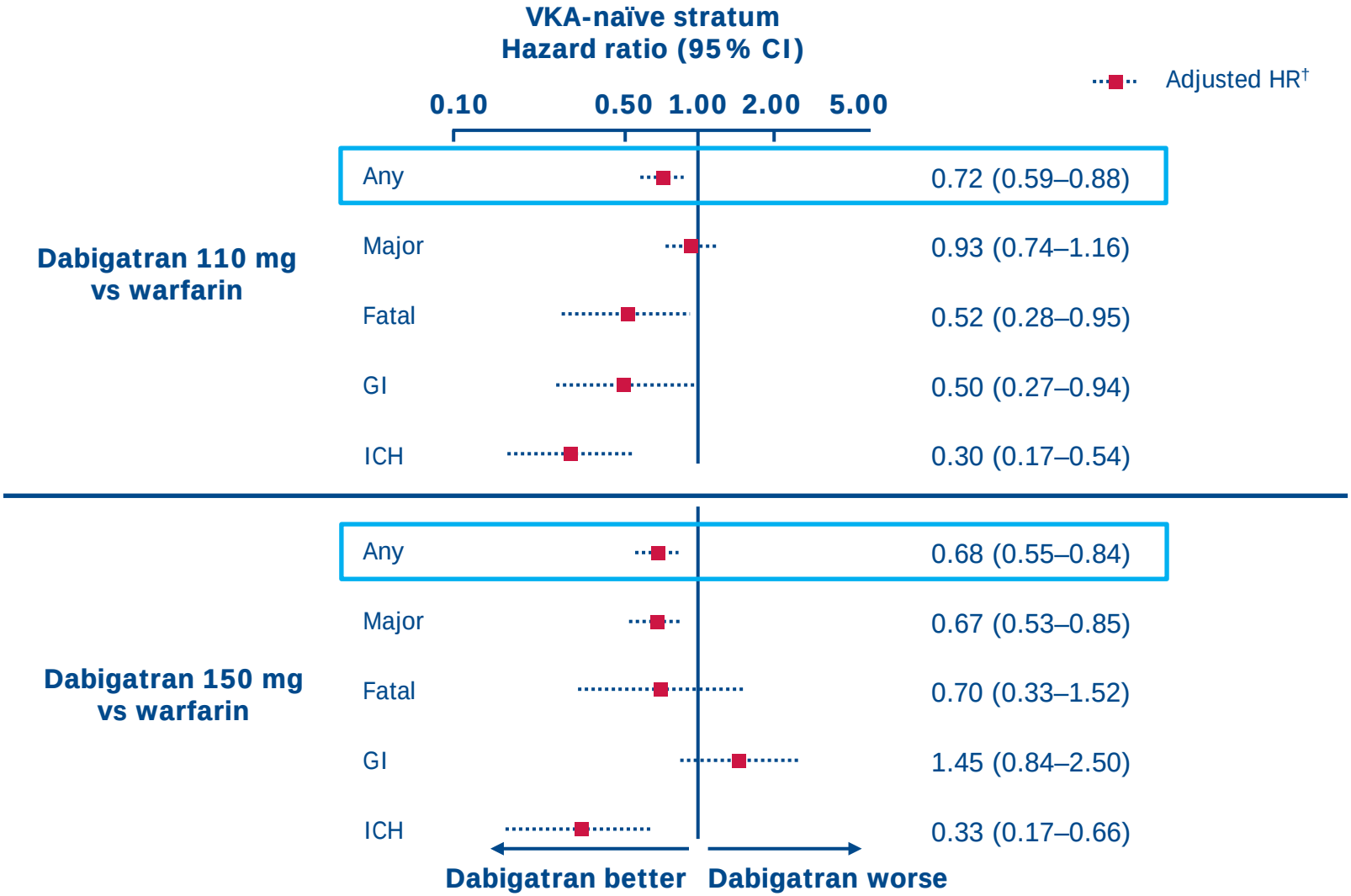
D110 users were older, more often female, and at higher bleeding and stroke risk than D150 users (VKA-naïve stratum: applying new-user design [see slide 2])

Characteristic	VKA-naïve stratum		
	D110	D150	Warfarin
Patients, n	3045	4018	14 126
Median age (IQR), yrs	82 (77–86)	67 (62–72)	73 (66–80)
Age ≥65 yrs, %	95.3	63.6	76.8
Age ≥75 yrs, %	80.1	13.7	42.5
Female, %	55.1	36.6	41.3
HAS-BLED score, mean (SD)	2.32 (1.04)	1.70 (1.11)	1.97 (1.18)
$CHADS_2$ score, mean (SD)	1.91 (1.21)	0.94 (1.05)	1.33 (1.21)
CHA_2DS_2VASc score, mean (SD)	3.70 (1.47)	2.12 (1.41)	2.80 (1.67)

D110 = dabigatran etexilate 110 mg BID; D150 = dabigatran etexilate 150 mg BID; IQR = interquartile range; SD = standard deviation

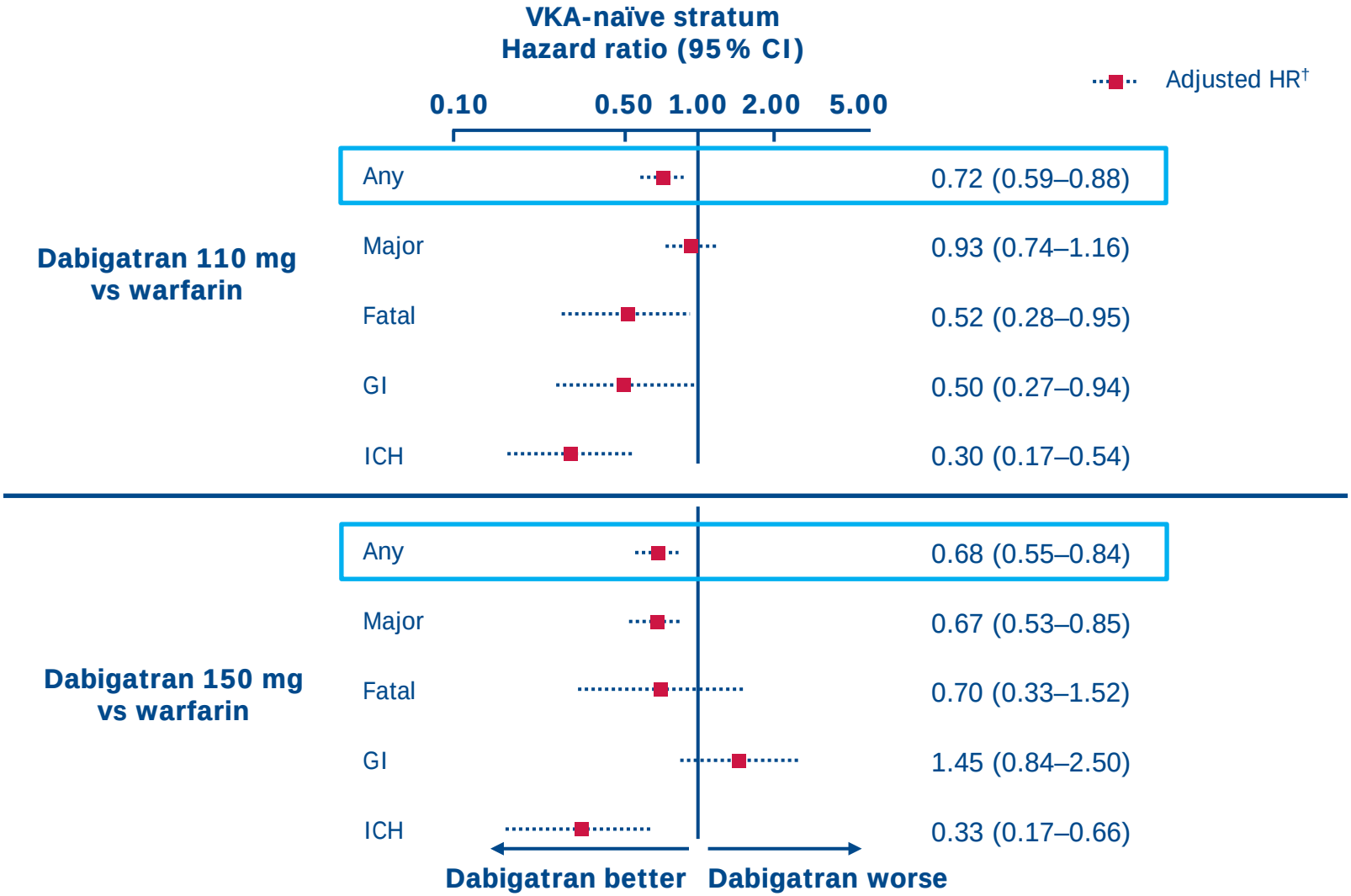
Larsen TB et al. Am J Med 2014;127:650–6.e5. doi: 10.1016/j.amjmed.2014.01.031

Both dabigatran doses showed significant reductions in risk of any bleeding vs warfarin* (VKA-naïve stratum)



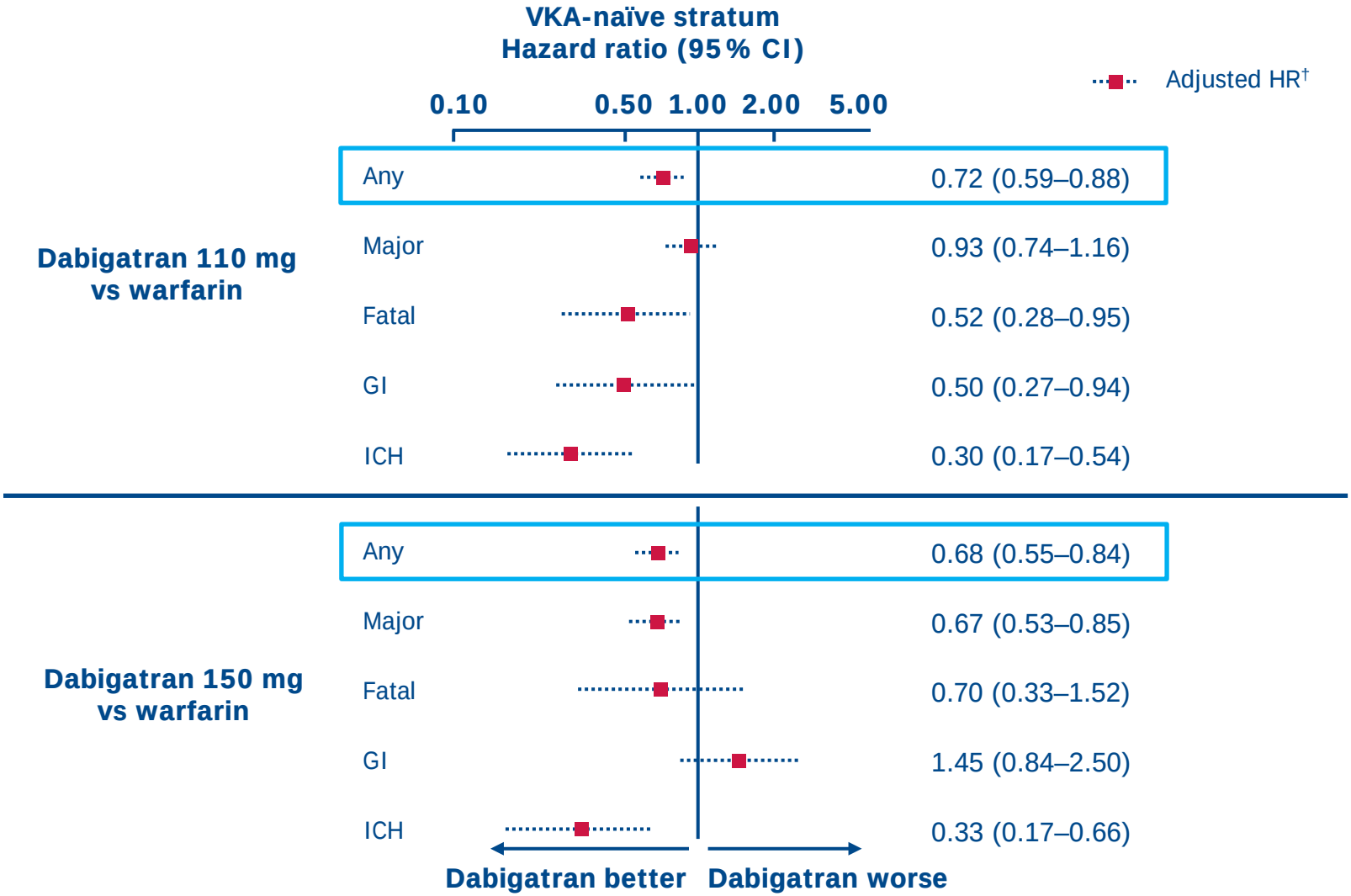
*Adjusted HR; †Age, components of CHA_2DS_2-VASc, HAS-BLED, months since August 2011, time since initiation of VKA therapy
VKA = Vitamin K antagonist; Larsen TB et al. Am J Med 2014;127:650–6.e5. doi: 10.1016/j.amjmed.2014.01.031

Both dabigatran doses showed significant reductions in risk of any bleeding vs warfarin* (VKA-naïve stratum)



*Adjusted HR; †Age, components of CHA_2DS_2-VASc, HAS-BLED, months since August 2011, time since initiation of VKA therapy
VKA = Vitamin K antagonist; Larsen TB et al. Am J Med 2014;127:650–6.e5. doi: 10.1016/j.amjmed.2014.01.031

Both dabigatran doses showed significant reductions in risk of any bleeding vs warfarin* (VKA-naïve stratum)



*Adjusted HR; †Age, components of CHA_2DS_2-VASc, HAS-BLED, months since August 2011, time since initiation of VKA therapy

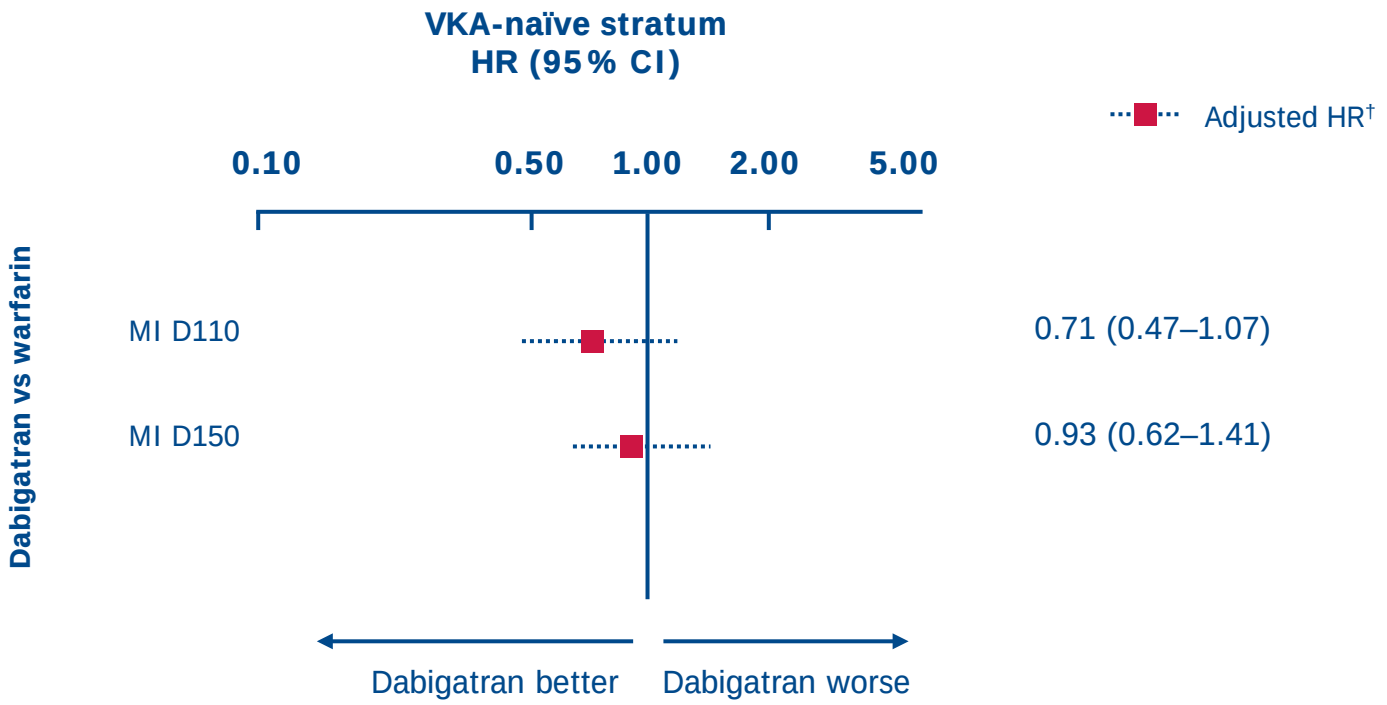
VKA = Vitamin K antagonist; Larsen TB et al. Am J Med 2014;127:650–6.e5. doi: 10.1016/j.amjmed.2014.01.031

Myocardial ischemic events in ‘real world’ patients with atrial fibrillation treated with dabigatran or warfarin: a nationwide cohort study

Larsen TB et al.

Am J Med 2014;127:329–36.e4
doi: 10.1016/j.amjmed.2013.12.005

Both dabigatran doses showed a non-significant trend to lower MI rates vs warfarin* (VKA-naïve stratum)



*Adjusted HR; †Age, components of CHA_2DS_2-VASc, HAS-BLED, history of any MI event, months since August 2011, time since initiation of VKA therapy

Larsen TB et al. Am J Med 2014;127:329–36.e4. doi: 10.1016/j.amjmed.2013.12.005

Patologie concomitanti e fattori di rischio nei pazienti con fibrillazione atriale nei diversi paesi europei

G Ital Cardiol 2014;15(2):99-109

	Francia (n=1532)	Germania (n=1771)	Italia (n=1888)	Spagna (n=858)	UK (n=1194)	Totale (n=7243)
Ipertensione arteriosa	63.8%	81.9%	75.3%	72.7%	62.1%	72.0%
Diabete mellito	16.8%	31.2%	19.2%	26.4%	18.8%	22.4%
Terapia insulinica	18.0%	26.3%	24.5%	20.0%	16.1%	22.3%
Obesità (BMI >30 kg/m^2)	24.8%	30.8%	21.9%	25.7%	36.0%	27.5%
BPCO	8.9%	9.8%	14.6%	12.8%	10.1%	11.3%
Attuale abitudine al fumo	5.7%	6.7%	8.4%	7.5%	7.0%	7.1%
Pregressa abitudine al fumo	30.5%	33.7%	36.6%	28.4%	50.0%	35.8%
Dislipidemia	41.0%	46.9%	38.7%	51.2%	42.9%	43.4%
Ipertiroidismo	3.9%	3.6%	5.8%	2.9%	3.4%	4.1%
Insufficienza renale cronica	10.1%	14.9%	12.5%	12.7%	14.0%	12.9%
Cardiopatia ischemica	18.2%	29.6%	20.6%	21.6%	26.6%	23.4%
Arteriopatia aortica o periferica	5.9%	5.0%	3.4%	4.3%	3.4%	4.4%
Scompenso cardiaco	18.2%	28.4%	19.4%	24.4%	15.4%	21.3%
Pregresso ictus	8.9%	10.7%	6.5%	7.7%	8.0%	8.4%

Caratteristiche generali dei pazienti (n=204) in terapia con Dabigatran etexilato (Pradaxa)

Eta' (anni; media±DS);	72 ±8		**Scompenso cardiaco**	85
>80 anni	51			
Sesso (maschi)	109		**Diabete mellito II**	55
CHA_2DS_2VASc (media±DS)	4,3±1,6		**Pregresso Ictus cerebrale/TIA/ Episodio trombo-embolico**	54
numero pazienti per classe di rischio	**1**	7	**Ipertensione arteriosa**	189
	2	19	**IM, malattia arteriosa periferica o placca aortica**	74
	3	48	**Insufficienza renale cronica**	35
	4	40	**Insufficienza epatica**	2
	5	43	**Storia di sanguinamento o diatesi emorragica o anemia**	33
	6	27	**Terapia concomitante con antiaggreganti piastrinici**	51
	7	15	**con ASA o clopidogrel**	19
	8	3	**con ASA e clopidogrel**	12
	9	2	**Pazienti Naive**	75
HAS-BLED (media±DS)	2,9±0,9		**Pazienti già in TAO**	129
numero pazienti per classe di rischio	**1**	16	**INR instabile con tempo in range terapeutico < 60%**	118
	2	46	**TTR (%; media±DS)**	48±14
	3	83	**Pazienti in terapia con 220 mg/die**	119
	4	51	**Pazienti in terapia con 300 mg/die**	85

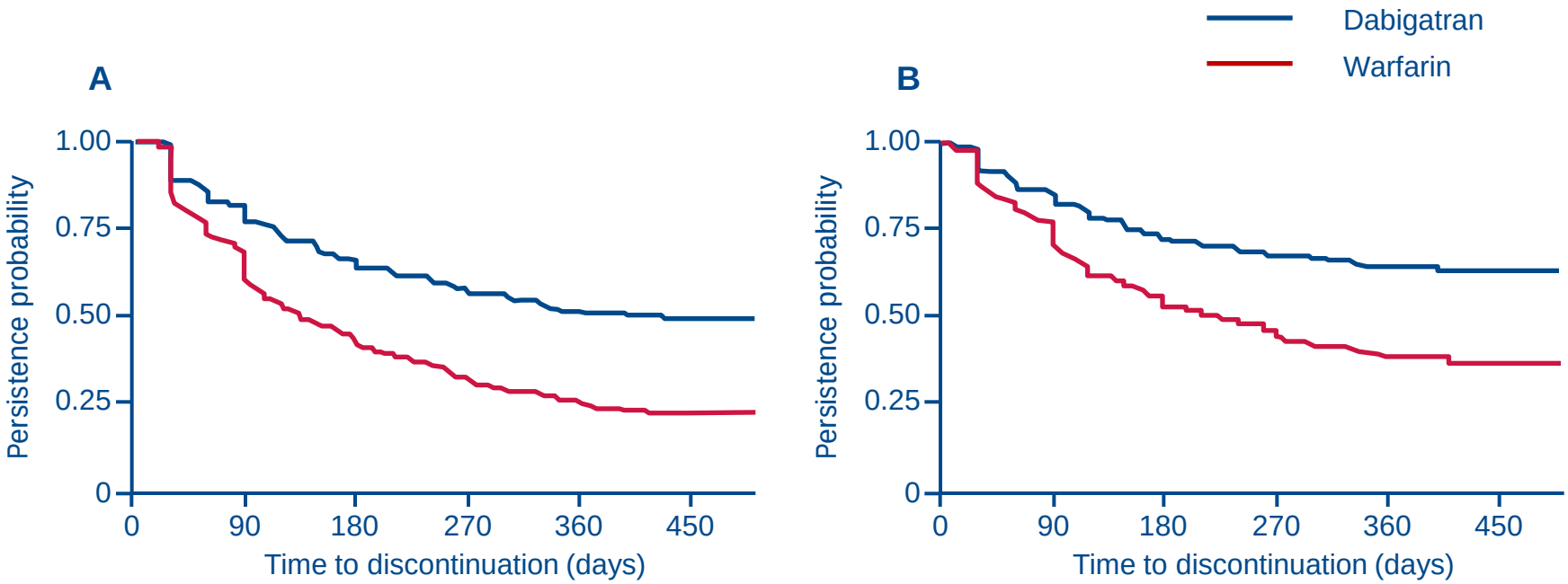
Caratteristiche generali dei pazienti (n=119) in terapia con Dabigatran etexilato 220 mg/die (Pradaxa)

Eta' (anni; media±DS)	75 ±6		**Scompenso cardiaco**	48 (41%)
Sesso (maschi)	60(51%)		**Diabete mellito II**	31 (26%)
CHA_2DS_2VASc (media±DS)	4,64±1,43		**Pregresso Ictus cerebrale/TIA/ Episodio trombo-embolico**	39 (33%)
numero pazienti per classe di rischio	**1**	0	**Ipertensione arteriosa**	111 (93%)
	2	4	**IM, malattia arteriosa periferica o placca aortica**	44(37%)
	3	30	**Insufficienza renale cronica**	32(27%)
	4	23	**Insufficienza epatica**	1 (0,1%)
	5	28	**Storia di sanguinamento o diatesi emorragica o anemia**	22 (19%)
	6	20	**Terapia concomitante con antiaggreganti piastrinici**	35 (29%)
	7	12	**con ASA o clopidogrel**	14
	8	2	**con ASA e clopidogrel**	11
	9	0	**Pazienti Naive**	51(43%)
HAS-BLED (media±DS)	3,1±0,91		**Pazienti già in TAO**	67 (56%)
numero pazienti per classe di rischio	**1**	6	**INR instabile con tempo in range terapeutico < 60%**	68 (57%)
	2	20	**TTR (%; media±DS)**	50±12
	3	50	**Effetti collaterali**	1(0,1%)
	4	38	**Epigastralgia**	1

Caratteristiche generali dei pazienti (n=85) in terapia con Dabigatran etexilato 300 mg/die (Pradaxa)

Eta' (anni; media±DS)	69 ±8		**Scompenso cardiaco**	37 (43%)
Sesso (maschi)	49 (57%)		**Diabete mellito II**	23 (27%)
CHA_2DS_2VASc (media±DS)	3,8±1,80		**Pregresso Ictus cerebrale/TIA/ Episodio trombo-embolico**	16(13%)
numero pazienti per classe di rischio	1	7	**Ipertensione arteriosa**	78(66%)
	2	15	**IM, malattia arteriosa periferica o placca aortica**	30(25%)
	3	18	**Insufficienza renale cronica**	3(0,3%)
	4	17	**Insufficienza epatica**	1(0,1%)
	5	15	**Storia di sanguinamento o diatesi emorragica o anemia**	11 (13%)
	6	7	**Terapia concomitante con antiaggreganti piastrinici**	16(14%)
	7	3	**con ASA o clopidogrel**	13
	8	1	**con ASA e clopidogrel**	3
	9	2	**Pazienti Naive**	23(27%)
HAS-BLED (media±DS)	2,62±0,99		**Pazienti già in TAO**	62(72%)
numero pazienti per classe di rischio	1	10	**INR instabile con tempo in range terapeutico < 60%**	50(60%)
	2	26	**TTR (%; media±DS)**	46±15
	3	33	**Effetti collaterali**	1(0,1%)
	4	13	**Epigastralgia**	1

Time to discontinuation by treatment group in matched patients



A) 30-day medication gap

- Median persistence was longer for dabigatran (389 days) than warfarin (135 days) (P<0.001)

B) 60-day medication gap

- Median persistence was longer for dabigatran (>400 days) than warfarin (222 days) (P<0.001)

Kaplan–Meier survival curves for propensity score-matched patients by treatment group
Zalesak M et al. Circ Cardiovasc Qual Outcomes 2013;6:567–74

Electrophysiology

Adherence to dabigatran therapy and longitudinal patient outcomes: Insights from the Veterans Health Administration

Supriya Shore, MD,[a,b,c] Evan P. Carey, MS,[a,c,d] Mintu P. Turakhia, MD, MAS,[e,f] Cynthia A. Jackevicius, PharmD, MSc,[g,h] Fran Cunningham, PharmD,[i] Louise Pilote, MD, MPH, PhD,[j] Steven M. Bradley, MD, MPH,[a,b,c] Thomas M. Maddox, MD, MS,[a,b,c] Gary K. Grunwald, PhD,[a,d] Anna E. Barón, PhD,[d] John S. Rumsfeld, MD, PhD,[a,b,c] Paul D. Varosy, MD,[a,b,c] Preston M. Schneider, MD,[a,b,c] Lucas N. Marzec, MD,[a,b,c] and P. Michael Ho, MD, PhD[a,b,c]

Denver, and Aurora, CO; Palo Alto, Stanford, Los Angeles, and Pomona, CA; Hines, IL; and Québec, Canada

Association between adherence (PDC) and outcomes

Outcome	Number of events	Unadjusted HR (95% CI) per 10% decrease in PDC	Adjusted HR (95% CI) per 10% decrease in PDC
Combined all-cause mortality and stroke	247	1.13 (1.07-1.19)	1.13 (1.08-1.19)
Stroke	31	1.09 (0.94-1.27)	1.13 (0.97-1.33)
Non-fatal bleeding events	96	1.05 (0.95-1.15)	1.04 (0.94-1.13)
Myocardial infarction	20	1.03 (0.83-1.27)	0.97 (0.78-1.21)

Am Heart J 2014 Jun;167(6):810-7

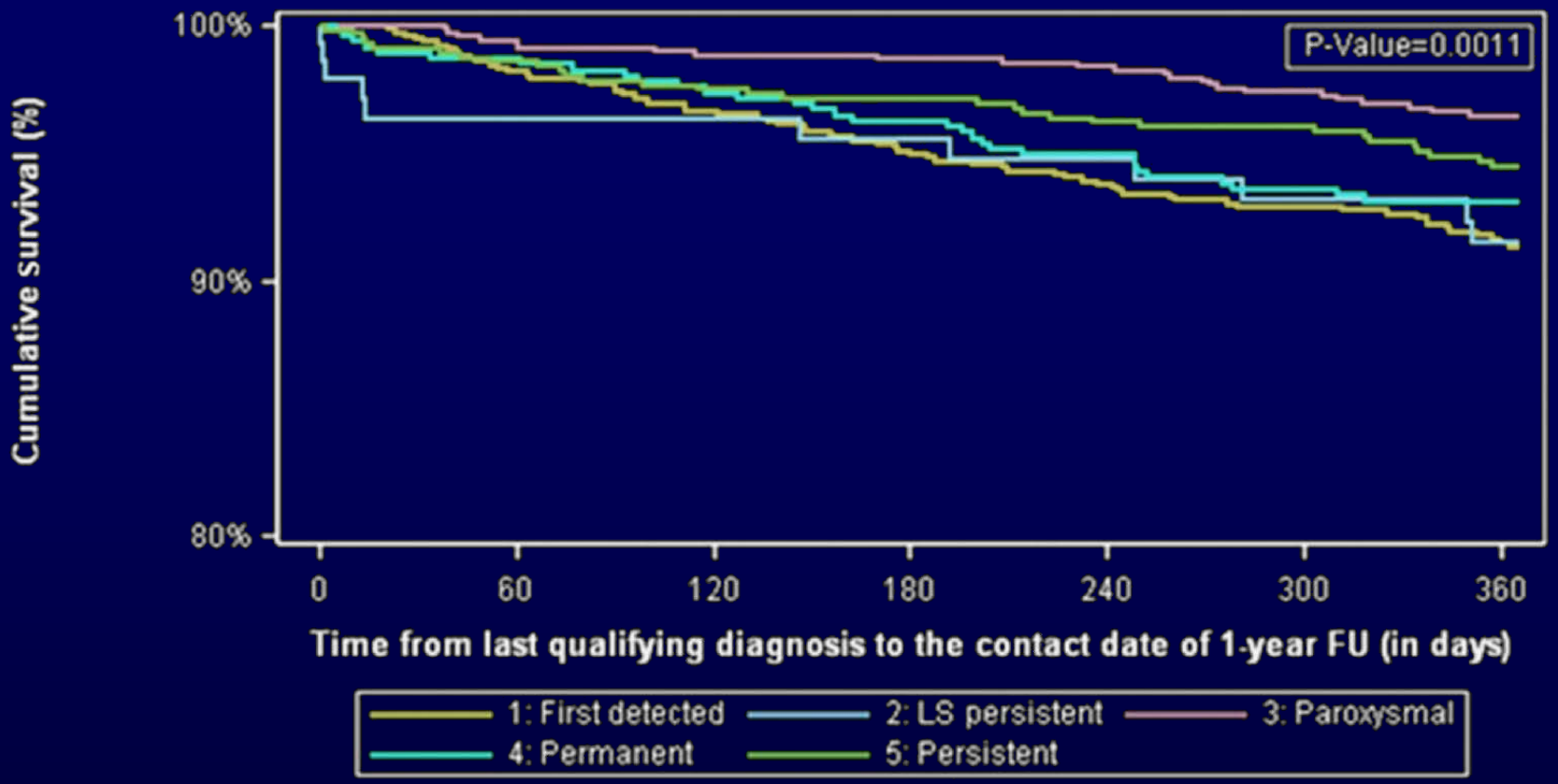
European Heart Journal
doi:10.1093/eurheartj/ehu374

CLINICAL RESEARCH
ESC Clinical Trial and Registry Update FASTTRACK

Prognosis and treatment of atrial fibrillation patients by European cardiologists: One Year Follow-up of the EURObservational Research Programme-Atrial Fibrillation General Registry Pilot Phase (EORP-AF Pilot registry)

Gregory Y.H. Lip[1]*, Cécile Laroche[2], Popescu Mircea Ioachim[3], Lars Hvilsted Rasmussen[4], Laura Vitali-Serdoz[5], Lucian Petrescu[6], Dan Darabantiu[7], Harry J.G.M. Crijns[8], Paulus Kirchhof[9], Panos Vardas[10], Luigi Tavazzi[11], Aldo P. Maggioni[12,13], and Giuseppe Boriani[14]

Mortality in relation to atrial fibrillation subtype



Number of subjects at risk

1: First detected	923	764	750	735	721	707	595
2: LS Persistent	145	121	121	120	119	116	97
3: Paroxysmal	805	694	687	684	677	657	570
4: Permanent	526	448	442	433	426	411	358
5: Persistent	646	547	539	534	528	523	450

Eur Heart J 2014 Aug 31 doi:10.1093/eurheartj/ehu374

European Heart Journal (2014) **35**, 250–256
doi:10.1093/eurheartj/eht483

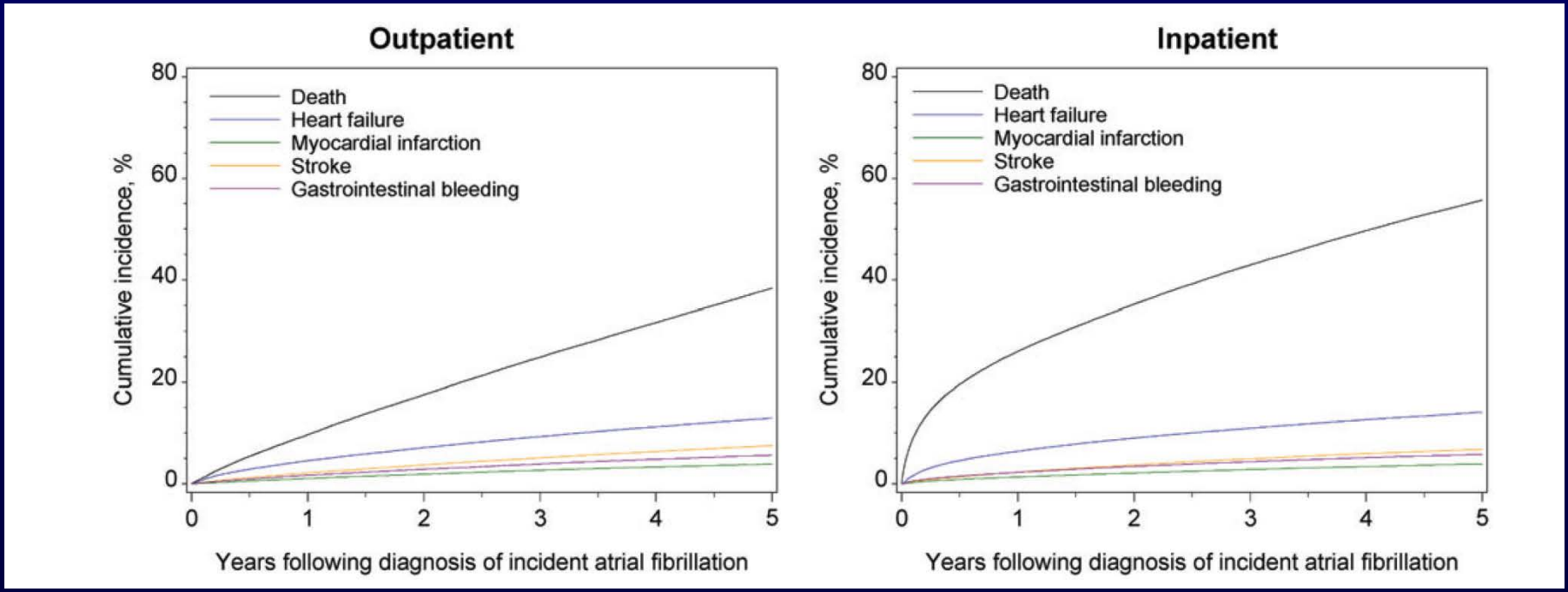
CLINICAL RESEARCH
Atrial fibrillation

Clinical course of atrial fibrillation in older adults: the importance of cardiovascular events beyond stroke

Jonathan P. Piccini[1,2*], Bradley G. Hammill[1], Moritz F. Sinner[3], Adrian F. Hernandez[1,2], Allan J. Walkey[4], Emelia J. Benjamin[4,5], Lesley H. Curtis[1,2], and Susan R. Heckbert[6]

[1]Duke Clinical Research Institute, Duke University School of Medicine, Durham, NC, USA; [2]Department of Medicine, Duke University School of Medicine, Durham, NC, USA; [3]Department of Medicine I, University Hospital Grosshadern, Ludwig-Maximilians University Munich, Munich, Germany; [4]Department of Medicine, Boston University School of Medicine, Boston, MA, USA; [5]Department of Epidemiology, Boston University School of Public Health, Boston, MA, USA; and [6]Department of Epidemiology, University of Washington School of Public Health, Seattle, WA, USA

Risk of stroke, HF, AMI and GI bleeding in pts with AF



Piccini JP, Duke University, Eur Heart J 2014, 35: 250-6

REMARKS

- The vast majority of real world atrial fibrillation patients should be anticoagulated according to Guidelines
- VKA therapy remains problematic in many patients
- Use of new oral anticoagulants is increasing but still suboptimal in Italy
- A substantial number of perceived contraindications to anticoagulation therapy appear not justified
- Data from registries of NOA indicate and efficacy and safety profile even more favorable than that observed in clinical trials
- However, despite stroke risk reduction, prognosis of AF is influenced by comorbidities, mainly heart failure and CAD