Management of anticoagulation in frail and complex patients

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Declaration of interests

- The practice has received funding from: Abbott, Bayer, Boehringer-Ingelheim, Bristol Myers Squibb, Dawn, INRStar, Medtronic, Oberoi Consulting, Pfizer, Roche, Sanofi-Aventis, Servier.
- An advisor to: Anticoagulation Europe, Arrhythmia Alliance, Heart Valve Voice, National Stroke Association, Syncope Trust
- A trustee of Thrombosis UK, AF Association

What do you think of when you think of “Geriatrics”?

Quotes

- ***Benjamin Franklin:***
  - *"All would live long, but none would be old."*
- ***Abraham Lincoln:***
  - *"And in the end, it's not the years in your life that count. It's the life in your years."*

Geriatric “Catch Phrases”

- **Start Low and Go Slow…**
- **The Dying Patient**
- **Life Expectancy**
- **Quality of Life**
- **Falls Risk**
- **Polypharmacy**

Geriatric “Realities”

- **“Graying” of America**
- **Increasing population of oldest of the old (number of people over age 80 will increase from 6.9 million in 1990 to 25 million by 2050).**

Geriatric “Realities”

- **With an increase in older adults comes an increase in chronic diseases.**
- **Many older adults are not “dying” but are living healthy, active lives with several chronic diseases.**

Do We “Undertreat” Older Adults with Chronic Conditions?

- **Probably Yes….**

Outline

- **Why we might undertreat older patients**
- **Problems with clinical trials**
- **New perspectives on life expectancy**
- **Examples**
- **Importance of Absolute Risk reduction and determination of baseline risk**

Objectives

- **Appreciate the need to individualize care of older patients with complex medical problems**

- **Understand the importance of Baseline Risk in determining the overall impact, or absolute risk reduction, that any certain therapy may have– patients at highest risk for a bad outcome stand to gain the most from a treatment that has even modest benefit!**

Why would we undertreat?

- Ageism
- Exclusion of older adults from clinical trials
- Assumption that the older adult may not want “aggressive” treatment
- Ideas based upon Life Expectancy
- Concern for Polypharmacy
- Concern that relative efficacies may be less for certain treatments in older subgroups
- Overestimation of Risks of Treatment and underestimation of Benefits of Treatment

Ageism

- **Coined 1969 by Dr. Robert Butler (first director of the National Institute on Aging)**
- **“Systematic stereotyping of and discrimination against people because they are old”**

- **Fostered in clinical training**
  - **Students and residents see older adults from nursing homes and in the hospital**
  - **The Aging Game**
  - **The “Unwritten Curriculum”**
- **Age is NOT EQUAL to frailty.**

Exclusion of Older Adults from Clinical Trials

- **1/3 of all major, original research papers in 1997 and 15% in 2004 excluded older people without justification**
- **Potential concerns:**
  - **More comorbid illnesses, more difficulty to follow, higher drop out**
  - **Increased risks with treatment**
  - **Polypharmacy**
  - **Protocol restrictions on comorbidities**
  - **Older population as “vulnerable” study group**
  - **Barriers with transportation and mobility**

Assumption that Older Adult May Not Want "Aggressive" Therapy

- **The literature suggests that we tend to underestimate "Quality of Life" equivalents for others.**

- **There is data showing that physicians tend to assume that older adults do not want certain treatments, including ICU care, even though older patients, when asked, actually do want such care.**

Ideas Based upon Life Expectancy

- **"Average Life Expectancy" can be misleading**
  - **Overall average 77 years in 2002**
  - **But, a 70-year-old woman on average can expect to live another 18 years!**
  - **10% of 90 year olds will live to 100**

Polypharmacy

- **Legitimate concern**
- **Medications seem to exponentially increase with each additional diagnosis!**
- **Balance standard of care**
- **Risk for Adverse Drug Event directly related to number of medications**
- **Need to actively discontinue any unnecessary medications**

Common Theme

- **Increasing age is associated with increased bad outcome (stroke with afib, death/recurrent MI with acute coronary syndrome, cardiovascular event with hyperlipidemia).**
- **With increase in age, there is a decrease in the number of eligible patients who receive the standard of care treatment.**

Atrial Fibrillation and Anticoagulation

- **Prevalence: 5% of people over age 65**
- **10% of people over age 80**
- **50% of all patients with afib are over age 80**
- **Dreaded outcome: Stroke**
  - **Strokes with afib have higher mortality/disability**

Age and Stroke Risk

- **Incidence of stroke with afib increases with age:**
  - **1.3 %/year in patients 50–59**
  - **2.2 %/year in 60–69**
  - **4.2 %/year in 70–79**
  - **5.1 %/year in 80–89**

  - **But it is much more complicated…**

Predicting Risk of Stroke

- **CHADS2**
  - CHF: 1 point
  - HTN: 1 point
  - Age over 75: 1 point
  - DM: 1 point
  - Prior Stroke/TIA: 2 point
  - Score 0 = annual stroke risk <1% (ASA alone)
  - 2 or more: annual stroke risk over 4%: warfarin
  - Score 1= individualized treatment decision
  - Score 5 = over 10%/year stroke rate
  - Score 6 = over 15%/year stroke rate

Benefit of Warfarin

- **Overall decreases risk of stroke by 60–70%, ARR of 2.7–3 %/year**
- **Beneficial in all age groups, even those over age 75**
- **?Quality of life of preventing a stroke**

Risks of Warfarin

- **Risk of warfarin associated bleeding increases with age**
- **Risk ICH:**
  - **0.34 %/year in age less than 60**
  - **0.76% /year in those over 80**
- **Absolute risk of major bleeding = 2.2% /year (increases to near 3% in those on warfarin plus asa)**

Warfarin Use

- **Older patients less likely to receive anticoagulation**
- **Older patients more likely to be "underanticoagulated" -- even though data is clear that there is no significant stroke protection at an INR of less than 2.**
- **Overestimation of "Falls Risk"**

Warfarin in Older Patients: Bigger Bang for the Buck…

- **Patients under age 65 with afib and risk factors for stroke: warfarin decreases risk of stroke from 4.9 %/year to 1.7 %/year**
- **In patients over 75 with risk factors (highest risk group), warfarin reduces risk of stroke from 12 %/year to 2–4 % /year.**
- **Those at highest risk for stroke (older, prior stroke, chf, dm, htn) are less likely to be given warfarin because of concerns for their "comorbidities."**

DEMENTIA

Dementia as a risk

- Some evidence to support worse control but not why (*Circ Cardiovasc Qual Outcomes. 2010;3:277-283* doi: 10.1161/CIRCOUTCOMES.109.884171)
- No trials identify any specific increased risk of complications
- Suggestions that dementia is more common in people with AF

FALLS

Falls as a risk

- Cost benefit analysis shows the number of falls on average likely to cause greater risk than benefits with warfarin = 295
  - *Arch Intern Med.* 1999;159(7):677-685. doi:10.1001/archinte.159.7.677
- Beware fallers with significant injury
  - Major head injury with proven SDH
  - Major bruising resulting in surgery

Falls and anticoagulation

CLINICAL RESEARCH STUDY

THE AMERICAN JOURNAL of MEDICINE®

Risk of Falls and Major Bleeds in Patients on Oral Anticoagulation Therapy

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ABSTRACT

BACKGROUND: The risk of falls is the most commonly cited reason for not providing oral anticoagulation, although the risk of bleeding associated with falls on oral anticoagulants is still debated. We aimed to evaluate whether patients on oral anticoagulation with high falls risk have an increased risk of major bleeding.

METHODS: We prospectively studied consecutive adult medical patients who were discharged on oral anticoagulants. The outcome was the time to a first major bleed within a 12-month follow-up period adjusted for age, sex, alcohol abuse, number of drugs, concomitant treatment with antiplatelet agents, and history of stroke or transient ischemic attack.

RESULTS: Among the 515 enrolled patients, 35 patients had a first major bleed during follow-up (incidence rate: 7.5 per 100 patient-years). Overall, 308 patients (59.8%) were at high risk of falls, and these patients had a nonsignificantly higher crude incidence rate of major bleeding than patients at low risk of falls (8.0 vs 6.8 per 100 patient-years, $P = .64$). In multivariate analysis, a high falls risk was not statistically significantly associated with the risk of a major bleed (hazard ratio 1.09; 95% confidence interval, 0.54-2.21). Overall, only 3 major bleeds occurred directly after a fall (incidence rate: 0.6 per 100 patient-years).

CONCLUSIONS: In this prospective cohort, patients on oral anticoagulants at high risk of falls did not have a significantly increased risk of major bleeds. These findings suggest that being at risk of falls is not a valid reason to avoid oral anticoagulants in medical patients.

 • The American Journal of Medicine (2012) 125, 773-778

KEYWORDS: Accidental falls; Adverse drug events; Anticoagulants; Hemorrhage; Risk factor

Despite their proven efficacy in both prevention and treatment of cardiovascular and cerebrovascular diseases, oral anticoagulants are under-prescribed.[1-4] The most commonly cited reason for not providing oral anticoagulants is a risk of falls.[5,6] Few prior studies, however, specifically address the question of whether a high falls risk is associated with major bleeds in patients receiving oral anticoagulants; these also are limited by retrospective design, a focus on special subpopulations such as inpatients or those with atrial fibrillation, and are based on falls risks as assessed by physician reports or International Classification of Diseases, 9th Revision, Clinical Modification codes.[7-10] Moreover, patients at high risk of falls are themselves often excluded from clinical anticoagulation trials.[11] Our aim was to prospectively evaluate whether medical patients on oral anticoagulants who are considered at high risk of falls based on 2 validated questions have an increased risk of major bleeds compared with patients at low risk of falls.

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Conflict of Interest: None.

Authorship: All authors had access to the data and had a role in writing the manuscript.

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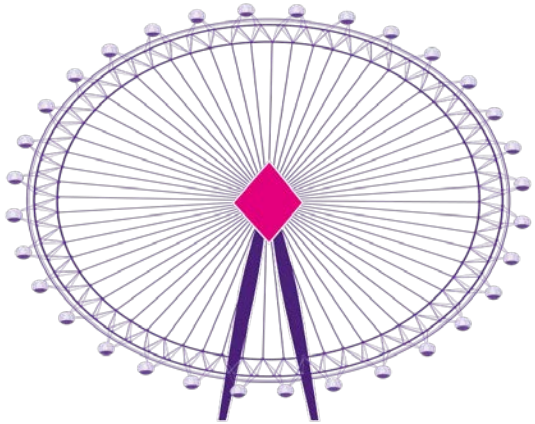
XANTUS: a Real World, Prospective, Observational Study of Patients Treated With Rivaroxaban for Stroke Prevention in Atrial Fibrillation



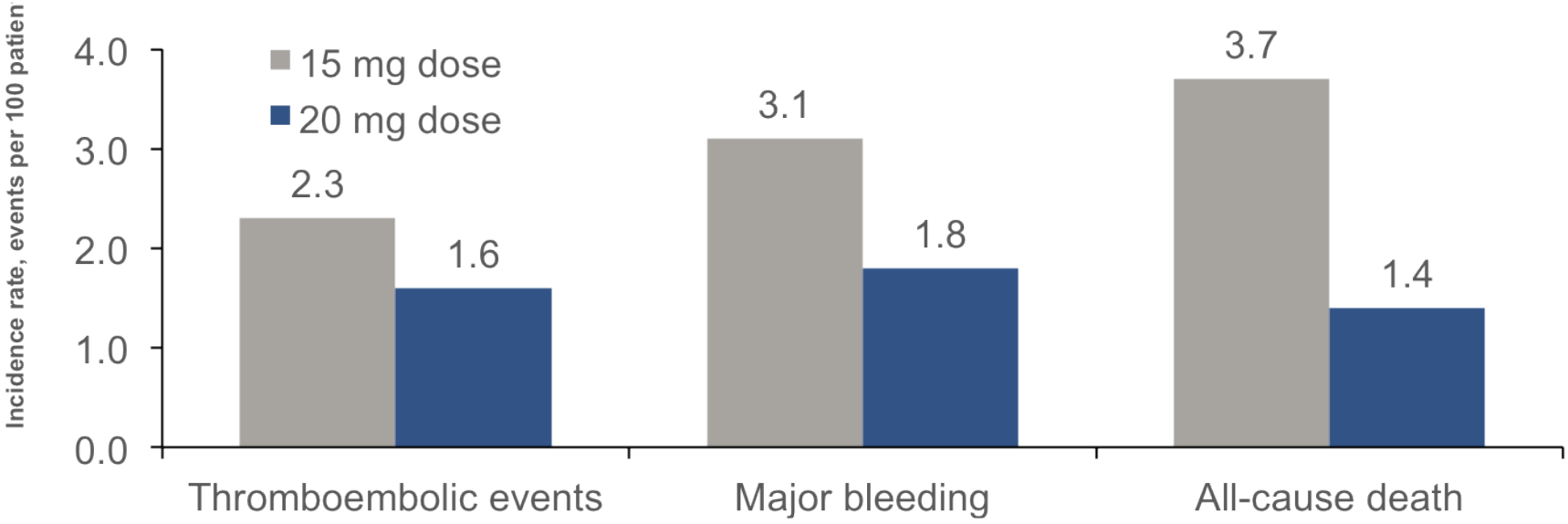
Content

- Why is Real World Evidence Needed Given the Positive Outcomes of Phase III trials?

- XANTUS:
  - Study rationale, Objective and Design
  - Patient Disposition and demographics
  - Treatment-Emergent Outcomes and Event Rates
  - Distribution of Events By Stroke Risk Score
  - Treatment Persistence and Patient Satisfaction
  - Comparison with ROCKET AF
  - Strengths and Limitations

XANTUS: Outcomes According to Dosing (20/15 mg od)

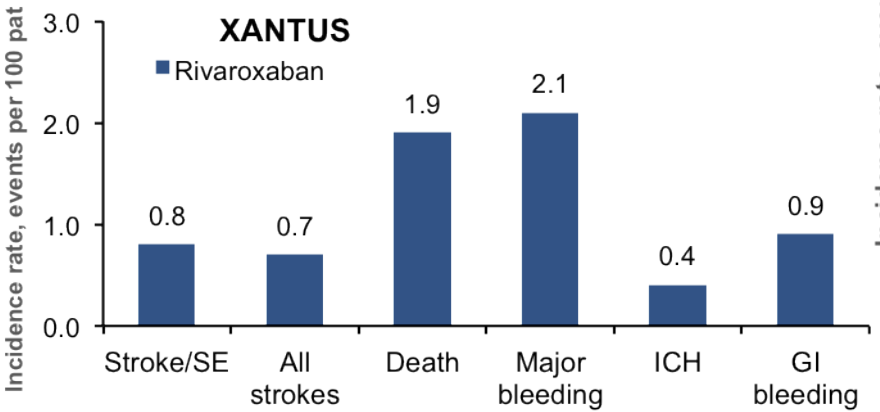
- Major bleeding, all-cause death and thromboembolic events (stroke/SE/TIA/MI) occurred at higher incidence rates for the 15 mg od versus the 20 mg od dose

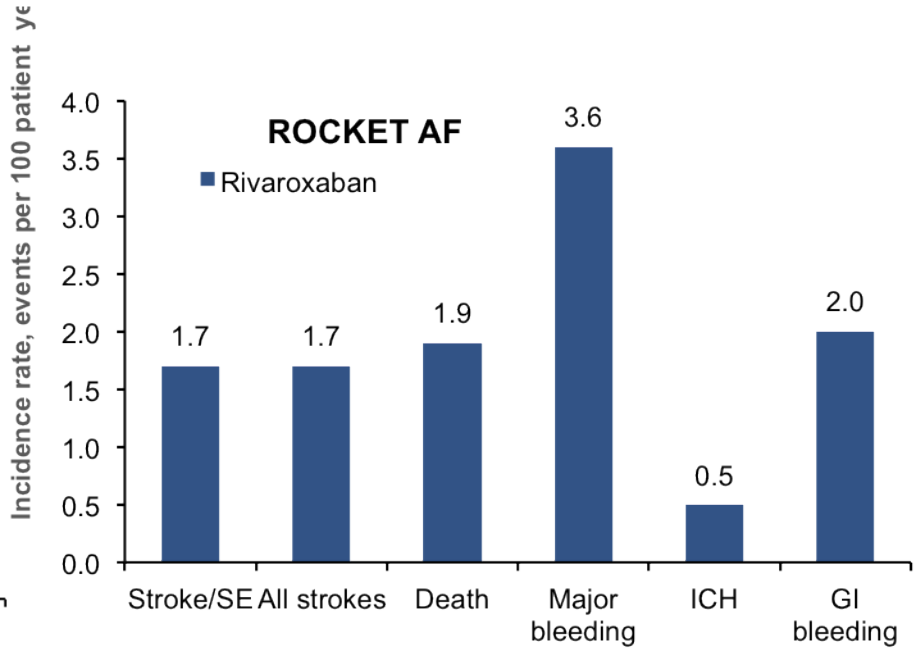


Camm AJ *et al*, *Eur Heart J* 2015; doi: 10.1093/eurheartj/ehv466;

Comparison of Main Outcomes: XANTUS versus ROCKET AF

	$CHADS_2$	Prior stroke[#]
ROCKET AF[1]	3.5	55%
XANTUS[2]	2.0	19%





[#]Includes prior stroke, SE or TIA;

1. Patel MR *et al, N Engl J Med* 2011;365:883–891; 2. Camm AJ *et al*, *Eur Heart J* 2015; doi: 10.1093/eurheartj/ehv466; 3. *Chest.* 2012;142(4_MeetingAbstracts):84A. doi:10.1378/chest.1388403

Comparison of Main Outcomes: XANTUS versus ROCKET AF

Alternative slide

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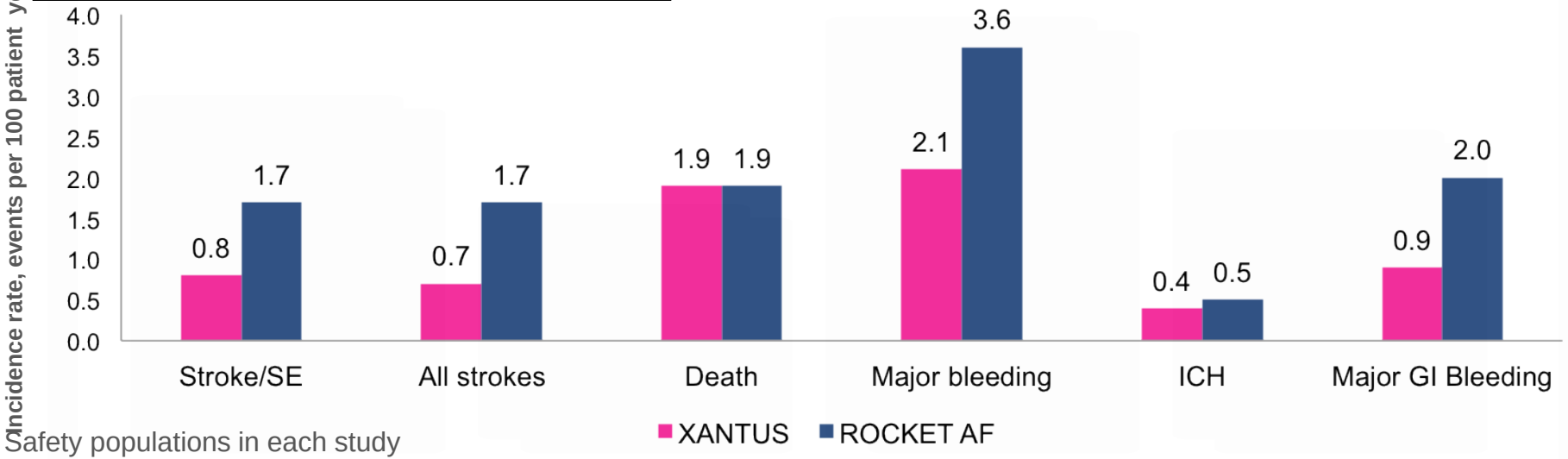


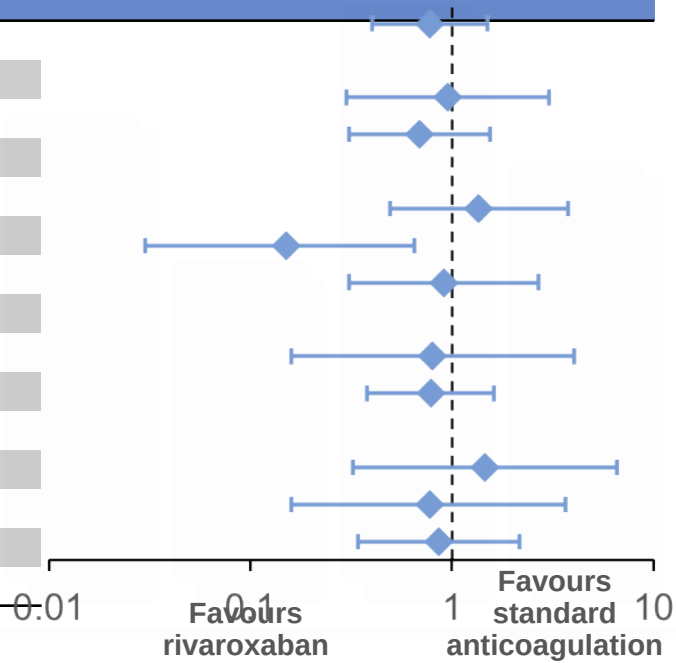
Safety populations in each study

[#]Includes prior stroke, SE or TIA;

1. Patel MR *et al, N Engl J Med* 2011;365:883–891; 2. Camm AJ *et al*, *Eur Heart J* 2015; doi: 10.1093/eurheartj/ehv466; 3. *Chest.* 2012;142(4_MeetingAbstracts):84A. doi:10.1378/chest.1388403

Treatment-Emergent Major Bleeding Across Subgroups

	Rivaroxaban		Standard anticoagulation	
	n/N	(%)	n/N	(%)
All patients	19/2505	(0.8)	43/2010	(2.1)
Age				
<60 years	8/1286	(0.6)	11/785	(1.4)
≥60 years	11/1219	(0.9)	32/1225	(2.6)
Weight				
≤70 kg	7/522	(1.3)	14/495	(2.8)
>70–<90 kg	3/843	(0.4)	14/663	(2.1)
≥90 kg	6/599	(1.0)	12/482	(2.5)
Active cancer at baseline				
Yes	2/144	(1.4)	13/338	(3.8)
No	17/2361	(0.7)	30/1672	(1.8)
First available CrCl				
<50 ml/min	3/98	(3.1)	9/194	(4.6)
≥50–<80 ml/min	3/410	(0.7)	10/366	(2.7)
≥80 ml/min	12/1047	(1.1)	16/757	(2.1)



Note: some demographic parameters have data missing
Propensity score-adjusted population

Recurrent Venous Thromboembolism Across Subgroups

	Rivaroxaban		Standard anticoagulation	
	n/N	(%)	n/N	(%)
All patients	36/2505	(1.4)	47/2010	(2.3)
Age				
<60 years	17/1286	(1.3)	16/785	(2.0)
≥60 years	19/1219	(1.6)	31/1225	(2.5)
Weight				
≤70 kg	8/522	(1.5)	13/495	(2.6)
>70–<90 kg	8/843	(0.9)	18/663	(2.7)
≥90 kg	11/599	(1.8)	12/482	(2.5)
Active cancer at baseline				
Yes	5/144	(3.5)	14/338	(4.1)
No	31/2361	(1.3)	33/1672	(2.0)
First available CrCl				
<50 ml/min*	1/98	(1.0)	3/194	(1.5)
≥50–<80 ml/min	6/410	(1.5)	11/366	(3.0)
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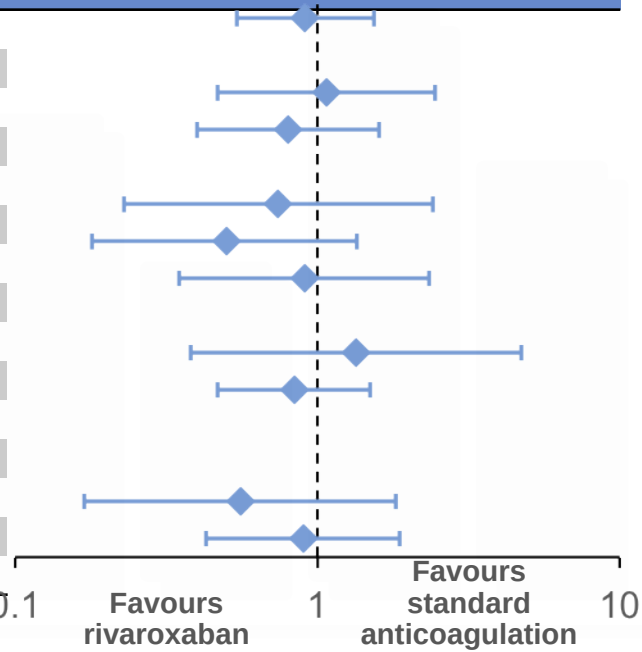


Note: some demographic parameters have data missing;
* HR not calculated because of too few events
Propensity score-adjusted population

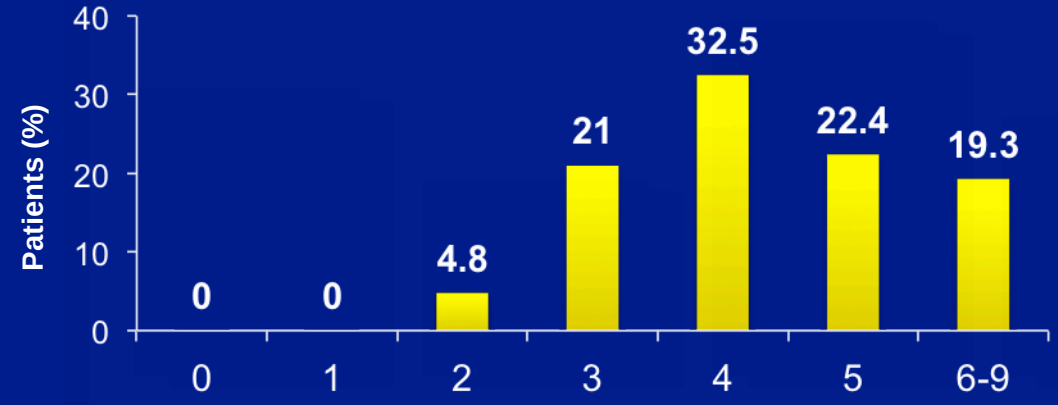
Date of preparation January 2016
L.GB.MKT.01.2016.14475

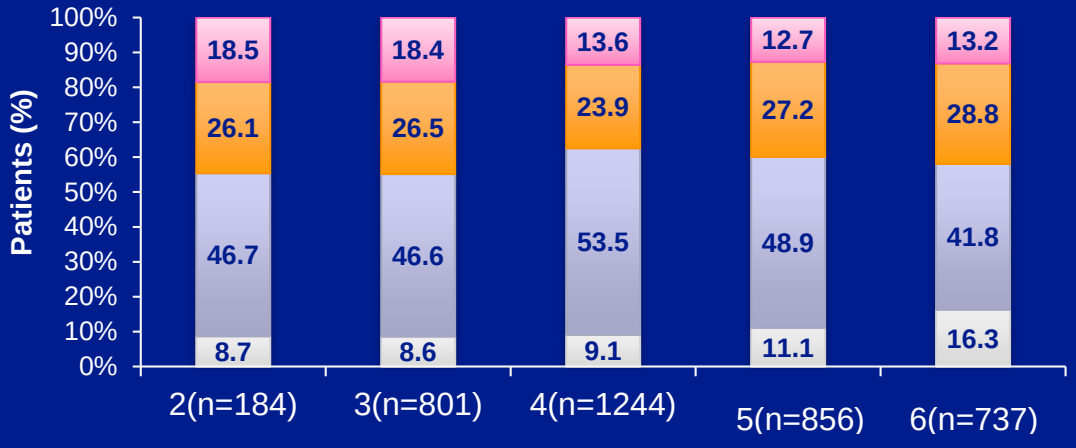
Global Anticoagulant Registry in the FIELD (GARFIELD)

GARFIELD is supported by an unrestricted research grant from Bayer Pharma AG to the Thrombosis Research Institute

GARFIELD-AF Cohort 1 : Outcomes in elderly newly diagnosed AF patients (1)

Date of preparation January 2016
L.GB.MKT.01.2016.14475





- 36.2% of patients in Cohort 1 were 75 y.o. or older (n=3813)
- ¾ of this population had CHA_2DS_2-VASc ≥ 4

Mantovani et al. AHA 2012

GARFIELD-AF Cohort 1 :
Outcomes in elderly newly diagnosed AF patients

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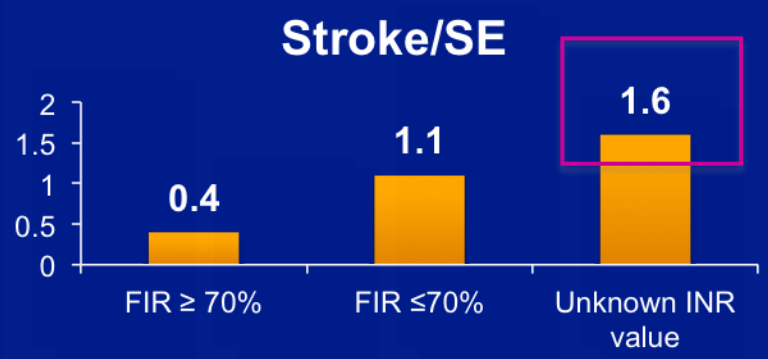
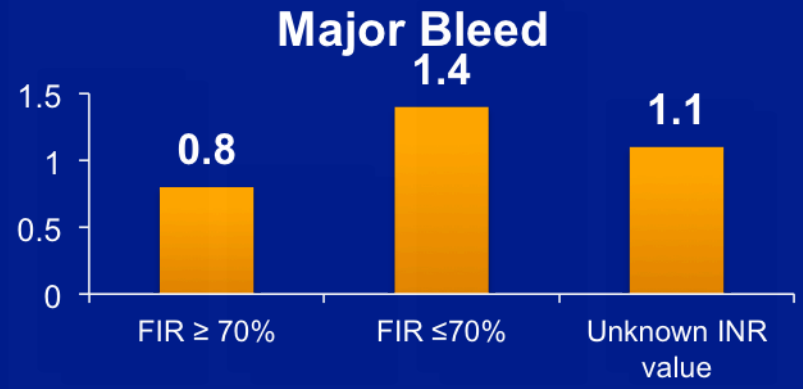
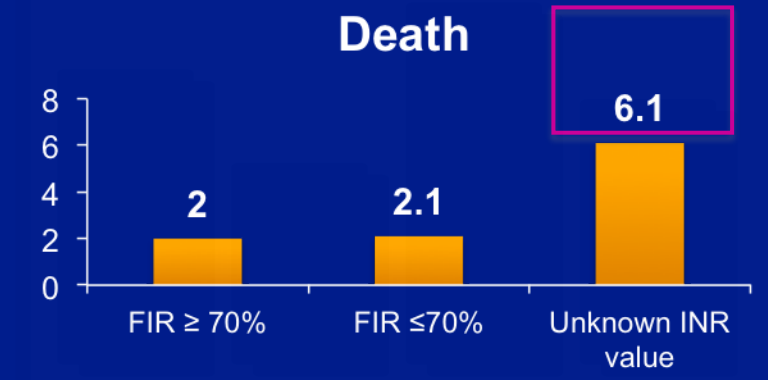






Patients without INR information had highest rates of stroke and death

FIR = frequency in range

Mantovani et al. AHA 2012

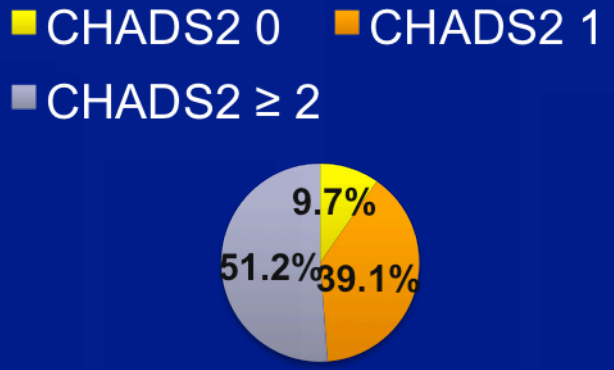
GARFIELD-AF Cohort 1:
Gender differences in use of antithrombotic therapy in AF

Date of preparation January 2016
L.GB.MKT.01.2016.14475

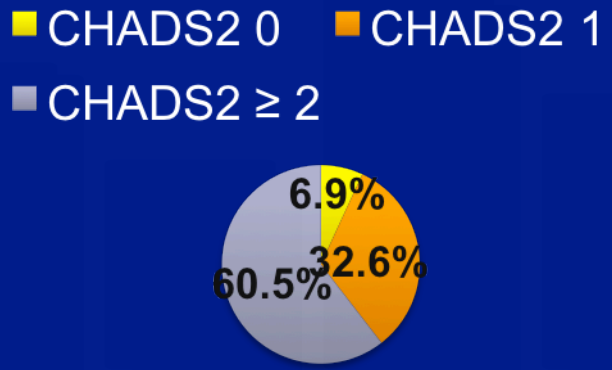
	Total population	Men	Women
$CHADS_2$	1.8 (1.2)	1.7 (1.1)	2.0 (1.2)
CHA_2DS_2-VASc	2.9 (1.5)	2.4 (1.4)	3.7 (1.4)
HAS-BLED	2.0 (0.9)	1.9 (0.9)	2.1 (0.8)

Data are mean (SD)

Men



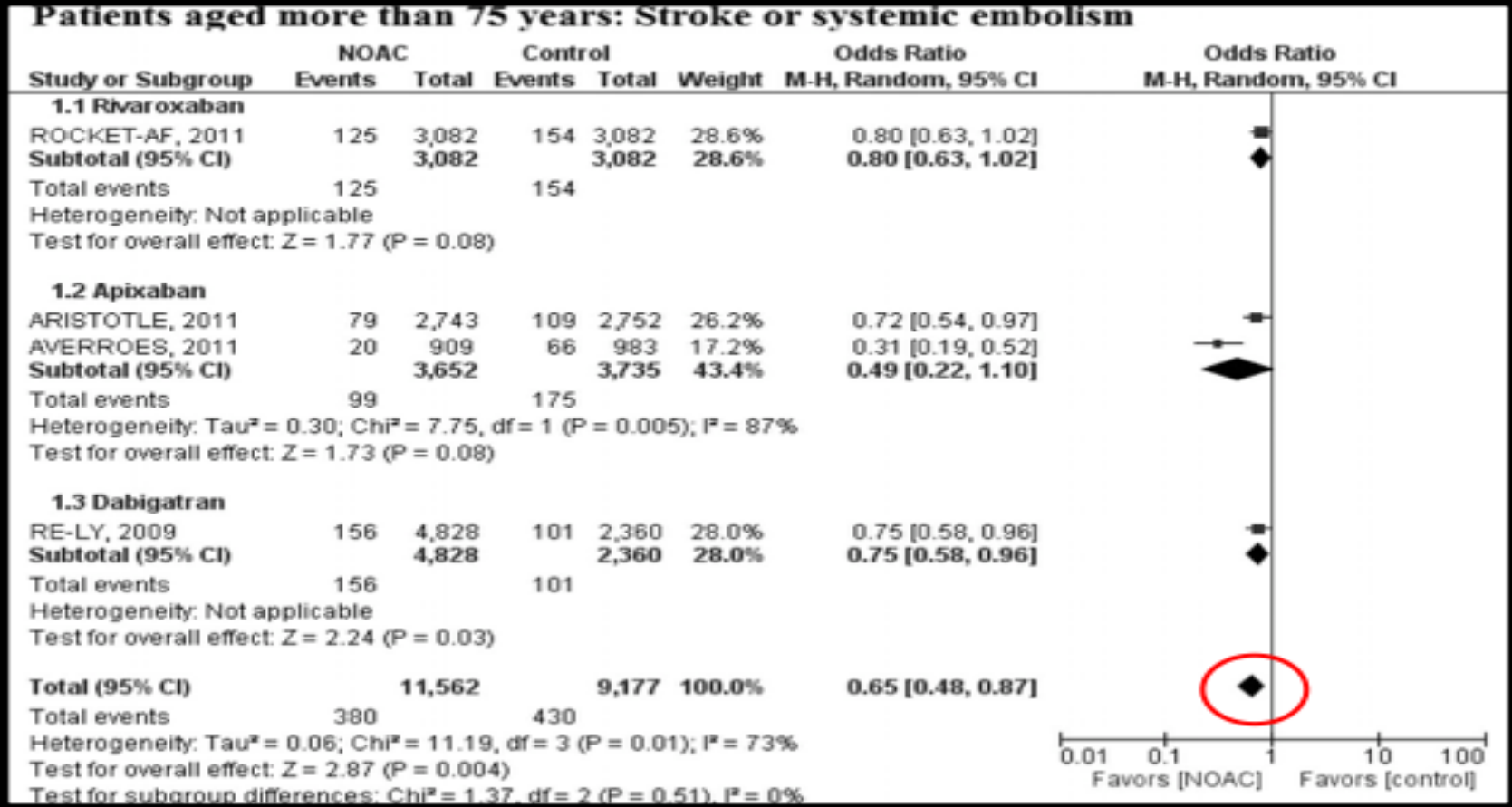
Women



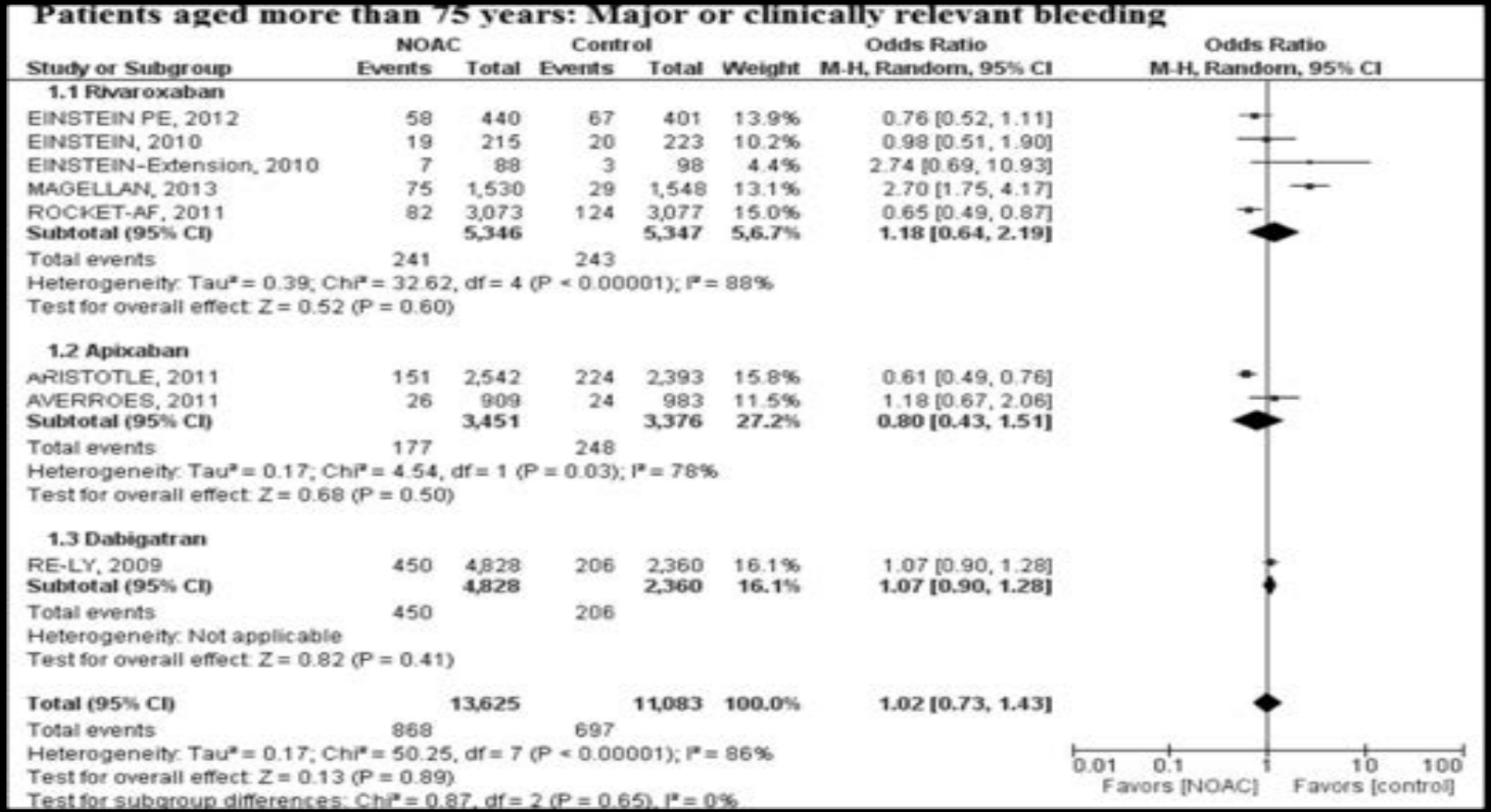
Lip et al. ESC 2012

Dresden Registry

Dresden: Bleeding in the over 75 on DOAC



Dresden: Bleeding in the over 75 on DOAC



Summary

- Age is a risk factor
- Age is a risk of under-treatment
- Warfarin is an effective treatment in the old
- Warfarin is an effective treatment in the frail
- DOACs are as effective in warfarin
- DOACs perform well in the real world in the old and frail

Thank you for your attention

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 @fatherofhan