RETROSPECTIVE CLAIMS DATABASE STUDIES OF DIRECT ORAL ANTICOAGULANTS (DOACS) FOR STROKE PREVENTION IN NONVALVULAR ATRIAL FIBRILLATION

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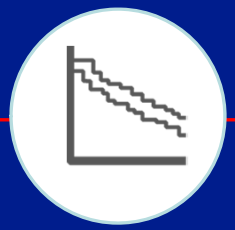
For a Medicine (i.e., a DOAC) to Gain Approval, It Must Demonstrate a Positive Benefit-Risk Profile



Phase III clinical trials have demonstrated the positive benefit-risk profile of DOACs in comparison to VKAs in NVAF[1-4]

DOACs have been approved by regulatory authorities, (e.g. FDA), based on pivotal phase III clinical trial findings

FDA=Food and Drug Administration; VKA=vitamin K antagonist

1. N Engl J Med 2011; 365:883-891; 2. N Engl J Med 2011; 365:981-992; 3. N Engl J Med 2009; 361:1139-1151; 4., N Engl J Med 2013; 369:2093-2104

Pharmacological Characteristics of DOACs for NVAF (US)

Properties	Apixaban	Dabigatran	Edoxaban	Rivaroxaban
Therapeutic target	Factor Xa	Factor II (Thrombin)	Factor Xa	Factor Xa
Bioavailability	50%	3–7%	62%	66% without food ~100% with food
T_{max}	3–4h	0.5–2h	1–2h	2–4h
Half-life	12h	12–17h	10–14h	5–9h (young) 11–13h (elderly)
Renal clearance of absorbed active drug	27%	~80%	50%	35%
Dose reduction	If 2-out-of-3 criteria meet: serum creatinine ≥1.5 mg/dL, age≥80 years, weight ≤60kg or co-administration with a strong dual inhibitors of CYP3A4 and P-gp: 2.5 mg BID (50% of full dose)	If CrCl 15–30 mL/min or if CrCl 30-50 mL/min and co-administered with a P-gp inhibitor (e.g. dronedarone, ketoconazole): 75 mg BID (50% of full dose)	CrCl 15–50 mL/min: 30 mg OD (50% of full dose)	CrCl 15-50 mL/min: 15 mg OD (75% of full dose)

US prescribing information for each DOAC as of September 4, 2016

My Personal View: "Real-World Evidence is Complementary to Rigorous But Tightly Controlled Randomized Clinical Trials"

- Real-world evidence is a broad term for many different study designs, including:
  - Pragmatic (or naturalistic) randomized clinical trials
  - Prospective registries (e.g., GARFIELD AF, ORBIT, Dresden, XANTUS)
  - Retrospective clinical studies
  - **Claims database analyses**
- Not all real-world evidence studies are created equal
  - Internal and external validity can change markedly between and within real-world study designs
  - Methodological differences and their impact are not always obvious to the reader
  - Understanding the strengths and limitations of real-world studies is paramount for their proper interpretation

Understanding the Methods, Strengths and Limitations of Retrospective Claims Database Analyses is of Particular Importance!

- Some of the simpler methodological and interpretation considerations for claims database analyses of DOACs for stroke prevention in NVAF
  - Does it report both ischemic and bleeding endpoints?
  - Are components of composite endpoints of equal clinical importance?
  - Does the study provide data on DOAC dosing (i.e., % receiving reduced dosage)
  - Are validated coding schemas used for identification of NVAF patients, co-morbidities (e.g., CHA2DS2-VASC, HAS-BLED) and endpoints?

What Do Claims Database Studies Tell Us About the Effectiveness and Safety of DOACs for Stroke Prevention in NVAF?

Recently Published Claims Databases*

	REVISIT-US 2016[1]	Yao 2016[2]	Larsen 2016[3]
Database (Country)	Truven MarketScan (USA)	OLDW (USA)	Danish Nationwide Databases (Denmark)
Dates	January 2011 to December 2014	October 2010 to June 2015	August 2011 to October 2015
Participants	Patients with non-valvular AF who were naïve to oral anticoagulants	Patients with non-valvular AF who were **either naive to oral anticoagulants or had prior warfarin-experience**	Patients with non-valvular AF who were naïve to oral anticoagulants and **were receiving a standard (not reduced) dose of a DOAC**

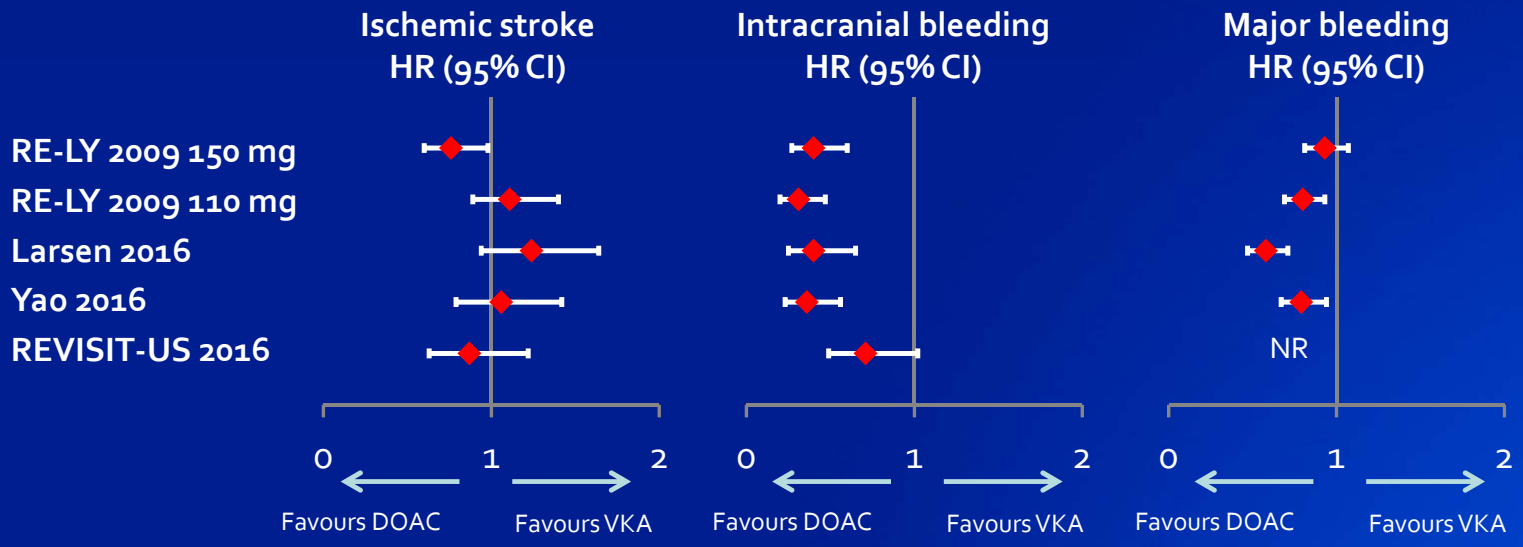
***Cross comparisons of statistically independent claims analyses (even when published in the same paper) are not appropriate**

USA=United States of America

1. Curr Med Res Opin. 2016 Sep 20:1-7; 2. J Am Heart Assoc 2016;5:e003725; 3. BMJ 2016;353:i3189

Recently Published Claims Database Analyses of Dabigatran Versus VKA for NVAF and Comparison of Results to RE-LY

	REVISIT-US 2016[1]	Yao 2016[2]	Larsen 2016[3]	RE-LY 2009[4]
Reduced dose, %	10.3%	8.8%	0%	NA
N (DOAC 150/110//VKA)	15,679/15,679	14,307/14,307	12,701/35,436	6,076/6,015/6,022



CI=confidence interval; HR=hazard ratio; NR=not reported; USA=United States of America

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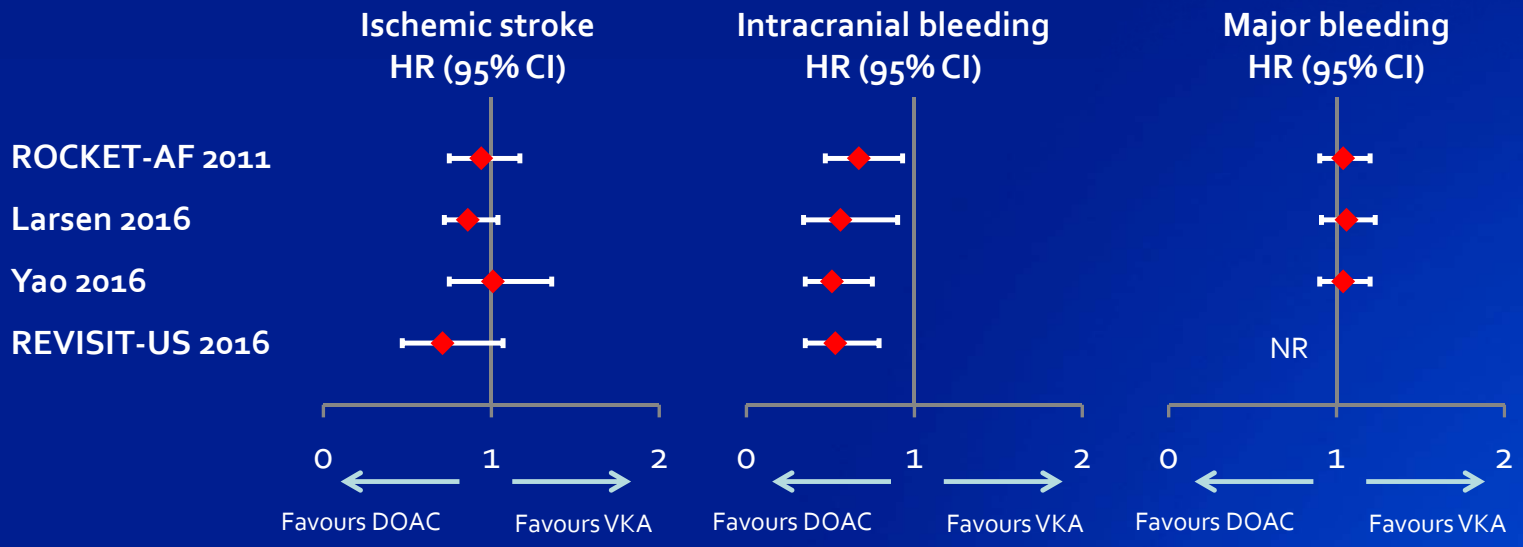
Recently Published Claims Database Analyses of Rivaroxaban vs. VKA for NVAF and Comparison of Results to ROCKET-AF

	REVISIT-US 2016[1]	Yao 2016[2]	Larsen 2016[3]	ROCKET AF 2011[4]
Reduced dose, %	17.3%	21.5%	0%	21.1%
N (DOAC/VKA)	11,411/11,411	16,175/16,175	7,192/35,436	7,131/7,133



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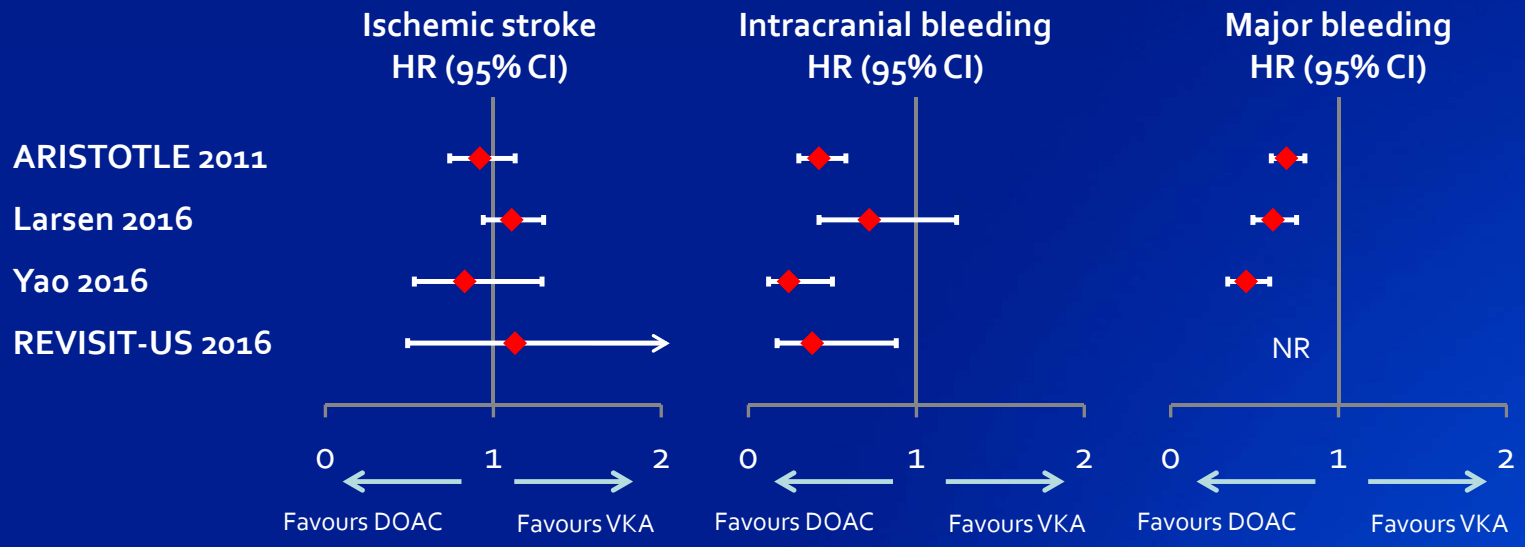
Recently Published Claims Database Analyses of Apixaban vs. VKA for NVAF and Comparison of Results to ARISTOTLE

	REVISIT-US 2016[1]	Yao 2016[2]	Larsen 2016[3]	ARISTOTLE 2011[4]
Reduced dose, %	15.5%	18.1%	0%	4.7%
N (DOAC/VKA)	4,083/4,083	7,695/7,695	6,349/35,436	9,120/9,081



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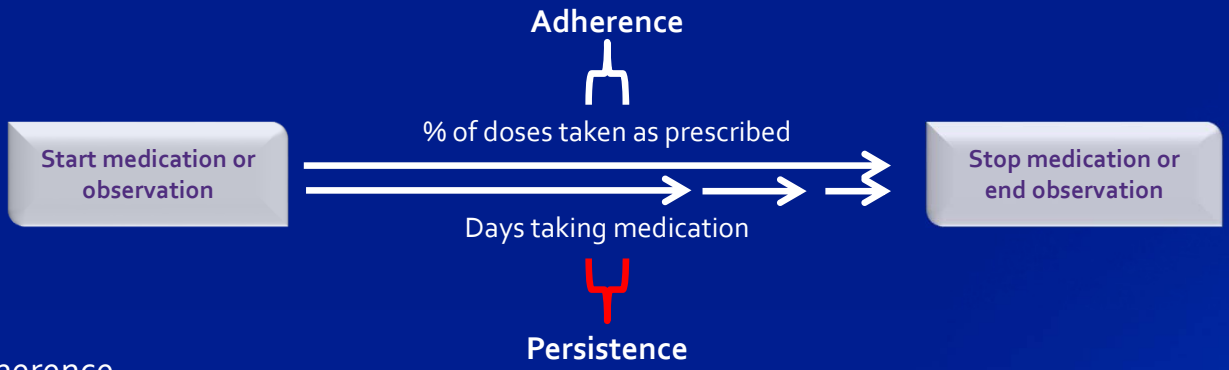
DOAC Use by Strength and Country

	Apixaban			Rivaroxaban			Dabigatran	
	Q2 2015			Q2 2015			Q2 2015	
Country	2.5 MG	5 MG	10 MG	15 MG	20 MG	75 MG	110 MG	150 MG
UNITED STATES	**25%**	**75%**	**5%**	**20%**	**75%**	**17%**	**0%**	**83%**
JAPAN	60%	40%	55%	45%	0%	40%	60%	0%
GERMANY	45%	55%	4%	34%	62%	2%	60%	38%
CANADA	38%	62%	5%	26%	69%	1%	52%	48%
AUSTRALIA	40%	60%	2%	30%	68%	0%	63%	36%
UNITED KINGDOM	39%	61%	5%	22%	74%	2%	50%	47%
SPAIN	38%	62%	5%	31%	64%	2%	59%	38%
FRANCE	45%	55%	7%	36%	57%	4%	66%	30%
BELGIUM	31%	69%	2%	42%	57%	0%	60%	40%
ITALY	41%	59%	3%	37%	60%	0%	62%	38%

IMS MIDAS Q2 2015 (unpublished)

Evidence From Claims Database Studies on Medication-Taking Behaviors of NVAF Patients

A Shared Understanding of Different Medication-Taking Behavior Terminology



- Adherence
  - The extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen
  - Percentage of doses taken as prescribed
  - Medication possession ratio (MPR): the sum of the medication days of supply divided by the exposure to therapy
  - Proportion of days covered (PDC): differs from MPR because it is measured over fixed periods of exposure; for example, 3, 6 or 12 months
- Persistence
  - Duration of time from initiation to discontinuation of therapy
  - Days taking medication (without exceeding permissible gap)

Value Health 2008;11:44–47

Estimated Persistence* to OACs in Patients with NVAF

27,514 OAC-naïve patients with incident NVAF between January 2011 and May 2014 in the UK primary care Clinical Practice Research Datalink (CPRD) database

Type of OAC	N	90-days %	180-days %	270-days %	365-days %
NOAC	914	94.7	85.9	82.4	79.2
VKA	12,307	87.2	76.5	69.3	63.6
P-value		<0.0001	<0.0001	<0.0001	<0.0001

*Defined as no more than a 30-day gap in OAC prescription fills

Thromb Haemost 2016; 115: 31–39

Adherence to DOACs in NVAF is Important

Claims-based analysis in MarketScan of propensity-score matched QD (100% rivaroxaban with 82% receiving 20 mg/ 0% edoxaban) and BID (24.5% apixaban with 83% receiving the 5 mg dose/75.5% dabigatran with 80% receiving the 150 mg dose) DOAC users with NVAF

DOAC	Proportion <80% adherent#	Adjusted* HR (95%CI) for ischemic stroke
All DOAC users (N=36,868)	29.7%	1.50 (1.30–1.73)
Once-daily users (N=18,434)	27.2%	1.47 (1.20–1.80)
Twice-daily users (N=18,434)	32.1%∫	1.50 (1.23–1.83)¶

∫p<0.001 for twice- versus once-daily DOAC use

¶ Interaction p-value for once- vs. twice daily hazard ratios for ischemic stroke=0.89

<80% represents suboptimal adherence (calculated as proportion of days covered using the Pharmacy Quality Alliance methodology)

*Cox proportion hazard regression adjusted for categorical age, gender, history of hypertension, diabetes mellitus, congestive heart failure, prior myocardial infarction, prior stroke, chronic kidney disease, liver disease, predisposition to bleeding, depression, alcohol and drug abuse and prior warfarin use

Int J Cardiol. 2016;215:11-3

As C. Everett Koop, former US Surgeon General said…

“Drugs don’t work in patients who don’t take them.”

Conclusions

- Real-world evidence (in all its forms) is "informative" as long as it is interpreted correctly
- Careful dissection of a claims database study is required
- The results of DOAC claims database analyses in NVAF patients are generally consistent with their pivotal, phase III randomized controlled trials
  - DOACs appear at least "non-inferior" to VKA for prevention of ischemic stroke
  - DOACs are associated with a significant reduction in the hazard of developing intracranial bleeding (the bleeds most associated with prolonged neurologic deficit and high case fatality rates)
- The reduced dose of DOACs are prescribed quite frequently
- The story is far from over…No doubt additional real-world (including claims database) studies will be published

Thank You for Your Attention!