Deaths and Vascular Outcomes with non-Vitamin K Oral Anticoagulants versus Warfarin in Patients with Heart Failure in the Food and Drug Administration Adverse Event Reporting System

Victor Serebruany, MD, PhD
Heart*Drug*™ Research LLC;
Johns Hopkins University;
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Background

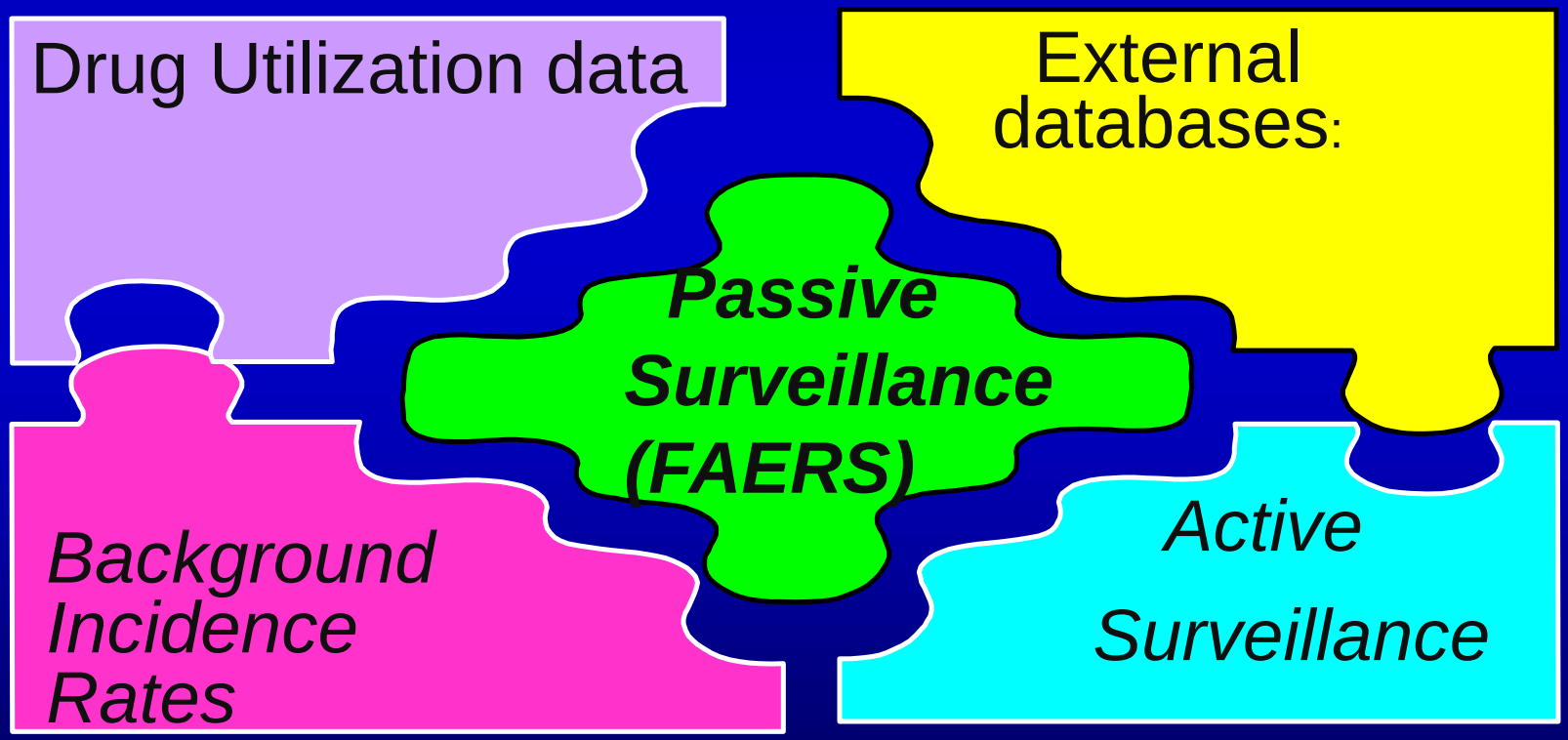
Many patients with heart failure (HF) are treated with warfarin or non-vitamin K antagonist oral anticoagulants (NOACs). The NOACs with its protagonist agents dabigatran, rivaroxaban, apixaban, and edoxaban have been tested in large-scale randomized clinical trials (RCT) in atrial fibrillation against warfarin, but no large-scale randomized head-to-head comparisons of these NOACs have been performed.

In HF in particular, randomized outcome-driven comparisons of different anticoagulant strategies are scarce. Data from international, government-mandated registries may be useful in understanding the real-life use of various anticoagulants and how they are linked to outcomes.

OBJECTIVE:

We aimed to assess 2015 annual all-cause mortality, myocardial infarction, and stroke rates co-reported for warfarin and NOACs in subjects with HF in the US Food and Drug Administration Adverse Event Reporting System (FAERS) database.

FDA Postmarketing Surveillance



FDA should monitor FAERS

- Daily “in-box” review of reports
  - All serious unlabeled reports;
  - Serious direct reports;
  - Periodic and “enhanced pharmacovigilance” reports
- Periodic safety reports
- Main mission: identify and monitor “Safety Signals”
- Work with epidemiologists, and doctors

Demographics and clinical characteristics in 11,324 subjects with HF co-reported with NOACs or warfarin in FAERS.

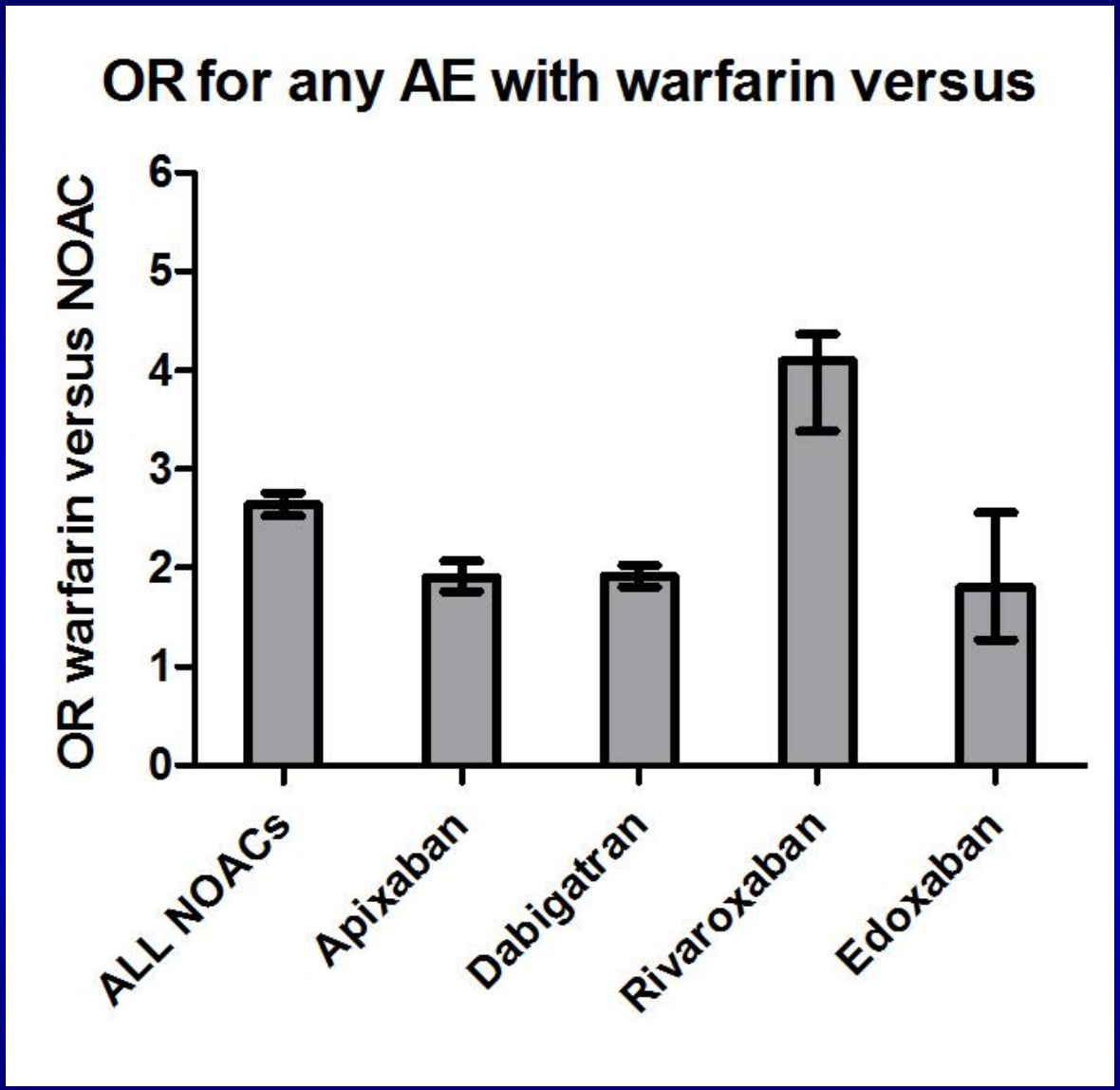
Variable	Warfarin n=8260 (%)	All NOACs n=3064 (%)	Apixaban n=666 (%)	Dabigatran n=1361 (%)	Rivaroxaban n=1005 (%)	Edoxaban n=32 (%)
Age (> 75 y.o.)	2627* (31.8%)	1424 (46.5%)	325 (48.8%)	646 (47.5%)	446 (44.4%)	7 (21.9%)
Female gender	3741 (50.4%)	1448 (47.3%)	314 (49.1%)	622 (47.5%)	503 (51.5%)	9 (56.3%)
Diabetes	414 (5.0%)	37 (1.2%)	4 (0.6%)	18 (1.3%)	15 (1.5%)	0 (0.0%)
Hypertension	1243 (15.0%)	170 (5.6%)	41 (6.2%)	56 (4.1%)	72 (7.2%)	1 (3.1%)
Renal failure	35 (0.4%)	22 (0.7%)	7 (1.1%)	5 (0.4%)	9 (0.9%)	1 (3.1%)
Aspirin use	2095 (25.4%)	598 (19.5%)	121 (18.2%)	246 (18.1%)	228 (22.7%)	3 (9.4%)
Other antiplatelet use	635 (7.7%)	177 (5.8%)	33 (5.0%)	83 (6.1%)	61 (6.1%)	0 (0.0%)

Numerical overview of reports on mortality and cardiovascular outcomes in subjects with HF co-reported with NOACs or warfarin.

Outcome	Warfarin (%)	All NOACs (%)	Apixaban (%)	Dabigatran (%)	Rivaroxaban (%)	Edoxaban (%)
All-cause mortality	2595 (31.4)	939 (31.1)	175 (26.3)	475 (34.9)	301 (30.0)	3 (0.0)
Myocardial infarction	718	87	17	41	29	0
Stroke	200	65	12	28	25	0
Ischemic stroke	169	40	5	18	17	0
Hemorrhagic stroke	16	7	2	1	4	0
Total Events	8260 (72.9)	3064	666 (5.9)	1361 (12.0)	1005 (8.9)	32 (0.3)

Risk of adverse outcomes co-reported with warfarin compared to NOACs in HF patients

OR (95% CI)	Warfarin vs all NOACs	Warfarin vs Apixaban	Warfarin vs Dabigatran	Warfarin vs Rivaroxaban
All-Cause mortality	2.69 (2.49-2.90)***	2.15 (1.83-2.52)***	2.19 (1.98-2.42)***	3.71 (3.28-4.19)***
Myocardial infarction	4.91 (3.95-6.10)***	2.57 (1.62-4.08)***	4.81 (3.60-6.45)***	5.74 (4.01-8.23)***
Stroke	8.85 (6.61-11.84)***	3.83 (2.12-6.91)***	8.46 (5.67-12.62)***	10.4 (6.83-15.82)***
Hemorrhagic stroke	5.32 (2.07-13.66)***	1.08 (0.24-4.76)	8.43 (1.11-63.85)*	5.43 (1.81-16.33)***
Ischemic stroke	12.73 (8.87-18.27)***	8.47 (3.45-20.79)***	12.91 (7.90-21.10)***	11.69 (7.06-19.36)***
Total Events	2.64 (2.53-2.76)***	1.91 (1.76-2.07)***	1.92 (1.81-2.03)***	4.09 (3.38-4.37)***


OR for any AE with warfarin versus
OR warfarin versus NOAC
0
1
2
3
4
5
6
ALL NOACs
Apixaban
Dabigatran
Rivaroxaban
Edoxaban

Conclusion

Annual 2015 FAERS profiles in HF patients reveal that warfarin was associated with higher risk of death, myocardial infarction and stroke compared to NOACs.

These observational data provide real-world insight into a potential safety benefit of NOACs over warfarin in the setting of HF.