Adverse Event Profiles and Filing Sources After Antiplatelet Agents in FAERS

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Limitations of Clinical Trials

Small sample size;

Heavily selective/restricted population;

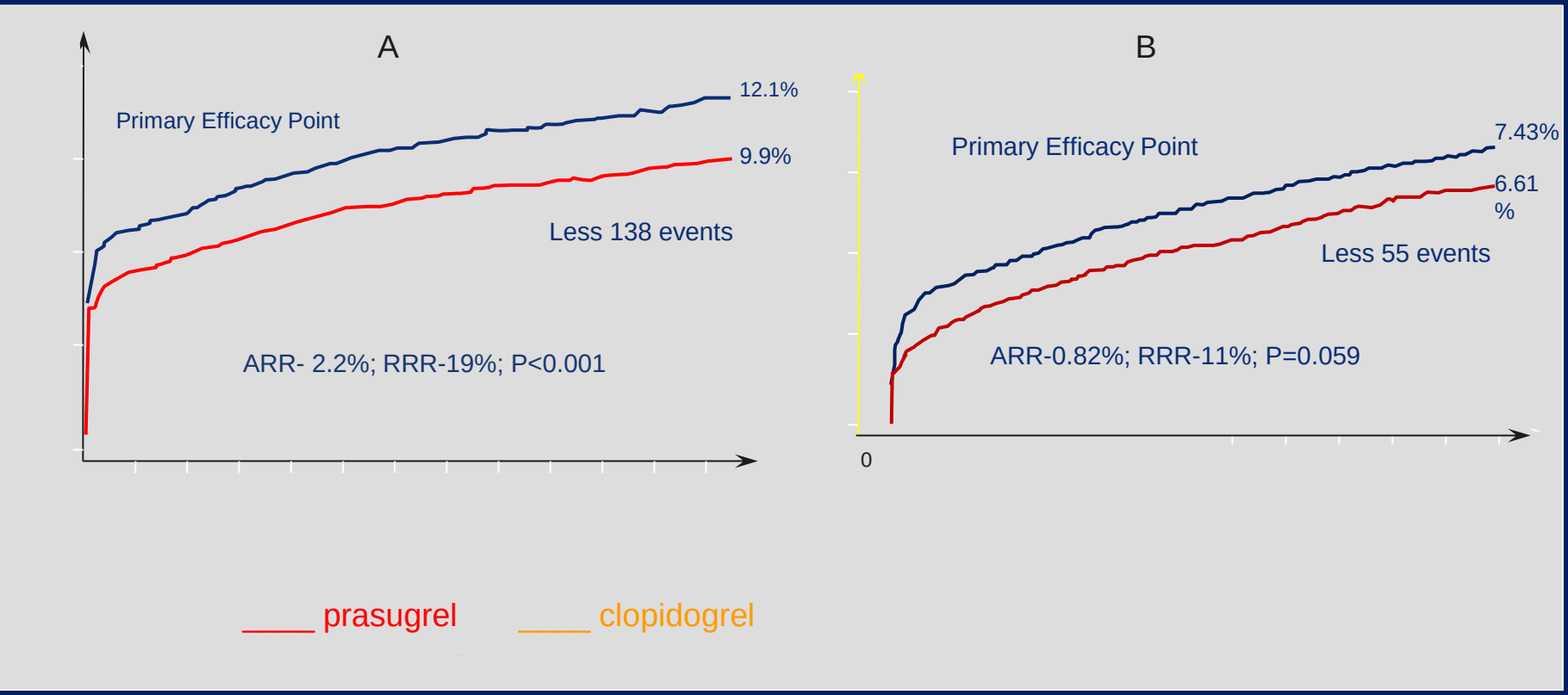
Lack of elderly, children, pregnancy, co-morbidities, impaired renal function;

Narrow indications, short duration, no chronic use;

Massive discontinuations and lost patients;

Potential sponsor bias

The TRITON Trial Controversy

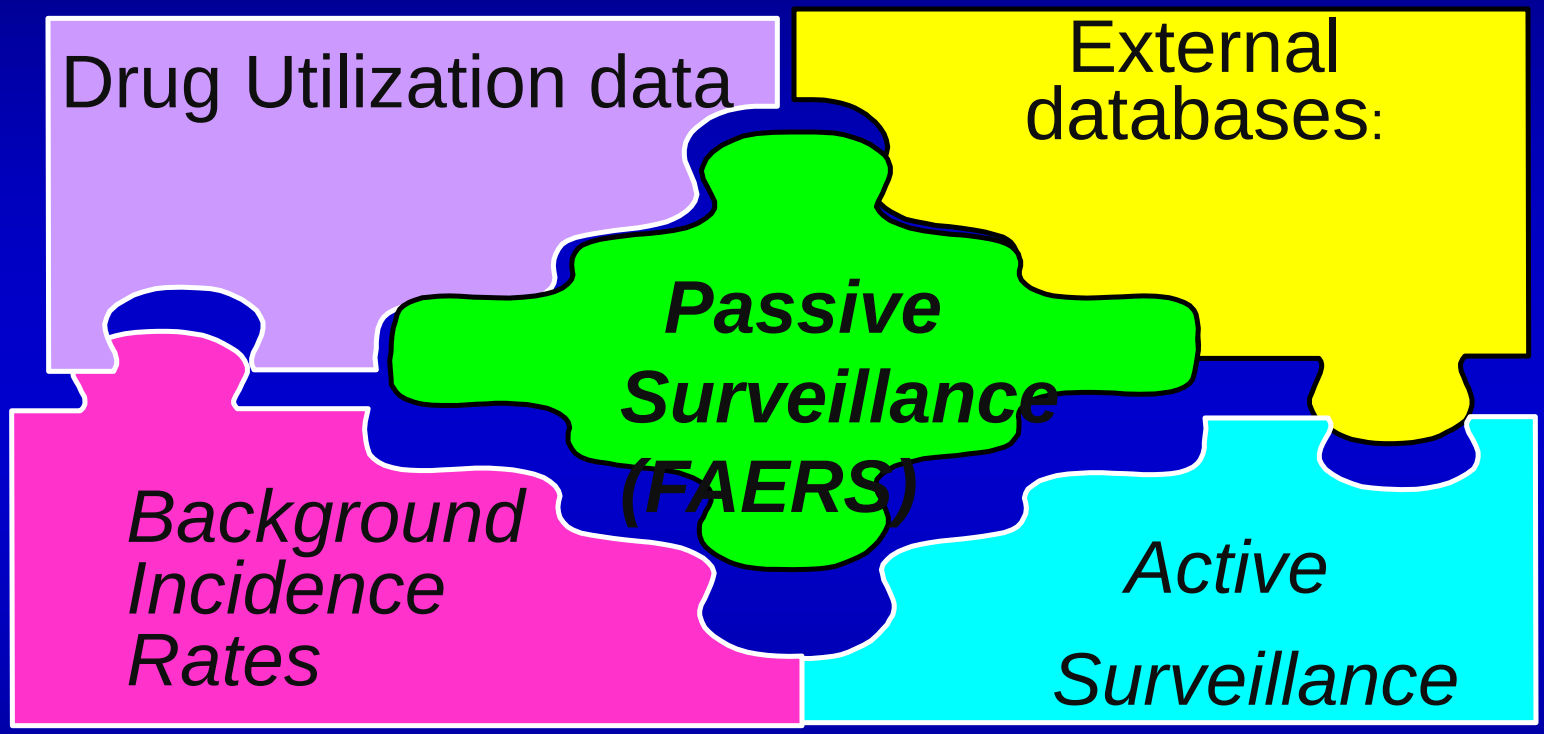


A : All Adjudicated Events NEJM; 2007

B: Site Reported Events FDA; 2009

124 *post hoc* and 74 meta analyses in PubMed

FDA Postmarketing Surveillance



- FDA Adverse Event Reporting System (FAERS)
- Voluntary, “spontaneous” reporting system
- Sponsors required to report (21CFR314.80)
- Computerized database
- Origin 1969; > 8.2 million reports
- Contains human drug and “therapeutic” biologics
- Exception - vaccines (VAERS)

FAERS Strengths

- Includes all U.S. marketed products
- Simple, inexpensive reporting system
- Detection of events not seen in clinical trials (“signal generation”)
- Critical for events with rare background rate, short latency
- Case series evaluation: identification of trends, drug indication, population, and other emerging safety concerns
- Open to public

FAERS Limitations

- Duplicate reporting;
- Extensive underreporting;
- Quality of report is variable;
- Reporting biases;
- Difficult to attribute events with a high background rate, confounders, long latency outcomes
- Hard to mine effectively

Total fatalities co-reported with oral P_2Y12 inhibitors in FAERS

Drug	Cases (n)	Deaths (n/%)	Chi-square	p-value	PRR (95%-CI)	ROR (95% - CI)
Clopidogrel	108,081	12,538; 11.6%	5.59	0.018	0.935 (0.885- 0.988)	0.927 (0.870- 0.987)
Prasugrel	7,562	635; 8.4%	71.35	< 0.00001	0.678 (0.619- 0.742)	0.648 (0.586-0.717)
Ticagrelor	9,860	1.222; 12.4%	-	-	1.000	1.000

Annual 2015 deaths co-reported with oral P_2Y12 inhibitors in FAERS

Drug	Cases (n)	Deaths (n/%)	Chi-square	p-value	PRR (95%-CI)	ROR (95% - CI)
Clopidogrel	13,234	1,156; 8.7%	86.33	<0.00001	0.596 (0.535- 0.664)	0.558 (0.492- 0.631)
Prasugrel	2,927	151; 5.2%	93.49	< 0.00001	0.425 (0.355- 0.508)	0.386 (0.317-0.471)
Ticagrelor	2,607	382; 14.7%	-	-	1.000	1.000

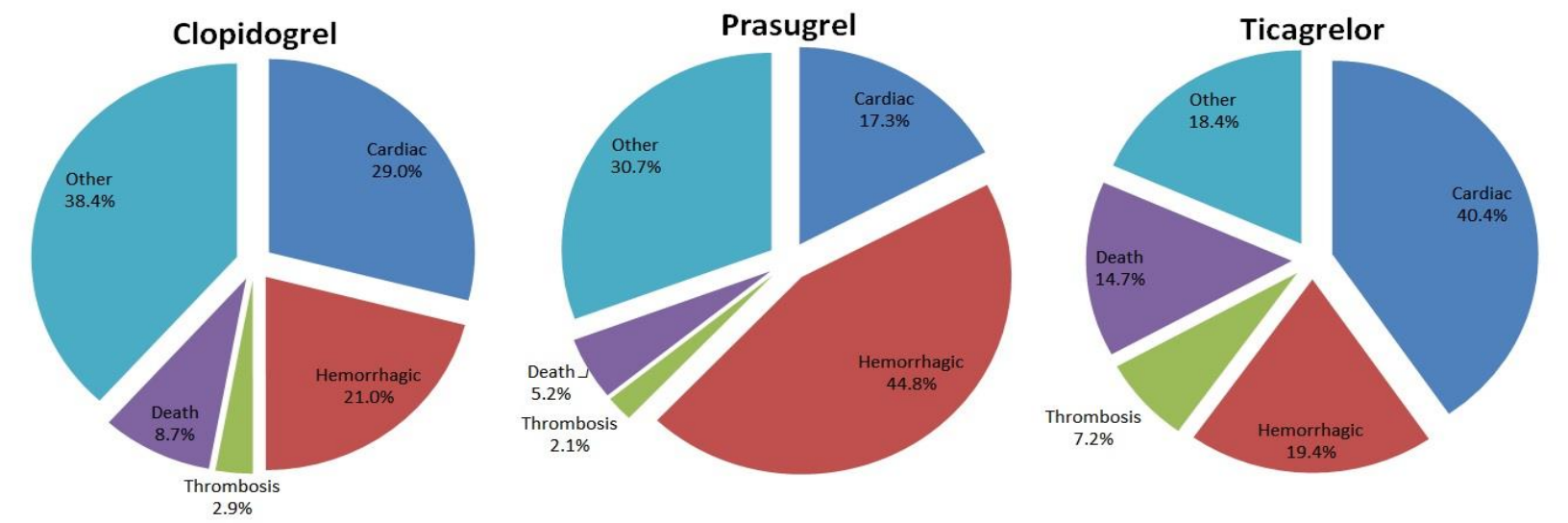
OBJECTIVE:

To assess adverse event profiles and filing sources after clopidogrel vs. prasugrel vs. ticagrelor

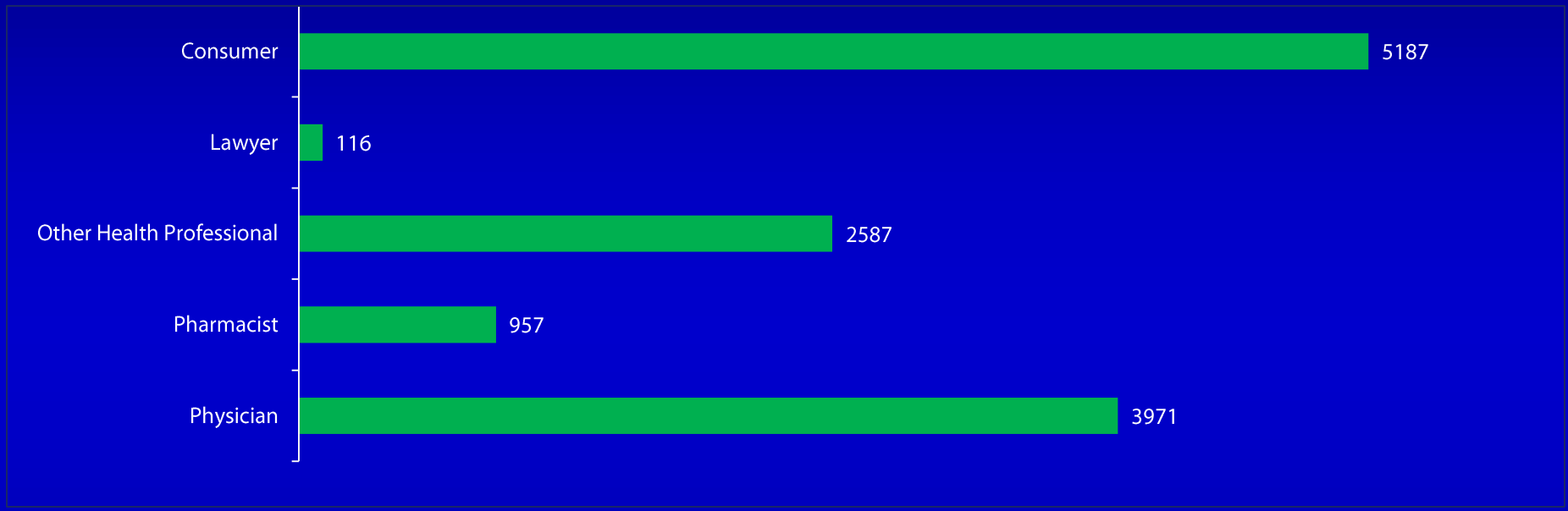
Annual 2015 adverse event types co-reported with oral P_2Y12 inhibitors in FAERS

Adverse Event	Clopidogrel (%)	Prasugrel (%)	Ticagrelor (%)
Cardiac	3,839 (29.0%)	505 (17.3%)	1,054 (40.4%)
Hemorrhagic	2,777 (21.0%)	1,312 (44.8%)	505 (19.4%)
Thrombotic	386 (2.9%)	61 (2.1%)	187 (7.2%)
All-Cause Death	1,156 (8.7%)	151 (5.2%)	382 (14.7%)
Other	5,076 (38.4%)	898 (30.6%)	479 (18.3%)
Total Events	13,234 (100%)	2,927(100%)	2,607(100%)

Spectrum of annual (2015) events co-reported with oral P_2Y12 inhibitors in FAERS

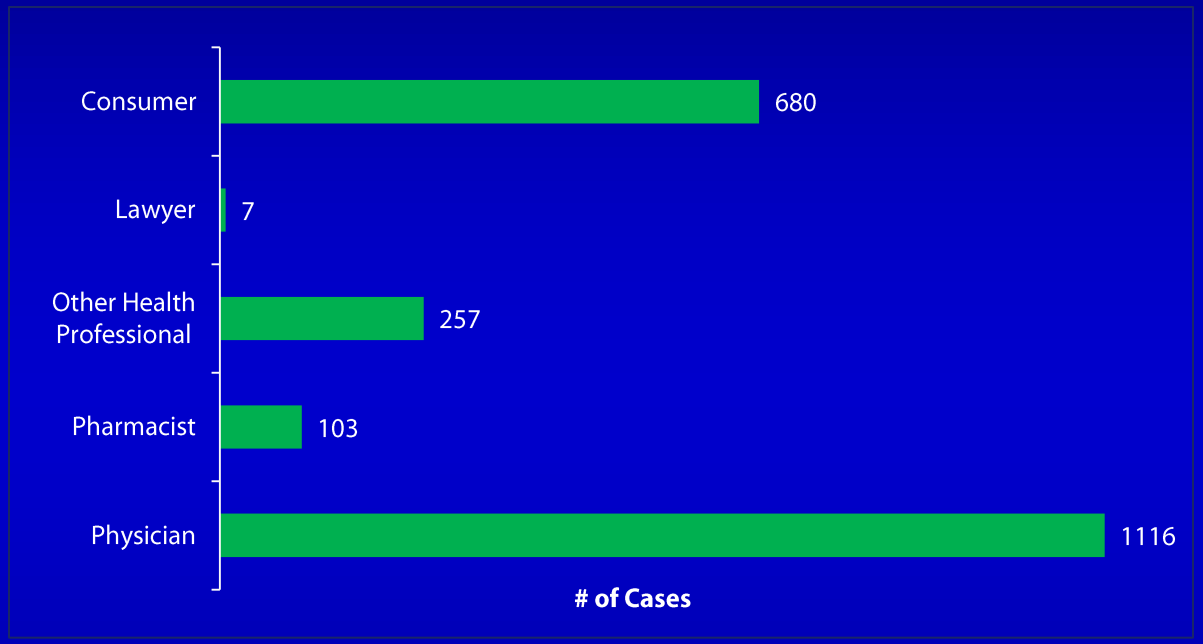


Annual 2015 filers identifying clopidogrel as a “prime suspect” in FAERS



Prasugrel filers in 2015

Ticagrelor filers in 2015



Conclusions:

- The adverse event FAERS profiles, the reporting quality and initial sources differed considerably among oral antiplatelet agents.
- All-cause death, cardiac, and thrombotic events were more common after ticagrelor than after clopidogrel, and especially after prasugrel for which the dominant and expected adverse event was bleeding.
- Patients or their family members filed most adverse events for clopidogrel and prasugrel, while physicians originated most ticagrelor complaints.These differences may be attributed to the confusion of treating physicians with unexpected events linked to ticagrelor.