Worldwide Reporting of Fatal Outcomes After Ticagrelor to the US Food and Drug Administration in FAERS

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Background

By law (21CFR314.80), manufacturers should mandatory report deaths to FAERS within 15 days, however, the geography patterns and quality of worldwide reporting are unclear. Expecting normal distribution of FAERS international fatal cases dependent on overall mortality, country population, economy, incidence of acute coronary syndromes, accepted recommendations, and drug utilization will be highly beneficial for independent outcome research since these data are public.

Ticagrelor has been chosen due to a single global sponsor, patent exclusivity, lack of generic formulations, uniformed priority placement into worldwide ACS guidelines, aggressive global marketing, growing clinical use, and massive current implementation of the PARTHENON clinical program seeking extra indications.

OBJECTIVE:

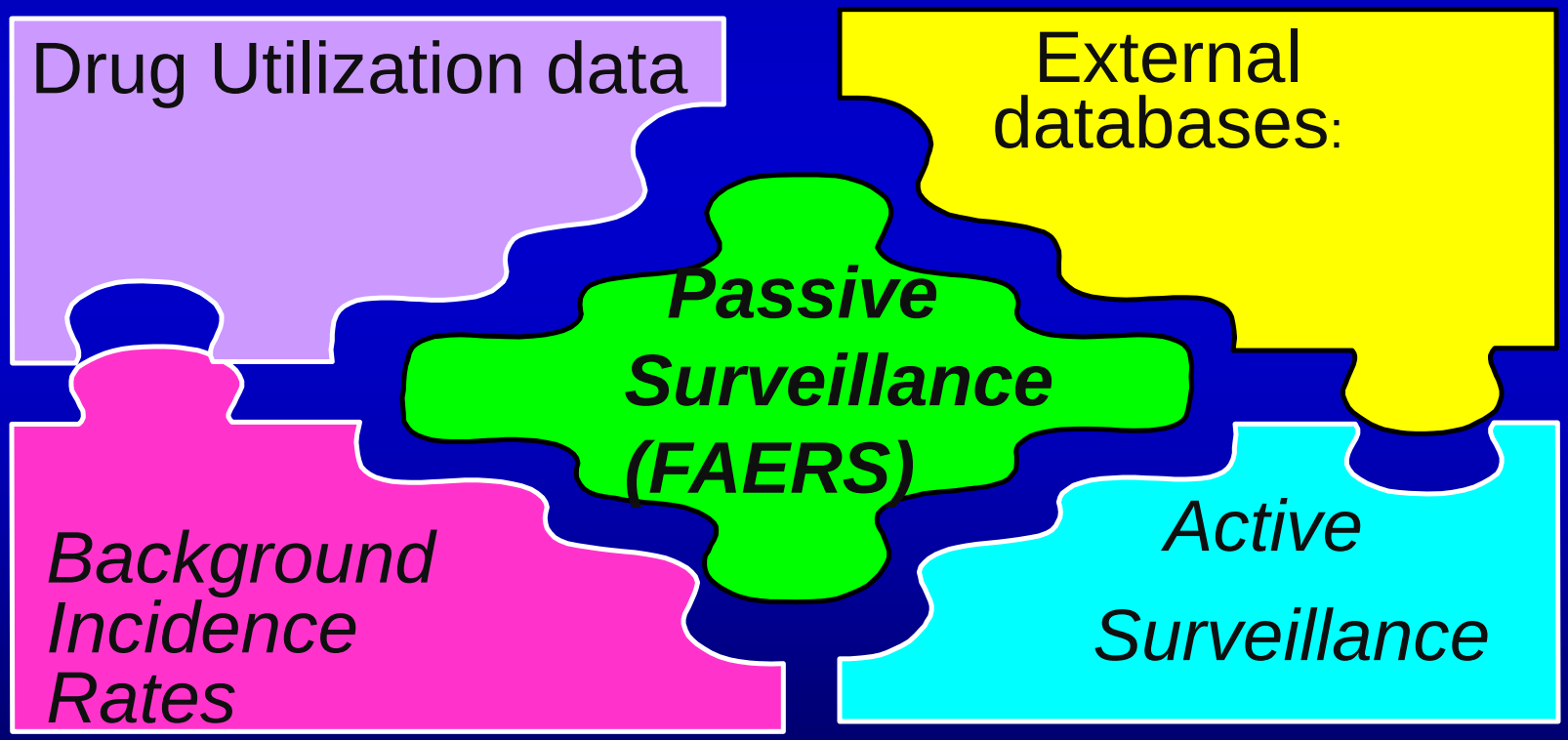
- We extracted and analyzed FAERS cases indicative of ticagrelor being considered as a primary cause of death over 4 years (2013-2016) from 59 countries or territories.

Results

Overall, there were 1,027 ticagrelor-associated FAERS fatalities. Most countries (n=37) reported less than 10 events, while many (n=22) countries reported 3 or less fatal cases. A single annual death event over four consecutive quarters was lacking in 36 countries.

Average reporting (11-24 deaths) occurred in 13 countries, and the highest numbers were yielded from 9 countries, namely, Bulgaria (n=25), Germany (n=26), UK (n=29), France (n=31), New Zealand (n=34), Brazil (n=57), Russia (n=71), Columbia (n=151), and finally was the highest in US (n=318).

FDA Postmarketing Surveillance



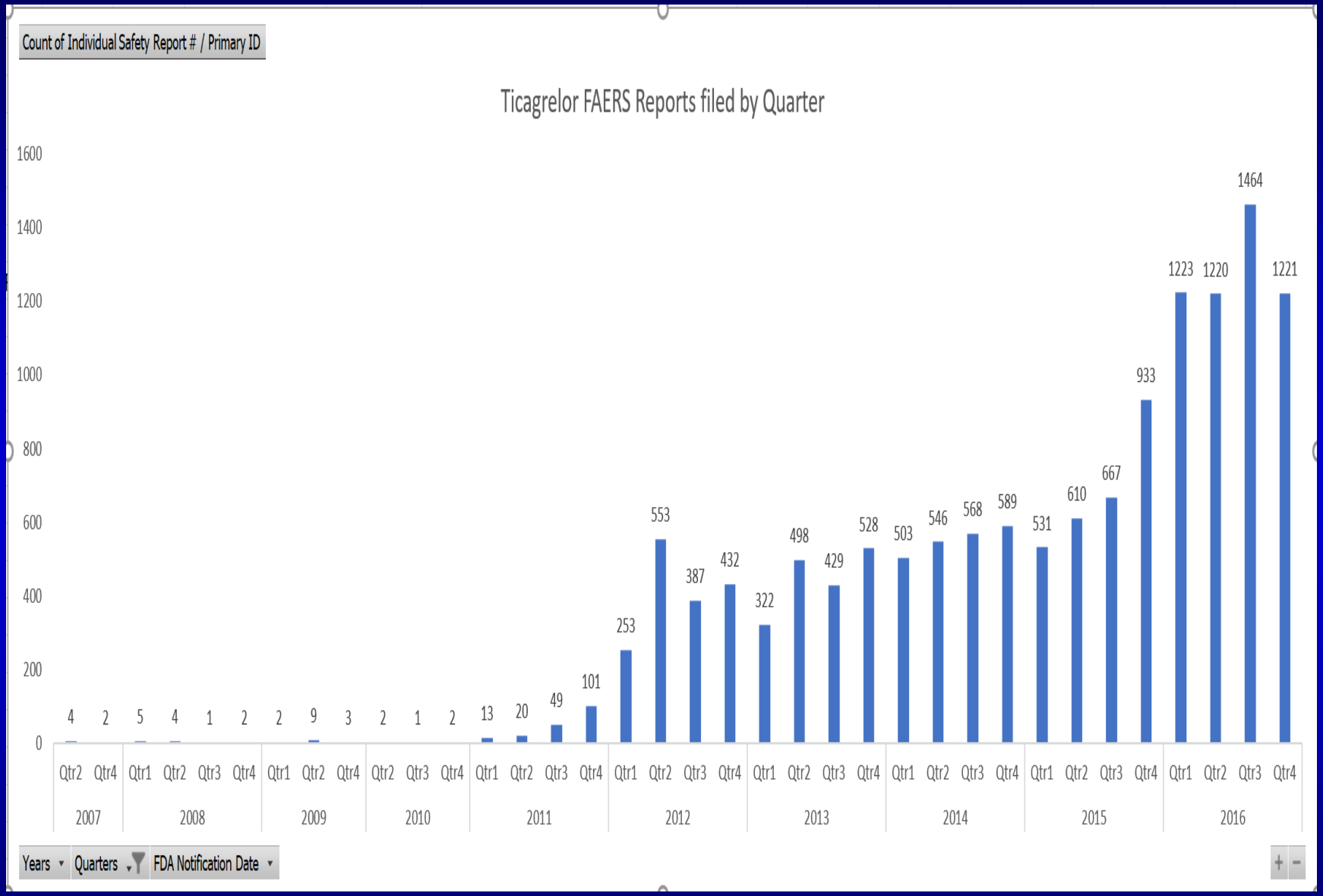
FDA should monitor FAERS

- 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

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

Serebruany V, et al. Am J Med, 2016


Count of Individual Safety Report # / Primary ID
Ticagrelor FAERS Reports filed by Quarter
1600
1400
1200
1000
800
600
400
200
0
4 2 5 4 1 2 2 9 3 2 1 2 13 20 49 101 253 553 387 432 322 498 429 528 503 546 568 589 531 610 667 933 1223 1220 1464 1221
Qtr2 Qtr4 Qtr1 Qtr2 Qtr3 Qtr4 Qtr1 Qtr2 Qtr4 Qtr2 Qtr3 Qtr4 Qtr1 Qtr2 Qtr3 Qtr4 Qtr1 Qtr2 Qtr3 Qtr4 Qtr1 Qtr2 Qtr3 Qtr4 Qtr1 Qtr2 Qtr3 Qtr4 Qtr1 Qtr2 Qtr3 Qtr4 Qtr1 Qtr2 Qtr3 Qtr4 Qtr1 Qtr2 Qtr3 Qtr4
2007 2008 2009 2010 2011 2012 2013 2014 2015 2016
Years
Quarters
FDA Notification Date

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

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Notable Countries

Country/Territory	Total Reports (2013-2016), (n)	Quarters with no reports (n)
Argentina	5	12
Australia	10	9
China	16	5
Jaoan	4	12
Indonesia	3	14
S. Korea	12	7
Columbia	151	2
USA	318	0

Conclusion

- Ticagrelor fatality patterns are reported differently around the globe, and some causative cases may be missing from FAERS.
- The notion for direct submission of reports to the FDA rather than via the manufacturer should be strongly considered, and promoted.