

Antithrombotics and Cancer: Are We Missing Something?



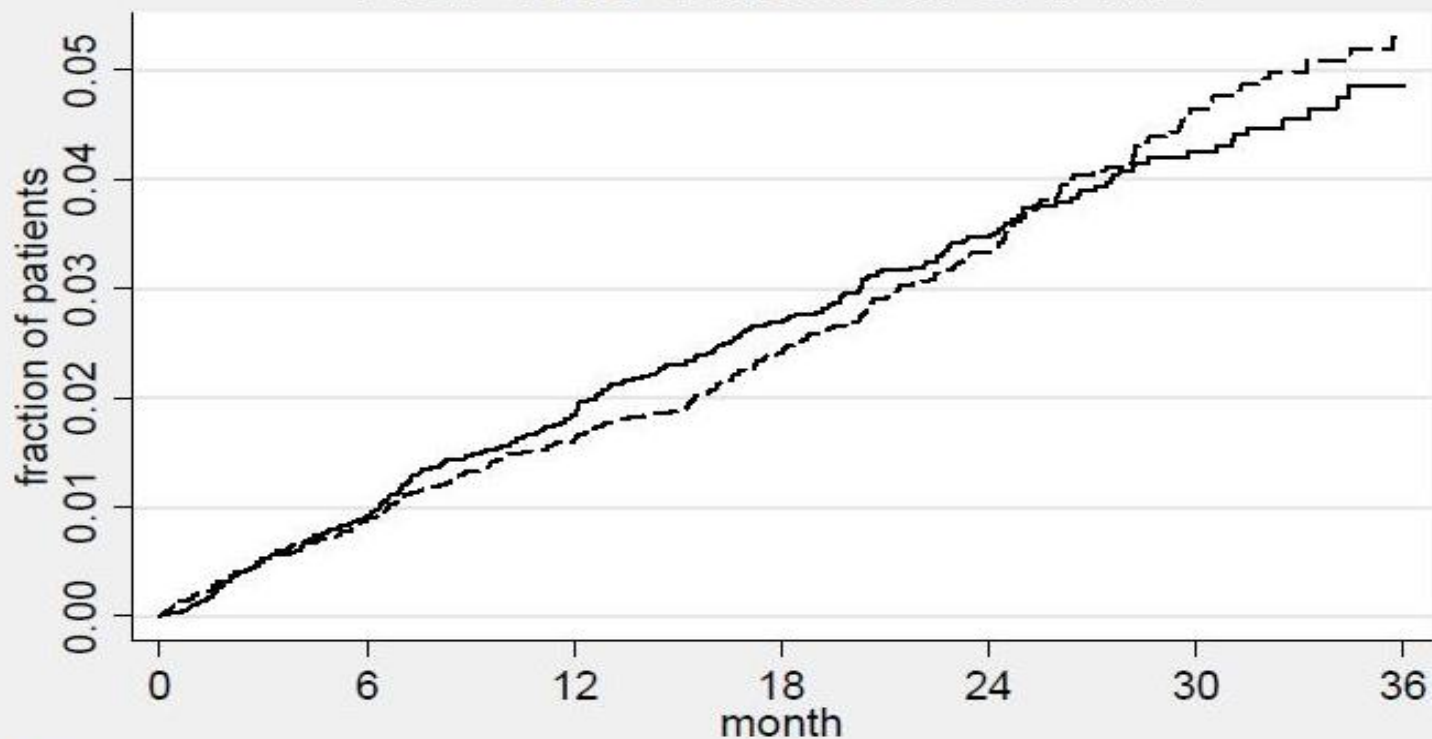
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Assistant Professor of Medicine

Johns Hopkins University School of Medicine – Baltimore, USA
JCR- Busan, Korea, December 11, 2015

Disclosures:

- **Ownership: HeartDrug™ Research, LLC**
- **Grants: Pfizer, Sanofi-BMS, Novartis, Lundbeck, Boehringer Ingelheim, Eli Lilly, AtheroGenics, Guilford, J&J, Bayer, Merck, Fibrex, Cardax, Eisai, Abbott, Brain Pool Program (Ministry of Science & Technology, Korea)**
- **Consulting: FDA, Pfizer, Sanofi-BMS, McNeil, NPS Pharma, Bayer, Eisai, mutual funds, hedge funds**
- **Speaking Bureau: Pfizer, Sanofi-BMS**
- **Patents: British Technology Group, Novartis, Boehringer Ingelheim, Eli Lilly, Pfizer, AtheroGenics, Eisai, PAR receptors and statins**
- **Unlabeled/Unapproved use: none**

New Solid Cancers in CAPRIE

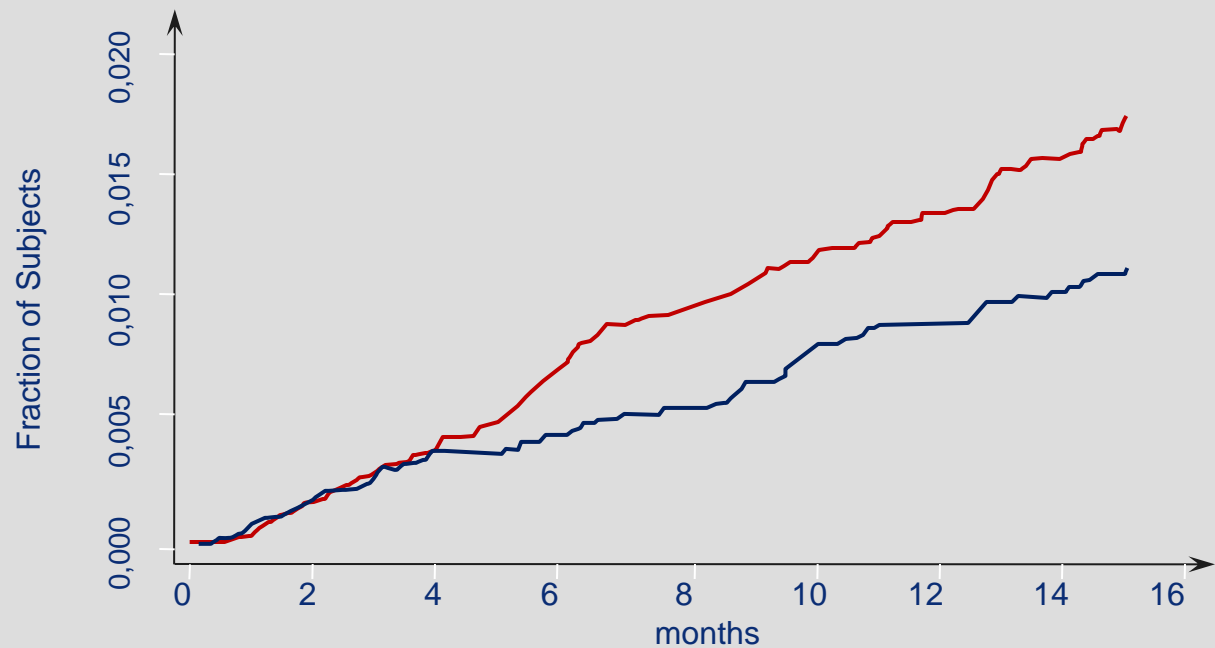


Number at risk

rx = aspirin	9553	8443	7680	5296	3831	1782	865
rx = clopidogel	9543	8424	7658	5276	3800	1774	853

— rx = aspirin - - - - rx = clopidogel

Solid Cancers in TRITON

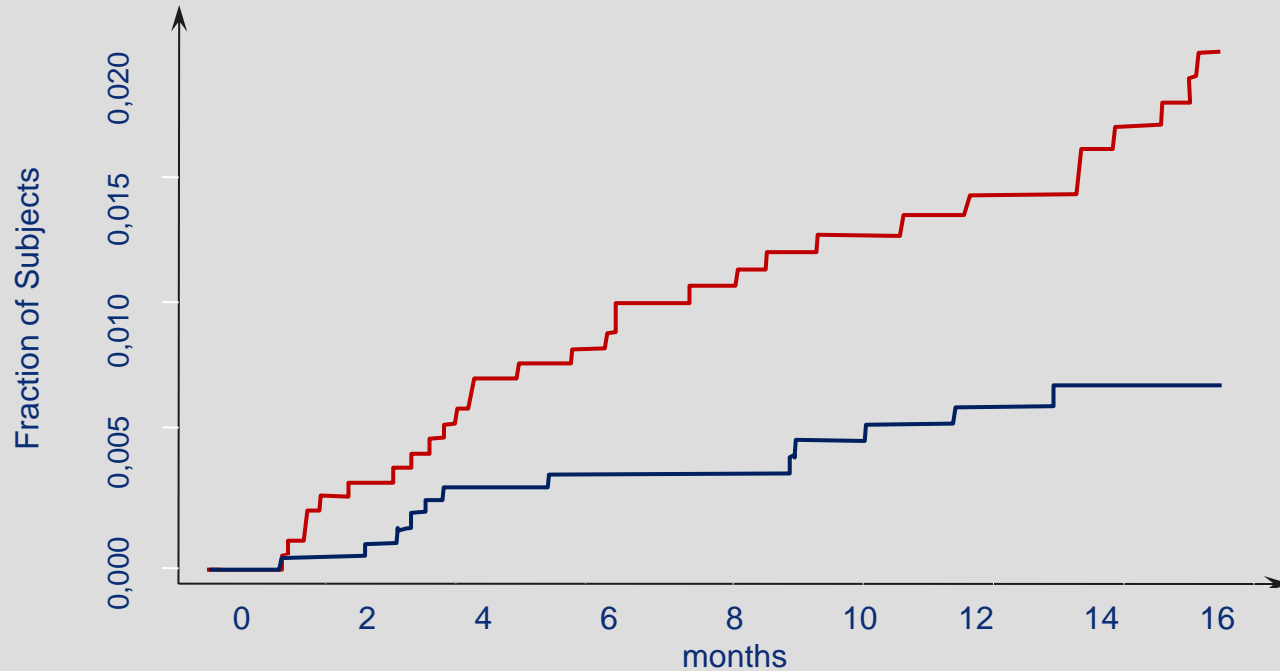


Number at risk	0	2	4	6	8	10	12	14	16
rx=Clopidogrel	6795	6508	6439	6327	5773	5120	4773	4286	0
rx=Prasugrel	6813	6558	6463	6318	5725	5097	4729	4227	0

— rx=Clopidogrel — rx=Prasugrel

The FDA Secondary Prasugrel Review, 2009

Solid Cancers in Women in TRITON

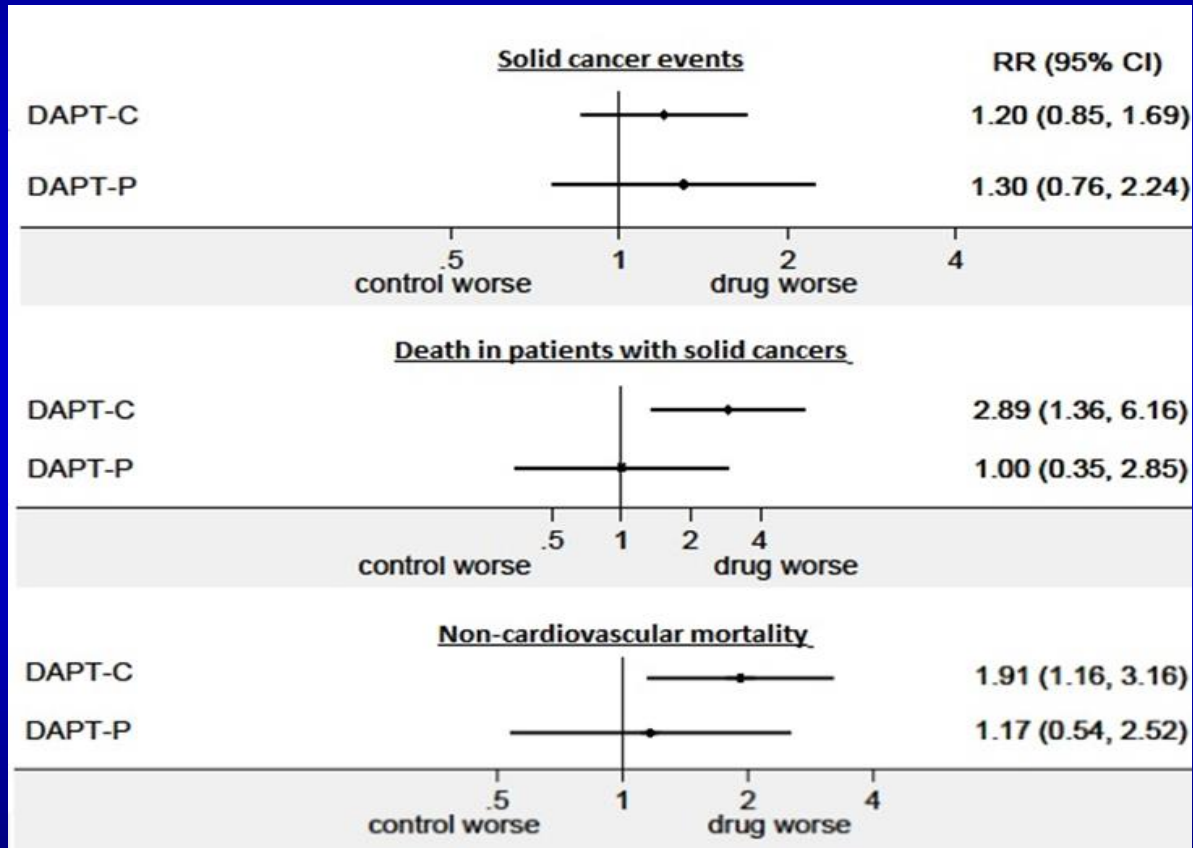


Number at risk		0	2	4	6	8	10	12	14	16
rx=Clopidogrel	1818	1727	1700	1669	1526	1345	1249	1105	0	
rx=Prasugrel	1705	1624	1589	1549	1389	1213	1112	991		

— rx=Clopidogrel

— rx=Prasugrel

DAPT Trial Cancers

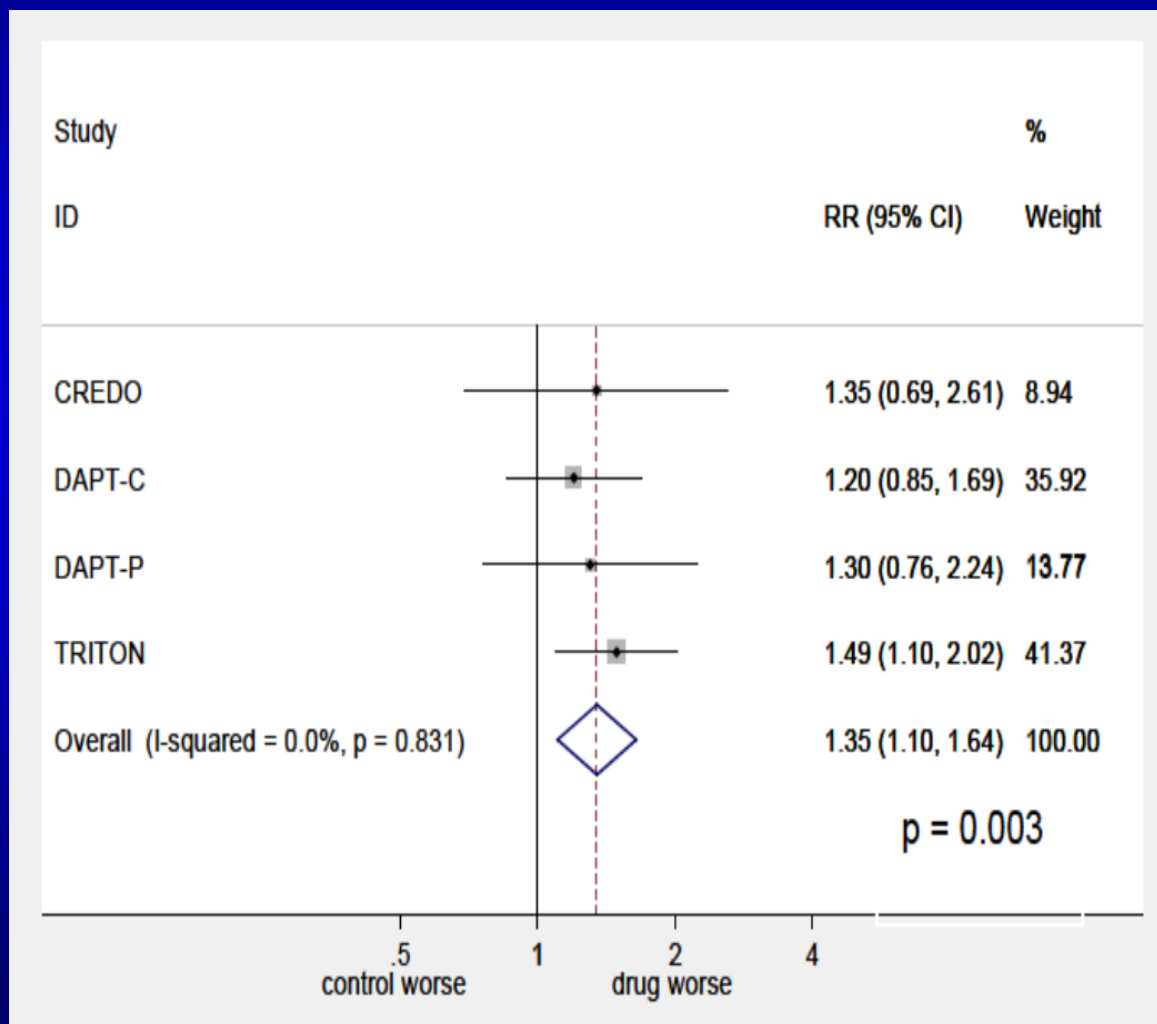


GUSTO Bleeding in DAPT Trial (The FDA Analyses): Massive Prasugrel Discontinuations?

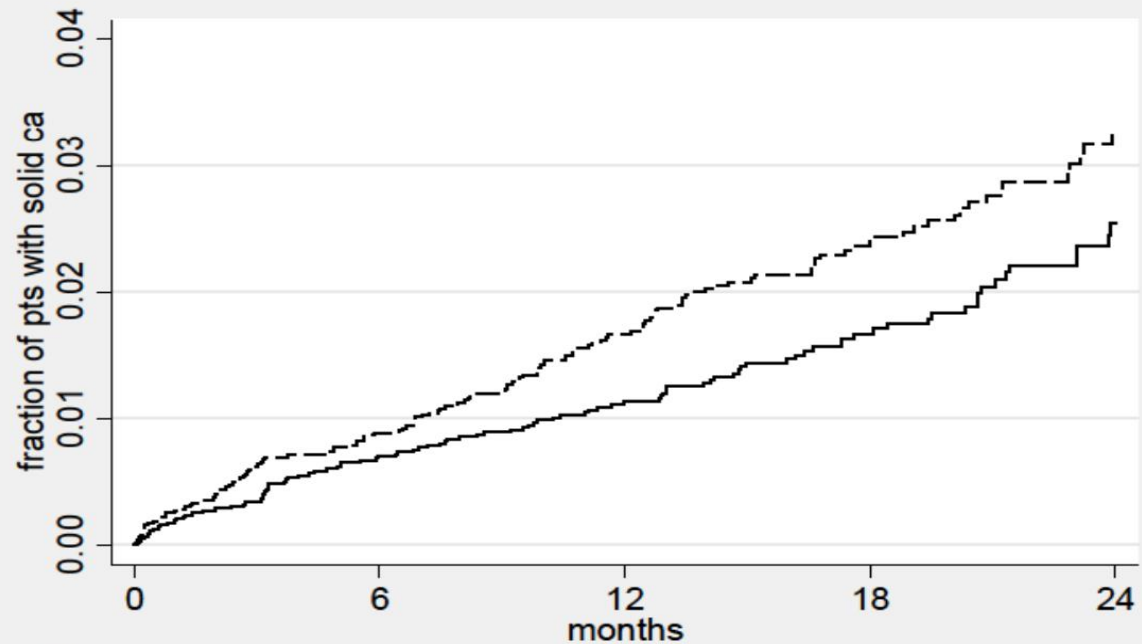
	clopidogrel	prasugrel	either
30m	2.66%	2.28%	2.5%
12m	1.68%	1.36%	1.6%
diff	0.98%	0.92%	0.96%
RR*	1.6	1.7	1.6
p	0.01	0.048	0.001

*RR = risk ratio 30m/12m

Solid Cancers after Thienopyridines



Solid Cancers in TRACER



Number at risk

rx = placebo 6471

5897

4450

2677

1082

rx = vorapaxar 6473

5914

4471

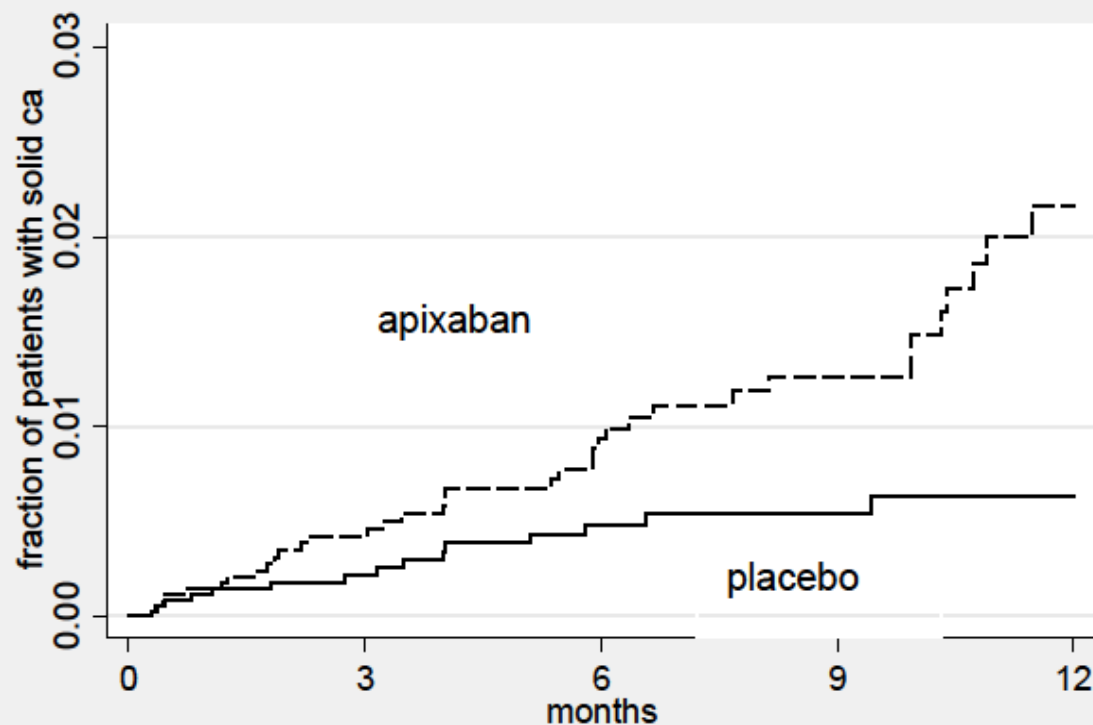
2659

1076

— rx = placebo - - - - rx = vorapaxar

Hazard ratio 1.4 (95% CI 1.1 to 1.8, p = 0.012)

Solid Cancers in APPRAISE



Number at risk

rx = placebo 3687

2615

1885

1139

533

rx = apixaban 3705

2556

1787

1101

508

— rx = placebo - - - - rx = apixaban

Hazard Ratio=2.5 (95% CI 1.4-4.6; p=0.002)

Solid Cancer Locations in APPRAISE

Location (Alphabetical Order)	Placebo	Apixaban
Anus	1	0
Bile duct	0	1
Bladder	0	5
Breast	0	1
Colon	5	4
Esophagus	0	1
Gastrointestinal (other)	0	1
Head and Neck	1	0
Kidney	0	2
Lung	2	8
Ovary	0	1
Pancreas	1	3
Prostate	2	1
Stomach	2	6
Testicles	0	1
Unknown	1	1
Uterus	0	1
TOTAL	15	37

Figure 17: Solid Cancer Event Incidence in ARISTOTLE

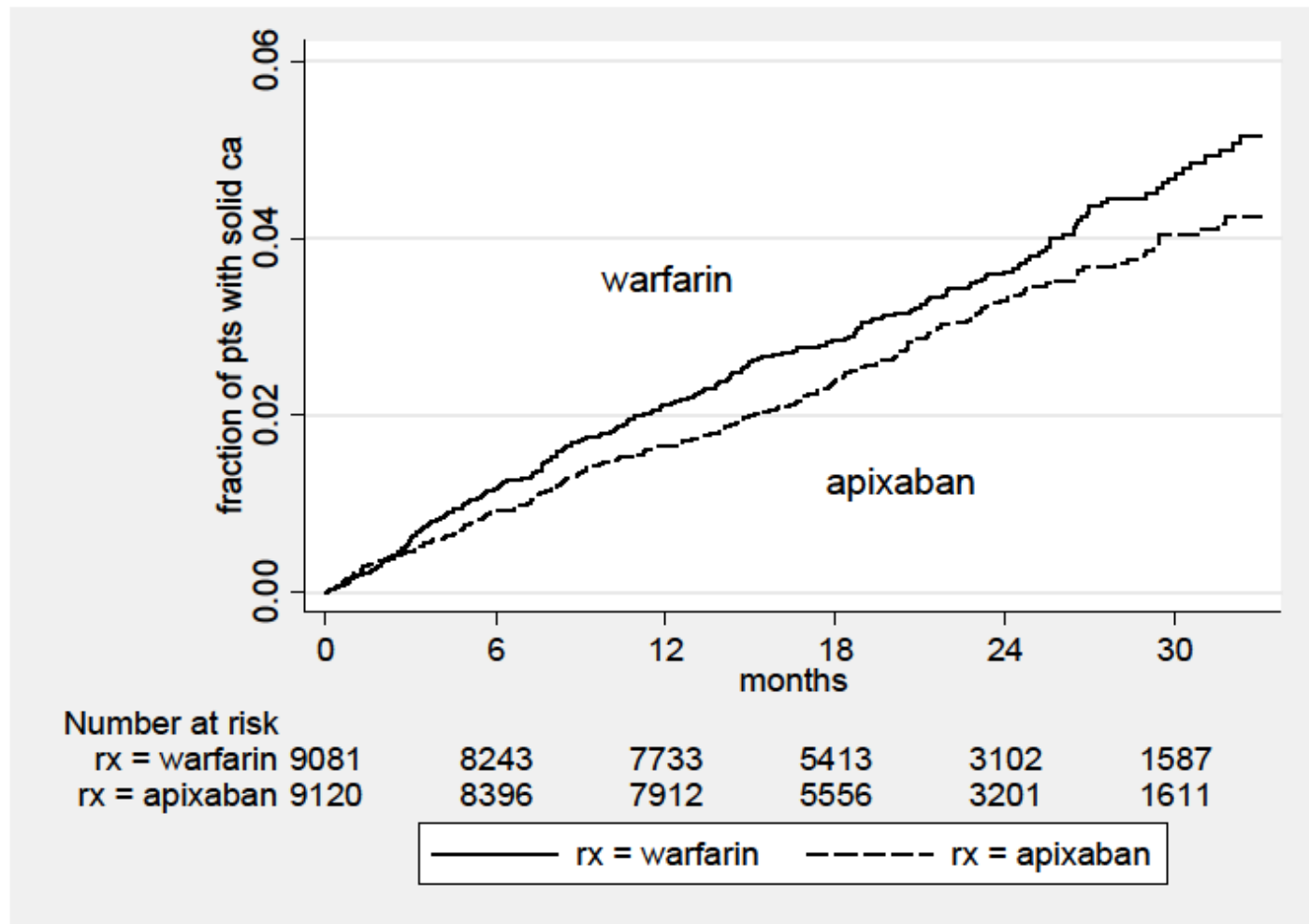


Figure 20: Solid Cancer Event Incidence in ATLAS

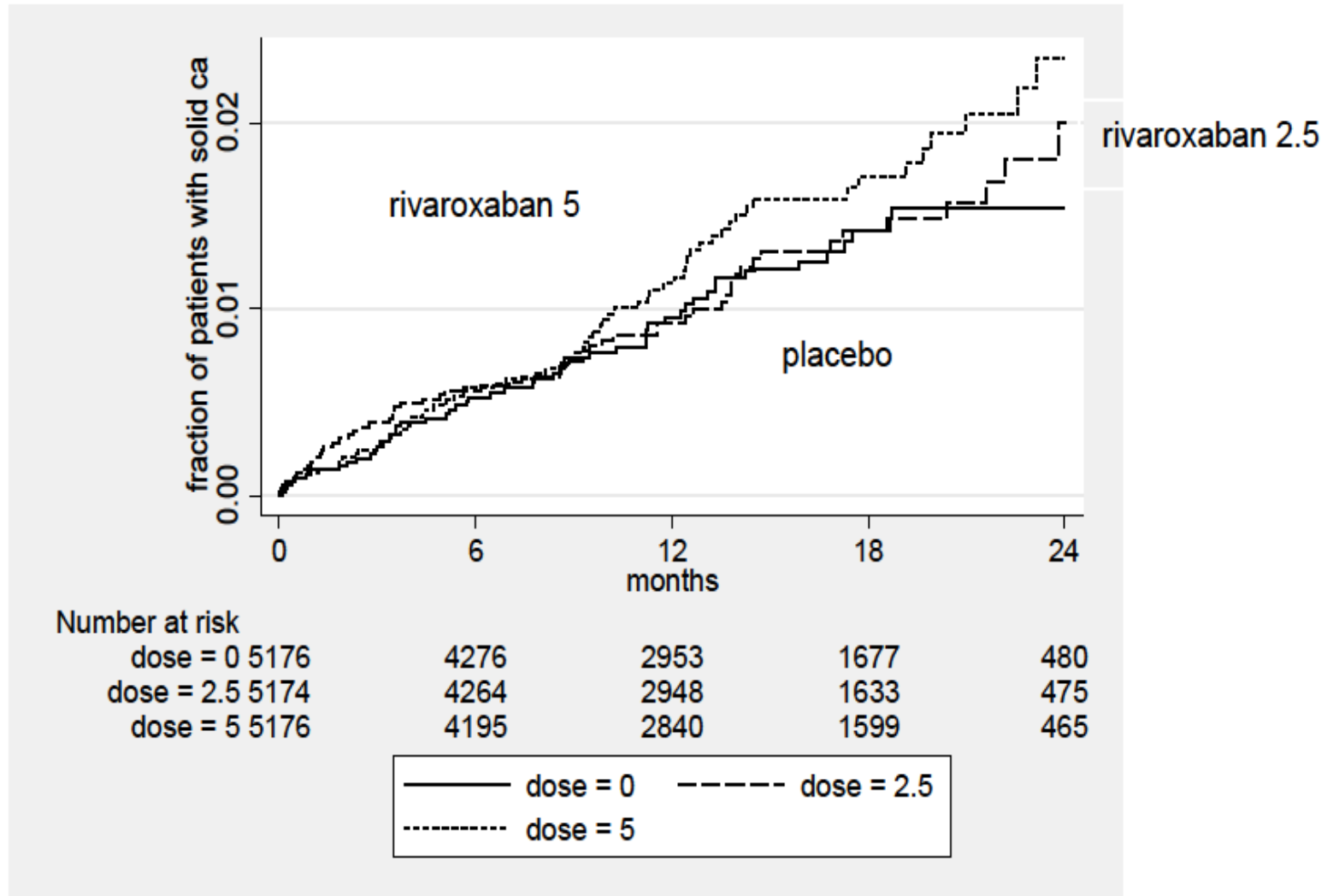
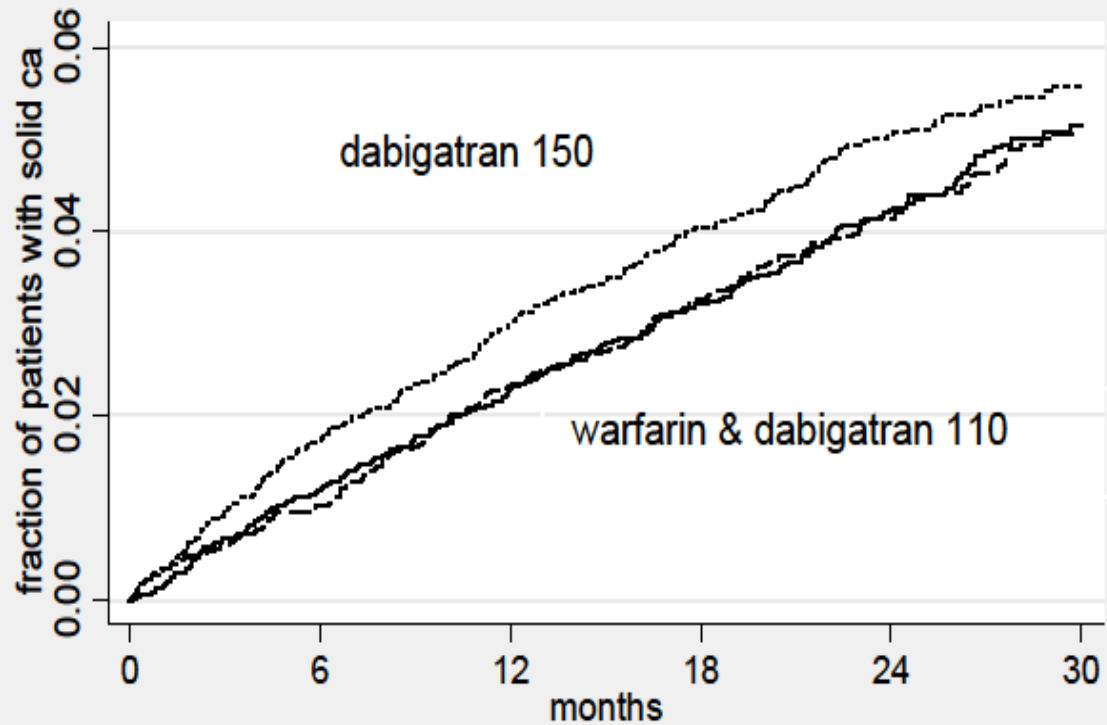


Figure 22: Solid Cancer Event Incidence in RELY



Number at risk

dose = 0	6022	5646	5387	4270	2832	1241
dose = 110	6015	5645	5379	4271	2883	1314
dose = 150	6076	5685	5420	4320	2925	1317

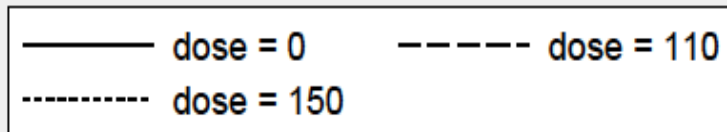
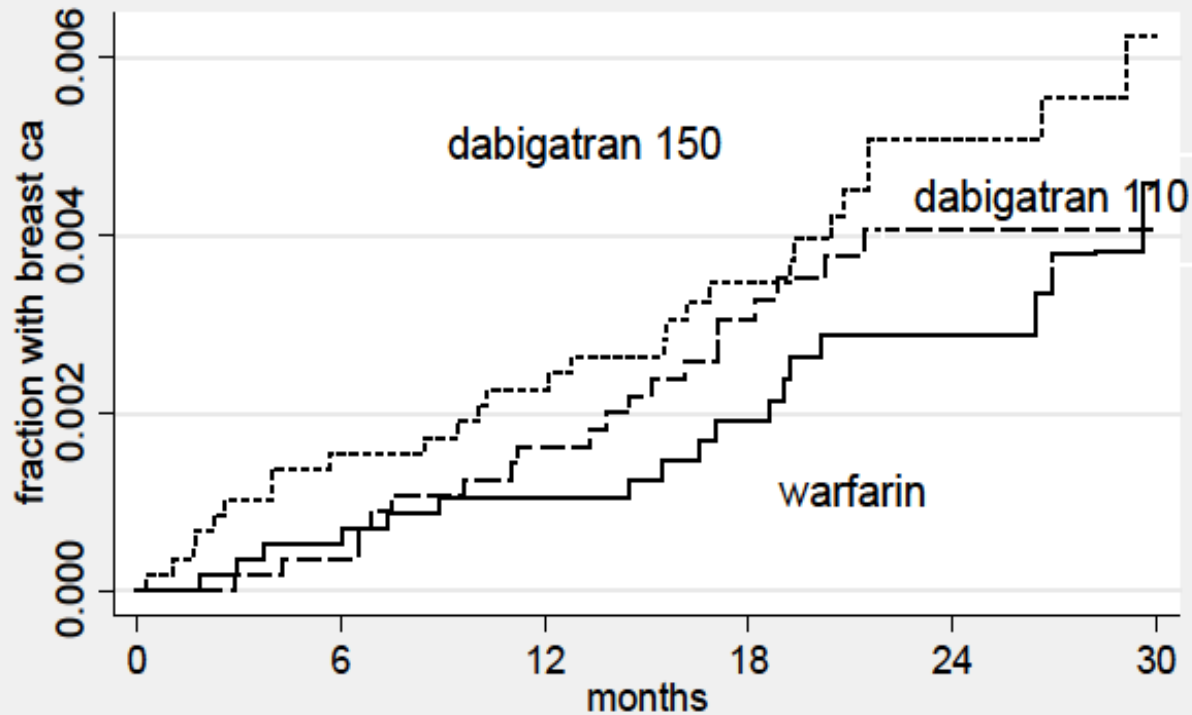


Figure 23: Breast Cancer Event Incidence in RELY



Number at risk

dose = 0	6022	5646	5387	4270	2832	1241
dose = 110	6015	5645	5379	4271	2883	1314
dose = 150	6076	5685	5420	4320	2925	1317

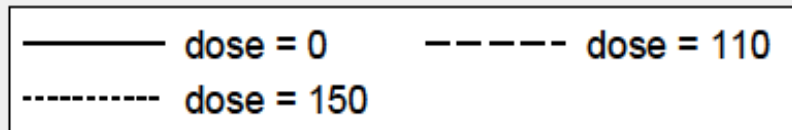
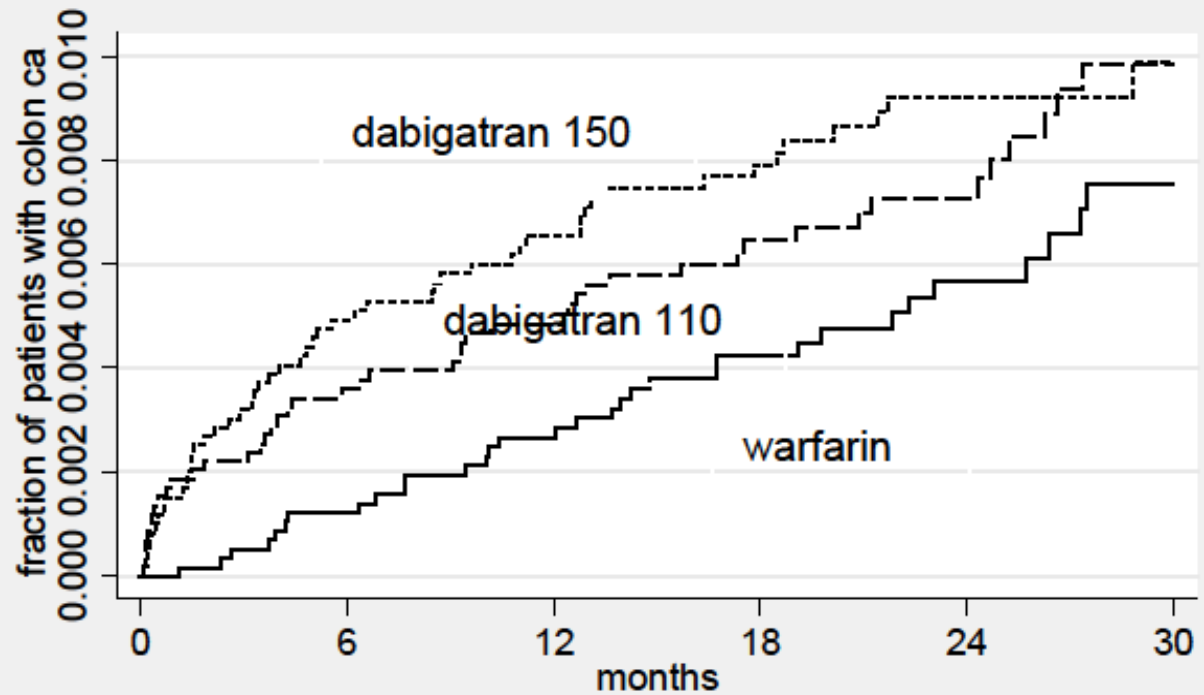


Figure 24: Colon Cancer Event Incidence in RELY



Number at risk

dose = 0	6022	5646	5387	4270	2832	1241
dose = 110	6015	5645	5379	4271	2883	1314
dose = 150	6076	5685	5420	4320	2925	1317

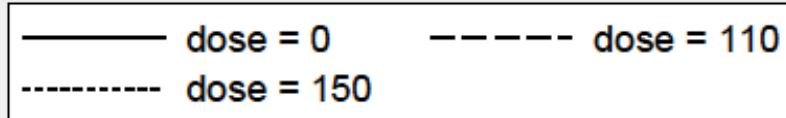
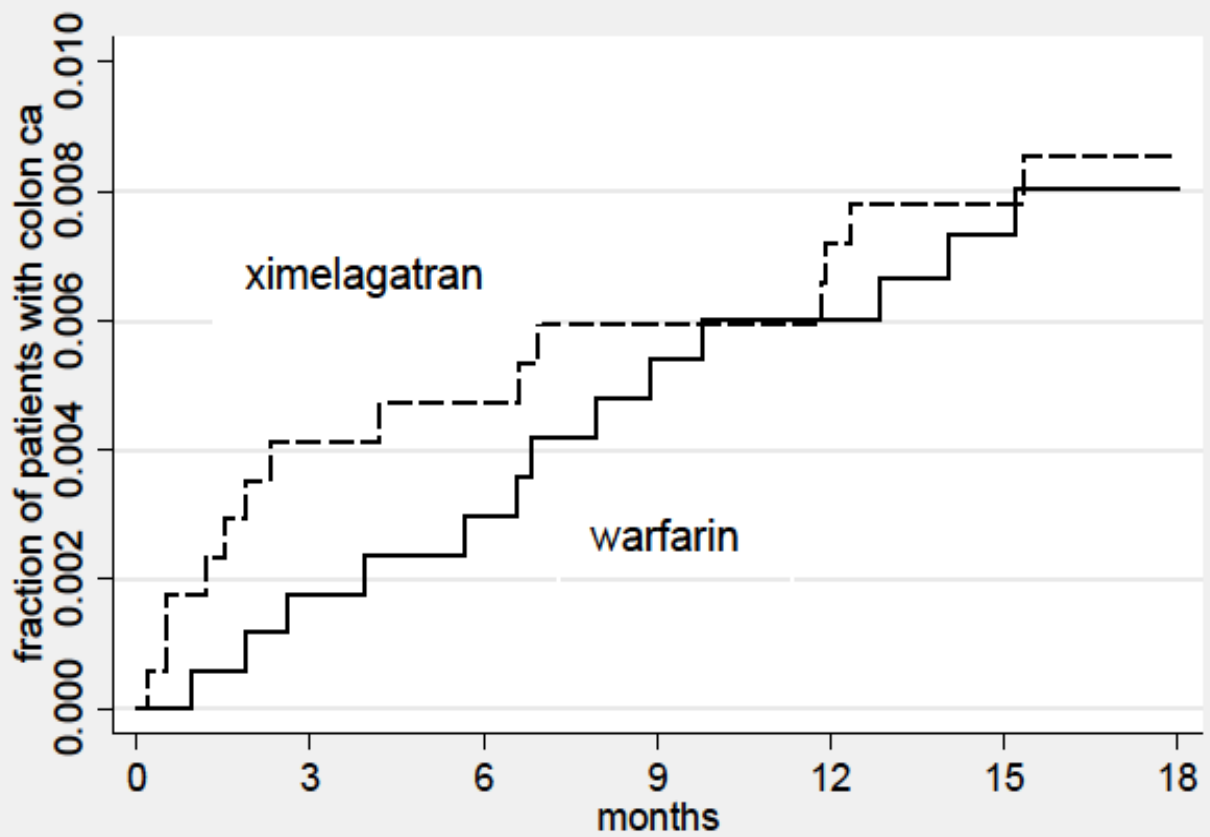


Figure 33: Colon Cancer Event Incidence in SPORTIF III

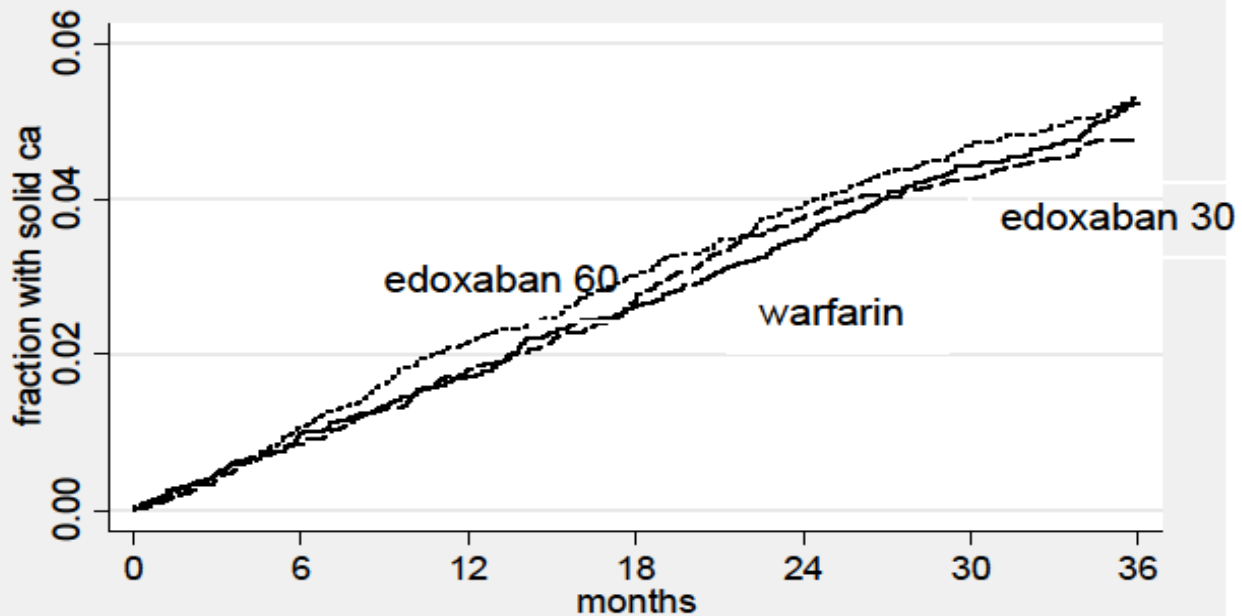


Number at risk

rx = warfarin	1703	1675	1649	1626	1610	1445	926
rx = exanta	1704	1670	1644	1620	1596	1439	920

— rx = warfarin - - - - rx = exanta

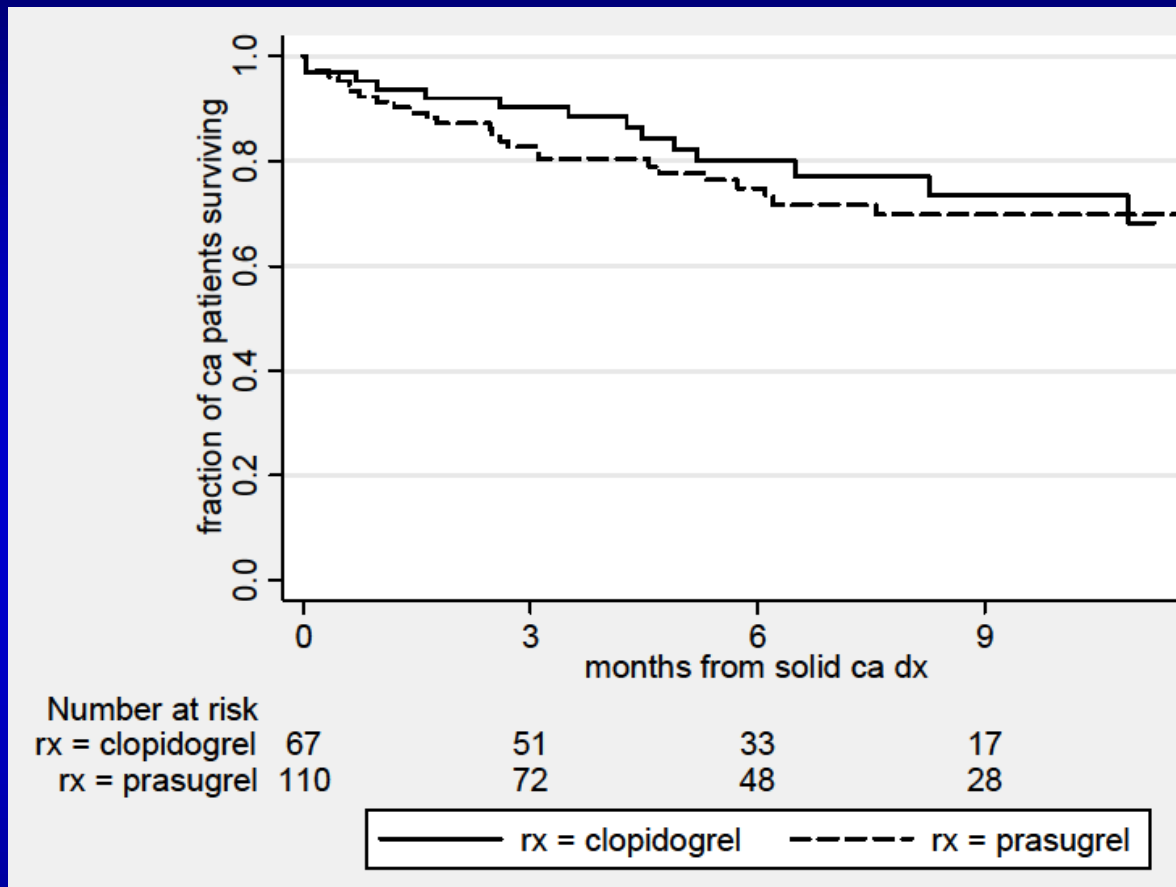
Figure 28: Solid Cancer Event Incidence in ENGAGE



Number at risk							
dose = warfarin	7036	6532	6216	5977	5747	4607	2665
dose = 30	7034	6575	6275	6023	5785	4695	2739
dose = 60	7035	6522	6223	5971	5733	4638	2684



Cancer Survival in TRITON



1-year Cancer Mortality

TRITON	30%
APPRAISE-2	31%
ARISTOTEL	30%
SEERS	31%
WHO	32%

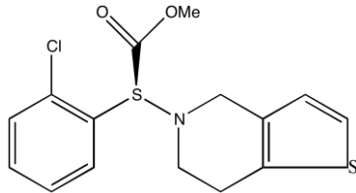
Major Non-Bleeding Solid Cancers

Location	Antithrombotic	Placebo
Breast	73	57
Pancreatic	72	39
Prostate	114	78

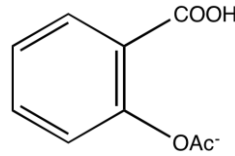
Where We Are Now on Cancer?

Drug/Trial	Fact	Bleeding
Clopidogrel: CAPRIE / CREDO/DAPT	After 2 years more solid cancers and cancer deaths	More
Prasugrel:TRITON / DAPT	Immediate cancer risks especially in women	Much more
Ticagrelor: PEGASUS	Significant increase of solid cancer death after 1 year therapy	Much more
Vorapaxar: TRACER/TRA2P	More solid cancers in TRACER, but not in TRA2P	Extreme
Apixaban: APPRAISE-2	More solid cancers (37 vs.15)	Stopped due to
Warfarin: ARISTOTEL	301 vs. 260 (p=0.034) more solid cancers	More
Rivaroxaban: ATLAS	More solid cancers RR=1.3 for higher dose	More
Dabigatran: RELY	More solid cancers (280 vs.237)	More
Edoxaban: ENGAGE	No signal	Less

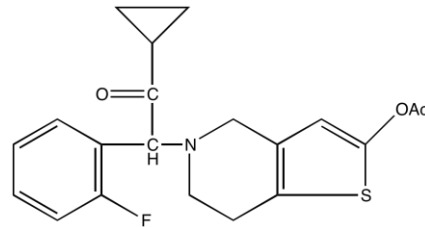
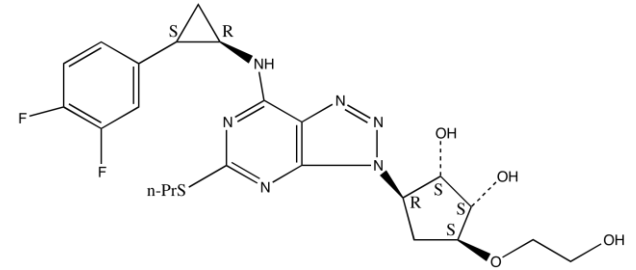
Clopidogrel



Aspirin

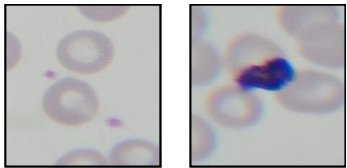


Ticagrelor

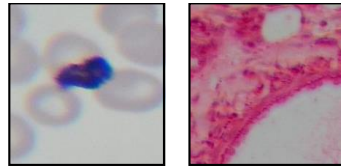


Prasugrel

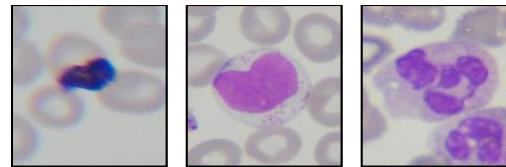
Dual Antiplatelet + NOAC



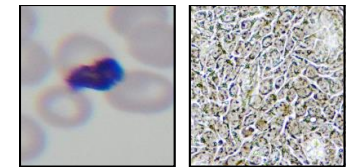
Bleeding



Wound Healing



Infections



Cancer

Impressions:

- **Extra cancers on top of antithrombotics is a scary reality**
- **These solid tumors are not agent specific, but follow the bleeding**
- **These cancers are iatrogenic, therefore, FDA bureaucracy will fight admitting potential association**

