Solid cancers after antiplatelet therapy: Confirmations, controversies, and challenges

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Summary
The role of anticoagulants and antiplatelet agents in tumour growth and prognosis is not new, and currently under intense investigation. Some randomised data strongly suggest that this association exists, but it is complex, and not necessarily pointed at the same direction. The potential mechanisms responsible for such harmful association include a direct hazard of novel antithrombotics on cancer, indirect promotion of tumour growth, easier metastatic dissemination due to instability of platelet-tumour cell aggregates, or inability to keep cancer cells locally in situ are considered. The latest randomised evidence ultimately rejected the drug-specific cancer risks, clearly indicating the class-effect. In lay terms “cancers follow bleeding”, which seems to be true for antithrombotic agents in general. Significant excess of solid cancers which was similar after prasugrel in TRITON, and with vorapaxar in TRACER trials was confirmed by the FDA reviews. Later, extra cancer deaths reported following clopidogrel and prasugrel in DAPT, and after ticagrelor in PEGASUS are also of concern. However, there are remaining controversies with regard to published cancer risks after ticagrelor (PLATO), or another vorapaxar trial (TRA2P), while full disclosure of separate clopidogrel and prasugrel cancer data in DAPT is still lacking. In short, if we apply moderate antiplatelet strategies for over two years, or aggressive regimens including triple therapy for much less than one year, the solid cancer risks emerge. Currently, more delicate platelet inhibition, and shorter exposure to dual oral antiplatelet agents should prevail.

Keywords
Prasugrel, clopidogrel, aspirin, ticagrelor, vorapaxar, cancer, clinical trials, duration of antiplatelet therapy, triple antiplatelet therapy

Introduction
Platelets are highly reactive components of the circulatory system, which exert not only haemostatic activity but also contribute to inflammation, atherosclerosis and cancer dissemination through the release of cytokines, chemokines and expression of several adhesion receptors (1). The first alarming signal that dual antiplatelet therapy may cause excess of solid cancers was observed in the prasugrel arm of TRITON-TIMI 38 trial (2, 3). Later, until TRACER Food and Drug Administration (FDA) review, the randomised evidence remains inconclusive, probably due to the awareness of drug manufacturers of such catastrophic association resulted in missing delayed outcomes of many patients, suggesting bias. Nevertheless, numerically more cancers were observed after prasugrel in TRILOGY-ACS trial (4), but since it was a negative trial, no detailed FDA reviews are available for public. Notably, the rate of patients lost to follow-up was as high as 14.7% in PLATO (5), and about 12% in ATLAS ACS2 (6), somewhat challenging our comprehension of outcomes after ticagrelor and rivaroxaban. Lately, however, two important pieces of the puzzle emerge, namely vorapaxar’s New Drug Application reviewed by the FDA (7), and publication of the DAPT trial (8). We will update the current evidence on what is known, and what is missing on solid cancer risks and antiplatelet therapy focusing on the potency and length of chronic platelet inhibition.

Aspirin
With regard to antiplatelet agents and cancer risk, there are plenty of data on aspirin, while any reliable historic evidence linking aspirin for prevention of coronary artery occlusions with neoplasms is not conclusive. Early animal data suggest that aspirin can block potent urine bladder carcinogens (9) and even protect against cancer proliferation (10). Clinical studies usually yield consistent slightly positive results with regard to the ability of long-term aspirin to prevent several cancer types. The ukCAP trial suggest that aspirin (300 mg/day) but not folate (0.5 mg/day) use was found to reduce the risk of colorectal adenoma recurrence, with evidence that aspirin could have a significant role in preventing the development of advanced lesions (11). Moreover, the Australian Cancer Study found that frequent use of aspirin is associated with reduced...
occurrence of esophageal cancers, particularly among those with frequent symptoms of gastroesophageal reflux (12). In contrast, a current large registry found no association between the regular aspirin use and reduction of lung cancer risk (13), and that aspirin has no preventive effect on breast cancer in a randomised study (14). An over 20 years long prospective study of almost 50,000 patients suggested that regular, long-term aspirin use reduces risk of colorectal cancer among men. However, the benefit of aspirin necessitates at least six years of consistent use, with maximal risk reduction occurs at higher aspirin doses (15). Overall, long-term follow-up of previous randomised trials of aspirin suggest that it decreases cancer incidence and mortality with the greatest effects seen on cancers that arise from the gastrointestinal tract (16) and prostate (17). Reduction in distant metastasis (18) and improvements in cancer outcomes (19) appear within five years of randomisation indicating that aspirin affects tumour growth and/or the development and spread of metastases from existing cancers or both. These data were later confirmed by the Women’s Health Study applying alternate-day 100 mg/daily dose aspirin reduce risk for colorectal cancer in healthy women (20). Some experts even suggest that in patients with hereditary nonpolyposis colon cancer (Lynch syndrome), aspirin reduces cancer incidence and should be considered standard care (21).

Despite such favourable profile, the mechanism by which aspirin may exert cancer protective properties is unclear. This may include direct inhibition of cyclooxygenase (COX)-2, prevention of the carcinogens activation via sulphation by the P phenolsulphotransferase (22), reduced flux through ornithine decarboxylase may participate in the antiproliferative activity of aspirin towards colonic tumoural cells (23), or blocking the inflammatory response at the gene transcription level (24), by reducing apoptosis through release of mitochondrial cytochromes (25) or via upregulation of Bcl-2 and Bax and suppression of VEGF (26).

Clopidogrel

Despite being one of the most prescribed drugs in the world, the cancer data and clopidogrel are sparse. Systematic evidence with regard to active metabolite, dosage, and length of exposure are lacking. Clopidogrel significantly inhibited the development of metastases in mice model of pancreatic cancer via inhibition of tissue factor TF, as well as the integrins αvβ1 and αvβ3 blockade (27). Clopidogrel is also known to prevent hepatocellular carcinoma and improves survival in a mouse model of chronic hepatitis B (28). However, a small randomised phase II clinical study failed to prove clopidogrel impact of the number of circulating tumour cells in patients with metastatic breast cancer (29). Lately, clopidogrel was shown to enhance tumour penetration for cisplatin based nano-formulations delivery (30).

The clopidogrel’s New Drug Application submission to the FDA revealed no carcinogenicity concerns (31). In fact, a long 78-week study in mice suggested no excess of tumours when exposed to 27 to 47 times human clopidogrel dose. Rats tolerated clopidogrel up to 123 mg/kg for one and two years with no tumorigenic response. Baboons given up to 200 mg/kg (approximately 52 times clinical dose) clopidogrel daily for one year revealed only slight reversible changes in red blood cells, serum albumin, or liver weight. The FDA takes very seriously the unexpected solid cancer signal after prasugrel in TRITON (3). Solid cancers included all non-haematologic malignancies except for non-melanoma skin cancers and primary brain tumours. Non-melanoma skin cancers were excluded a priori based on preclinical findings because they carry a generally benign prognosis and because ascertainment can be erratic. The Agency was also in search for thienopyridine class effect, reviewed the data from the clopidogrel development program in detail, and found no apparent effect of clopidogrel on cancer rates. Therefore, the analyses of of cancer rates in CAPRIE (32) (Figure 1), and CHARISMA (33) (Figure 2) trials were plotted.

These data suggest that the rates of new solid cancers are similar, and actually slightly lower after monotherapy with clopidogrel when compared to aspirin until 30 months in CAPRIE. Later, for the last six months of follow-up (30 to 36 months) clopidogrel did worse than aspirin exhibiting somewhat higher solid cancer risks. Worth mentioning, is that in CHARISMA (Figure 2), cancer risks follow-up was shorter (30 months) than in CAPRIE (36 months). In fact 30 months was the exact time when cancer rates diverged in CAPRIE, being the exact time-point when clopidogrel cancer signal was noticed in CAPRIE. Another important observation, is that CHARISMA analysis suggests that dual antiplatelet therapy with low-dose aspirin and clopidogrel exhibits slightly less new solid cancer rates than low-dose aspirin and placebo. This fact is critical for challenging the hypothesis that better cancer diagnosis was due to more bleeding after prasugrel in TRITON (2). In fact, clopidogrel + aspirin combination in CHARISMA has been numerically associated with more fatal (26 vs 17); severe (130 vs104); or moderate (164 vs 101) GUSTO bleeding, but less cancer.

Figure 1: Incidence plot of new solid cancers (excluding non-melanoma skin and brain cancer) in CAPRIE.
Importantly, known gastrointestinal bleeding preceded the diagnosis of colonic neoplasms only in half of the patients, and breast or prostate solid cancers in TRITON were not affiliated with bleeding, but were still higher after prasugrel (3). Therefore, the more bleeding causing better cancer diagnoses hypothesis has been overwhelmingly rejected. CAPRIE and CHARISMA exonerated clopidogrel for up to 30 months from any cancer signal; however, numerically CURE (34) showed a doubling in the rate of colorectal cancer with clopidogrel compared to placebo (16 vs 8), which was not observed in CAPRIE or CHARISMA. Clopidogrel was associated with excess lung cancer in CURE (12 vs 7) and CREDO (35) (5 vs 0), but not in the larger CAPRIE (72 vs 74) or CHARISMA (70 vs 63). The differences between no cancer signal (CAPRIE and CHARISMA) vs slight signal in two other trials (CURE and CREDO) lacks reasonable explanation, and may represent play of chance.

However, this clopidogrel controversy is important since delayed cancer risks after clopidogrel are now confirmed by the DAPT trial (8). Obviously, DAPT investigators take the cancer issue very seriously, since they included four respected oncologists from Dana Farber Cancer Institute and Boston Medical Center as official trial adjudicators. That concern was well justified since DAPT revealed significant (p=0.02) increase of cancer-related deaths (31 vs 14) after prolonged dual antiplatelet therapy vs conventional regimen. As with any large trial, DAPT was slightly disbalanced with more cancers prior to enrollment in the long term (n=488) when compared to conventional (n=466) therapy. Most importantly, DAPT showed similarity with CAPRIE revealing lack of early (0–12 months) cancer signal (20 vs 25), but more cancers (102 vs 80) late (12–33 months) in the trial. It seems cancer deaths are responsible for the majority of most non-cardiovascular deaths (48 vs 22; [confidence interval (CI)=2.23; 1.32–3.78]; p=0.02) in DAPT. Unfortunately, the trial published only the combined (clopidogrel and prasugrel) data, not dichotomising evidence dependent on which thienopyridine has been used. Apparently, it is a very sensitive issue, since separate clopidogrel or prasugrel effects were reported for stent thrombosis (S3A), major adverse events (S3B), GUSTO severe/moderate bleeding (S3C), or myocardial infarction (S3D), but not for cancer in the trial Supplementary Materials (8). The FDA issued a statement that “higher rate of death was largely explained by an increase in deaths from non-cardiovascular causes, primarily cancer and trauma deaths. The increased risk of death with longer treatment was seen in the patients given clopidogrel, but not those given prasugrel. It should be noted that increases in non-cardiovascular death have not been reported in previous large trials examining clopidogrel for other cardiovascular diseases” (36). Such a strong statement thus seems premature, and brings more confusion to the issue since cancer facts in DAPT are not fully disclosed, but clopidogrel was used in the majority of patients (over 64%) at the start of the open-label period. It is entirely unknown how many patients truly are still on the assigned medications at the end of such a lengthy trial, what was the percent of real drug discontinuations due to deliberate withdrawals, and/or partial non-compliance. Since long-term prasugrel caused more GUSTO severe/moderate bleeding (CI=1.75; 1.02 to 3.0) than clopidogrel (CI=1.55, 1.08 to 2.22), and documented compliance verification with drug metabolite screening was not done, more prasugrel non-compliance and missed outcomes including cancers should not be excluded. Importantly, the risks for non-cardiovascular deaths in DAPT were predominantly attributed to cancer, and emerged 24 months after therapy (8). Therefore, up to two years dual antiplatelet therapy with clopidogrel seems to be safe with regard to potential cancer risks.

**Prasugrel**

Two-year carcinogenicity studies were conducted in both mice and rats, with lower doses of prasugrel studied in rats due to decreased tolerability of the drug in that species. Although the rat study was essentially negative, the mice study showed a statistically significant positive dose response relationship in the incidence of both hepatocellular adenomas and hepatocellular carcinomas with prasugrel in both sexes (3). With 110 animals per group, the numbers of hepatic adenomas were 25 in the control group vs 16, 46, and 83 in the prasugrel 50, 100, and 300 mg/kg/day groups. The numbers of hepatocellular carcinomas were 12 in the control group, vs 16, 15, and 21 in the prasugrel 50, 100, and 300 mg/kg/day groups. Overall, prasugrel was associated with a roughly 50% increase in liver malignancies over placebo. In addition, the mice study suggested a weak dose-relationship between prasugrel and cancers of the intestine and lung, while skin cancers were more common in the control group. The FDA review states that while the positive rodent study in one species did not prohibit regulatory approval, it was useful in generating the hypothesis that prasugrel may act as a tumour promoter for a
variety of solid cancers. In TRITON the baseline malignancies were well-balanced, with 174 in the prasugrel group and 175 in the clopidogrel group, representing 2.6% of the study population (3). Excluding non-melanoma skin cancers and brain tumours, 92 new solid cancers were adjudicated in the prasugrel group, compared to 64 in the clopidogrel group, for a relative risk of 1.44 by log rank test (p = 0.024). Kaplan-Meier plots for overall new solid cancers, and solid cancers in women are displayed in ▶ Figure 3 and ▶ Figure 4, respectively.

New solid cancers were associated with a mortality rates of 38% in the prasugrel group and 34% in the clopidogrel group, compared to < 3% in cancer free patients. Excluding non-melanoma skin cancers and brain tumours, 112 new and worse cancers occurred in the prasugrel group, compared to 69 in the clopidogrel group, for a relative risk of 1.62 by log rank test (p = 0.001). Kaplan-Meier plots are displayed in ▶ Figure 5.

In both ▶ Figure 3 and ▶ Figure 5 the Kaplan-Meier plots diverge at four months, consistent with the hypothesis that prasugrel promotes solid cancers, and arguing against the increase in cancer rates being a chance finding.

Because of discrepancies between the FDA’s initial analysis of cancer data and the sponsor’s, a further review of cases was conducted, with little change in findings. The reconciliation resulted in 86 solid cancers with prasugrel, compared to 61 with clopidogrel, for a relative risk of 1.41 (p = 0.038). Including non-melanoma skin cancers, haematologic malignancies, and brain tumours, the total was 102 cancers with prasugrel and 79 with clopidogrel, for a relative risk of 1.29 (p = 0.08).

Ticagrelor

Similar to prasugrel, ticagrelor carcinogenicity has been tested in rats and mice. The rat study used doses of 0, 20, 60, and 120 mg/kg/day (for males) and 0, 20, 60, and 180 mg/kg/day (for females). The mouse study used doses of 0, 50, 100 and 250 mg/kg/day for both sexes. The rat study demonstrated a significant decrease in female survival (Cox: p=0.018, Kruskal-Wallis: p=0.0424), possibly due to metastatic uterine neoplasms, mostly adenocarcinomas, and squamous cell carcinomas. Fourteen of the 31 female animals in the high-dose ticagrelor group who died ahead of scheduled termi-
nation had uterine adenocarcinoma listed as the cause of death, based upon the pathologic criteria for metastasis. The increased incidence for mortality was statistically significant when compared to the combined controls (p<0.001). The major tumour findings were in females and included hepatocellular adenoma and uterine malignancies. Additional in vivo studies to investigate the mechanism of the uterine tumours reported in the rat study were carried out. Ticagrelor did not show significant affinity for oestrogen, progesterone, testosterone, thyrotropin releasing hormone or vasopressin receptors. The submitted to the FDA information on major metabolites, including AR-C124910XX was not sufficient to draw any definite conclusions. It has been proposed that changes in circulating prolactin may be responsible mechanism for the animal tumour findings (5). Moreover, excess of gynaecomastia in the ticagrelor PLATO arm (0.19 % vs 0.03 %, relative risk=6.0) suggest prolactin involvement, and estrogen burst to increase the size of male breast tissue. The submitted data suggest no evidence for ticagrelor effects upon rates of sex organ malignancies, although PLATO was relatively short study with only 277 days mean follow-up (37). One testicular cancer was reported in ticagrelor patient, while prostate cancer was balanced (13 vs 12). Breast cancer events favoured ticagrelor (4 vs 10), while ovari al cancer was balanced (2 vs 1), with no uterine, or cervical cancers reported. In contrast to the balanced and mildly concerned FDA reports, the official PLATO publication present the cancer data as a trend towards ticagrelor benefit. Any new neoplasms during PLATO were 132 vs 155 (p=0.17), including malignant (115 vs 121, p=0.69), and benign (18 vs 35; p=0.02) all in favour of ticagrelor (37). Since all ticagrelor patients in PLATO received aspirin as well, and cause more bleeding than clopidogrel, there is no biological plausibility for less cancer risks after ticagrelor, especially considering positive animal studies. One should also remember that cancer signal after prasugrel in TRITON was an unexpected pitfall, therefore later trials were well aware of this setback, and may filter the evidence via incomplete follow-up, and early discontinuations which were high in the PLATO FDA review (5). In contrast to PLATO, there were significantly more cancer deaths after ticagrelor in recent PEGASUS trial (39). The differences in PLATO and PEGASUS cancer-related outcomes ([39], Supplement) are presented in Table 1.

The PEGASUS data are in full agreement with the DAPT trial exhibiting similar to prasugrel or clopidogrel extra cancer risks after ticagrelor beyond one year therapy.

### Vorapaxar

Recently approved for post myocardial infarction, and peripheral artery disease (PAD) indications, vorapaxar, as a first-in class thrombin PAR-1 inhibitor, underwent detailed FDA review (7). With regard to the animal tumourigenic findings, in male rats there was no evidence of drug-related tumours, but female rats had increased incidence of hepatocellular adenoma at 28 times human exposure. However, the Executive Carcinogenicity Advisory Committee found no definite evidence for carcinogenicity based on their conclusion that hepatic adenomas are a common tumour in rats, necessitating a lower p-value than what was observed. The Agency reviewed two large trials, namely TRACER (39) and TRA2P (40). The primary clinical reviewers commented upon deaths caused by solid cancers. In TRACER they reported 27 such deaths for vorapaxar vs 18 for placebo. In TRA2P there were 111 such deaths for vorapaxar, and 97 for placebo. The times to first solid cancer events by arm are presented in Figure 6 for TRACER, and Figure 7 for TRA2P.

The excess of solid cancers after vorapaxar in TRACER (hazard ratio 1.4 (95 % CI 1.1 top 1.8, p=0.012) look very similar to those for prasugrel in TRITON (Figure 1), the trial that initiated the focus on aggressive antiplatelet strategies, bleeding and cancer. In TRACER, as in TRITON, the recounted deaths numbers in all patients with solid cancer were high: 37 in vorapaxar patients vs 24 in the placebo group. However, TRA2P revealed that times to first solid cancer events were virtually identical by arm, as shown in Figure 6. Obviously, the solid cancer incidence in TRA2P (Figure 7) is completely different from TRACER (Figure 6). It

![Figure 6. Times to first solid cancer events by arm in TRACER.](https://www.thrombosis-online.com/)

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<table>
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<tr>
<th>Trial/Arm</th>
<th>Outcomes (n,%)</th>
<th>RR</th>
<th>95 % CI</th>
<th>P-value</th>
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<td>PLATO</td>
<td>New Cancers</td>
<td>0.95</td>
<td>0.73–1.22</td>
<td>0.69</td>
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<tr>
<td>Ticagrelor 180 mg/daily</td>
<td>115 (1.2 %)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clopidogrel 75 mg/daily</td>
<td>121 (1.3 %)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PEGASUS</td>
<td>Death</td>
<td>1.46</td>
<td>1.02–2.06</td>
<td>0.034</td>
</tr>
<tr>
<td>Ticagrelor 180 mg/daily</td>
<td>77 (1.1 %)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>53 (0.76 %)</td>
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Figure 6: Times to first solid cancer events by arm in TRACER.

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is hard to comprehend the disparate results for solid cancers in two vorapaxar trials. As a rule of thumb, more potent antiplatelet regimens cause more bleeding, and more solid cancers. In TRA2P, the vorapaxar arm definitely had more bleeding, but solid cancer rates were similar. Importantly, differences in patient populations between trials may be responsible for cancer disparity. In fact, TRACER enrolled >90% of non-STEMI ACS patients, while TRA2P was predominantly focused on myocardial infarction (>67%), ischaemic stroke (>18%), or documented PAD (>14%). Complete thrombotic occlusions were associated with higher degree of platelet activation, when compared with less thrombotic burden in TRACER. In other words, vorapaxar finds more truly suitable patients for extra antiplatelet protection in TRA2P than in TRACER, yielding much better vascular outcomes, and less cancer. Also, overall, the potency of antiplatelet therapy was much higher in TRACER, when triple antiplatelet therapy in the experimental arm (aspirin + clopidogrel + vorapaxar) exceeded 87% (39), compared to less than 37% in TRA2P (40). Finally, serious adverse events in both TRACER and TRA2P were only to be reported until 60 days after the last dose of study drug. While this limitation is less critical for bleeding, it is problematic for delayed events, such as cancers, that take time to develop and be detected. Incomplete follow-up of 3.5% in TRA2P compared to less than 2% in TRACER (7) may also be a confounding factor.

Figure 7: Times to first solid cancer events by arm in TRA2P.

Figure 8: A flow diagram on the potential biological plausibility linking solid cancers and antiplatelet therapy.
Impressions

The available body of evidence indicates that the most reasonable and likely clinical scenario linking antithrombotic therapy and solid cancer is due to persistent platelet inhibition promoting easier dissemination of younger unclassified cancer cells, and elevated metastasis risks (41). In fact, the constantly emerging cancer data are novel, and not explicitly discussed in the literature. We are gaining more knowledge with every large published trial. Most if not all cancer data are yielded from the detailed FDA reviews, and some evidence is still not in public domain making it difficult to draw any definite conclusions. Moreover, it is entirely unknown whether the cancer signals observed in trials can be expected in a comparable non-treated cohort of patients. We currently do not have enough evidence to prove that the numbers of solid tumours are really related to the agents tested. We do know, however, that longer time of exposure to antithrombotic therapy is linked to more new solid cancers, and cancer-related deaths. Obviously, direct comparisons will definitely suffer from drug withdrawals and heavy non-compliance especially after cancer diagnosis. Since all the trials with the exception of CAPRIE, include aspirin in the experimental arm(s), no data on monotherapy with novel antithrombotic agents exist. Considering that aspirin per se may be protective, triaging the exact role of prasugrel, ticagrelor, vorapaxar or future agents on cancer promotion is problematic. On the other hand, excess of reported non-cardiovascular deaths observed in TRITON, TRACER, DAPT, and PEGASUS is of concern because cancer is responsible for about half of such fatalities. We may effectively prevent cardiovascular events, but if cancer risks are higher, and it seems they are, then balancing the risk/benefit ratio of modern antithrombotic strategies is way more complex than just matching vascular occlusions with bleeding. To make it perfectly clear, the existing cancer signal will not eliminate dual antithrombotic therapy after acute vascular events, but may impact duration and potency of optimal therapy.

As initially observed with prasugrel, the longer we use such therapy, and the more aggressive the strategy we choose, the more solid cancer risks will occur (42). The good news is that prasugrel as a chemical entity, and prime “suspect” can now be exonerated from being a unique cancer promoter among antithrombotic agents. The bad news is that long-term any dual antithrombotic regimen holds extra solid cancer risks. Even worse is that solid cancer risks may not be exclusively attributed to antithrombotic agents, but anticoagulants as well. In fact, solid cancer rates after apixaban were more than doubled in the halted APPRAISE-2 trial, but did not differ in successful ARISTOTEL (43), suggesting cancer follows bleeding. Chronic antithrombotic therapy impairs the essential abilities of clot formation (higher bleeding rates) and stabilising tumour cell arrest in the vasculature (higher cancer risks). Maintaining the tumour-platelet barrier, at least in part, is of compensatory nature, limiting tumour dissemination and keeping cancer cells in situ. A flow diagram on the potential biological plausibility linking solid cancers and antithrombotic therapy is presented in Figure 8.

Aggressive platelet inhibition disintegrates these benign protective mechanisms resulting in the significantly higher cancer rates after profoundly and repeatedly exhausted platelets will surrender. This hypothesis is indirectly supported by the emerging evidence of higher cancer risks in women (Figure 4), and unclassified cancer morphology with very early dissemination and quick death (44). Since pharmacokinetics in women are affected by lower body weight, slower gastrointestinal motility, less intestinal enzymatic activity, and slower glomerular filtration rate (45), it takes less time and less antithrombotic therapy potency to provoke solid cancers. For example, because renal clearance is slower in women, some renally-excreted medications, may require a dosage adjustment which is uncommon with antithrombotics. The summary of available evidence is presented in Table 2.

In summary, excess of solid cancers after modern antithrombotic therapy, especially after DAPT partial publication (8), is no longer just a hypothesis. It is an alarming reality which can be reasonably explained, with critical clinical and legal implications regarding the optimal potency and duration of existing and future chronic antithrombotic strategies. This harmful association is not an artifact, is probably attributable to all agents, does not represent pure chance, or can be explained by better cancer diagnostics due to more bleeding. Based on the current knowledge, we should not

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Table 2: Solid cancer risk and oral antithrombotic agents.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Animal studies</th>
<th>Clinical trials</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>No evidence</td>
<td>No evidence</td>
<td>No extra risks, potential protection against colorectal cancer</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>No evidence</td>
<td>No risks in CAPRIE or CHARISMA, some signal in CURE and CREDO, strong late signal in DAPT</td>
<td>Safe for 2 years, delayed risks thereafter</td>
</tr>
<tr>
<td>Prasugrel*</td>
<td>hepatocellular adenomas and carcinomas in mice</td>
<td>Significant (p = 0.024, RR=1.44) excess of new solid cancers in TRITON, numerically more in TRILOGY</td>
<td>With the 10 mg/daily dose definite risks, especially in women</td>
</tr>
<tr>
<td>Ticagrelor*</td>
<td>Uterine metastatic adenocarcinomas, and squamous cell carcinomas in rats</td>
<td>No evidence in PLATO, significant excess of cancer deaths (RR=1.46; p=0.034) in PEGASUS</td>
<td>Short term risks unknown, long term risk comparable to clopidogrel or prasugrel</td>
</tr>
<tr>
<td>Vorapaxar*</td>
<td>Hepatocellular adenomas in female rats</td>
<td>Significant (RR=1.4, p=0.012) in TRACER, and small numeric signal in TRA2P</td>
<td>Definite risks with triple therapy, much lower with DAPT</td>
</tr>
</tbody>
</table>

* on top of aspirin; RR, relative risk.
omit aspirin at all because the other drugs might otherwise increase solid tumour risks even further if used as monotherapy. Adequately sized randomised controlled trials designed specifically to look at cancer should be performed to fully elucidate the risk of dual antiplatelet therapy, especially with the newer antiplatelet agents. The exact recommendations with regard to the optimal content and duration can not be issued at this time. The evidence is clearly not sufficient to avoid long-term antithrombotic regimens, but cancer risks should be kept in mind especially in patients prone to bleeding. Future guidelines and real-life clinical practice should seriously consider solid cancer risks, advocating for more delicate and shorter antithrombotic strategies.

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Conflicts of interest

Dr. Serebruany is listed as an inventor for the issued US patent “Treating vascular events with statins by inhibiting PAR-1 and PAR-4” (7,842,716) assigned to HeartDrug. Research; and two pending applications: “Treating cardiac arrhythmias, heart failure, peripheral vascular disease and stroke with cyclopentyl-triazolo-pyrimidine or derivative thereof (USN 61/253, 829) assigned to HeartDrug”; and “Method for treatment of platelet activity with E5555” (USN 61/080,791); assigned to Eisai and HeartDrug”. He received compensation for the issued US patent 11/996,380 “Use of PAR-1/PAR-4 inhibitors for treating and preventing vascular diseases” on prasugrel assigned to Lilly. Dr Serebruany received funding for research studies with clopidogrel, and prasugrel; and consultant fees from clopidogrel and ticagrelor manufacturers. None of the other authors have any conflicts of interest to declare.

This Viewpoint Article reflects the view of its authors and is not representative of the view of the Editorial Board or the Publishers.

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