Cancer after intense and prolonged antiplatelet therapies – fact or fiction?

Raffaele De Caterina
University Cardiology Division, G. d’Annunzio University – Chieti, Italy

In this issue of *Thrombosis and Haemostasis*, Serebruany, in his Viewpoint paper, raises the hypothesis that – based on a compilation of current evidence – intense and prolonged antiplatelet therapy, mostly achieved with the combination of aspirin and a P2Y<sub>12</sub> inhibitor or with the addition of the platelet-activating receptor (PAR)-1 antagonist vorapaxar on top of aspirin and clopidogrel beyond two years, might increase the incidence of solid cancer (1). The issue is of relevance in the light of the uncertain efficacy/safety balance of antiplatelet therapy more intense than achievable with the time-honoured combination of aspirin and clopidogrel for the first year after an acute coronary syndrome or coronary stenting.

This Editorial Commentary will put these data in perspective, as well as point out weaknesses and inconsistencies in the data thus far available. This commentary also points out the importance of maintaining attention to this topic when we are dealing with antiplatelet drug treatments that are intense or prolonged, or both, in the face of progressively diminishing efficacy returns on cardiovascular endpoints compared with more conservative treatment strategies.

**Aspirin protection from solid cancer**

The background standard-of-care for secondary prevention of cardiovascular disease remains aspirin (2). Aspirin has now repeatedly and consistently shown protective effects on incidence and also mortality against several types of solid cancer, mostly – but not only – gastrointestinal (3-5). Even low doses of aspirin, in the order of 100 mg/daily, doses at which the drug can be considered a pure cyclo-oxygenase (COX)-1 inhibitor, mostly – if not only – determining pure antiplatelet effects due to the permanent acetylation of platelet COX-1, have been associated with protection from solid cancers (5).

The comparison of cancer incidence on aspirin against that after prolonged treatment with vitamin K antagonists tends to exclude the possible explanation that this anti-cancer effect of aspirin is due to early detection of cancer due to increased bleeding. Indeed, in the Thrombosis Prevention Trial (TPT) (6), more bleeding events were observed with prolonged warfarin therapy in primary cardiovascular disease prevention, but there was a much lower incidence of colon cancer in the aspirin group (4). The similarity of the effect with low- and higher doses of aspirin, these latter also inhibiting COX-2, has suggested that a COX-1-mediated antiplatelet effect may in turn mediate an anti-COX-2 effect indirectly, thus inhibiting tumour growth (7).

Indeed, mechanistic data now are supporting the epidemiological and clinical evidence (8, 9). The anti-cancer effect of aspirin is now considered by some (10), including ourselves (11), to be sufficiently relevant to warrant being considered as part of our advice to prescribe aspirin for the primary prevention of cardiovascular disease. Here, the net clinical benefit, simply estimated as protection from ischaemic events vs induction of major bleeding, is overall uncertain. We would argue that the use of aspirin in patients at high risk of death, myocardial infarction and stroke in primary cardiovascular disease prevention is warranted in patients with an estimated risk of this composite >20% at 10 years. We also maintain that in lower risk categories, a family history of gastrointestinal cancer may reasonably orient informed patients’ choice towards the use of aspirin (11). While we are still awaiting more conclusive results deriving from specifically designed and now ongoing trials, we cannot at this point in time disregard the currently available evidence for long-term treatment.

**Is the effect of aspirin on cancer specific for aspirin, or is it due to platelet inhibition?**

No sufficiently large trial of clopidogrel alone vs placebo, with long-term results on cancer or mortality, is available. The CAPRIE study was a head-to-head comparison of aspirin and clopidogrel in over 21,000 patients with evidence of atherosclerotic vascular disease (12). The lack of differences in cancer incidence or death in the two arms of the study is compatible with the idea of clopidogrel also possibly being protective against cancer (12). There are also data for an involvement of the platelet P2Y<sub>12</sub> receptor in murine pulmonary metastases (13).

Thus, some evidence might suggest that mild platelet inhibition, by aspirin or P2Y<sub>12</sub> inhibitors, can in some way interfere with cancer growth or progression, or metastatic dissemination, which are different processes possibly differentially affected by different antiplatelet treatments (9). Various
pleotropic effects of platelet P2Y\textsubscript{12} inhibitors have been proposed, but whether these are related to a pro- or anti-cancer effect is uncertain (14).

What about more intense or prolonged antiplatelet therapy?

More potent P2Y\textsubscript{12} inhibitors clearly impact on platelet function and associated cardiovascular outcomes (15, 16), but not enough is known on relevant outcomes. The impact of more intense or prolonged antiplatelet therapy combining aspirin and a P2Y\textsubscript{12} inhibitor and/or a third antiplatelet agent on cancer-related outcomes is here being scrutinised by Serebruany (1). He suggests that more prolonged antiplatelet therapy, as achievable with the combination of aspirin and clopidogrel long-term, as in DAPT (17), or more intense or potent antiplatelet therapy as with prasugrel in TRITON-TIMI 38 (18) and TRILOGY (19), or with ticagrelor in PEGASUS-TIMI 54 (20), is associated with a numerically increased incidence of deaths due to solid cancer, which is truly the opposite of the anti-cancer effect observed with milder levels of platelet inhibition.

Should one base the evaluation of this hypothesis only on the solidity of statistical testing, admittedly weak? I argue that statistics can help, but only up to a certain point. Cancer death was not a pre-specified endpoint in any of the trials, and P values for direct comparisons of cancer deaths in the two arms of those studies were not adjusted for multiple comparisons. Thus, “significant differences” in some of the trials might still be the result of the play of chance. The issue here is whether to dismiss this signal completely—interpreting it as “background noise” and “play of chance” —or to keep the attention on it, while waiting for further evidence. I would argue that—with no pretension of being conclusive—such data should not be disregarded.

While biological plausibility remains vague, it would not be the first case whereby hypotheses of biological plausibility are raised after the suggestion of unexpected effects of a drug or treatment.

Diminishing returns with more intense or prolonged antiplatelet treatments

These data need to be put in the context of the still unclear overall net clinical benefit for more intense or prolonged antiplatelet treatments. Some such treatments, such as the use of ticagrelor instead of clopidogrel for one year (21), have been associated with a reduction in all-cause mortality. Independent of whether pre-specified or not, death is the most undisputable of all study outcomes. “Death is a fact, while the causes of death are opinions”. One should never dismiss the possibility that a benefit on some – expected – ischaemic outcomes, such as myocardial infarction or ischaemic stroke, may be outweighed, in the course of a trial, by other – unexpected and unwanted – outcomes, pointing in an opposite, unfavourable direction.

Reduction in total mortality was achieved in PLATO with ticagrelor (21), but not in TRITON-TIMI 38 with prasugrel (18). In this latter trial, however, there were still numerically less deaths by all causes in the prasugrel arm than in the clopidogrel arm (18), arguing for a net clinical benefit also of prasugrel over clopidogrel in the study cohort. This was not however the case in DAPT (17). Here the rationale for prolonging dual antiplatelet therapy with aspirin and clopidogrel in patients after an acute coronary syndromes and/or treated with a coronary stent would be a reduction in stent thrombosis and acute myocardial infarction; but at the price of numerically increased deaths, part of which may be due to increased incidence of cancer. PEGASUS also treated a cohort of selected patients at distance from an ischaemic event for a prolonged (median 33 months) time period (20). Here the use of ticagrelor beyond one year was associated with a reduction in non-fatal myocardial infarction, but with no reduction in all-cause deaths (20) and with a suggestion, as highlighted by Serebruany (1), of increased cancer mortality.

The rationale for prolonging treatment with ticagrelor beyond one year might still be of value in certain selected patient categories, but it is not immediately obvious and generalizable. This also appears to be the case for vorapaxar trials, whereby a significant increase in cancer deaths occurred in TRA-CER (22) and a numerically increased rate of cancer deaths occurred in TRA-2°P (23). One has to emphasize that net clinical benefit analyses still point in the right (favourable) direction overall for vorapaxar, with an overall reduction in total deaths (23). Still the issue requires continuing attention to provide the best possible information to patients and health providers on the long-term consequences of treatments that are all expensive additions to the previous drug armamentarium, and for which concern for the overall patients’ health remains the most important issue at stake.

Net clinical benefit analyses

In the absence of conclusive data on mortality, more and more emphasis should be given to analyses on the net clinical benefit of treatments. Such analyses are useful to inform personalized management (11, 24). Such analyses should no longer be presented as the simple addition of fatal and non-fatal events of different nature, but rather should attempt at weighing the prognostic value of non-fatal events. This can be done by evaluating the prognostic value of non-fatal events on the risk of subsequent death (25, 26), in order to give value to the fact that an intra-cranial haemorrhage has, for example, a much heavier prognostic impact than an ischaemic stroke or a myocardial infarction. In the setting of anticoagulant therapy, for example, such analyses disclose the interesting fact that treatments with lower anticoagulant doses of dabigatran etexilate and edoxaban in the setting of RE-LY (27) and ENGAGE-AF (28) trials are associated with a similar and actually possibly more favourable net clinical benefit vs warfarin.
than the higher dosages (29), strongly arguing for the inadequacy of judging treatments predominantly based on their ability to prevent ischaemic stroke. As in several other cases, here “less is more”. We advocate more and more of such analyses, with the accrual of long-term outcomes, also in the setting of prolonged or more intense antiplatelet therapies, where the health benefit in terms of mortality remains equivocal.

The importance of whistle blowers

With all the uncertainties and limitations of the analyses presented by Serebruany on the risk of solid cancer related to intense/prolonged antiplatelet therapies (1), I value the author’s role of whistle-blower, raising the level of attention to issues not usually focused in the primary analyses of the various trials. I also applaud Thrombosis and Haemostasis for allowing publication of his Viewpoint, with the awareness that it will ignite discussion and controversies. These discussions are healthy, are actually welcome, and might eventually confirm or deny the hypotheses generated by such analyses. There is much more to lose from not being sufficiently alert than from being unduly blind.

Acknowledgment

The Author expresses gratitude to Paola Patrignani, Ph.D., for insightful exchange of information and opinions on the topic.

Conflict of interest

Has received research fees and honoraria from AstraZeneca, Lilly, Daiichi-Sankyo, Boehringer-Ingelheim, Bayer, BMS/Pfizer, Novartis and Roche.

Note added in proof

As of November 6, 2015, the American Food and Drug Administration released a statement according to which using clopidogrel with aspirin for over a year does not increase or decrease risk of overall death in patients with coronary heart disease or who are at risk for developing the disease—and it does not change the risk of cancer death or of developing cancer (30).

The announcement was based on a review of the Dual Antiplatelet Therapy (DAPT) trial, as well as of other large clinical trials that also examined adverse events from clopidogrel use. The FDA’s meta-analyses of 56,799 patients showed no difference in all-cause death between clopidogrel and aspirin used for 12 months or longer (6.7% incidence) vs use of both medications or aspirin alone for six months or less (6.6% incidence).

Long-term use of the dual antiplatelet therapy also showed no increase in any cancer-related adverse event (4.2% vs 4.0%, respectively) or death (0.9% vs 1.1%, respectively).

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References


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Trial glossary

CAPRIE: Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (12)
DAPT: Dual Anti-Platelet Therapy (17)
ENGAGE-AF: Global Study to Assess the Safety and Effectiveness of Dosed With Warfarin in Patients With Atrial Fibrillation (Engage-AF-TIMI 48) (28)
PEGASUS-TIMI 54: Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin (20)
PLATO: Platelet Inhibition and Patient Outcomes (2)
RE-LY: Randomized Evaluation of Long Term Anticoagulant Therapy (RE-LY) With Dabigatran (27)
TPT: Thrombosis Prevention Trial (6)
TRA 2°P: Trial to Assess the Effects of Vorapaxar (SCH 530348; MK-5348) in Preventing Heart Attack and Stroke in Patients With Atherosclerosis (TRA 2°P – TIMI 50) (23)
TRA-CER: Trial to Assess the Effects of Vorapaxar (SCH 530348; MK-5348) in Preventing Heart Attack and Stroke in Participants With Acute Coronary Syndrome (TRIACLE-TRA-CER) (22)
TRILGIO: TaRgeted platelet Inhibition to Clarify the Optimal strateGy to medically manage Acute Coronary Syndromes (19)
TRITON-TIMI 38: Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction 38 (18)


