Mortality and cancer risk on long-term antiplatelet treatment: What is known and what we still don’t know

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Despite various large-scale clinical trials and particularly large amounts of data coming from different independent studies (1, 2) and meta-analyses (3–5), the optimal duration of dual antiplatelet treatment (DAPT) is still considered unknown for both acute coronary syndrome (ACS) and stable patients undergoing PCI. Historically, the initiation and conduction of randomised trials on prolonged (>12 months) DAPT was essentially triggered about a decade ago by data suggesting an increased risk of late stent thrombosis and higher mortality with first generation drug-eluting stents (6, 7). A 30- versus 12-month DAPT duration was therefore tested in the pivotal randomised DAPT trial (1) and it did not come as a surprise that the longer DAPT duration reduced ischaemic risk including stent thrombosis and myocardial infarction, while it increased the risk of minor and major bleeds. However, what came as a surprise from the DAPT trial was the observed increased risk of death from any cause in patients with prolonged thienopyridine therapy (2.0 % vs 1.5 %, hazard ratio [HR] 1.36, 95 % confidence interval [CI] 1.00 to 1.85; p = 0.05). Of note, this risk difference was entirely driven by non-cardiovascular mortality (1.0 % vs 0.5 %, HR 2.23, 95 % CI 1.32 to 3.78; p = 0.002). This apparent increase in non-cardiovascular deaths on long-term thienopyridine treatment leads one to speculate whether it is the risk of developing cancer that may trigger this phenomenon. Indeed, in supplementary material to the main DAPT trial publication (1) the cancer-related mortality risk was reported to be higher under prolonged thienopyridine treatment (31 cases (0.62 %) vs 14 cases (0.28 %); p = 0.02). However, the authors acknowledged that a relevant number of patients in the 30-month DAPT group had cancer diagnosed already before their randomisation, leading to an imbalance of cancer rates between groups when entering the trial (1). After secondary analysis (8), the authors basically dismissed the excess cancer-signal in the 30-month thienopyridine group by excluding patients with known cancer at the time of randomisation. However, despite being the largest randomised trial regarding optimal duration of antiplatelet therapy, the total incidence of cancer events in the DAPT trial population was low and the risk of a chance finding was relevant. With this in mind it is a valid approach to study mortality and cancer risk of prolonged DAPT treatment independently and in large cohorts of PCI-treated patients. In this issue of Thrombosis and Haemostasis, Serebruany et al. provide outcome data on mortality and cancer risk after 30 versus 12 months DAPT from 25,938 PCI-treated patients from the KOREA registry (9). The study follows prior reports from this author on cancer risk and ADP receptor blockers in this and other journals (10, 11). Key results can be summarised as follows: The overall mortality risk was similar between patients with 30 versus 12 months DAPT (1.24 % vs 1.28 %, HR 0.99, 95 % CI 0.73 to 1.14; p = 0.99), while cancer risk was slightly but significantly higher on prolonged DAPT (4.15 % vs 4.04 %, HR 1.22, 95 % CI 1.06 to 1.41; p = 0.005). Based on the reported results the authors conclude that their data does not support continuing DAPT for >1 year in East Asians and that the cancer risk warrants further investigations.

Serebruany et al. are to be congratulated for this important and well-done analysis from a large cohort of patients. One important strength of the publication is the careful and broad (>90 %) exclusion of patients potentially carrying biases towards the analysis. However, some important caveats should be considered to put the reported data into perspective: First, the absolute difference in cancer risk between the two study groups is 0.11 %, which much be considered as minor and would correspond to a number need to harm (NNH) of 909 patients. Moreover, it may well be that differences in baseline characteristics of the two study groups may be the underlying reason for the minor difference in cancer risk and utilised statistical methods like propensity score matching or inverse probability of treatment weighting may not be able to fully adjust for this. In consequence, these results must be considered as important but hypothesis-generating and future studies should specifically address this observation. Second, all data from this analysis stems from a complex database, where we may assume that compliance and actual intake of antiplatelet treatment may not be placed in the centre of attention. If the actual intake of DAPT and its duration perfectly matches with the recordings in the database is at least uncertain and leaves room for systematic biases. Third, published observational and randomised data is conflicting with respect to the issue in how far (prolonged) thienopyridine treatment may trigger cancer. In a recently pub-
lished population-based historical cohort study from Israel in 183,912 subjects, >20,000 cancer cases were captured and DAPT (aspirin plus clopidogrel) was associated with an even lower cancer risk versus monotherapy with aspirin (HR 0.92, 95% CI 0.86 to 0.97) (12). In fact, this study suggested that clopidogrel treatment may reduce cancer risk, which would be in complete contradiction to the results of Serebruany et al. reported here (9). In a meta-analysis from nine studies with 282,084 participants Kotronias et al. analysed data on cancer event rate and mortality with thienopyridines (13). Key results of that analysis were that thienopyridine treatment showed no association with cancer rate and subsequent mortality. Further on, when comparing potent platelet inhibition with prasugrel versus clopidogrel, no significant association was noted for cancer event rate as well. In line with this, the TRILOGY-ACS investigators reported (14) that cancer events were infrequent during long-term DAPT after ACS and events did not differ in prasugrel versus clopidogrel treatment patients (1.8% vs 1.7%, p=0.79, median treatment exposure of 15 months). Finally, the KOREA registry is limited by having only clopidogrel-treated patients included. Independent registry data from cohorts of similar size with prasugrel and ticagrelor treated patients is urgently needed. Randomised data on mortality and cancer risk for a long-term use of ticagrelor in patients with prior myocardial infarction comes from the PEGASUS trial (15). In that study, overall mortality did not differ for ticagrelor- versus placebo-treated patients (HR 1.00 95% CI 0.86–1.16, p=0.99 for ticagrelor 90 mg vs placebo; HR 0.89 95% CI 0.76–1.04, p=0.14 for ticagrelor 60 mg vs placebo). However, cancer-related death was numerically higher in the ticagrelor versus placebo groups of the study (77 cases (1.10%) in ticagrelor 90 mg arm, 64 cases (0.92%) in ticagrelor 60 mg group and 53 cases (0.76%) in placebo group). Serebruany et al. hypothesise that the potential excess in cancer-related diagnoses and deaths may be “a class effect” of antithrombotic agents as cancer follows bleeding (9, 10). Although possible mechanisms might link bleeding to an increased risk of developing cancer, introducing a class effect for all antithrombotic agents might be an over-simplification of the true interaction. One example of that is the beneficial effect of aspirin on colorectal cancer development in patients with previous colorectal neoplasia (16).

In conclusion, a possible increase in cancer risk on prolonged DAPT might be considered as minor or maybe negligible based on published data. Not losing sight of the big picture, we should keep focusing on a possible increase in overall mortality with prolonged DAPT (1, 4). While Serebruany et al. reported no direct evidence into that direction here (9), a recent meta-analysis including 31,666 patients from 10 randomised clinical trials specifically focused on different DAPT durations after drug-eluting stent implantation (4). In that analysis, especially prolonged DAPT beyond one year was associated with increased overall mortality due to an increased risk of non-cardiovascular death that was not offset by a reduction in cardiac mortality. This must be understood as a note of caution and “the longer the better” does not seem to be the way to go with DAPT. Instead, we should also realise that clinical certainty for an individual patient and the “perfect DAPT duration” after PCI cannot be achieved. It is therefore time to revisit a more individualised approach to DAPT duration (17, 18) and to move away from a one-size-fits-all strategy. For future treatment it could be useful to introduce scoring systems like the DAPT score (19) into this decision-making, in a similar way as the CHA2DS2-VASc and HAS-BLED scores are being used for initiation and guidance of treatment with anticoagulants and antiplatelet agents (20).

Conflicts of interest
Dr. Sibbing: Speaker fees and honoraria for consulting from Eli Lilly, MSD, Pfizer, Daiichi Sankyo, Bayer Vital, AstraZeneca and Roche Diagnostics, and research grants from Roche Diagnostics; Dr. Aradi: Lecture fees from AstraZeneca, Daiichi Sankyo, Eli Lilly, Roche Diagnostics.

References