and aspirin.[148] Thus, for clopidogrel, we advise the same decision-making strategy based upon the degree of TP, as depicted above for low-dose aspirin. However, clopidogrel is a prodrug with a complex cytocrome p450-dependent (3A4, 2B6, 2C19, 2C9) bioactivation, known to cause clinically relevant DDIs (Suppl. Table S1). DDIs with clopidogrel may either increase variability in its antiplatelet effect,[149] or even increase the toxicity of chemotherapeutic agents such as taxanes.[150] Consistently, we advise, if possible, to cautiously use clopidogrel in cancer patients on chemotherapeutical drugs, considering potential clinically relevant DDIs (Suppl. Table S1).

Beyond secondary prevention, low-dose aspirin is also the reference treatment in patients who have undergone revascularization for a significant arterial stenosis in the absence of a symptomatic MI or stroke and in patients with documented, clinically significant arterial stenosis (usually ≥50%).[135] For these patients, deemed at very-high CV risk because of unequivocally documented relevant atherosclerotic disease, we advise to use the same reasoning pattern as in secondary prevention.

Recommendations

8. SAPT in secondary prevention

- **a.** For grade 1 TP, we recommend to maintain SAPT with low-dose aspirin. ***Level 2b, grade B***
- **b.** For grade 2 TP, we recommend to maintain SAPT with low-dose aspirin, providing that the patient has no other major bleeding risk factors (**Table 4**). ***Level 2b, grade C***
- **c.** For grade 3 TP, SAPT with low-dose aspirin should be continued only if additional CV thrombotic risk factors are present (**Table 3**). ***Level 4, grade C***
- **d.** Grade 4 TP, we recommend to temporarily withhold SAPT, independently of the thrombotic risk level. ***Level 5, grade D***
- **e.** If withheld, SAPT should be resumed as soon as platelet count reaches ≥25 to 50×10^9/L, according to the thrombotic risk. ***Level 5, grade D***

Primary prevention

In primary CV prevention low-dose aspirin use should be restricted to patients with multiple CV risk factors, estimated to be at high or very-high CV risk[137,151] or for patients with risk-enhancing factors (high Coronary Artery Calcium score) or in patients with no history of MI or stroke but with significant carotid and/or femoral plaque stenosis documented by imaging especially with diabetes.[151] Considering that the absolute yearly risk of CV complications is lower in primary than secondary prevention, we advise to keep ongoing aspirin for grade 1 TP patients in the absence of other bleeding risk factors, and to temporarily withhold aspirin for grades 2–4, restarting the drug when platelets raise to $>75 \times 10^9$/L.

Recommendations

9. Low-dose aspirin in primary prevention

- a. Grade 1 TP: we recommend maintaining SAPT with low-dose aspirin, if indicated, unless other bleeding risk factors are present. ***Level 5, grade D***
- b. Grade ≥2: we recommend holding SAPT and resuming as soon as platelet count is $\geq 75 \times 10^9$/L. ***Level 5, grade D***

Dual antiplatelet therapy

Patients can be on DAPT (low-dose aspirin plus a $P2Y_{12}$ inhibitor, either clopidogrel or prasugrel or ticagrelor) according to current guidelines[136,139] for the following indications: acute minor ischemic stroke or high-risk TIA within the first 21 days; prior TIA/stroke with intracranial arterial culprit lesion within 90 days; percutaneous coronary intervention (PCI) and stent implantation for stable CAD within 6 months; ACS with or without revascularization within 12 months. Overall, there is scarce and low-quality evidence on patients with a clear indication for DAPT who have cancer and concurrent TP, especially grade 3–4. In addition to the bleeding risk in this setting (**Table 4**), the potential utility of DAPT in improving CV and cerebrovascular outcomes has been proven in RCT, which excluded TP patients. There is no evidence supporting the use of platelet function assays for any of the therapeutic decisions.[152,153]

DAPT in stroke prevention

Current stroke prevention guidelines emphasize the importance of identifying the underlying stroke mechanism (eg, small vessel disease, large artery atherosclerosis, cardioembolism), since each mechanism warrants distinct antithrombotic regimens.[136] In contrast to cardioembolic strokes that necessitate anticoagulation, prevention of strokes related to small or large arteries requires APT. Long-term SAPT, usually with aspirin, is the mainstay secondary prevention strategy for ischemic stroke or TIA.[136] In contrast, the role of DAPT in early recurrent stroke prevention is time-limited in the acute setting[154–156] or mechanism-specific[141,156,157] (eg, intracranial large artery stenosis).

Acute ischemic stroke or TIA

Several multicenter RCTs including patients with acute minor ischemic stroke or high-risk TIA have demonstrated a short-term reduction in ischemic stroke recurrence with DAPT-clopidogrel[154,155] or DAPT-ticagrelor[156] compared to low-dose aspirin alone. Compared to the aspirin-only group, DAPT-clopidogrel reduced the event rate especially during the first 21 days of therapy (5.2% versus 7.8%; HR 0.66, 95% CI, 0.56-0.77) with a nonsignificant increase in major bleeding (0.3% versus 0.1%; HR 2.11, 95% CI, 0.86-5.17), resulting in a favorable risk-benefit profile (NNT 38; NNH 500).[158] Accordingly, international stroke guidelines recommend DAPT-clopidogrel for 21 days after noncardioembolic acute minor ischemic stroke or high-risk TIA.[136]

There is no evidence on the effect of TP (with or without cancer) on the risk-benefit ratio in this context. A single retrospective cohort study provided data on TP patients ($<100 \times 10^9$/L) with acute ischemic stroke (AIS) (n = 28) and demonstrated a high risk of intracranial hemorrhage (14.3% versus 1.5%) compared with patients without TP (n = 1,205), as detailed in **Table 6**.[159] Although fraught with potential bias, this study provides reason for caution. The risk-benefit ratio in non-TP patients and the time-limited nature of the DAPT (21 d), despite uncertainty and some concern regarding the bleeding risk in TP and cancer, led us to recommending continuing DAPT with clopidogrel for up to 21 days after minor stroke or high-risk TIA in grade 1 TP and in grade 2 TP in the absence of additional bleeding risk factors. Because of a modest NNT, we recommend SAPT (low-dose aspirin) over DAPT in grade 3 TP in this context, and holding all APT in grade 4 TP.

Recommendations

10. AIS or TIA in the past month without a significant intracranial arterial lesion

- **a.** For stable grade 1 TP, DAPT with clopidogrel should be used for 21 days after the event followed by low-dose aspirin only.[136] ***Level 5, grade D***
- **b.** For grade 2 TP, DAPT with clopidogrel should be used for 21 days followed by low-dose aspirin only, unless additional bleeding risk factors are present (**Table 4**). If additional bleeding risk factors are present SAPT with