REVIEW ARTICLE

Optimal management of cancer patients with acute coronary syndrome

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KEY WORDS

acute coronary syndrome, anticoagulation, antiplatelet therapy, bleeding management, thrombocytopenia

ABSTRACT

Cancer at various stages and therapy is observed in about 15% of patients with acute coronary syndrome (ACS). Current guidelines for invasive and conservative treatment of ACS cannot be applied to all patients with cancer. The choice of antiplatelet and anticoagulant drugs should be individualized with clopidogrel as a key $P2Y_{12}$ inhibitor in this population. Major challenges of therapy in patients with ACS and cancer include limitations for the use of the recommended antithrombotic therapy (particularly in case of cancer-related thrombocytopenia or when anticoagulation is needed due to concomitant atrial fibrillation or venous thromboembolism), the management of bleeding complications, eligibility criteria for cancer surgery, and reinitiation of chemotherapy or radiotherapy after ACS. This review summarizes the current evidence and our own experience in the treatment of ACS in cancer patients. Since prognosis has considerably improved in many cancer patients in the last decade, optimal therapy of ACS may increase the life expectancy and reduce the risk of adverse coronary events after ACS in this high-risk population.

Epidemiology and mechanisms of acute coronary syndrome in cancer A modern approach to the diagnosis of acute coronary syndrome (ACS) is not limited to confirming the presence of critical coronary artery stenosis and myocardial ischemia due to atherosclerotic plaque rupture or erosion (type 1 myocardial infarction [MI]). The clinical spectrum of ACS encompasses also type 2 MI secondary to ischemia caused by an imbalance between oxygen demand and supply, type 3 MI resulting in sudden cardiac death, type 4a associated with percutaneous coronary interventions (PCIs), type 4b associated with stent thrombosis, and finally, type 5 associated with cardiovascular surgery.[1,2] The key to understanding the pathophysiology of ACS is ischemia, which is also caused by endothelial and microcirculatory dysfunction, vasospasm, as well as enhanced inflammatory state and inherited or acquired prothrombotic tendency.[3] The pathogenesis of ACS often involves the simultaneous presence of several different causes of ischemia. All these considerations on the pathophysiology of ACS are particularly important in patients with concomitant cancer at various stages of its diagnosis and treatment.[4] A new common mechanism linking cancer with ACS is formation of neutrophil extracellular traps, chromatin fibers released from dying neutrophils, leading to a prothrombotic state, oxidative stress, and atherosclerosis progression.[5] The association between cancer and ACS is complex. ACS may occur before or after establishing the diagnosis of cancer. Sometimes the diagnosis is made during hospitalization for ACS.

ACS may be induced by cancer treatment (ie, chemotherapy, radiotherapy, or surgical treatment). Highly prothrombotic effects have been observed in patients treated with cisplatin (ACS in up to 2% of patients), erythropoietin, gemcitabine, 5-fluorouracil (ACS in up to 10%), granulocyte colony-stimulating factors, and bevacizumab (ACS in up to 4%). Use of pyrimidine analogues requires close monitoring for ACS. Overall, previous chemotherapy should be considered a risk factor of coronary artery disease. In most cases, ACS in cancer patients develops in the arteries affected by atherosclerosis as a manifestation of coronary artery disease in the presence of cardiovascular risk factors, predominantly in elderly patients, and it occurs independently of anticancer treatment. It may be also associated with complications from cancer or not be associated

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Received: April: 19, 2018.
Accepted: April 19, 2018.
Published online:
Conflict of interest: none declared.
Pol Arch Intern Med. 2018; 128 (4): 244-253
doi:10.20452/pamw.4254

with cancer at all. Cancer at various stages and therapy is observed in about 15% of patients with ACS.[6] Clinical data show that cardiovascular death is one of the main causes of in-hospital mortality in cancer and noncancer patients with ACS undergoing PCI.[7]

Unfortunately, so far prospective studies assessing the efficacy and safety of ACS treatment have excluded patients with active cancer. As a result, current guidelines for invasive and conservative treatment of ACS cannot be easily applied to all patients with cancer. There is growing awareness that cancer treatment has negative effects on the optimal management of ACS, and vice versa.[8] Therefore, from a clinical perspective, it is extremely important to assess the cardiovascular and noncardiovascular risk in patients with ACS and concomitant cancer.[9] Such an approach allows to avoid complications of aggressive antiplatelet and anticoagulant therapy or revascularization with PCI or coronary artery bypass grafting (CABG).

The incidence of ACS in patients with newly diagnosed cancer increases in the first 6 months since diagnosis and then decreases after a year to increase again in more advanced stages.[10,11] ACS occurs in patients with various cancers, most often in those with lung, gastric, or pancreatic cancer. The occurrence of ACS in patients with cancer is associated with classic risk factors such as hypertension, diabetes, obesity, or smoking, but also with several prothrombotic factors secreted by the tumor itself or expressed on its surface; chemotherapy and radiotherapy can also exert prothrombotic, proinflammatory, and vasospastic actions.[4,11]

The occurrence of ACS in the cancer patient raises numerous concerns about the management, which should not only be effective but also safe.[12,13] The common questions are as follows: Are complaints reported by the patient typical for ACS? Which antiplatelet and anticoagulant drugs and what regimens should be used? How to balance the risk of thrombosis against the risk of bleeding? How to manage patients with bleeding complications? How to modify treatment of ACS in patients with thrombocytopenia? How to perform invasive revascularization (PCI, CABG)? What should be the indications and eligibility criteria for cancer surgery following ACS? When to restart chemotherapy or radiotherapy after ACS?

Key messages

- Cancer at various stages of development and therapy is observed in about 15% of patients with ACS.
- The incidence of ACS in patients with newly diagnosed cancer increases in the first 6 months since diagnosis and decreases at 1 year.
- ACS most often occurs in patients with lung, gastric, and pancreatic cancer.
- Each patient with cancer should be screened for classic cardiovascular risk factors.

Clinical presentation of acute coronary syndrome in cancer The clinical presentation of ACS in cancer patients is often different from that observed in the general population.[14-16] The prevalence of silent ischemia is higher in cancer patients, possibly due to neurotoxic effects of chemotherapy and altered perception of angina. Dyspnea is observed more often than angina in cancer patients. There are various misleading abnormalities on electrocardiograms that may be caused by tumor infiltration of the myocardium, cerebral bleeds, chemotherapy, pulmonary embolism, and others. Elevated cardiac troponin levels do not necessarily indicate ACS. In 85% of cases, ACS manifests as non–ST-segment elevation MI (NSTEMI), and in 15%, as ST-segment elevation MI (STEMI). Moreover, 1 in 10 patients presents with Takotsubo cardiomyopathy.

According to current management guidelines, every patient with ACS and cancer should be considered for interventional treatment, with optimal medical therapy prior to admission and during hospitalization. Importantly, the presence of cancer in patients with ACS undergoing PCI increases the risk of cardiovascular events and bleeding complications, especially gastrointestinal hemorrhage and hematuria as well as adversely affects in-hospital and long-term prognosis.[16-20] In the BleeMACS project, a multicenter observational registry that enrolled patients with ACS, it has been reported that 6.4% suffered from concomitant cancer, and they were older, and more frequently had NSTEMI and severe comorbidities compared with the remainder.[17] Importantly, death or reinfarction as well as bleedings after 1-year follow-up were more common in the cancer group (15.2% vs 5.3% and 6.5% vs 3.0%, respectively), leading to the conclusion that cancer is the strongest predictor of the 2 endpoints.[17] A study on a large Canadian cohort of 22 907 cancer patients with acute MI recruited between 1995 and 2013 and followed for 10 years reported that at 30 years, cancer, but not recurrent ACS or stroke, is associated with higher morality (adjusted hazard ratio, 1.12; 95% confidence interval, 1.01–1.17) and to a similar extent after 1 year and during long-term follow-up.[18] There was no difference in the rate of death with regard to the time from cancer diagnosis to MI, which underscores the value of cardiac assessment in cancer survivors.[18] Higher mortality in patients with MI with a history of cancer is multifactorial. This finding probably results not only from cancer itself but is also associated with the clinical characteristics of these patients, who are more often older, suffer from arterial hypertension, diabetes, chronic kidney disease, and have a history of ACS and CABG as well as bleeding complications. Moreover, the outcomes of PCI and conservative treatment may differ depending on the stage of cancer, diagnostic evaluation, and treatment.[7] Stage 1 (ie, from diagnosis to treatment completion) is associated with higher thrombotic risk. Stage 2 (ie, prolonged

survival after treatment completion) is associated with increased thromboembolic risk due to thrombocytosis, leukocytosis, and infection. Finally, stage 3 (ie, long-term survival) may be associated with cardiotoxic effects of chemotherapy, in particular anthracyclines and kinase inhibitors, and radiotherapy.

To optimize interventional treatment and minimize bleeding events, it is important to use the transradial and not the transfemoral approach.[21] The transradial access is much safer in case of bleeding and is more convenient for the patient. On the other hand, the transfemoral access poses a higher risk of retroperitoneal bleeding, a major event, which may be fatal, especially if dual antiplatelet therapy (DAPT) is used in a patient with thrombocytopenia. The transfemoral approach should not be used in such patients except those in whom the transradial access had been used several times before, in women after total mastectomy, in those with abnormal Allen test results, and in individuals on hemodialysis.[22]

Importantly, long-term cardiovascular prognosis in patients with ACS undergoing PCI does not differ between individuals with newly diagnosed cancer and those with a history of cancer (most often lung, breast, and prostate cancer).[23] Moreover, patients with metastatic cancer who develop STEMI or NSTEMI benefit from PCI in terms of a 2- to 3-fold reduction in in-hospital mortality.[24] However, based on the available data, PCI is performed only in every fourth cancer patient with STEMI and in every tenth cancer patient with NSTEMI. Of note, it has been demonstrated that invasive therapy of ACS results in 5-year survival of 99% of patients with metastatic prostate cancer, and as few as 7% of those with metastatic pancreatic cancer.[25] Therefore, each ACS patient with cancer, regardless of the presence of distant metastases or not, should be considered for invasive strategy. The potential clinical benefits of PCI in these patients are not affected by radiotherapy.[26] However, previous radiotherapy for breast cancer in patients with ACS has been shown to increase the risk of recurrent ACS in a 12-year follow-up.[27]

Key messages

- The clinical presentation of ACS in cancer patients is often different from that observed in the general population.
- ACS manifests predominantly as NSTEMI.
- The stage of cancer since diagnosis to treatment completion is associated with higher venous thromboembolic risk.
- Anticancer treatment may increase thrombotic risk and lead to cardiotoxic effects of chemotherapy and radiotherapy.
- The presence of cancer in patients with ACS undergoing PCI increases cardiovascular and bleeding risk (especially gastrointestinal and urinary bleeding), as well as adversely affects in-hospital and long-term prognosis.
- Patients with metastatic cancer who develop STEMI or NSTEMI benefit from PCI.

Medical therapy in patients with acute coronary syndrome and cancer To maintain the beneficial effects of revascularization in patients with ACS, optimal medical therapy is required, which has been shown to be effective in reducing serious cardiovascular events during long-term follow--up.[28] Each patient with ACS, both with and without cancer, should be considered for the recommended antiplatelet treatment along with a statin, angiotensin-converting enzyme inhibitor (ACEI) (or angiotensin receptor blockers [ARBs] in case of ACEI intolerance), mineralocorticoid receptor antagonist, and β-blocker.[29] Optimal medical therapy was shown to reduce the rate of serious cardiovascular events by 32% during a 12-month follow-up in patients with ACS and cancer undergoing PCI.[30] However, both invasive treatment and optimal medical therapy have been shown to be underused in cancer patients with ACS.[17-19] Nevertheless, in the BleeMACS study, β-blockers, ACEIs/ARBs, statins, and antiplatelet agents were shown to reduce the risk of death and reinfarction at 1 year since ACS.[17] In Canada, ACEIs (or ARBs) and statins have been found to be slightly less often prescribed in cancer patients after ACS, while the use of clopidogrel, nitrates, spironolactone, calcium channel blockers, and β-blockers was similar in cancer and noncancer patients.[18]

In the case of long-term secondary prevention after ACS in patients with cancer, potential drug interactions with chemotherapeutics should be considered.[31-33] In particular, paclitaxel affects CPY2C8-mediated metabolism of simvastatin, atorvastatin, lovastatin, and fluvastatin.[34] Clopidogrel, a prodrug metabolized in the liver to its active form, may have lower antiplatelet activity in patients with liver injury due to cancer or the use of chemotherapeutics.[8] The androgen--receptor blocker spironolactone reduces the effectiveness of chemotherapy in patients with breast cancer, and therefore it should be replaced by the selective mineralocorticoid receptor antagonist eplerenone.[35,36]

Due to several drug–drug interactions and common unstable anticoagulation in part driven by interactions with diet, warfarin could be less effective than low-molecular-weight heparin (LMWH) in stable cancer patients with ACS; therefore, LMWH is the preferred option in such patients when, apart from DAPT, anticoagulation is recommended (particularly in venous thromboembolism [VTE]).[8,37,38] Finally, the use of class 3 antiarrhythmic drugs (ie, amiodarone and sotalol) in combination with angiogenesis inhibitors may prolong the QT interval leading to life-threatening ventricular arrhythmia.[39]

Key messages

- Each cancer patient with ACS should be considered for optimal medical therapy with antiplatelet drug or drugs, statins, ACEIs (or ARBs in case

TABLE 1 Interactions between anticancer drugs and non–vitamin K antagonist oral anticoagulants

Contraindicated/not recommended Increased/decreased anticoagulant effects		No relevant drug–drug interaction anticipated
Vinblastine	↓	Metotrexate
Doxorubicin	↓	Pemetrexed, purine analogs[a], pyrimidine analogs[b]
Imatinib, crizotinib	↑	Topotecan
Vandetanib, sunitinib	↓	Irinotecan
Abiraterone	↑	Daunorubicin
Enzalutamide	↓	Mitoxantrone
Cyclosporine	↑	Busulfan
Dexamethasone	↓	Bendamustine
Tacrolimus	↑	Chlorambucil
		Melphalan
		Carmustine
		Procarazine
		Dacarbazine
		Temozolomide
		Carboplatin
		Bleomycin
		Dactinomycin
		Mitomycin C
		Erlotinib, gefitinib
		Monoclonal antibodies (eg, rituximab, bevacizumab)
		Flutamide
		Letrozole
		Fulvestrant
		Raloxifene
		Leuprolide, Mitotane

a Purine analogs: mercaptopurine, thioguanine, pentostatin, cladribine, clofarabine, fludarabine

b Pyrimidine analogs: fluorouracil, capeticabine, cytarabine, gemcitabine, azacitadine, decitabine

of ACEI intolerance), mineralocorticoid receptor antagonists, and β-blockers.

- In the case of long-term secondary prevention after ACS in cancer patients, potential interactions with chemotherapeutics should be considered.

Antiplatelet therapy of patients with acute coronary syndrome and cancer Antiplatelet therapy, which is a standard management in the general population with ACS, constitutes a challenge in patients with cancer. These patients are at high risk of stent thrombosis and bleeding complications that are often aggravated by the presence of thrombocytopenia.[40] Currently, the first-choice antiplatelet drugs in ACS patients with cancer are acetylsalicylic acid (ASA; 300/75 mg) and clopidogrel (300–600/75 mg) (FIGURE 1A).[41] Ticagrelor and prasugrel should not be used owing to higher risk of bleeding in cancer patients. As conservative treatment, ASA with clopidogrel should be used for at least 1 month, while the decision to continue treatment for 3 to 6 months should depend on additional factors increasing the risk of recurrent ischemia related to the extent of coronary lesions and procedure performed, as well as the presence of clinically relevant bleeding complications. After this period, clopidogrel should be stopped and ASA alone should be continued. In the case of ASA intolerance or bleeding, ASA should be switched to clopidogrel. In patients with cancer who experience ACS, PCI with bare metal stent implantation should be performed, and DAPT should be administered if the platelet count exceeds 30 000/μl. It is recommended that chemotherapy or surgery should be delayed by 4 weeks. After drug-eluting stent (DES) implantation, DAPT should be administered for 12 months provided no bleeding occurs[42]; however, the implantation of third-generation DESs implicates shortening of the duration of DAPT that can be safely reduced to 3 to 6 months. Such a therapy should be considered if the platelet count exceeds 30 000/μl and the patient does not require an urgent surgery or aggressive chemotherapy.[43] Baloon angioplasty is recommended if the platelet count ranges from 10 000 to 30 000/μl, or if DAPT cannot be used, or if chemotherapy or surgery is scheduled within the next 4 weeks.[22] With balloon angioplasty, DAPT should be administered for at least 2 weeks (provided that the platelet count exceeds 30 000/μl).

The need for urgent surgery following ACS in cancer patients is a challenge. Irrespective of the stent implanted, clopidogrel should be stopped and ASA should be continued in the perioperative period. After the surgery, typically after 24 to 48 hours, clopidogrel at a loading dose of 300 mg can be restarted and then tapered to 75 mg/d provided the hemostasis is maintained.

The duration of DAPT after stent implantation in patients on chemotherapy and radiotherapy is still under debate, as the data on the effect of this treatment on reendothelization of stents are lacking.[12] It is recommended to assess the possibility of optimal stent extension in these patients, using intravascular ultrasound or optical coherence tomography.[22] In general, the decision on the choice of antiplatelet drugs should be tailored to individual patients depending on the stage of cancer and the need for surgery after ACS and/or PCI.

Anticoagulant therapy combined with antiplatelet agents in patients with acute coronary syndrome and cancer The management of patients with ACS and cancer who have indications for chronic anticoagulation (eg, mechanical heart valve, nonvalvular atrial fibrillation [NVAF], VTE, or high-risk thrombophilia [eg, antiphospholipid syndrome, antithrombin deficiency]) is particularly challenging due to high risk of bleeding and thrombosis.

Cancer occurs in about 2.5% of patients with NVAF, the most common indication for anticoagulation, and this arrhythmia is associated with a 5-fold increase in stroke risk, poor prognosis,

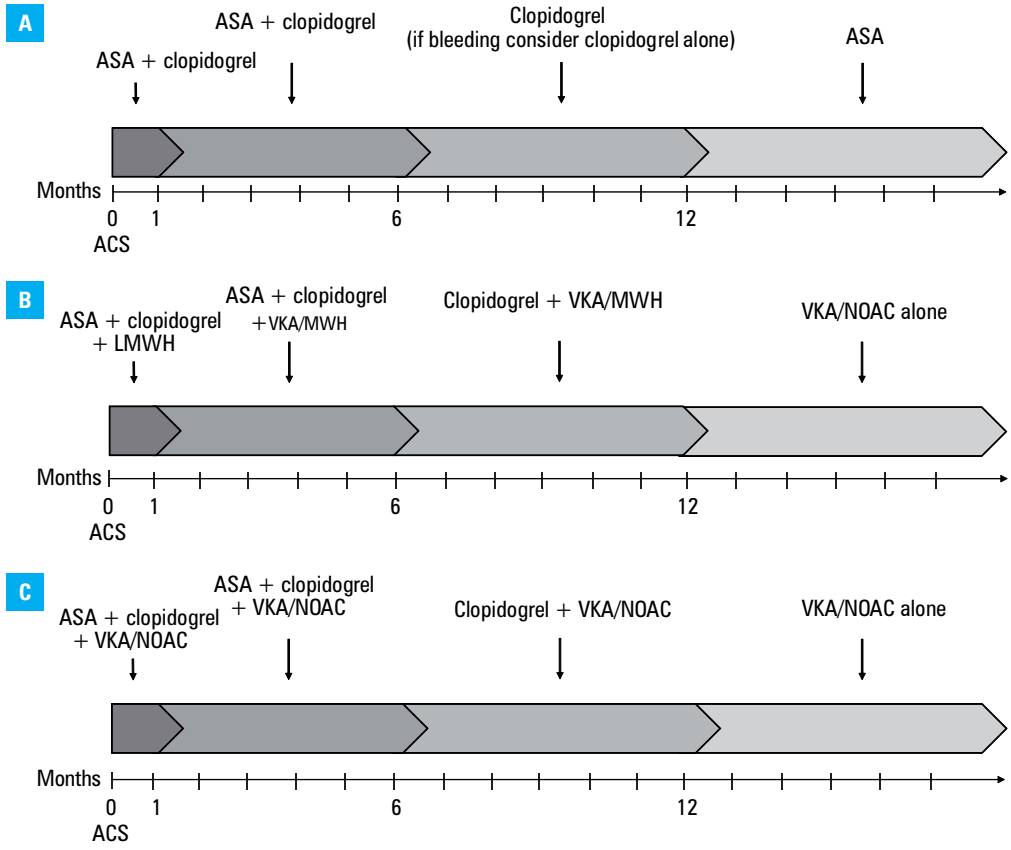

FIGURE 1 Antithrombotic treatment of cancer patients with acute coronary syndromes (ACSs) based on current guidelines and own experience; **A** – patients without indication for anticoagulation; **B** – patients with previous venous thromboembolism or other indications for anticoagulation, who may be treated with dual antiplatelet therapy up to 12 months depending on bleeding risk; **C** – patients with atrial fibrillation treated with oral anticoagulants with low to moderate bleeding risk (mainly patients after more than 1 year since cancer diagnosis). Low-molecular-weight-heparin could be considered as an alternative to oral anticoagulants if bleeding risk is high.
Acetylsalicylic acid (ASA): 75–100 mg/d once daily; vitamin K antagonist (VKA; warfarin, acenocoumarol) with a target international normalized ratio between 2 to 2.5, with its measurements every 1 to 2 weeks; low-molecular-weight heparin (LMWH; enoxaparin, preferentially subcutaneously) at an intermediate dose; optimization using anti-Xa activity could be used; non–vitamin K antagonist oral anticoagulant (NOAC): dabigatran, 2 × 110 mg/d; rivaroxaban, 15 mg/d; apixaban, 2 × 5 mg/d or 2 × 2.5 mg/d (reduction if 2 of the 3 criteria are met: weight ≤60 years, age ≥80 years, or creatinine ≥133 uM). Prolonged use of antiplatelet agents at high risk of myocardial ischemia following ACS including stenting of the left main coronary artery, or proximal descending artery, proximal bifurcation, stent thrombosis etc, and low bleeding risk.

and mortality rates of 20% to 25% at 30 days.[44] It has been reported that cancer and its therapy contribute to increased prevalence of NVAF, in part due to comorbidities, anticancer treatment, and cancer-associated factors, including dehydration, inflammation, and others, and the risk of thromboembolic complications.

In cancer patients, non–vitamin K antagonist oral anticoagulants (NOACs), including dabigatran, rivaroxaban, apixaban, and edoxaban (unavailable in Poland until April 2018), should be used with caution.[45] Active cancer was an exclusion criterion in most studies performed in patients with AF and VTE to evaluate the efficacy and safety of all NOACs. Several drug–drug interactions can hamper the use of NOACs in cancer; however, strong interactions are infrequent, as shown in TABLE 1.[44] Despite limited evidence on the efficacy and safety of NOACs in this disease, they are increasingly used in cancer patients with NVAF, which poses problems in acute myocardial ischemia.[46] A recent Danish population-based cohort study has demonstrated that 1-year risks of bleeding and thromboembolic events were similar in patients with NVAF with and without cancer receiving NOAC and vitamin K antagonist (VKA).[46] Of note, as few as 27% of cancer patients were diagnosed within 2 years preceding the ACS.[46] In American NOAC users with AF and cancer, lower or similar rates of bleeding and stroke were observed compared with warfarin users.[47]

Cancer patients on anticoagulant therapy with VKA or a NOAC, who experience an ACS, should be considered to be temporarily switched to LMWH, particular patients on chemotherapy (FIGURE 1B). The rationale for such an approach is an easier control of anticoagulation with LMWH, which mostly does not require laboratory

monitoring as compared with VKAs. LMWH also facilitates the therapeutic decision of oncologists and surgeons, and it has been shown to be more effective than VKAs in cancer patients.[37] Of importance, subtherapeutic doses of LMWH commonly administered could be ineffective in stroke prevention among cancer patients with NVAF, given the lack of high quality data to support their use in this disease. Importantly, LMWH are even contraindicated in acute stroke in NVAF. On the other hand, ambulatory cancer patients who are stable and receive oral anticancer treatment along with oral anticoagulants, could continue VKA or NOAC after hospital discharge given the absence of bleeding prior to ACS. Most patients with breast or prostate cancer who receive anticancer therapy for a few years do not require a few months on heparins after ACS. During triple therapy in cancer patients, VKA should be titrated to obtain international normalized ratio (INR) of less than 2.5 or NOAC at reduced doses (**FIGURE 1C**). Appropriate patient selection for typically used triple therapy with an oral anticoagulant post ACS is of vital importance especially in cancer patients with good prognosis who should receive optimal management similar to that in noncancer individuals.

In some cases, triple antithrombotic therapy, involving ASA, clopidogrel, and LMWH/VKA, is not used because patients with ACS and cancer are commonly considered at high risk of bleeding. The duration of combination therapy with LMWH/VKA and clopidogrel varies depending on the cancer status of the patient and potential bleeding complications during therapy. The maximum duration is 12 months of dual antithrombotic therapy in cancer patients, followed by a monotherapy with oral anticoagulants or LMWH if accepted by a patient, mainly in VTE. LMWH is typically used for up to 6 weeks, followed by a VKA unless contraindicated due to the disease progression and poor prognosis. In everyday practice, LMWH is used on the long-term basis in patients with metastatic cancer in the case of high bleeding risk, frequent liver injury, and poor prognosis. Monitoring of renal function and blood cell count in cancer patients on LMWH is needed.

When deciding on a therapy with VKA, its limitations in patients with cancer should be considered.[8] It is much more difficult to achieve the therapeutic INR in these patients owing to the presence of cancer, use of chemotherapy and radiotherapy, possible surgical procedures, thrombocytopenia, or concomitant chronic kidney disease.[22,27] The INR also depends on the diet, progression of anorexia, vomiting, a decrease in albumin levels, difficult vascular access, and immobilization. Due to a higher risk of bleeding complications, including gastrointestinal bleeding, gastroprotection with proton pump inhibitors (PPIs), or H_2-receptor antagonists in case of intolerance, is recommended during combined antiplatelet and anticoagulant therapy.

In case of an urgent surgery for cancer in patients with ACS, clopidogrel should be stopped 5 days before the planned surgery, while ASA should be continued. After surgery, clopidogrel should be restarted, first at a loading dose of 300 mg, followed by a maintenance dose of 75 mg 24 to 72 hours after surgery provided that hemostasis is maintained.[12] In patients at high thrombotic risk, bridging therapy with intravenous (IV) glycoprotein (GP) IIb/IIIa-receptor inhibitors (tirofiban or eptifibatide) may be considered after discontinuation of clopidogrel. The bridging therapy should be started 3 days before the surgery and discontinued 4 to 6 hours before the procedure.[48] Such an approach is used within the first weeks since ACS, in particular within the first 28 days.

If an urgent life-saving surgery is required in patients on DAPT, the risk of excessive perioperative bleeding should be accepted, and platelet concentrate should be used if necessary. Prophylactic infusion of platelet concentrates in patients on DAPT is not recommended in this setting; only an extremely low platelet count requires such therapy prior to surgery.

Replacement of antiplatelet drugs with standard heparin or LMWH to reduce bleeding risk is not recommended because it has been reported that such a strategy is associated with a 10- to 12-fold higher risk of serious cardiovascular events and a 2-fold higher risk of bleeding.

Another issue is surgery in cancer patients with a history of ACS.[49] Preferably, such operations should be performed in the hospital where PCI could be performed on the 24/7 basis if needed. Of note, breast cancer surgery, thyroid gland operation, reconstructive, gynecological, and minor urological interventions are considered low-risk procedures.[12] On the other hand, stomach and major urological surgeries, as well as most transplantations, are moderate-risk procedures.

Key messages

- Patients with ACS and cancer are at high risk of stent thrombosis and bleeding that are often aggravated by the presence of thrombocytopenia.
- The choice of antiplatelet and anticoagulant drugs should be individualized depending on the stage of cancer and the need for surgery after ACS and/or PCI.
- Ticagrelor and prasugrel should not be used in cancer patients.
- In cancer patients who experience ACS, PCI with bare metal stents should be performed, and DAPT should be administered if the platelet count exceeds 30 000/μl.
- With third-generation DESs, the duration of DAPT can be safely shortened to 3 to 6 months and should be considered if the platelet count exceeds 30 000/μl and the patient has no indications for an urgent surgery or chemotherapy.
- Patients on previous anticoagulant therapy, either with a VKA or a NOAC, should be switched to LMWH if ACS occurs.

• In case of an urgent surgery for cancer in patients with ACS, clopidogrel should be stopped 5 days before the procedure, while ASA should be continued.
• After surgery, clopidogrel should be restarted, first at a loading dose of 300 mg, followed by a maintenance dose of 75 mg 24 to 72 hours after surgery provided that hemostasis is maintained.
• In patients at high thrombotic risk in whom clopidogrel is discontinued, bridging therapy with GP IIb/IIIa-receptor inhibitors (tirofiban or eptifibatide) administered intravenously should be considered. The therapy should be administered 3 days before the surgery and stopped 4 hours before the procedure.
• Replacement of antiplatelet drugs with standard heparin or LMWH is not recommended in cancer patients post ACS.

Bleeding events during antithrombotic therapy in cancer patients The occurrence of bleeding or a higher risk of bleeding at baseline in patients with ACS increases in-hospital mortality.[50,51] Importantly, the clinical consequences of bleedings vary depending on the type of bleeding. Clinically relevant, severe or life-threatening bleedings require modifications of management. The issue becomes even more complicated in cancer patients with ACS because recent major bleeding has so far been an exclusion criterion in all randomized clinical trials on ACS.[51] The question whether to continue, withdraw, or temporarily discontinue the antiplatelet or anticoagulant therapy (or both) in ACS patients who experienced major bleeding is challenging and an individualized approach is recommended. The risk of thrombosis should be balanced against the risk of bleeding, and the clinician should be prepared to substantially modify the decision depending on the clinical scenario.

If severe bleeding occurs in ACS patients on triple therapy, the first step is to decide on the use of an antidote and blood transfusion.[52,53] However, red blood cell transfusion increases the risk of thrombotic events and enhances inflammatory state, which is particularly important in patients with ACS and cancer.[22,54] Therefore, the decision to perform red blood cell transfusion should be guided by hemoglobin levels (<7 g/dl), but also by the presence of clinical symptoms of anemia. If a bleeding complication occurs in a patient on antiplatelet therapy, platelet transfusion should be considered. If the patient was on a VKA, then vitamin K, frozen plasma, prothrombin complex concentrate should be used. If the patient was on dabigatran, anticoagulant effects of this drug can be reversed by a humanized monoclonal antibody fragment, idarucizumab, that binds unbound and thrombin-bound dabigatran.[55-58] Idarucizumab is administered at 2 doses of 2.5 mg IV given no more than 15 minutes apart. In the REVERSE-AD study, 8.5% of dabigatran-treated patients who required reversal of its activity suffered from cancer, and no signal of lower efficacy or safety in this subgroup was noted.[58] Andexanet alfa, a reversal agent for rivaroxaban and apixaban administered intravenously, awaits approval by the Food and Drug Administration.[55] At present, life-threatening bleeding in patients treated with factor Xa inhibitors should be treated with 1500 to 2000 U of 4-factor prothrombin complex concentrate (like in patients receiving VKA). Recombinant activated factor VII (off-label indication) might be used if other agents are ineffective.[55,56]

Bleeding complications in patients with ACS and cancer are often an indication for a temporary or total withdrawal of antiplatelet and/or anticoagulant therapy, which may result in an increased risk of thrombotic complications. The risk of stent thrombosis increases after 5 days since withdrawal of the antiplatelet drugs in the first 30 days after PCI.[59] The final decision should be based on the severity of bleeding.[41,60,61,62] In the case of minor bleeding (mucocutaneous or subconjunctival bleeding, large hematomas), DAPT can be continued. If the patient was on oral anticoagulation, the therapy can be continued or stopped for 24 hours. In the case of clinically relevant nonmajor bleeding (nosebleed, hemoptysis, lower or upper gastrointestinal bleeding, bleeding from the urinary or genital tract that require medical contact), which do not require hospitalization, DAPT can be continued or its duration can be reduced. Oral anticoagulation should be stopped for 24 to 48 hours, and when restarted, a VKA with an INR of 2 to 2.5 is preferred.

Triple antithrombotic therapy can be replaced by dual therapy with clopidogrel plus VKA and simultaneous use of a PPI. In patients with severe bleeding (defined as a decrease in hemoglobin levels by more than 2 g/dl and a need for hospitalization), the cause of bleeding should be established. DAPT can be restarted after 3 to 7 days, and a shorter duration of this combination therapy should be considered. In patients on oral anticoagulation, its withdrawal for 5 to 7 days or the use of an antidote should be considered (in patients with mechanical heart valve or left ventricular assist device, unfractionated heparin [UFH] or LMWH should be used instead, for 4 to 8 days). The cause of bleeding should be established. Triple therapy should be switched to UFH/LMWH treatment (for the duration of diagnostic workup or active cancer treatment) plus clopidogrel. Then, clopidogrel alone should be used. In case of upper gastrointestinal bleeding, a PPI should be used (intravenous and then oral). Severe bleeding in all patients, including cancer patients, requires aggressive treatment including red blood cell and platelet transfusion, endoscopic and surgical procedures. Before restarting antiplatelet drug or drugs (3 to 7 days in stable clinical condition), the risk-to-benefit ratio of this therapy should be assessed. Most often, DAPT should be discontinued and clopidogrel alone should be used.

In individuals receiving oral anticoagulation, the therapy should be stopped for 7 days and the use of an antidote should be considered,

except in patients with mechanical heart valve or left ventricular assist device. UFH or LMWH should be introduced again, and VKA therapy (INR of 2 to 2.5) should be started after the completion of cancer treatment. Triple therapy should be switched to LMWH, followed by a VKA in combination with clopidogrel. If the bleeding occurs during the use of an oral anticoagulant and antiplatelet drug, LMWH alone, followed by a VKA alone, should be used after the bleeding is stopped. In the case of life-threatening bleeding, fluid infusion, blood product transfusion, endoscopic or surgical procedures, and discontinuation of DAPT are recommended. Before restarting the patient on clopidogrel alone (>5 days), the thrombotic risk should be balanced against the risk of bleeding. If the patient is on oral anticoagulation, the anticoagulant should be withdrawn, and an antidote should be used. Once the bleeding is stopped, UFH/LMWH can be used after 7 days, but the patient's clinical condition should be carefully monitored. As gastroprotective treatment, a PPI may be used (eg, pantoprazole, an IV bolus of 80 mg, followed by an IV infusion of 8 mg/h for 72 hours and then 20 to 40 mg orally twice daily). An alternative treatment (preferred in our center) is a bolus infusion of pantoprazole at a dose of 80 mg and then 40 mg IV every 12 hours for 72 hours, followed by oral administration of 20 to 40 mg twice daily.[63]

Key messages

- The occurrence of bleeding complications or the higher risk of bleeding at baseline in patients with ACS increases in-hospital mortality.
- The clinical consequences of bleedings are varied and depend on the type of bleeding.
- The decision whether to continue, temporarily discontinue, or withdraw the antiplatelet and/or anticoagulant therapy should be based on the severity of bleeding, careful risk-to-benefit assessment, and the clinical status.

Cardiac surgery in cancer patients with acute coronary surgery Some patients with ACS and cancer require urgent CABG. It is well known that CABG in the first 7 days after ACS is associated with high risk of mortality and MI. Therefore, the optimal time to perform CABG after ACS is 2 to 6 weeks in clinically stable patients.[15,64,65] For safety reasons, the platelet count at the time of CABG should exceed 50 000/µl.[29] A mini-invasive surgery should be considered to minimize bleeding in all cancer patients who require cardiac surgery. In patients who have undergone prior radiation therapy, computed tomography to evaluate the degree of mediastinal fibrosis should be performed and an angiographic assessment of the internal thoracic artery should be made before deciding on CABG.[66]

Key messages

- CABG should be scheduled 2 to 6 weeks after ACS in clinically stable patients with cancer.
- CABG should be performed in patients with a platelet count exceeding 50 000/µl.

Thrombocytopenia in cancer patients with acute coronary syndrome About 10% to 25% of cancer patients have thrombocytopenia, defined as a platelet count of less than 100 000/µl.[22,67-69] Thrombocytopenia induced by chemotherapy or treatment with heparin, fibrinolytic drugs, clopidogrel, or GP IIb/IIIa receptor inhibitors increases the risk of major bleeding and other cardiovascular events.[70] There is currently no convincing evidence for the minimum platelet count that would constitute an absolute contraindication to coronary angiography.[68] Therefore, it is assumed that if a platelet count is between 40 000/µl and 50 000/µl and there are no other thrombotic disorders, PCIs are safe.

It seems that in the context of antiplatelet therapy the platelet function is more important than the platelet count. Unfortunately, there are currently no tests that would allow a reliable assessment of platelet function in patients with cancer and thrombocytopenia or that would guide the decision making in terms of platelet transfusion or the duration of DAPT.[22] Thromboelastography might be used to assess blood coagulation if the platelet count is lower than 30 000/µl; however, the method is poorly standardized, not widely available, and data interpretation could be difficult. If the platelet count is above 10 000/µl, ASA therapy can be continued and prophylactic platelet transfusion should not be performed; discontinuation of ASA would worsen the prognosis of patients with ACS. If the platelet count is lower than 10 000/µl, platelet transfusion is recommended.[71] Prophylactic platelet transfusion should be considered if the platelet count is lower than 20 000/µl and the patient has high fever, leukocytosis, a sudden decrease in platelet count (heparin-induced thrombocytopenia should be expected if any heparin is used) or other coagulation disorders, or if the patient is on chemotherapy due to bladder, reproductive, or large intestine cancer, or melanoma. Combination of ASA with clopidogrel is allowed if the platelet count is higher than 30 000/µl.[72] The starting dose of UFH if the platelet count is 50 000/ml or lower should be 30 to 50 U/kg.[22] If the platelet count exceeds 50 000/µl, UFH at a dose of 50 to 70 U/kg or bilivarudin IV should be used. If the activated clotting time (ACT) is less than 250 seconds during the infusion of UFH, the heparin dose should be increased. ACT monitoring is crucial for patient safety in this clinical setting.

Key messages

- Thrombocytopenia induced by chemotherapy or treatment with heparin, thrombolytic drugs, clopidogrel, or GP IIb/IIIa-receptor blockers increases the risk of bleeding complications and other cardiovascular events.
- PCIs are safe in patients with a platelet count between 40 000 and 50 000/µl and no thrombotic disorders.
- If the platelet count is higher than 10 000/µl, ASA can be continued and prophylactic platelet transfusion should not be used in patients with

ACS, while at the platelet count below 10 000/μl, platelet transfusion should be performed.

- Prophylactic platelet transfusion can be performed if the platelet count is below 20 000/μl and the patient has high fever, leukocytosis, a sudden decrease in the platelet count or other coagulation disorders, or if the patient is on chemotherapy due to bladder, ovarian, colon cancer, or melanoma.
- Combination of ASA with clopidogrel is allowed if the platelet count exceeds 30 000/μl given the absence of active bleeding.

Conclusions The current limited evidence indicates that each patient with cancer, at any stage of its diagnosis and treatment, who develops ACS should be managed according to the guidelines recommended for noncancer patients, including invasive strategy whenever possible. In each case, the risk-to-benefit ratio of the recommended treatment should be carefully assessed before making the therapeutic decision and regularly reassessed. Chemotherapy and surgery as potent prothrombotic factors that disturb therapy post ACS require specialist consults, particularly within the first weeks following acute myocardial ischemia. Given increased bleeding risk in cancer patients, antithrombotic treatment following ACS should be carefully monitored and not prolonged above the recommended duration.

Since prognosis has considerably improved in many cancer patients in the last decade, optimal therapy of ACS may increase the life expectancy and reduce the risk of adverse coronary events after ACS in this high-risk population.

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