ORAL PRESENTATIONS

S1 – ESC CARDIO-ONCOLOGY GUIDELINES – A CARDIOLOGIST'S PERSPECTIVE

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Over the past two decades, survival rates for patients with malignant diseases have increased due to advancements in chemotherapy protocols, the introduction of targeted biological therapies, improved surgery, radiotherapy, and novel interventional radiology techniques. However, this improved survival often comes at the cost of damage to other organs, including the cardiovascular (CV) system, and today, CV diseases are the second leading cause of long-term morbidity and mortality among cancer patients.

Initially, cardiotoxicity was almost exclusively associated with the development of irreversible systolic dysfunction of the left ventricle (LV) leading to symptomatic heart failure (HF) as a result of anthracycline therapy. With the advent of biological anti-HER therapy, it was discovered that it could cause largely reversible damage to cardiac function. On the other hand, cardiotoxicity cannot be linked solely to LV systolic dysfunction, as cancer therapy can cause a range of CV diseases such as new or worsened hypertension, vasospastic and/or thrombotic myocardial ischemia, worsening atherosclerosis, rhythm and conduction disorders, and myocarditis.

Given all of the above, it was clear that there was a need for the development of guidelines in cardio-oncology. Therefore, after issuing a *Position Paper* in 2016, the European Society of Cardiology proceeded to develop comprehensive guidelines that were published in 2022 . The guidelines took into account all aspects of cardio-oncology, so instead of the old term cardiotoxicity, the new term cancer therapy-related cardiovascular toxicity (CTR-CVT) is used. They also introduce new standards for defining CTR-CVT, and protocols for monitoring patients during and after cancer treatment, as well as diagnosing and treating CTR-CVT. In addition to the six basic pathophysiological mechanisms for the development of CTR-CVT, exceptions of cardiovascular toxicity that can be caused by individual cancer drugs are listed. The emphasis is on prevention, or rather risk assessment for the development of cardiovascular toxicity before the administration of cancer therapy, thereby minimizing unnecessary interruptions of cancer treatment. It must always be kept in mind that any interruption or change in cancer treatment can significantly alter the outcomes of cancer treatment and the prognosis of the disease. The approach to CTR-CVT must be multidisciplinary, and the development of cardio-oncology subspecialists with broad knowledge of cardiology, oncology, and hematology is recommended. The biggest drawback of the guidelines is that most of the recommendations are based on expert opinion or registries (level of evidence C). It is simply impossible to conduct enough randomized clinical trials.

With an increasing number of patients being treated with chemotherapy and biological drugs, the incidence of cardiovascular toxicity is continuously rising. The scope of the problem is even greater because some patients must take a combination of multiple cardiotoxic drugs. Cancer patients at increased risk of developing cardiovascular toxicity require a multidisciplinary approach and regular cardiological follow-up to identify and treat CV side effects in a timely manner. In this way, improved clinical outcomes and quality of life are achieved, and if possible, optimal continuation of specific cancer treatment.

Keywords: cardio-oncology, cancer therapy-related cardiovascular toxicity, ESC gudelines

S2 – ESC GUIDELINES ON CARDIO-ONCOLOGY: OVERVIEW BY MEDICAL ONCOLOGIST

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The guidelines from the European Society of Cardiology (ESC) on cardio-oncology highlight the relation between cardiovascular diseases (CVD) and cancer, which remain the leading causes of death in developed countries despite advancements in prevention and treatment. There is a bidirectional relationship between CVD and cancer, influenced by risk factors such as hypertension, diabetes, obesity, smoking, diet, and physical inactivity. Common pathophysiological mechanisms include chronic inflammation, oxidative stress, metabolic and hormonal dysregulation, and cellular aging.

The growing cancer patient population is projected to reach approximately 32.6 million by 2045, up from about 20 million currently. New therapeutic options in oncology are extending life expectancy, particularly among those over 65 years old; however, these treatments can be cardiotoxic and may adversely affect cardiac health. Studies indicate that cancer survivors face a higher risk of cardiovascular diseases (CVD) with worse outcomes compared to non-cancer patients. Until 2022, there was an unmet need within the oncology and cardiology communities to define clearly cardiotoxicity associated with cancer treatments and to establish monitoring and preventive strategies.

European Society of Cardiology (ESC) in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS) released comprehensive guidelines in 2022 that included 272 new recommendations addressing different cardiovascular disease entities resulting from oncological therapy toxicity. The core concept of these guidelines is to evaluate cardiovascular risk as a dynamic variable before initiating cancer treatment, modify this risk through prevention strategies, and monitor it according to established algorithms for each potentially cardiotoxic drug group. This includes agents like anthracyclines, anti-HER2 therapies, anti-angiogenic treatments, CDK4/6 inhibitors, fluoropyrimidines, and immunotherapy.

Understanding cardiovascular risk factors and lifestyle is crucial alongside clinical assessments and complementary tests such as cardiac biomarkers (troponin, NT-pro BNP), ECGs, lipid profiles, and transthoracic echocardiography (TTE).

Patients are stratified into low, moderate, high, and very high-risk categories. Those at low or moderate risk can begin cancer treatment following monitoring algorithms, while high-risk patients require initial collaboration between oncology and cardiology to balance treatment risks and benefits while considering patient preferences. Standardized tools for assessing cardiovascular risk in oncology patients are available on the HFA-ICOS digital platform.

This patient-individualized approach aims to enhance quality of life while reducing the burden of cardiac side effects. Continuous cardiac monitoring is essential for oncology patients throughout their surveillance, especially those at high risk for cardiovascular events, since cardiac side effects may arise later after cancer treatment has concluded. Collaboration between cardiologists and oncologists is vital

when cardiotoxicity develops during cancer treatment to improve heart health and adjust oncological therapy options.

The complexity of oncological treatments necessitates a multidisciplinary approach with intensive cooperation from the cardiology community and individualized strategies for each patient that include cardioprotective measures and lifestyle modifications.

The ESC guidelines from 2022 address unmet needs in the cardio-oncology community significantly impacting care and improving outcomes for cancer patients.

Keywords: cancer, cardiovascular diseases (CVD), cardio-oncology, cardiotoxicity

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S3 – VASCULAR TOXICITY

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Cancer therapy has undergone significant advancements, improving survival rates across a broad range of cancers. However, the spectrum of therapy-related toxicities has changed, particularly cardiovascular toxic effects. While cardiac toxicities remain a primary concern, vascular toxicities have emerged as the second most commonly reported cardiovascular side effects of cancer therapies, now receiving comparable attention. Vascular toxicities are also the second leading cause of death among cancer patients undergoing outpatient treatment. These toxicities can manifest as acute vasospasm, acute thrombosis, or accelerated atherosclerosis, with varying mechanisms and clinical significance. Historically, venous thromboembolism (VTE) was the primary vascular toxicity of interest, but recent therapies have highlighted arterial toxicities. Acute vasospasm is commonly linked to therapies such as 5-FU, cisplatin, paclitaxel, and VEGF inhibitors. Management typically involves vasodilators like nitrates and calcium-channel blockers, with specific strategies tailored to microvascular dysfunction. While pre-treatment coverage with vasodilators may help prevent vasospasm, it is not universally effective, suggesting additional underlying mechanisms. In cases of re-exposure to 5-FU after cardiotoxicity, close monitoring through electrocardiograms and echocardiography is crucial to detect ischemic changes and arrhythmias. Acute thrombosis, often associated with cisplatin and VEGF inhibitors, appears to result from endothelial injury, blood flow disruptions, and a prothrombotic state. These therapies can induce endothelial damage while reducing repair capacity, contributing to arterial thrombosis. Risk factors such as pre-existing cardiovascular disease, vessel stenoses, and altered blood flow dynamics play a critical role in determining individual susceptibility. Additionally, the interplay between cancer cells, platelets, and coagulation pathways further exacerbates the prothrombotic environment, particularly in advanced or aggressive cancers like pancreatic or lung cancers. VTE continues to be a significant complication in cancer patients, with risks peaking around the time of diagnosis and remaining elevated in metastatic disease. While tools like the Khorana score help predict VTE risk, balancing the benefits of prophylactic anticoagulation against bleeding risks remains challenging. Studies on anticoagulants such as edoxaban, apixaban and rivaroxaban show promise, though they also reveal increased bleeding risks. Pulmonary hypertension has also been observed with therapies like dasatinib and bleomycin, linked to endothelial injury and structural pulmonary vascular changes. Although screening is not routine, patients experiencing dyspnea or right heart failure symptoms should undergo echocardiography and further evaluation. Despite growing awareness, many questions remain unanswered, including how to identify at-risk patients, define optimal screening protocols, and develop strategies for primary prevention of arterial toxicities. The lack of standardized guidelines complicates efforts to manage vascular toxicities effectively. Research is needed to establish precise estimates of incidence, risk factors, and preventive measures tailored to specific therapies and patient populations. Greater understanding of the mechanisms underlying vascular toxicities will enable the development of personalized strategies, ensuring that cancer treatments can continue without compromising cardiovascular health. Insights into the pathophysiology of vascular damage may also provide broader implications for managing cancer therapy-related cardiotoxicities. Future efforts should prioritize well-designed studies and registries to address these critical gaps and improve outcomes for cancer patients.

Keywords: cancer therapy; cardiovascular toxicity; arterial thrombosis; venous thromboembolism; pulmonary hypertension

S4 – ARTERIAL HYPERTENSION ASSOCIATED WITH ONCOLOGICAL TREATMENT

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According to the assessment of the World Health Organization, hypertension is the leading risk factor for overall mortality. In the study *Epidemiology of arterial hypertension in Croatia* (EHUH), the frequency of hypertension was 37.5% with significant regional differences. Furthermore, almost 2/3 of all deaths in Croatia annually are caused by cardiovascular (CV) or oncological diseases. Based on the above, it is clear that the incidence of CV comorbidities, especially hypertension, is high in the population of oncology patients.

Possible clinical scenarios; a) patients with previously known hypertension + malignant disease – stable, b) patients with previously known hypertension + malignant disease – destabilization of regulation during active treatment of malignant tumors, c) patients with new-onset hypertension associated with oncological treatment.

The guidelines of the European Society of Cardiology for the treatment of hypertension (2024) and cardio-oncology (2022) state that the frequency of hypertension related to certain therapeutic protocols for the treatment of malignant tumors is significant. The development of hypertension during active oncological treatment is especially evident in patients treated with vascular endothelial growth factor inhibitors (VGEFi – 80–90%) and tyrosine kinase inhibitors, also with adjuvant therapies (corticosteroids, antiandrogen hormone therapy, etc.). Hypertension caused by anticancer drugs is often dose limiting and reversible after therapy interruption or discontinuation.

The systolic pressure values when hypertension must be treated regardless of the stage of the oncological disease is 160 mm Hg (diastolic 100 mm Hg), and most often already when the systolic pressure is > 140 mm Hg.

During every examination and prescription of oncology therapy, it would be ideal to evaluate the patient's condition, including blood pressure measurement, and to encourage the patient to measure it at home. The recommended values for optimal blood pressure regulation are < 140/90, and if the patient tolerates it, < 130/80 mm Hg. The first line of treatment is angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) and dihydropyridine calcium channel blockers (CCBs).

A dynamic and individualized approach is necessary in these groups of patients; antihypertensive therapy should be optimized (doses), ev. temporarily suspend and modify depending on the current condition of the patient (anemia, dehydration, eGFR, potassium level, tachycardia, etc.)

Managing these complex patients requires multidisciplinary healthcare involving oncologists, cardiologists, nephrologists, etc. Evidence-based clinical trials specifically addressing patients who develop hypertension due to oncological treatment are lacking and are necessary to assess the outcome and quality of life of this subgroup of patients.

Keywords: arterial hypertension; oncology; therapy

S5 – CARDIOTOXICITY OF CANCER CHEMOTHERAPY IN TREATMENT OF SOLID TUMOURS

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Cardiovascular diseases (CVD) and cancer are two leading causes of death worldwide with an increasingly recognised interrelationship. Both share numerous overlapping risk factors and pathophysiologic mechanisms including smoking, obesity, metabolic syndrome, hypertension, diabetes, and inflammation. This suggests a bidirectional relationship where each condition can potentially influence the onset and progression of the other.

Cardiovascular complications involve a range of issues beyond myocardial dysfunction and heart failure, such as valvular disease, pulmonary hypertension, pericardial complications, coronary artery disease, arrhythmias, hypertension, thromboembolic events, peripheral vascular disease, and stroke. Cardiotoxic effects can arise either shortly after treatment or later in the follow up period, and they may be transient or irreversible. Assessing the risk of cancer patients before starting therapy is essential to identify those at high risk for cardiotoxicity. The main patient-related risk factors appear to be the pre-existence of cardiac risk factors such as diabetes, hypertension, dyslipidemia, smoking, increased body weight as well as previous history of CVD.

Anthracyclines are cytotoxic agents that have been associated with several cardiovascular toxicities, including left ventricular systolic dysfunction and heart failure which is the leading cause of death among cancer patients who develop symptoms. The exact mechanism of anthracycline-induced cardiotoxicity remains unclear, but it is likely to be multifactorial. Regardless of the type of anthracycline, the cumulative exposure is a consistent risk factor for cardiotoxicity, with the risk significantly rising once the upper lifetime dose limit for each agent is exceeded.

Fluorouracil is the second most common chemotherapeutic agent associated with cardiotoxicity, after anthracyclines. The underlying mechanism and optimal management is not well defined. The most common clinical manifestation is angina but myocardial infarction, arrhythmias, heart failure, acute pulmonary edema, cardiac arrest and pericarditis were reported. Repeated administration of flourouracil in patients with undiagnosed cardiotoxicity may lead to potentially avoidable permanent damage and even death.

Cisplatin is an alkylating agent with a wide spectrum of antineoplastic activity. Cardiotoxicity is a relatively uncommon complication but atrial fibrillation, supraventricular tachycardia, intra-ventricular left block and myocardial infarction have been reported. These events don't seem to be dose-dependent and can occur anytime, from hours after the first infusion up to 18 months after therapy ends.

Conduction abnormalities, cardiovascular collapse and angina have been reported in patients treated with docetaxel, and sinus bradycardia is the most common cardiotoxic manifestation of paclitaxel, a plant derived chemotherapeutic. Like docetaxel, paclitaxel appears to potentiate the cardiotoxicity of antracyclines.

Bleomycin, an antitumor antibiotic has been associated with several different forms of cardiotoxicity such as coronary artery disease, myocardial ischemia, and myocardial infarction. Topoisomerase inhibitor

etoposid has been linked to the development of myocardial infarction and vasospastic angina in several case reports.

Frequent monitoring during and after treatment is necessary to promptly address any cardiovascular effect. Close collaboration between oncologists, cardiologists, hameatologists and other health care professionals through a multidisciplinary team will ensure optimal care for cancer patients with cardiac and non-cardiac toxicities. Cardiologist should have a thorough understanding of the prognosis, treatment plan, benefits and goals of the proposed treatment. Conversely, oncologists and haematologists should be informed of the patient's cardiovascular risk factors.

Keywords: cardiotoxicity, cancer, chemotherapy

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S6 – CARDIAC DYSFUNCTION RELATED TO HER2-TARGETED THERAPIES

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Human epidermal growth factor receptor 2 (HER2) is a member of a family of four receptor tyrosine kinases. Upon activation, HER proteins undergo homodimerization or heterodimerization, initiating complex cellular signaling cascades, including the PI3K/AKT and RAS/MAPK (ERK) pathways, which govern cell proliferation, survival, and tumor cell metastasis(1). The HER2-signaling pathway is crucial for cardiomyocyte survival and adaptation to diverse stresses. Anti-HER2 agents affect various cell types in the myocardium that express HER2 receptors, hence triggering pathogenic pathways. These include interstitial fibrosis, cellular dysfunction, apoptosis, microvascular damage, oxidative stress, and inflammation(2). All of these processes contribute to cardiac remodeling and the development of heart failure with decreased or retained ejection fraction(3,4).

HER2-targeted drugs include monoclonal antibodies (trastuzumab, pertuzumab, and margetuximab), antibody-drug conjugates (trastuzumab emtansine -T-DM1 and trastuzumab deruxtecan T-DXd) and tyrosine kinase inhibitors (lapatinib, neratinib, and tucatinib). Treatments that target HER2 receptor have considerably improved clinical outcomes for patients with early and metastatic HER2-positive breast cancer (BC). Trastuzumab, an anti-HER2 medication, can also be used in patients with HER2-overexpressing metastatic gastric adenocarcinomas in combination with platinum-based chemotherapy, capecitabine, or 5-fluorouracil (5-FU).

The potential for cardiotoxicity with HER2-targeted drugs, which clinically presents as heart failure (2.5%-4%) or, more typically, asymptomatic declines in left ventricular ejection fraction (LVEF) up to 20%, has challenged clinicians to determine an appropriate balance between effective cancer therapy and potential cardiotoxicity risk(5).

The extent most commonly used cardiotoxicity definition in clinical practice and clinical trials is LVEF decrease >10% to below 50%, with or without symptoms of CHF. Following the 2022 ESC guidelines, the cardiotoxicity definition is precise and ambiguous. Cancer therapy-related cardiac dysfunction (CTRCD) may present as symptomatic – heart failure (HR) or asymptomatic. LV function surveillance based on LVEF and global longitudinal strain (GLS) is suggested before and every three months throughout HER2-targeted treatment(6).

As research on the topic of cardio-oncology is growing, cardiotoxicity diagnosis is no longer limited to functional imaging of the heart, and the use of cardiac serum markers as natriuretic peptides (NT) and cardiac troponin (cTn) is becoming more widespread in clinical practice, as well as implemented in ESC Guidelines(6).

Antioxidants, ACE inhibitors, angiotensin II receptor blockers, β-blockers, and statins may have a cardioprotective effect when used with HER2-targeting drugs(7).

Oncologists generally consider the potential risk of cardiotoxicity associated with cancer therapies, including anthracyclines and HER2-targeted agents, in their treatment recommendations. However, with the implementation of ESC Guidelines on cardio-oncology and enhanced collaboration with cardiologists, there has been an emphasis on the impact of an individual's pre-existing cardiovascular risk factors or conditions.

Keywords: cardiotoxicity, cardiac dysfunction, HER2-targeted therapies

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S7 – CARDIOTOXICITY OF NOVEL HER2 TARGETED AGENTS IN TREATMENT OF BREAST CANCER

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HER2-positive breast cancer, which accounts for about 15–20% of all breast tumors, is highly aggressive neoplasm with poor prognosis. From the clinical point of view, HER2 typification is an example of breast cancer precision oncology and a successful therapeutic target. The approval of trastuzumab for use in metastatic breast cancer marked a breakthrough in the understanding of the biology of the disease. However, like most cancer therapies, the disease finds a way to advance despite the treatments developed to eradicate it.

Many therapies are being developed to target the mechanisms of resistance in patients with HER2-positive, trastuzumab-resistant breast cancer. Treatment options for HER2 positive breast cancer patients have increased steadily in recent years, and with a myriad of novel approaches under preclinical investigation or clinical validation. It is expected that in a few years, the conventional anti-HER2 antibodies and tyrosin kinase inhibitors (TKIs) will be replaced by more effective and innovative therapies, such as antibody-drug conjugates (ADCs), bispecific antibodies, CAR-T cells, nanotherapy, and immunotherapy. However, it is also anticipated that new toxicities may also arise form these novel agents.

Novel agents that have already entered the clinical practice are tucatinib (oral, reversible inhibitor of HER2) and antibody-drug conjugates (ADCs), such as trastuzumab emtansine (T-DM1) and trastuzumab deruxtecan (T-Dxd). A large list of other ADCs, including trastuzumab duocarmazine, are under clinical evaluation. Techniques that use the HER2 molecule as the target for recognition by immune cells, such as HER2 vaccines, bispecific antibodies, and HER2-targeted chimeric antigen receptor T-cell therapy (CAR-T), are very promising, but none of them have been clinically approved so far.

Little is known about potential long-term cardiovascular toxicities of novel HER2-targeted agents. Given the trastuzumab component of antibody-drug conjugates, they carry a warning for left ventricular dysfunction, with a recommendation for LVEF assessments at baseline and at regular intervals during treatment. Additional recommendations regarding continuation, discontinuation, or holding of therapy are provided based on the degree or severity of LVEF change. Despite containing trastuzumab, thus far the reported rates of cardiotoxicity associated with TDxd have been low. The low cardiotoxicity rates seen with TDxd are similar when compared to another antibody-drug conjugate, T-DM1. In clinical trials with tucatinib the incidence of all-grade, as well as grade > 3 treatment-related adverse events, was similar between arms, specifically in regards to LVEF reduction and QTc prolongation.

Cardiac monitoring strategy is recommended for patients treated with HER2-targeted therapies. incorporating patient's baseline cardiovascular risk, cardiac symptoms, cardiac imaging, and biomarkers

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S8 – CARDIOVASCULAR TOXICITY INDUCED BY VASCULAR ENDOTHELIAL GROWTH FACTOR INHIBITORS

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Angiogenesis inhibitors targeting the vascular endothelial growth factor (VEGF) signaling pathway have revolutionized cancer therapy, particularly for renal cell carcinoma and colorectal cancer. Despite their clinical success, these inhibitors, including bevacizumab and tyrosine kinase inhibitors (TKIs) like sorafenib and sunitinib, have been associated with specific toxicity profiles. Cardiotoxicity is a significant concern when using VEGF inhibitors like bevacizumab, sorafenib, and sunitinib, which are commonly used in cancer therapy. These drugs, while effective as anticancer treatment, have been linked to various cardiovascular issues, including heart failure, hypertension, and arterial thromboembolism. The underlying mechanisms mainly inhibit VEGF signaling, crucial for maintaining vascular health and myocardial perfusion.

The clinical manifestations of cardiotoxicity can range from heart failure, observed in 2-4% of patients on bevacizumab and 3-8% on VEGF-TKIs, to arterial thromboembolism and cardiac ischemia. Managing these risks involves aggressive blood pressure control and regular cardiac monitoring, including echocardiography and biomarkers like troponin. A multidisciplinary approach involving a cardio-oncology team is essential for optimizing cancer treatment while minimizing cardiovascular risks. Understanding these mechanisms and risk factors is crucial for improving patient outcomes and ensuring that the benefits of VEGF inhibitor therapy outweigh the potential cardiovascular risks.

A review of cardiac adverse events conducted on patients with metastatic renal cell carcinoma treated with sunitinib showed that 9.7% of patients experienced grade 3 hypertension, with most cases developing after the third cycle of sunitinib. Additionally, 18.9% of patients developed some degree of cardiac abnormality, with 6.9% experiencing grade 3 LVEF dysfunction and/or congestive heart failure (CHF). Significant predictors of CHF included a history of hypertension and coronary heart disease, as well as prior treatment with an angiotensin-converting enzyme inhibitor.

Several risk factors contribute to the cardiotoxicity associated with VEGF inhibitors. Hypertension is almost universally observed in patients undergoing this treatment, with severe hypertension occurring in about 7.4% of cases. Coronary artery disease (CAD) is another significant predictor, with patients having a history of CAD being at a higher risk of developing heart failure. Preexisting conditions like diabetes and obstructive sleep apnea also increase the risk due to their impact on the vascular reserve.

Furthermore, TKIs are associated with increased circulating endothelin-1 (ET-1) levels, a potent vasoconstrictor. ET-1 exerts its vasoconstrictive effects through interactions with ETA and ETB receptors. Vascular rarefaction, characterized by reduced capillary density, contributes to hypertension. Microvessels, including arterioles and capillaries, play a crucial role in peripheral vascular resistance, and their disruption can lead to elevated blood pressure. Several studies have shown that functional and structural vascular rarefaction are linked to VEGF inhibitors. Additionally, reduced sodium excretion by the kidneys can result in volume-dependent hypertension.

However, many questions remain to be answered, e.g., when antiangiogenic therapy should be initiated after an acute coronary incident and how the risk can be assessed and quantified, i.e., when such treatment should be avoided entirely.

Keywords: angiogenesis inhibitors; cancer therapy; VEGF signaling pathway; cardiotoxicity; hypertension; coronary artery disease

S9 – IMUNOTHERAPY AND CDK4/6I IN CONTEXT OF HEART HEALTH

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CDK4/6 inhibitors (ribociclib, abemaciclib and palbociclib) are drugs that have made a significant breakthrough in the treatment of hormone receptor-positive, HER2-negative breast cancer, both in the metastatic phase and in the treatment of early-stage breast cancer. These drugs belong to a class that targets the cell cycle by blocking the activity of cyclin-dependent kinases 4 and 6. The role of these kinases is crucial for the transition of cells from the G1 to the S phase of the cell cycle, a process that allows cells to continue dividing. In tumor cells, this process is often disrupted, leading to uncontrolled cell division.

Their use is often connected to hematologic side effects, leukopenia and neutropenia with all ciclibs. They are also often connected to side effects such as diarrhea, fatigue or hepatotoxicity, but they differ in the extent to which they cause them. It is known that ribociclib relates to extension of QTC interval, in medical literature it is mentioned in up to 3% of the cases. For ribociclib, special recommendations apply for monitoring electrocardiograms and electrolytes in all patients to prevent serious arrhythmia in a timely manner. In an analysis of reports from the FDA Adverse Event Reporting System (FAERS), hypertension and heart failure were highlighted as the most commonly reported cardiovascular side effects, and all ciclibs were associated with serious cardiac events.

To conclude, cardiotoxicity of ciclibs is among the rarer side effects associated with them as a class of drugs. To reduce the risk of cardiotoxicity, careful patient selection based on cardiovascular status prior to the start of treatment is required, along with close monitoring of patients during therapy.

Immune checkpoint inhibitors, such as CTLA-4, PD-1, and PD-L1 inhibitors, work by blocking specific molecules of the immune system that normally help the immune system avoid uncontrolled, excessive reactions that could lead to damage of healthy organs. Cancer cells exploit these checkpoints to evade recognition and destruction by the immune system. By blocking the interaction between molecules like PD-1, PD-L1, or CTLA-4 and their ligands, a *release of the brakes* on the immune system occurs, allowing T lymphocytes to recognize and destroy cancer cells. These inhibitors are used in the treatment of various types of cancer, often in combination with other oncological drugs, and are indicated for the treatment of both early and metastatic stages of cancer. In addition to being administered alongside other oncological drugs, there are protocols in which two checkpoint inhibitors are given simultaneously. Their use is associated with numerous side effects, as they can cause inflammatory reactions in all organ systems. Cardiotoxicity associated with their use is less common compared to other side effects, but due to the high risk of mortality, it remains a particularly significant side effect. Among the cardiotoxic side effects, myocarditis is most frequently mentioned in the literature, occurring in up to 1.14% of cases. According to the 2022 Guidelines of the European Society of Cardiology, it is necessary to assess cardiovascular status before initiating their use (electrocardiogram, troponin, and NTproBNP for all patients, and for high-risk patients, an echocardiogram should also be performed). The risk of cardiovascular events is highest in the first three months, so careful monitoring is particularly important during this period. Suspecting an adverse cardiovascular event requires a prompt response from the oncologist, discontinuation of ICI therapy, and involvement of a cardiologist or a multidisciplinary team for further diagnosis and treatment.

Keywords: CDK4/6 inhibitors, Immune checkpoint inhibitors, cardiotoxicity

S10 – LIFESTYLE: A FACTOR IN IMPROVING CARDIO-VASCULAR HEALTH

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Cardiovascular diseases (CVDs) remain a global health challenge, with lifestyle modifications emerging as a critical intervention strategy. This lecture explores the profound impact of lifestyle factors on cardiovascular health, highlighting key mechanisms for risk reduction. Research demonstrates that targeted lifestyle interventions can significantly mitigate cardiovascular risk through multiple pathways, including blood pressure regulation, lipid profile improvement, and metabolic health optimization.

Cardiovascular health and longevity are critically influenced by comprehensive lifestyle interventions targeting physiological mechanisms underlying mortality risk. This research synthesizes evidence demonstrating the profound impact of strategic health optimization approaches, with particular emphasis on body composition, muscle mass, and fitness parameters.

Key intervention strategies:

- Comprehensive physical activity protocols
- Resistance training for muscle mass preservation
- Metabolic health optimization
- Nutritional modulation
- Stress management techniques

Clinical trials, including the Diabetes Prevention Program and DASH-Sodium Trial, provide robust evidence supporting lifestyle modifications' effectiveness in reducing cardiovascular risk factors. Notably, individuals following comprehensive lifestyle practices can achieve up to 80% reduction in cardiovascular disease risk.

Emerging research demonstrates that integrated lifestyle approaches can substantially mitigate cardiovascular risk, targeting multiple physiological pathways simultaneously. The intervention model emphasizes proactive health management, moving beyond traditional reactive medical approaches.

Muscle strength and body composition emerge as pivotal indicators of longevity, with potential to modulate chronic disease risk and overall life expectancy. Strategic interventions focusing on these parameters offer promising prospects for comprehensive health optimization.

Critical findings demonstrate:

- 15-30% decrease in cardiovascular-related mortality through dietary modifications
- Inverse relationship between muscular strength and all-cause mortality
- Significant CVD risk reduction through strategic nutritional interventions

The lecture explores and explains how factors of modern lifestyle – sedentary lifestyle, food environment full of ultra-processed foods which, among other factors, fundamentally disrupt human metabolic health. By examining the intricate relationships between obesity, dietary patterns and chronic low-grade inflammation, it will be shown how modern life accelerates the development of various metabolic disorders.

The presentation will critically analyze the mechanisms underlying metabolic dysfunction caused by a dominantly modern lifestyle, emphasizing the importance and effectiveness of prevention strategies and multidisciplinary interventions, including targeted, scientifically proven supplementation, to mitigate the

risk of developing numerous chronic non-communicable diseases that are rapidly increasing in the current century.

Nowadays, need is to emphasize a holistic approach to cardiovascular health, targeting multiple risk factors simultaneously and providing long-term benefits with help but beyond pharmaceutical interventions.

Keywords: cardiovascular health; longevity; muscle mass; mortality reduction; nutritional interventions

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S11 – PERICARDIAL EFFUSIONS IN CANCER PATIENTS

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Pericardial involvement in cancer patients is not uncommon, occurring with an incidence ranging from 2% to 15-30%, and it is associated with a poorer prognosis. This involvement can manifest as acute or constrictive pericarditis, pericardial effusion, or other conditions such as benign pericardial tumors. It is most frequently linked to tumors within the chest cavity, such as lung cancer, breast cancer, B-cell lymphoma, and melanoma. The spectrum of pericardial involvement ranges from asymptomatic effusion to cardiac tamponade, and while pericardial effusion can occasionally be the first sign of occult malignancy, it is more commonly observed in the later stages of known metastatic disease. Common characteristics of pericardial effusion in cancer patients include recurrence, large volumes of fluid—often hemorrhagic—progression to cardiac tamponade in approximately 30% of cases, and the absence of acute-phase reactants. Pericardial effusion can result from direct invasion of the pericardium, lymphatic or hematogenous spread of cancer, or obstruction of lymphatic flow in the mediastinum due to infiltration of mediastinal lymph nodes. When cancer cells infiltrate the pericardium via small vessels and capillaries, they promote the transudation of extracellular fluid into the pericardial space and stimulate inflammation. In immunocompromised cancer patients, additional causes of pericardial effusion include infections and primary pericardial tumors. Furthermore, certain cancer treatments—such as chemotherapy, radiotherapy, and immunotherapy with immune checkpoint inhibitors (ICIs)—can also lead to pericardial involvement. However, pericardial effusion is less frequently required to be treated with pericardiocentesis in these cases, with an incidence ranging from 0.2% for cytostatic drugs to 0.3% for ICIs. Echocardiography is the standard diagnostic tool, allowing for the assessment of effusion size and signs of cardiac tamponade. However, CT and MRI of the heart are complementary methods, primarily used to evaluate pericardial thickening, calcifications, or signs of constrictive pericarditis. Pericardiocentesis is essential for hemodynamically unstable patients and remains the standard of care. For patients with large pericardial effusions but who are stable, conservative management is typically preferred. The mediastinal connective tissue has low resistance to the expansion of the parietal pericardium, so when fluid accumulates gradually, large amounts may be contained. In contrast, if fluid accumulates rapidly, it can lead to cardiac tamponade by impairing the filling of cardiac chambers. The goal of pericardiocentesis is to alleviate symptoms, improve the patient's quality of life, prevent recurrence, and allow for the continuation of cancer treatment. Cytological evaluation remains the gold standard for diagnosing neoplastic pericardial effusion, with a sensitivity of 71% to 92.1% and nearly 100% specificity, as reported in various studies. Recurrence of pericardial effusion is common in cancer patients (approximately 38%). Approaches to reduce recurrence include the creation of a pericardial window via percutaneous balloon pericardiotomy or surgery, or the installation of intrapericardial cytostatics, though there is no consensus on the optimal method. Decisions should be made by a cardio-oncology team based on the patient's specific characteristics and the available resources at the healthcare facility.

Keywords: pericardial effusion; cardiac tamponade; cancer patients; pericardiocentesis

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S12 – CARDIOTOXICITY ASSOCIATED WITH DUAL HER2 BLOCKADE IN NEOADJUVANT TREATMENT OF HER2-POSITIVE BREAST CANCER: A CASE SERIES

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Introduction: The introduction of targeted therapies, such as trastuzumab and pertuzumab, has greatly enhanced the outcomes for patients with HER2-positive breast cancer. These monoclonal antibodies, utilized in both neoadjuvant and adjuvant settings, have shown exceptional effectiveness in shrinking tumors, reducing recurrence rates, and improving overall survival. However, their use is associated with potential risks. Among the most concerning adverse effects is cardiotoxicity, which can influence further treatment decisions, delay surgery, and require modifications in cancer therapy. In this report, we present a series of seven female patients who experienced significant cardiotoxicity during or after treatment with these agents.

Case Series: This report describes seven patients diagnosed with HER2-positive breast cancer who developed cardiotoxicity during neoadjuvant therapy. They received treatment according to a regimen that included doxorubicin/cyclophosphamide, paclitaxel, and dual HER2 blockade with trastuzumab and pertuzumab. The patients had a mean age of 59.3 years. Cardiotoxicity occurred after the completion of the full treatment protocol in only two patients, whereas the remaining five experienced it before completing their planned therapy. On average, cardiotoxicity developed 176 days after the initiation of chemotherapy, and the time from cardiotoxicity onset to surgery was approximately 50 days. Baseline left ventricular ejection fraction (LVEF) averaged 61%, which declined to 23% at the time of cardiotoxicity diagnosis. After the implementation of optimal heart failure management, LVEF improved to an average of 43%.

Conclusion: Cardiotoxicity continues to pose a significant challenge for patients receiving neoadjuvant therapy for HER2-positive breast cancer with trastuzumab and pertuzumab, especially when combined with anthracyclines. In this series, most patients developed cardiotoxicity before completing their treatment. However, early diagnosis and prompt intervention contributed to partial recovery of left ventricular function in the majority of cases. These findings highlight the critical need for consistent cardiovascular monitoring throughout therapy to reduce the risk of long-term cardiac complications.

Key words: cardiooncology, breast cancer, neoadjuvant therapy, trastuzumab and pertuzumab, delay from surgery

S13 – MEASUREMENT OF CARDIAC-SPECIFIC BIOMARKERS IN THE FIRST MORNING URINE AS A NEW METHOD OF EARLY DETECTION OF CARDIOTOXICITY OF CHEMOTHERAPY

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Background: In the last few years, research investigating the use of measuring cardiac-specific markers in first morning urine as a new diagnostic tool in the early detection of cardiac damage has been significantly increasing. Our previous results in patients who have a condition that damages the heart, such as unregulated arterial hypertension, indicate an increase in cardiac specific markers, predominantly cardiac troponin I (hsTnI) in the first morning urine. The aim of this summary is to highlight the potential and possibilities of measuring hsTnI in first morning urine as a new method for early detection of chemotherapy cardiotoxicity.

Patients and methods: A commercially available highly sensitive cardiac troponin I test (Abbott ARCHITECT STAT High Sensitive Troponin-I) was used to analyze cardiac troponin I in the first morning urine. Blood and first morning urine samples of voluntary subjects were used to create preliminary results of a healthy population. First morning urine and blood samples of two patients who were treated with cardiotoxic chemotherapy protocols at UH Merkur were used for preliminary analysis. The patients were treated at the Department of Hematology and suffered from Hodgkin's and Non-Hodgkin's lymphoma. They were treated according to the R-CHOP protocol (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Prednisone) and the ABVD protocol (Adriamycin, Bleomycin, Vinblastine, Dacarbazine). Samples were collected after each chemotherapy cycle for the next consecutive three days. A total of 60 urine samples were collected and analyzed. All respondents included in the study signed informed consent.

Results: Preliminary data in a healthy group of subjects indicate that hsTnI values in the first morning urine are significantly higher than in blood and range up from 0.3 to 35ng/L. In patients receiving cardiotoxic chemotherapy, hsTnI values were even higher, with maximum values reaching up to 59.2ng/L, and minimal range of 0.3ng/L. Concentrations of hsTnI in the blood did not significantly differ between the subjects and the healthy population.

Conclusion: First morning urine hsTnI concentrations in patients treated with cardiotoxic chemotherapy indicate a significant increase in hsTnI in the days immediately following chemotherapy administration. This may indicate silent myocardial injury that cannot be detected in a timely manner by existing cardiotoxicity tests and could represent a new method of early detection of chemotherapy cardiotoxicity.

Key words: Cardiotoxicity, chemotherapy, first morning urine, cardiac troponin I

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S14 – LATE ONSET ANTHRACYCLINE CARDIOTOXICITY

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Introduction: A well-known fact is that the global cancer burden is growing, but so is our capability to cope with it. New chemotherapeutic agents help reduce cancer-related mortality. Unfortunately, it goes hand in hand with treatment-related side effects of which cardiovascular toxicity has great impact on long term morbidity and mortality of cancer patients(1,2). This has caught interest of cardiologists and led to publishing the first ESC guidelines on cardio-oncology in 2022.

Although new therapeutic advances give us hope in diminishing cancer burden, anthracyclines have been, for several decades now, an integral part of most chemotherapeutic regimens. They are also the first class of chemotherapeutics that comes to our mind when thinking of cardiotoxicity. Anthracycline cardiotoxicity is dose-dependent and their use is limited by the maximum lifetime cumulative dose(3). Therapy, prevention and pathophysiology of it are still not well addressed(4). This makes them an interesting topic of scientific and clinical interest to date.

Case report: A 59-year-old women was diagnosed with triple negative invasive right breast carcinoma (pT1bN0M0), first detected on the national screening program mammography. Quadrantectomy with sentinel lymph node biopsy of the right axilla was done. She received adjuvant chemotherapy AC-T regimen (doxorubicin, cyclophosphamide and paclitaxel) and radiotherapy of the right breast.

Due to successful treatment of acute myeloid leukemia with anthracycline based regimen 16 years ago, her equivalent of total cumulative doxorubicin dose was 348mg/m^2. During chemotherapy for breast cancer, regular oncology follow-up with electrocardiogram and laboratory results were made. Echocardiography was made 2 and 13 months on completion of chemotherapy and report was within the normal limits, with EF of 60%. The oncology follow-ups were without relapse.

Four years later she was admitted to our department and diagnosed with heart failure with reduced left ventricular ejection fraction due to anthracycline cardiotoxicity. Her family history and previous medical history were without cardiovascular diseases. Invasive coronary angiography revealed no significant coronary artery stenosis. There were no significant arrhythmias. The optimal medical therapy was introduced. After discharge cardiac magnetic resonance report was consistent with dilatative cardiomyopathy of nonischemic etiology.

On cardiology follow-ups she was asymptomatic with optimal heart failure therapy and her left ventricular ejection fraction improved from 20% to 43%.

Consclusion: Dose dependent anthracycline cardiotoxicity has become a companion to anthracycline regimens ever since they proved very successful in the treatment of vast majority of cancers(4,5). Attempts to classify it regarding timing of symptom onset and its reversibility, were made over the years. Advances of diagnostic and therapeutic options changed its prognosis. Timely detection of subclinical lesions and

introduction of adequate therapy influences their reversibility, leading to a more appealing hypothesis of one pathophysiologic continuum in one disease rather than three distinct types(6,7).

Anthracyclines have major part in cancer therapy-related cardiovascular toxicity poses a considerable obstacle in further reducing cancer burden(6). This clinical challenge has been existing for decades now and it still persists. There is a need to adopt more efficient follow-up strategies and tighten collaboration of oncologists and cardiologists.

Keywords: Anthracycline; Cardiotoxicity, Doxorubicin, Breast Cancer

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S15 – IMPROVED OUTCOMES WITH PERCUTANEOUS CORONARY INTERVENTION IN ONCOLOGY PATIENTS WITH ACUTE CORONARY SYNDROME

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Introduction: Cardiovascular diseases are the leading cause of mortality and morbidity in the developed world, followed closely by oncological diseases. Consequently, cardio-oncology patients have become increasingly common. The rising prevalence of such patients is a result of improved treatment for both cardiovascular and oncological conditions, which has subsequently extended the life expectancy of these individuals. Moreover, the higher prevalence of comorbidities associated with these conditions, along with their respective treatments, contributes to an increased incidence of cardiovascular diseases in oncology patients and vice versa.

Aim of the Study: The primary objective of this study was to investigate the impact of treatment approach (invasive vs. conservative) on clinical outcomes in oncology patients with acute coronary syndrome (ACS), depending on the ACS subtype. Additionally, the study aimed to assess the influence of the primary tumor site on patient prognosis following ACS and to determine the prevalence of type 2 myocardial infarction (T2MI) in the cardio-oncology patient population.

Methods and Participants: A total of 269 participants treated at the Clinical Hospital Center Zagreb (KBC Zagreb) under the diagnosis of ACS, who had active cancer at the time of hospitalization or within the five-year period prior to hospitalization, were included in the study. The study period spanned from January 2012 to December 2023. The data source for this retrospective study was the hospital information system (BIS) of KBC Zagreb.

Results: Oncology patients with STEMI myocardial infarction were most frequently treated with percutaneous coronary intervention (74,6%), whereas patients with NSTE-ACS were more often managed conservatively (50,4%) (P<0,001). Conservatively treated patients were significantly associated with higher in-hospital mortality (12,4% vs. 4%) and lower six-month survival rates (52,8% vs. 79%). These trends were observed in both STEMI and NSTE-ACS patients. The lungs were the most common primary cancer site (22,8%). Patients with metastatic disease had, as expected, higher in-hospital mortality (16,6% vs. 5,2%) and consequently lower six-month survival (53,2% vs. 74,1%) compared to those without metastases. T2MI was identified in 24,2% of the patients.

Conclusion: Cardio-oncology patients with ACS are at increased risk due to their oncological disease, resulting in higher mortality compared to non-oncology ACS patients. The study indicates that half of the NSTE-ACS patients and a quarter of STEMI patients were treated conservatively, which negatively impacted their prognosis. Invasive treatment had a positive effect on outcomes for all oncology patients with ACS, regardless of the primary cancer site. T2MI was more frequently observed in the cardio-oncology subpopulation in this study compared to cardiology patients without cancer, as reported in the literature. To better understand the detailed pathophysiological mechanisms contributing to the higher prevalence of this infarction type in these patients, larger multicenter studies are required.

Keywords: acute coronary syndrome; type 2 myocardial infarction; oncological diseases; percutaneous coronary intervention

S16 – CASE OF SEVERE PERSISTENT HYPERTRIGLYCERIDEMIA IN A PATIENT ON IMATINIB TREATMENT

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Imatinib mesylate is a tyrosine kinase inhibitor commonly used in the treatment of chronic myeloid leukemia (CML) and c-Kit (CD117)-positive metastatic gastrointestinal stromal tumors (GISTs) in adults. In addition to its antileukemic and antitumoral effects, imatinib also binds to other receptors, including platelet-derived growth factor receptor (PDGF-R), c-Fms, and non-receptor tyrosine kinases. While imatinib has been shown to reduce serum lipids and glucose levels, its lipid-lowering effects are noteworthy.

Several studies have demonstrated that imatinib can lower and normalize hyperlipidemia within 4 weeks of treatment, suggesting that it may have a protective role against conditions like atherosclerosis. One proposed mechanism for these effects involves the inhibition of PDGFR-dependent phosphorylation of the low-density lipoprotein (LDL)-receptor-related protein (LRP). This inhibition has been shown to prevent intimal hyperplasia after vascular injury and reduce fibrovascular proliferation in animal models of hypercholesterolemia.

We present the case of a 42-year-old man undergoing imatinib treatment for gastric metastatic GIST, who developed severe persistent hypertriglyceridemia. Despite not having a history of type 2 diabetes or metabolic syndrome, and with normal lipid levels prior to treatment, the patient's triglycerides remained elevated. He was treated with high-dose rosuvastatin alongside a high-dose regimen of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), totaling 4 grams per day.

After 3 months of treatment with rosuvastatin and EPA+DHA, the patient's triglyceride levels normalized.

Keywords: Imatinib, hypertriglycerdiemia, EPA, DHA