# ANTIBODY–DRUG CONJUGATES IN BREAST CANCER TREATMENT: IS THERE CONCERN FOR CARDIOVASCULAR HEALTH?

CHIARA ĆELIĆ[1]

[1]*Division of Medical Oncology, University Hospital for Tumors, Sestre milosrdnice University Hospital Center, Zagreb, Croatia*

Antibody–drug conjugates (ADCs) have transformed the treatment landscape of HER2-positive and metastatic breast cancer by enabling targeted delivery of cytotoxic agents while reducing systemic toxicity. Agents such as trastuzumab emtansine (T-DM1) and trastuzumab deruxtecan (T-DXd) have demonstrated substantial improvements in progression-free and overall survival, leading to their increasing use in both advanced and earlier-stage disease settings (1,2). Although ADCs were initially developed to minimize the cardiotoxicity associated with conventional HER2-targeted therapies and chemotherapy, emerging evidence suggests that cardiovascular adverse events remain an important clinical concern (3).

Recent meta-analytic data involving 9,538 patients demonstrated that T-DM1 was associated with the lowest incidence of left ventricular ejection fraction (LVEF) decline (0.94%), whereas T-DXd showed a higher incidence of LVEF reduction (4.20%), comparable to trastuzumab-based chemotherapy regimens (3). Most cardiotoxic manifestations were asymptomatic decreases in LVEF, although symptomatic heart failure may occur, particularly in patients with pre-existing cardiovascular disease or prior anthracycline exposure (4). ADC-related cardiotoxicity appears less frequent than with conventional HER2-targeted therapies, yet long-term cardiovascular safety data remain limited (5).

Pharmacovigilance analyses based on the FDA Adverse Event Reporting System (FAERS) further identified a broad spectrum of ADC-associated cardiac adverse events, including cardiac failure, arrhythmias, cardiomyopathy, myocarditis, pericardial effusion, and left ventricular dysfunction (6,7). Another large FAERS-based study reported that cardiac adverse events represented approximately 11.77% of ADC-related reports, with breast cancer patients accounting for the majority of affected cases (7). Female sex and older age were associated with increased risk, while most cardiovascular events occurred within the first three months of treatment initiation (7). Mechanistic analyses also suggested a potential role of heat shock protein pathways and HSP70 dysregulation in ADC-associated cardiotoxicity (7).

Despite these concerns, current evidence indicates that ADC-related cardiotoxicity remains relatively uncommon compared with conventional chemotherapy and earlier HER2-targeted regimens (3,5). Experts emphasize that ADCs represent a more sophisticated method of cytotoxic drug delivery rather than a completely toxicity-free approach (8). As ADCs continue to move into first-line and curative-intent settings, careful cardiovascular assessment and monitoring become increasingly important, particularly in patients with pre-existing cardiovascular risk factors (4,5).

In conclusion, ADCs have significantly improved outcomes in breast cancer treatment while demonstrating a generally favorable cardiovascular safety profile. Nevertheless, clinically relevant cardiotoxicity may still occur and warrants continued surveillance, multidisciplinary cardio-oncology collaboration, and further prospective research to optimize prevention and management strategies.

**Keywords:** antibody–drug conjugates; breast cancer; cardiotoxicity; HER2-positive breast cancer; left ventricular ejection fraction; cardio-oncology

REFERENCES

1. Verma S, Miles D, Gianni L, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. N Engl J Med. 2012;367(19):1783–1791.
2. Cortés J, Kim SB, Chung WP, et al. Trastuzumab deruxtecan versus trastuzumab emtansine for breast cancer. N Engl J Med. 2022;386(12):1143–1154.
3. Seth L, Bhave A, Kollapaneni S, et al. Cardiotoxic effects of antibody drug conjugates vs standard chemotherapy in ERBB2-positive advanced breast cancer: a systematic review and meta-analysis. JAMA Netw Open. 2025;8(11):e2540336.
4. Lyon AR, Dent S, Stanway S, et al. Baseline cardiovascular risk assessment in cancer patients scheduled to receive cardiotoxic cancer therapies. Eur J Heart Fail. 2020;22(11):1945–1960.
5. Zamorano JL, Lancellotti P, Rodriguez Muñoz D, et al. 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity. Eur Heart J. 2016;37(36):2768–2801.
6. Abbas T, Rehman WU, Shaukat MT, et al. Cardiotoxicity of antibody–drug conjugates: A FAERS-based pharmacovigilance study (2023–2024). J Clin Oncol. 2026;44(suppl):443.
7. Zheng X, Song Y, Cao Y, et al. Systematic analysis and mechanistic investigation of cardiac adverse events associated with antibody–drug conjugates using FAERS database. Int J Surg. 2026;112:1436–1447.
8. Tarantino P. Top 5 takeaways from the future of antibody-drug conjugates in solid oncology. Presented at: Binaytara Detroit 2026 Hematology and Oncology Practice Symposium; 2026.

## CAPECITABINE-TRIGGERED CARDIOMYOPATHY ON A BACKGROUND OF PRIOR ANTHRACYCLINE EXPOSURE WITH REVERSE REMODELING FOLLOWING EARLY QUADRUPLE THERAPY

MARIN BOBAN[1], Krešimir Crljenko[1], Helena Jerkić[1,2]

[1]*Department of Cardiology, University Hospital Centre Sestre Milosrdnice, Zagreb, Croatia*
[2]*School of Medicine, University of Zagreb, Croatia.*

**Background:** Fluoropyrimidine-associated cardiotoxicity, including that related to capecitabine, is relatively uncommon but clinically relevant, with an incidence of approximately 5%. The risk is significantly increased in patients with prior exposure to cardiotoxic agents, particularly anthracyclines, due to pre-existing subclinical myocardial injury. This creates a vulnerable substrate in which additional cardiotoxic therapies may precipitate overt heart failure. Contemporary heart failure management, including early initiation of quadruple guideline-directed medical therapy (GDMT), offers the potential for myocardial recovery even in toxic cardiomyopathy.

**Case Presentation:** A 66-year-old female with metastatic breast cancer (diagnosed in 2013) presented with progressive dyspnea and reduced exercise tolerance over 4–5 weeks during ongoing capecitabine therapy. Her oncologic history included prior anthracycline-based chemotherapy, followed by paclitaxel and fulvestrant.

On admission, the patient was hemodynamically stable. Laboratory findings revealed markedly elevated NT-proBNP (2540 ng/L) with normal high-sensitivity troponin levels. Transthoracic echocardiography demonstrated a dilated left ventricle (LVEDD 60 mm) with severely reduced systolic function (LVEF 30%) and markedly impaired global longitudinal strain (GLS −5.7%), along with grade III diastolic dysfunction and moderate functional mitral regurgitation. Chest X-ray showed cardiomegaly and pulmonary congestion. Coronary angiography excluded obstructive coronary artery disease.

Given the temporal relationship with capecitabine therapy and the background of prior anthracycline exposure, a diagnosis of capecitabine-triggered cardiomyopathy on a pre-injured myocardial substrate was established.

**Management and Outcome:** Capecitabine was promptly discontinued following multidisciplinary oncologic evaluation. The patient was treated with intravenous diuretics and levosimendan, followed by early initiation of quadruple GDMT including an ACE inhibitor, beta-blocker, mineralocorticoid receptor antagonist, and SGLT2 inhibitor. At 8-week follow-up, the patient demonstrated marked clinical improvement (NYHA II), with NT-proBNP reduction to 600 ng/L. Repeat echocardiography revealed significant reverse remodeling, with LVEF improvement to 45% and GLS to −10.7%, accompanied by regression of diastolic dysfunction.

**Discussion:** This case highlights the synergistic cardiotoxic effect of sequential cancer therapies. While capecitabine-associated cardiotoxicity is relatively rare, its occurrence is more likely in patients with prior anthracycline exposure, reflecting cumulative myocardial injury. The temporal association with capecitabine initiation strongly supports its role as the triggering factor in this patient. Importantly, the absence of troponin elevation does not exclude significant myocardial dysfunction in chemotherapy-related cardiomyopathy. Early recognition and rapid initiation of quadruple GDMT, were associated with substantial and early reverse remodeling, in line with current ESC heart failure recommendations. These findings emphasize the importance of a cardio-oncology approach that integrates oncologic history, timing of therapies, and cardiovascular risk stratification.

**Conclusion:** Capecitabine can act as a trigger for overt cardiomyopathy in patients with prior anthracycline exposure. Early discontinuation of the offending agent and prompt initiation of quadruple GDMT can result in significant recovery of cardiac function. This case underscores the importance of recognizing cumulative cardiotoxicity and ensuring long-term cardiovascular surveillance in oncology patients.

**Keywords:** capecitabine cardiotoxicity; anthracycline; HFrEF; reverse remodeling

## CARDIAC RHYTHM DISORDERS IN CARDIO-ONCOLOGY: RISK STRATIFICATION, MONITORING AND INDIVIDUALIZED MANAGEMENT

MARIJANA KNEŽEVIĆ PRAVEČEK[1,2], Katica Cvitkušić Lukenda[1,2], Domagoj Vučić[1,2]

[1]*Department of Cardiology, General Hospital "Dr. Josip Benčević", Slavonski Brod, Croatia*
[2]*Faculty of Dental Medicine and Health Osijek, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia*

**Abstract**

Cancer treatment has increasingly transformed malignant disease into a chronic condition, but this benefit is accompanied by a rising burden of cardiovascular toxicity, including cardiac rhythm disorders. Arrhythmias in patients with active cancer and survivors are driven by a complex interaction between patient-related factors, the malignancy itself, systemic inflammation, electrolyte and autonomic disturbances, drug–drug interactions and the direct or indirect electrophysiological effects of anticancer therapy. Atrial fibrillation is the most frequent arrhythmia, while QTc prolongation, ventricular arrhythmias,

bradyarrhythmias, conduction disorders and sudden cardiac death, although less common, may have major clinical consequences. Contemporary cardio-oncology practice therefore requires early identification of high-risk patients before treatment, careful review of anticancer and supportive medications, baseline electrocardiography, correction of reversible triggers and individualized surveillance during therapy.

Management should aim not only to treat arrhythmias, but also to prevent unnecessary interruption of effective oncological treatment. In atrial fibrillation, rate or rhythm control must be balanced with cancer-related symptoms, hemodynamic status, expected prognosis and interactions between antiarrhythmic drugs, anticoagulants and anticancer agents. Anticoagulation decisions are particularly challenging because thromboembolic risk, bleeding risk, thrombocytopenia, renal and hepatic dysfunction and invasive procedures often coexist. QTc prolongation requires systematic monitoring, electrolyte optimization and avoidance of cumulative QT-prolonging medication when possible. Ventricular arrhythmias and high-grade conduction disturbances demand prompt evaluation for myocarditis, ischemia, cardiomyopathy, radiation-related disease or drug toxicity. In selected patients, catheter ablation, pacemakers, implantable cardioverter-defibrillators or cardiac resynchronization therapy may be appropriate, but decisions should incorporate cancer status, life expectancy, infection risk, vascular access and radiotherapy considerations.

A multidisciplinary model integrating cardiology, oncology, hematology, electrophysiology, pharmacy and palliative care is essential. Practical pathways should be based on arrhythmia phenotype, cancer therapy, reversibility of triggers and patient goals. Further prospective cardio-oncology registries and clinical trials are needed to define evidence-based prevention, monitoring and treatment strategies. Until such data are available, individualized risk assessment and close collaboration remain the cornerstone of safe and uninterrupted cancer care.

**Keywords:** Cardio-Oncology; Arrhythmias, Cardiac; Atrial Fibrillation; Long QT Syndrome; Cardiotoxicity; Pacemaker

REFERENCES:

1. Romano LR, Polimeni A, Indolfi C, Curcio A. Management of cardiac rhythm disorders in cardio-oncology. Arrhythm Electrophysiol Rev. 2025 Feb 20;14:e05. doi:10.15420/aer.2024.20.
2. Torbey E, Cheung JW, Abideen Asad ZU, Tamirisa K, Tisdale JE, Copeland-Halperin R, et al. Arrhythmias and cardiac devices management in oncology patients. Heart Rhythm. 2026 Mar 31:S1547-5271(26)02227-7. doi:10.1016/j.hrthm.2026.03.1944. Epub ahead of print.
3. Wright JC, Sharma S, Potter AS. Arrhythmia challenges in cardio-oncology: high-risk therapies, management, and anticoagulation. Cardiol Clin. 2025 Feb;43(1):43-56. doi:10.1016/j.ccl.2024.09.001.
4. Keramida K, Kariki O, Angelopoulou E, Kalafatis I, Lafaras C, Letsas KP, et al. Arrhythmias, conduction disorders and sudden cardiac death in cancer patients and survivors: expert opinion of the working groups on cardio-oncology and on electrophysiology of the Hellenic Cardiac Society. Cardiooncology. 2025;11:71. doi:10.1186/s40959-025-00363-0.
5. Asteggiano R, Norbiato C, Marengo S, Parrini I. Cancer and arrhythmias. E-Journal of Cardiology Practice. 2021 May 5;19(21)

# CARDIAC SAFETY OF PEMBROLIZUMAB-BASED NEOADJUVANT CHEMOIMMUNOTHERAPY IN EARLY TRIPLE-NEGATIVE BREAST CANCER

PETRA SERTIĆ[1]

[1]*Department of Medical Oncology, Division for Medical Oncology, University Hospital for Tumors, University Hospital Sestre Milosrdnice, Zagreb, Croatia*

The immune system plays a crucial role in regulating tumor growth, and the goal of immunotherapy is to harness the specificity and long-term memory of the adaptive immune response to achieve durable cancer control. Immune checkpoints are signaling pathways that maintain self-tolerance and prevent autoimmunity; however, their overexpression in tumor cells enables immune evasion by inhibiting cytotoxic T-cell activity and promoting tumor progression. Immune checkpoint inhibitors (ICIs) block these inhibitory pathways, restoring T-cell function and enhancing antitumor immunity. Common ICIs include anti-PD-1/PD-L1 monoclonal antibodies (pembrolizumab, nivolumab, durvalumab, atezolizumab), anti-CTLA-4 (ipilimumab), and anti-LAG-3 (relatlimab), which may also be used in combination. Due to their mechanism of action, ICIs can cause immune-related adverse events (irAEs), resulting from excessive immune activation. These toxicities are more frequent with combination immunotherapy, with severe events (grade 3–4, according to CTCAE) occurring in approximately 10–20% of patients. IrAEs are heterogeneous, ranging from common manifestations such as dermatologic, endocrine, and gastrointestinal toxicities (e.g., rash, thyroid dysfunction, diarrhea, colitis) to less frequent but potentially life-threatening cardiopulmonary and neurological complications. Cardiovascular toxicities represent a particularly important group of irAEs and include myocarditis, pericarditis, pericardial effusion, myocardial infarction, arrhythmias, heart failure, and accelerated atherosclerosis. Additionally, indirect cardiovascular effects may arise from other irAEs, particularly endocrine disorders (thyroid dysfunction, hypophysitis, adrenal insufficiency), immune-mediated diabetes, and thromboembolic events. Among these, myocarditis is a rare but severe complication with high mortality, reported to occur most commonly within the first 30 days of ICI therapy, although late-onset cases may also develop. Mortality rates can reach up to 50%. Later cardiovascular complications (after 90 days) include heart failure, hypertension, and progressive atherosclerosis. Diagnosis is based on clinical presentation, elevated cardiac biomarkers (especially troponin), and electrocardiographic abnormalities such as conduction disturbances or arrhythmias, requiring prompt cardiologic evaluation and exclusion of other causes such as myocardial infarction. Imaging with echocardiography and cardiac magnetic resonance is essential. Treatment typically involves high-dose corticosteroids (e.g., methylprednisolone), with additional immunosuppressive therapy in severe cases. The phase III KEYNOTE-522 trial demonstrated statistically and clinically significant improvements in outcomes for patients with stage II–III early triple-negative breast cancer treated with pembrolizumab in combination with anthracycline-based chemotherapy. Although the incidence of myocarditis in the trial was low (0.4%), it was higher compared to chemotherapy alone, highlighting the need for careful baseline cardiovascular assessment and close monitoring, particularly in high-risk patients. A higher incidence of endocrine disorders, which may indirectly affect cardiovascular health, was also observed. In our retrospective study of 45 patients with early triple-negative breast cancer treated at our University Hospital Centre, cardiac events occurred in 6.6% of patients. Reported events included atrial fibrillation, immune-mediated myositis with severe hypothyroidism and mild pericardial effusion, and pulmonary embolism. One additional patient developed suspected ICI-related myocarditis after neoadjuvant therapy. These

findings are consistent with real-world data, indicating relatively low but clinically relevant cardiotoxicity and underscoring the importance of baseline risk assessment and early monitoring.

**Keywords:** immune checkpoints, breast cancer, pembrolizumab, myocarditis

REFERENCES:

1. Mezzanotte-Sharpe J, Hsu C-Y, Choi D, Sheffield H, Zelinskas S, Proskuriakova E, et al. Adverse events in patients treated with neoadjuvant chemo/immunotherapy for triple negative breast cancer: results from seven academic medical centers. Breast Cancer Res Treat [Internet]. 2025;213(1):71–80.
2. Yin Q, Wu L, Han L, Zheng X, Tong R, Li L, et al. Immune-related adverse events of immune checkpoint inhibitors: a review. Front Immunol [Internet]. 2023;14:1167975.
3. Schmid P, Cortes J, Pusztai L, McArthur H, Kümmel S, Bergh J, et al. Pembrolizumab for early triple-negative breast cancer. N Engl J Med [Internet]. 2020;382(9):810–21.
4. Mazloom A, Asturias JA, Manan H, Prodduturvar P. Investigation of cardiotoxicity with concomitant use of anthracyclines and checkpoint inhibitors. J Clin Oncol [Internet]. 2024;42(16_suppl):e24022–e24022.
5. Lyon AR, López-Fernández T, Couch LS, Asteggiano R, Aznar MC, Bergler-Klein J, et al. 2022 ESC guidelines on cardio-oncology developed 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). Eur Heart J [Internet]. 2022;43(41):4229–361.

## CARDIAC TISSUE ANALYZES USING MAGNETIC RESONANCE IMAGING

MARKO BOBAN[1,2,3]

[1]*Department for cardiomyopathies, valvular heart diseases and heart failure, Cardiology Clinic, „Sestre Milosrdnice“ University hospital Center, Vinogradska 29, Zagreb 10000, Croatia*
[2]*Department of cardiology, University clinic „Bonto“, Medvedgradska ulica 49, Zagreb 10000, Croatia*
[3]*Faculty of dental medicine and health Osijek, University „J.J. Strossmayer“ of Osijek, Crkvena ulica 21, Osijek 31000, Croatia*

**Summary:**

Owing to the advancements in oncology, especially within the last decade or two, great deal of cancerous diseases became chronic illnesses. On the other side, although heart normally operates on long endurant scales, there are numerous modalities of cardiac toxicity associated with oncology treatments. These, often subtle changes can nowadays be visualized and detected in early phases using magnetic resonance imaging, offering potential to mediate or arrest from potential further damage to cardiomyocytes, via selecting alternative treatment options. Some routes of cancer treatments might cause irreversible damage to myocardial cells; hence awareness and early detection are clinically important and relevant. In general, magnetic resonance offers highly precise and non-invasive assessment of cardiac morphology, functions, as well as tissue analyzes. Standard tools for tissue analysis include T1, T2, T2* sequences, in addition to early and delayed post contrast phases. In the latter tissue deposits of gadolinium offer potential for characterization of fibrosis. Nowadays several modalities of mapping offered fine tune characterizations and potential for early and reproducible detection of tissue water, inflammation, and fibrotic replacements, due to cell death. Mapping gave us quantitative insight into lesions characterized by subtle and/or diffuse cardiomyocyte damage, which failed to be screened using conventional sequences.

**Keywords**: cardiac toxicity; cardiac magnetic resonance imaging; tissue analyzes; heart failure

# CARDIOVASCULAR EMERGENCIES IN CARDIO-ONCOLOGY

KREŠIMIR KORDIĆ[1,2]

[1]*Department of Cardiology, University Hospital Centre Sestre Milosrdnice, Zagreb, Croatia*
[2]*School of Medicine, Catholic University of Croatia, Zagreb, Croatia*

Cardio-oncology has become an important clinical field at the intersection of contemporary cancer therapy and cardiovascular medicine. Modern anticancer treatments, such as anthracyclines, anti-HER2 agents, immune checkpoint inhibitors (ICIs), anti-VEGF drugs, CDK4/6 inhibitors, and fluoropyrimidines, can lead to a wide range of potentially life-threatening cardiovascular complications. As cancer outcomes improve and patients live longer, cardiovascular complications related to treatment are being seen more often, including acute and severe conditions that demand rapid identification and intervention.

Most common cardiovascular emergencies in cardio-oncology are acute heart failure and cardiomyopathy, often caused by anthracycline-induced myocardial toxicity, anti-HER2 agents (such as trastuzumab and pertuzumab), and anti-VEGF drugs (like bevacizumab). Anthracycline-related cardiotoxicity is usually dose-dependent and may be irreversible, while cardiac dysfunction from anti-HER2 therapy can often be reversed, especially if recognized early. Myocarditis, particularly linked to immune checkpoint inhibitors, is rare but very serious, with high mortality if not diagnosed promptly. Symptoms are often vague and may include arrhythmias, conduction problems, or rapid worsening of ventricular function. Acute coronary syndrome can develop through several pathways: fluoropyrimidine-induced coronary vasospasm (without underlying atherosclerosis), arterial thrombosis due to anti-VEGF agents, and accelerated atherosclerosis following mediastinal radiotherapy. Arrhythmias may present as ventricular tachycardia and fibrillation, QT prolongation and torsades de pointes (from arsenic trioxide, vandetanib, or CDK4/6 inhibitors like ribociclib), atrial fibrillation (associated with ibrutinib), or high-degree AV block in ICI-related myocarditis. Thromboembolic events, particularly cancer-associated thrombosis (CAT), impact up to 20% of cancer patients and include massive pulmonary embolism, deep vein thrombosis, and arterial thromboembolism. Hypertensive emergencies, seen mostly with anti-VEGF therapies, can be complicated by acute renal failure. Less common but important emergencies are valvular and endocardial disease (such as non-bacterial thrombotic endocarditis and carcinoid heart disease) and structural complications from tumors (including direct cardiac invasion, intracardiac masses causing hemodynamic obstruction, and superior vena cava syndrome).

Acute management of cardiovascular emergencies in oncological patients follows standard cardiovascular protocols and should not be delayed due to the underlying malignancy. A multidisciplinary cardio-oncology approach is essential for balancing cardiovascular risk against oncological benefit.

**Conclusion**: Cardiovascular emergencies in cardio-oncology are diverse and increasingly encountered in clinical practice. Early recognition, structured differential diagnosis, and a multidisciplinary approach are key to improving outcomes, particularly as many of these conditions may be reversible when treated promptly.

**Keywords**: cardio-oncology; cardiovascular emergencies; cardiotoxicity

# CARDIOVASCULAR TOXICITY INDUCED BY VASCULAR ENDOTHELIAL GROWTH FACTOR INHIBITORS

JELENA PROŠEV[1]

[1]*Department of Clinical Oncology, Division for Medical Oncology, University Hospital for Tumors, Sestre milosrdnice University Hospital Center, Zagreb, Croatia*

Vascular endothelial growth factor (VEGF) inhibitors have been an essential part of cancer treatment for many years. Their main mechanism of action is by supressing pathological angiogenesis- a crucial part of tumor growth. They are used alone or in combination with chemotherapy. Agents targeting the VEGF signaling pathway–including monoclonal antibodies such as bevacizumab or tyrosine kinase inhibitors including sunitinib and sorafenib–have demonstrated therapeutic benefit. However, by now we have substantial evidence that these drugs are associated with significant cardiovascular toxicity, creating an important challenge in oncology and cardiovascular medicine.

Anti-VEGF–induced cardiotoxicity consists of several adverse cardiovascular effects, including hypertension, left ventricular dysfunction, heart failure, myocardial ischemia, thromboembolic events, arrhythmias, and, less commonly, cardiomyopathy. The risk of developing cardiovascular toxicity is individual for every patient an depends on their lifestyle, preexisting cardiovascular comorbidities and previous oncological treatment.

Hypertension is the most frequent manifestation. Although the mechanism through which it develops during anti VEGF treatment isn't completely ascertained, evidence suggests it results from reduced nitric oxide production, endothelial dysfunction and increased vascular resistance. Sustained elevations in blood pressure may subsequently contribute to structural and functional cardiac impairment. In addition, VEGF signaling plays a critical role in maintaining myocardial capillary density and endothelial cell survival; therefore, its inhibition may impair myocardial perfusion and adaptive cardiac remodeling, especially in patients with pre-existing cardiovascular disease.

Tyrosine kinase inhibitors generally exhibit a higher incidence of direct myocardial toxicity compared with monoclonal antibodies. Risk is further increased in older patients and in those with prior exposure to anthracyclines, radiation therapy, hypertension, diabetes mellitus, or established coronary artery disease. Importantly, some cardiovascular effects may be reversible following discontinuation of therapy and initiation of guideline-directed cardiac management, though irreversible dysfunction has also been reported.

Early identification and monitoring are essential to minimizing morbidity and mortality associated with anti-VEGF therapy. Baseline cardiovascular assessment, periodic blood pressure monitoring, electrocardiography, cardiac biomarkers, and echocardiographic evaluation of left ventricular ejection fraction are recommended in high-risk populations. Cardio- oncology teams have therefore become an essential part of optimizing cancer treatment. Current management strategies focus on aggressive control of cardiovascular risk factors, prompt treatment of hypertension and heart failure, dose modification when necessary, and individualized risk–benefit assessment regarding continuation of anticancer therapy.

Future research in the field of cardio-oncology is focued on understanding the molecular mechanisms underlying cardiotoxicity, identify predictive biomarkers, and develop targeted cardioprotective interventions. Those will be essential information for optimizing cancer outcomes while preventing long term consequenses for patients.

**Keywords**: VEGF inhibitors; cardiotoxicity; hypertension;

REFERENCES:

1. Chen H. H., Klemens M. Meyer. *VEGF signaling and cardiovascular toxicity in cancer therapy*. Nature Reviews Cardiology. 2021;18(9):608–621.
2. Joerg Herrmann. *Vascular toxic effects of cancer therapies*. Nature Reviews Cardiology. 2020;17(8):503–522.
3. Daniel J. Lenihan, Tomas G. Neilan. *Cardiovascular toxicity of targeted cancer therapies: mechanisms and management*. Journal of the American College of Cardiology. 2023;81(5):489–505

## DISSEMINATED NON-SMALL CELL LUNG CARCINOMA FOLLOWING CARDIAC TRANSPLANTATION

MARTA TUČKAR[1], Katarina Toljan[1], Matias Trbušić (mentor)[1,2]

[1]*University of, Zagreb, School of Medicine, Zagreb, Croatia*
[2]*Department for Cardiomyopathies, Heart Failure and Valvular Heart Diseases, Department of Cardiology, University Hospital Centre Sisters of Charity, Zagreb, Croatia*

Post-transplant malignancy is a well-recognised complication of long-term immunosuppression. In this case report, we present a case of disseminated non-small cell lung carcinoma (NSCLC) diagnosed two years post-cardiac transplantation, highlighting the complex interplay between cardio-oncological risk factors and immunosuppression-related sequelae.

A 62-year-old male with ischaemic cardiomyopathy and end-stage advanced heart failure (LVEF 25%) underwent orthotopic cardiac transplantation in April 2023. At the time, pre-transplant evaluation revealed no contraindications or existing malignancies. Post-operatively, immunosuppression was initiated with mycophenolic acid and by January 2024, echocardiography showed excellent allograft function with a normalised LVEF of 60%.

In May 2024, the patient was hospitalised due to nausea and vomiting. Oesophagogastroduodenoscopy revealed mucosal abnormalities consistent with infectious aetiology, and CMV viraemia exceeding 160,000 copies was detected. Ganciclovir was started alongside temporary discontinuation of immunosuppressive therapy, resulting in successful viral suppression.

In June 2025, the patient presented to the ER with acute-onset confusion, aphasia, and suspected seizure activity. Emergency brain CT identified a 21 × 20 × 21 mm lesion in the left frontal region. However, neither CT nor MRI were able to establish a definitive diagnosis, with the lesion initially raising concern for cerebral abscess. The differential diagnosis included toxoplasmosis, nocardia infection, aspergilloma, abscess, and tumour. Urgent stereotactic brain biopsy confirmed cerebral squamous cell carcinoma metastases, and thorax CT identified a primary pulmonary process.

In July 2025, bronchoscopy confirmed squamous cell NSCLC. Follow-up brain MRI revealed progressive cerebral metastases, with additional lesions identified in the right cerebellar hemisphere, left parietal, and right frontal regions. The patient subsequently underwent stereotactic radiosurgery (SRS) for brain metastases and stereotactic ablative radiotherapy (SABR) targeting the paraesophageal lymph node and bronchoproliferative process in the right upper lobe. From January 2026, systemic treatment with carboplatin/paclitaxel combination chemotherapy was initiated, whilst immunosuppression with ciclosporin, prednisolone, and mycophenolic acid was maintained at a reduced dose.

Throughout his illness, the patient remained functionally active and professionally engaged. An episode of dysphagia, likely due to tumour compression, showed regression after administration of first chemotherapy cycle, following which the patient returned to full professional activity.

This case illustrates the diagnostic and therapeutic challenges inherent to cardio-oncology. Long-term immunosuppression increases the risk of post-transplant malignancies, while concomitant CMV viraemia primarily reflects a profound net-state of immunosuppression, and may indirectly contribute to tumour progression through immunomodulatory effects on cellular immunity. In such cases, squamous cell carcinomas tend to be more aggressive, more locally invasive, and more prone to metastases, as seen in this case presentation. Here, the diagnosis was ultimately established only by prompt stereotactic brain biopsy, highlighting the limitations of laboratory and serologic tests and imaging techniques. This case further highlights the necessity of vigilant oncological surveillance in transplant recipients as well as the value of multidisciplinary collaboration across cardiology, oncology, infectious diseases, and neurosurgery.

Through careful minimization of immunosuppression combined with contemporary oncological and radio therapeutic treatment, patient survival may be meaningfully extended and quality of life preserved, whilst simultaneously preventing allograft rejection.

**Keywords**: heart transplantation, immunosuppression therapy, lung neoplasms, brain neoplasms

## EARLY CARDIOVASCULAR TOXICITY: TO CONTINUE OR MODIFY ONCOLOGICAL TREATMENT?

LJUBICA VAZDAR[1,2,3], Mihaela Trajbar[1]

[1]*University Hospital for Tumors, Sestre milosrdnice University Hospital Center, Division for Medical Oncology, Ilica 197, 10 000 Zagreb, Croatia*
[2]*University of Zagreb, School of Medicine, Šalata 2, 10 000 Zagreb, Croatia*
[3]*Josip Juraj Strossmayer University of Osijek, Faculty of Food Technology, F. Kuhača 18, 31000 Osijek, Croatia*

**Summary**

Early cardiovascular toxicity related to oncological treatment (CTR-CVT) represents a major challenge in modern oncology and cardio-oncology. According to the ESC guidelines, early cardiotoxicity is defined as the occurrence of cardiovascular complications during or within 12 months of completing oncological therapy. The most common forms include left ventricular dysfunction, myocarditis, arrhythmias, QTc interval prolongation, arterial hypertension, and thromboembolic events. Early identification enables timely introduction of cardioprotective measures, preservation of cardiac function, and continuation of effective oncological therapy.

Assessment of the grade of cardiotoxicity is based on symptoms, cardiac biomarkers (troponin, NT-proBNP), and imaging methods, particularly assessment of left ventricular ejection fraction (LVEF) and global longitudinal strain (GLS). ESC criteria distinguish mild, moderate, and severe dysfunction associated with oncological therapy. Severe forms, including symptomatic heart failure, LVEF <40%, acute coronary syndrome, or suspected ICI myocarditis, require immediate discontinuation of oncological treatment.

In milder forms of cardiotoxicity, such as isolated GLS decline or asymptomatic LVEF decline, it is often possible to continue oncological treatment with enhanced cardio-oncological monitoring and administration of cardioprotective therapy. The decision to continue or discontinue treatment depends on the type of anti-tumor therapy, reversibility of cardiotoxicity, and the context of the oncological disease. In patients with early, potentially curable disease, the tolerance threshold for cardiotoxicity is lower, whereas in metastatic disease, the concept of permissive cardiotoxicity is more often applied to preserve disease control and quality of life.

Particular challenges are posed by anthracyclines, anti-HER2 therapy, immunotherapy, and anti-VEGF drugs, which require an individualized approach to treatment and monitoring. The ESC guidelines recommend the use of ACE inhibitors, ARBs, and beta-blockers in high-risk patients as a primary prevention strategy for cardiotoxicity.

In conclusion, cardiotoxicity does not necessarily mean permanent discontinuation of oncological treatment. A multidisciplinary approach, early risk identification, and timely cardioprotection enable optimization of both oncological and cardiovascular outcomes.

**Keywords:** early cardiotoxicity; oncological treatment; CTRCD; cardioprotection

## EMERGING CARDIAC RISKS OF IMMUNOTHERAPY: CASE REPORT ON A CHECKPOINT INHIBITOR-INDUCED MYOCARDITIS

ANDRIJA MATIJEVIĆ[1*], Ivo Darko Gabrić[1,3], Matias Trbušić[1,2], Krešimir Kordić[1,3], Ozren Vinter[1,3], Matej Nedić[1]

[1]*University Hospital Center "Sisters of charity", Zagreb, Croatia*
[2]*School of Medicine University of Zagreb, Šalata 3b, Zagreb, Croatia*
[3]*School of Medicine Catholic University of Croatia, Ilica 244, Zagreb, Croatia*

**Introduction:** Recent progress in modern oncology highlights the importance of immunotherapeutic agents, treatments that enhance the body's immune response against neoplastic cells. Among the most significant of these are checkpoint inhibitors–monoclonal antibodies fabricated to block inhibitory pathways that normally suppress immune activation. By targeting these regulatory receptors, checkpoint inhibitors enable the immune system to more effectively identify and destroy malignant cells. Despite their significant clinical benefits, these agents are also associated with a spectrum of immune-related adverse events. Of particular concern are major adverse cardiovascular events (MACE), which are increasingly reported in patients undergoing such treatments. One of the most serious complications is myocarditis, an inflammatory condition of the heart muscle that can lead to severe cardiac dysfunction, arrhythmias and even death. As the usage of checkpoint inhibitors grows, the rising incidence of cardiovascular toxicity underscores the importance of early detection, careful monitoring and interdisciplinary management to mitigate potential risks.

* Corresponding author: Andrija Matijević, andrija.matijevic@kbcsm.hr, +385915850329

**Case Presentation:** We report the case of a 74-year-old male who presented with clinical signs and symptoms consistent with heart failure including dyspnea, fatigue, and reduced exercise tolerance. His medical history was notable for disseminated lung cancer, for which he had been receiving treatment with cemiplimab for 12 months. Upon admission, transthoracic echocardiography revealed biventricular systolic dysfunction, with a left ventricular ejection fraction (LVEF) of 30% and a tricuspid annular plane systolic excursion (TAPSE) of 12 mm, indicating significant biventricular systolic impairment. No new regional wall motion abnormalities or valvular pathology were identified. Guideline-directed medical therapy for heart failure with reduced ejection fraction (HFrEF) was promptly initiated, including the introduction of an angiotensin receptor-neprilysin inhibitor. Given the patient's risk profile, coronary angiography was performed, which demonstrated a hemodynamically significant stenosis in the right coronary artery (RCA). A drug-eluting stent was successfully implanted, restoring adequate coronary blood flow. To further characterize myocardial involvement, cardiac magnetic resonance imaging (MRI) was conducted. The imaging revealed a transmural region of late gadolinium enhancement in the inferolateral wall of the basal segment, consistent with a prior ischemic insult. In addition, there were extensive areas of mesocardial and subepicardial late enhancement involving the anteroseptal wall, interventricular septum, and inferoseptal regions. The distribution and morphology of these findings were suggestive of concomitant myocarditis, likely immune-mediated in origin. Given the suspicion of checkpoint inhibitor–associated myocarditis, cemiplimab therapy was immediately discontinued. During the follow-up period, the patient experienced notable clinical improvement, with stabilization of symptoms and gradual recovery of functional status under continued cardiologic care.

**Conclusion:** This case highlights the crucial importance of extensive cardiovascular monitoring in patients undergoing checkpoint inhibitor therapy. Early recognition of myocarditis and other forms of MACE is essential to enable timely intervention and prevent potentially life-threatening complications. The dual presence of ischemic and inflammatory myocardial injury in this patient further emphasizes the complexity of cardiovascular presentations in the context of cancer immunotherapy. Establishing standardized screening protocols, including baseline and periodic cardiac evaluation, may improve patient safety and clinical outcomes. Ongoing research into the immunopathological mechanisms underlying these adverse effects will be essential for developing targeted prevention and management strategies in this rapidly evolving field.

**Keywords:** cardiotoxicity, immune checkpoint inhibitors, MACE, myocarditis

## HYPERTENSION IN CANCER PATIENTS

HELENA JERKIĆ[1,2]

[1]*Department of Cardiology, Sestre milosrdnice University Hospital Center Zagreb, Croatia*
[2]*School of Medicine, University of Zagreb, Zagreb, Croatia*

The prevalence of arterial hypertension is higher in patients with cancer and in cancer survivors than in the general population. Hypertension in this group of patients is a consequence of cancer treatments, concomitant medications and other contributing factors including stress, pain, renal impairment and unhealthy lifestyle habits.

**Chemotherapy Associated Hypertension**

Alkylating and alkyl-like agents such as ifosfamide, cyclophosphamide, platinum compounds, busulfan, bendamustine and procarbazine can cause hypertension primarily through mechanisms involving vascular injury and nephrotoxicity. Hypertension has been reported in 25% to 36% of adults treated with busulfan and in up to 58% of pediatric patients. Bendamustine has been associated with hypertensive emergencies in approximately 2.4% of treated patients. Ifosfamide is known for its nephrotoxic effects, particularly in children and in cancer survivors previously treated with this agent. Similarly, platinum-based agents have been associated with nephrotoxicity through vascular endothelial damage.

**Targeted anticancer agents**

Vascular endothelial growth factor receptor (VEGFR) inhibitors are antiangiogenic agents that induce hypertension by reducing nitric oxide production and increasing vascular resistance. The incidence of anti-VEGFR-induced hypertension is approximately 23%, although it varies depending on the specific agent and dosage.

**Management of Hypertension in Cancer Patients**

First line antihypertensive treatment in cancer patients includes angiotenzin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), as they provide both cardioprotective and renoprotective effects. ACEIs or ARBs are also the first-line treatment for anti-VEGFR-induced hypertension due to their renoprotective effects and beneficial effects on proteinuria associated with anti-VEGFR treatment. For patients with BP>160/100 mmHG, combination therapy with an ACEI or ARB and a dihydropyridine calcium channel blocker (CCB) is recommended. The use of fixed-dose combinations should be advised to improve treatment adherence. In cases of resistant hypertension (uncontrolled BP despite ≥3 antihypertensive agents, including a diuretic), mineralocorticoid receptor antagonists are recommended. However, caution is warranted when using diuretics in patients at risk of volume depletion secondary to chemotherapy-related adverse effects. If BP remains uncontrolled despite optimal antihypertensive treatment, modification of the anticancer treatment regimen may be necessary, including dose reduction or mporary discontinuation of anticancer agents. Prohypertensive anticancer agents should be withheld if BP exceeds 180/110 mmHG and should not be restarted until BP is controlled (<160/100 mmHG). Additionally, other contributing medications, including nonsteroidal anti-inflammatory drugs, corticosteroids, and erythropoiesis-stimulating agents should be carefully reviewed. Effective pain management also plays a critical role in BP control. Non-dihidropyridine CCB (verapamil, diltiazem) should be avoided in patients receiving therapies metabolized via P-glycoprotein and cytochrome P450 (e.g., sorafenib or sunitinib) due to the increased risk of drug-drug interactions and enhanced chemotherapy toxicity.

**Conclusion**

Untreated cancer therapy-induced hypertension is associated with an increased risk of coronary artery disease, heart failure, arrhythmias, and cardiovascular mortality. Given the risk of serious adverse events, early detection and an individualized, multidisciplinary approach are crucial in this group of patients.

**Keywords**: cardio-oncology; cancer therapy-induced hypertension; antihypertension treatment;

# IS THERE SUCH A THING AS CARDIONEPHROTOXICITY?

JOSIPA JOSIPOVIĆ[1,2]

[1]*Department of Nephrology and Arterial Hypertension, Clinic for Internal Medicine, Sestre milosrdnice University Hospital Center, Zagreb, Croatia*
[2]*Catholic University of Croatia, School of Medicine, Zagreb, Croatia*

Advances in modern oncology have substantially improved cancer survival, but have also increased recognition of renal and cardiovascular complications related to anticancer therapies. Although cardiotoxicity and nephrotoxicity have traditionally been viewed as separate entities, growing evidence supports the concept of cardionephrotoxicity, characterized by interconnected injury to both the heart and kidneys during cancer treatment (1,2).

The kidney is particularly vulnerable to anticancer therapies because of its high blood flow, metabolic activity, and central role in drug elimination. Renal injury may involve all kidney compartments, including vascular endothelium, glomeruli, tubules, and interstitium. Clinical manifestations range from acute kidney injury (AKI), proteinuria, electrolyte and acid–base disturbances, hypertension, and tubulointerstitial nephritis (TIN), to thrombotic microangiopathy (TMA), glomerulopathies, and progression to chronic kidney disease (CKD) (3,4).

Several anticancer agents may simultaneously induce renal and cardiovascular toxicity through shared mechanisms such as endothelial dysfunction, oxidative stress, inflammation, and mitochondrial injury. VEGF inhibitors are among the most important examples, frequently causing hypertension, proteinuria, endothelial injury, and TMA (5). Anthracyclines and HER2-targeted therapies may trigger cardiorenal syndrome secondary to chemotherapy-induced heart failure, while immune checkpoint inhibitors can induce simultaneous myocarditis and nephritis through immune-mediated mechanisms (1,5). Cardiovascular toxicity remains highly prevalent among cancer survivors and significantly affects long-term morbidity and mortality (6).

Accurate assessment of kidney function in oncology patients remains particularly challenging. Serum creatinine alone is often insufficient because muscle wasting and altered body composition may lead to overestimation of renal function. Current recommendations emphasize the use of estimated glomerular filtration rate (eGFR), preferably incorporating creatinine- and cystatin C-based equations, while measured GFR (mGFR) remains the gold standard in selected high-risk patients and clinical situations requiring precise drug dosing (3). Quantification of albuminuria and proteinuria using albumin-to-creatinine (ACR) and protein-to-creatinine ratios (PCR) also represents an important component of renal monitoring, particularly during VEGF inhibitor therapy (3,5).

Preventive strategies include optimization of cardiovascular risk factors, blood pressure control, individualized anticancer drug dosing, adequate hydration, and early recognition of renal injury. Renin–angiotensin–aldosterone system blockade may be beneficial in selected patients with proteinuria or VEGF inhibitor-associated hypertension. Emerging evidence also suggests a potential role for integrated cardionephroprotective therapies, including sodium-glucose cotransporter-2 inhibitors and mineralocorticoid receptor antagonists.

Renal dysfunction may directly influence cardiovascular risk and limit continuation of potentially life-saving oncologic therapies. Conversely, cardiovascular complications such as heart failure may worsen renal perfusion and precipitate further kidney injury, creating a self-perpetuating cardiorenal axis. Early recognition and multidisciplinary collaboration between oncologists, nephrologists, and cardiologists are therefore essential for individualized risk stratification, prevention, and treatment optimization (1,2).

Understanding cardionephrotoxicity is becoming increasingly important in modern oncology practice. Greater focus on renal outcomes, precise kidney function assessment, and integrated cardio-renal monitoring may improve both treatment safety and long-term patient outcomes.

**Keywords:** cardionephrotoxicity; onco-nephrology; acute kidney injury; thrombotic microangiopathy; cardio-oncology; kidney function assessment

REFERENCES

1. Attieh RM, Nunez B, Copeland-Halperin RS, Jhaveri KD. Cardiorenal impact of anti-cancer agents: the intersection of onco-nephrology and cardio-oncology. Cardiorenal Med. 2024;14:281-293. doi:10.1159/000539075
2. Salati S, Firouzbakht B, Daneii P, Azarpey A, Hatami B, Johari Moghadam MM, et al. Oncocardiology: close collaboration between oncologists, cardiologists, and nephrologists. J Nephropharmacol. 2024;13(1):e11660. doi:10.34172/npj.2023.11660
3. Renaghan AD, Ostermann M, Ronco C, Ballen K, Cosmai L, Fenoglio R, et al. The nephrotoxic effects of anti-cancer therapies: consensus report of the 34th Acute Disease Quality Initiative workgroup. Nat Rev Nephrol. 2026;22:283-300. doi:10.1038/s41581-025-01031-3
4. Chen C, Xie D, Gewirtz DA, Li N. Nephrotoxicity in cancer treatment: an update. Adv Cancer Res. 2022;155:77-129. doi:10.1016/bs.acr.2022.03.005
5. Mihalcea D, Memis H, Mihaila S, Vinereanu D. Cardiovascular toxicity induced by vascular endothelial growth factor inhibitors. Life (Basel). 2023;13(2):366. doi:10.3390/life13020366
6. Wong-Siegel JR, Hayashi RJ, Foraker R, Mitchell JD. Cardiovascular toxicities after anthracycline and VEGF-targeted therapies in adolescent and young adult cancer survivors. Cardiooncology. 2023;9:30. doi:10.1186/s40959-023-00181-2

## MANAGING CARDIOVASCULAR RISK IN PROSTATE CANCER TREATMENT

JURE MURGIĆ[1,2]

[1]*Department of Oncology and Nuclear Medicine, Sestre milosrdnice University Hospital Center, Zagreb, Croatia*
[2]*School of Medicine, Croatian Catholic University, Zagreb, Croatia*

Therapeutic advances in prostate cancer have significantly improved survival, particularly with the widespread use of androgen deprivation therapy (ADT), androgen receptor pathway inhibitors (ARPIs), chemotherapy, and radiotherapy. As patients live longer, non-cancer comorbidities–especially cardiovascular disease (CVD)–have emerged as a leading cause of morbidity and mortality. Cardiovascular risk is both pre-existing and treatment-related, necessitating a multidisciplinary cardio-oncology approach.

This narrative review summarizes current evidence on cardiovascular toxicity associated with systemic and local therapies for prostate cancer, with a focus on mechanisms, clinical risk factors, and risk mitigation strategies. Data from randomized trials, meta-analyses, and real-world studies are integrated to provide a clinically relevant overview.

ADT remains the backbone of treatment across disease stages but is associated with metabolic changes, including insulin resistance, dyslipidemia, and increased fat mass, contributing to elevated cardiovascular risk. Observational studies have demonstrated higher rates of myocardial infarction, stroke, and sudden cardiac death among men receiving ADT, particularly those with pre-existing CVD. Emerging

data suggest that GnRH antagonists may be associated with lower cardiovascular event rates compared with GnRH agonists in high-risk populations.

Second-generation ARPIs, including abiraterone, enzalutamide, apalutamide, and darolutamide, further improve oncologic outcomes but carry distinct cardiovascular toxicity profiles. Abiraterone is associated with hypertension, hypokalemia, and fluid retention due to mineralocorticoid excess, while enzalutamide and apalutamide have been linked to increased rates of hypertension and, less commonly, ischemic events. Darolutamide appears to have a more favorable cardiovascular safety profile, although long-term real-world data are still evolving.

Taxane-based chemotherapy, particularly docetaxel, is generally well tolerated from a cardiovascular standpoint but may rarely cause arrhythmias or heart failure. Radiotherapy, especially when involving pelvic lymph nodes, may contribute indirectly to cardiovascular risk through systemic inflammation and endothelial dysfunction, although its impact is less pronounced than in thoracic irradiation.

Importantly, patients with prostate cancer are often older and have a high baseline burden of cardiovascular risk factors, including hypertension, diabetes, and prior coronary artery disease. The interaction between patient-related factors and treatment-related toxicity underscores the need for individualized risk assessment.

Cardiovascular risk is a critical consideration in the management of prostate cancer. Baseline cardiovascular evaluation, optimization of modifiable risk factors, and careful selection of systemic therapies are essential to minimize adverse outcomes. Close collaboration between oncologists, cardiologists, and primary care physicians is key to implementing effective prevention and monitoring strategies. Future research should focus on prospective risk stratification tools and tailored interventions to improve both oncologic and cardiovascular outcomes.

**Keywords:** Prostate cancer, Androgen deprivation therapy, Cardiovascular toxicity

## MYOCARDIAL INFARCTION WITH NON-OBSTRUCTIVE CORONARY ARTERIES (MINOCA) DURING 5-FLUOROURACIL INFUSION: A CASE REPORT

LEA SKORUP ĆUTIĆ[1,2], Koraljka Benko[1,2], Tihana Salopek[3], Tamara Hlača Caput[1], Laura Afrić[1]

[1]*Clinic for cardiovascular diseases, Clinical Hospital Center Rijeka, Rijeka, Croatia*
[2]*The Faculty of Medicine, University of Rijeka, Rijeka, Croatia*
[3]*Tumor Clinic, Clinical Hospital Center Rijeka, Rijeka, Croatia*

**ABSTRACT:**

**Introduction:** Acute cardiovascular (CV) disease in patient with cancer are increasing in incidence due to multiple factors; cancer mediated prothrombotic milleu and cardiotoxic effect of cancer treatment. Acute CV complication requires prompt recognition and multidisciplinary aproach to define the underlying mechanism and guide both cardivoascular and cancer treatement (1).

Key component of noumerous chemoterapeutic regimens for solid cancers is 5- fluorouracil (5-FU). However, it is also one of the most common causes of cardiotoxicity, second only to anthracyclines (2).

**Case report:** A 57-year-old women was diagnosed with metastatic colon adenocarcinoma following detection of lung mass on rutine preoperative chest radiography prior to elective orthopedic operation. Her past history included resection of sigmoid colon due to colon adenocarcionoma (Dukes B, pT3N0 (0/23)Mx; no perineural invasion, LKI negative)) nine years earlier. Current staging revealed lung and right adrenal gland metastases. Transthoracic biopsy of lung mass confirmed diagnosis. Colonoscopy revealed sessile polyp in ascending colon and colon anastomosis without signs of recidive. She was scheduled to recive FOLFOX chemotherapy protocol and bevacizumab. Pretreatment testing confirmed normal dihidropyrimidine dehydrogenase metabolism.

During her first chemotherapy cycle, approximately 40 hours into continious 5- fluorouracil (5-FU) infusion and more than 24 hours after oxaliplatin infusion the patient developed chest pain. The infusion was imediately discontinued. Serial electrocardiograms (ECG) revealed ST depression and negative T waves in precordial leads. Serial troponin I mesurements showed upward dinamic (hsTnI 48 ng/L to hsTnI 334.1 ng/L). She recived acetylsalycic acid 300mg and amlodipine 2.5mg and was transfered to cardiology departement for further treatement of acute miocardial infarction without ST elevation. Transtoracic ehocardiography (TTE) revealed global hypokinesia with akinesia of apex and moderately reduced systolic function of left ventricle. Invasive coronarography, without functional coronary testing, was described as normal. The patient remained hemodinamicaly stable without recurrent chest pain. Cardiac magnetic resonance (CMR) imaging performed three days later demostrated now normal systolic function without signs of fibrosis and with myocardial mapping within normal limits. Chemotherapy was modified to oxaliplatin and panitumumab, along with radiotherapy of metastatases. On cardiology follow up, she remained asymptomatic with near-normal TTE findings. Despite treatment, disease progression occured over six months with developement of bone and brain metastases and the patient ultimately died forom her illnes.

**Conclusion:** Fluoropirimidine – associated cardiotoxicity has been recognised over more that five decades. Its etiopathogenesis remains incompletely understood, with propsed mechanisms including coronary vasospasm, endotelial dysfunction, mitochondrial dysfunction and ferroptosis. Acute coronary syndrome is among the most common CV complication and MINOCA is a frequent manifestation in cancer patients (3).

Risk factors for myocardial ishaemia include dose, route and administration schedule. Notably, cardiotoxicity may occur days after drug administration, complicating causal atribution. Immediate discontinuation of 5-FU is mandatory when cardiotoxicity is suspected. Decision regarding rechallenge is not easy and should be made by cardio-oncology team, bearing in mind the re-treatment risks and the aim of cancer treatment in that specific patient (4).

**Keywords**: 5- fluorouracil, MINOCA, cancer therapy-related cardiovascular toxicity

REFERENCES:

1. Gevaert, S. A. *et al.* Evaluation and management of cancer patients presenting with acute cardiovascular disease: a Consensus Document of the Acute CardioVascular Care (ACVC) association and the ESC council of Cardio-Oncology–Part 1: acute coronary syndromes and acute pericardial diseases. *European Heart Journal Acute Cardiovascular Care* 10, 947–959 (2021).
2. Morelli, M. B. *et al.* Cardiotoxicity of Anticancer Drugs: Molecular Mechanisms and Strategies for Cardioprotection. *Front. Cardiovasc. Med.* 9, 847012 (2022).
3. Zalaquett, Z. *et al.* Cardiovascular Toxicity of Fluoropyrimidines: What We Know. *Mayo Clinic Proceedings* 101, 136–155 (2026).
4. Lyon, A. R. *et al.* 2022 ESC Guidelines on cardio-oncology developed 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). *European Heart Journal* 43, 4229–4361 (2022).

# NUTRITIONAL STRATEGIES IN THE PREVENTION AND REHABILITATION OF CARDIOTOXICITY

LJUBICA VAZDAR[1,2,3]

[1]*University Hospital for Tumors, Sestre milosrdnice University Hospital Center, Division for Medical Oncology, Ilica 197, 10 000 Zagreb, Croatia*
[2]*University of Zagreb, School of Medicine, Šalata 2, 10 000 Zagreb, Croatia*
[3]*Josip Juraj Strossmayer University of Osijek, Faculty of Food Technology, F. Kuhača 18, 31 000 Osijek, Croatia*

**Summary**

Cardiotoxicity associated with oncological treatment represents a major challenge in cardio-oncology due to the potential long-term cardiovascular consequences and its impact on patients' quality of life. Its development is influenced not only by oncological therapy but also by the presence of risk factors such as chronic inflammation, insulin resistance, oxidative stress, sarcopenia, and reduced physical activity. Nutritional interventions play an important role in the prevention and rehabilitation of cardiotoxicity by acting on cardiometabolic risk, inflammatory processes, and treatment tolerance.

The ESC guidelines emphasize the importance of controlling cardiovascular risk factors before, during, and after oncological therapy, with proper nutrition and physical activity playing a key preventive role. The strongest evidence supports the Mediterranean diet, based on the intake of vegetables, fruits, whole grains, legumes, nuts, olive oil, and fish/seafood. A meta-analysis of 238 randomized studies involving nearly 198,000 participants showed a reduction in the risk of fatal cardiovascular diseases by 10–67% and of non-fatal events by 21–70%, particularly in secondary prevention.

Furthermore, a meta-analysis of prospective cohort studies with over 800,000 participants showed that regular consumption of olive oil reduces all-cause mortality and cancer mortality by 15% and cardiovascular mortality by 25%. Nuts also have a beneficial effect, associated with a 25% reduction in coronary artery disease risk and a 20% reduction in cardiovascular mortality. A diet rich in fruits, vegetables, and fiber is associated with a reduced risk of stroke, cardiovascular disease, and all-cause mortality.

Natural polyphenols from berries, olive oil, green tea, and cocoa contribute to improving cardiometabolic parameters and reducing inflammation. Regarding omega-3 fatty acid supplementation, benefit has been confirmed only for highly purified EPA in the secondary prevention of high-risk patients, while there is insufficient evidence for standard fish oil supplements. At the same time, routine use of antioxidant dietary supplements during oncological treatment is not recommended due to possible interactions with anti-tumor therapy.

In addition to nutrition, regular physical activity, including aerobic exercise and strength training, also plays an important role. The synergy of proper nutrition and physical activity represents the foundation of the modern approach to the prevention and rehabilitation of cardiotoxicity in cancer patients.

**Keywords:** cardiotoxicity; Mediterranean diet; nutritional intervention; cardiovascular prevention

# PERSONALIZATION OF ANTHRACYCLINE AND FLUOROPYRIMIDINE USE – WHO IS AT RISK OF CARDIOTOXICITY?

PETRA SERTIĆ[1]

[1]*Department of Medical Oncology, Division for Medical Oncology, University Hospital for Tumors, University Hospital Sestre Milosrdnice, Zagreb, Croatia*

Anthracyclines remain essential in treating lymphomas, acute leukemias, soft tissue sarcomas, and certain breast cancer subtypes, despite advances in targeted and immunotherapies. These cancers often affect younger patients, making long-term toxicity especially relevant. Higher cumulative anthracycline doses are associated with delayed cardiotoxicity, which is critical in potentially curable populations. Breast cancer is the most common malignancy in women, and anthracyclines are still widely used, particularly in luminal and triple-negative subtypes. Gastrointestinal cancers, comprising 20–25% of malignancies, mainly affect older individuals who already have a higher cardiovascular risk. In this group, 5-fluorouracil (5-FU) is commonly used and is the second leading cause of chemotherapy-related cardiotoxicity after anthracyclines. Anthracycline-induced cardiotoxicity results primarily from direct cardiomyocyte damage and metabolic disruption. It can occur during or after treatment. Early toxicity often presents as an asymptomatic reduction in left ventricular ejection fraction (LVEF), while late toxicity manifests as hypokinetic cardiomyopathy and heart failure. Cardiotoxicity from 5-FU varies widely depending on dose, administration, drug combinations, and patient risk factors. Although coronary vasospasm is the most common explanation–sometimes presenting as acute coronary syndrome–the mechanism is multifactorial. It may include endothelial dysfunction, microvascular impairment, coagulation disturbances, and direct mitochondrial toxicity. Clinical manifestations include angina, ischemic ECG changes, hypertension, Takotsubo syndrome, and myocardial infarction, while myocarditis and arrhythmias are less common. Cardiovascular risk prevention should begin at cancer diagnosis. Risk assessment tools such as HFA-ICOS may help stratify patients before treatment. For anthracyclines, a cumulative doxorubicin dose ≥250 mg/m² requires close cardiovascular monitoring. Risk increases more steeply at higher doses and in patients with pre-existing cardiovascular risk factors. Preventive strategies for high-risk patients include dexrazoxane and liposomal anthracycline formulations. During fluoropyrimidine therapy, aggressive management of cardiovascular risk factors and screening for coronary artery disease are recommended, along with baseline echocardiography. Regular clinical assessments based on baseline risk–including physical examination, 12-lead ECG, transthoracic echocardiography, and cardiac biomarkers–are recommended for monitoring patients during treatment with anthracyclines and fluoropyrimidines and can help identify both symptomatic and asymptomatic cardiovascular toxicity. After completion of cardiotoxic cancer therapies, ongoing surveillance is necessary, especially in high-risk patients. These are defined based on clinical characteristics, a history of therapy-related cardiovascular toxicity, elevated cardiac biomarkers, or abnormal findings on cardiovascular imaging. Education of patients about their potentially increased cardiovascular risk is essential, along with encouragement of healthy lifestyle habits.

**Key words:** Anthracyclines, fluoropyrimidines, cardiotoxicity

REFERENCES:

1. Li H, Wang M, Huang Y. Anthracycline-induced cardiotoxicity: An overview from cellular structural perspective. Biomed Pharmacother [Internet]. 2024;179(117312):117312.

2. Blaes A, Nohria A, Armenian S, Bergom C, Thavendiranathan P, Barac A, et al. Cardiovascular considerations after cancer therapy: Gaps in evidence and JACC: CardioOncology expert panel recommendations. JACC CardioOncol [Internet]. 2025;7(1):1–19.
3. Sara JD, Kaur J, Khodadadi R, Rehman M, Lobo R, Chakrabarti S, et al. 5-fluorouracil and cardiotoxicity: a review. Ther Adv Med Oncol [Internet]. 2018;10(1758835918780140):1758835918780140.
4. Lyon AR, López-Fernández T, Couch LS, Asteggiano R, Aznar MC, Bergler-Klein J, et al. 2022 ESC guidelines on cardio-oncology developed 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). Eur Heart J [Internet]. 2022;43(41):4229–361.

## PLACE AND ROLE OF CARDIAC REHABILITATION IN CARDIO-ONCOLOGY PATIENTS; CARDIO-ONCOLOGY REHABILITATION (CORE)

NENAD LAKUŠIĆ[1,2], Ivana Sopek Merkaš[1], Mateja Pracaić[1], Luka Lakušić[3]

[1]*Department of Cardiac Rehabilitation, Hospital for Medical Rehabilitation Krapinske Toplice, Krapinske Toplice,Croatia*
[2]*Faculty of Dental Medicine and Health Osijek, J. J. Strossmayer University of Osijek, Osijek, Croatia*
[3]*University of Zagreb, School of Medicine, Zagreb, Croatia*

In accordance with the European and global cardiology associations, comprehensive cardiac rehabilitation (CR) stands as an officially endorsed and highly recommended therapeutic approach (class I recommendations; level of evidence A) for a diverse spectrum of cardiac patients. Nevertheless, it is a cause for concern to observe that fewer than 50% of eligible patients are being effectively referred for CR, whether in an outpatient or inpatient setting. Concurrently, studies reveal that a substantial proportion of individuals with atherosclerotic cardiovascular disease maintain unhealthy lifestyles and exhibit suboptimal management of modifiable cardiovascular risk factors, including hypertension, lipid levels, and diabetes. Beyond the conventional patient profile encompassing those recovering from acute coronary syndrome with or without percutaneous coronary intervention, as well as patients who have undergone coronary or valvular surgery, contemporary CR now emphasizes specialized subgroups of patients such as frail elderly patients, those with chronic heart failure as well as cardiac patients with concomitant oncological disease.

CR in cardio-oncology, known as Cardio-Oncology Rehabilitation (CORE), is a multidisciplinary model of care designed to prevent and alleviate cardiovascular damage caused by cancer treatment. While classical CR is standard for patients after heart attacks or heart surgery, the CORE model adapts these methods to the specific needs of cancer patients who are at risk for cardiotoxicity. CORE integrates cardiac care with cancer treatment through several levels: a) individualized training: programs combine aerobic and resistance training to improve cardiorespiratory fitness and muscle strength, which often decline during chemotherapy, b) risk factor management: monitoring and aggressive treatment of hypertension, dyslipidemia, and diabetes, which can be exacerbated by certain therapies such as VEGF inhibitors or steroids, c) nutritional counseling: focuses on cancer-specific nutritional needs, including management of muscle loss and changes in body composition d) psychosocial support: addressing anxiety, depression, and cancer fatigue through counseling and stress management techniques.

The application of the CORE model has shown significant clinical benefits in recent research such as preservation of cardiac function, improved quality of life, better functional capacity compared to those receiving usual care, reduced cardiovascular and overall mortality in cancer survivors.

Research confirms that center-based rehabilitation programs are cost-effective despite higher initial costs compared to community-based exercise. Given that these programs are still underrepresented, interest in telerehabilitation (exercise at home with remote supervision) is growing, which could increase the availability of care for patients in rural areas or those with weakened immune systems.

In conclusion, CORE represents a bridge that connects the fight against malignant disease with the preservation of the vitality of the heart. While modern oncological therapies save lives, they sometimes pose severe challenges to the heart in the form of cardiotoxicity. Rehabilitation here ceases to be just "recovery" and becomes an active shield that allows the patient to endure treatment and return to the fullness of life.

**Keywords**: cardiooncology; cancer; cardiovascular disease; cardiotoxicity; cardiac rehabilitation

REFERENCES:

1. Lakušić N, Sopek Merkaš I. Quo vadis cardiac rehabilitation; the role of comprehensive cardiac rehabilitation in modern cardiology. World J Cardiol. 2023; 15(12): 627-632.
2. Adams SC, Rivera-Theurel F, Scott JM, Nadler MB, Foulkes S, Leong D. et al. Cardio-oncology rehabilitation and exercise: evidence, priorities, and research standards from the ICOS-CORE working group. Eur Heart J 2025; 46: 2847–2865.
3. Bisceglia I, Venturini E, Canale ML, Ambrosetti M, Riccio C, Giallauria F et al. Cardio-oncology rehabilitation: are we ready? Eur Heart J Suppl. 2024;26(Suppl 2):ii252-ii263.
4. Wilson, R, Christopher, C, Yang, E, Yang EH, Barac A, Scott CA. et al. Incorporating Exercise Training into Cardio-Oncology Care: Current Evidence and Opportunities: JACC: CardioOncology State-of-the-Art Review. J Am Coll Cardiol CardioOnc. 2023; 5(5): 553–569.
5. Lyon AR, Lopez-Fernandez T, Couch LS, Asteggiano R, Aznar MC, Bergler-Klein J. et al. 2022 ESC Guidelines on cardio-oncology developed 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): Developed by the task force on cardio-oncologyof the European Society of Cardiology. European Heart Journal 2022; 43: 4229-4361.

## PREVENTION AND THERAPY OF EARLY CARDIOVASCULAR TOXICITY

IVO DARKO GABRIĆ[1,2]

[1]*University Hospital Centre "Sestre milosrdnice", Zagreb, Croatia*
[2]*Catholic University of Croatia, School of Medicine, Zagreb, Croatia*

**Summary:**

Early cardiovascular toxicity is an important challenge in modern cancer care. New chemoterapeutic protocols have greatly improved cancer outcomes, but can also cause clinical or subclinical cancer therapy-related cardiac dysfunction (CTRCD). For this reason, cardiovascular protection is an essential part of oncologic treatment, not only as a later supportive measure.

The main goal of prevention is at first to identify high risk patients reciving high risk chhemotherapy protocole. Close monitoring of such patients allows us to detect cardiac injury at an early, subclinical stage, before a relevant fall in left ventricular ejection fraction occurs. In daily practice, this is best achieved by a combination of echocardiographic monitoring and biomarkers. Global longitudinal strain (GLS) is a sensitive marker of early myocardial dysfunction, while troponin and NT-proBNP can detect myocardial

stress or injury before overt heart failure develops. When these tests show early changes, treatment can be started sooner and cardiac damage may be limited.

Cardioprotective therapy traditionally includes ACE inhibitors and beta-blockers. These drugs remain the basis of prevention in patients at increased risk of cardiotoxicity. More recent data, however, suggest that statins may also have a useful role, especially in patients exposed to anthracyclines. Their anti-inflammatory and antioxidant effects may help reduce early myocardial injury and preserve cardiac function. In addition, SGLT2 inhibitors are becoming an interesting new option in cardio-oncology. Early studies and meta-analyses suggest that these agents may improve GLS, reduce oxidative stress, and support myocardial energy balance during cancer treatment.

Alongside pharmacological treatment, lifestyle measures are also important. Regular physical activity and balanced nutrition can help reduce inflammation, improve functional capacity, and support the heart during cancer therapy. These measures are especially valuable in patients receiving intensive treatment or those with pre-existing cardiovascular risk factors.

The best results are achieved through a multidisciplinary cardio-oncology team that can identify high-risk patients, start early monitoring, and adjust therapy. A strategy based on early detection, prompt treatment, and coordinated care may reduce the burden of cardiovascular toxicity and help patients complete life-saving cancer therapy safely.

**Keywords:** Cardio-oncology; early cardiotoxicity; prevention; GLS; statins; SGLT2 inhibitors

## QT INTERVAL ASSESSMENT IN CDK4/6 INHIBITOR RIBOCICLIB THERAPY – HOW IMPORTANT IS IT?

SINIŠA CAR[1]

[1]*Department of Arrhythmias, Clinic for Cardiovascular Diseases, University Hospital Centre Sestre Milosrdnice, Zagreb, Croatia*

**Abstract**

CDK4/6 inhibitors – palbociclib, ribociclib, and abemaciclib – represent the standard of care in HR+/HER2– breast cancer, but their cardiovascular safety profiles differ significantly, making drug-specific rather than class-based monitoring mandatory.

Ribociclib carries the highest risk of QTc interval prolongation within the class, with Grade 3 prolongation (defined as QTcF >500 ms or an increase of >60 ms from baseline, per CTCAE v5.0) reported exclusively with this agent. A pooled analysis of MONALEESA-2, -3, and -7 (Ball et al., 2,062 patients) demonstrated a nearly 8-fold increased relative risk for QTcF prolongation >60 ms from baseline (RR 7.96; 95% CI 3.68–17.19) and a 4-fold increased risk for post-baseline QTcF >480 ms (RR 4.00; 95% CI 2.16–7.41; $I^2$=0). Only 1.38% of patients required dose reduction, interruption, or discontinuation. A 2024 meta-analysis (Murad B et al., JNCI Cancer Spectrum; 14 RCTs, 16,196 patients) confirmed a 3.12-fold increased relative risk of QTc prolongation (95% CI 2.09–4.65) and a 5.84-fold increased risk of QTcF rise >60 ms from baseline, with Grade 3 events observed exclusively with ribociclib. A 2025 meta-analysis (Hoo YY et al., Cancer Treatment

Reviews) confirmed that approximately 80% of prolongations occur within the first four weeks and are reversible upon dose modification. No cases of „torsades de pointes“ have been reported across all trials.

QTc prolongation represents only part of the cardiotoxicity burden of ribociclib. A meta-analysis by Aziri et al. (JACC, 2024; 6 RCTs, 6,974 patients) identified hypertension as a second clinically relevant cardiotoxic effect (~8% incidence) and confirmed a dose-dependent relationship – prolongation rates were 9% at 600 mg versus 5% at 400 mg. Real-world pharmacovigilance data (Li et al., International Journal of Cancer, 2025; FAERS Q1/2015–Q1/2024) confirmed QTc prolongation as a strong ribociclib signal (IC 2.11; 95% CI 1.90–2.29) and uniquely identified conduction defects as an additional ribociclib-specific signal (IC 2.07; 95% CI 1.87–2.23) – not previously captured in RCTs. Age ≥65 years and type of CDK4/6 inhibitor were identified as significant risk factors.

The primary mechanisms include hERG potassium channel blockade, moderate CYP3A4 inhibition, and potential modulation of cardiac ion channel gene expression, with a confirmed concentration-dependent effect. Risk stratification before initiation is essential, encompassing baseline QTcF, electrolyte status, concomitant QT-prolonging medications, and patient-specific factors. ECG monitoring is mandatory per ESC guidelines (Class I/A): at baseline, Day 14 of Cycle 1, and Day 1 of Cycle 2, with additional monitoring at each dose increase. Dose management follows a structured algorithm up to permanent discontinuation in cases of TdP or symptomatic arrhythmia.

QT interval monitoring in ribociclib therapy is not a formality – it is a safety-critical protocol enabling continuation of effective oncological treatment. Emerging real-world evidence suggests the cardiotoxicity profile of ribociclib extends beyond QTc prolongation, reinforcing the need for comprehensive and individualized cardiovascular surveillance.

**Keywords:** ribociclib; QTc prolongation; cardio-oncology; CDK4/6 inhibitors; ECG monitoring; pharmacovigilance

## RECEPTIVE MUSIC THERAPY AND FRACTAL CHROME MUSIC THERAPY IN CARDIO-ONCOLOGY

GORAN KRSTAČIĆ[1,3], Antonija Krstačić[2,3]

[1]*Polyclinic for Prevention of Cardiovascular Diseases and Rehabilitation, Zagreb*
[2]*Department of Neurology, Clinic of Traumatology, KBC Sestre milosrdnice, Zagreb*
[3]*Faculty of Dental Medicine and Health, J. J. Strosmayer University of Osijek, Croatia*

If we are talking about continuous communication between the brain and the heart, then the influence of art in cardiology (cardio-oncology) is indispensable. Can we not only inherit the application of some artistic methods in cardiovascular or neurological rehabilitation, but also expand it with some new, mostly holistic methods, which in turn contain art in themselves? Chromotherapy (light and color therapy) has been a known method of treatment for centuries, and is increasingly being discovered in various branches of medicine. The most commonly used colors are (red, green, blue, orange and yellow) and stimulate the soul and psyche. The importance of chromotherapy was also highlighted by Dr. John Ott, who said: “Light is a foodstuff similar to food – the wrong type will make us sick, and the right one will

keep us healthy. "The existence of every living being depends on light. Scientific research has shown that all matter, including every cell in our body, consists of energy and that every cell in the body emits light. Color flows through us, it is an active force and has a huge impact on our spirit and body.

On the other hand, music therapy (music therapy, music therapy or melotherapy) is a method of treatment with music that is used to achieve a better physical, spiritual, social or emotional state of a person, without the targeted development of personal musical singing or playing skills. Music therapy is an officially recognized holistic discipline in about fifty countries. Music therapy has been known since ancient times, and developed especially in the second half of the 20th century. Modern music therapy includes ethnomusicology, aesthetics and music psychology. Music therapy directly affects the autonomic nervous system, is intended for everyone, regardless of intelligence, reduces anxiety and stress, strengthens the mechanisms of coping with illness. Music therapy, which some authors consider to be a young medical discipline, has used various musical instruments for centuries to treat diseases and revive the spirit. From the Aboriginal use of the didgeridoo to treat physical ailments, to the ancient oriental use of the gong to treat the spirit. Pythagoras believed that music can significantly contribute to human health, and he called the process of healing with music "purification". He was the first founder of a school that dealt with the study of the effects of music, or rhythm, on human passions, and he called music that had a positive effect on humans "music of the spheres". He believed that with the help of music, both the body and the mind can be purified. It was also believed in ancient China that music has healing powers. Zen teacher Su Ma Tsien also wrote about this in his memoirs: "Sounds and music move the arteries and veins. The so-called "ton che" affects the heart and brings to man the harmony of ideal customs and rituals. Music therapy as a form of expressive art therapy, which uses music to improve and maintain the physical, psychological and sociological well-being of an individual, includes a wide range of activities, such as listening to music, singing, playing a musical instrument, writing songs, etc. Music therapy is a profession that has become part of comprehensive medical practice and is carried out in cooperation and agreement with other members of the medical team as part of the overall rehabilitation of the patient. In the cardiovascular rehabilitation program (CVR), the music therapist is a member of the cardiology team, participates in every phase of patient care and helps in the process of maintaining good heart health. With KVR, receptive music therapy is most often used, which implies active and focused listening to selected music in order to achieve therapeutic goals. Contemporary evidence-based music therapy practice emphasizes the importance of the patient's choice of music to ensure the most effective treatment, and the application of music therapy is primarily aimed at calming, alleviating and reducing stress and anxiety, and improving mood. Systematic and targeted use of music is an effective psychological intervention whose effects are also reflected in physiological outcomes such as lowering blood pressure and heart rate. These effects are attributed to the activity of the brain and the autonomic nervous system, but the relationship between musical features and the activity of the autonomic nervous system is not yet completely clear. Further studies have yet to answer questions about the limitations, as well as recommendations for the application of this type of intervention within the framework of cardiovascular rehabilitation programs.

Fractal chromomusicotherapy is a completely new method that simultaneously includes a digital health method, i.e. nonlinear dynamics, chaos theory and biosignal processing of patient records, such as ECG, and holistic methods of chromotherapy and music therapy. Something completely new and revolutionary, this combination of music and images, but music and images of the patient's own heart. This means that we could give the patient the so-called "three-in-one" therapy, i.e. chromotherapy based on images and colors of his heart generated from digital data of the ECG signal (basic ECG, telemetric ECG or 24-hour ECG recording) and music therapy composed especially for the patient by an academic musi-

cian who has experience in music therapy of various forms of disease. Patients listen to "composed music" for and from the heart and at the same time observe the images and colors of the fractals of their heart. This combination of therapy could be particularly useful for a newer group of patients who require cardiac rehabilitation, namely the so-called cardio-oncology patients (patients after chemotherapy or immunotherapy for malignant diseases that can result in cardiotoxicity, i.e. damage to the heart muscle and heart structures). This group of patients is already very "vulnerable" because they have already undergone severe therapy with possible harmful consequences. Therefore, they need some new methods and a gentler approach. We hope that a combination of standard and new techniques could achieve better patient engagement in the CVR program, better rehabilitation outcomes, and longer-term sustainability of positive results.

Chromotherapy, music therapy, and fractal chromomusicotherapy are effective psychological interventions whose effects are manifested in physiological outcomes such as reduced blood pressure, heart rate, and respiratory rate. The basis is brain activity and the autonomic nervous system, but scientific explanations of these connections are new scientific challenges and the subject of further research.

**Keywords**: chromotherapy; music therapy; fractal chromomusicotherapy

## REVERSIBLE CARDIOTOXICITY – WHEN CAN WE EXPECT RECOVERY?

LANA MARIČIĆ[1,2]

[1]*Department of General Cardiology and Ischemic Heart Disease; Division of Cardiology; University Hospital Centre Osijek, Osijek, Croatia*
[2]*Faculty of Medicine Osijek, University J.J. Strossmayera; Osijek; Croatia*

**Background:** Reversible cardiotoxicity refers to a transient impairment of cardiac function, most commonly associated with the use of chemotherapeutic agents such as trastuzumab or anthracyclines during the early phases of treatment. This condition may resolve after discontinuation of therapy or with appropriate medical management. Improvement is typically expected within a period ranging from several weeks to a few months following removal of the causative agent. In some patients, recovery of left ventricular function may begin within 1 to 3 months, while complete normalization may take up to 6 months or longer. The rate of recovery depends on several factors, including the type and dose of the administered drug, duration of therapy, timely recognition of cardiac dysfunction, and initiation of cardioprotective treatment such as ACE inhibitors and beta-blockers.

**Case Report:** A 40-year-old woman was diagnosed in 2018. with HER2-positive right breast cancer (Ki-67 25%) with axillary lymph node metastases. A mastectomy was performed, followed by adjuvant chemotherapy, radiotherapy and adjuvant therapy with trasuzumab for one year. Baseline echocardiography showed a preserved left ventricular ejection fraction (LVEF 73%). Until 2023. received LHRH agonists, then continued endocrine therapy.

In November 2023, disease recurrence was confirmed, presenting as hormone receptor-negative invasive breast carcinoma infiltrating the pectoral muscle Treatment with pertuzumab and trastuzumab was started.

After six cycles of chemotherapy, adjuvantly with pertuzumab and trastuzumab, the patient was hospitalized with a clinical picture of cardiac decompensation in August 2024. Echocardiography revealed a significantly reduced systolic function of LV EF BP 27%, with reduced function of right ventricular, TAPSE 14 mm, S' 0.06 m/s, NTproBNP 6742 ng/L. After discontinuation of oncology therapy and initiation of heart failure treatment, gradual recovery was observed. At 3-month follow-up, LVEF improved to 48%, and after 6 months, complete recovery was achieved (LVEF 60%), with NT-proBNP reduced to 908 ng/L.

**Conclusion:** Regular cardiac monitoring and early intervention enable full recovery of cardiac function and may allow the safe continuation of oncologic management.

**Keywords:** Breast neoplasms; drug-related cardiotoxicity; anti-HER2 therapy; trastuzumab; heart failure

## VASCULAR TOXICITY OF CANCER THERAPY

KARLO GOLUBIĆ[1,2]

[1]*Department of Cardiology, University Hospital Centre Sestre milosrdnice, Zagreb, Croatia*
[2]*Catholic University of Croatia, School of Medicine, Zagreb, Croatia*

**Abstract**

Vascular toxicity of cancer therapy is the second most common cardiovascular complication of oncological treatment and represents a significant cause of non-cancer mortality in patients undergoing therapy. It is as prevalent as cardiotoxicity in scientific publications of the targeted therapy era. The spectrum of vascular toxicity encompasses three main categories: arterial toxicity (vasospasm and microvascular dysfunction, thrombosis, and accelerated atherosclerosis), venous thromboembolism (VTE), and pulmonary hypertension.

Acute vasospasm and microvascular dysfunction are most frequently associated with conventional chemotherapy agents such as 5-fluorouracil (5-FU) and capecitabine, paclitaxel, bleomycin, and cisplatin. Targeted agents, particularly VEGF inhibitors (bevacizumab) and tyrosine kinase inhibitors (sunitinib, sorafenib), impair endothelial nitric oxide signalling and reduce coronary flow reserve. Immunotherapy, including CAR T-cell therapy and immune checkpoint inhibitors (ICIs), has minimal direct effect on acute vascular dysfunction. Treatment of vasospasm relies primarily on vasodilators, including nitrates and calcium channel blockers.

Arterial thrombosis is predominantly associated with cisplatin and VEGF inhibitors through endothelial surface erosion, platelet activation, and impaired endothelial repair. BCR-ABL1 inhibitors, particularly nilotinib and ponatinib, carry a prothrombotic profile with increased risk of myocardial infarction and stroke. Management includes anticoagulation, fibrinolysis, antiplatelet therapy, and revascularisation, with drug-eluting stents preferred over bare metal stents in cancer patients with high bleeding risk.

Accelerated atherosclerosis is a long-term complication, particularly following cisplatin-based regimens and anthracyclines. Testicular cancer survivors treated with cisplatin face up to a sevenfold increased risk of coronary artery disease, persisting decades after treatment. VEGF inhibition and certain TKIs (nilo-

tinib, ponatinib) further accelerate atherosclerosis, while ICI therapy promotes plaque destabilisation through enhanced T-cell-mediated inflammation. All patients should be managed according to current cardiovascular guidelines with optimal medical therapy.

Cancer patients face a 4–7-fold increased risk of VTE compared to the general population, with the highest risk in the first months after diagnosis and in metastatic disease. Prophylaxis with LMWH or direct oral anticoagulants (apixaban, rivaroxaban) is indicated in high-risk patients (Khorana score ≥3). Treatment should be individualised based on bleeding risk, tumour type, and thrombocytopenia. Dasatinib-induced pulmonary hypertension is a recognised complication requiring echocardiographic surveillance and potential haemodynamic evaluation.

Optimal screening methods, prevention strategies, and monitoring protocols for vascular toxicity remain to be defined. Future research should focus on identifying risk factors, establishing screening thresholds, and clarifying the pathophysiological mechanisms underlying cancer therapy-associated vascular toxicity to enable safe and effective oncological treatment.

**Keywords:** vascular toxicity; cancer therapy; vasospasm; arterial thrombosis; venous thromboembolism; accelerated atherosclerosis