Onko-kardiológia highlights

DR. NAGY ANDRÁS CSABA PHD

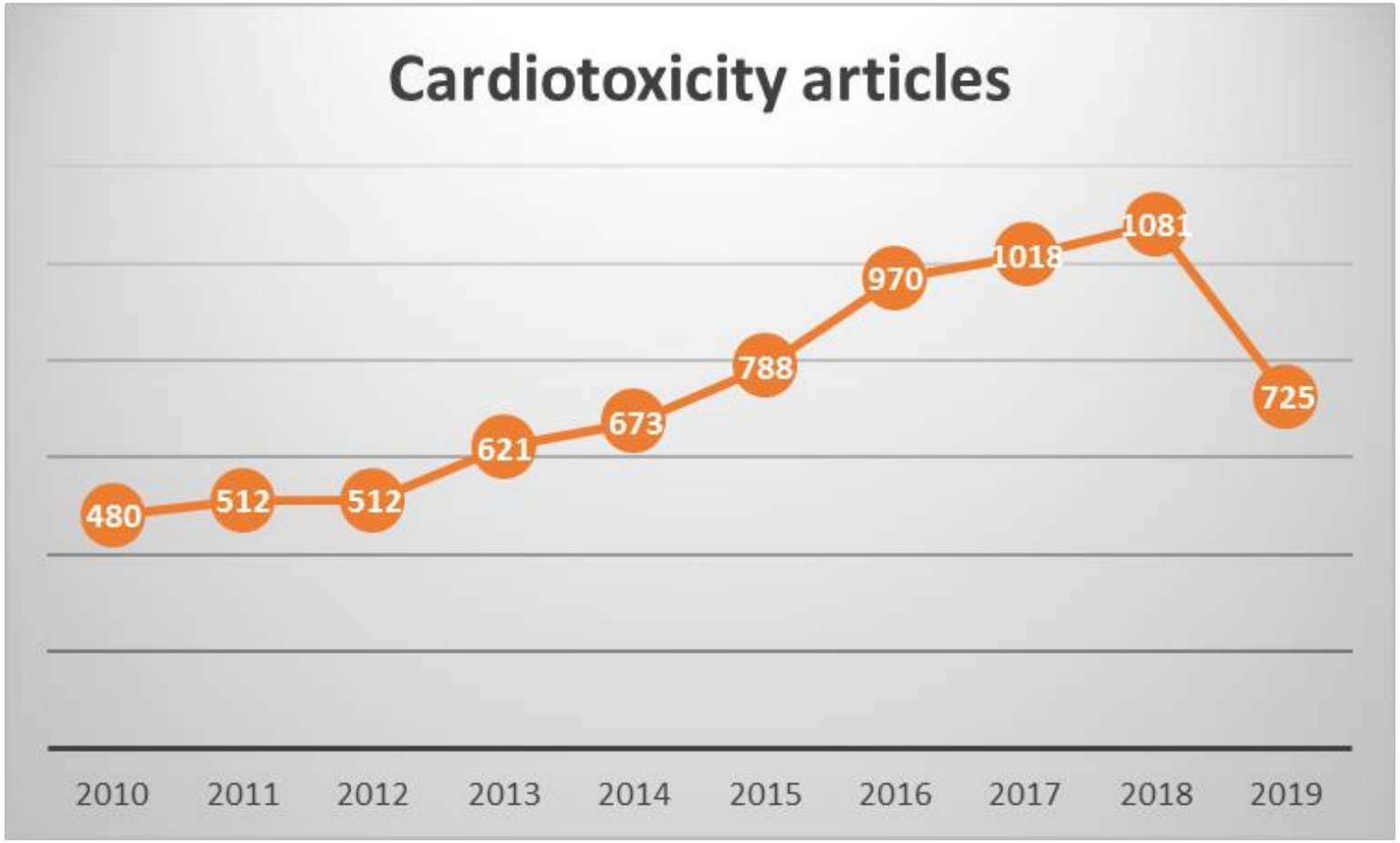
ZUGLÓI EGÉSZSÉGÜGYI SZOLGÁLAT

2019 SZEPTEMBER 13.

Újdonságok. Újdonságok?

1. Epidemiológia: közös halmaz
2. A legújabb szerekkel is foglalkoznunk kell?
3. Szívelégtelenség és kardiotoxicitás
4. Precíziós gyógyszerek?
5. Sisyphus mítosza
6. Biomarkerek?
7. Újabb preventív szerek?

Cardiotoxicitás publikációk



Forrás: Pubmed

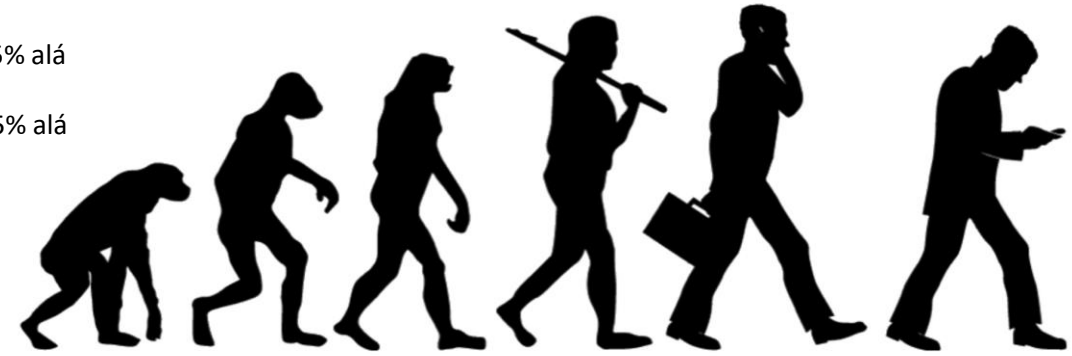
Kardiotoxicitás definíció evolúciója

The National Cancer Institute: "toxicity that affects the heart" (www.cancer.gov/dictionary/)

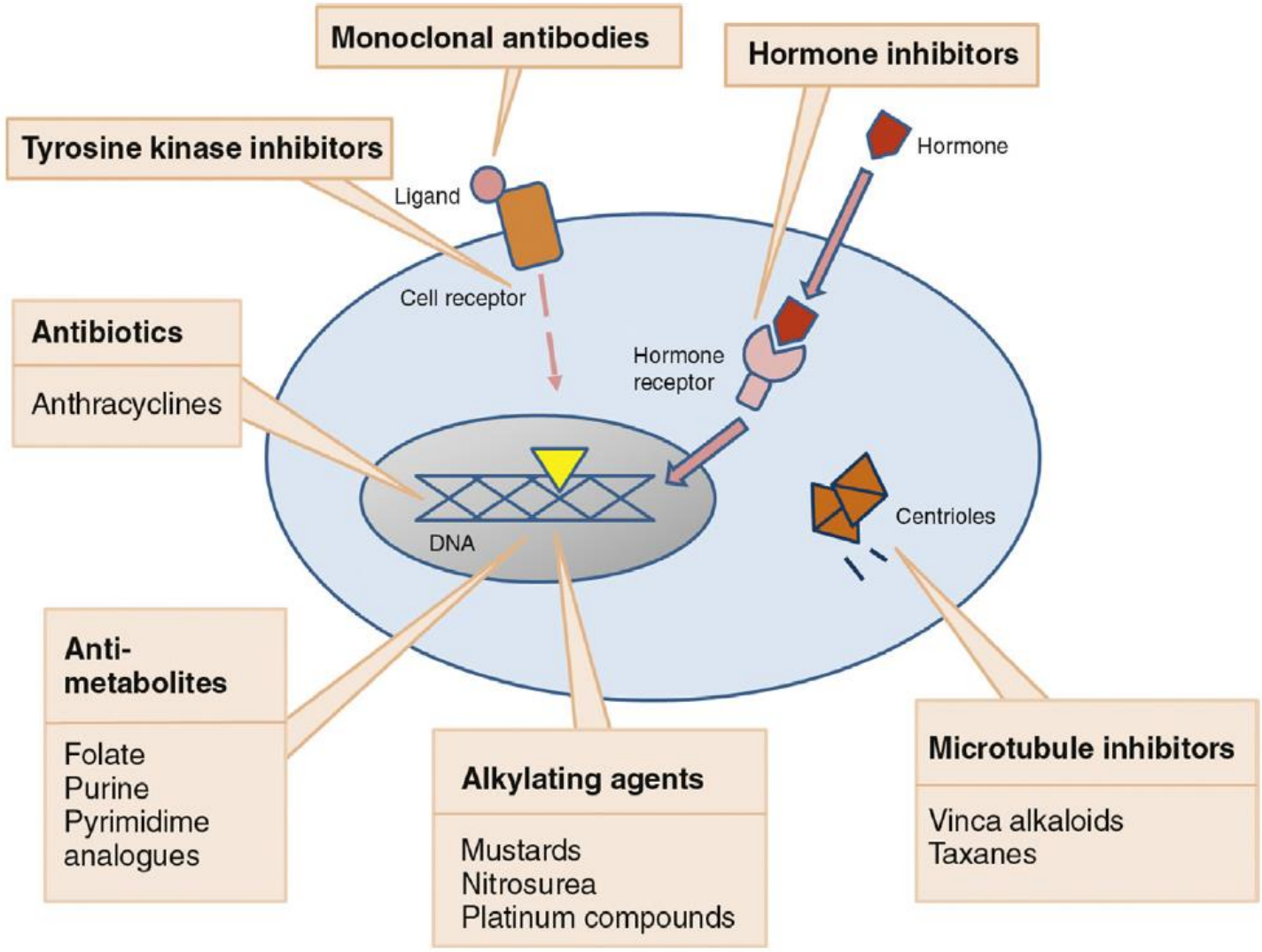
Korábbi definitio egy trastuzumab trial alapján (Cardiotoxicitás legalább egy az alábbiak közül):

- 1. CM csökkent (globalis vagy súlyosabb segmentalis - septalis) LVEF
- 2. szívelégtelenség tünetei
- 3. szívelégtelenség jele (S3 gallop, tachycardia, vagy mindkettő)
- 4. LVEF 5%-os csökkenése, vagy 55% alá esése tünetekkel,
- vagy 10%-os csökkenése, illetve 55% alá esése tünetmentes betegnél

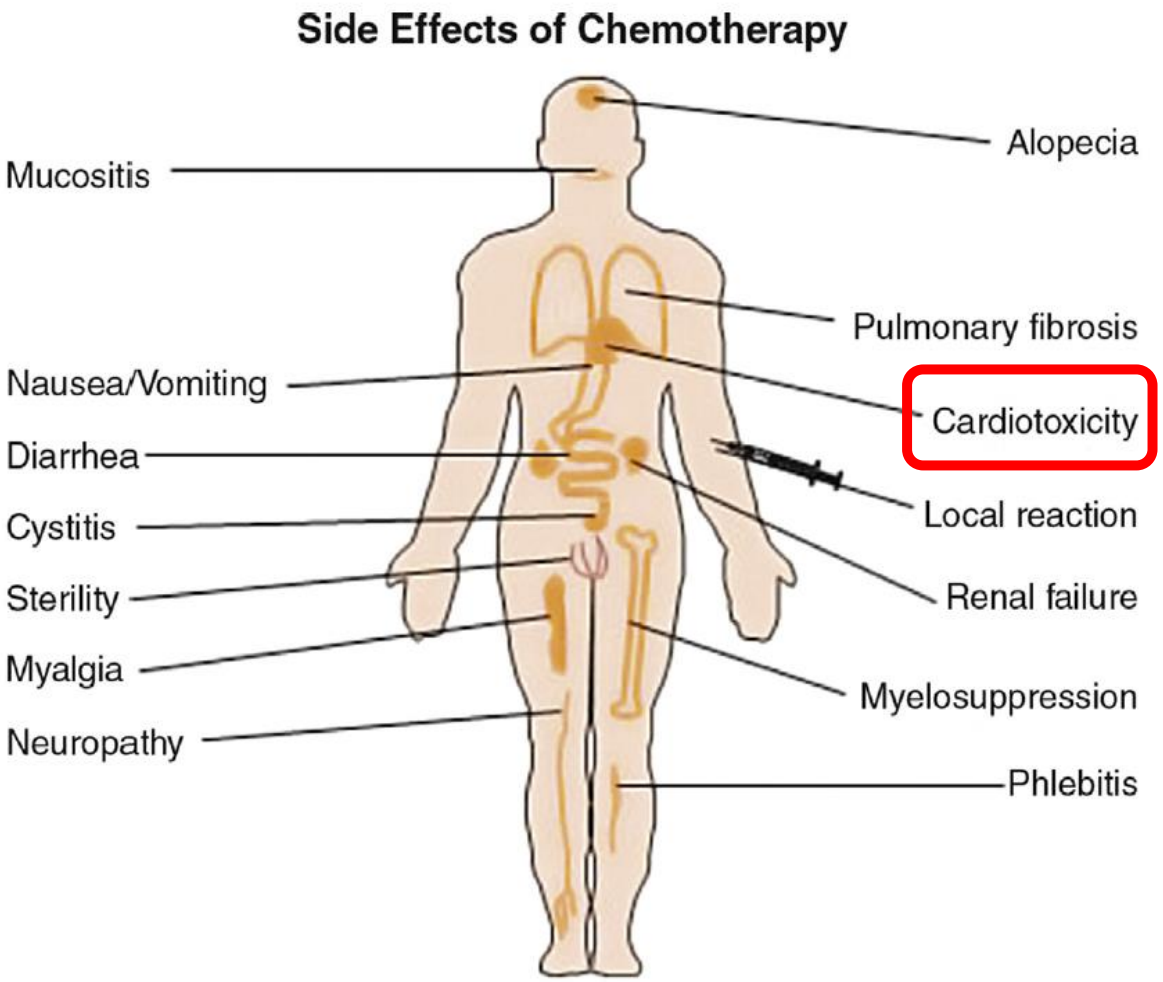
CTRCD – bármilyen kardiovaszkuláris mellékhatás, mely daganatellenes kezeléssel függ össze

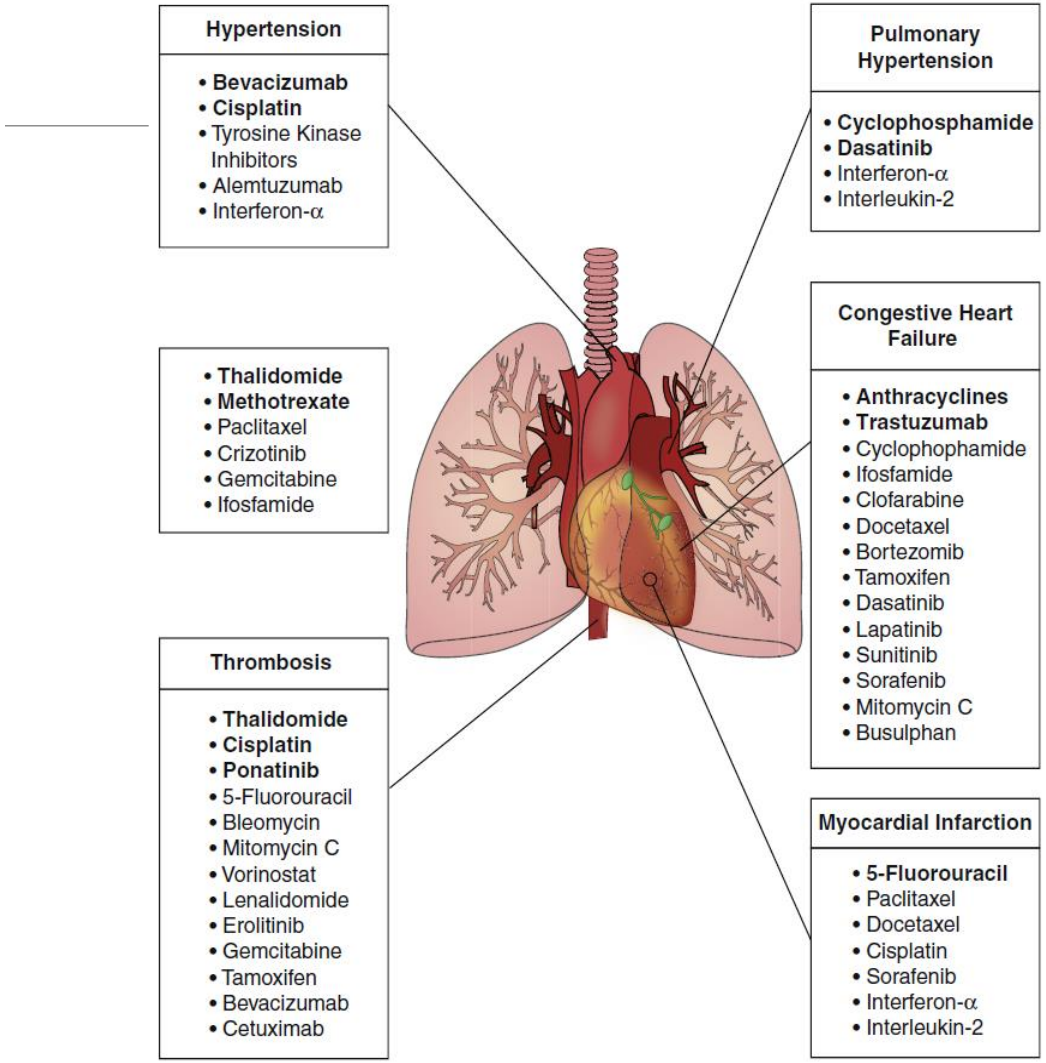


A daganatellenes kezelések legfontosabb hatásai



A daganatellenes kezelések legfontosabb mellékhatásai





CV és daganatos betegségek: közös halmaz?

Current Oncology Reports (2019) 21:47
https://doi.org/10.1007/s11912-019-0796-0

CARDIO-ONCOLOGY (EH YANG, SECTION EDITOR)

Cardiovascular Disease and Cancer: Is There Increasing Overlap?

Logan Vincent[1] · Douglas Leedy[2] · Sofia Carolina Masri[1] · Richard K. Cheng[1,3]

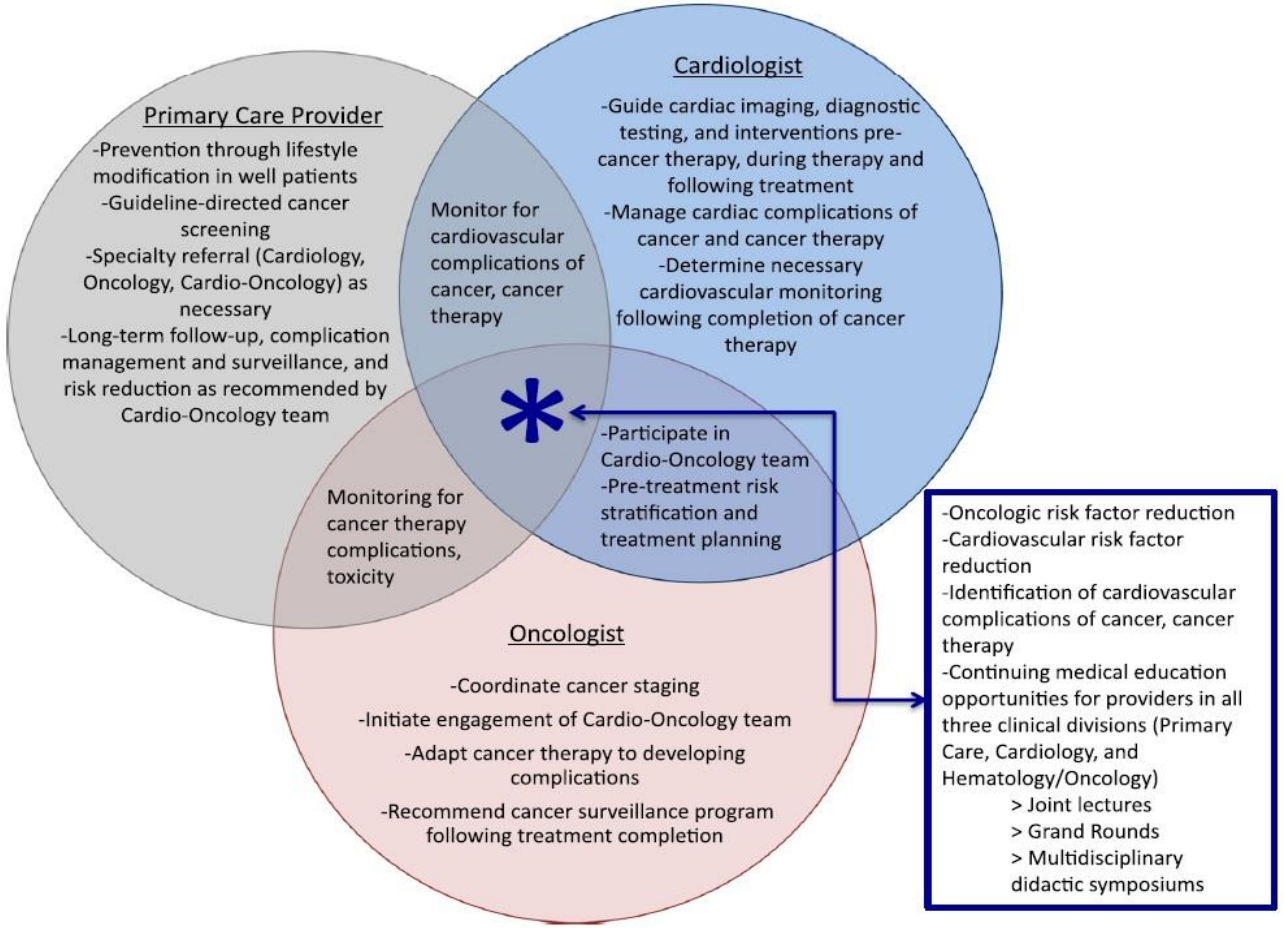
CV és daganatos betegségek: közös halmaz?

Shared modifiable risk factors for CVD and cancer

Risk factor	CVD	Cancer
Tobacco	Implicated in 30% of CVD; 50% reduction in CHD risk after 1 year of cessation. Impairs nitric oxide bioavailability, promotes a prothrombotic and inflammatory state, and leads to endothelial damage	Single largest modifiable risk factor. Implicated in 30% of all cancer-related deaths. Strongly associated with lung, esophageal, pancreatic, and bladder cancer.
Alcohol	J-shaped curve with improved CVD outcomes in moderate consumption.	No safe limit. Increase risk of colorectal, oropharynx, esophageal, liver, and breast cancer.
Obesity	Independent risk factor when others controlled. Often associated with other risk factors—dyslipidemia, insulin resistance, sedentary lifestyle, hypertension.	Second largest modifiable risk factor. Implicated in 20% of all cancer. Increased risk with increasing BMI.
Physical inactivity	Less than 30% of adults meet recommended physical activity. Responsible for 12.2% of the global burden of MI.	Increased risk of breast, colorectal, bladder, endometrial, esophagus, kidney, lung, and stomach.
Hypertension	Single largest preventable cause of CVD. Effects one-third of the adult population, two-thirds of adults aged ≥ 60 years.	Weakly linked to increased risk of renal cell carcinoma. Prolonged exposure to ACEIs may have an increased risk of lung cancer.
Hyperlipidemia	Contributes to atherosclerotic plaque formation. Affects over one-third of adults age ≥ 40 years. Only about 50% of patients recommended for treatment are on cholesterol medication.	Mixed results, strongest evidence supports a possible association with breast cancer. Statins may have a role in preventing recurrence in cancer, particularly breast cancer.
Diabetes mellitus	Regarded as a CVD risk equivalent. Contributes to atherosclerosis through hyperglycemia-induced glycosylation, free-radical oxidative damage, and dyslipidemia.	Increased cancer-related death; particularly breast, endometrial, colorectal, and intrahepatic cholangiocarcinoma.
Chronic inflammation	Cornerstone of atherosclerosis and underlying mechanism of many CVD risk factors. Future area of pharmacologic targets.	Underlying mechanism of carcinogenesis. Future area of pharmacologic targets.
CHIP	Associated with CAD, early MI, and ischemic stroke.	Associated with hematologic malignancies.

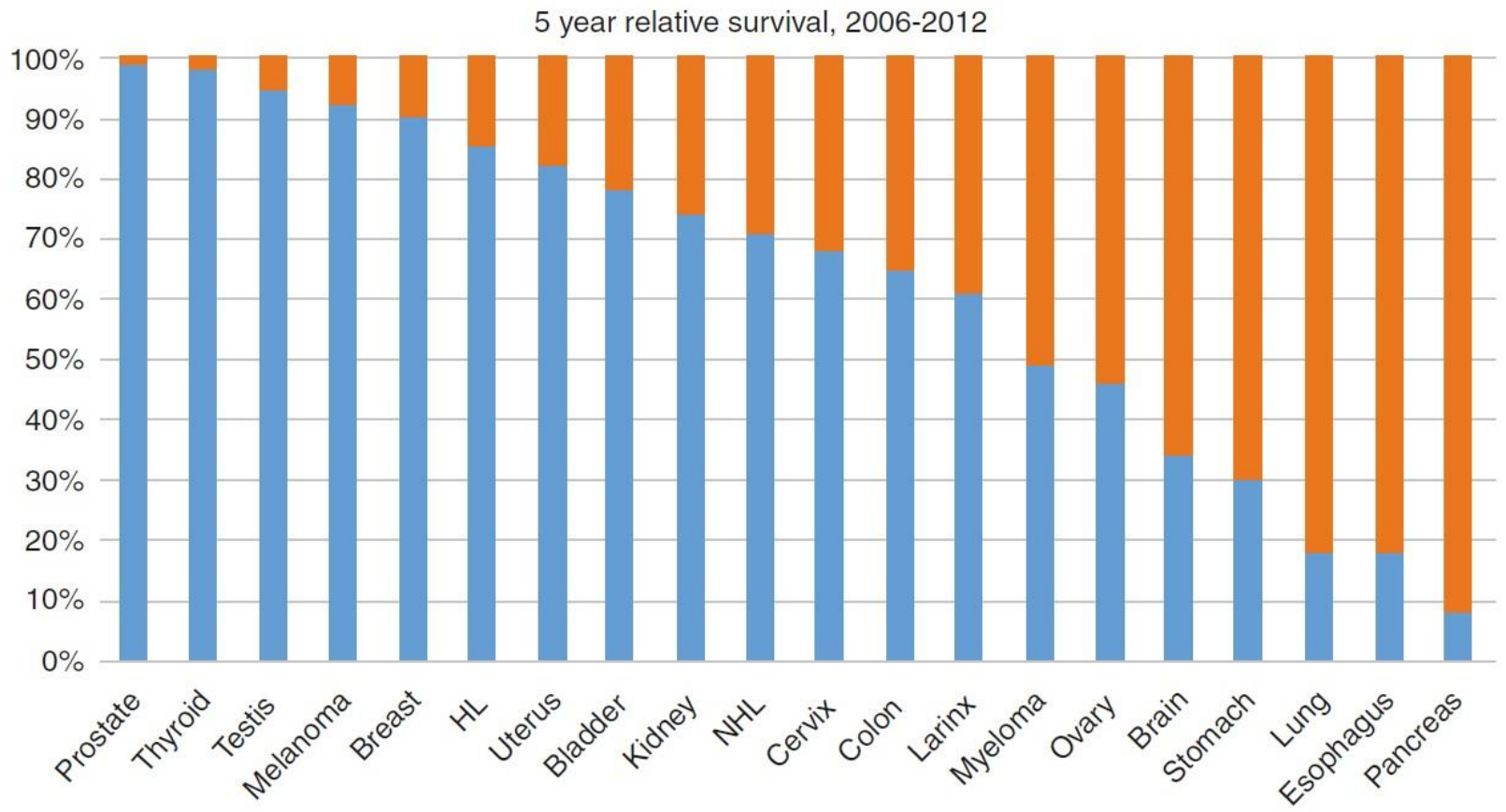
Vincent L. et al: Current Oncology Reports (2019) 21:47

Fontos az együttműködés!



Vincent L. et al: Current Oncology Reports (2019) 21:47

5 éves relatív túlélés (2006-2012) daganatonként



SEER 18 registries, National Cancer Institute. 2016

ESC Állásfoglalás 2016

European Heart Journal Advance Access published August 26, 2016

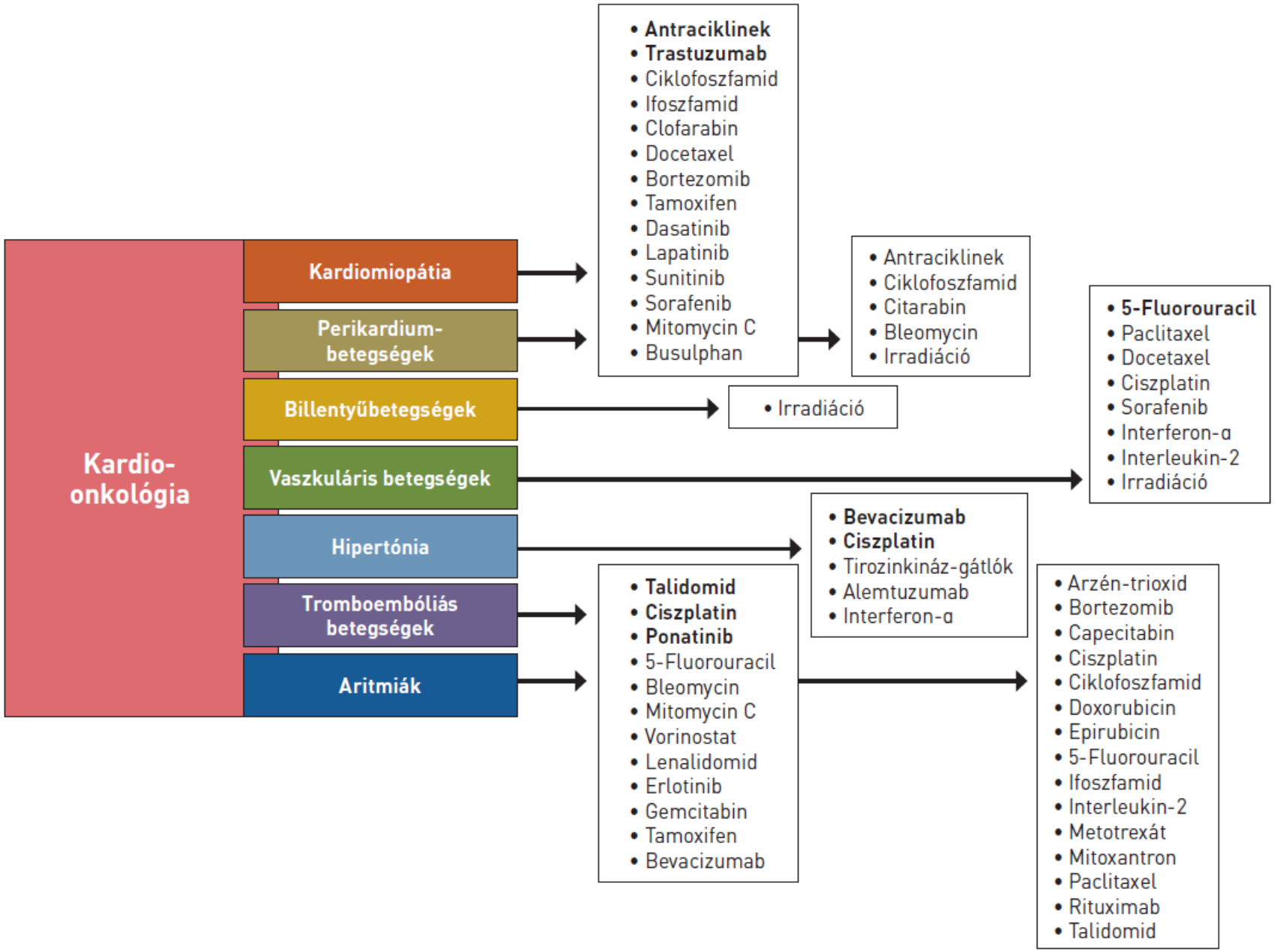
European Heart Journal
doi:10.1093/eurheartj/ehw211

ESC CPG POSITION PAPER

2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines

The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC)

Authors/Task Force Members: Jose Luis Zamorano* (Chairperson) (Spain), Patrizio Lancellotti* (Co-Chairperson) (Belgium), Daniel Rodriguez Muñoz (Spain), Victor Aboyans (France), Riccardo Asteggiano (Italy), Maurizio Galderisi (Italy), Gilbert Habib (France), Daniel J. Lenihan[1] (USA), Gregory Y. H. Lip (UK), Alexander R. Lyon (UK), Teresa Lopez Fernandez (Spain), Dania Mohty (France), Massimo F. Piepoli (Italy), Juan Tamargo (Spain), Adam Torbicki (Poland), and Thomas M. Suter (Switzerland)


Kardio-onkológia
Kardiomiopátia
Perikardium-betegségek
Billentyűbetegségek
Vaszkuláris betegségek
Hipertónia
Tromboembóliás betegségek
Aritmiák
• Antraciklinek
• Trastuzumab
• Ciklofoszfamid
• Ifoszfamid
• Clofarabin
• Docetaxel
• Bortezomib
• Tamoxifen
• Dasatinib
• Lapatinib
• Sunitinib
• Sorafenib
• Mitomycin C
• Busulphan
• Antraciklinek
• Ciklofoszfamid
• Citarabin
• Bleomycin
• Irradiáció
• Irradiáció
• 5-Fluorouracil
• Paclitaxel
• Docetaxel
• Ciszplatin
• Sorafenib
• Interferon-α
• Interleukin-2
• Irradiáció
• Bevacizumab
• Ciszplatin
• Tirozinkináz-gátlók
• Alemtuzumab
• Interferon-α
• Talidomid
• Ciszplatin
• Ponatinib
• 5-Fluorouracil
• Bleomycin
• Mitomycin C
• Vorinostat
• Lenalidomid
• Erlotinib
• Gemcitabin
• Tamoxifen
• Bevacizumab
• Arzén-trioxid
• Bortezomib
• Capecitabin
• Ciszplatin
• Ciklofoszfamid
• Doxorubicin
• Epirubicin
• 5-Fluorouracil
• Ifoszfamid
• Interleukin-2
• Metotrexát
• Mitoxantron
• Paclitaxel
• Rituximab
• Talidomid

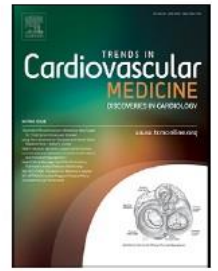
Új daganatellenes szerek

Trends in Cardiovascular Medicine 29 (2019) 29–39

Contents lists available at ScienceDirect

Trends in Cardiovascular Medicine

journal homepage: www.elsevier.com/locate/tcm



Update on cardio-oncology: Novel cancer therapeutics and associated cardiotoxicities☆,☆☆,☆☆☆

Avirup Guha, MBBS[a], Merna Armanious, MD[b,c], Michael G. Fradley, MD[b,c,*]

[a] Division of Cardiovascular Medicine, Ohio State University, USA
[b] Cardio-Oncology Program, Division of Cardiovascular Medicine, University of South Florida, 2 Tampa General Circle, Tampa, FL, 33606, USA
[c] Cardio-Oncology Program, H. Lee Moffitt Cancer Center and Research Institute, 12902 USF Magnolia Drive, Tampa, FL, 33612, USA

Új daganatellenes szerek

1. Klasszikus citosztatikumok

2. “Molekulárisan célzott terápiák”
   1. Hormonterápiák
   2. Antitestek
   3. Tirozin kináz gátlók
   4. Egyebek (pl. **CDK 4/6 gátlók**, stb.)

3. **Immuno-onkológiai terápiák**

Common cardiovascular toxicities of novel cancer therapeutics.

Toxicity
Cardiac Dysfunction
Cardiomyopathy
Myocarditis
Arrhythmias
QT prolongation
Bradycardia or Heart Block
Atrial arrhythmias
Ventricular arrhythmias or sudden death
Vascular Disease
Ischemic Vascular Events
Venous thromboembolism
Pulmonary Hypertension
Hypertension
Metabolic Disorders
Hyperlipidemia
Impaired Glucose Tolerance
Pericardial disease

Új daganatellenes szerek

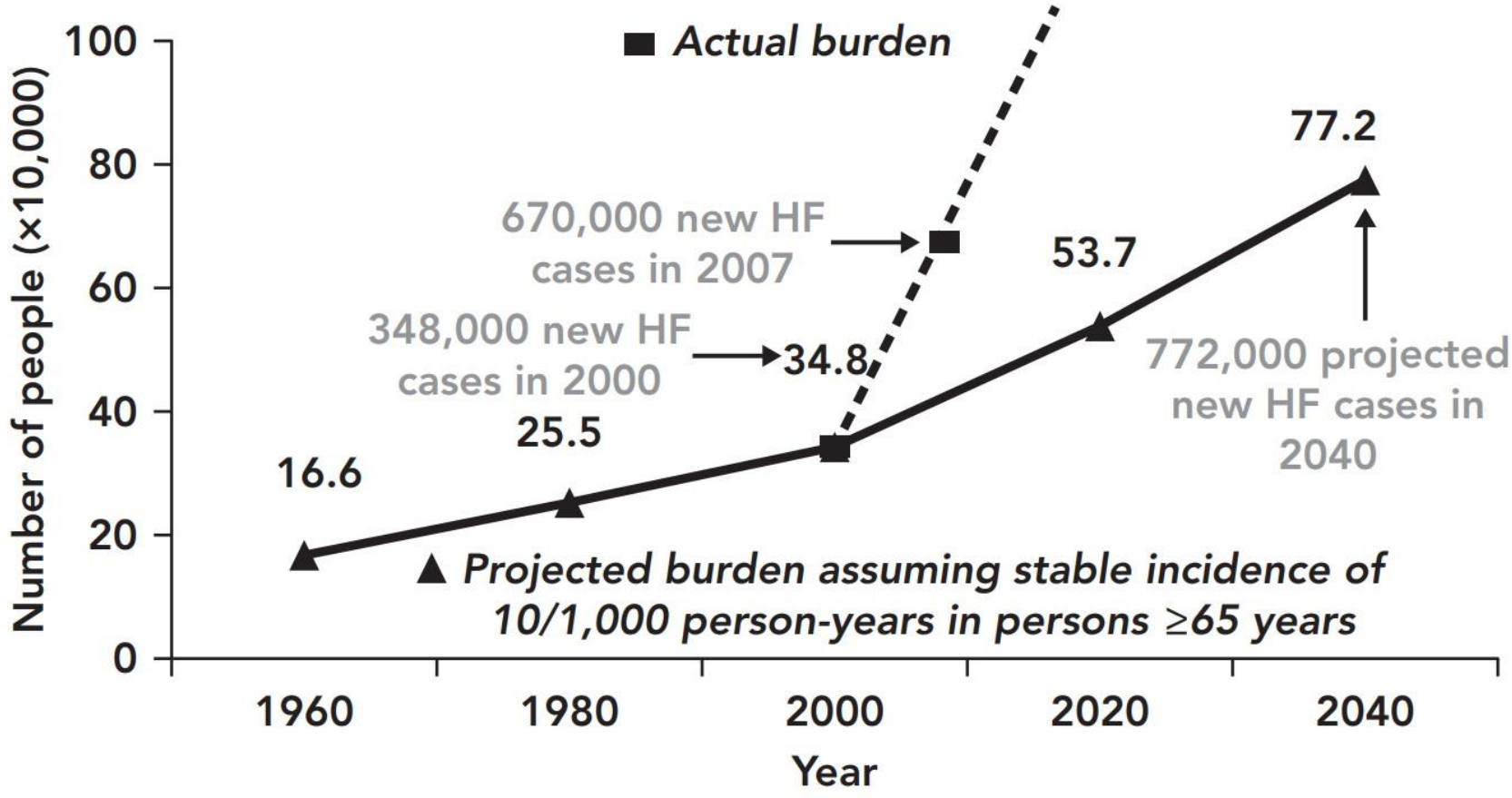
Table 2
Cardiotoxicities of recently approved cancer therapeutics.

Agent, Class	Cancer/Cancers approved for	Side effects	Reference
Receptor Tyrosine Kinase inhibitor (TKI)			
Afatinib (epidermal growth factor receptor (EGFR) inhibitor)	Non-small cell lung cancer (NSCLC)	No cardiovascular side effects	[156]
Erlotinib (EGFR inhibitor)	EGFR positive NSCLC	Heart failure (HF)	[157]
Neratinib (dual Her2 and EGFR inhibitor)	HER2 + breast cancer	Ischemic vascular events (IVE), QT prolongation (QTP), HF	[158,159]
Osimertinib (EGFR inhibitor)	EGFR positive (NSCLC)	QTP	[136,160]
Small molecule TKI			
Acalabrutinib (second generation BTK inhibitor)	mantle cell lymphoma (MCL), Chronic lymphocytic leukemia (CLL)	IVE	[161]
Alectinib (anaplastic lymphoma kinase (ALK) inhibitor)	ALK-positive NSCLC	QTP, pulmonary embolism (PE)	[162]
Bosutinib (BCR-Abl inhibitor)	Chronic myelogenous leukemia (CML)	Hypertension (HTN), IVE, QTP, atrial fibrillation (AF)	[163]
Brigatinib (ALK and EGFR inhibitor)	Metastatic ALK-positive NSCLC	IVE, PE	[135]
Cabozantinib (c-Met, VEGFR2*, AXL and RET inhibitor)	advanced renal cell carcinoma (RCC)	HTN, Hyperlipidemia (HLD)	[164,165]
Ceritinib (ALK inhibitor)	ALK-positive NSCLC	IVE, sinus bradycardia (SB)	[166]
Crizotinib (ALK and ROS1 inhibitor)	Metastatic ALK-positive NSCLC	SB	[167]
Dabrafenib (BRAF inhibitor)	Melanoma, NSCLC with BRAF V600E mutation	HTN, HF, PE, QTP	[168-171]
Dasatinib (BCR/Abl*, Src, c-Kit, ephrin receptor inhibitor)	CML	Pleural effusion, pulmonary hypertension, IVE, QTP	[172]
Ibrutinib (first generation BTK inhibitor)	chronic graft versus host disease, CLL, MCL, Waldenström's Macroglobulinemia	AF, VT, VF, sudden cardiac death (SCD)	[55]
Lenvatinib (VEGFR1-3 inhibitor)	advanced RCC	HLD, IVE, intracranial hemorrhage (ICH)	[173]
Nilotinib (BCR-ABL*, KIT, LCK, EPHA3, EPHA8, DDR1, DDR2, PDGFRB, MAPK11 and ZAK inhibitor)	CML	HTN, IVE, QTP, HLD, hyperglycemia	[35,174,175]
Ponatinib (BCR-Abl inhibitor)	CML, Philadelphia chromosome + acute lymphoblastic leukemia	HTN, HF, IVE, PE	[38,45,163]
Regorafenib (VEGFR2-TIE2 tyrosine kinase inhibitor)	hepatocellular carcinoma (HCC)	HTN, IVE, cardiac death	[176-179]
Sunitinib (PDGF and VEGF inhibitor)	RCC Gastrointestinal Stromal Tumor	HTN	[180,181]
Trametinib (MEK inhibitor)	Melanoma, NSCLC with BRAF V600E mutation	HTN, HF, PE, QTP, SCD	[168,170,172]
Vemurafenib (BRAF inhibitor)	Melanoma, Erdheim-Chester Disease	QTP, pericarditis	[182-185]
Protein Kinase Inhibitor			
Midostaurin (FMS-like tyrosine kinase 3 receptor (FLT3) inhibitor)	FLT3 + acute myeloid leukemia (AML)	No cardiovascular events	[186]
poly (ADP-ribose) polymerase (PARP) inhibitor			
Olaparib	HER2 negative breast cancer Recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer	Pericarditis, PE and syncope	[187-189]
Rucaparib	BRCA positive advanced ovarian cancer	HTN, QTP, HLD	[190]
Niraparib	Recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer	HTN	[191]
Cyclin Dependent Kinase (CDK) inhibitor			
Abemaciclib (CDK4/CDK6 inhibitor)	Hormone Receptor (HR)-positive, HER2-negative advanced or metastatic breast cancer	PE	[192,193]
Palbociclib (CDK4/CDK6 inhibitor)	HR-positive, HER2- negative advanced or metastatic breast cancer	PE, HTN, AF	[110,194]
Ribociclib (CDK4/CDK6 inhibitor)	HR-positive, HER2-negative advanced or metastatic breast cancer	QTP	[195,196]
Histone DeAcytylase (HDAC) inhibitor			
Panabinostat	Multiple myeloma	No reported cardiac side effects	[197]
Romidepsin	Cutaneous T-cell lymphoma (TCL)	QTP	[198,199]
Belinostat	Peripheral TCL	QTP	[200]
Mitochondrial enzyme inhibitor			
Enasidenib (isocitrate dehydrogenase-2 inhibitor)	Relapsed or refractory AML with an isocitrate dehydrogenase-2 (IDH2) mutation	No reported cardiac side effect	[201]
PI3K inhibitor			
Copanlisib (PI3K-α/PI3K-δ inhibitor)	Relapsed follicular lymphoma	HTN	[202,203]
HER2 inhibitor			
Pertuzumab	HER-2 positive breast cancer in	HF, cardiac death	[204]
Checkpoint Inhibitor			
Atezolizumab (PD-L1 inhibitor)	Metastatic NSCLC; advanced urothelial carcinoma	Myocarditis, HF, HTN, PE, AF, heart block, SCD	[142-144,205]
Avelumab (programmed cell-ligand death (PD-L1) inhibitor)	Advanced urothelial carcinoma; metastatic Merkel cell carcinoma	Myocarditis, HF, AF, heart block, SCD	[132,133]
Durvalumab (PD-L1 inhibitor)	Advanced urothelial carcinoma, NSCLC	Myocarditis, HF, HTN, PE, AF, heart	[134,206]

1. Klasszikus citosztatikumok: Cabazitaxel-no; Carfilzomid-HT,HF,arrhytmia
2. “Molekulárisan célzott terápiák”
   1. Hormonterápiák: Abiraterone ac.-HT,AF,HF
   2. Antitestek: Brentuximab-PE; Obinutuzab-AF,HF,PE
   3. Tirozin kináz gátlók:Erlotinib-HF; Neratinib-QTP,HF
   4. Egyebek (pl. CDK 4/6 gátlók, stb.): Ribociclib-QTP, Palbociclib-PE,HT,HF
3. Immuno-onkológiai terápiák (chekpoint inhibitors): Avelumab, Nivolumab, Pembrolizumab –myocarditis, HF, AF, heart block

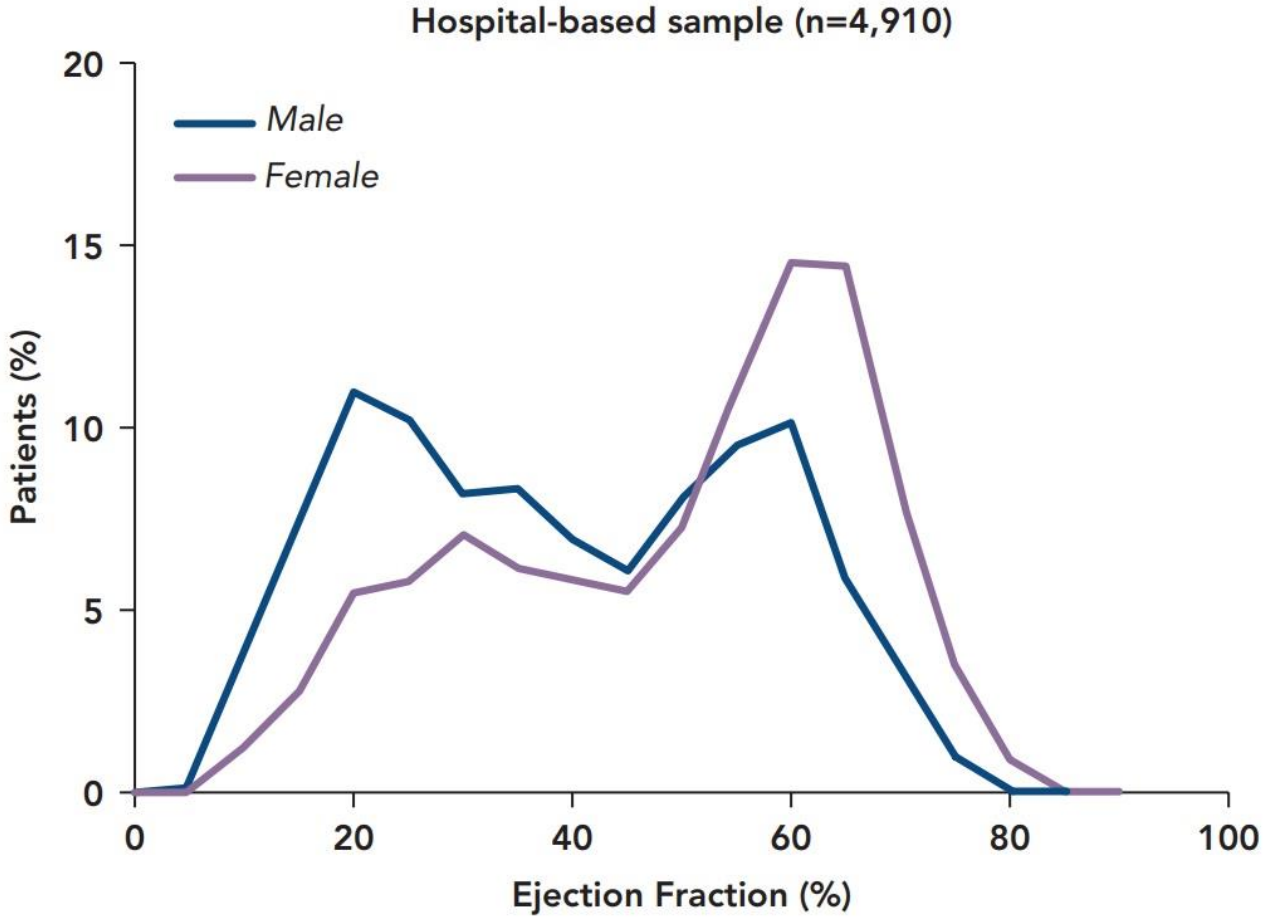
A. Guha et al. / Trends in Cardiovascular Medicine 29 (2019) 29–39

Szívelégtelenség epidemiológiája



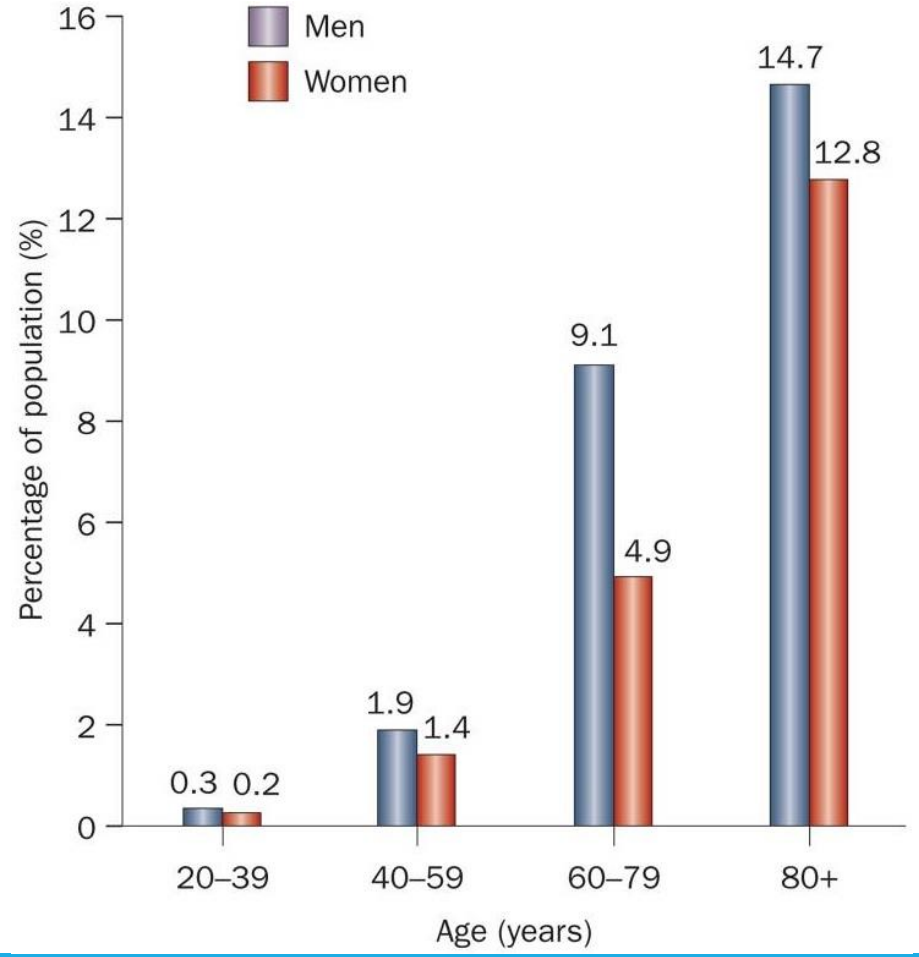
Savarese G. et al. Cardiac Failure Review 2017;3(1):7–11.

Szívelégtelenség epidemiológiája



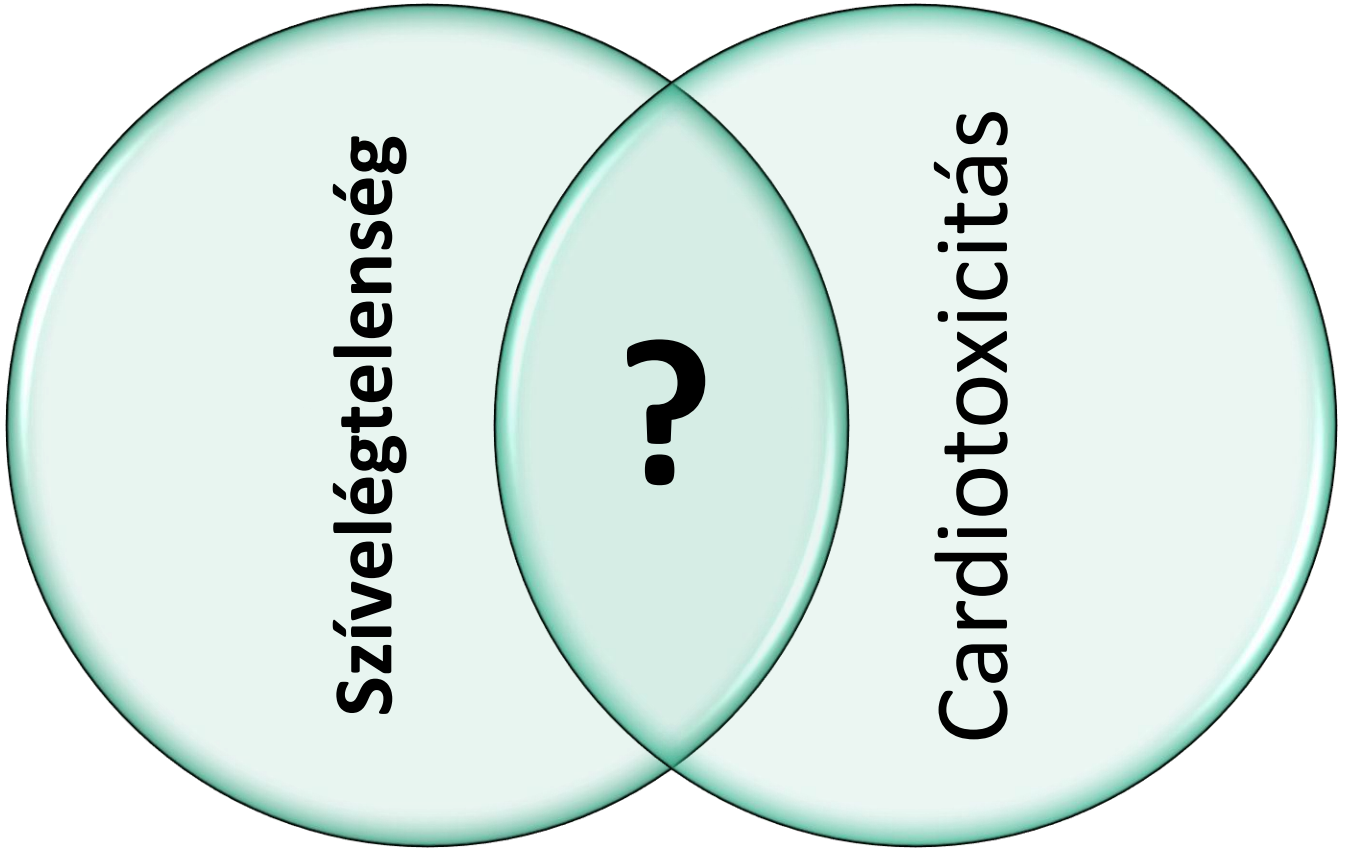
Savarese G. et al. Cardiac Failure Review 2017;3(1):7–11.

Szívelégtelenség epidemiológiája

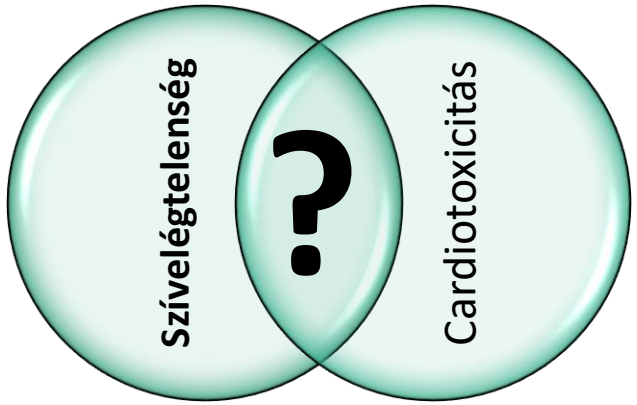


Bui AL. Et al. Nat Rev Cardiol. 2011 January ; 8(1): 30–41.

A közös előfordulás aránya?



A közös előfordulás okai



- Közös rizikófaktorok:
  - Életkor
  - Dohányzás
  - Inaktivitás
  - Obesitás
- HF önmagában elősegíti a carcinogenesist
  - HF-related low-grade inflammation
  - Sympaticus idegrendszeri hyperaktivitás
  - RAAS túlműködés
- HF-ben használt bizonyos szereknél felmerül a carcicogenitás
  - ARB?
  - Digoxin
  - ACE gátlók?

ESC
European Society of Cardiology

European Journal of Heart Failure (2019)
doi:10.1002/ejhf.1539

REVIEW

Cancer and heart disease: associations and relations

Rudolf A. de Boer*, Wouter C. Meijers, Peter van der Meer, and Dirk J. van Veldhuisen

University of Groningen, University Medical Center Groningen, Department of Cardiology, Groningen, The Netherlands

Received 28 January 2019; revised 13 May 2019; accepted 24 May 2019

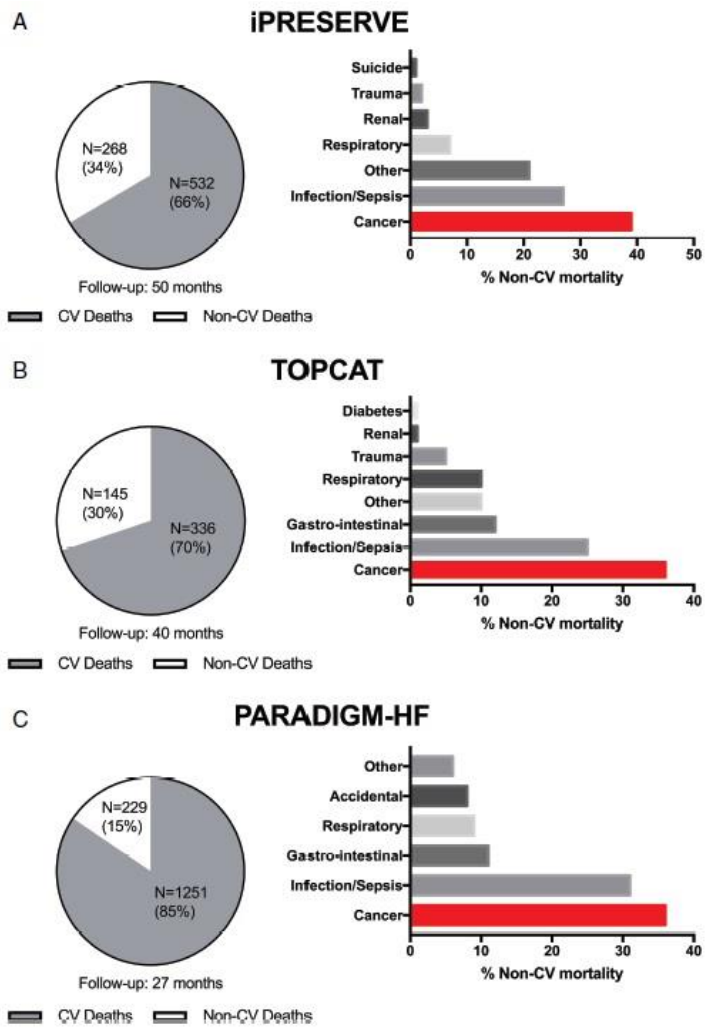
Szívelégtelenség tanulmányok npl. előfordulás

Study	Design	Population	Patients, *n*	Follow-up period (years)	Primary outcome	Secondary outcomes
Hasin *et al.*[8]	Case-control	General population with or without HF	Total: 1192 HF: 596 Cancer: 102	7.7 ± 6.4	HR 1.68, 95% CI 1.13–2.50 adjusted for BMI, smoking, and co-morbidities	Incident cancer increased the risk of death: HR 1.56, 95% CI 1.22–1.99 adjusted for age, sex, index year, and co-morbidities
Hasin *et al.*[9]	Prospective cohort study	Post-MI with or without HF	Total: 1081 HF: 228 Cancer: 28	4.9 ± 3.0	HR 1.71, 95% CI 1.07–2.73 adjusted for age, sex, and Charlson co-morbidity index	Incident cancer increased the risk of death: HR 3.91, 95% CI 1.88–8.12
Rinde *et al.*[10]	Prospective population-based study	Patients with either a MI or not	Total: 28 763 MI: 1747 Cancer: 146	15.7	HR 1.46, 95% CI 1.21–1.77 adjusted for age, sex, BMI, systolic blood pressure, diabetes mellitus, HDL cholesterol, smoking, physical activity and education level	Increased cancer incidence highest during the first 6 months post-MI: HR 2.15, 95% CI 1.29–3.58 3 years post-MI risk of incidence cancer: HR 1.60, 95% CI 1.27–2.03
Banke *et al.*[11]	Prospective study	HF subjects (LVEF < 45%) compared to the general population	Total: 4 949 968 HF: 9307 Cancer: 975	4.5 ± 2.3	IRR 1.24, 95% CI 1.15–1.33 adjusted for age, sex	After 180 days: IRR 1.17, 95% CI 1.08–1.27 After 365 days: IRR 1.14, 95% CI 1.05–1.24
Berton *et al.*[12]	Prospective study	Post-MI	Total: 589 MI: 589 Cancer: 99	17	IR 17.8 cases/1000 person-years	Incident cancer increased the risk of death: HR 1.8, 95% CI 1.1–2.9
Selvaraj *et al.*[13]	Pooled RCTs	PHS I: control vs. low-dose aspirin and β-carotene PHS II: control vs. vitamin supplementation Self-reported HF, no data on cardiac function	Total: 28 341 HF: 1420 Cancer: 177	19.9 [25th–75th percentile: 11.0–26.8]	HR 1.02, 95% CI 0.84–1.25 adjusted for enrolment group, race, cigarette smoking (never, former, current), alcohol use, aspirin use, family history of cancer, cirrhosis, proton pump inhibitor or H2 blocker use, and sun exposure	No increased risk of cancer death: HR 1.16, 95% CI 0.82–1.65 adjusted for the same model as the primary outcome

Rudolf AB. Et al: European Journal of Heart Failure (2019) doi:10.1002/ejhf.1539

Halálozás szívelégtelenségben

- a prognosis szegényes
  5 vs 10 éves túlélés 50% vs 25%
- HFrEF és HFpEF is!
- korábban úgy gondolták, hogy a halálozás nagy része a szívelégtelenség közvetlen eredménye
- Valójában kortól és októl függően a non-CV halálozás 20%-50% is lehet!



Rudolf AB. Et al: European Journal of Heart Failure (2019) doi:10.1002/ejhf.1539

Rizikófaktorok relativ kockázata HF/cc

Risk factor	Incidence of heart failure[a]	Incidence of cancer
BMI[b], per kg/m^2	1.03 (1.01–1.06)	1.08 (1.06–1.10)
Smoking	1.84 (1.46–2.32)	1.68 (1.65–1.72)
Diabetes mellitus	1.41 (1.12–1.79)	1.10 (1.03–1.18)
Hypertension	1.65 (1.33–2.06)	1.03 (0.98–1.09)
Heart rate[b]	1.02 (1.01–1.03)	1.09 (1.01–1.18)[c]

BMI, body mass index.
[a]Study population (Health ABC, PREDICTOR, PROSPER).
[b]Hazard ratios are expressed per 1-unit increase in continuous risk factors.
[c]Per 10 b.p.m. increase.

Rudolf AB. Et al: European Journal of Heart Failure (2019) doi:10.1002/ejhf.1539

Clinical Research in Cardiology (2018) 107:271–280
https://doi.org/10.1007/s00392-018-1202-x

REVIEW

Cardio-oncology: conflicting priorities of anticancer treatment and cardiovascular outcome

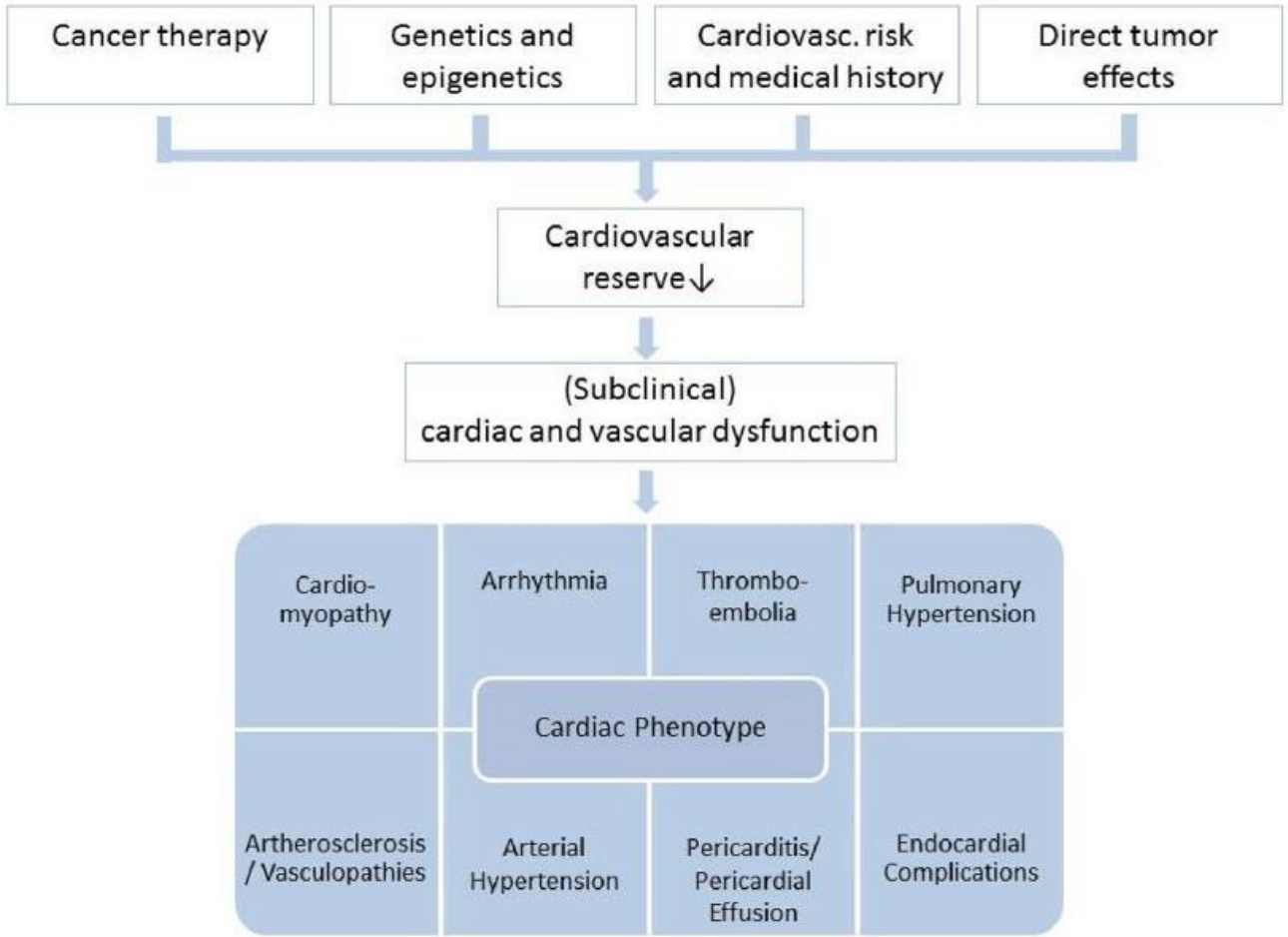
Lisa M. Tilemann[1,2] · Markus B. Heckmann[1,2] · Hugo A. Katus[1,2] · Lorenz H. Lehmann[1,2] · Oliver J. Müller[1,2,3]

Egyre több beteg éli túl a daganatos betegségét, az onkológiai terápiák hosszú távú mellékhatásait mérlegelni kell.

Különösen a rákkezelést követő kardiotoxikus mellékhatások jelentik az életminőség és a túlélés csökkenését.

A kombinált kemoterápia vagy az adjuváns sugárterápia szinergista vagy additív hatással lehet a szívszövődmények kockázatára, és fokozhatja a kardiotoxikus potenciált.

Egy adott terápia kardiotoxicitását az egyes betegek számára nehéz megjósolni, mivel több tényező ismeretlen mértékben járul hozzá:



Tilemann LM. Et al: Clinical Research in Cardiology (2018) 107:271–280

Kardiotoxicitás: precíziós gyógyszer pontatlan definíciókkal

Cardio-oncology recognises that *today's cancer patient is tomorrow's cardiac patient* and aims to prevent, diagnose and treat cardiotoxicity.

Chung R, et al. Open Heart 2018;5:e000774. doi:10.1136/openhrt-2018-000774

Kardiotoxicitás: precíziós gyógyszer pontatlan definíciókkal

Table 1 Variation in definitions of cardiotoxicity across standards organisations

Standards organisation	Definition of cardiotoxicity	Comments
ASE/EACVI	LVEF fall by >10% to absolute EF <53%	Change in LV function may be global or regional (septum) Symptomatic or asymptomatic for HF
ESC	LVEF fall by >10% from baseline to EF <50%	Symptomatic or asymptomatic for HF
NCI	CTCAE HF grade 1–5	Grade 1 (asymptomatic) Grade 2 (mild to moderate symptoms) Grade 3 (symptomatic on minimal exertion or at rest) Grade 4 (life-threatening) Grade 5 (death)
CCS	LVEF fall by >10% from baseline or LVEF <53%	Guidelines also recommend (1) 3D echocardiography or same imaging modality during cancer therapy, (2) myocardial strain imaging and (3) cardiac biomarkers (N-terminal pro brain natriuretic peptide, troponin) for early detection
ESMO	Symptomatic decline in LVEF of at least 5% to <55% or asymptomatic decline in LVEF of at least 10% to <55%	Symptoms for congestive HF with signs including but not limited to S3 gallop, tachycardia or both Decline in LVEF either global or more severe in the septum

Chung R, et al. Open Heart 2018;5:e000774. doi:10.1136/openhrt-2018-000774

Kardiotoxicitás: precíziós gyógyszer pontatlan definíciókkal

Table 2 'Cardiotoxicity' of common cancer therapies

	LVSD	HTN	Angina	ACS	Takotsubo	Stroke	PAD	PHTN	DVT/PE
Anthracyclines	X								
5-FU	X		X	X	X				
Gemcitabine			X	X					
Paclitaxel		X	X	X					X
Cisplatin		X	X	X		X	X		
Bleomycin			X	X		X		X	
Vincristine		X	X	X					
Cyclophos-phamide	X		X					X	
mTOR inhibitors		X	X						X
Carfilzomib	X	X		X				X	
Bevacizumab	X	X	X	X	X	X			X
Sunitinib	X	X	X	X	X	X			X
Nilotinib			X	X		X	X		X
Dasatanib	X							X	
Thalidomide									X
Rituximab		X	X	X	X				

Chung R, et al. Open Heart 2018;5:e000774. doi:10.1136/openhrt-2018-000774

Cardio-onkológia – Sisyphus mítosza

Heart Failure Reviews
https://doi.org/10.1007/s10741-019-09805-1

Cardio-oncology, the myth of Sisyphus, and cardiovascular disease in breast cancer survivors

Sophie I. Mavrogeni [1] · Elisa Sfendouraki [2] · George Markousis-Mavrogenis [1] · Angelos Rigopoulos [3] · Michel Noutsias [3] · Genovefa Kolovou [1] · Constantina Angeli [2] · Dimitrios Tousoulis [2]

Cardio-onkológia – Sisyphus mítosza

- ugyan emelkedik a daganatos túlélők száma, a kései komplikációk okozta halálozás is növekszik!
- a diagnosztika teljes arzenáljával rendelkezünk, de újra kell alkotni a szabályokat ebben a speciális betegcsoportban!
- ugyanolyan fontos a prevenció, mint a legtöbb betegcsoportban, de mégis számos különbség lelhető fel, mivel akkor kell gondolni rá, amikor még el sem kezdődött!
- a terápia széles köre evidenciákkal, tapasztalatokkal mit sem ér sokszor ebben a betegcsoportban!
- újra és újra neki kell fogni, és a már ismert sziklafalon fel kell gurítani a nagy követ!!!

Mavrogeni SI. Et al: Heart Failure Reviews. https://doi.org/10.1007/s10741-019-09805-1

Cardio-onkológia – Sisyphus mítosza

Számos állásfoglalást láttunk a CTRCD megfelelő megközelítéséről az elmúlt években. Ezek szerint a CTRCD menedzselésének az alábbi kulcspontokra kell összpontosítania:

1) a kockázat felismerés,

2) megelőzés (elsődleges vagy másodlagos),

3) korai diagnosztizálás,

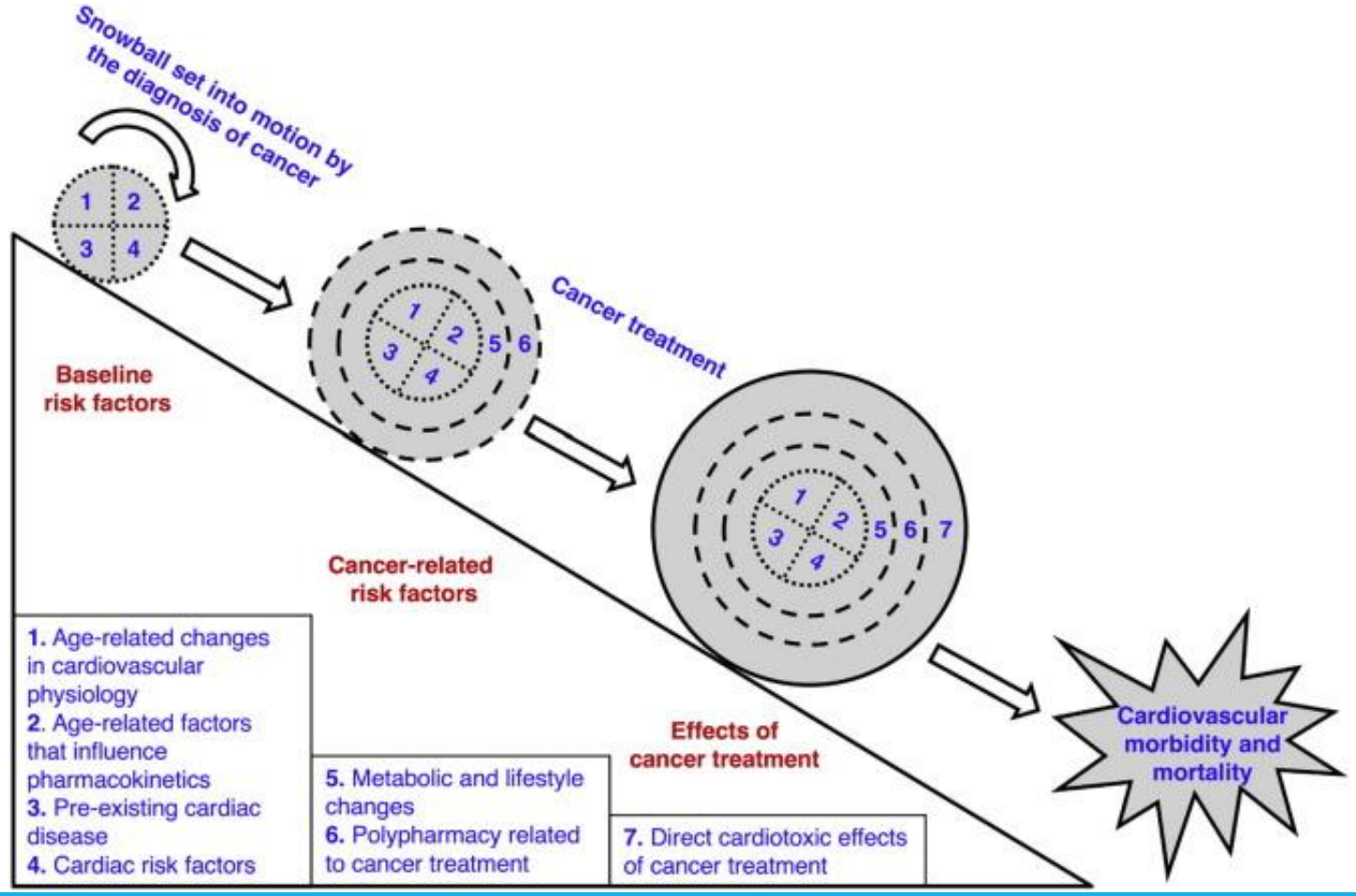
4) a kardiológiai kezelés korai megkezdése,

5) egyensúly az onkológiai kezelés és a kardiovaszkuláris biztonság között

6) azon betegek azonosítása, akik profitálnak a szorosabb megfigyelés és / vagy korai kezelés folyamatából.

Mavrogeni SI. Et al: Heart Failure Reviews. https://doi.org/10.1007/s10741-019-09805-1

„Hógolyó effektus”



Reddy et al: Journal of Geriatric Oncology, 2017, Available online 9 May 2017

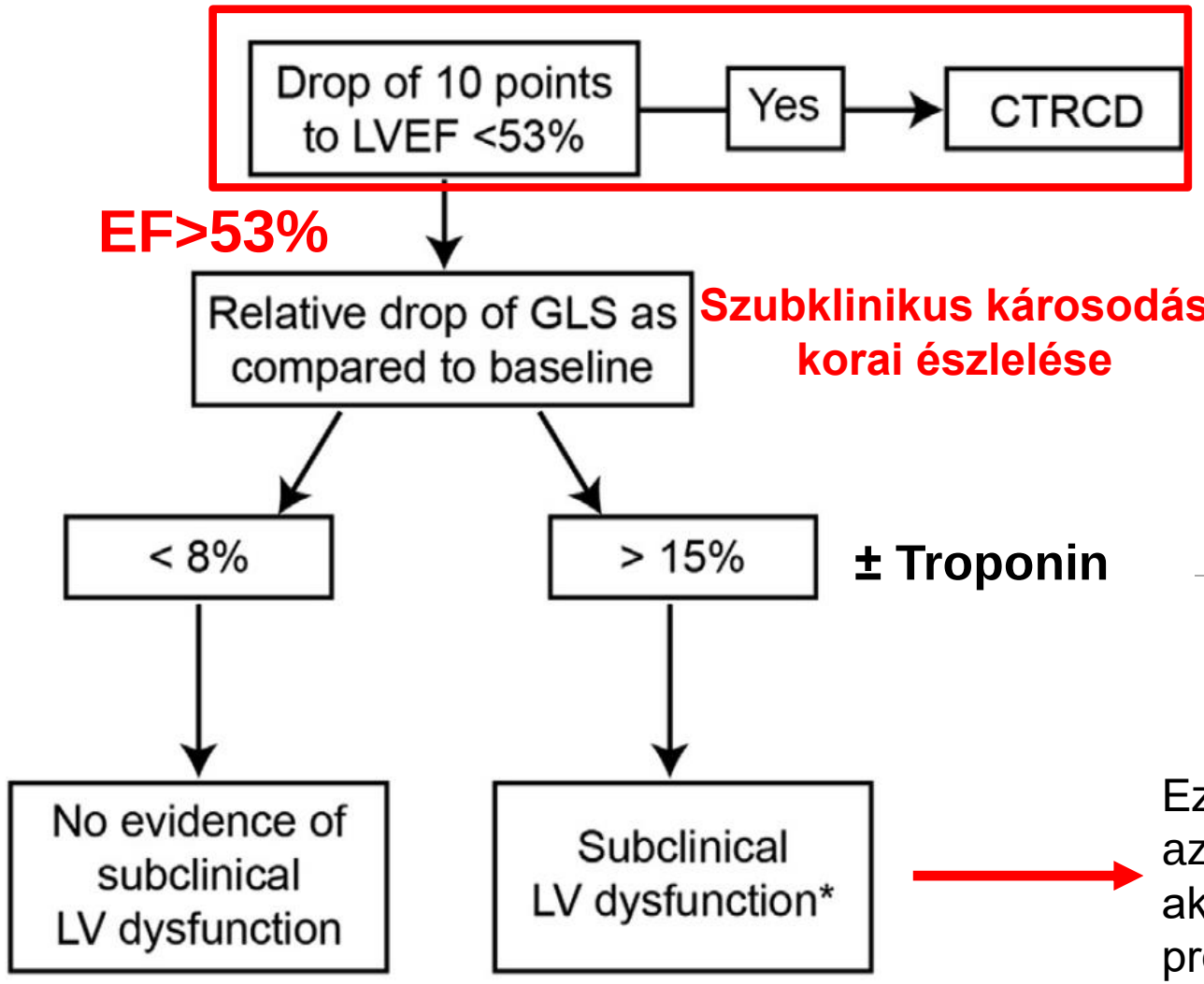
Cardio-onkológia – Sisyphus mítosza

Mavrogeni SI. Et al: Heart Failure Reviews. https://doi.org/10.1007/s10741-019-09805-1

Cardio-onkológia – Sisyphus mítosza

Mavrogeni SI. Et al: Heart Failure Reviews. https://doi.org/10.1007/s10741-019-09805-1

ASE és EACI guideline - 2014



3D-EF
CMR

Szubklinikus károsodás korai észlelése

± Troponin

Ezzel lehet kiválasztani azokat a betegeket, akiknél a korai kardio-protektív kezelés előny

Plana JC et al. J Am Soc Echocardiogr 2014;27:911-39

Congress News

ESC Congress Paris 2019
Together with World Congress of Cardiology

Day 2

Sunday 1 September

Spotlight Global Cardiovascular Health

ESC Congress Paris 2019
Together with World Congress of Cardiology
31 August - 4 September

World Heart Federation

ESC European Society of Cardiology

Cardio-oncology – a new subspecialty for a growing problem

Dr. Alexander Lyon

Fuelled by the combination of improved long-term survival of cancer patients, the cardiovascular side effects of cancer treatment and an increasing elderly population, cardio-oncology has developed out of necessity as a new subspecialty within modern cardiology.

Last year, the ESC formed the ESC Council of Cardio-Oncology to help address the new clinical challenge of a growing number of patients presenting to cardiology services during or after cancer treatment. ESC Cardio-Oncology Council Treasurer, Doctor Alexander Lyon (Royal Brompton Hospital, London, UK), explains, "The aim of this new Council is to improve the standard of care for oncology patients and cancer survivors treated with cardiotoxic cancer therapies or radiotherapy. This involves developing an ESC strategy for training, education, patient care and management to treat and prevent the cardiovascular complications of cancer therapies. Given the broad scope and rapid growth of the field, a multidisciplinary membership–representing cardiology, oncology, haematology, radiotherapy and related disciplines–from Europe and beyond was felt to be crucial."

New cancer therapies are being developed at a rapid pace, and so cardio-oncology is a fast-moving area adapting to these new advances. Over the next few days at ESC Congress 2019, several symposia will discuss different aspects of cardio-oncology. Dr. Lyon is Co-Chair of a symposium today and he provides a flavour of what to expect. "The symposium will discuss risk factors common to both cardiovascular disease and cancer, including inflammation, and mechanisms of toxicity that can guide new cardiovascular drug development. The different cardiovascular toxicities of new anti-tumour therapies will be reviewed. Finally, approaching cancer and cardiovascular disease from the opposite direction, research will be presented showing an increased risk of cancer in patients with heart failure, and the interesting search for potential mechanisms–some of these will be discussed this morning."

A symposium on Monday will further explore the cardiovascular toxicity of anticancer treatments, says Dr. Lyon. "Cardiovascular toxicities are changing with the use of new cancer treatments. Many cardiologists will be familiar with anthracycline- and trastuzumab-associated cardiotoxicity. However, new cardiovascular diseases are emerging as a result of treatment with targeted cancer agents, such as the checkpoint inhibitors and tyrosine kinase inhibitors. And the effects of radiotherapy, commonly used to treat many cancers, should not be neglected."

A session on Tuesday morning will focus on cardio-oncology clinical pathways and patient management. Dr. Lyon, who will be discussing the role of cardiovascular biomarkers in patients receiving cancer treatment, stresses the importance of this symposium for clinical practice. "The session is designed to help cardiovascular healthcare professionals to recognise the complexity of risk associated with cancer treatment, and its continuation during survivorship, and to provide guidance on incorporating expert recommendations into clinical practice."

He concludes, "The field of cardio-oncology is only going to grow, and in the coming years, all cardiologists can expect to see increasing numbers of patients with cardiovascular issues related to cancer and its treatment. We should all be aware of the problems facing these patients and how we can manage them, and ideally prevent them, where possible."

Don't miss!

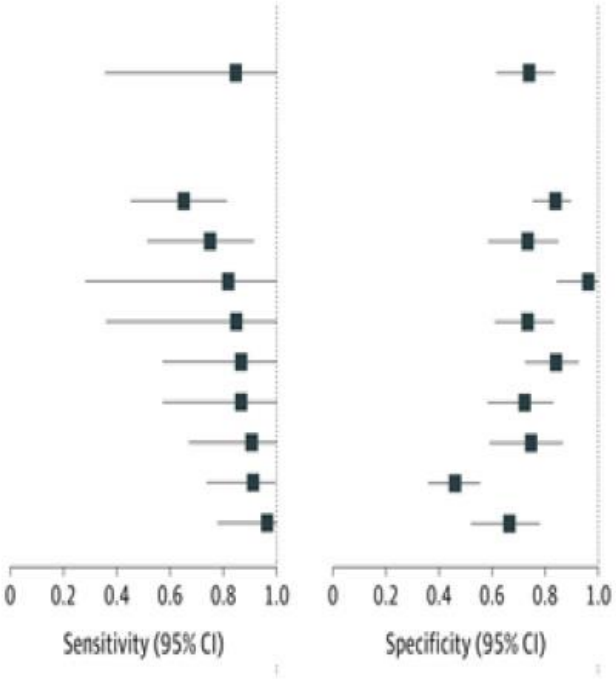
- **Cardio-Oncology: Novel mechanisms and clinical implications**
  Today, 11:00 - 12:30; Athens - Village 3
- **Cardio-oncology: what every cardiologist should know about cardiovascular effects of cancer treatment**
  Monday, 08:30 - 10:00; Colette - The Hub
- **Cardiovascular health in cancer patients and survivors**
  Tuesday, 11:00 - 12:30; Colette - The Hub

Want to be involved with the ESC Council of Cardio-Oncology? Find out more at the ESC Stand

CTRCD: strain – baseline cutoffs

21 prognosztikai tanulmány szisztematikus áttekintése
GLS – chemotherápia
CTRCD incidencia: 9,3-43,8%
4-23 hónap alatt
Poolozott incidencia: 21%

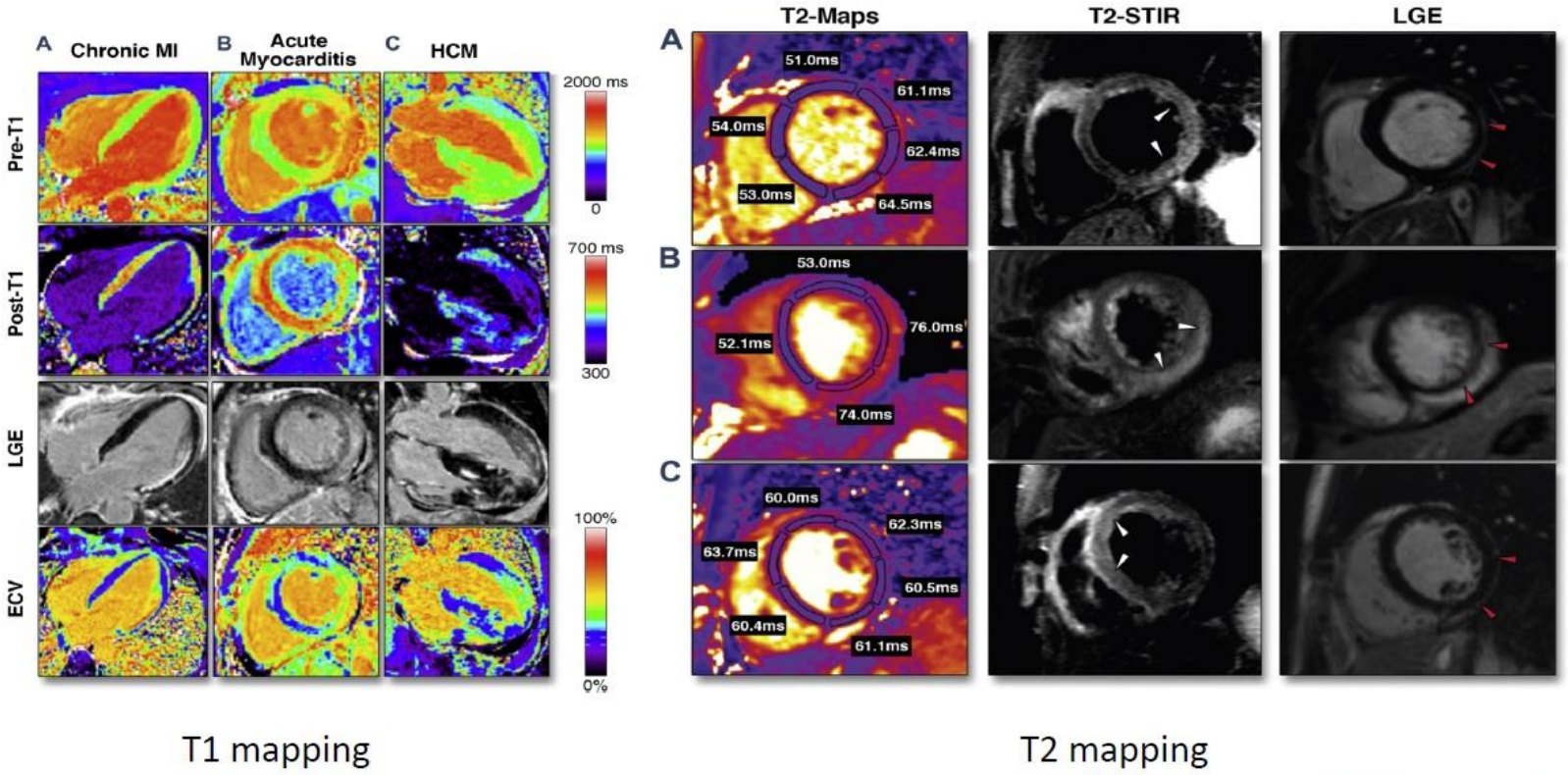
Study	Decreased GLS: No. of Events	Decreased GLS: No. of Nonevents	Increased GLS: No. of Events	Increased GLS: No. of Nonevents	Cancer Type	Cutoff, %	Vendor	Sensitivity (95% CI)	Specificity (95% CI)
Absolute GLS before treatment initiation									
Charbonnel et al,[20] 2017	5	22	1	58	Hematologic	-19.95	GE	0.83 (0.36-1.00)	0.72 (0.61-0.82)
Absolute GLS value during treatment									
Milks et al,[26] 2018	21	26	12	124	Breast	-19.00	Tomtec	0.64 (0.45-0.80)	0.83 (0.76-0.88)
Sawaya et al,[31] 2012	17	15	6	40	Breast	-19.00	GE	0.74 (0.52-0.90)	0.73 (0.59-0.84)
Gripp et al,[21] 2018	4	2	1	42	Breast	-16.60	GE	0.80 (0.28-0.99)	0.95 (0.85-0.99)
Charbonnel et al,[20] 2017	5	22	1	58	Hematologic	-17.45	GE	0.83 (0.36-1.00)	0.72 (0.61-0.82)
Tang et al,[33] 2017	12	12	2	60	Breast	-13.84	GE	0.86 (0.57-0.98)	0.83 (0.73-0.91)
Paraskevaidis et al,[29] 2017	12	19	2	47	Hematologic	-18.40	GE	0.86 (0.57-0.98)	0.71 (0.59-0.82)
Guerra et al,[24] 2016	17	13	2	37	Breast	-18.00	GE	0.89 (0.67-0.99)	0.74 (0.60-0.85)
Portugal et al,[30] 2017	27	70	3	58	Breast	-18.00	GE	0.90 (0.73-0.98)	0.45 (0.36-0.54)
Negishi et al,[12] 2013	23	19	1	38	Breast	-21.00	GE	0.96 (0.79-1.00)	0.67 (0.53-0.79)



Assessment of Prognostic Value of Left Ventricular Global Longitudinal Strain for Early Prediction of Chemotherapy-Induced Cardiotoxicity: A Systematic Review and Meta-analysis.

Oikonomou EK, et al. JAMA Cardiol. 2019.

CTRCD: Szöveti megjelenítés - CMR

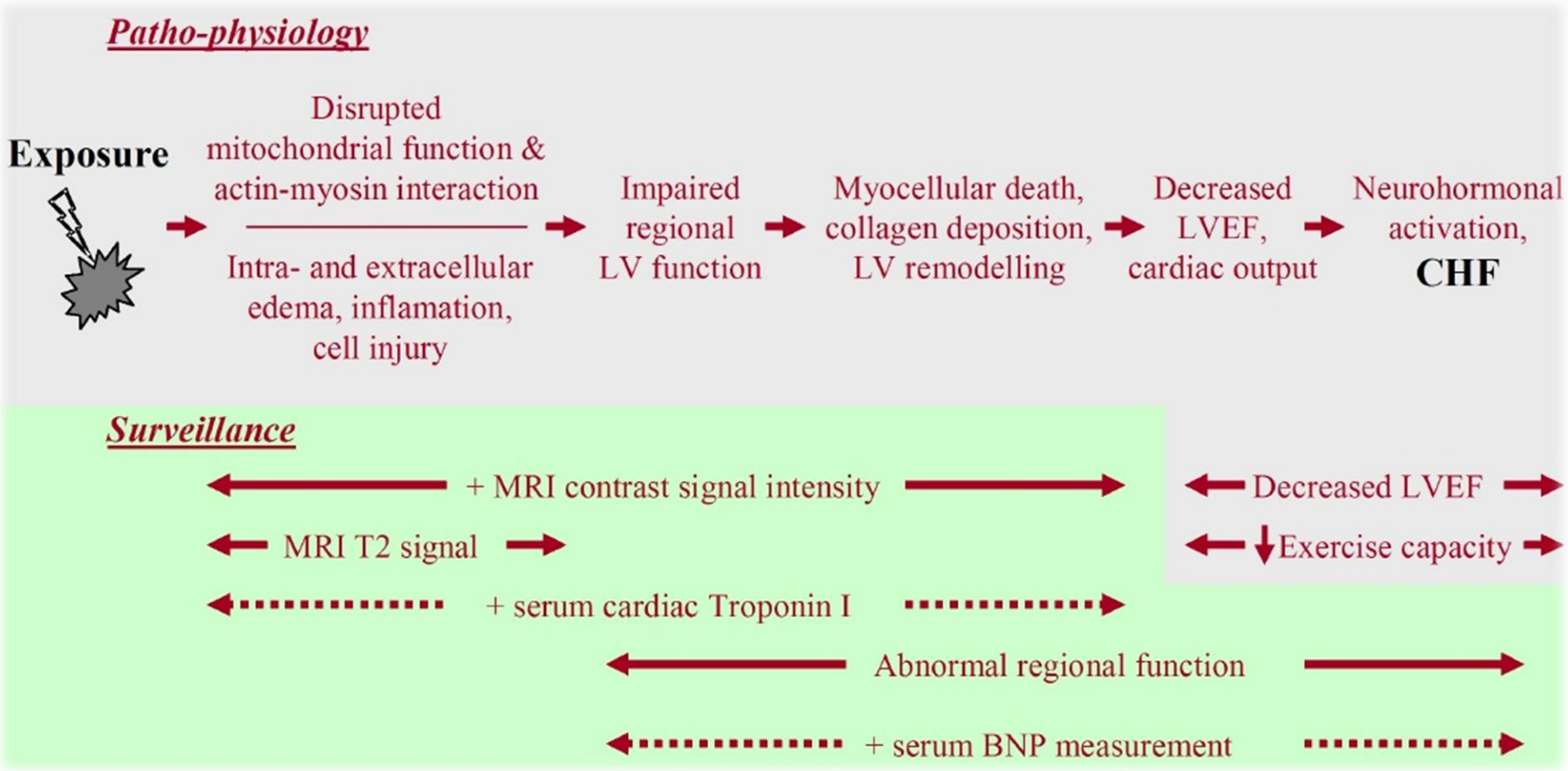


T1 mapping

T2 mapping

Salerno, et al. Advances in Parametric Mapping with CMR Imaging. *JACC Imaging* 2013.

CTRCD: Szöveti megjelenítés - CMR



Cardio-onkológia – Sisyphus mítosza

Az onkológia jelenlegi helyzete nagyon emlékeztet Sisyphus mítoszára abban az értelemben, hogy az egyik problémát (neoplazia) csak akkor oldják meg, hogy egy másik kialakulásával kell szembenézni (CTRCD).

De hogyan lehetünk képesek elkerülni a Sziszifust hordozó sorsot?

- Primer prevenció – direkt cardiotoxicitás elkerülése
  - anthracaclin kumulativ dosis limitáció
  - kevésbé cardiotoxicus analog használata
  - alternatív szer – pl. trastuzumab
  - gyógyszeres prevenció
    - dextrazoxán
    - ACEi, ARB (enalapril, perindopril [MANTICORE], telmisartan, candesartan [PRADA])
    - Béta blokkoló (carvedilol, nebivolol, bisoprolol [MANTICORE])
    - Statin – pleiotrop hatás?
    - Aldosteron antagonista (spironolacton)
- Secunder prevenció
  - Enalapril
  - ARNI??

Mavrogeni SI. Et al: Heart Failure Reviews. https://doi.org/10.1007/s10741-019-09805-1

Biomarkers?

ESC European Society of Cardiology

European Journal of Heart Failure (2018)
doi:10.1002/ejhf.1292

RESEARCH ARTICLE

Activity and outcomes of a cardio-oncology service in the United Kingdom—a five-year experience

Nilesh Pareek[1†], Joaquim Cevallos[1†], Pedro Moliner[2], Mit Shah[1], Li Ling Tan[1,3], Vicki Chambers[1], A. John Baksi[1], Rajdeep S. Khattar[1], Rakesh Sharma[1], Stuart D. Rosen[1,4], and Alexander R. Lyon[1,4*]

Myocardium toxicitási felosztás a Royal Brompton Hospital C-O szolgálatától

Kardiotoxicitás csoport	Klasszifikáció	Definíció	Biomarker	E/E'>12 vagy GLS>-18%	LVEF csökkenés	Tünetek
1	korai biokémiai kardiotoxicitás	új BNP vagy Troponin I emelkedés normális imaging-el (ha alapból jó, akkor 20%-os emelkedés)	+	-	-	-
2	korai funkcionális kardiotoxicitás	Új GLS csökkenés vagy DD gr.III-IV és normális biomarkerek	-	+	-	-
3	korai kevert kardiotoxicitás	normál LVEF abnromális biomarkerekkel és GLS/DD	+	+	-	-
4	tünetes HFpEF	tünetes HFpEF	+	+	-	+
5	tünetmentes LVSD	új LVEF csökkenés vagy <50% vagy 10%-nál nagyobb LVEF csökkenés 55%-ig	+/-	+	+	
6	tünetes LVSD	tünetes LVEF csökkenés 50% alatt vagy 10%-nál nagyobb LVEF csökkenés 55% alatt	+	+	+	+

Lyon A. et al.: E-journal of Cardiology Practice vol 16; No 40, 2019.

Myocardium toxicitási felosztás a Royal Brompton Hospital C-O szolgálatától

Kardiotoxicitás csoport	Klasszifikáció	Definíció	Menedzsment stratégiák Onkológiai kezelés	Kardiológiai kezelés
1	korai biokémiai kardiotoxicitás	új BNP vagy Troponin I emelkedés normális imaging-el (ha alapból jó, akkor 20%-os emelkedés)	folyamatos	C-O vizsgálat szorosabb monitorozás, vagy ACEI vagy BB, kardioprotekció
2	korai funkcionális kardiotoxicitás	Új GLS csökkenés vagy DD gr.III-IV és normális biomarkerek	folyamatos	ld. 1-es
3	korai kevert kardiotoxicitás	normál LVEF abnromális biomarkerekkel és GLS/DD	folyamatos	C-O vizsgálat alacsony dózisú ACEI vagy BB, kardioprotekció
4	tünetes HFpEF	tünetes HFpEF	megszakítás és risk/benefit elemzés*	C-O vizsgálat Furosemid és alacsony dózisú ACEI vagy BB, kardioprotekció, ha a KT folytatódik
5	tünetmentes LVSD	új LVEF csökkenés vagy <50% vagy 10%-nál nagyobb LVEF csökkenés 55%-ig	elemzés és risk/benefit balansz*	C-O vizsgálat ACEI és/vagy BB kezelés 50-100%-ig feltitrálva
6	tünetes LVSD	tünetes LVEF csökkenés 50% alatt vagy 10%-nál nagyobb LVEF csökkenés 55% alatt	megszakítás és risk/benefit elemzés*	C-O vizsgálat ACEI és/vagy BB kezelés 100%-ig feltitrálva

Lyon A. et al.: E-journal of Cardiology Practice vol 16; No 40, 2019.

Ranolazine

European Journal of Heart Failure (2014)
doi:10.1002/ejhf.50

Ranolazine protects from doxorubicin-induced oxidative stress and cardiac dysfunction

Carlo G. Tocchetti[1]*, Andrea Carpi[2], Carmela Coppola[3], Cristina Quintavalle[4], Domenica Rea[5], Marika Campesan[2], Antonella Arcari[8], Giovanna Piscopo[3], Clemente Cipresso[3], Maria Gaia Monti[7], Claudia De Lorenzo[6], Claudio Arra[5], Gerolama Condorelli[4], Fabio Di Lisa[2], and Nicola Maurea[3]

Ranolazine Attenuates Trastuzumab-Induced Heart Dysfunction by Modulating ROS Production

Gennaro Riccio[1], Salvatore Antonucci[2], Carmela Coppola[3], Chiara D'Avino[4,5], Giovanna Piscopo[3], Danilo Fiore[4], Carlo Maurea[3], Michele Russo[6], Domenica Rea Claudio Arra[7], Gerolama Condorelli[4], Fabio Di Lisa[2], Carlo G. Tocchetti[6*], Claudia De Lorenzo[4,5*] and Nicola Maurea[3*]

OncoTargets and Therapy 2018

Cardiotoxic effects of the novel approved anti-ErbB2 agents and reverse cardioprotective effects of ranolazine

Claudia De Lorenzo[1,2,*]
Rolando Paciello[1,2,*]
Gennaro Riccio[3]
Domenica Rea[4]
Antonio Barbieri[4]
Carmela Coppola[4]
Nicola Maurea[4]

Empagliflozin

JACC
JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

Journal of the American College of Cardiology

Volume 73, Issue 9 Supplement 1, March 2019
DOI: 10.1016/S0735-1097(19)31266-5

PDF Article

CARDIOPROTECTIVE AND ANTI INFLAMMATORY EFFECTS OF A SELECTIVE INHIBITOR OF THE SODIUM GLUCOSE COTRANSPORTER 2 (EMPAGLIFOZIN) IN DOXORUBICIN INDUCED CARDIOTOXICITY

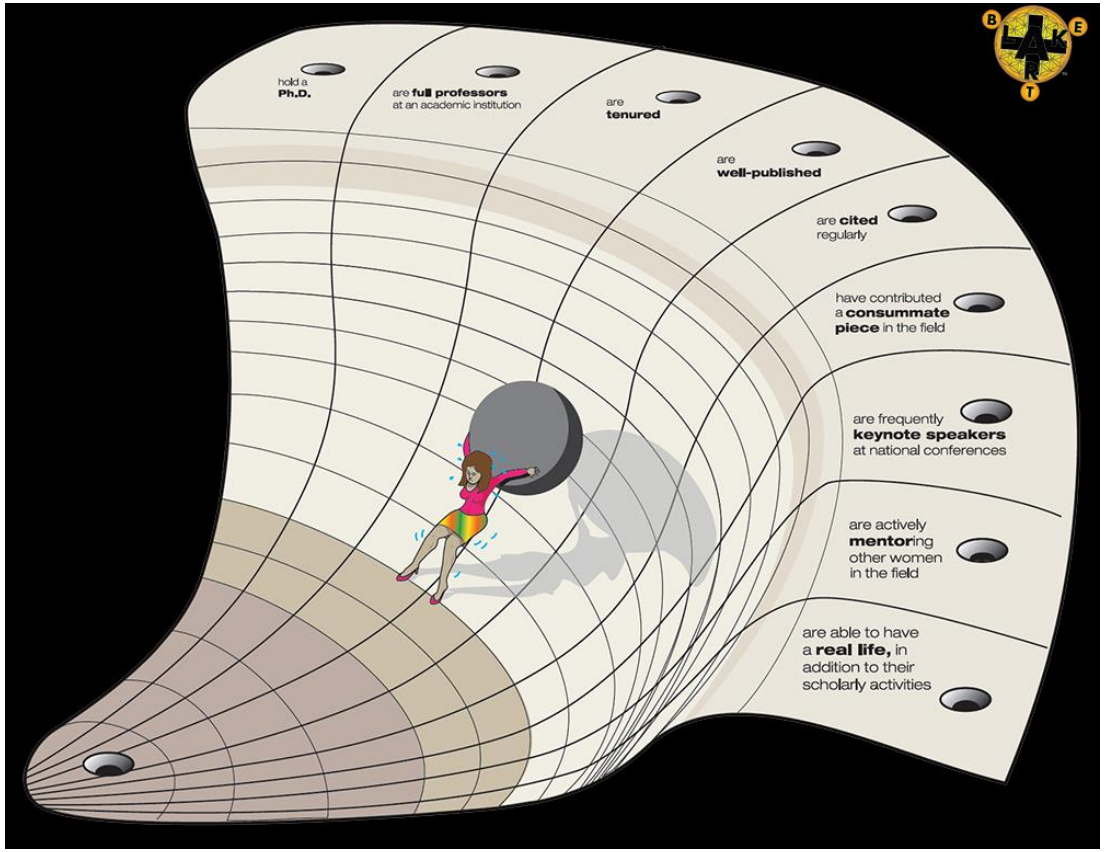
Nicola Maurea, Vincenzo Quagliariello, Carmela Coppola, Giovanna Piscopo, Rosario Vincenzo Iaffaioli and Gerardo Botti

Background: Empagliflozin (EMPA), a selective inhibitor of the sodium glucose co-transporter 2 (SGLT2), reduced the risk of hospitalization for heart failure or cardiovascular death in type 2 diabetic patients. The mechanism by which EMPA induces cardiovascular benefits is obscure but it could have also cardioprotective effects in Doxorubicin-Induced cardiotoxicity.

Methods: Herein we tested effects of EMPA (at 100 or 500 nM) alone or in combination with Doxorubicin (20 μM) in HL-1 cells (mouse adult cardiomyocytes) evaluating: mitochondrial viability (at 24h of incubation), lipid peroxidation (quantifying cellular Malondialdehyde [MDA] and 4-hydroxynonenal [4-HNA]) , Leukotriene-B4 expression, p65-NF-κB activation and Interleukin 1β, 8 and 6 secretion.

Results: We demonstrated for the first time that EMPA, co-incubated with Doxorubicin, is able to increase cardiomyocyte viability of 33,6 and 89,3 % at 100 and 500 nM, respectively (compared to only Doxorubicin treated cells). EMPA is able to inhibit lipid peroxidation by decreasing MDA and 4-HNA production of around 23,6 and 28,7 %, at 100 nM and of 47,8 and 52,1 % at 500 nM ,respectively, compared to untreated cells ($p<0,01$ for all). Moreover, EMPA has anti-inflammatory activity in a concentration dependent manner with a reduction of Leukotriene B4 expression and p65-NFkb activation of 37,4 % and 31,6 % at 100 nM and of 58,4 and 64,3 % at 500 nM, respectively (all compared to only Doxorubicin treated cells). EMPA also decreased the expression of Interleukin 1β (of 28,5 and 68,8 %), Interleukin-8 (of 21,2 and 57,3 %)and Interleukin-6 (of 28,1 and 49,8 %) at 100 and 500 nM, respectively, compared to only Doxorubicin exposed cells ($p<0,05$ for all).

Conclusion: EMPA has strong anti-inflammatory and cardioprotective effects in Doxorubicin-Induced cardiotoxicity and these effects are mainly mediated by a reduction of the lipid peroxidation, Leukotriene-B4 activation, NF-κB activation bringing, consequently, to a strong inhibition of the Interleukin 1β, 8 and 6 production in adult cardiomyocytes. Significance of this preliminary study is based on the possible use of EMPA in the management of cardiovascular risk factors in cancer patients.


hold a
Ph.D.
are **full professors**
at an academic institution
are
tenured
are
well-published
are **cited**
regularly
have contributed
a **consummate**
piece in the field
are frequently
keynote speakers
at national conferences
are actively
mentoring
other women
in the field
are able to have
a **real life,** in
addition to their
scholarly activities

Köszönöm megtisztelő figyelmüket!