

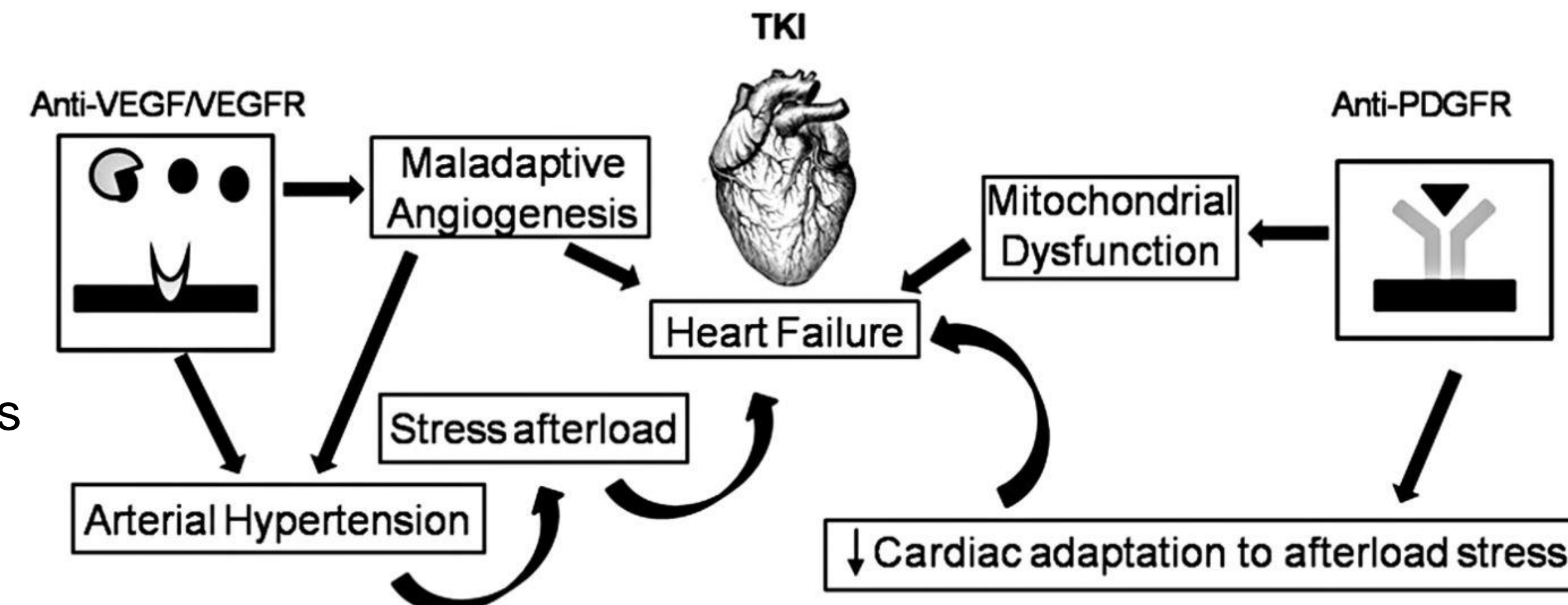
Tivozanib: Saving Kidneys but Breaking Hearts: A Case Report

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Background

- Tivozanib is a tyrosine kinase inhibitor (TKI) indicated for the treatment of advanced renal cell carcinoma¹
 - Food and Drug Administration (FDA) approval date: March 10, 2021¹
 - Mechanism of Action: via potent and selective inhibition of **vascular endothelial growth factor receptor (VEGFR)-1, -2, & -3**, along with inhibition of c-kit and PDGFR β , tivozanib **inhibits angiogenesis, vascular permeability, and tumor growth**¹
- As a class, VEGFR inhibitors have demonstrated efficacy across numerous oncologic disease states, with robust data in the treatment of renal cell cancer. They exert their effects by halting neo-angiogenesis that is required to supply blood to growing tumors.²
- VEGFR inhibitors are known to cause cardiac toxicity including hypertension and heart failure, as well as thromboembolism. However, only some VEGFR inhibitors have specific cardiac monitoring parameters published in their FDA prescribing information. VEGFR inhibitor cardiotoxicity is documented to be at least partially reversible. Cardiac failure is reported in 1.6% of patients treated with tivozanib.¹⁻²



Tocchetti CB, et al. How TKI antagonists induce cardiac damage. Figure. *Antioxid Redox Signal.* 2019;30(18):2117. doi: 10.1089/ars.2016.6930

Patient Case

Patient AZ is a 72 year-old female with past medical history of hypertension and hypothyroidism

Baseline ECHO 8/29/22: LVEF 60-65%

- Grossly normal biventricular function with estimated LV ejection fraction of 60-65%
- Small circumferential pericardial effusion (0.72 cm) without evidence of pericardial tamponade
- Compared to the prior study dated 06/16/2022, severity of pericardial effusion is less

Follow-up ECHO 5/17/23: LVEF 20%

- Left ventricular systolic function is severely decreased. The quantitative EF by 2D Simpson biplane is 20%. Left atrial filling pressure is elevated.
- Right ventricular systolic function is reduced
- Compared to previous study on 08/29/2022, LV systolic function has acutely declined. Moderate or severe MR is now present.

2018

2020 – March 2023

April 26, 2023

May 13, 2023

May 17, 2023

May 24, 2023

Initial diagnosis

Diagnosed with Stage III renal cell cancer and underwent nephrectomy but declined adjuvant sunitinib

Recurrence

Cancer recurred as metastatic disease
1st-line: axitinib plus pembrolizumab
2nd-line: cabozantinib
3rd-line: everolimus

Tivozanib

4th-line: tivozanib at a reduced dose of 0.89 mg daily for 21 days every 28 days (due to poor performance status)

Emergency

Admitted for shortness of breath, lower extremity edema, altered mental status, and hypertension

Echocardiogram

Acute systolic heart failure with a **severely depressed LVEF of 20%**. Diagnosis of **tivozanib-induced cardiomyopathy** by cardio-oncology service

Discharged

Patient was ultimately discharged on home hospice care

Discussion

- This case highlights the importance of cardiac monitoring in patients on VEGFR inhibitors
- Particular attention should be given to ensure appropriate cardiac monitoring in patients receiving treatment with tivozanib due to:
 - Recent FDA approval in 2021
 - Lack of echocardiogram monitoring recommendations in the prescribing information
 - Potential for the rapid onset of cardiac adverse effects, as demonstrated in our patient case
 - Potentially reversible cardiac adverse effects with timely diagnosis and treatment
- For tivozanib, the European Society of Cardiology recommends the following: baseline echocardiography in high- and very high-risk patients (repeat every 3 months during the first year and every 6 to 12 months thereafter); consider baseline echocardiography in low- and moderate-risk patients (consider repeating every 4 months during the first year and every 6 to 12 months thereafter for moderate-risk patients)³
- As the drug information experts on the interdisciplinary healthcare team, clinical pharmacists play a key role in understanding the potential cardiac adverse effects of VEGFR inhibitors and advocating for patient safety by updating clinic-specific practice guidelines to include more robust, evidence-based cardiac monitoring recommendations

Future Directions

- Standardize cardiac monitoring for tivozanib across the healthcare system
- Identify other VEGFR inhibitor TKIs/treatments that could be optimized with standardized cardiac monitoring

References

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- Dobbin SJH, et al. Cardiotoxic effects of angiogenesis inhibitors. *Clin Sci (Lond)*. 2021;135(1):71-100. doi: 10.1042/CS20200305.
- Lyon AR, 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*. 2022;43(41):4229-4361. doi: 10.1093/eurheartj/ehac244.