

# Sunitinib Related Cardiac Toxicity in Renal Cell Carcinoma: An experience in Northern Ireland

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## Background:

Renal cell carcinoma is the 7th commonest malignancy in Northern Ireland. Surgery is the treatment of choice with amenable tumours, whereas in metastatic disease systemic therapy is used.

The Von Hippel Lindau protein plays a key role in the pathogenesis of RCC & normally induces expression of genes associated with angiogenesis and proliferation in hypoxic conditions, such as VEGF, PDGF, and TGF-alpha.

Sunitinib is an inhibitor of multiple tyrosine kinases, including VEGF, & has been shown to have a significant improvement on overall and progression-free survival in patients with metastatic RCC.

Physiologically, It is thought that the development of hypertension occurs as inhibition of VEGF causes a decrease in production of nitric oxide and prostacyclin in vascular endothelial cells.

Cardiac dysfunction is proposed to occur through a combination of a microvascular dysfunction mediated through growth factor blockade, AMP kinase blockade that depletes cardiac mitochondrial ATP, & pro-apoptotic kinase activation in the myocardium.

## Study design:

This is a retrospective study examining the experience within the Northern Ireland Cancer Centre with patients who had advanced renal cell carcinoma who were prescribed Sunitinib between 2015-2018. Advanced RCC was defined as stage III and IV disease.

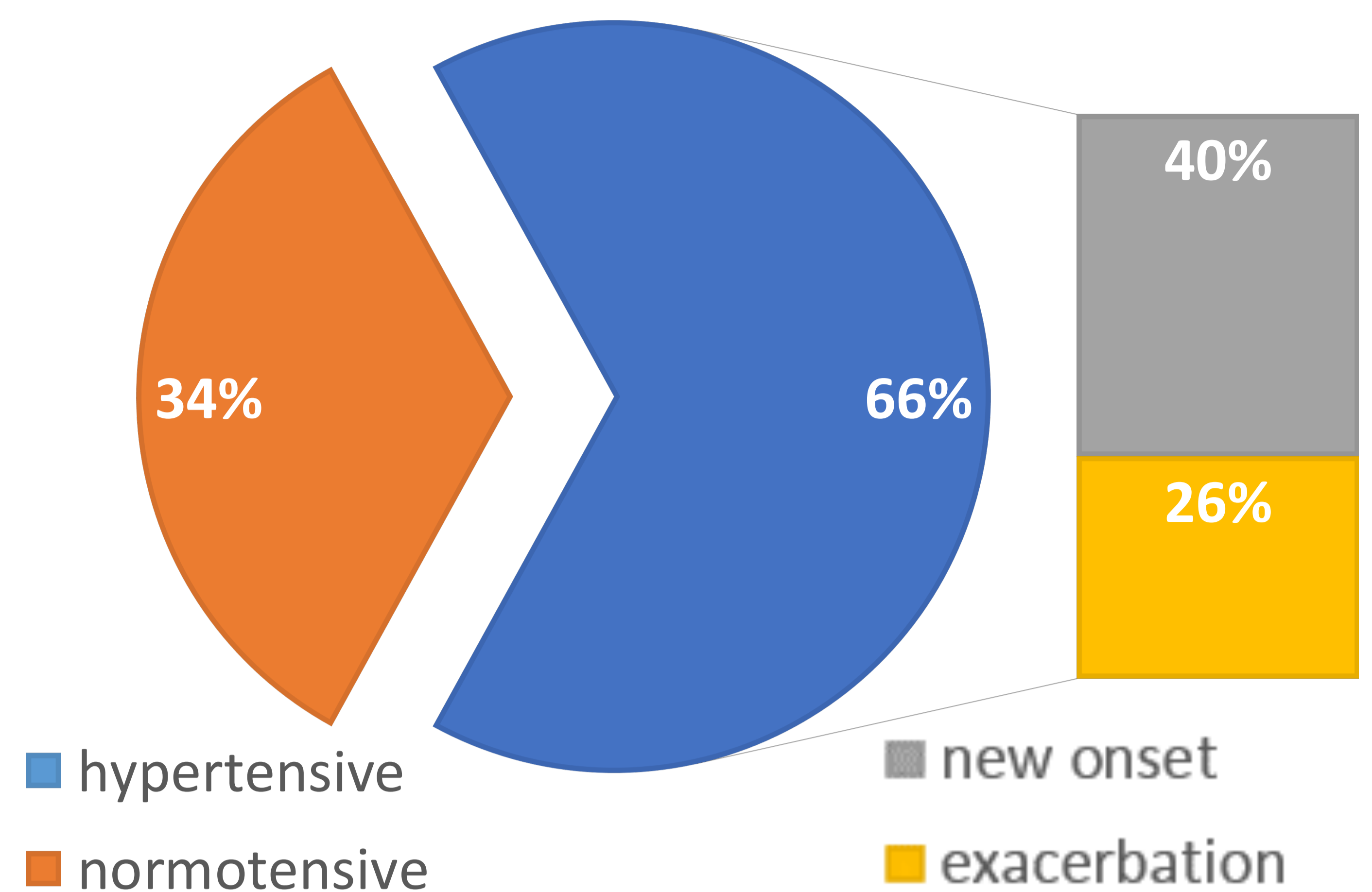
Patients were identified anonymously through the local electronic medical notes system. Data was acquired about peri-treatment factors aiming to identify risk factors & predictive biomarkers. Intra-therapy arterial hypertension & deterioration in left ventricular function Indications for cessation of treatment were collected.

## Results

| Demographic              | frequency           | Range          |
|--------------------------|---------------------|----------------|
| <b>Gender</b>            |                     |                |
| - Male                   | 45 pts              |                |
| - Female                 | 27 pts              |                |
| <b>Age</b>               | 50.5 years (median) | 36 to 88 years |
| <b>Cycles of therapy</b> | 15.7 cycle (mean)   | 1 – 85 cycles  |

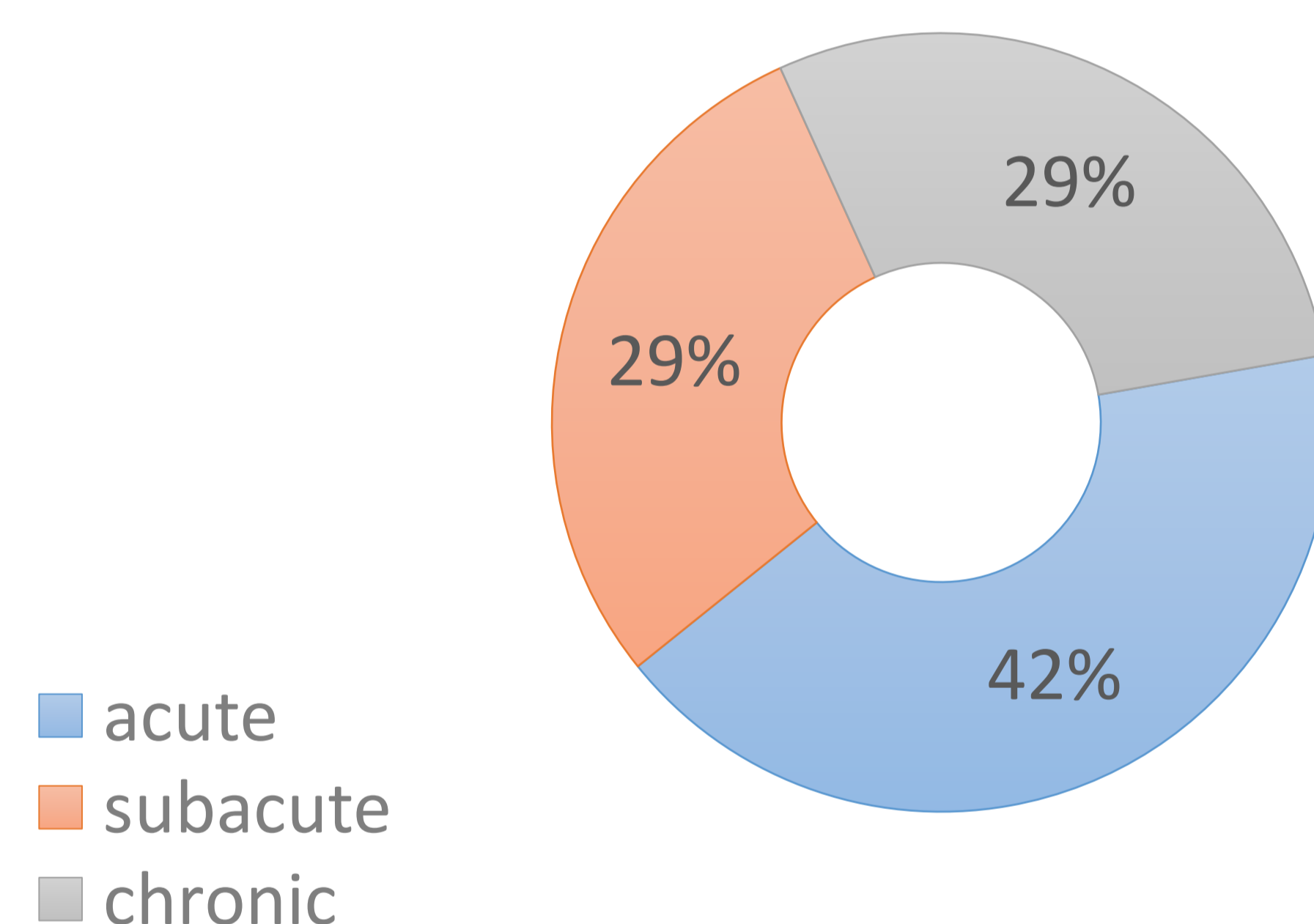
| Risk factors                | patients |
|-----------------------------|----------|
| - Pre-existing HTN          | 26       |
| - Type II diabetes mellitus | 6        |
| - Hyper-cholesterolaemia    | 4        |
| - Tobacco use               | 6        |

## INCIDENCE OF HYPERTENSION



| Cessation indication | frequency |
|----------------------|-----------|
| Disease progression  | 84.8%     |
| Cardiotoxicity       | 6.7%      |
| Other Toxicity       | 8.5%      |

## Distribution of LVED



## Conclusion & Discussion:

- The incidence of hypertension and cardiomyopathy reflects that in literature.
- Pre-existing hypertension was not predictive of hypertension whilst prescribed Sunitinib & was present in the majority of patients in our centre.
- Cardiomyopathy was **the third** most common indication for cessation of therapy after progression. Most cases of cardiomyopathy were detected in the acute setting with a subsequent rapid recovery whilst chronic onset appeared to be associated with a poorer prognosis.
- No association between serum biomarkers and cardiomyopathy was observed.
- The majority of our patients who developed arterial hypertension, were managed with non-dihydropyridine Calcium channel blockers.
- There is a paucity of data recommending specific agents in anticancer therapy induced hypertension.
- Sunitinib related hypertension acts mainly through a vasoconstrictive mechanism, as such, the use of vasodilatory agents in physiologically sound. However there is a rationale for preference of cardio-protective anti-hypertensives such as ACEis or ARBs given the risk of left Ventricular dysfunction.
- Reluctance to use these agent maybe be centred around to association of ACEi/ARBs and acute kidney injury in a patient group that are likely to possess reduced functional renal mass, however observation data suggests that ACEi/ARBs in patients with a nephrectomy can be cardioprotective and renoprotective.
- Prospective randomised controlled trial data in this domain is required.