

# Dronedarone-induced hyperkalemia

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## Background

Dronedarone is an anti-arrhythmic agent indicated for atrial fibrillation. In signal detection of VigiBase, the WHO global individual case safety report database at Uppsala Monitoring Centre, dronedarone associated hyperkalemia was identified as a signal.

## Objectives

To assess causality and possible risk factors for dronedarone associated hyperkalemia.

## Methods

Reports of dronedarone associated hyperkalemia in VigiBase up to April 2019 were reviewed. The Bradford-Hill criteria were applied in the assessment of the case series.

## Results

VigiBase contained **18 unique cases** of hyperkalemia with dronedarone as a suspected or interacting drug (expected 8). Dronedarone was **single suspected in 12 cases**. The reports came from **10 countries** involving **5 females and 13 males**, age range **45 to 86 years** (mean 71). The dronedarone dose (known in 10) was **400 mg** twice daily in nine cases. **Most of the cases (89%) were serious** with four life-threatening and one fatal.

**The mean time** from dronedarone start to the event onset (TTO) **was 19 days** (median 13 days, n=11) ranging from 3 days to 9 weeks. **Positive dechallenge** was reported in **six cases** when information was available. Based on the temporal relationship including positive dechallenge, there seems to be a **possible causal relation for dronedarone associated hyperkalemia**.

In **11 cases, (acute) renal failure** was a co-reported event, with creatinine increased in two other cases, while in five there were no co-reported renal events and in four of these dronedarone was single suspected. While creatinine increased is clearly included in the label as an adverse reaction of dronedarone, renal failure is not.

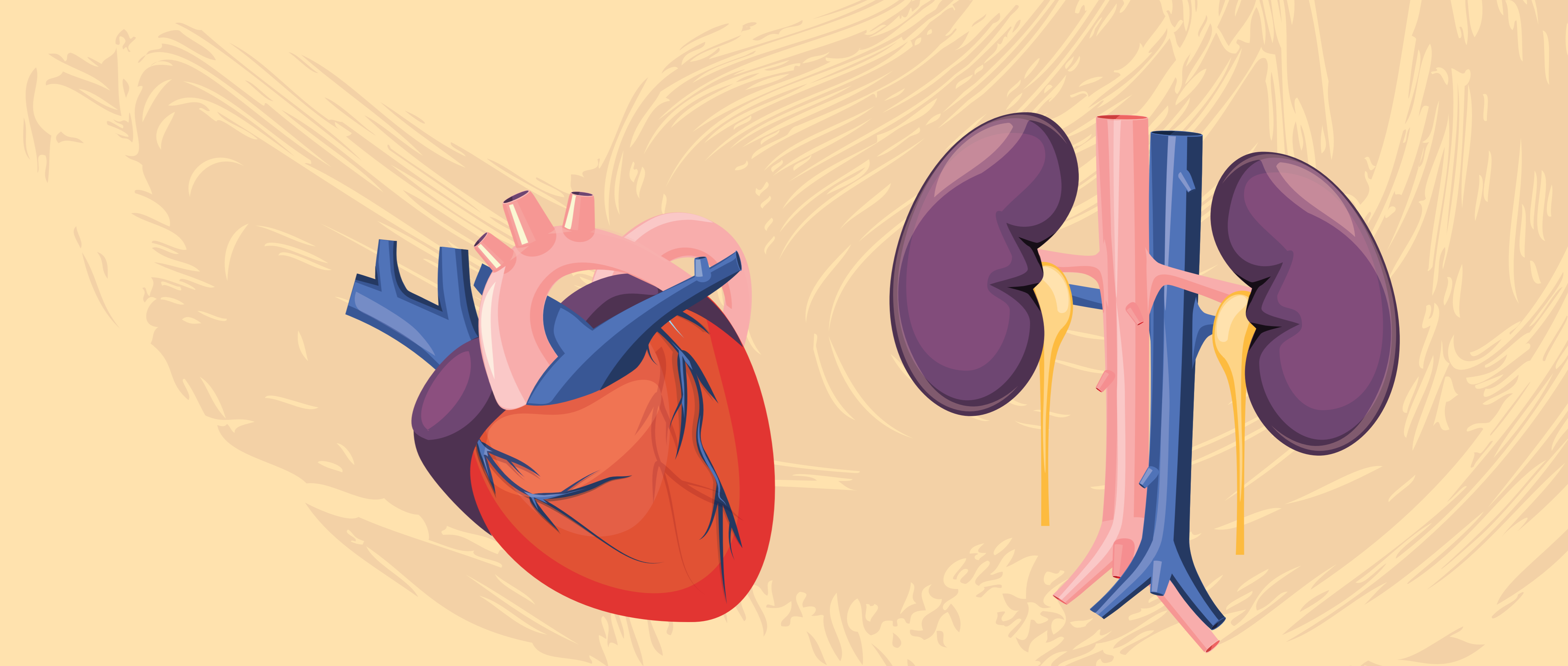
Other drugs known to cause hyperkalemia were reported as suspected (four cases) or concomitant (10 cases) drugs: such as beta-blockers and calcium channel blockers (alter transmembrane potassium movement); ACE-inhibitors, angiotensin-II receptor blockers, NSAIDs, potassium-sparing diuretics (impair renal potassium excretion); and potassium-containing agents (increase supply).

## Conclusions

Based on the Bradford-Hill criteria, and especially the reporting disproportionality, close temporal relationship including positive dechallenge, and similar literature cases, a causal relationship for dronedarone and hyperkalemia seems possible. The mechanism is unclear, but likely multifactorial: e.g. renal failure with dronedarone and concomitant medications known to cause hyperkalemia as contributing factors. Health care professionals should be aware of this possible risk. Renal function should be monitored periodically as recommended during dronedarone treatment.

## Disclaimer

The authors are indebted to the national centres which make up the WHO Programme for International Drug Monitoring and contribute reports to VigiBase. The opinions and conclusions of this study are not necessarily those of the various centres nor of the WHO.



**18** unique cases (expected 8)

**12** cases Dronedarone - single suspected

**89%** of cases serious

**19** days TTO (mean)



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