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Lessons from the trials

ROCKET AF adds more concerns about Digoxin safety in patients with atrial fibrillation

Mohamed ElMaghawry*

Department of Cardiology, Aswan Heart Centre, Kasr ElHajjar, Aswan, Egypt
*Email: maghawry79@gmail.com

ABSTRACT

In a recent article in the Journal, we have reviewed the adverse cardiovascular outcomes observed with digoxin use in the PALLAS study.[1] The PALLAS study was designed to determine if dronedarone would reduce major vascular events in patients with permanent atrial fibrillation (AF).[2] However the study was stopped early because of safety reasons, as a significant number of patients on the dronedarone arm reached the co-primary end point composite of stroke, myocardial infarction, systemic embolism, or cardiovascular death. Data sub-analyses suggested that digoxin-dronedarone interaction was responsible for the higher arrhythmic death rate observed in the trial. These observations are consistent with several other studies that demonstrate the potential hazard of the use of digoxin in heart failure and/or atrial fibrillation.

A more recent article published in the Lancet studied the use and outcomes of digoxin in the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism in Atrial Fibrillation (ROCKET AF) trial.[3] The investigators concluded that digoxin treatment was associated with a significant increase in all-cause mortality, vascular death, and sudden death in patients with AF.

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ROCKET AF DESIGN AND OUTCOMES

ROCKET AF was a multicentre, randomised, double-blind, double-dummy, trial comparing fixed-dose rivaroxaban with adjusted-dose warfarin (target international normalized ratio 2.0–3.0) for prevention of all stroke (ischaemic or haemorrhagic) or systemic embolism. The study randomized 14171 patients from 1178 clinical sites and hospitals at 45 countries with electrocardiographically documented paroxysmal, persistent, or permanent AF. Increased stroke risk was indicated by a history of stroke, transient ischaemic attack, or systemic embolism, or at least two of the following risk factors: heart failure or left ventricular ejection fraction 35% or lower; hypertension; age 75 years or older; or diabetes (CHADS2 score ≥ 2). Patients were randomly assigned with to receive rivaroxaban (20 mg or 15 mg daily in patients with a creatinine clearance of 30–49 mL/min) or dose-adjusted warfarin (target international normalized ratio of 2.0–3.0).

The main results of ROCKET AF concluded that rivaroxaban was non inferior to warfarin for the prevention of stroke or systemic embolism. There was no significant difference between the study arms in the risk of major bleeding. However, less intracranial hemorrhage rates were observed in the rivaroxaban arm.

In ROCKET AF, 5239 (37%) of 14 171 patients were on digoxin at time of randomisation. Patients with AF given digoxin were significantly more likely to be female, have a history of heart failure, have diabetes, and have persistent AF than those who were not. These patients also tended to have a higher baseline heart rate than those not given digoxin. Median duration of follow-up was 707 days (95% CI 519–885). The overall rate of stroke or systemic embolism, the primary endpoint of ROCKET AF, was similar in patients given digoxin at baseline compared with those that were not (2.11 vs 2.37 events per 100 patient-years; adjusted hazard ratio [HR] 0.92; 95% CI 0.77–1.10; adjusted $p = 0.34$). Adjusted rates of the primary safety endpoint (major and non-major clinically relevant bleeding) were similar between patients on baseline digoxin and those that were not.

Baseline digoxin use was associated with increased all-cause mortality (5.41 vs 4.30 events per 100 patient-years; adjusted HR 1.17 [95% CI 1.04–1.32]; adjusted $p = 0.0093$), vascular death (3.55 vs 2.69; 1.19 [1.03–1.39]; $p = 0.0201$), and sudden death (1.68 vs 1.12; 1.36 [1.08–1.70]; $p = 0.0076$). On the other hand, baseline use of digoxin was not associated with increased all-cause admission to hospital (14.83 vs 15.40 events per 100 patients-years; adjusted HR 1.02 [95% CI 0.95–1.10]; $p = 0.64$).

CRITIQUE

Some recent reports have noted a possible hazard with digoxin. The recent ROCKET AF subanalyses further confirms these observations. However, given the retrospective nature of most of these observations, and the large amount of potential confounders, the question whether digoxin is harmful would be hard to answer without a large randomized trial of the drug in patients with AF. Furthermore, non of the recent studies showing worse outcomes with digoxin use, including the current ROCKET AF subanalyses, have had detailed information about how digoxin was used. Knowing more about digoxin dosages, how often digoxin levels were checked, and how often were the digoxin levels outside the therapeutic ranges would add an important clinical insight to the consistent observed adverse outcomes. Some clinicians claim they never encounter these adverse outcomes in their daily practice if they have enough knowledge and experience on how to adminster digoxin properly to their patients. Yet, bearing in mind the current data, it is unlikely that digoxin would yield a clinical improvement for patients.

For the time being, in patient with AF, digoxin should be a last-line agent and should be used with prudence when there are no other available options.

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