Cardiovascular Effects of Androgen Receptor Signalling Inhibitors in the Treatment of Advanced and Metastatic Prostate Cancer

A Systematic Review and Meta-analysis of Randomised Controlled Trials

Omar El-Taji1,2, Samih Taktak3, Craig Jones1,3, Mick Brown1, Noel Clarke1,3, Ashwin Sachdeva1,2

1Genito Urinary Cancer Research Group, Division of Cancer Sciences, University of Manchester; 2Department of Surgery, The Christie NHS Foundation Trust, Manchester, United Kingdom; 3Department of Urology, Salford Royal Hospital, Northern Care Alliance NHS Foundation Trust, Manchester, United Kingdom; Wirral University Teaching Hospitals NHS Foundation Trust, Wirral, United Kingdom.

Introduction

Cardiovascular (CV) events remain a significant cause of non-cancer related mortality amongst men with advanced and metastatic prostate cancer (PCa) with up to 40% of patients dying from a CV related cause. The impact of these novel agents on CV toxicity remains unclear.

Real world data has shown that up to 60% of patients receiving an androgen receptor signalling inhibitor (ARSI), have at least one CV comorbidity.

We aimed to assess the incidence of CV events with addition of ARSI to standard of care (SOC) in locally-advanced (MO) and metastatic (M1) PCa.

Methods

Searches were performed from inception to May 2023 and in accordance with PRISMA guidance.

Eligible RCTs including patients with MO HSPC, M1 HSPC, M0 CRPC and M1 CRPC treated with novel abiraterone acetate, and second-generation (enzalutamide, apalutamide, darolutamide) ARSIs.

All non-randomised studies, and those including an ARSI agent in the control arm were excluded.

Results 1: Eligible studies & incidence of CV events

Figure 1. PRISMA flow chart

Figure 2. Included Studies

25 RCTs (n=22,353 participants)
- 3 RCTs mCRPC (n=4,794)
- 9 RCTs nmHSPC (n=4,256)
- 9 RCTs nmCRPC (n=6,745)

Figure 3. Incidence rates for (A) primary and (B) secondary outcomes.

A. Primary outcomes

CV toxicity

B. Secondary outcomes

Methods

Pairwise meta-analysis was performed using the MetaBase package in R. Data was analysed using the Mantel–Haenszel method and expressed as a risk ratio (RR), with 95% confidence intervals, p<0.05 was considered statistically significant.

A pre-planned subgroup analysis based on disease state and type of ARSI treatment was conducted.

Weighted meta-regression analysis with a mixed-effects model was performed to quantify the potential moderating influence of participant and trial characteristics.

Results 3: Secondary outcomes & subgroup analysis

Figure 6. Secondary Outcomes.

Table 1. Subgroup analysis of ARSI treatment

Addition of ARSIs to traditional ADT significantly increases risk of CV events across the prostate cancer disease spectrum.

Discussion

Our contemporary analysis provides up-to-date evidence of increased CV events in PCa patients receiving ARSIs with conventional ADT.

Significant increase in grade ≥3 hypertension, ACS, cardiac dysrhythmia, cerebrovascular events, and CV-related death.

As use of combination therapy becomes more widespread, particularly in earlier disease settings, there is greater need to evaluate and optimise baseline CV risk prior to commencing ARSI therapy.