Cardiovascular Safety of Roxadustat Versus Erythropoiesis-Stimulating Agents for Treatment of Anemia in Patients With Chronic Kidney Disease Incident to or Not Receiving Dialysis: Pooled Subgroup Analysis of Four Phase 3 Studies

Ciro Esposito, Jonathan Barratt, Frank Dellanna, Jose Portoles, Gabriel Choukroun, Luca de Nicola, Michael Reusch, James Young, Alina Jiletcovici, Nada Dimkovic

cebo-controlled run-in period, enrolled patients were randomized to one of three doses of dexfadrostat phosphate taken orally, once daily. After 8 weeks, patients were switched to placebo and followed for an additional 2 weeks. Blood samples were taken at 2-week intervals and evaluated in a central laboratory for steroid and peptide hormones as well as electrolytes. Blood pressure was measured during each clinic visit. Ambulatory systolic blood pressure (aSBP) was monitored over 24-hours at baseline and after 8 weeks of treatment.

Results or Learning points: All endpoints of the study were met with high significance. Dexfadrostat phosphate treatment was generally safe and well tolerated. We present the effects on the aldosterone-to-renin ratio (ARR) and blood pressure reduction, correction of hypokalemia, and reversal of therapeutic effects upon drug withdrawal.

Conclusions: The phase 2 study evaluated the ability of dexfadrostat phosphate to deliver both biochemical (ARR, potassium) and subsequent clinical (aSBP) correction of the consequences of uncontrolled aldosterone production. By demonstrating clinical utility in an indication of extreme aldosterone dysregulation, the potential of dexfadrostat phosphate may well expand to address essential hypertension, chronic kidney disease, hypokalemia, volume expansion and organ remodeling.

OC 46 / P 29

Living kidney donor evaluation and coronary risk assessment with low radiation dose computed tomography as a one-stop-shop examination*

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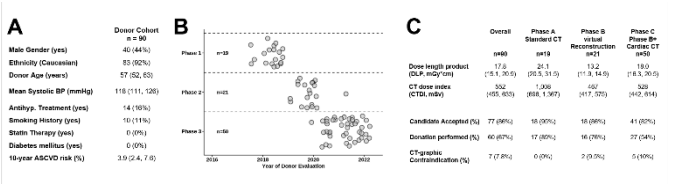
Background: To compare a standard triple phase computer tomography (CT) protocol with a combined dual-energy, split-bolus CT protocol with cardiothoracic assessment of living kidney donor candidates.

Methods or Case description: This was an analysis of pre-selected living kidney donor candidates in a single transplantation center in Switzerland. CT scans of candidates were analyzed and compared between patients with a standard abdominal triple phase CT acquisition (Protocol A), an abdominal dual phase CT acquisition with virtual non-contrast reconstruction and a split-bolus contrast medium administration for assessment of the urinary tract (Protocol B) and a protocol B with additional cardiothoracic CT acquisition (Protocol C). Cardiothoracic and abdominal CT findings, as well as CT dose estimations were compared between the groups.

Results or Learning points: A total of 90 kidney donor candidates were included. The highest radiation dose was observed with CT protocol A (n = 19, DLP 1008 mGy*cm; CTDI 24.1 mGy), while radiation dose was lower in the dual energy, split bolus CT protocol B (n = 21, 467 mGy*cm; CTDI 13.2 mGy), even when combined with the additional cardiothoracic CT in protocol C (n = 50, DLP 528 mGy*cm; CTDI 18.0 mGy; p <.001). 17/50 (34%) donor candidates with the combined cardiothoracic and abdominal CT protocol C had coronary artery calcifications, while 3/50 (6%) had previously unknown significant coronary stenosis that led to subsequent invasive coronary angiography and coronary stent insertion. Other relevant cardiothoracic findings included aortic root ectasia (12%), bicuspid aortic valve (2%) and emphysema (8%). Abdominal CT findings were not significantly different between the three groups (p = >.81). Overall, 77/90 (86%) of donor candidates were accepted as kidney donors. In 7 donors (7.8%), CT-graphic contraindications were identified.



Conclusions: Combined cardiothoracic and abdominal CT assessment with low radiation dose is feasible and shows a relevant prevalence of clinically significant cardiothoracic findings in kidney donor candidates. This procedure allows identification of contraindications for kidney donation with high precision.

*Student paper

OC 47 / P 30

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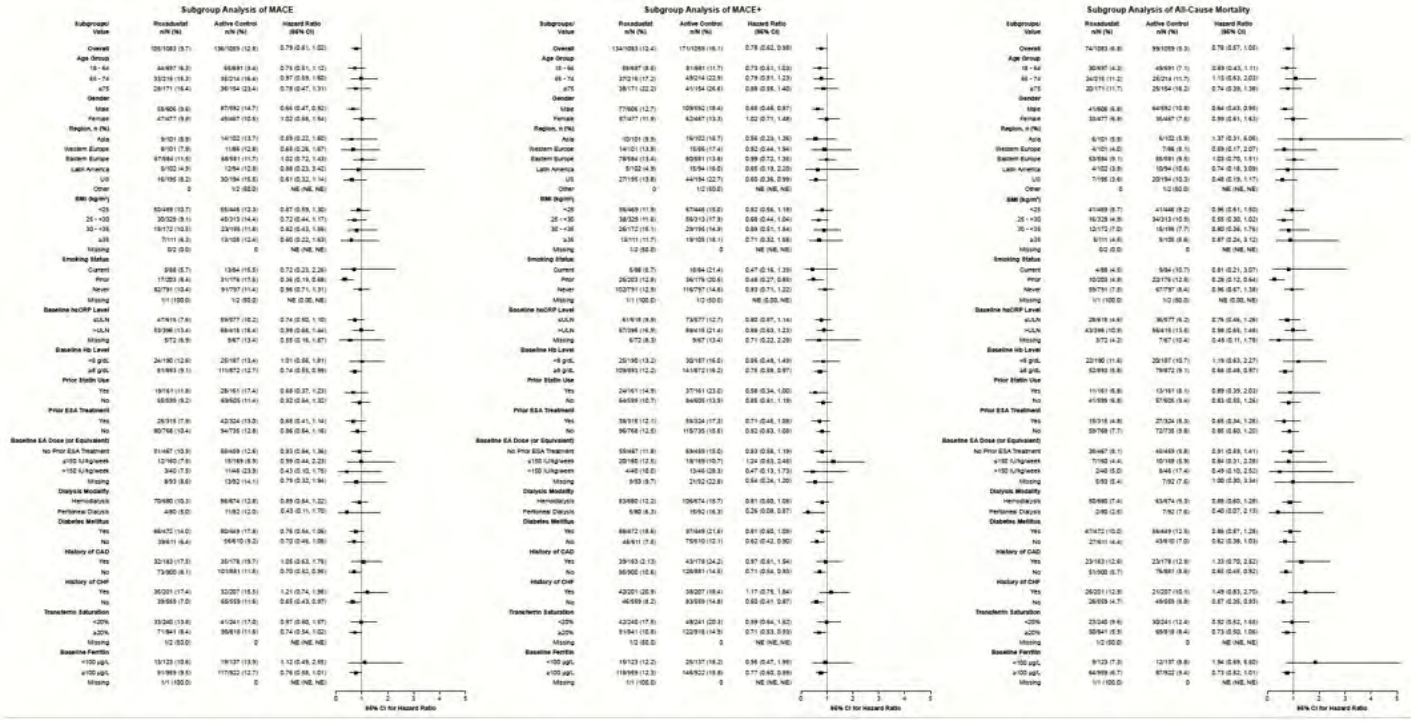
Background: Cardiovascular safety of roxadustat is established in the non–dialysis-dependent (NDD) and incident-to-dialysis (ID)- dialysis-dependent (DD) chronic kidney disease (CKD) populations compared to erythropoiesis-stimulating agents (ESAs); however, the effect of baseline characteristics on cardiovascular safety requires further elucidation.

Methods or Case description: In this post hoc exploratory analysis, cardiovascular safety results from eligible patients with anemia of CKD enrolled in four phase 3, randomized, open-label studies (NDD [DOLOMITES] or ID-DD [SIERRAS, HIMALAYAS, ROCKIES]) were pooled and compared between roxadustat and an ESA. Time to major adverse cardiovascular event (MACE), MACE+ (MACE plus congestive heart failure or unstable angina requiring hospitalization), and all-cause mortality (ACM) was evaluated in subgroups established from baseline characteristics. These endpoints were evaluated descriptively for consistency with the main cardiovascular safety analyses in the pooled NDD or ID-DD CKD population previously reported. Hazard ratios derived using a meta-analysis method that combined individual study log-hazard ratios with weights inversely proportional to the variance of the study-specific log-hazard ratios and 95% confidence intervals were compared between roxadustat and ESA.

Results or Learning points: In total, 2142 patients were evaluated (1083 roxadustat, 1059 ESA; 616 NDD, 1526 ID-DD). Roxadustat was comparable to ESA for risk of MACE and MACE+ with a consistent finding for ACM in most subgroups, which was consistent with outcomes from the main cardiovascular safety analyses, including male sex, United States region, prior smoker, baseline hemoglobin ≥8 g/dL, prior statin use, peritoneal dialysis, no history of diabetes mellitus, no history of coronary artery disease, no history of congestive heart failure, transferrin saturation ≥20%, and ferritin ≥100 mcg/L (Figure).

Conclusions: The risks of MACE, MACE+, and ACM between roxadustat and ESA were consistent with the main cardiovascular safety analyses in the pooled NDD or ID-DD CKD population across most baseline characteristic subgroups with no evidence of increased cardiovascular risk compared with ESA.



OC 48 / P 31

Association of Renin Angiotensin System (RAS) Gene Polymorphisms in Type 2 Diabetic Subjects with Proteinuric and Non-proteinuric Nephropathy

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Background: The genotype frequency of polymorphisms in RAAS genes are varied in different types of nephropathies. Their polymorphic variations may have association with magnitude of proteiuria and progression of disease. In this study the SNPs in ACE, AGT and Aldosterone Synthase gene (CYP11B2) is compared between type 2 diabetic subjects with nephropathy having proteinuria or not.

Methods or Case description: In pre-diagnosed diabetic subjects nephropathy was defined by presence of albuminuria (UrAlb >30 mg/day) and/or CCr <60 ml/min without significant hematuria, pyuria and disproportionate kidneys. The proteinurics are designated as PDN and non-proteinuric nephropathy as NPDN. Genomic DNA was extracted from blood and then amplified using appropriate primers by PCR for evaluation. The insertion-deletion of ACE (ID, DD, II); polymorphisms of AGT in M235T (MM,TT,MT) and Aldosterone Synthase (CYP11B2) gene (TT,CC,TC) was investigated in this study.

Results or Learning points: The nephropathy subjects with proteinuria (PDN) vs normo-proteinuria (NPDN) were 379 vs. 115; age 57±8 vs 58±8 years (p = NS); CCR 58±38 vs. 50±25 ml/min (p = NS) and 24hr UrAlb 956±1452 vs. 11±8 mg/d (p <0.001). The distribution of genotype frequencies for ACE and AGT were similar between PDN vs. NPDN (p = 0.37 and p = 0.959). The distribution of polymorphysms for CYP11B2 was significantly different between the two study groups (TC was 45 vs. 69%; CC 11 vs. 6% and TT 44 vs. 25%; p <0.001) respectively for PDN vs NPDN

Conclusions: The genotype frequency of angiotensinogen (AGT) gene and angiotensin converting enzyme (ACE) gene is not different among diabetic subjects with or without proteinuric nephropathy. The significant difference in Aldosterone synthase (CYP11B2) gene polymorphisms need further exploration for development and progression of nephropathy among Bangladeshi type 2 diabetics with nephropathy.

OC 49 / P 32

Is nephrolithiasis a systemic disorder ? Evidence from a prospective cohort study.

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Background: There is increasing evidence that many renal stone formers (SF) exhibit 'non-urologic' abnormalities such as metabolic syndrome (MS) or cardiovascular disease.

Methods or Case description: A disease is defined as systemic if several organs/tissues or the whole body are affected. We analyzed additional anthropometric/metabolic data from 531 non-selected consecutive renal stone formers investigated over 11 years for incomplete distal renal tubular acidosis (idRTA) [1]. Eight cystine stone patients and 130 calcium stone formers with various secondary causes [1] including idRTA