ASBMR (2017) ABSTRACT

TITLE: Oral bisphosphonate use and risk of acute Kidney Injury, gastrointestinal events and hypocalcaemia in patients with moderate-advanced chronic kidney disease: a population-based cohort study.

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BACKGROUND

The risks and benefits of oral bisphosphonates (oBP) are unclear in patients with moderate to severe chronic kidney disease (CKD): while they could reduce fracture risk, some reports suggest they could worsen renal function.

OBJECTIVES

To study the association between oBP use and the risk of acute kidney injury (AKI), gastrointestinal events (GIE) and hypocalcaemia in moderate-severe CKD.

METHODS

Design: *Cohort study including all subjects with an estimated glomerular filtration rate (eGFR)<45 (stage IIIB+ CKD) at age 50 years or older, with 1+ years run-in data available. Previous users of anti-osteoporosis drugs were excluded.*

Setting: UK Primary Care computerised records in the Clinical Practice Research Datalink linked to Hospital Episode Statistics (HES) and Office for National Statistics (ONS) mortality data.

Exposure/s: GP prescriptions of oral bisphosphonates (oBP) were identified using National (BNF) drug codes. Treatment episodes (in BP users) were created by concatenating prescriptions until patients switched or stopped therapy (refill gap in prescriptions of 180+ days), or were censored (end of study or transfer out). A wash-out of 30 days was added to date of last prescription to account for carry-over effects.

Outcome/s: AKI leading to hospital admission, GIE (bleeding or ulcer/s), or hypocalcaemia leading to hospital admission.

Statistical analyses: Cox regression models were fitted to estimate Hazard Ratios (HR) and 95% Confidence Intervals (95CI) according to BP use after 1:5 matching on propensity scores (PS). Different PS models were constructed for each of the outcomes using a priori defined confounders including baseline demographic characteristics, co-morbidities and co-medications, previous fracture and hospital admissions in the previous year. Pre-specified interactions by gender, fracture history and CKD stage were tested.

RESULTS

A total of 19,315 oBP users and 210,568 non-users were included, with 8846, 499 and 682 patients developing AKI, GI events and hypocalcaemia respectively during follow-up (Table 1). After PS matching, the HR for AKI, GIE and hypocalcaemia were 0.95(95%CI 0.84 -1.07), 0.85(0.48, 1.52), and 1.11(0.77, 1.62), respectively. None of the interactions were significant.

CONCLUSIONS

BP use is not associated with AKI, GIE or hypocalcaemia amongst patients with moderate to severe (stage IIIB+) CKD. More data are needed on the potential risks and benefits of BP therapy in this increasing population.

Table 1. Crude incidence rates of acute kidney injury, gastrointestinal events or hypocalcaemia (N= Number of outcome events and IR= incidence rates).

	oBP Users					
	Number of eVENTS	IR	95%CI	Number of eVENTS	IR	95%CI
AKI-Hospital	387	0.99	0.14, 7.1	8459	0.94	0.12, 7.1
AKI-CPRD_HES	513	1.31	0.24, 7.1	11074	1.24	0.21, 7.21
GI-Events	15	0.04	0, 721.35	484	0.05	0, 320.43
Hypocalcemia	41	0.1	0, 49.18	641	0.07	0, 115.45

This research was funded by the NIHR HTA (project number or ref 14/36/02). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.