A Systematic Literature Review to Understand the Impact of Calcium-Containing Phosphate Binders and Sevelamer on Mortality, Cardiovascular Disease, and Bone Related Disorders in Patients with Kidney Disease

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INTRODUCTION

- Hyperphosphatemia and vascular calcification (VC) are common complications of patients with chronic kidney disease (CKD) and end-stage renal disease (ESRD) with high total body burden of calcium being an important factor for these complications which include including cardiovascular (CV) events and mortality
- Calcium containing phosphate binders (CPBs) are effective in reducing increased serum phosphate levels and are inexpensive, but emerging evidence suggests that, when compared to non-CPBs, such as sevelamer, the CPBs can increase serum calcium levels, resulting in complications

OBJECTIVES

- To summarize the impact of CPBs and resulting hypercalcemia on cardiovascular calcification, mortality, and bone related disorders, in patients with kidney disease and to highlight the advantages of sevelamer in these populations compared to CPBs

METHODS

- A systematic search was run in the OvidSP search platform in the MEDLINE and Embase databases and the Wiley search platform in the Cochrane database
- Two reviewers independently screened relevant references obtained from the literature search, using the inclusion criteria

outlined below. No additional exclusion criteria were applied

- Eligible were any peer-reviewed randomized studies (full text articles only) that presented research on the impact of CPBs on mortality, CV effects (e.g. calcification), and bone related disorders
- Patients had to be adults (>18 years) with kidney disease. Papers in any language published after 1995 were accepted
- Studies had to investigate the effects of sevelamer or had to include at least one study arm with a CPB if compared to other agents
- Studies that reported on phosphate binders for other indications were not included

RESULTS

- The literature search identified 2549 references of which 859 duplicates were removed
- The remaining 1690 references were reviewed in EndNote against the inclusion criteria. No additional studies were identified in hand searches.
- From the 1,690 identified references, 56 were included for full text review and data were summarized from 28 studies

Study Outcomes

Cardiovascular Effects

- There is evidence demonstrating that elevated serum phosphate and calcium levels are important factors involved in the pathogenesis of CVD, eventually resulting in death in patients with ESRD

- Seventeen randomized studies were included for data summary that reported mainly on CV effects
- Three studies reported no differences between sevelamer and CPBs. Other studies confirmed that CPBs cause coronary artery calcification (CAC) and many studies reported advantages of sevelamer in regard to CV effects

Mortality

- Five randomized studies were included for data summary that reported mainly on mortality related outcomes
- All studies reported advantages of sevelamer versus CPBs in regard to (all-cause and/or CVD related) mortality
- Additionally, one of the studies also reported fewer hospitalizations and hospital days for patients on sevelamer

Bone Related Disorders

- In addition to hyperphosphatemia, CKD can also result in disturbances related to the calcium-phosphate homeostasis, referred to as CKD-MBD
- Disturbances in bone turnover, architecture and mineralization result in reduced bone quality and density, with increased risk of fractures
- Six studies were included for data summary that reported mainly on bone related disorders
- All of the studies reported sevelamer's safety and highlighted better bone related outcomes versus CPBs

DISCUSSION AND LIMITATIONS

- No statistical analyses were conducted comparing outcomes for specific patient populations
- Nonetheless, important lessons can be learned from this research, especially regarding the negative impact of CPBs and the safety disadvantages versus sevelamer
- Our study came to similar conclusions as two recently published network meta-analyses.^{1,2} In line with these meta-analyses, our study also reported higher mortality rates with CPBs compared with sevelamer
- The benefits of sevelamer compared to CPB in CKD patients have also been reported by the Canadian Agency for Drugs and Technologies in Health (CADTH).³

CONCLUSIONS

- Based on this study, it can be concluded that sevelamer has clinical advantages versus CPBs in regards to cardiovascular effects and mortality. Sevelamer should therefore be considered as preferential treatment option for the management of hyperphosphatemia in CKD patients

REFERENCES

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