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Proton pump inhibitors and chronic kidney disease: Reevaluating the evidence from a randomized controlled trial

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Proton Pump Inhibitors and Chronic Kidney Disease: Reevaluating the Evidence from a Randomized Controlled Trial

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"Take home" messages

- Proton pump inhibitors (PPIs) are among the most widely prescribed medicines worldwide.
- Observational studies have suggested that PPIs increase the risk of acute kidney injury and chronic kidney disease.
- A recent randomized controlled trial claims to provide evidence of renal safety.
- However, the RCT in question suffers from several limitations and, even on face value, does not contradict the evidence from the observational studies.

Conflict of interest statement

Dr. Gerstman serves as an expert witness on behalf of the plaintiffs in Proton-Pump Inhibitor Multi-District Litigation 2789, United States District Court, District of New Jersey. He has received no fees for writing this commentary and has not shared this manuscript before its publication.

Acronyms and abbreviations

RCT	randomized controlled trial
CKD	chronic kidney disease
COMPASS	Cardiovascular OutcoMes for People using Anticoagulant StrategieS [clinical trial]
eGFR	estimated glomerular filtration rate
KDIGO	Kidney Disease Improving Global Outcomes [organization]
MACE	major cardiovascular events
OR	odds ratio
PPI	proton pump inhibitors

Background

Proton pump inhibitors (PPIs) are among the most widely prescribed medications worldwide.[1,2] However, these products are often over-prescribed and used for unwarranted long durations,[2,3] contributing to substantial expense, polypharmacy, and potential adverse reactions.[4,5]

Evidence from observational studies suggest that PPIs are associated with interstitial nephritis, acute kidney injury, and chronic kidney disease (CKD). For example, Antoniou and colleagues found that hospital admissions for acute kidney injury occurred with more than twice the frequency in PPI users than in non-users (HR = 2.52; 95% CI: 2.27, 2.79).[6] Lazarus and colleagues found a hazard ratio of 1.50 (1.14, 1.96) for CKD in PPI users compared to non-users.[7] These associations have been replicated in numerous studies.[8-14] In contrast, a randomized controlled trial (RCT) by Moayyedi and colleagues concluded that the PPI "pantoprazole is not association with any adverse event [including chronic kidney disease] when used for 3 years, with the possible exception of an increased risk of enteric infections."[15] This reassurance was greeted with welcome relief.[16,17]

While it is convenient to assume that a relationship established by an experiment trumps those of observational studies, this may be "an oversimplification of the actual facts."[18] RCTs, like any type of study, can be designed in ways that have strengths and limitations. Because of the importance of the RCT in question, I believe it warrants a further look.

The COMPASS Trial

For the sake of brevity and clarity, I will refer to the RCT in question as "Moayyedi 2019."[15] To understand the strengths and limitation of this study, is important to place it in the context of the trial from which it was derived. The trial in question is called COMPASS, which stands for "Cardiovascular OutcoMes for People Using anticoagulant StrategieS." As the name implies, COMPASS was designed to test whether the anticoagulant rivaroxaban (Xarelto®) alone or in combination with aspirin was more effective than aspirin alone in preventing major cardiovascular events (MACE) in patients with stable atherosclerotic disease.[19] COMPASS also sought to determine whether the PPI pantoprazole (PROTONIX®) reduces the risk of upper gastrointestinal bleeding and ulceration in its participants. Thus,

the primary study endpoints in COMPASS were MACE, major bleeding, and upper GI bleeding/ulceration. These primary endpoints were carefully defined and adjudicated.[19-22]

Renal endpoints in COMPASS

The only renal endpoint in the COMPASS protocols was "acute nephritis (not caused by infection), nephrotic syndrome, and acute renal failure (only if not related to cardiovascular event or bleeding)."[20,21] In contrast, the renal endpoint in Moayyedi 2019 is chronic kidney disease (CKD). No case definition for CKD is provided in the article, its online supplements, or study protocol.[15,20,21] The first mention of CKD in COMPASS appears in a separate article about its rationale and design published in August 2017.[23] This separate article also offer no criteria for ascertaining CKD.

So how was CKD ascertained in Moayyedi 2019? The article states that participants were questioned every 6 months about whether they encountered new onsets of "safety outcomes of special interested." One of the 9 outcomes of special interest was CKD. The article also states that "medical records were reviewed as appropriate." However, it does not specify how and when such reviews took place, or if independent adjudication ever took place.

According to the Kidney Disease Improving Global Outcomes (KDIGO), "CKD is defined as abnormalities of kidney structure or function present for > 3 months with implications for health."[24] Also, according to KDIGO, the estimated glomerular filtration rate (eGFR) is the best overall index of kidney function with eGFRs < 60 ml/min indicating decreased kidney function, and eGFRs < 30 ml/min indicating severely decreased kidney function.[24] Thus, a standard epidemiologic case definition for CKD is two eGFRs < 60 at least 3 months apart. Within this context, it is important to note that CKD is often silent. The CDC estimates that 9 in 10 adults with CKD are not aware that they have the condition.[25]

Other than at the initial screening and randomization, COMPASS did not routinely measure serum creatinine in its participants [Online Note 1]. At these initial screenings, 22% of participants had eGFRs below 60 and above 30. An additional 1% had eGFRs below 30.[19] These participants were not excluded from the PPI trial. It is therefore likely that a sizable proportion of COMPASS participants were prevalent CKD cases before follow-up began. Given the randomization, blinding, lack of admissibility criteria to screen out prevalent cases (incidence-prevalence bias), and the lack of an objective case definition during follow-up, one can expect endpoint misclassifications to be substantial and nondifferential. This

will tend to bias odds ratios toward the null. While a sizable bias toward the null is relatively acceptable in studies that seek to determine efficacy (strengthen inferences of any effect), it is incoherent a study of safety.

Additional biases toward the null

In addition to problems with case ascertainment, the article incorporates several additional biases toward the null. These biases are related to prior exposure to PPIs, reliance on intention to treat follow-up, exposure misclassification, and failure to consider alternative induction periods.

A 2015 study suggested that 8% of adults between 40 and 64 had used a PPI in the prior 30 days and 18% over 65 had done the same.[1] The initial COMPASS protocol called for participants with a need for PPIs to be excluded from the PPI element of the trial.[20] However, a revised protocol of August of 2015 made clear that only subjects with a *continuous* need for PPIs were to be excluded from the PPI trial.[21] It is therefore likely that many of the participants had used a PPI at some time in their past. Failure to capture these prior exposures is a form of "left truncation" which, in term, would further tend to bias results toward the null. In addition, prior exposure could be associated with the phenomenon known as "attrition of susceptibles."[26]

The ORs in the article are based on modified intention-to-treat follow-up. The permanent discontinuation rate of PPIs was 21%.[15] We normally expect intention-to-treat analyses to attenuate measures of effect. To be fair, however, a sensitivity analysis in Moayyedi 2019 that excluded permanent discontinuers only weakened the association.

PPIs are widely available without a prescription. Given their widespread use, it is possible that placebo users either unknowingly or surreptitiously took PPIs during follow-up. This, too, would tend to bias results toward the null.

The interval from exposure to disease detection is called the empirical induction period. Follow-up of participants in Moayyedi 2019 was for a semi-fixed period (median 3.0 years with an IQR of 2.5 to 3.6 years). Time to event was not considered in the logistic regression used in the article. Inappropriate assumptions about the empirical induction period adds to the potential for a bias toward the null.[27]

Statistical misinterpretations

The best estimate of CKD risk in Moayyedi 2019 excludes participants with eGFRs below 30 ml/min (severely decreased kidney function) at the beginning of follow-up [Online Note 2]. This OR is 1.20 (95% CI: 0.96, 1.51; p = .11). The authors interpret this to indicate "no association." However, results are more consistent with a 20% increase in risk than with no increase at all.[28,29] In any event, "non-significance" should *not* be interpreted as evidence in favor of the null hypothesis.[30-33]

The authors also provide a calculation of 80% power for a significance test at alpha .05 and an expected OR of 1.41. Like *p*-values and confidence intervals, power calculations are easily misinterpreted.[33] Power is a *pre-study* probability. Once the results are in, we cannot cross back over that divide and use the calculation as the probability of a correct decision.[34] Pretest power does not work that way and does obliviate the need for direct tests of alternative hypotheses. For example, a test of H_0: OR = 1.41 with the current data derives a *p* value 0.171 [Online Note 3]. In other words, data are not very incompatible with an OR of 1.41.

Most readers will be aware that non-differential misclassification tends to bias results toward the null. They may not however be aware that it also inflates perceived power and precision.[35] The data are actually "noisier" than one might assume based on the study's confidence interval lengths and power calculations.

Of even more importance is that frequentist statistics do nothing to address what William Sealy Gosset ("Student") referred to as "real error."[36] That is, they do not consider problems with the case definitions, incidence-prevalence bias, prior exposure, misclassification of the induction period, and other the forms of systematic error.

Where does the current study fit in with prior results?

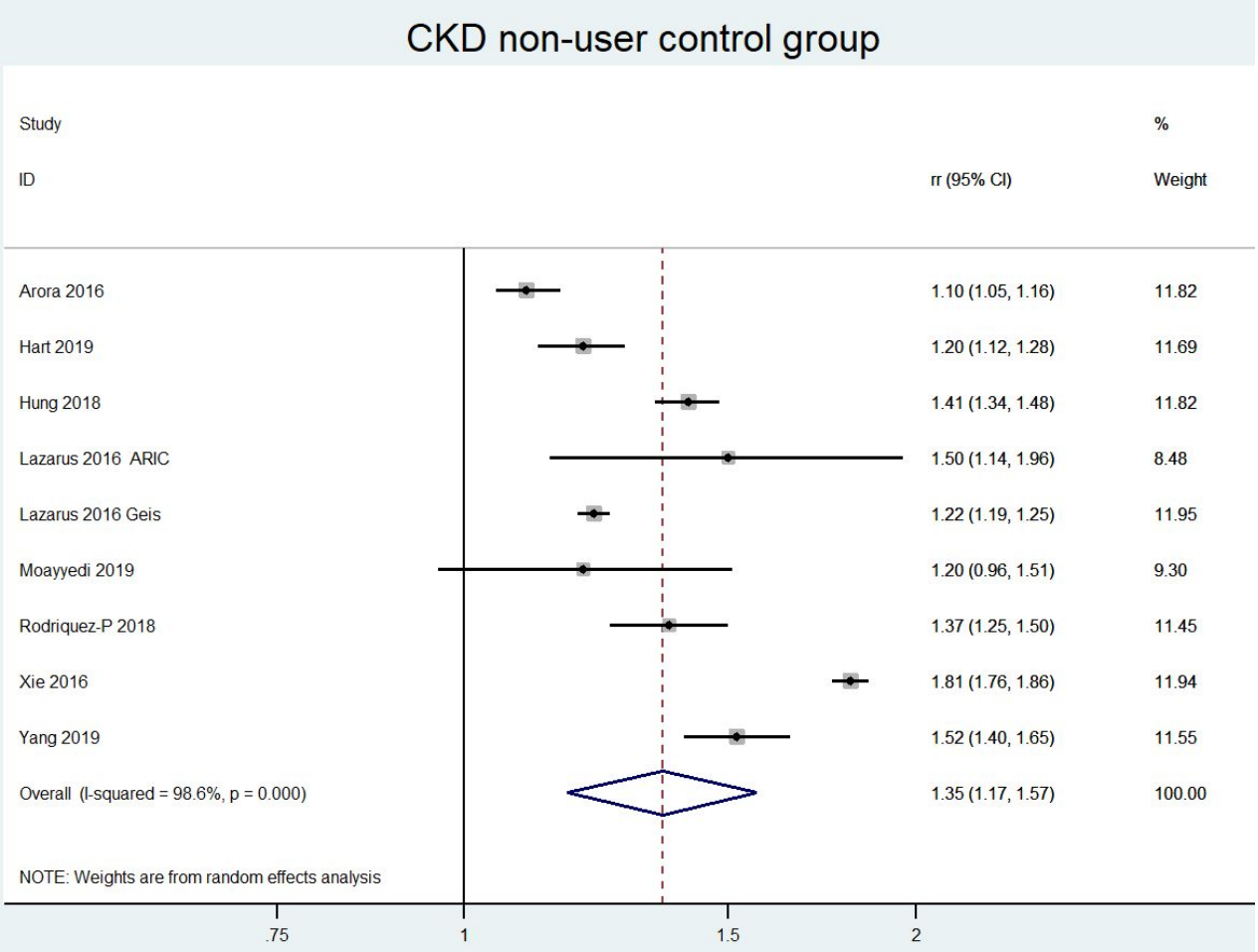
Even when taken at face value, the results from Moayyedi 2019 do not contradict those of the prior observational studies. Figure 1 is a forest plot that includes the RCT's results among those of observational studies in which PPI users were compared to non-users for CKD occurrence. Studies are presented in alphabetic order by first author.[7-9,14,15,37-39] The results results show that the study's results

fit in with the many of the prior studies and the overall relative risk of 1.36 (95% CI: 1.17, 1.57) [Online Note 4].

To sum up, the COMPASS trial was designed to determine whether the anticoagulant rivaroxaban alone or in combination with aspirin was more effective than aspirin alone in preventing major cardiovascular events in patients with stable cardiovascular disease. It was also designed to test whether the addition of pantoprazole would cut down on upper GI bleeding and ulceration in these individuals. Ultimately, the study included more than 17 thousand participants PPI arms of the trial. It hardly needs to be said that carrying out an experiment on this scale requires a great deal of organization and is a credit to all those concerned. It may therefore seem ungracious of me to highlight the study limitations while ignoring the studies strengths (e.g., randomization, blinding, low loss to follow-up). Word limitations require otherwise. However, I must suggest that just because we call this study is an RCT, it is not fallible to other limitations. If an amount of attention equivalent to that which was applied to trial's primary objectives had been applied to its renal safety results, it results in this regard would have carried far greater weight. However, as it is, this study does not provide strong evidence of renal safety.

Figure

Forest plot Relative risks of CKD associated with PPI use with non-user referent groups. Studies are listed in alphabetical order by first author. Moayyedi 2019 is the 6th study listed.



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Online Notes

Note 1

The commentary that accompanied Moayyedi 2019 in *Gastroenterology* states that kidney disease was "directly measured using estimated glomerular filtration rate."[16] This is not true. The only scheduled collection of blood chemistries in COMPASS occurred during the run-up period to the trial and at the time of randomization (COMPASS trial protocol, version 3, Table 7-1). Moayyedi 2019 provides information only on these baseline eGFRs.

Note 2

In a letter to the editor, Lazarus & Carrero request recalculations in the patients with an eGFR of >60 mL/min/1.73 m^2 at baseline.[40] The reply from the authors does not provide these estimates.[41] The letter from Lazarus & Carrero also raise concerns analogous to those expressed in this commentary, including limitations in the study's precision/power and in terms of nondifferential misclassification and the induction period.

Note 3

The standard error of the ln OR is derived from the reported confidence limits. The two-sided *p*-value is calculated from a *z* statistic based on the difference between the observed and null OR divided by the standard error on a natural log scale.

Note 4

Studies in the meta-analysis are a superset of the studies in which PPI use was compared to non-use in previously published meta-analyses.[42-48] Previously published meta-analyses ceased searching for component studies as of September of 2017. The current meta-analysis includes studies through December of 2019. The forest plot was produced with the STATA (v. 14.2) using a DerSimonian & Laird random effects pooling.[49,50]

As an example, the meta-analysis by Nochaiwong and colleagues ceased its literature search as of October 2016.[44] Studies in which CKD is compared in PPI users and nonusers since this time include Hart

2019, Hung 2018, Rodrigues-Poncelas 2018, and Yang 2019.[8,14,38,39] Also note that the current meta-analysis excludes the study by Peng and colleagues because its endpoint is end stage renal disease, not CKD.[51] Nevertheless, the meta-analysis by Nochaiwong 2018 derives an overall relative risk of 1.36 (1.07, 1.72), which is nearly identical to the current overall relative risk of 1.35 (1.17, 1.57).

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