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TITLE PAGE

Title: Effect of ACE Inhibitors and Angiotensin II Receptor Blockers on Disease Outcomes in Inflammatory Bowel Disease.

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Abbreviations:	5-ASA	5-aminosalicylate
	ACE-I	angiotensin converting enzyme inhibitors
	ARB	angiotensin receptor blocker
	IBD	inflammatory bowel disease
	RAS	renin-angiotensin system

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Editor;

We read the recent paper by Garg et al. with interest. [1] The renin-angiotensin system (RAS) has an established role in the pathogenesis of fibrosis and inflammation in renal and cardiovascular disease. However, high concentrations of angiotensin-converting enzyme (ACE) and renin are also found in the small and large intestine. These, along with angiotensin-II, are elevated further within the inflamed colonic tissue of patients with inflammatory bowel disease (IBD), compared with healthy controls. [1, 2] ACE inhibitor (ACE-I) or angiotensin II receptor blocker (ARB) therapy may inhibit the effects of RAS in IBD. In their study Garg et al. demonstrated lower rates of hospitalisation and surgery among patients with IBD receiving these drugs. [1] We aimed to examine the relationship between ACE-I or ARB use and longitudinal disease activity outcomes in a large number of patients with IBD.

Subjects were a well-characterized cohort of 764 patients with IBD (ulcerative colitis = 321, Crohn's disease = 443) recruited into a study between November 2012 and June 2015, and followed up prospectively for a minimum of 2 years. [3, 4, 5, 6] Demographic data and patient-reported disease activity indices were recorded at baseline, and longitudinal disease activity outcomes, including flare or glucocorticosteroid use, escalation of medical therapy, hospitalisation, and intestinal resection, were obtained from electronic health records. Faecal calprotectin levels at baseline were provided by a subset of 382 patients, with $<250\text{mcg/g}$ used to define biochemical remission. Multivariate Cox regression analyses were performed to adjust for selected baseline data (sex, age, 5-aminosalicylate (5-ASA) use, thiopurine use, biologic use, and type of IBD), with results expressed as hazard ratios with 95% confidence intervals.

In total, 104 (13.6%) patients were prescribed ACE-I or ARB therapy at baseline. There were no significant demographic differences between those prescribed ACE-I or ARB therapy and those not prescribed either drug, with the exception of a higher mean age (60.1 ± 13.5 vs. 41.4 ± 15.5 , $P=0.042$). Significantly more patients on ACE-I or ARB therapy were taking 5-ASAs (63.5% vs.

44.2%, $P < 0.001$), but fewer were receiving biologics (10.6% vs. 20.9%, $P = 0.013$). There were no differences in clinical disease activity indices or rates of biochemical remission at baseline.

After univariate analysis, there was a trend towards improved outcomes in those prescribed ACE-I or ARB therapy (Table 1), in terms of reduced rates of flare or need for glucocorticoid prescription, and hospitalisation, and likelihood of intestinal resection was significantly lower (1.9% vs. 7.6%, $P = 0.03$). However, after multivariate Cox regression analysis, adjusting for sex, age, 5-ASA use, thiopurine use, biologic use, and type of IBD, these effects were no longer evident (Table 1).

Although our study demonstrated that rates of adverse disease activity outcomes were generally lower in patients with IBD prescribed ACE-I or ARB therapy, the results were less striking than those of previous smaller studies. [1, 7] It may be that longer follow-up in this cohort of patients will provide more conclusive evidence that these drugs have a beneficial effect on the natural history of IBD.

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Competing Interests:

KMF: none to declare. DH: none to declare. DJG: none to declare. ACF: none to declare.

Table 1. Effect of ACE-I or ARB use on longitudinal disease activity in univariate and multivariate Cox regression analysis.

	Univariate Analysis			Multivariate Cox Regression Analysis	
	ACE-I or ARB Use	No ACE-I or ARB Use	P value*	Hazard Ratio	95% Confidence Interval
Flare of disease activity or need for glucocorticosteroids	25.6%	35.7%	0.06	0.79	0.50 – 1.24
Escalation of therapy	31.6%	40.0%	0.12	0.96	0.64 – 1.45
Hospitalisation	9.6%	16.5%	0.07	0.86	0.43 – 1.70
Intestinal resection	1.9%	7.6%	0.03	0.45	0.10 – 1.90

* χ^2 test

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