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Angiotensin Inhibition and Gastrointestinal Bleeding Prevention in Patients with Left Ventricular Assist Devices

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Abstract

Gastrointestinal bleeding remains a common complication in advanced heart failure patients following implantation of continuous-flow left ventricular assist devices. While the cause is likely multifactorial, development of arterial venous malformations in the gastrointestinal mucosa are a key factor. Inhibition of angiotensin II activity has been postulated to disrupt the signaling that promotes angiogenesis in these patients. We aim to review the theoretical basis for angiotensin receptor blockade, which has been proposed and explore the published evidence regarding this therapy and gastrointestinal bleeding in LVAD patients.

Summary of Presentation

Gastrointestinal (GI) bleeding remains a commonly encountered complication in patients who receive implantable continuous-flow left ventricular assist devices (CF-LVADs), encountered in 25% to 40% of these patients [1-6]. Factors thought to contribute to GI bleeding in CF-LVAD patients include acquired Von Willebrand syndrome, arterial-venous malformation (AVM) development, anticoagulant and antiplatelet medications, advanced age, and other comorbidities that include peptic ulcer disease, liver dysfunction, and malnutrition [3-4,7]. The occurrence of GI bleeding is associated with significant morbidity, hospital admissions, blood transfusion, and potentially increased risk of thromboembolic complications, including ischemic stroke [5-6,8-9]. Despite the significant association with morbidity and increased use of hospital resources, studies to date has not identified a direct link to increased mortality. Consequences of blood transfusions may increase allosensitization, which can have a significant impact on donor availability in bridge-to-transplant patients. Additionally, the need to temporarily reduce anticoagulation and antiplatelet therapy may partially explain the increased risk of thrombotic events and stroke in patients with GI bleeding.

ACE-inhibitor (ACE-I) and angiotensin receptor blocker (ARB) therapy have been proposed to reduce the occurrence of GI bleeding in LVAD patients through inhibition of angiotensin type 1 receptor- (AT1R) mediated increases of angiopoieitin-2 (Ang2) and transforming growth factor-β (TGF-β) [10-12]. Vascular endothelial growth factor (VEGF) expression is enhanced by TGF-β (Figure 1). It is postulated that both increased expression of VEGF and Ang2 are part of the chemical signaling through which AVM proliferation occurs [10-13].

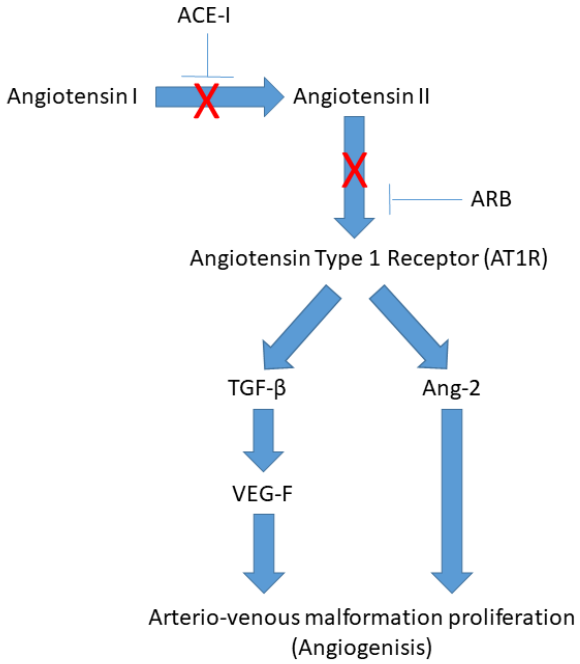

Figure 1*. Proposed mechanistic pathway*

Evaluation of ACE-I and ARB use and effects on GI bleeding in CF-LVAD patients has been undertaken in two single-center retrospective studies in recent years. The first study included 131 patients: 100 received ACE-I or ARB while 31 received no ACE-I or ARB [14]. Patients were considered to have received ACE-I or ARB if they received >30 days of consecutive therapy. In the total cohort, 39 patients (30%) experienced at least one GI bleeding episode. In the unadjusted analysis, ACE-I or ARB use was associated with an odds ratio of 0.36 (95% confidence interval [CI]: 0.16–0.85) compared with no ACE-I or ARB on post-discharge GI bleeding. An adjusted analysis was conducted to account for age at implant, sex, cardiomyopathy etiology, type of LVAD, mean arterial pressure at the first post-discharge appointment, and serum creatinine and international normalized ratio (INR) on day of discharge. In the adjusted analysis, the odds ratio remained 0.29 (95% CI: 0.12–0.72) for any GI bleeding episodes. This study further analyzed GI bleeding secondary to arteriovenous malformation (AVM) and found similarly that ACE-I-and ARB-treated patients had an odds ratio of 0.25 (95% CI: 0.085–0.74) for AVM-related GI bleeding in the unadjusted analysis; and an odds ratio of 0.23 (95% CI: 0.07–0.71) in the same adjusted model.

A later study was undertaken, which included 121 patients with an LVAD and compared patient groups of those receiving an ACE-I or ARB within the first 30 days following implant compared with those that did not receive any ACE or ARB postoperatively [15]. Two-year incidence of major GI bleed and AVM-related GI bleed was compared, indicating a hazard ratio of 0.46 (95% CI: 0.23–0.93) and 0.45 (95% CI 0.20–0.98), respectively. Adjusted hazard ratios were 0.43 (95% CI 0.19–0.97) for major GI bleed and 0.37 (95% CI: 0.16–0.84) for AVM-related GI bleed, with adjustments for age, sex, kidney injury or renal replacement therapy, INR, mean arterial pressure, intent of LVAD therapy, history of bleeding, and INTERMACS score at time of implant included. ***Both studies concluded that the use of ACE-I or ARB therapy could reduce the occurrence of GI bleeding in patients with implanted CF-LVADs.***

While the preliminary data is favorable regarding the effects of ACE-I and ARB on GI bleeding in CF-LVAD patients, definitive randomized studies must be performed to prove any certain benefits of these classes of medications on reducing this risk. Despite the inconclusive nature of this evidence in GI bleeding outcomes, ACE-inhibitor and ARB remain a preferred therapy for blood pressure management and afterload reduction due to their long-established safety profile and well-known benefits across multiple cardiovascular disease subpopulations, most notably of which are heart failure patients.

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