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Mineralocorticoid Receptors: An Appealing Target to Treat Coronary Microvascular Dysfunction in Diabetes

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Cardiovascular disease (CVD), particularly coronary vascular disease, is a primary contributor to diabetes-related morbidity and mortality worldwide. Specifically, dysfunction of coronary microcirculation is common in this patient population, often occurring in the absence of or preceding epicardial coronary atherosclerosis, thereby leading to impaired coronary blood flow (CBF) regulation and increased risk of myocardial ischemia/infarct. Clinically, coronary microvascular function can be assessed by determination of coronary flow reserve (CFR) (ratio of maximal hyperemic to basal CBF), and impaired CFR is a powerful independent correlate of cardiac mortality in diabetic patients (1). Importantly, recent evidence revealed that diabetic patients with preserved CFR (above the median) have cardiac event rates similar to nondiabetic patients (1). Thus, treatment strategies designed to restore CFR (i.e., coronary microvascular function) hold promise to reduce acute and long-term cardiac mortality in patients with diabetes.

Diabetes is associated with increased activation of the renin-angiotensin-aldosterone system (RAAS), and evidence suggests that the aldosterone-binding mineralocorticoid receptor (MR) contributes to obesity and diabetes-related vascular dysfunction (2,3). Even modest elevations in circulating aldosterone levels correlate with increased acute ischemic events and cardiovascular death in diabetic patients with coronary artery disease (4). Furthermore, accumulating evidence demonstrates that inhibition of angiotensin II (AngII) action, via ACE inhibition or angiotensin receptor blockade (ARB), does not appreciably lower circulating aldosterone levels, suggesting a residual role for MR activation in CVD pathogenesis (5). This is consistent with initial clinical trials demonstrating reduced mortality with MR antagonist treatment in heart failure patients already receiving ACE inhibitors or ARBs (6,7). Increased and persistent MR activation is likely even more pertinent in obesity and diabetes due to increased production of aldosterone and aldosterone secretagogues by adipose tissue (8,9). These data highlight the potential of MR antagonists to confer cardiovascular protection above that provided by standard ACE inhibition and ARB therapy in obesity and diabetes.

In this issue of *Diabetes*, Garg et al. (10) specifically addressed the clinical utility of interrupting the RAAS in a double-blind, randomized, controlled study of well-controlled diabetic patients without ischemic heart disease. Specifically, CFR derived from quantitative positron emission tomography was assessed in 64 men and women with diabetes before and after 6-month treatment with an ACE inhibitor (enalapril) combined with the MR antagonist spironolactone compared with treatment with enalapril plus hydrochlorothiazide (matching the blood pressure–lowering effect of spironolactone). An enalapril plus placebo group was also included. Results demonstrate that the addition of spironolactone to enalapril improved CFR, extending a previous crossover design study by this group showing that 6-week treatment with enalapril plus the MR antagonist eplerenone increased CFR in a smaller cohort of diabetic patients (11). Moreover, in the current study, the increase in CFR with spironolactone occurred absent of changes in systemic metabolic and lipid parameters and cardiac function, mass, and extracellular volume and remained significant after controlling for baseline CFR, change in BMI, race, and statin use. In conjunction

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with the lack of increased CFR following hydrochlorothiazide treatment, these results support a blood pressure–independent effect of spironolactone to improve coronary microvascular function in diabetes, presumably via its action on MR within the coronary vascular wall.

While the study by Garg et al. (10) did not include long-term follow-up to determine whether improved CFR leads to reduced cardiovascular event rates in diabetic patients, it does provide important insight into the relationship of AngII and the MR (Fig. 1). A major strength of this study is the use of the ACE inhibitor enalapril in combination with spironolactone as ACE inhibitors themselves, unlike ARBs, improve CFR in patients with diabetes (12,13). Therefore, we can speculate that the improved CFR following spironolactone was additive to that already present due to ACE inhibition, although the latter was not determined during the run-in portion of the current study. Furthermore, as AngII-dependent activation of coronary vascular smooth muscle MR in vitro has been previously reported (14), a portion of the benefit of ACE inhibition on CFR may result from reduced AngII action via the MR. However, the study by Jaffe and Mendelsohn (14) demonstrated that AngII activation of the MR is inhibited by ARB treatment, suggesting complex interactions underlying the discrepancy of the CFR benefit in ACE inhibition versus ARBs in diabetes. Further studies are necessary to directly evaluate the pre- and posttreatment effects of ACE inhibition with and without MR blockade on coronary function in diabetes. Regardless, the current study supports combination ACE/MR inhibition as a powerful therapy to improve CFR in patients with diabetes.

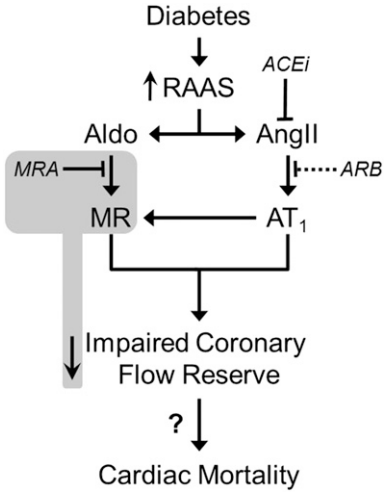

Figure 1—Diabetes-related impairment of CFR is improved by certain inhibitors of RAAS. Increased RAAS activation in diabetes impairs CFR, and this impairment can be reduced by MR antagonists (MRA) (gray box; reported in Garg et al. [10]) and ACE inhibitors (ACEi), but not ARBs. The effect of these antagonists on long-term cardiac mortality in patients with diabetes remains unclear. Solid lines indicate effective treatment options; dashed lines indicate ineffective treatment options. Aldo, aldosterone; AT_1, AngII receptor, type 1.

It should be noted that the study population examined included both men (~63%) and women (~37%) and, unfortunately, is likely underpowered to examine for distinct sex differences. Future studies should evaluate whether there are differential female/male benefits for MR-related therapies in light of recent evidence. In particular, recent analysis of the Women's Ischemia Syndrome Evaluation (WISE) trial revealed that adding eplerenone to ACE inhibition did not improve coronary endothelial function or CFR in women with symptoms of ischemia but without obstructive coronary artery disease (15). Furthermore, direct inhibition of MR-dependent proinflammatory gene expression by estrogen-bound estrogen receptor α was recently reported as demonstrating a novel mechanism of protection for premenopausal women from deleterious vascular MR signaling and subsequent CVD (16).

Finally, the study by Garg et al. (10) adds to accumulating data suggesting a distinct role for vascular MR as a mediator of coronary, but not peripheral, vascular dysfunction in patients with obesity and diabetes. Indeed, an earlier study from this group demonstrated no increase in brachial artery flow-mediated dilation following ACE/MR inhibition in the same patients exhibiting increased CFR (11). Several recent studies also report no benefit of MR blockade on peripheral flow-mediated dilation in obese patients (17,18). The basis for this discrepancy remains unclear but may be a consequence of the unique developmental origins of coronary vascular cells (19).

In summary, the study by Garg et al. (10) presents important evidence in diabetic patients of an additive benefit of ACE/MR inhibition to improve CFR. Ongoing studies should focus on delineating the cell type–specific deleterious effects of coronary vascular MR signaling and whether MR blockade improves coronary responses to (patho)physiologic perturbations (i.e., metabolic and ischemic dilation), particularly in obesity and diabetes.

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