Although the renin angiotensin system (RAS) is a well-established regulator of blood pressure and intravascular volume, considerable evidence has emerged demonstrating the importance of the RAS directly on the cardiovascular system (please refer to the Figure for description of the enzymatic pathways involved in RAS regulation). Indeed, angiotensin converting enzyme (ACE) inhibitors, which prevent the conversion of angiotensin I into angiotensin II (Ang II), and Ang II receptor type 1 (AT1R) antagonists, which inhibit the receptor-mediated actions of Ang II, have demonstrated direct favorable effects on the heart. These include a reduction in cardiac fibrosis during hypertensive left ventricular (LV) hypertrophy, protection against LV enlargement following myocardial infarction, and reduced LV remodeling following coronary artery bypass graft surgery. Hence, ACE1 is generally thought of as a villain contributing to the development of cardiovascular disease due to its generation of Ang II. Fortunately, the RAS may also have a potential hero in ACE2, which can counter many of the negative consequences of ACE1-produced Ang II. In this issue of Circulation Research, Patel et al demonstrate an important role for the RAS in the development of diabetic cardiomyopathy. If diabetic Akita mice are deficient for ACE2 (Akita/ACE2KO), the enzyme responsible for converting Ang II into Ang 1–7, a progressive systolic dysfunction occurred that is associated with oxidative stress, excessive extracellular matrix degradation, vascular dysfunction, and impairment of the Akt-signaling pathway. Ang II activation of the AT1R was implicated in these actions, since a 1-month treatment with the AT1R antagonist, irbesartan, reversed this systolic dysfunction, oxidative stress, vascular dysfunction, and Akt signaling in the Akita/ACE2KO mice.

These findings add to the growing body of evidence implicating a cardioprotective role for ACE2 in cardiovascular diseases. Initial interest in ACE2 as a potential therapeutic target for cardiovascular diseases was engendered by the observation that ace2 mapped to several putative genetic quantitative trait loci associated with hypertension in 3 rodent models of elevated blood pressure. Moreover, the generation of mice deficient for ACE2 (ACE2KO) was associated with a phenotype exhibiting LV contractile dysfunction. Subsequent studies illustrated that ACE2 may be a potential cardioprotective target in a variety of cardiac pathologies. Indeed, ACE2KO mice are more susceptible to ischemic injury, adverse LV remodeling, and LV contractile dysfunction following permanent occlusion of the left anterior descending coronary artery. These effects are prevented by treatment with irbesartan for 3 days prior to left anterior descending coronary artery occlusion and for the duration of the study. Chronic infusion of Ang II into mice also exacerbates pathological hypertrophy, oxidative stress, myo-
cardiac fibrosis, and diastolic dysfunction in ACE2KO mice compared to their wild type littermates. Intriguingly, treatment of wild type mice with recombinant human ACE2 reverses Ang II-induced pathological hypertrophy and oxidative stress. In addition, recombinant human ACE2 therapy also attenuates the deterioration in cardiac function and development of pathological hypertrophy in wild type mice subjected to pressure overload via aortic banding. Aortic banding of ACE2KO mice exacerbates the progression of LV hypertrophy, LV dilatation, and systolic dysfunction, which is associated with increased NADPH oxidase activity and subsequent oxidative stress, and is amendable to reversal following Ang 1–7 supplementation. Utilizing a different approach, Mercure et al also demonstrated beneficial effects for Ang 1–7 against Ang II-induced adverse remodeling, as transgenic mice that overexpress Ang 1–7 specifically in the heart exhibit a reduction in ventricular fibrosis and LV hypertrophy following a 19-day Ang II infusion.

In the Patel et al study, the authors crossed ACE2KO mice with diabetic Akita mice to determine the contribution of ACE2 in the progression of diabetic cardiomyopathy. Although the cardiac phenotype of Akita mice involves diastolic dysfunction, these authors demonstrate that on a background of ACE2 deficiency, Akita mice will also progress to systolic dysfunction. These observations were associated with increased NADPH oxidase activity and subsequent oxidative stress, as well as increased matrix metalloproteinase activity and subsequent degradation of the extracellular matrix. Thus, inhibiting ACE2 activity in the cardiovascular system accentuates a number of mechanisms involved in precipitating cardiac injury. However, antagonism of the AT1R with irbesartan was able to reverse these effects, highlighting the involvement of increased Ang II levels in mediating the cardiac dysfunction in Akita/ACE2KO mice.

Interestingly, in the study by Patel et al, ACE2 was actually upregulated in the Akita mice. The authors suggest that this upregulation of ACE2 activity in Akita mice is a compensatory adaptation to limit Ang II-induced systolic dysfunction. However, the study does not provide evidence to support this concept, and the reason for the upregulation of ACE2 in these animals remains unknown.

It should be noted that although the phenotype of Akita mice does encompass certain characteristics of type 2 diabetes, the mice used in the Patel et al study primarily reflect a type 1 diabetic phenotype. It would therefore be interesting in future studies to explore the role of ACE2 in diabetic cardiomyopathy following diet-induced models of obesity, insulin resistance, and subsequent type 2 diabetes.

Recent studies have demonstrated the potential for lipotoxicity in mediating the cardiovascular complications of obesity and diabetes. The authors suggest that the systolic dysfunction as a result of ACE2 deficiency in Akita mice (Akita/ACE2KO) is not the result of cardiac lipotoxicity, as intramyocardial levels of long-chain acyl CoA and ceramide were similar between Akita and Akita/ACE2KO mice. However, the authors did not measure diacylglycerol in their studies, and it has recently been demonstrated that obesity in mice results in the accumulation of diacylglycerol in the heart, which activates protein kinase C alpha and plays a key role in mediating cardiac insulin resistance.

Many of the beneficial effects of ACE2 appear to be due to its metabolism of Ang II into Ang 1–7 (Figure), as Ang 1–7 binding to its Mas receptor opposes many of the actions of Ang II/AT1R and can also potentiate bradykinin action and subsequent nitric-oxide-dependent vasodilation. In contrast, in the Patel et al study, a 1-month infusion of Ang 1–7 did not reverse the systolic dysfunction in Akita/ACE2KO mice. Therefore, the reported findings illustrate that limiting Ang II-mediated AT1R signaling is more important than stimulating Ang 1–7-mediated Mas receptor signaling with regards to preventing RAS-induced diabetic cardiovascular complications. Furthermore, as ACE2 is capable of metabolizing a number of peptides, some of which include apelin-13 and apelin-36, and apelin receptors are present in the heart, it will be important for future studies to delineate the possible contribution of apelin and other ACE2 substrates in regulating LV function during diabetic cardiomyopathy.

Because current ACE inhibitors only inhibit ACE, optimal therapeutic management of the RAS in the patient population may require dual therapy to inhibit ACE and activate ACE2. As novel ACE2 agonists are developed, it will be important to compare their efficacy as monotherapies against ACE inhibitors and AT1R antagonists and to determine whether manipulating the Ang II axis from both ends via combination therapies can provide additional benefit. Taken together, the findings of Patel et al are very interesting and have a high clinical relevance. Because of the increasing incidence of obesity and diabetes in our patient population, there is the need for novel therapies to limit diabetic cardiomyopathy and its subsequent complications. Combined with previous studies demonstrating a beneficial role for ACE2 in islet function and subsequent glucose tolerance, as well as systolic and diastolic heart failure, strategies aimed at increasing peripheral ACE2 activity seem well suited to address the growing burden of diabetic cardiomyopathy.

Sources of Funding
This editorial was supported by a grant from the Canadian Institutes of Health Research to Gary D. Lopaschuk. Gary D. Lopaschuk is an Alberta Heritage Foundation for Medical Research Medical Scientist. John R. Ussher is a fellow of Alberta Innovates Health Solutions and the Canadian Institutes of Health Research.

Disclosures
None.

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Circ Res. 2012;110:1270-1272
doi: 10.1161/CIRCRESAHA.112.269951
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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