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RESEARCH ARTICLE

The use of aliskiren as an antifibrotic drug in experimental models: A systematic review

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Abstract

Aliskiren is an oral antihypertensive medication that acts by directly inhibiting renin. High levels of circulating renin and prorenin activate the pathological signaling pathway of fibrosis. This drug also reduces oxidative stress. Thus, the aim of this systematic review is to analyze experimental studies that show the actions of aliskiren on fibrosis. PubMed and LILACS databases were consulted using the keywords aliskiren and fibrosis within the period between 2005 and 2017. Fifty-three articles were analyzed. In the heart, aliskiren attenuated remodeling, hypertrophy, inflammatory cytokines, collagen deposition, and oxidative stress. In the kidneys, there was a reduction in interstitial fibrosis, the infiltration of inflammatory cells, apoptosis, proteinuria, and in the recruitment of macrophages. In diabetic models, an improvement in the albumin/creatinine relationship and in the insulin pathway in skeletal muscles was observed; aliskiren was beneficial to pancreatic function and glucose tolerance. In the liver, aliskiren reduced fibrosis, steatosis, inflammatory cytokines, and collagen deposition. In the lung and peritoneal tissues, there was a reduction in fibrosis. Many studies have reported on the beneficial effects of aliskiren on endothelial function and arterial rigidity. A reduction in fibrosis in different organs is cited by many authors, which complies with the results found in this review. However, studies diverge on the use of the drug in diabetic patients. Aliskiren has antifibrotic potential in several experimental models, interfering with the levels of fibrogenic cytokines and oxidative stress. Therefore, its use in diseases in which fibrosis plays an important pathophysiological role is suggested.

KEYWORDS

aliskiren, antifibrotic drug, fibrogenic cytokine, fibrosis, renin-angiotensin-aldosterone system

Abbreviations: ACEIs, ACE inhibitor; ACR, Albumin creatinine relation; Akt, Kinase protein; AMPK, 5′ Adenosine monophosphate-activated protein kinase; Ang II, Angiotensin II; ANP, Atrial natriuretic peptide; ARB, Angiotensin receptor blocker; BP, Blood pressure; COL1α1, Collagen type1 α1; COX-2, Cyclooxygenase −2; CTGF, Connective tissue growing factor; DNMT1, DNA Methyltransferase 1; ECM, Extracellular membrane; ERK, Extracellular signal-regulated protein kinase; GPX1, Glutathione peroxidase; 4-HNE, Hydroxynonenal; IFN, Interferon; iNOS, Inducible nitric oxide synthase; MCP-1, Monocyte chemoattractant protein-1; MEK1, Mitogen-activated protein kinase; MHC, Major histocompatibility complex; MMP, Metalloproteinase; NADP, Nicotinamide adenine dinucleotide phosphate; OPN, Osteopontin; PAI-1, Plasminogen activator inhibitor-1; PPARα, Peroxisome proliferator-activated receptor α; (P)RR, Pro-renin receptor; RAAS, Renin angiotensin aldosterone system; p-SAPK/JNK, Stress-activated protein kinase/Jun-amino-terminal kinase; α-SMA, α-Smooth muscle actin; SMAD, Small mother against decapentaplegic; SOD, Superoxide dismutase; TBARS, Thiobarbituric acid reactive substances; TGF-β1, Transforming growth factor-β1; TIMPs, Tissue inhibitor of metalloproteinase; TLR4, Toll-like receptor; TNF-α, Tumor necrosis factor-α; VEGF, Vascular endothelial growth factor.

1 | INTRODUCTION

Aliskiren (ALI) was approved by the U.S. Food and Drug Administration (FDA) in 2007 as the first oral antihypertensive medication that acts by directly inhibiting renin (Frampton & Curran, 2007; Wiggins & Kelly, 2009). Different than other drugs that target the renin-angiotensin-aldosterone system (RAAS), it acts on the system in such a way that it directly inhibits renin, and, as a result, reduces blood pressure (Azizi, Webb, Nussberger, & Hollenberg, 2006; Nussberger, Wuerzner, Jensen, & Brunner, 2002). The drug is not metabolized by the liver isoenzyme CYP3a4; therefore, there is little interaction with other drugs (Vaidyanathan, Jarugula, Dieterich, Howard, & Dole, 2008).

This medication has been mentioned in many different studies owing to the fact it reduces blood pressure and considerably protects some organs as a consequence of this reduction (Abuelezzy, Hendawy, & Osman, 2016). Moreover, it shows a great beneficial antifibrotic potential in different models of fibrosis, including peritoneal, renal, and cardiac fibrosis (Gross et al., 2011; Ke et al., 2010; Zhi et al., 2013).

High levels of circulating renin and its precursor (prorenin) probably activate the pathological signaling pathway of fibrosis via stimulation of the prorenin receptor, whose mechanism is completely independent not only of the production of angiotensin II (Ang II), but also of the stimulation of type I Ang II receptor. Thus, one of the profibrotic effects of renin (Ichihara et al., 2006; Nguyen, 2006), which is attenuated by ALI, can be explained. In addition, ALI reduces the expression of prorenin receptors (Ferri, Greco, Maiocchi, & Corsini, 2011).

Transforming growth factor β1 (TGFβ1) is the most potent fibrogenic cytokine, and it is expressed at high levels even at late stages of lung fibrosis (Bonniaud et al., 2005; Broekelmann, Limper, Colby, & Mcdonald, 1991). With the administration of ALI, it could be observed that these levels are reduced. Both renin and prorenin are capable of stimulating the production of TGF β1 via p42/p44 mitogen-activated protein (MAP) kinase, resulting in the positive regulation of pro-fibrotic molecules, such as fibronectin and Type I collagen (Huang et al., 2006). Cytokine stimulation such as TGF-β1, produced by macrophages and other cells, makes fibroblasts synthesize fibers and achieve differentiation into myofibroblasts with the resultant progression to interstitial fibrosis (Chevalier, Forbes, & Thornhill, 2009; Chevalier, Thornhill, Forbes, & Kiley, 2010). Additionally, macrophages are able to synthesize extracellular membrane proteins, such as collagen and fibronectin (Nathan, 1987).

The literature reports that ALI has an antioxidant capacity. Therefore, it provides protection against oxidative stress effects that may result in the onset of fibrosis (Santuzzi et al., 2015; Virdis et al., 2012).

ALI also reduces fibrosis owing to the fact it decreases levels of MMPs (metalloproteinases), which are proteases involved in the physiopathology of fibrosis and abnormal remodeling of the extracellular matrix (ECM) (Abuelezzy et al., 2016; Kunugi, Fukuda, Ishizaki, & Yamanaka, 2001; Pardo & Selman, 2012).

The activity of metalloproteinases is catalyzed by a specific family of inhibitors called tissue inhibitors of metalloproteinases (TIMPs). An imbalance between MMPS and TIMPs triggers the fibrogenesis process (Woessner, 1994). ALI is also known for its capacity to reduce TIMP-6. (Figure 1).

Taking the beneficial antifibrotic effect of ALI into account, according to the above data found in the literature, the aim of this systematic review was to analyze those experimental studies that demonstrated the effects of ALI on fibrosis.

2 | METHODS

The PubMed and LILACS databases were consulted using the keywords #aliskiren and #fibrosis within the period between 2005 and 2017. Articles found between August 15, 2005 and October 29, 2017 were taken into consideration. A total of 66 articles were obtained from PubMed, and their abstracts were analyzed. Within these 66 articles, 62 were also found on LILACS.

Exclusion criteria comprised the following: language in which the article was written unknown by the reviewers (Czech); literature

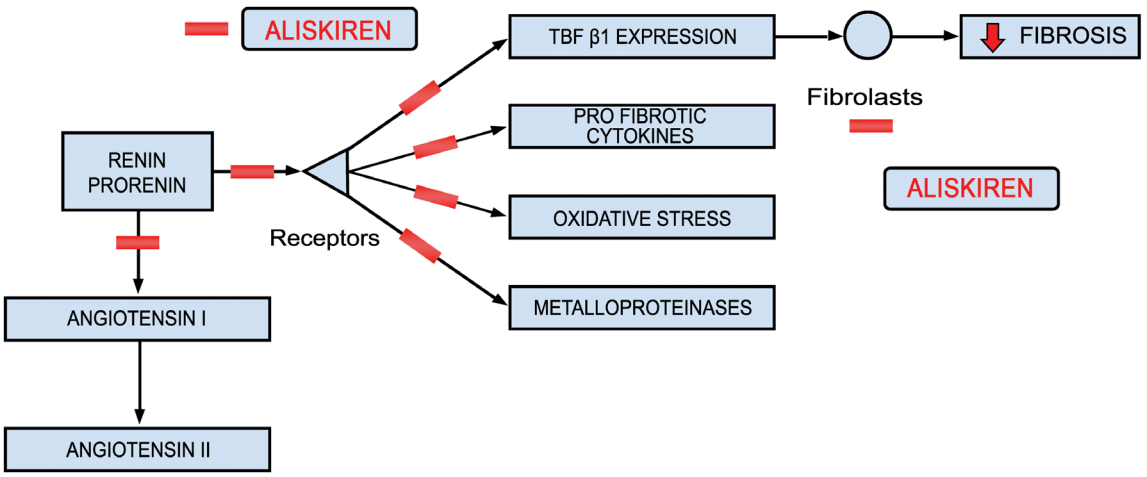

FIGURE 1 Mechanisms of action of Aliskiren

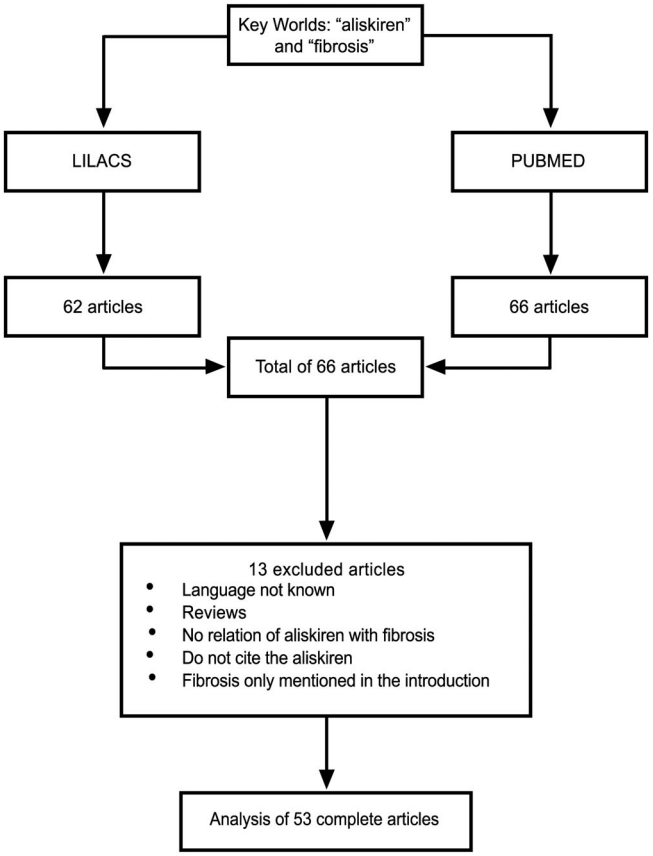

FIGURE 2 Flowchart showing the screening and exclusion of articles for the systematic review

reviews; ALI unrelated to fibrosis; fibrosis not mentioned; ALI not mentioned; fibrosis only mentioned in the introduction; lack of references to ALI in the full-text article due to the fact they did not report the effects of the drug on fibrosis. A total of 13 articles were excluded, leaving 53 articles to be analyzed according to the scheme as shown in Figure 2 were included in this review the articles that studied the ALI's effect in experimental models, in English, published between 2005 and 2017.

3 | RESULTS

For the sake of better understanding, the results were compiled and divided into tables according to the experimental model used.

Table 1 shows experimental models of myocardial injury. In these studies, remodeling and hypertrophy were attenuated and reductions in inflammatory cytokines, collagen deposition, and oxidative stress could be seen. There was less degeneration of myocytes and a reduction in interstitial and perivascular fibrosis. An improvement in cardiac function was seen.

Table 2 refers to experimental models of renal injury, in which reductions in collagen deposition, VEGF, α-SMA, inflammatory cytokines, inflammatory cell infiltration, apoptosis, and macrophage recruitment could be observed. There was also a decrease in tubulointerstitial fibrosis, interstitial volume, hypertrophy, and proteinuria as well as a normalization of interleukin status.

The effects of ALI in experimental diabetes models are reported in Table 3. There was a reduction in matrix protein deposition, an improvement in interstitial fibrosis and oxidative stress, a reduction in metalloproteinase and fibronectin expression, in collagen deposition and albuminemia as well as the promotion of an antisclerosis effect. An improvement in albumin and creatinine levels could also be observed. Additionally, there was an increase in the compliance of heart chambers and a reduction in hypertrophy and cardiac apoptosis. Beneficial effects on pancreatic function and glucose tolerance were also reported, as well as an improvement in the insulin metabolic pathway in skeletal muscles.

Table 4 shows the studies on ALI in experimental hepatic injury models. There was a reduction in fibrosis, steatosis, inflammatory cytokines, and collagen deposition. There was also an improvement in liver function.

Table 5 shows the studies that evaluated the use of ALI in experimental lung injury models. Reductions in fibrosis, collagen fibers, and inflammatory cytokines could be observed.

Table 6 refers to studies on the use of ALI in experimental peritoneal injury models. In these studies, it was noted that there was a reduction in the expression of fibronectin, collagen, proapoptotic factors, metalloproteinases, and VEGF. Mesothelial cell damage was prevented, and there was a decrease in inflammation, fibrosis, and peritoneal thickness.

Finally, Table 7 shows the effect of ALI in experimental injury models. There was tube dilation and a reduction in hypertrophy, proteinuria, interstitial and perivascular fibrosis, albuminuria and inflammation. ALI prevented glomerulosclerosis, pancreatic structural changes, diastolic dysfunction, and cardiac hypertrophy. A decrease in inflammatory cells and macrophage infiltration was observed.

4 | DISCUSSION

The renin-angiotensin-aldosterone system (RAAS) plays a fundamental role in arterial pressure (AP) regulation; therefore, drugs that target the stages in the cascade, such as angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), are vastly used as antihypertensive agents. Renin is the first and highly regulated step that limits the system, and its inhibition has been the objective of pharmacotherapy for almost 60 years (Nicholls et al., 2013).

Many randomized control trials have shown significant results when ALI in monotherapy is administered for the reduction of AP (Danser et al., 2008; Gradman et al., 2005; Gradman et al., 2007; Kushiro et al., 2006; Nussberger et al., 2002; Stanton, Jensen, Nussberger, & O'brien, 2003; Strasser et al., 2007). Actually, such effects were similar to those provided by losartan (Stanton et al., 2003), valsartan (Gradman et al., 2007), irbesartan (Palatini et al., 2010), and lisinopril (Danser et al., 2008), as well as a tolerability profile similar to placebo.

TABLE 1 Results obtained from the use of aliskiren in experimental myocardial injury models

References	Animal model	Results/conclusions
Zhao et al., 2016	Mongrel dogs receiving high and low doses.	The high-dose attenuated abnormal tissue more efficiently, but the low-dose also protected from remodeling. It reduced TGF-β1, MEK1, ERK1/2, IL-18, and TLR4.
Satoh et al., 2017	Beagle female dogs	Suppression of increased left atrial volume and fibrosis. Reduction in the upregulation of fibronectin, MCP-1, periostin, and type 3 collagen. Suppressive effect on interstitial fibrosis and myocyte degeneration.
Sadek, Rashed, Bassam, & Saida, 2015	Sprague–Dawley albino mice	The concentrations of Type I collagen and Type III collagen were reduced.
Takamura et al., 2016	BALB mouse	Reduction of the ratio heart to body weight, and thinned the wall of the left ventricle. It attenuated the inflammatory cells infiltration and myocardial fiber destruction. Reduced expression of the cardiac genes IL-2, IFN-γ, TNF-α, and collagen Type I. Suppression of proinflammatory cytokines and CD4 + T cell proliferation.
Yamada et al., 2016	dnNRSF-Tg mice or wild-type (WT)	Reduction of left ventricular systolic and diastolic diameters and of myocyte mean size. Decreased expression of TGFβ-1, TGFβ-3, Type I collagen, fibronectin, TIMP, and MMP-2.
Weng et al., 2014	C57BL/6J mice in induced hypertrophy overload	Reduction of TGF-β1 and α1 type 1 collagen. Attenuation of cardiac hypertrophy and fibrosis.
Zhi et al., 2013	C57BL6 male mice with hyperhomocysteinemia (Hhe)-induced fibrosis	Reduction of perivascular and interstitial fibrosis, of the expression COL1A1, COL1A2 and COL3A1. Direct effects on the cardiac fibroblasts biology; normalization of diastolic function.
Whaley-Connell et al., 2012	Ren2 Sprague–Dawley rats	There were no areas of organized collagen with the treatment. Improved mechanisms related to metabolic signaling, myocardial tissue, fibrosis, and hypertrophy.
De Mello, Rivera, Rabell, & Gerena, 2013	Heterozygous TG rats (mRen-2)	Decreased left ventricle final diastolic volume and its thickness, left ventricular interstitium and perivascular fibrosis. Reduced remodeling.
Ma et al., 2012	Sprague–Dawley rats with DOCA (deoxycorticosterone)-induced fibrosis	Improved myocardial fibrosis. Reduced the expression of ERK1/2, PERK1/2, and MMP-9 and collagen production. Decreased Ang II level, inhibition of ERK1/2 signaling pathway phosphorylation.
Whaley-Connell et al., 2008	Ren2 and SD rats	NADPH oxidase activity was reduced, as did mitochondria. Decreased perivascular fibrosis and abnormal intercalated discs.
Fischer et al., 2008	dTGRs (RCC ltd.) rats and nontransgenic Sprague–Dawley rats (SD).	Prevented cardiac hypertrophy, inflammation, fibrosis, and the long QT segment. Normalization of ANP expression. Reduced Type I collagen and fibronectin deposition, the expression of ED-1 and gap junction Cx43 relocation.
Campbell et al., 2011	Female heterozygous rats (mRen-2) 27	Reduced fibrosis and cardiac hypertrophy. Protected against ischemia, oxidative stress, inflammatory and hemodynamic damage.
De Mello, 2015	TGR(mRen2) 27 rats	Improvement of cardiac function and remodeling reduction. Interstitial and perivascular fibrosis were reduced.

Abbreviations: ANP, atrial natriuretic peptide; MEK1, mitogen-activated protein kinase; TLR4, toll-like receptor 4.

The AQUARIUS study, which analyzed the effects of the drug in prehypertensive individuals with coronary atherosclerosis, concluded that it did not offer any additional benefit to patients (Nicholls et al., 2013). However, many studies reported beneficial effects of ALI in regard to endothelial function and arterial rigidity (Bonadei et al., 2014; Fukutomi, Hoshide, Mizuno, & Kario, 2014; Raptis et al., 2015). Furthermore, it reduces ventricular mass according to the ALLAY study, which revealed that ALI is as effective as losartan in the reduction of hypertrophied ventricular mass in hypertensive patients with BMI >25 kg/m^2 (Solomon et al., 2009). Myocardial thickness was reduced, according to many articles that analyzed the effects of ALI (Table 1) in cardiac experimental models (Campbell et al., 2011; De Mello, 2015; Fischer et al., 2008; Takamura et al., 2016; Weng et al., 2014; Yamada et al., 2016).

VEGF is a mediator of angiogenesis, which consists of vascular expansion formed by new blood vessels (Carmeliet & Jain, 2011). The formation of new vessels occurs under normal circumstances, such as regeneration, but it is an important factor in many pathological processes (Hoeben, Landuyt, & Highley, 2004). VEGFs have a wide range of effects related to infarction, which are involved in the pathogenesis

TABLE 2 Studies on the use of aliskiren in experimental kidney injury models

References	Animal model	Results/conclusions
Prókai et al., 2016	C57B16 mice-induced CNI nephropathy	Prevented the damaging VEGF increase and collagen deposition.
Chung et al., 2017	C57BL/6J mice with UUO	Significant decrease in tubulointerstitial fibrosis and ERK phosphorylation. Reduction of Type IV collagen, α-SMA expression, and prevention of Nox1 and Nox2 increase.
Bae et al., 2014	Male Sprague–Dawley rats with gentamicin nephropathy.	Reduction of the ED-1 and iNOS proteins, renal expression in TNF-α mRNA, IL-1β, IFN-γ, TGF-β1 (by inhibition of TNF-κB), α-SMA, ERK 1/2 and p38. Reduction of inflammatory cell infiltration. Attenuation of fibrosis.
Sakuraya et al., 2014	Male Sprague Dawley rats with UUO	Significant attenuation in tubulointerstitial damage after UUO. The interstitial volume and number of ED-1 positive cells infiltration decreased. Reduced expression of α-SMA, TGF-b1, OPN, and MCP-1. Aliskiren has a significant but not complete protective action on renal fibrosis.
Kavvadas et al., 2013	RenTg mice	Decreased expression of F4/80. Return to normal values of tissue adhesion molecules, tumor necrosis factor-a, monocyte chemoattractant protein 1, SMAD1/5/8 phosphorylation levels. Reduction of cell infiltration and collagen deposition (Types I and III), α-smooth, plasminogen 1, TGF-β, connective tissue growth factor (CTGF), MEC and atrial natriuretic peptide. It normalized the upregulation levels of the factor induction of 1α and DNMT1 hypoxia, kidney injury molecule 1, proteinuria, hypertrophy, fibrosis and inflammation. It increased the morphogenetic protein expression of bones 4 and 7, resulting in phosphorylation and activation of SMAD1/5/8 (anti-fibrotic). Positively regulated hepatocyte growth factor.
Whaley-Connell et al., 2013	Transgenic mice TG (mRen2) 27 (Ren2) and Sprague–Dawley rats	Improvement in interstitial tubule fibrosis. Reduction in fibronectin and collagen III.
Sun et al., 2012	Female B6 mice with renal artery attachment	Reduced the atrophic effect of chronic renal ischemia. Reduction in TGF-β1, CTGF, Type I collagen, collagen deposition, (P)RR mRNA expression, klotho, fibrogenic cytokine production, apoptosis, and renal fibrosis.
Choi et al., 2011	C57BL/6 mice with UUO	Reduction in inflammatory cell infiltration, tubule epithelial cell damage, macrophage recruitment, α-SMA and TGF-β expression. Preserved tubular morphology. Improved renal inflammation and fibrosis.
Gross et al., 2011	COL4A3−/− mice	Reduced proteinuria. Decrease in TGFβ1 and CTGF. Glomerular architecture preservation, less mesangial expansion. Improvement in glomerulosclerosis. Reduction in fibrosis.
Wu et al., 2010	Male Sprague–Dawley rats with ureter attachment	Decreased levels of tubular dilatation, interstitial volume, collagen deposition, and fibrosis. Reduction of α-SMA, collagen type IV, ERK, Snail1 and TGF-β1 expression. Decreased macrophage ED-1 infiltration.
Baracho et al., 2017	Nephrectomized (¾) rats Wistar	Urinary levels of IL-1β, IL-6, TGF-β, and IL-10 were normalized without altering TGF-β levels. Reduced glomerular and tubular damage, inflammatory interstitial infiltrate, glomerular disorder, and hypotrophy/abnormal tubular dilation with hyaline material in the tubular lumen.

Abbreviations: UUO, unilateral ureteral obstruction; VEGF, vascular endothelial growth factor.

of atherosclerosis, a common cause of cerebrovascular accident (CVA) (Greenberg & Jin, 2013). Studies with ALI in which renal and peritoneal tissues were analyzed, and the release of this mediator was decreased (Ke et al., 2010; Prókai et al., 2016).

The use of ALI not only promoted a reduction in TGF-β1 in the lung, liver, and peritoneum, it also reduced TGF-β1 urinary excretion. TGF-β1 plays fundamental roles in the following processes: modulation of cell growth, maturation and differentiation, the formation of ECM, homeostasis, plasticity of endothelial cells, immune regulation, apoptosis, angiogenesis and cancer progression (Heldin, Landström, & Moustakas, 2009; Ikushima & Miyazono, 2011; Moses & Barcellos-Hoff, 2011; Parvani, Taylor, & Schiemann, 2011; Van Meeteren & Ten Dijke, 2012). Its reduction in cardiac, renal, hepatic, lung and peritoneal tissues and in diabetic animals treated with the

TABLE 3 Studies on the use of aliskiren in experimental diabetes models

References	Animal model	Results/conclusions
Zhou, et al. 2015	BKS.Cg-Dock7m +/+ Leprdb/J mice homozygous	Reduction in glomerular matrix protein deposition, TGFβ1, PAI-1, fibronectin, collagen α1 (IV) expression, and NADPH oxidase activity.
Erena et al., 2014	Male Sprague Dawley rats with diabetes - nephropathy induced	Improvement in interstitial fibrosis.
Erena et al., 2014	KK/Ta Jcl mice and KK/Ta Jcl diabetic mice	Reduction in MMP-2, MMP-9, TIMP-1, TIMP-2, fibronectin, collagen Type IV, MCP-1, and (P)RR in the kidneys, as well as p-p38, p-ERK1/2, and p-SAPK/JNK. It improved urinary levels of ACR and renal fibrosis by improving inflammation. Reduced albuminemia.
Matavelli & Siragy, 2014	Sprague–Dawley male rats	Reduction in fibronectin, renal 8-isoprostane, and fibrosis. Increased NO-cGMP production.
Lizakowski et al., 2012	Humans aged 18–65 years, without diabetic nephropathy	Reduced urinary excretion of TGF-β1. Antisclerosing effect.
Elrashidy, et al. 2012	Albino Wistar rats induced to develop nephropathy	Reduced levels of creatinine, NO, TGF-β1 mRNA, and TIMP-2 mRNA. Decreased collagen fibers deposition in cardiac tissue. Increased extracellular matrix turnover. Regulation of the MMP-2/TIMP-2 system in cardiac tissue.
Connelly et al., 2011	Sprague–Dawley rats	Reduced mRNA (P) RR expression, cardiac hypertrophy, and fibrosis. Improvement in the compliance of the chambers.
Dong et al., 2010	Male db/db mice (C57BLKS/J-leprdb/leprdb)	It improved cardiac and pancreatic damage, macrophage infiltration, interstitial fibrosis, coronary artery thickness, and peri-coronary fibrosis. Improved glucose tolerance. Cardiac superoxide reduction of NADPH oxidase and reduction of p22phox. Attenuation of interstitial and perivascular fibrosis.
Lastra et al., 2009	Ren2 transgenic mice and Sprague Dawley rats	Reduced NADPH oxidase activity and perivascular fibrosis; the number of mitochondria declined. Beneficial effect on insulin metabolic signaling in skeletal muscles.
Singh, et al. 2008	Sprague Dawley rats with streptozotocin-induced diabetes	It completely blocked the oxidative stress, protected against cardiac apoptosis, and reduced fibrosis.
Kelly, et al. 2007	Heterozygous female mice (mRen-2) 27	Albuminuria, diffuse and nodular glomerulosclerosis, and fibrosis were reduced.

Abbreviations: ACR, albumin creatinine ratio; PAI-1, plasminogen activator inhibitor-1; (P)RR, prorenin receptor; p-SAPK/JNK, phosphorylated stress-activated protein kinase/Jun-terminal-amino kinase.

drug is a beneficial effect (Aihara et al., 2013; Asker et al., 2015; Bae et al., 2014; Baracho et al., 2017; Choi et al., 2011; Elrashidy, Asker, & Mohamed, 2012; Gross et al., 2011; Kavvadas et al., 2013; Ke et al., 2010; Kishina et al., 2014; Lee, Chan, Hsieh, Huang, & Lin, 2012; Lizakowski et al., 2012; Sakuraya et al., 2014; Sun et al., 2012; Wang et al., 2015; Weng et al., 2014; Wu et al., 2010; Yamada et al., 2016; Zhao et al., 2016; Zhou, Liu, Cheung, & Huang, 2015).

The pathology resulting from the extracellular regulated kinase (ERK) pathway dysfunction is better studied in mammals. The cascading signals result in protein synthesis, culminating in changes in cell proliferation and survival (Chang, Steelman, & Lee, 2003; Dhillon, Hagan, Rath, & Kolch, 2007; Scholl, Dumesic, & Khavari, 2005; Shaw & Cantley, 2006; Yoon & Seger, 2006). If the signaling via this pathway is deregulated, an increase in cell proliferation occurs along with an extension of cell lifespan, which contributes to tumorigenesis (Chang et al., 2003; Dhillon et al., 2007; Roberts & Der, 2007; Shaw & Cantley, 2006; Yoon & Seger, 2006). The direct renin inhibitor caused, as one of its effects, a decrease in ERK phosphorylation in the heart, kidneys, and liver as well as in experimental diabetes mellitus models (Aihara et al., 2013; Bae et al., 2014; Chung et al., 2017; Furukawa et al., 2013; Lee et al., 2012; Ma et al., 2012; Wu et al., 2010; Zhao et al., 2016).

However, in 2011, the ALTITUDE study, which tested the use of ALI in Type 2 diabetic patients, had to be interrupted due to cases of renal dysfunction, hyperkalemia, and hypotension, with no additional benefits, and a higher incidence of non-fatal CVA in comparison with the placebo group (Mcmurray et al., 2012). Besides these adverse effects, Parving et al. also mentioned cases of diarrhea, hypoglycemia, and infarction. It could be observed that the albumin/creatinine ratio was reduced by ALI in comparison with placebo, indicating a decrease in microalbuminuria, a great benefit to diabetic patients (Parving, Brenner, & Mcmurray, 2012). Similar effects were found by McMurray et al. (Mcmurray et al., 2012). Interestingly, beneficial effects in experimental diabetes models were found in this review, such as those on pancreatic function and glucose tolerance, an improvement in insulin signaling in skeletal muscles, as well as antisclerotic and antifibrotic

TABLE 4 Findings regarding the use of aliskiren in hepatic injury models

References	Animal model	Results/conclusions
Karcioglu et al., 2016	Male albino Wistar rats; Paracetamol-induced injury	Hepatic protective effect with normal histology in treated animals and reduction of TNF-αin hepatocytes.
Kishina et al., 2014	Ob/Ob rats	Decreased fibrosis area. Reduced α-SMA, TGF-β1 mRNA levels, MCP-1 gene expression, TNF-α; collagen type I; Kupffer cells. It attenuated hepatic steatosis and total hepatic cholesterol content. Inhibited the activation of liver stellate cells. Reduced oxidative stress, inflammatory cytokine levels, and fibrosis.
Lee et al., 2013	Mice deficient in methionine and choline	Decreased triglyceride levels, inflammatory focus and hepatocytes balloons; reduced apoptotic hepatocytes, collagen deposition, fibrosis and oxidative stress. Reduced levels of TBARS, 4-HNE and p47 phox, catalase 1, GPX1 and SOD, TNF-α 1, α-SMA, COL1α1 and TIMP-.1 increased insulin sensitivity, expression of Akt and catalase 1. Activated PPARα and AMPK.
Aihara et al., 2013	Male Fischer 344 mice	Reduction in fibrosis, α-SMA expression, hepatocarcinogenesis, TGF-β1, and procollagen α1 and ERK1/2 phosphorylation. Suppression of stellate cells and of neovascularization.
Lee, Chan, Hsieh, Huang & Lin, 2012	C57BL mice with chronic liver disease	Reduction in ALT and tendency to reduce AST. Reduction of apoptotic hepatocytes from TNF-α, iNOS, COX-2, TGF-β1, α-SMA, collagen Type I α1, TIMP-1, phosphorylated ERK genes. Reduction in oxidative stress, stellate cell activation, and Kupffer cell activation. It attenuated liver inflammation and fibrosis.
Ramalho et al., 2017	C57BL/6 rats	It reduced liver weight, total liver fat, triglyceride and cholesterol accumulation, AST and ALT dosage, steatosis levels, and lipid deposition. It decreased neutrophil influx and inflammation, as well as collagen deposition. It halted the increase in plasma glucose levels and stimulated insulin increase. It prevented increased expression of the IL-1β and TNF-α genes.

Abbreviations: 4-HNE, hydroxynonenal; Akt, kinase protein; AMPK, 5′ adenosine monophosphate-activated protein kinase; COL1α1, collagen type 1 α1; COX-2, cyclooxygenase −2; ERK1/2 = extracellular signal-regulated protein kinases 1 and 2; GPX1, glutathione peroxidase; iNOS, inducible nitric oxide synthase; MCP-1, monocyte chemoattractant protein-1; PPARα, peroxisome proliferator-activated receptor α; SOD, superoxide dismutase; TBARS, thiobarbituric acid reactive substances; TIMP-1, tissue inhibitor of metalloproteinases; TNF-α, tumor necrosis factor.

effects (Table 3) (Connelly et al., 2011; Dong et al., 2010; Erena et al., 2014; Kelly, Zhang, Moe, Naik, & Gilbert, 2007; Lastra et al., 2009; Lizakowski et al., 2012; Matavelli & Siragy, 2014; Singh, Le, Khode, Bazer, & Kumar, 2008).

Furthermore, the drug reduced MCP-1 concentrations in diabetic models (Furukawa et al., 2013; Kishina et al., 2014; Sakuraya et al., 2014; Satoh et al., 2017). MCP-1 attracts monocytes to inflammatory sites of the vascular subendothelial space, initiating the migration of these cells into the arterial wall and leading to the formation of foam cells. Many studies have pointed to a significant correlation between circulating MCP-1 and other traditional risk factors for atherosclerosis, such as high-sensitivity C-reactive protein (hs-CRP) and fibrinogen (De Lemos et al., 2003; Deo et al., 2004; Piemonti et al., 2009). High concentrations of this molecule are also related to the complications caused by atherosclerosis, like ischemic infarction, myocardial infarction, and cardiovascular mortality (Arakelyan et al., 2005; De Lemos et al., 2003; Piemonti et al., 2009). The circulating MCP-1 concentration is increased in diabetic patients (Bláha et al., 2006; Nomura, Shouzu, Omoto, Nishikawa, & Fukuhara, 2000; Piemonti et al., 2009; Simeoni et al., 2004; Zietz et al., 2005), and it is greater in the vitreous humor of patients with diabetic retinopathy, thus indicating its role in the development of the disease, according to Mitamura et al. (2001). Local production of MCP-1 has been reported as a contributor to the development of advanced diabetic nephropathy due to the recruitment and activation of monocytes/macrophages (Chow, Ozols, Nikolic-Paterson, Atkins, & Tesch, 2004; Morii et al., 2003).

According to the ASTRONAUT study, patients who received ALI had a higher rate of hyperkalemia, episodes of hypotension and worsening in renal function (Gheorghiade et al., 2013). On the other hand, some studies conducted by Persson et al. showed that ALI has antiproteinuric effects that became evident at different moments of the treatment, suggesting a renoprotective action independent from the antihypertensive action (Bolger & Anker, 2000; Persson et al., 2008; Zhao & Xu, 1999).

Tumor necrosis factor alpha (TNF-α) cytokine is involved in the pathogenesis of different clinical conditions, including cardiovascular disease. Its expression increases in mononuclear cells of patients with congestive cardiac failure, and high concentrations are associated with cardiac failure progression (Bolger & Anker, 2000; Dedoussis et al., 2005; Vendrell et al., 2003; Zhao & Xu, 1999). It is known that TNF-α plays an important role in the activation of different inflammatory factors (Lozano et al., 2003). Recent studies have pointed to the

TABLE 5 Results obtained from the use of aliskiren in experimental lung injury models

References	Animal model	Results/conclusions
Abuelezzy, et al. 2016	Rats; bleomycin-induced fibrosis	Reduction in fibrosis and inflammation
Fletcher et al., 2017	Fat embolic rats	Reduction in inflammatory cells and fibrosis markers
Asker, Mazroa, Boshra, & Hassan, 2015	Mouse; bleomycin-induced fibrosis	Reduction in collagen fibers. TGFβ1 and hydroxyproline
Wang et al., 2015	Transgenic mice RenTgMK	Pulmonary architecture normalization and significant reduction of pro-fibrotic factors (TGFβ1 and CTGF), myofibroblast marker (α-SMA), and extracellular matrix proteins (fibronectin, Types I and II collagen)
Díaz-Pina et al., 2015	Commercial fibroblast strain, which was exposed to the drug for 6 hr	Aliskiren had no effect on the induction of extracellular matrix molecules

Abbreviations: α-SMA, α-smooth muscle actin; CTGF, connective tissue growth factor; TGFβ1, transforming growth factor β1.

TABLE 6 Studies on the use of aliskiren in experimental peritoneal injury models

References	Animal model	Results/conclusions
Pérez-Martinez et al., 2012	Sprague–Dawley female rats	Reduced expression of fibronectin, collagen type III, C-reactive protein and amyloid-P protein. Suppression of the pro-apoptotic factors genetic expression. Increase of mRNA Bcl-2, D2/D0 glucose ratio. It prevented peritoneal mesothelial cell damage and subsequent inflammation and fibrosis.
Koçak et al., 2012	Nonuremic albino Wistar rats with encapsulated peritonitis, chlorhexidine gluconate-induced sclerosis	Reduction in peritoneal fibrosis and MMP-2 tissue levels.
Ke et al., 2010	Male Sprague–Dawley rats with chlorhexidine digluconate-induced fibrosis	Reduction in TGF-β1, α-SMA, fibronectin, collagen, and VEGF. Decreased peritoneal thickness.

TABLE 7 Studies on the use of aliskiren in experimental injury models

References	Animal model	Results/conclusions
Moniwa et al., 2013	mRen2 mice	Correlation with renal damage. Tubular proliferation and lymphocyte infiltration were noted. Tubular dilatation. Reduction in cardiac hypertrophy and proteinuria
Yakamoto et al., 2009	ENOS _/_ and wild-type mice (C57BL/6J)	Reduction in interstitial fibrosis, coronary artery thickness, perivascular fibrosis, macrophages infiltration, and superoxide levels. Reduction in albuminuria by NADPH oxidase. It prevented cardiac hypertrophy, glomerulosclerosis, inflammation, and vascular intima hyperplasia.
Habibi et al., 2008	Ren2 heterozygous rats and control SD	Reduction in fibrosis and mitochondrial content. Reduction in NADPH oxidase and nitrotyrosine content, improved pancreatic structure.
Pilz et al., 2005	DTGR mice with hypertension	Albuminuria remained constant or was improved. Reduction in cardiac hypertrophy, wall thickness, and diastolic dysfunction. Decreased numbers of macrophages, CD4, CD8, dendritic, CD86+ and MHC II+ cells, α-MHC, β-MHC, and ANP in the heart. Reduced infiltration of inflammatory cells in the kidneys

abnormal activity of TNF-α as an important factor in the mechanism of liver injury (Muto et al., 1988; de la Mata et al., 1990; Sun, Tokushige, Isono, Yamauchi, & Obata, 1992). In this review, ALI was capable of reducing cytokine levels in cardiac, hepatic, and renal tissues (Bae et al., 2014; Karcioglu et al., 2016; Kishina et al., 2014; Lee et al., 2012; Lee et al., 2013; Ramalho et al., 2017; Takamura et al., 2016). Collagens are the main structural protein of the ECM (Pozzi, Wary, Giancotti, & Gardner, 1998; Yeh, Lin, & Tang, 2012). The

cell-collagen interaction controls a variety of cell activities, including proliferation, migration, and invasion through integrin and discoidin domain receptors (Canty & Kadler, 2005; Lochter & Bissell, 1995; Pozzi et al., 1998; Provenzano et al., 2006; Yeh et al., 2012; Zhang et al., 2013). Many diseases result in collagen accumulation. In Duchenne muscular dystrophy (DMD), for example, muscle tissue injuries are persistent, leading to the activation of fibrinogenic cells and culminating in connective tissue deposition and subsequent fibrosis (Zanotti et al., 2015). An increase in collagen production also occurs in scleroderma, an autoimmune disease characterized by skin and internal organ fibrosis, vasculopathy and the production of antibodies (Bossini-Castillo et al., 2013; Lopez-Isac et al., 2014; Radstake et al., 2010). The reduction in collagen deposition by ALI may be an advantage in such conditions.

During the fibrotic process, the ECM goes through remodeling via MMP-mediated collagen degradation (Genovese, Manresa, & Leeming, 2014; Zhen, Brittain, & Laska, 2008). Deregulation in MMPs is observed in many experimental models and human disorders, and their increased expression accompanies renal fibrosis (Catania, Chen, & Parrish, 2007; Tan & Liu, 2012). ALI reduced MMP levels and collagen deposition in the kidneys, heart and peritoneum in many experimental models (Elrashidy et al., 2012; Furukawa et al., 2013; Ma et al., 2012; Yamada et al., 2016).

ALI was primarily created for the control of systemic arterial hypertension. It should be orally administered at a dose of 150–300 mg once daily (Whelton et al., 2017). It was especially used in patients with high levels of renin and/or in cases of hyperaldosteronism that need to be investigated for renal or renovascular causes (Spence, 2010).

According to the 2017 American College of Cardiology guidelines, ALI is a long-lasting medication that should not be used in combination with ACE or ARB inhibitors. It should not be used during pregnancy, and it increases the risk of hyperkalemia, and may cause acute renal failure in patients with severe bilateral renal artery stenosis (Whelton et al., 2017).

Therefore, it is a medication that has been little used for the control of arterial pressure. However, it brings about many other effects that were explored in this review. Such effects can be useful in many comorbidities, especially reducing tissue fibrosis.

5 | CONCLUSIONS

ALI is a medication that has been little used for the control of arterial pressure. It has demonstrated antifibrotic potential in several experimental models, interfering with levels of fibrogenic cytokines and oxidative stress. Therefore, its use in many diseases in which fibrosis plays an important pathophysiological role is suggested.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

AUTHORS CONTRIBUTION

Thainá A. Marin: conception and design of the study, literature review, analysis and interpretation of the data, wrote the text, Bruno Bertassoli: literature review, text correction, Alzira Siqueira: collaboration in the discussion, text correction, David Feder: conception and design, collaboration in the discussion of the results, collaboration in the discussion.

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REFERENCES

Abuelezzy, S. A., Hendawy, N., & Osman, W. M. (2016). Aliskiren attenuates bleomycin-induced pulmonary fibrosis in rats: Focus on oxidative stress, advanced glycation end products, and matrix metalloproteinase-9. *Naunyn-Schmiedeberg's Archives of Pharmacology*, *389*(8), 897–909.

Aihara, Y., Yoshiji, H., Noguchi, R., Namisaki, T., Shirai, Y., Douhara, A., … Fukui, H. (2013). Direct renin inhibitor, aliskiren, attenuates the progression of non-alcoholic steatohepatitis in the rat model. *Hepatology Research*, *43*(11), 1241–1250.

Arakelyan, A., Petrkova, J., Hermanova, Z., Boyajyan, A., Lukl, J., & Petrek, M. (2005). Serum levels of the MCP-1 chemokine in patients with ischemic stroke and myocardial infarction. *Mediators of Inflammation*, *2005*(3), 175–179.

Asker, S. A., Mazroa, S. A., Boshra, V., & Hassan, A. M. (2015). Biochemical and histological impact of direct renin inhibition by aliskiren on myofibroblasts activation and differentiation in bleomycin induced pulmonary fibrosis in adult mice. *Tissue & Cell*, *47*(4), 373–381.

Azizi, M., Webb, R., Nussberger, J., & Hollenberg, N. K. (2006). Renin inhibition with aliskiren: Where are we now, and where are we going? *Journal of Hypertension*, *24*(2), 243–256.

Bae, E. H., Kim, I. J., Joo, S. Y., Kim, E. Y., Choim, J. S., Kim, C. S., … Kim, S. W. (2014). Renoprotective effects of the direct renin inhibitor aliskiren on gentamicin-induced nephrotoxicity in rats. *Journal of the Renin-Angiotensin-Aldosterone System*, *15*(4), 348–361.

Baracho, N. C. D. V., Silveira, K. D. D., Rocha, N. P., Cordeiro, T. M., Feracin, V., Pereira, R. M., … Silva, A. C. S. E. (2017). Urinary cytokine profiles according to the site of blockade of the renin-angiotensin system in nephrectomized rats. *Jornal Brasileiro de Nefrologia*, *39*(2), 108–118.

Bláha, V., Andrýs, C., Smahelová, A., Knízek, J., Hyspler, R., Solichová, D., … Zadák, Z. (2006). Effect of atorvastatin on soluble CD14, CD40 ligand, sE- and sP-selectins and MCP-1 in patients with type 2 diabetes mellitus: Relationship to cholesterol turnover. *Pharmacological Research*, *54*(6), 421–428.

Bolger, A. P., & Anker, S. D. (2000). Tumors necrosis factor in chronic heart failure: A peripheral view on pathogenesis, clinical manifestations and therapeutic implications. *Drugs*, *60*(6), 1245–1257.

Bonadei, I., Vizzardi, E., D'aloia, A., Sciatti, E., Raddino, R., & Metra, M. (2014). Role of aliskiren on arterial stiffness and endothelial function in patients with primary hypertension. *Journal of Clinical Hypertension (Greenwich, Conn.)*, *16*(3), 202–206.

Bonniaud, P., Margetts, P. J., Ask, K., Flanders, K., Gauldie, J., & Kolb, M. (2005). TGF-beta and Smad3 signaling link inflammation to chronic fibrogenesis. *Journal of Immunology*, *175*(8), 5390–5395.

Bossini-Castillo, L., Martin, J. E., Broen, J., Simeon, C. P., Beretta, L., Gorlova, O. Y., … Spanish Scleroderma Group. (2013). Confirmation of TNIP1 but not RHOB and PSORS1C1 as systemic sclerosis risk factors

in a large independent replication study. *Annals of the Rheumatic Diseases*, *72*(4), 602–607.

Broekelmann, T. J., Limper, A. H., Colby, T. V., & Mcdonald, J. A. (1991). Transforming growth factor beta 1 is present at sites of extracellular matrix gene expression in human pulmonary fibrosis. *Proceedings of the National Academy of Sciences of the United States of America*, *88* (15), 6642–6646.

Campbell, D. J., Zhang, Y., Kelly, D. J., Gilbert, R. E., McCarthy, D. J., Shi, W., & Smyth, G. K. (2011). Aliskiren increases bradykinin and tissue kallikrein mRNA levels in the heart. *Clinical and Experimental Pharmacology & Physiology*, *38*(9), 623–631.

Canty, E. G., & Kadler, K. E. (2005). Procollagen trafficking, processing and fibrillogenesis. *Journal of Cell Science*, *118*(Pt 7), 1341–1353.

Carmeliet, P., & Jain, R. K. (2011). Molecular mechanisms and clinical applications of angiogenesis. *Nature*, *473*(7347), 298–307.

Catania, J. M., Chen, G., & Parrish, A. R. (2007). Role of matrix metalloproteinases in renal pathophysiologies. *American Journal of Physiology. Renal Physiology*, *292*(3), F905–F911.

Chang, F., Steelman, L. S., & Lee, J. T. (2003). Signal transduction mediated by the Ras/Raf/MEK/ERK pathway from cytokine receptors to transcription factors: Potential targeting for therapeutic intervention. *Leukemia*, *17*(7), 1263–1293.

Chevalier, R. L., Forbes, M. S., & Thornhill, B. A. (2009). Ureteral obstruction as a model of renal interstitial fibrosis and obstructive nephropathy. *Kidney International*, *75*(11), 1145–1152.

Chevalier, R. L., Thornhill, B. A., Forbes, M. S., & Kiley, S. C. (2010). Mechanisms of renal injury and progression of renal disease in congenital obstructive nephropathy. *Pediatric Nephrology*, *25*(4), 687–697.

Choi, D. E., Jeong, J. Y., Lim, B. J., Chang, Y., Na, K., Shin, Y., & Lee, K. W. (2011). Aliskiren ameliorates renal inflammation and fibrosis induced by unilateral ureteral obstruction in mice. *The Journal of Urology*, *186*, 694–701.

Chow, F., Ozols, E., Nikolic-Paterson, D. J., Atkins, R. C., & Tesch, G. H. (2004). Macrophages in mouse type 2 diabetic nephropathy: Correlation with diabetic state and progressive renal injury. *Kidney International*, *65*(1), 116–128.

Chung, S., Kim, S., Kim, M., Koh, E. S., Shin, S. J., Park, C. W., … Kim, H. S. (2017). Treatment combining aliskiren with paricalcitol is effective against progressive renal tubulointerstitial fibrosis via dual blockade of intrarenal renin. *PLoS One*, *12*(7), e0181757.

Connelly, K. A., Advani, A., Kim, S., Advani, S. L., Zhang, M., White, K. E., … Gilbert, R. E. (2011). The cardiac (pro)renin receptor is primarily expressed in myocyte transverse tubules and is increased in experimental diabetic cardiomyopathy. *Journal of Hypertension*, *29*(6), 1175–1184.

Danser, A. H. J., Charney, A., Feldman, D. L., Nussberger, J., Fisher, N., & Hollenberg, N. (2008). The renin rise with aliskiren: It's simply stoichiometry. *Hypertension*, *51*(4), E27–E28.

De Lemos, J. A., Morrow, D. A., Sabatine, M. S., Murphy, S. A., Gibson, C. M., & Antman, E. M. (2003). Association between plasma levels of monocyte chemoattractant protein-1 and long-term clinical outcomes in patients with acute coronary syndromes. *Circulation*, *107* (5), 690–695.

De Mello, W., Rivera, M., Rabell, A., & Gerena, Y. (2013). Aliskiren, at low doses, reduces the electrical remodeling in the heart of the tgr(mren2) 27 rat independently of blood pressure. *Journal of the Renin-Angiotensin-Aldosterone System*, *14*(1), 23–33.

De Mello, W. C. (2015). Spironolactone enhances the beneficial effect of aliskiren on cardiac structural and electrical remodeling in tgr(mren2) 27 rats. *Journal of the Renin-Angiotensin-Aldosterone System*, *16*(3), 488–494.

Dedoussis, G. V., Panagiotakos, D. B., Vidra, N. V., Louizou, E., Chrysohoou, C., Germanos, A., … Stefanadis, C. (2005). Association between TNF-alpha −308g>a polymorphism and the development of acute coronary syndromes in Greek subjects: The CARDIO2000-GENE study. *Genetics in Medicine*, *7*(6), 411–416.

Deo, R., Khera, A., McGuire, D. K., Murphy, S. A., Meo Neto Jde, P., Morrow, D. A., & De Lemos, J. A. (2004). Association among plasma levels of monocyte chemoattractant protein-1, traditional cardiovascular risk factors, and subclinical atherosclerosis. *Journal of the American College of Cardiology*, *44*(9), 1812–1818.

Dhillon, A. S., Hagan, S., Rath, O., & Kolch, W. (2007). MAP kinase signalling pathways in cancer. *Oncogene*, *26*(22), 3279–3290.

Díaz-Pina, G., Montes, E., Checa, M., Becerril, C., Alba, C. G., Veja, A., … Ruiz, V. (2015). Profibrosing effect of angiotensin converting enzyme inhibitors in human lung fibroblasts. *Lung*, *193*(2), 199–202.

Dong, Y. F., Liu, L., Kataoka, K., Nakamura, K., Fukuda, M., Tokutomi, Y., … Kim-Mitsuyama, S. (2010). Aliskiren prevents cardiovascular complications and pancreatic injury in a mouse model of obesity and type 2 diabetes. *Diabetologia*, *53*(1), 180–191.

Elrashidy, R. A., Asker, M. E., & Mohamed, H. E. (2012). Beneficial effects of pioglitazone against cardiovascular injury are enhanced by combination with aliskiren in a rat model of diabetic nephropathy. *The Journal of Pharmacy and Pharmacology*, *64*(6), 862–871.

Erena, Z., Günal, M. Y., Bakir, E. A., Coban, J., Çağlayan, B., Ekimci, N., … Kantarci, G. (2014). Effects of paricalcitol and aliskiren combination therapy on experimental diabetic nephropathy model in rats. *Kidney & Blood Pressure Research*, *39*(6), 581–590.

Ferri, N., Greco, C. M., Maiocchi, G., & Corsini, A. (2011). Aliskiren reduces prorenin receptor expression and activity in cultured human aortic smooth muscle cells. *Journal of the Renin-Angiotensin-Aldosterone System*, *12*(4), 469–474.

Fischer, R., Dechendm, R., Qadri, F., Markovic, M., Feldt, S., Herse, F., … Muller, D. N. (2008). Dietary N-3 polyunsaturated fatty acids and direct renin inhibition improve electrical remodeling in a model of high human renin hypertension. *Hypertension*, *51*(2), 540–546.

Fletcher, A. N., Molteni, A., Ponnapureddy, R., Patel, C., Pluym, M., & Poisner, A. M. (2017). The renin inhibitor aliskiren protects rat lungs from the histopathologic effects of fat embolism. *Journal of Trauma and Acute Care Surgery*, *82*(2), 338–344.

Frampton, J. E., & Curran, M. P. (2007). Aliskiren: A review of its use in the management of hypertension. *Drugs*, *67*(12), 1767–1792.

Fukutomi, M., Hoshide, S., Mizuno, H., & Kario, K. (2014). Differential effects of aliskiren/amlodipine combination and high-dose amlodipine monotherapy on endothelial function in elderly hypertensive patients. *American Journal of Hypertension*, *27*(1), 14–20.

Furukawa, M., Gohda, T., Hagiwara, S., Tanimoto, M., Horikoshi, S., Funabiki, K., & Tomino, Y. (2013). Effect of the direct renin inhibitor aliskiren on urinary albumin excretion in the spontaneous type 2 diabetic KK-A(Y) mouse. *International Journal of Nephrology*, *2013*, 519130.

Genovese, F., Manresa, A. A., & Leeming, D. J. (2014). The extracellular matrix in the kidney: A source of novel non-invasive biomarkers of kidney fibrosis? *Fibrogenesis & Tissue Repair*, *7*(1), 4.

Gheorghiade, M., Bohm, M., Greene, S. J., Fonarow, G. C., Lewis, E. F., Zannad, F., … Astronaut Investigators and Coordinators. (2013). Effect of aliskiren on postdischarge mortality and heart failure readmissions among patients hospitalized for heart failure: The ASTRONAUT randomized trial. *JAMA*, *309*(11), 1125–1135.

Gradman, A. H., Schmieder, R. E., Lins, R. L., Nussberger, J., Chiang, Y., & Bedigian, M. P. (2005). Aliskiren, a novel orally effective renin inhibitor, provides dose-dependent antihypertensive efficacy and placebo-like tolerability in hypertensive patients. *Circulation*, *111*(8), 1012–1018.

Gradman, A. H., Schmieder, R. E., Lins, R. L., Nussberger, J., Chiang, Y., & Bedigian, M. P. (2007). Aliskiren, an orally effective renin inhibitor, provides antihypertensive efficacy alone and in combination with valsartan. *American Journal of Hypertension*, *20*(1), 11–20.

Greenberg, D. A., & Jin, K. (2013). Vascular endothelial growth factors (VEGFS) and stroke. *Cellular and Molecular Life Sciences*, *70*(10), 1753–1761.

Gross, O., Girgert, R., Rubel, D., Temme, J., Theissen, S., & Müller, G. A. (2011). Renal protective effects of aliskiren beyond its antihypertensive property in a mouse model of progressive fibrosis. *American Journal of Hypertension*, *24*(3), 355–361.

Habibi, J., Whaley-Connel, A., Hayden, M. R., Demarco, V. G., Schneider, R., Sowers, S. D., … Sowers, J. R. (2008). Renin inhibition attenuates insulin resistance, oxidative stress, and pancreatic remodeling in the transgenic ren2 rat. *Endocrinology*, *149*(11), 5643–5653.

Heldin, C. H., Landström, M., & Moustakas, A. (2009). Mechanism of TGF-β signaling to growth arrest, apoptosis, and epithelial-mesenchymal transition. *Current Opinion in Cell Biology*, *21*(2), 166–176.

Hoeben, A., Landuyt, B., & Highley, M. S. (2004). Vascular endothelial growth factor and angiogenesis. *Pharmacological Reviews*, *56*(4), 549–580.

Huang, Y., Wongamorntham, S., Kasting, J., Mcquillan, D., Owens, R. T., Yu, L., … Border, W. (2006). Renin increases mesangial cell transforming growth factor-beta1 and matrix proteins through receptor-mediated, angiotensin II-independent mechanisms. *Kidney International*, *69*(1), 105–113.

Ichihara, A., Kaneshiro, Y., Takemitsu, T., Sakoda, M., Nakagawa, T., Nishiyama, A., … Inagami, T. (2006). Contribution of nonproteolytically activated prorenin in glomeruli to hypertensive renal damage. *Journal of the American Society of Nephrology*, *17*(9), 2495–2503.

Ikushima, H., & Miyazono, K. (2011). Biology of transforming growth factor-β signaling. *Current Pharmaceutical Biotechnology*, *12*(12), 2099–2107.

Karcioglu, S. S., Palabiyik, S. S., Bayir, Y., Karakus, E., Mercantepe, T., Halici, Z., & Alba, A. (2016). The role of RAAS inhibition by aliskiren on paracetamol-induced hepatotoxicity model in rats. *Journal of Cellular Biochemistry*, *117*(3), 638–646.

Kavvadas, P., Weis, L., Abed, A. B., Feldman, D. L., Dussaule, J. C., & Chatziantoniou, C. (2013). Renin inhibition reverses renal disease in transgenic mice by shifting the balance between profibrotic and antifibrotic agents. *Hypertension*, *61*(4), 901–907.

Ke, C. Y., Lee, C. C., Lee, C. J., Subeq, Y. M., Lee, R. P., & Hsu, B. G. (2010). Aliskiren ameliorates chlorhexidine digluconate-induced peritoneal fibrosis in rats. *European Journal of Clinical Investigation*, *40*(4), 301–309.

Kelly, D. J., Zhang, Y., Moe, G., Naik, G., & Gilbert, R. E. (2007). Aliskiren, a novel renin inhibitor, is renoprotective in a model of advanced diabetic nephropathy in rats. *Diabetologia*, *50*(11), 2398–2404.

Kishina, M., Koda, M., Kato, J., Tokunaga, S., Matono, T., Sugihara, T., … Murawaki, Y. (2014). Therapeutic effects of the direct renin inhibitor, aliskiren, on non-alcoholic steatohepatitis in fattyliver Shionogi ob/ob male mice. *Hepatology Research*, *44*(8), 888–896.

Koçak, G., Azak, A., Astarci, H. M., Huddam, B., Karaca, G., Çeri, M., … Duranay, M. (2012). Effects of renin-angiotensin-aldosterone system blockade on chlorhexidine gluconate-induced sclerosing encapsulated peritonitis in rats. *Therapeutic Apheresis and Dialysis*, *16*(1), 75–85.

Kunugi, S., Fukuda, Y., Ishizaki, M., & Yamanaka, N. (2001). Role of MMP-2 in alveolar epithelial cell repair after bleomycin administration in rabbits. *Laboratory Investigation*, *81*(9), 1309–1318.

Kushiro, T., Itakura, H., Abo, Y., Gotou, H., Terao, S., & Keefe, D. L. (2006). Aliskiren, a novel oral renin inhibitor, provides dose-dependent efficacy and placebo-like tolerability in Japanese patients with hypertension. *Hypertension Research*, *29*(12), 997–1005.

Lastra, G., Habibi, J., Whaley-Connell, A. T., Manrique, C., Hayden, M. R., Rehmer, J., … Sowers, J. R. (2009). Direct renin inhibition improves systemic insulin resistance and skeletal muscle glucose transport in a transgenic rodent model of tissue renin overexpression. *Endocrinology*, *150*(6), 2561–2568.

Lee, K. C., Chan, C. C., Hsieh, Y. C., Huang, Y. H., & Lin, H. C. (2012). Aliskiren attenuates chronic carbon tetrachloride-induced liver injury in mice. *European Journal of Clinical Investigation*, *42*(12), 1261–1271.

Lee, K. C., Chan, C. C., Yang, Y. Y., Hsieh, Y. C., Huang, Y. H., & Lin, H. C. (2013). Aliskiren attenuates steatohepatitis and increases turnover of hepatic fat in mice fed with a methionine and choline deficient diet. *PLoS One*, *8*(10), e.77817.

Lizakowski, S., Tylicki, L., Renke, M., Rutkowski, P., Heleniak, Z., Slawinska-Morawska, M., … Tutkowski, B. (2012). Aliskiren and perindopril reduce the levels of transforming growth factor-β in patients with non-diabetic kidney disease. *American Journal of Hypertension*, *25*(6), 636–639.

Lochter, A., & Bissell, M. J. (1995). Involvement of extracellular matrix constituents in breast cancer. *Seminars in Cancer Biology*, *6*(3), 165–173.

Lopez-Isac, E., Bossini-Castillo, L., Simeon, C. P., Egurbide, M. V., Alegre-Sancho, J. J., Callejas, J. L., … Spanish Scleroderma Group. (2014). A genome-wide association study follow-up suggests a possible role for PPARG in systemic sclerosis susceptibility. *Arthritis Research & Therapy*, *16*(1), R6.

Lozano, J. M., Padillo, J., Montero, J. L., Peña, J., De La Mata, M., & Muntané, J. (2003). Immunomodulatory activity of TNF-alpha during acute liver injury induced by D-galactosamine and its protection by PGE1 in rats. *International Immunopharmacology*, *3*(2), 197–207.

Ma, L., Hua, J., He, L., Li, Q., Zhou, J., & Yu, J. (2012). Anti-fibrotic effect of aliskiren in rats with deoxycorticosterone induced myocardial fibrosis and its potential mechanism. *Bosnian Journal of Basic Medical Sciences*, *12*(2), 69–73.

de la Mata, M., Meager, M., Rolando, N., Daniels, H. M., Nouri-Aria, K. T., Goka, A. K., … Williams, R. (1990). Tumour necrosis factor production in fulminant hepatic failure: Relation to aetiology and superimposed microbial infection. *Clinical and Experimental Immunology*, *82*(3), 479–484.

Matavelli, L. E., & Siragy, H. M. (2014). Reduction of aldosterone production improves renal oxidative stress and fibrosis in diabetic rats. *Journal of Cardiovascular Pharmacology*, *61*, 17–22.

Mcmurray, J. J. V., Abraham, W. T., Dickstein, K., Køber, L., Massie, B. M., & Krum, H. (2012). Aliskiren, altitude, and the implications for atmosphere. *European Journal of Heart Failure*, *14*(4), 341–343.

Mitamura, Y., Takeuchi, S., Matsuda, A., Tagawa, Y., Mizue, Y., & Nishihira, J. (2001). Monocyte chemotactic protein-1 in the vitreous of patients with proliferative diabetic retinopathy. *Ophthalmologica*, *215*(6), 415–418.

Moniwa, N., Varagic, J., Ahmad, S., Voncannon, J. L., Simington, S. W., Wang, H., … Ferrario, C. M. (2013). Hemodynamic and hormonal changes to dual renin angiotensin system inhibition in experimental hypertension. *Hypertension*, *61*(2), 417–424.

Morii, T., Fujita, H., Narita, T., Shimotomai, T., Fujishima, H., Yoshioka, N., … Ito, S. (2003). Association of monocyte chemoattractant protein-1 with renal tubular damage in diabetic nephropathy. *Journal of Diabetes and its Complications*, *17*(1), 11–15.

Moses, H., & Barcellos-Hoff, M. H. (2011). TGF-β biology in mammary development and breast cancer. *Cold Spring Harbo Perspect Biol.*, *3*(1), 003277.

Muto, Y., Nouri-Aria, K. T., Meager, A., Alexander, G. J. M., Eddleston, A. L., & Williams, R. (1988). Enhanced tumor necrosis factor and interleukin-1 in fulminant hepatic failure. *Lancet*, *2*(8602), 72–74.

Nathan, C. F. (1987). Secretory products of macrophages. *The Journal of Clinical Investigation*, *79*(2), 319–326.

Nguyen, G. (2006). Renin/prorenin receptors. *Kidney International*, *69*(9), 1503–1506.

Nicholls, S. J., Bakris, G. L., Kastelein, J. J. P., Menon, V., Williams, B., Armbrecht, J., … Nissen, S. E. (2013). Effect of aliskiren on progression of coronary disease in patients with prehypertension: The Aquarius randomized clinical trial. *Jama*, *310*(11), 1135–1144.

Nomura, S., Shouzu, A., Omoto, S., Nishikawa, M., & Fukuhara, S. (2000). Significance of chemokines and activated platelets in patients with diabetes. *Clinical and Experimental Immunology*, *121*(3), 437–443.

Nussberger, J., Wuerzner, G., Jensen, C., & Brunner, H. R. (2002). Angiotensin II suppression in humans by the orally active renin inhibitor aliskiren (spp100): Comparison with enalapril. *Hypertension*, *39*(1), E1–E8.

Palatini, P., Jung, W., Shlyakhto, E., Botha, J., Bush, C., & Keefe, D. L. (2010). Maintenance of blood-pressure-lowering effect following a missed dose of aliskiren, irbesartan or ramipril: Results of a randomized, double-blind study. *Journal of Human Hypertension*, *24*(2), 93–103.

Pardo, A., & Selman, M. (2012). Role of matrix metalloproteases in idiopathic pulmonary fibrosis. *Fibrogenesis & Tissue Repair*, *5*(Suppl 1), S9.

Parvani, J. G., Taylor, M. A., & Schiemann, W. P. (2011). Noncanonical TGF-β signaling during mammary tumorigenesis. *Journal of Mammary Gland Biology and Neoplasia*, *16*(2), 127–146.

Parving, H. H., Brenner, B. M., & Mcmurray, J. J. (2012). Cardiorenal end points in a trial of aliskiren for type 2 diabetes. *The New England Journal of Medicine*, *367*(23), 2204–2213.

Pérez-Martinez, P., Pérez-Martinez, F. C., Carrión, B., Masiá, J., Ortega, A., Simarro, E., … Cena, V. (2012). Aliskiren prevents the toxic effects of peritoneal dialysis fluids during chronic dialysis in rats. *PLoS One*, *7*(4), e36268.

Persson, F., Rossing, P., Schjoedt, K. J., Juhl, T., Tarnow, L., Stehouwer, C. D., … Parving, H. H. (2008). Time course of the antiproteinuric and antihypertensive effects of direct renin inhibition in type 2 diabetes. *Kidney International*, *73*(12), 1419–1425.

Piemonti, L., Calori, G., Lattuada, G., Mercalli, A., Ragogna, F., & Garancini, M. P. (2009). Association between plasma monocyte chemoattractant protein-1 concentration and cardiovascular disease mortality in middle-aged diabetic and nondiabetic individuals. *Diabetes Care*, *32*(11), 2105–2110.

Pilz, B., Shagdarsuren, M. W., Fiebeler, A., Dechend, R., Gratze, P., Meiners, S., … Müller, D. N. (2005). Aliskiren, a human renin inhibitor, ameliorates cardiac and renal damage in double-transgenic rats. *Hypertension*, *46*(3), 569–576.

Pozzi, A., Wary, K. K., Giancotti, F. G., & Gardner, H. A. (1998). Integrin alpha1beta1 mediates a unique collagen-dependent proliferation pathway in vivo. *The Journal of Cell Biology*, *142*(2), 587–594.

Prókai, Á., Csohány, R., Sziksz, E., Pap, D., Balicza-Himer, L., Boros, S., … Szabó, A. J. (2016). Calcineurin-inhibition results in upregulation of local renin and subsequent vascular endothelial growth factor production in renal collecting ducts. *Transplantation*, *100*(2), 325–333.

Provenzano, P. P., Eliceiri, K. W., Campbell, J. M., Inman, D. R., White, J. G., & Keely, P. J. (2006). Collagen reorganization at the tumor-stromal interface facilitates local invasion. *BMC Medicine*, *4*(1), 38.

Radstake, T. R., Gorlova, O., Rueda, B., Martin, J. E., Alizadeh, B. Z., Palomino-Morales, R., … Mayes, M. D. (2010). Genome-wide association study of systemic sclerosis identifies CD247 as a new susceptibility locus. *Nature Genetics*, *42*(5), 426–429.

Ramalho, F. N., Sanches, S. C., Foss, M. C., Augusto, M. J., Silva, D. M., Oliveira, A. M., & Ramalho, L. N. (2017). Aliskiren effect on non-alcoholic steatohepatitis in metabolic syndrome. *Diabetology and Metabolic Syndrome*, *9*, 82.

Raptis, A. E., Markakis, K. P., Mazioti, M. C., Ikonomidis, I., Maratou, E. P., Vlahakos, D. V., … Dimitriadis, G. D. (2015). Effect of aliskiren on circulating endothelial progenitor cells and vascular function in patients with type 2 diabetes and essential hypertension. *American Journal of Hypertension*, *28*(1), 22–29.

Roberts, P. J., & Der, C. J. (2007). Targeting the RAF-MEK-ERK mitogen-activated protein kinase cascade for the treatment of cancer. *Oncogene*, *26*(22), 3291–3310.

Sadek, S. A., Rashed, L. A., Bassam, A. M., & Saida, E. S. (2015). Effect of aliskiren, telmisartan and torsemide on cardiac dysfunction in l-nitro arginine methyl ester (l-NAME) induced hypertension in rats. *Journal of Advanced Research*, *6*(6), 967–974.

Sakuraya, K., Endo, A., Someya, T., Hirano, D., Murano, Y., Fujinaga, S., … Shimizu, T. (2014). The synergistic effect of mizoribine and a direct renin inhibitor, aliskiren, on unilateral ureteral obstruction induced renal fibrosis in rats. *The Journal of Urology*, *191*(4), 1139–1146.

Santuzzi, C. H., Tiradentes, R. V., Mengal, V., Claudio, E. R., Mauad, H., Gouvea, S. A., & Abreu, G. R. (2015). Combined aliskiren and L-arginine treatment has antihypertensive effects and prevents vascular endothelial dysfunction in a model of renovascular hypertension. *Brazilian Journal of Medical and Biological Research*, *48*(1), 65–76.

Satoh, A., Niwano, S., Niwano, H., Aoyama, Y., Oikawa, J., Fukaya, H., … Ako, J. (2017). Aliskiren suppresses atrial electrical and structural remodeling in a canine model of atrial electrical and structural remodeling in a canine model of atrial fibrillation. *Heart and Vessels*, *32*(1), 90–100.

Scholl, F. A., Dumesic, P. A., & Khavari, P. A. (2005). Effects of active MEK1 expression in vivo. *Cancer Letters*, *230*(1), 1–5.

Shaw, R. J., & Cantley, L. C. (2006). Ras, PI(3)K and mTOR signalling controls tumour cell growth. *Nature*, *441*(7092), 424–430.

Simeoni, E., Hoffmann, M. M., Winkelmann, B. R., Ruiz, J., Fleury, S., Boehm, B. O., … Vassali, G. (2004). Association between the A-2518G polymorphism in the monocyte chemoattractant protein-1 gene and insulin resistance and type 2 diabetes mellitus. *Diabetologia*, *47*(9), 1574–1580.

Singh, V. P., Le, B., Khode, R., Bazer, K. M., & Kumar, R. (2008). Intracellular angiotensin II production in diabetic rats is correlated with cardiomyocyte apoptosis, oxidative stress, and cardiac fibrosis. *Diabetes*, *57*(12), 3297–3306.

Solomon, S. D., Appelbaum, E., Manning, W. J., Verma, A., Berglund, T., Lukashevich, V., … Dahlof, B. (2009). Aliskiren in left ventricular hypertrophy (ALLAY) trial investigators. Effect of the direct renin inhibitor aliskiren, the angiotensin receptor blocker losartan, or both on left ventricular mass in patients with hypertension and left ventricular hypertrophy. *Circulation*, *119*(4), 530–537.

Spence, J. D. (2010). Physiologic tailoring of treatment in resistant hypertension. *Current Cardiology Reviews*, *6*(2), 119–123.

Stanton, A., Jensen, C., Nussberger, J., & O'brien, E. (2003). Blood pressure lowering in essential hypertension with an oral renin inhibitor, aliskiren. *Hypertension*, *42*(6), 1137–1143.

Strasser, R. H., Puig, J. G., Farsang, C., Croket, M., Li, J., & Van Ingen, H. A. (2007). A comparison of the tolerability of the direct renin inhibitor aliskiren and lisinopril in patients with severe hypertension. *Journal of Human Hypertension*, *21*(10), 780–787.

Sun, C. Y., Cherng, W. J., Jian, H. Z., Hsu, H. H., Wu, I. W., Hsu, H. J., & Wu, M. S. (2012). Aliskiren reduced renal fibrosis in mice with chronic ischemic kidney injury beyond the direct renin inhibition. *Hypertension Research*, *35*(3), 304–311.

Sun, Y., Tokushige, K., Isono, E., Yamauchi, K., & Obata, H. (1992). Elevated serum interleukin-6 levels in patients with acute hepatitis. *Journal of Clinical Immunology*, *12*(3), 197–200.

Takamura, C., Suzuki, J., Ogawam, M., Watanabe, R., Tada, Y., Maejima, Y., … Isobe, M. (2016). Suppression of murine autoimmune myocarditis achieved with direct renin inhibition. *Journal of Cardiology*, *68*(3), 253–260.

Tan, R. J., & Liu, Y. (2012). Matrix metalloproteinases in kidney homeostasis and diseases. *American Journal of Physiology. Renal Physiology*, *302*(11), F1351–F1361.

Vaidyanathan, S., Jarugula, V., Dieterich, H. A., Howard, D., & Dole, W. P. (2008). Clinical pharmacokinetics and pharmacodynamics of aliskiren. *Clinical Pharmacokinetics*, *47*(8), 515–531.

Van Meeteren, L. A., & Ten Dijke, P. (2012). Regulation of endothelial cell plasticity by TGF-β. *Cell and Tissue Research*, *347*(1), 177–186.

Vendrell, J., Fernandez-Real, J. M., Gutierrez, C., Zamora, A., Simon, I., Bardaji, A., … Richart, C. (2003). A polymorphism in the promoter of the tumor necrosis factor-alpha gene (−308) is associated with coronary heart disease in type 2 diabetic patients. *Atherosclerosis*, *167*(2), 257–264.

Virdis, A., Ghiadoni, L., Qasem, A., Lorenzini, G., Duranti, E., Cartoni, G., … Taddei, S. (2012). Effect of aliskiren treatment on endothelium-dependent vasodilation and aortic stiffness in essential hypertensive patients. *European Heart Journal*, *33*(12), 1530–1538.

Wang, J., Chen, L., Chen, B., Meliton, A., Liu, Q. S., Shi, Y., … Li, Y. C. (2015). Chronic activation of the renin-angiotensin system induces lung fibrosis. *Scientific Reports*, *5*, 15561.

Weng, L. Q., Zhang, W. B., Ye, Y., Yin, P. P., Yuan, J., Wang, X. X., … Zoum, Y. Z. (2014). Aliskiren ameliorates pressure overload-induced heart hypertrophy and fibrosis in mice. *Acta Pharmacologica Sinica*, *35*(8), 1005–1014.

Whaley-Connell, A., Habibi, J., Cooper, S. A., Demarco, V. G., Hayden, M. R., Stump, C. S., … Sowers, J. R. (2008). Effect of renin inhibition and AT1r blockade on myocardial remodeling in the transgenic ren2 rat. *American Journal of Physiology. Endocrinology and Metabolism*, *295*(1), 103–109.

Whaley-Connell, A., Habibi, J., Cooper, S. A., Demarco, V. G., Hayden, M. R., Stump, C. S., … Sowers, J. R. (2013). Renin inhibition and AT(1)R blockade improve metabolic signaling, oxidant stress and myocardial tissue remodeling. *Metabolism*, *62*(6), 861–872.

Whaley-Connell, A., Habibi, J., Nistala, R., Hayden, M. R., Pulakat, L., Sinak, C., … Sowers, J. R. (2012). Combination of direct renin inhibition with angiotensin type 1 receptor blockade improves aldosterone but does not improve kidney injury in the transgenic Ren2 rat. *Regulatory Peptides*, *176*(1–3), 36–44.

Whelton, P. K., Carey, R. M., Aronow, W. S., Casey, D. E., Jr., Collins, K. J., Dennison Himmelfarb, C., … Wright, J. T. (2017). Acc/Aha/Aapa/Abc/Acpm/Ags/Apha/Ash/Aspc/Nma/Pcna guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: A case report of the American College of Cardiology/American Heart Association task force on clinical pratice guideline. *Hypertension*, *71*(6), e113–e115.

Wiggins, K. J., & Kelly, D. J. (2009). Aliskiren: A novel renoprotective agent or simply an alternative to ace inhibitors? *Kidney International*, *76*(1), 23–31.

Woessner, J. F. (1994). The family of matrix metalloproteinase family. *Annals of the new York Academy of Sciences*, *732*, 11–21.

Wu, W. P., Chang, C. H., Chiu, Y. T., Ku, C. L., Wen, M. C., Shu, K. H., & Wu, M. J. (2010). A reduction of unilateral ureteral obstruction-induced renal fibrosis by a therapy combining valsartan with aliskiren. *American Journal of Physiology. Renal Physiology*, *299*(5), 929–941.

Yakamoto, E., Kataoka, K., Dong, Y. F., Nakamura, T., Fukuda, M., Tokutomi, Y., … Kim-Mitsuyama, S. (2009). Aliskiren enhances the protective effects of valsartan against cardiovascular and renal injury in endothelial nitric oxide synthase-deficient mice. *Hypertension*, *54*(3), 633–638.

Yamada, C., Kuwahara, K., Yamazaki, M., Nakagawa, Y., Nishikimi, T., Kinoshita, H., … Kimura, T. (2016). The renin-angiotensin system promotes arrhythmogenic substrates and lethal arrhythmias in mice with non-ischaemic cardiomyopathy. *Cardiovascular Research*, *109*(1), 162–173.

Yeh, Y. C., Lin, H. H., & Tang, M. J. (2012). A tale of two collagen receptors, integrin beta1 and discoidin domain receptor 1, in epithelial cell differentiation. *American Journal of Physiology. Cell Physiology*, *303*(12), C1207–C1217.

Yoon, S., & Seger, R. (2006). The extracellular signal-regulated kinase: Multiple substrates regulate diverse cellular functions. *Growth Factors*, *24*(1), 21–44.

Zanotti, S., Gibertini, S., Curcio, M., Savadori, P., Pasanisi, B., Morandi, L., … Mora, M. (2015). Opposing roles of mir-21 and mir-29 in the progression of fibrosis in Duchenne muscular dystrophy. *Biochimica et Biophysica Acta*, *1852*(7), 1451–1464.

Zhang, K., Corsa, C. A., Ponik, S. M., Prior, J. L., Piwnica-Worms, D., Eliceiri, K. W., … Longmore, G. D. (2013). The collagen receptor discoidin domain receptor 2 stabilizes snail1 to facilitate breast cancer metastasis. *Nature Cell Biology*, *15*(6), 677–687.

Zhao, S. P., & Xu, T. D. (1999). Elevated tumor necrosis factor alpha of blood mononuclear cells in patients with congestive heart failure. *International Journal of Cardiology*, *71*(3), 257–261.

Zhao, Z., Chen, Y., Li, W., Wang, X., Li, J., Yang, W., … Li, G. (2016). Aliskiren protecting atrial structural remodeling from rapid atrial pacing in a canine model. *Naunyn-Schmiedeberg's Archives of Pharmacology*, *389*(8), 863–871.

Zhen, E. Y., Brittain, I. J., & Laska, D. A. (2008). Characterization of metalloprotease cleavage products of human articular cartilage. *Arthritis and Rheumatism*, *58*(8), 2420–2431.

Zhi, H., Luptak, I., Alreja, G., Shi, J., Guan, J., Metes-Kosik, N., & Joseph, P. (2013). Effects of direct renin inhibition on myocardial fibrosis and cardiac fibroblast function. *PLoS One*, *8*(12), e81612.

Zhou, G., Liu, X., Cheung, A. K., & Huang, Y. (2015). Efficacy of aliskiren, compared with angiotensin ii blockade, in slowing the progression of diabetic nephropathy in db/db mice: Should the combination therapy be a focus? *American Journal of Translational Research*, *7*(5), 825–840.

Zietz, B., Büchler, C., Herfarth, H., Müller-Ladner, U., Spiegel, D., Schölmerich, J., & Schaffler, A. (2005). Caucasian patients with type 2 diabetes mellitus have elevated levels of monocyte chemoattractant protein-1 that are not influenced by the −2518 A->G promoter polymorphism. *Diabetes, Obesity & Metabolism*, *7*(5), 570–578.

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