In-Depth Topic Review

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Targeting Immunity in End-Stage Renal Disease

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Abstract
Background: Despite the stable incidence of end-stage renal disease (ESRD), it continues to be associated with an unacceptably high cardiovascular risk. ***Summary:*** ESRD is characterized by enhanced oxidative stress and severe inflammation, which boost cardiovascular risk, thus increasing cardiovascular-associated mortality rate. While substantial effort has been made in the technological innovation of dialytic techniques, few significant advances have been made to reduce inflammation in patients with ESRD. Indeed, this contrasts with the extensive scientific breakthroughs made in the basic field of science in targeting inflammation. There is thus a pressing need for clinical trials to test the effect of reducing inflammation in patients with ESRD. Here, we will revisit the negative effect of ESRD on inflammation and explore the impact of enhanced inflammation on cardiovascular outcomes and survival in patients with ESRD. Finally, we will discuss the need for clinical trials that target inflammation in ESRD, as well as weigh potential disadvantages and offer novel innovative approaches. ***Key Message:*** We will try to understand why the issue of inflammation has not been successfully addressed thus far in patients with ESRD, while at the same time weighing the potential disadvantages and offering novel innovative approaches for targeting inflammation in patients with ESRD.

Introduction

Despite the fact that end-stage renal disease (ESRD) is stable in its incidence, suggesting some efficacy of preventive approaches (ERA/EDA Registry: www.era-edta-reg.org), ESRD remains associated with higher cardiovascular risk compared to normal individuals [1] and carries a mortality rate higher than in other chronic diseases (ERA/EDA Registry: www.era-edta-reg.org). Enhanced oxidative stress and severe inflammation boost cardiovascular risk, particularly in diabetic patients [2]. While an association between inflammation and cardiovascular risk has been established [3], little progress has been made in targeting elevated inflammation in ESRD. Here, we will revisit the negative effect of ESRD on inflammation, and explore its impact on cardiovascular outcomes and survival in dialyzed patients. Finally, we will also discuss possible clinical

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trials that target inflammation in patients with failing kidneys, while weighing the potential disadvantages and offering novel innovative approaches. We used the key words "inflammation," "ESRD," and "cardiovascular risk" in searches of the PubMed, Embase, and Cochrane databases and then selected literature from the last 10 years.

Causes of Increased Inflammation in ESRD

The incidence of high levels of inflammation in ESRD is not surprising, given that high-sensitivity C-reactive protein (hs-CRP) is elevated in the course of metabolic syndrome, diabetes, and smoking, all of which are prevalent in ESRD patients [4]. In this disease setting, a combination of oxidative burst [5], uremic toxicity, dyslipidemia, and oxidative stress resulting from dysfunctional mitochondrial electron transfer [6] generates free reactive species. These compounds induce oxidative modifications of carbohydrates such as advanced glycation end products (AGEs), advanced oxidation protein products (AOPPs), advanced lipoxidation end products (ALEs), oxidized low density lipoproteins (oxLDLs) and DNA, in turn recognized as damage-associated molecular patterns (DAMPs) by Toll-like receptors (TLRs), which are upregulated in many cell types in ESRD, including macrophages and neutrophils [7]. TLRs and nucleotide binding oligomerization domain-like receptors (NODs), particularly NOD2, recognize oxidized products, priming a deleterious cascade of proinflammatory signaling [8]. Inflammation is further worsened by the same blood–dialyzer contact, water impurities, anemia, and antioxidant loss during dialysis [9, 10], all of which activate the complement cascade and neutrophil granulocytes. Furthermore, iron administration, which is essential for anemia management, exerts direct mitochondrial toxicity [11], reacting with H_2O_2 and producing OH and AOPPs [12]. These effects are mitigated in part by neutrophil gelatinase-associated lipocalin (NGAL), a marker of iron status that also functions as a free iron scavenger [13]. Heparin, which may induce the release of myeloperoxidase from endothelial cells, has pro-oxidant and pro-inflammatory effects as well [10]. Among circulating factors involved in worsening inflammation in ESRD, the following should also be noted.

Advanced Glycation End Products

AGEs are augmented in ESRD and interact with their receptor (RAGE), thus enhancing NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells)-mediated production of cytokines (interleukin [IL]-1, IL-6, monocyte chemoattractant protein-1 [MCP-1], tumor necrosis factor-α [TNF-α]) and cell adhesion molecules on T-cells [14].

Homocysteine

Hyperhomocysteinemia has been observed in ESRD patients associated with impaired methyltransferase activity, which is essential to revert homocysteine to methionine and adenosyl methionine. The latter is mandatory for DNA and protein methylation, and a lack of this molecule may lead to DNA hypermethylation and inflammation [15, 16].

Indoxyl Sulfate and P-Cresyl Sulfate

These uremic toxins are increased in the advanced stages of renal disease and induce intercellular adhesion molecule-1 (ICAM-1) expression, activating NF-κB and reactive species production by endothelial cells [17], increasing leukocyte endothelial adhesion [18], endothelial E-selectin, MCP-1, and tissue factor expression [19].

Uremic Dyslipidemia

The association of uremic dyslipidemia with inflammation [20] is related to cellular expression of the receptors involved in immune response (TLRs, major histocompatibility complex-II [MHC-II], cluster of differentiation [CD]40, CD40 ligand, CD80, CD28, apoptosis antigen 1 [FAS], and FAS ligand), which may be influenced by fluidity of membrane structures called lipid rafts. Thus, the expression of the aforementioned receptors can be modulated by membrane cholesterol content, and it can be impaired by dysfunctional high density lipoprotein [HDL] reverse cholesterol transport [21]. This leads to enhanced membrane expression of MHC-II, CD80, CD86, and TLR4 [22] and inflammation. Low density lipoproteins (LDLs) are also oxidized to oxLDLs, largely because of lipoprotein-associated phospholipase A_2 (Lp-PLA_2) [23], which produces highly proinflammatory lysophosphatidylcholine and oxidized free fatty acids [24].

Adaptive and Innate Immunity Abnormalities in ESRD

Oxidative stress, dialysis, and uremic dyslipidemia induce immune incompetence in ESRD, causing detrimental and aimless hyperactivation of the immune system. The proof of this phenomenon is found in evidence of elevated levels of peripheral markers of immune activation (e.g., cytokines and chemokines) [25–32]. Other pro-

inflammatory cell products, like NGAL [13], galectin-3 (GAL-3) [33], and Lp-PLA_2 [34], the first released by polymorphonuclear leukocytes and the others by macrophages, have been shown to be augmented as well.

Inflammation is pivotally driven by TLRs and NODs on polymorphonuclear leukocytes (chronically activated and degranulated) [35], which release reactive species and myeloperoxidase (MPO) [10, 36]. The latter phenomenon is linked to leukocyte apoptosis and impaired phagocytosis [37], impaired antigen presentation function [38, 39], and increased cytokine production [7]. Dialytic treatment may activate antibodies and complements; indeed, dialyzers absorb albumin, complement component 3 (C3), C1q, immunoglobulin G and ficolin, leading to activation of the alternative [9, 40], classical, and lectin [41] pathways of complement. All these alterations in innate immunity unavoidably have affects in adaptive immunity as well, inducing elevated number of high IL-2-producing T-cells [27], low number of B-lymphocytes (due to apoptosis) [42], dysfunctional memory $CD4^+$ T-cells [43], reduced CD4/CD8 ratio, increased Th1/Th2 ratio, and depletion of memory CD4 and CD8 T-cells and regulatory T-cells (Tregs; more likely to exhibit an IL-17 pro-inflammatory phenotype) [44].

Mechanisms by Which Inflammation May Increase Cardiovascular and Mortality Risk in ESRD

In patients with ESRD, several mediators of inflammation share a link with cardiovascular disease [34, 45–63] (Table 1). Indeed, this is quite dubious for C reactive protein (CRP), either in terms of mere association or from a pathogenic perspective. In fact, while in some trials CRP did not merge as a strong independent cardiovascular risk factor (instead of IL-1, IL-6, TNF-α, albumin, and body mass index) [52, 53, 55, 60], the genetic analysis of polymorphisms leading to a gain of function of gene transcription of CRP failed to demonstrate a dose-dependent effect of this marker [64] and a possible causal role. Other biomarkers (sTWEAK, MIC-1, $CD4^+$CD28-null T-cells, RANKL, pentraxin3, CCR5, GAL-3, myeloperoxidase, Lp-PLA_2, and sCD14), have also been linked to cardiovascular risk in ESRD [32, 34, 45–48, 51, 57, 61–63]. Besides studies of association, there are evidences that uremic serum directly causes vascular damage [65] via activation of pro-inflammatory endothelial pathways (e.g., TLR4, NF-κB, NALP3 [NACHT, LRR and PYD domains-containing protein 3] and p38 MAPK [p38 mitogen-activated protein kinase]), which induce increased endothelial expression of ICAM-1, VCAM-1 (vascular cell adhesion molecule-1), von Willebrand factor [66, 67], reduced nitric oxide availability, generating endothelial dysfunction [68].

Though the association between inflammation and cardiovascular disease is undeniable and while there is some evidence of a possible pathophysiological role, a sure causal relationship can not be stated so far, given the lack of intervention trials with this end point.

Targeting Inflammation in ESRD: Preclinical Studies

Indirect Strategies

Oxidative stress drives inflammation in ESRD, and not surprisingly, targeting oxidative stress is associated with improved outcomes in preclinical models (Table 2). Wistar rats treated with antioxidants such as L-arginine [69], tocotrienol, or α-tocopherol [70] showed a decrease in plasmatic concentrations of endothelial and cardiovascular stress markers including sICAM-1, TNF-α, NF-κB, VCAM-1, MCP-1, and TGF-β. Similar results have been obtained with LF-4 (an ApoA-1 mimetic peptide) [71], telmisartan [72], the oral sorbent AST-120, by improving the uremic milieu in ApoE-deficient mice [73]. However, the lack of reliable ESRD murine models makes these results difficult to interpret or translate to humans.

Direct Strategies

Several strategies aimed at reducing inflammation directly were tested including the following: (i) the C3 antagonist Cp40, which blunts complement activation and increases IL-10 concentrations in Cynomolgus monkeys [74]; (ii) the proteasome inhibitor MG132 and the NF-κB inhibitor PDTC, which reduced the binding of NF-κB to DNA and TNF-α levels in New Zealand white rabbits [75]; (iii) thalidomide, which induced decreased expression of NF-κB in C57BL/6 mice [76]; (iv) IL-10, which reduced MCP-1 and RANTES (regulated on activation, normal T-cell expressed and secreted) in Sprague–Dawley rats [77]; and (v) ablation of chemokine receptors in inbred C57BL/6 mice, which prevented renal ischemia/reperfusion injury [78].

Targeting Inflammation in ESRD Clinical Trials

Indirect Strategies

Antioxidant therapies have been tested in human clinical trials as well to reduce cardiovascular risk. In the SPACE

Table 1. Evidence of a relationship between inflammation markers and cardiovascular risk

Patients	Pivotal findings
Dialysis patients (*n* = 176)	IL-6 independently predicts mortality (OD [95% CI] 2.7 [1.1–6.6]) [52]
Dialysis patients (*n* = 1,228)	CRP predicts mortality (HRs [95% CI] 1st tertile 2.2 [0.96–5.16], 2nd tertile 3.3 [1.49–7.33], 3rd tertile 4.19 [1.93–9.06]) [60]
Dialysis patients (*n* = 231)	High vs low IL-1, IL-6, and TNF-α levels predict mortality (HR [95% CI] 2.62 [1.44–3.69]) [53]
Dialysis patients (*n* = 218)	sTWEAK alone and with IL-6 predicts cardiovascular mortality (respective HRs [95% CI] 2.66 [1.24–5.62] each pg/mL and 7.45 [1.98–27.9] each pg/mL) [46]
Dialysis patients (*n* = 1,041)	Hs-CRP and IL-6 predict cardiac death (respective adjusted HRs [95% CI] 1.22 [0.96–1.55] each mg/dL and 1.21 [0.96–1.53] each pg/mL) [55]
Dialysis patients (*n* = 54)	Hs-CRP predicts silent cerebral infarction (HR [95% CI] 1.61 [1.17–2.85] each mg/dL) [56]
Dialysis patients (*n* = 470)	MIC-1 predicts mortality (OD [95% CI] 4.84 [1.09–21.62]) [45]
Dialysis patients	CRP and CD4 + CD28-null T-cells correlate with impaired flow-mediated vasodilatation and increased carotid intima-media thickness [57]
Dialysis patients (*n* = 68)	Inverse relationship between RANKL and vascular calcifications [47]
Dialysis patients (*n* = 105)	Hs-CRP, PTX3, IL-6/IL-10 ratio correlate with systolic dysfunction [62]
Dialysis and control patients	Inflammation correlates with endothelial glycocalyx damage [65]
Dialysis, CKD and control patients	VCAM-1, ICAM-1, vWF, and circulating endothelial cells correlate with p38 MAPK and NF-κB in ESRD [67]
Dialysis patients (*n* = 413)	CCR5 delta 32 and hs-CRP >10 mg/L predict mortality (HR [95% CI] 1.82 [1.29–2.58]) [61]
Dialysis patients (*n* = 1,168), patients submitted to coronary angiography (*n* = 2,579)	GAL-3 predicts cadiovascular mortality in LURIC and 4D studies (respective HRs [95% CI] 1.21 [1.01–1.44] and 1.12 [1.01–1.24] each SD) [48]
Dialysis patients (*n* = 102)	Lp-PLA_2 >194 nmol/min/mL predicts cardiovascular outcome (OD [95% CI] 2.54 [1.09–5.95]) [34]
Dialysis patients (*n* = 236)	Doubled MPO levels predict cardiovascular risk (HR [95% CI] 1.60 [1.17–2.18]) [51]
Dialysis patients (*n* = 211)	sCD14 predicts mortality (HR [95% CI] 3.11 [1.49–6.36] for 3rd tertile) [32]
Dialysis patients (*n* = 310)	sCD14 predicts mortality (HR [95% CI] 1.94 [1.01–3.75] for 3rd tertile [63]

sTWEAK, serum TNF-related weak inducer of apoptosis; MIC-1, macrophage inhibitory cytokine-1; RANKL, receptor activator of nuclear factor kappa-B ligand; CCR5, C-C chemokine receptor type 5.

study, a reduction of 64% for overall end points and of 70% for myocardial infarction was observed with vitamin E in ESRD patients [79]. The study by Jun et al. [80], in which 10 trials pooling nearly 2,000 patients with altered kidney function who were treated with several antioxidants (e.g., vitamin E, co-enzyme Q, acetylcysteine, bardoxolone methyl and human recombinant superoxide dismutase) were analyzed, showed a 43% reduction in cardiovascular end points (RR = 0.57), but only in dialysis patients. Disappointingly, anti-hypertensives, statins, and lifestyle changes failed to reduce cardiovascular risk in ESRD patients [81]. In particular, the efficacy of renin–angiotensin system inhibitors is far from being demonstrated. With regard to homocysteine-lowering treatments, while showing conflicting results on endothelial function [82, 83], results did not suggest improved prevention of cardiovascular events either in ESRD [84] or kidney transplanted patients [85]. However, it is possible that lowering hyperhomocysteinemia may be of value in diabetic patients [86, 87].

Targeting Complement

Pharmacological complement inhibition by anti-C1 and anti-C5a compounds may abrogate intradialytic inflammation, due to blood–dialyzer contact. However, the

Table 2. Experimental therapies aimed at reducing inflammation in preclinical models of CKD and ESRD

Experimental model	Study design	Results
Cynomolgus hemodialysis model	Complement activation treated with the C3 inhibitor Cp40	Reduced complement activation and increased levels of IL-10 [74]
Adenine-induced CKD in C57BL/6 mice (n = 30)	3 Groups: (a) Control group (b) Adenine diet group (c) Adenine + thalidomide group	Reduced expression of cytokines and activation of NK-kB in the kidney [76]
Subtotal nephrectomized rats	3 Groups: (a) Untreated group (b) Telmisartan group (c) Telmisartan antagonist GW9662 group	Telmisartan antagonized macrophage infiltration, osteopontin, and VCAM-1 expression, all blunted by GW9662 [72]
5/6 nephrectomy rats receiving the ApoA1 mimetic drug L4F	3 Groups: (a) Control sham operated rats (b) Placebo group (c) L4F group	L4F reduced MCP-1 and NF-κB expression [71]
Extensive renal mass reduction in rats	4 Groups: (a) CKD rats (b) L-arginine group (c) L-carnitine, catechin, vitamins E and C (d) group (e) L-carnitine, catechin, vitamins E and C + L-arginine group	L-arginine decreased cytokines Antioxidants decreased cytokines and sICAM-1, increasing IL-4 levels L-arginine + antioxidants recovered normal cytokines and sICAM-1 [69]
New Zealand white rabbits submitted to 5/6 nephrectomy or sham operation (n = 24)	3 Groups: (a) CKD untreated rabbits (b) Proteasome inhibitor MG132 group (c) NF-κB inhibitor PDTC group	Reduced NF-κB DNA binding capacity and reduction of TNF-α levels in the MG132 group, similarly to PDTC [75]
Streptozotocin-induced diabetic rats with CKD	2 Groups: (a) Tocotrienol and α-tocopherol group (b) Control group	Tocotrienol, associated with α-tocopherol, prevented the elevation of TNF-α, TGF-β, and the activation of NF-κB [70]
Rats	2 Groups: (a) IL-10-transfected group (b) Control group	IL-10 reduced the expression of MCP-1, IFN-γ, IL-2, and RANTES [77]
ApoE-deficient mice treated with AST-120	3 Groups: (a) Uninephrectomy (b) Subtotal nephrectomy (c) Sham operation	Reduced aortic expression of MCP-1, TNF-α, and IL-1β [73]

IFN-γ, interferon-γ; NTGF-β, transforming growth factor-β.

high costs of these drugs are a major concern for healthcare providers. Conversely, 5C6 peptide (binding to factor H coated to polystyrene materials) [88], PMX-53 (which bind to C5aR) [89], Compstatin and POT-4 (which antagonize C3) [90], may represent promising alternatives.

Targeting Cytokines

Few trials evaluating cytokine targeting in ESRD can be found. One is based on the administration of a recombinant human IL-1 receptor antagonist (Anakinra) [91]. Fourteen subjects were randomized to receive 100 mg Anakinra or placebo subcutaneously for 4 weeks. The trial was biased by the presence of more severe inflammation in the placebo arm. Treated patients exhibited 53 and 40% reduction in hs-CRP and IL-6 levels, respectively, as compared to 1% reduction and 20% increase in the placebo group [91]. In another trial, the TNF-α antagonist, etanercept, tested with 10 dialyzed patients treated for 44 weeks failed to produce any effect on inflammation [92].

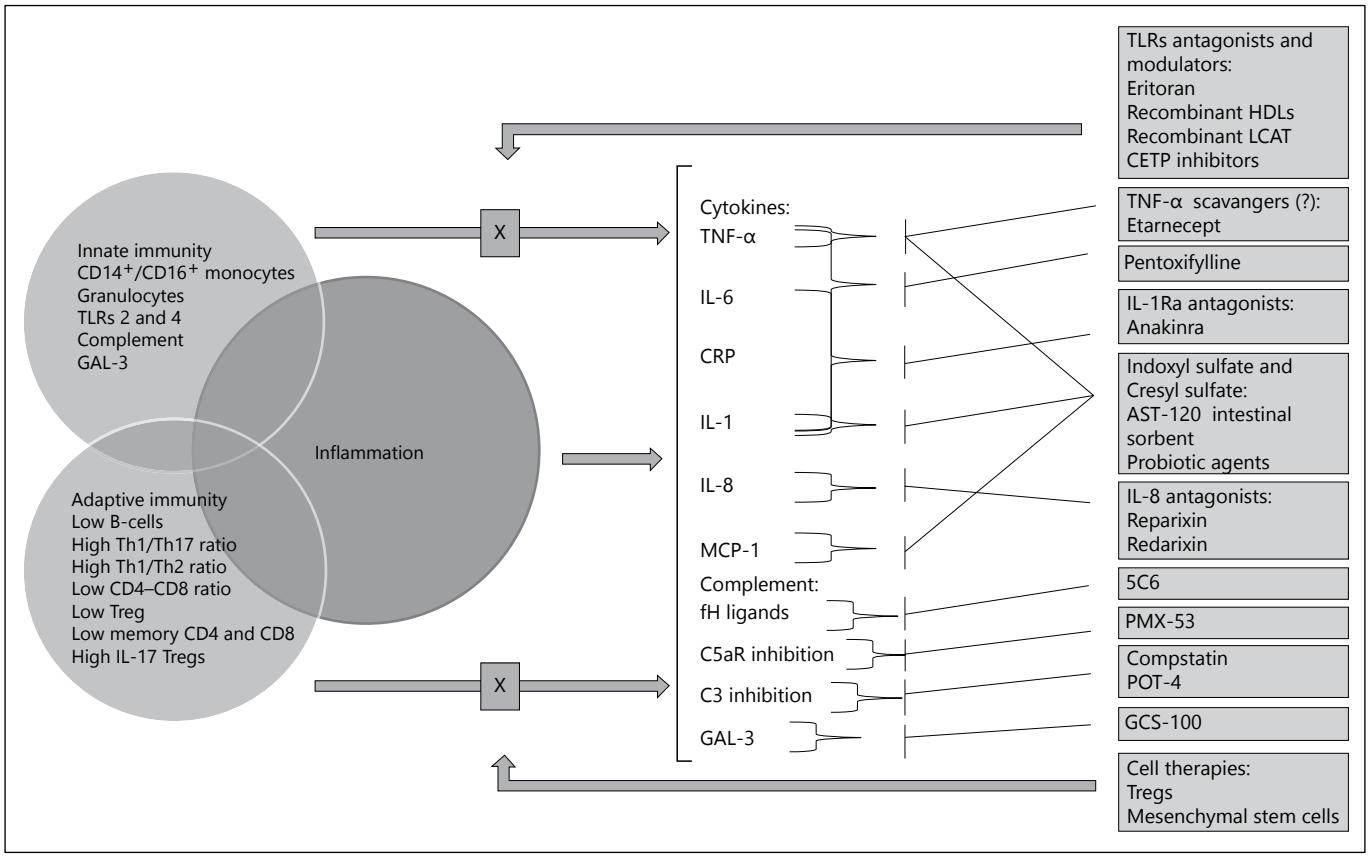

Fig. 1. Schematic attempt to show pathways that may be targeted or are currently being targeted in ESRD.

Lessons Learned from Trials and the Next Immunological/Anti-Inflammatory Trial in ESRD

The goal of improving cardiovascular risk in dialysis patients can be achieved with integrated management, ranging from strict blood pressure and glycemic control, through treatment with antioxidant compounds, to administration of novel anti-inflammatory molecules [93, 94]. Indeed, while an optimal blood pressure and glycemic control are difficult to achieve in real life, more anti-inflammatory treatments (Fig. 1) should be encouraged to confirm, for instance, the interesting results obtained with IL-1α receptor antagonists. The effect of novel TLR antagonists on the inflammatory response and cardiovascular risk in ESRD should be tested as well [95]. Likewise, therapies improving HDL concentrations (e.g., recombinant HDLs, recombinant lecithin-cholesterol acyltransferase [rLCAT], cholesteryl ester transfer protein [CETP] antagonists, torcetrapib, dalcetrapib and evacetrapib) should be evaluated. Strategies aiming at the lowering of uremic toxins, such as indoxyl sulfate and p-cresyl sulfate, by using intestinal probiotics may also prove interesting [96]. No data on the effect of galectin targeting in dialysis are available. The only reported experience is a trial developed by La Jolla Pharmaceutical Company in patients with chronic kidney disease stage 3b, treated with a complex polysaccharide (GCS-100), which binds to GAL-3 inhibiting profibrotic effects. A reduction in GFR decline was observed (see ASN 2014 abstract book). Also rGAL-1 which, contrarily to GAL-3, may have immunomodulatory and anti-inflammatory properties may be considered for use in this context [97]. Cell therapy may play an important role in the next clinical trials. Tregs have a crucial role in maintaining immunological self-tolerance and in limiting the inflammatory response to immune reactions [98], possibly containing the aimless immunological activation in ESRD [98]. Finally, mesenchymal stem cells, which possess immunomodulatory properties, may be harnessed to reduce inflammation as shown in diabetes, transplantation, and diabetic nephropathy [99–103].

Conclusions

Inflammation is one of the pivotal causes of mortality and morbidity in ESRD patients. Targeting of inflammation will be necessary to reduce the devastating cardiovascular complications observed in ESRD patients. Unfortunately, this has not been adequately addressed thus far in this population, particularly in diabetic patients, who may benefit the most from these approaches [104].

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Disclosure Statement

The authors have no conflicts of interests to declare.

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