Pharmacologic Approaches Against Advanced Glycation End Products (AGEs) in Diabetic Cardiovascular Disease

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Context: Advanced Glycation End-Products (AGEs) are signaling proteins associated to several vascular and neurological complications in diabetic and non-diabetic patients. AGEs proved to be a marker of negative outcome in both diabetes management and surgical procedures in these patients. The reported role of AGEs prompted the development of pharmacological inhibitors of their effects, giving rise to a number of both preclinical and clinical studies. Clinical trials with anti-AGEs drugs have been gradually developed and this review aimed to summarize most relevant reports.

Evidence Acquisition: Evidence acquisition process was performed using PubMed and ClinicalTrials.gov with manually checked articles.

Results: Pharmacological approaches in humans include aminoguanidine, pyridoxamine, benfotiamine, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, statin, ALT-711 (alagebrium) and thiazolidinediones. The most recent promising anti-AGEs agents are statins, alagebrium and thiazolidinediones. The role of AGEs in disease and new compounds interfering with their effects are currently under investigation in preclinical settings and these newer anti-AGEs drugs would undergo clinical evaluation in the next years. Compounds with anti-AGEs activity but still not available for clinical scenarios are ALT-946, OPB-9195, tenilsetam, LR-90, TM2002, sRAGE and PEDF.

Conclusions: Despite most studies confirm the efficacy of these pharmacological approaches, other reports produced conflicting evidences; in almost any case, these drugs were well tolerated. At present, AGEs measurement has still not taken a precise role in clinical practice, but its relevance as a marker of disease has been widely shown; therefore, it is important for clinicians to understand the value of new cardiovascular risk factors. Findings from the current and future clinical trials may help in determining the role of AGEs and the benefits of anti-AGEs treatment in cardiovascular disease.

Keywords: Glycosylation End Products, Advanced; Diabetic Cardiomyopathies; Pimagedine; Pyridoxamine; Benphothiamine; Hydroxymethylglutaryl-CoA Reductase Inhibitors; Alagebrium; Thiazolidinediones

1. Context

Advanced Glycation End-Products (AGEs) are ubiquitous signaling proteins related with vascular and neurological complications of diabetes. They include various compounds formed by the Maillard reaction, which is a non-enzymatic glycation of free amino groups by sugars and aldehydes. AGE formation begins under hyperglycemic or oxidative stress conditions and is characterized by conversion of reversible Schiff-base adducts to covalently bound Amadori products, which undergo further rearrangements that terminate in the formation of irreversibly bound compounds known as AGEs (1). These reactions can be triggered by glucose-6-phosphate, glyceralde-hydes-3-phosphate, glyoxal (GO), methylglyoxal (MGO) and 3-deoxyglucosone (3DG) (2). AGEs serum levels have been associated to several vascular and neurological complications, especially in the cardiovascular field and a flourishing production of literature is pointing at AGEs as a marker of negative outcome in both diabetes management and surgical procedures on these patients (3, 4). Detection and measurement techniques for AGEs have been gradually improved over the past 10 years starting from antibody and immune-based methods to the new readily available skin auto fluorescence techniques, which hold a promise for future bedside management of patients with diabetes (5). The reported role of AGEs in vascular complications of diabetes and cardiovascu-

lar disease also prompted the development of pharmacological inhibitors of their effects, giving rise to many experimental activities and a number of both preclinical and clinical studies. Although most studies confirm the usefulness of these pharmacological approaches, other reports produced contradictory findings. This review aimed to summarize most relevant issues in anti-AGE treatment, considering clinical experience in cardiovascular disease and discuss the potential benefits inhering their use in the clinical side.

1.1. AGEs Pathophysiology and Mechanisms of Action

AGEs damage cells and tissues through different mechanisms: intracellular glycation of proteins, which leads to impaired cell function; binding of circulating AGEs to cellular receptors, with activation of signal transduction cascade and alteration of genes expression; accumulation of AGEs in the extracellular matrix, which results in cross-linking and diminished vessels compliance.

1.1.1. Intracellular Glycation of Protein

Under high-glucose level conditions in endothelial cells, basic fibroblast growth factor (bFGF) undergoes increased glycation resulting in reduced mitogenic activity (6). Intracellular AGE formation reduces the expression of endothelial NO synthase (eNOS) and inactivates nitric oxide (NO); this explains the imparted vasodilatory response that occurs in diabetes (7). In diabetic rats, MGO-induced modifications of mitochondrial proteins were associated with increased superoxide formation in mitochondria (8). Furthermore, MGO modifies glutathione reductase and glutathione peroxidase, resulting in increased oxidative stress (9). MGO also impairs proteasome function (10) and alters overall cellular function (11).

1.1.2 Binding of Circulating AGEs to Cellular Receptors

After diffusion from the cell, circulating AGEs can bind to receptors on different cells, with activation of signaling pathways. Numerous AGE-binding proteins have been identified, such as macrophage scavenger receptors, AGE-R1, AGE-R2 and RAGE (12). The most studied receptor for AGEs is RAGE, a member of the immunoglobulin superfamily expressed in most tissues (13). Apart from AGEs, other ligands for RAGE include members of the S100/calgranulin family and high-mobility group box-1 (14). AGEs binding to RAGE induces signaling pathways of mitogen-activated protein kinases (MAPK) (15), cdc42/rac and Jak/STAT (16), which modulate expression of genes for endothelin-1, vascular cell adhesion molecule 1 (VCAM-1), E-selectin, vascular endothelial growth factor (VEGF), inflammatory cytokines and others (17). RAGE expression is down regulated by peroxisome proliferator-activated receptor

gamma (PPARγ) activation (18). Activation of AGE–RAGE axis increases self-expression of RAGE and NFkB-p65, which leads to a continuation and amplification of the signaling pathways and inflammation (19). Studies on diabetic mice confirmed the role of RAGE in the development of vascular alterations (20). The AGE–RAGE interaction determines a proliferation and activation of smooth muscle cell via angiotensin-2 pathway, with a possible explanation for accelerated atherosclerosis in diabetes (21).

1.1.3 Accumulation of AGEs in the Extracellular Matrix

AGE-RAGE activation increases transforming growth factor beta-1 (TGF-β1) levels, with enhanced activity of matrix metalloproteinase 2 (MMP-2); on the other hand, RAGE signaling promotes MMP-9 activity. These factors determine alterations in collagen IV turnover (22). Extra-cellular matrix (ECM) is highly susceptible for glycation because of its slow turnover rate, and AGE accumulation is responsible for the formation of cross-links (23), with subsequent mechanical alterations (24) leading to decreased elasticity and increased stiffness of vessels (25) and myocardium (26), increased thickness, narrowing of the vessel lumen (27), development of glomerular sclerosis and atherosclerosis. AGE formation in ECM also interferes with matrix–cell interactions, with alterations in signaling and adhesion; these may be an important initial event in diabetic microangiopathy (28). AGE production induces apoptosis in macrophages followed by the osteogenic differentiation of aortic smooth muscle cells, resulting in atherosclerotic vascular calcifications (29).

1.2. AGEs in Cardiovascular Disease

AGEs have been shown to induce inflammation and intracellular Reactive Oxygen Species (ROS), which leads to the expression of many atherosclerosis-related genes, including VEGF (30). AGE increases the levels of Low-Density Lipoprotein (LDL) through a reduction in its plasma clearance, contributing to atherosclerosis (31). Elevated serum AGEs were found in patients with coronary artery disease (32) and associated with aortic stiffness and correlated with disease severity (33). AGE deposits have been found in atherosclerotic plaques and within myocardium fibers (34, 35). Serum levels of AGEs are associated with markers of left ventricular diastolic dysfunction (36). Furthermore, AGE levels are higher in case of peripheral artery disease in patients with diabetes (3). Receptors for AGEs (RAGE) have been found to be overexpressed in carotid artery explants, as the vulnerable area of the plaque and have been related with inflammatory reactions (37). The soluble form of the extracellular domain of RAGE is known as sRAGE, which is able to prevent AGE-RAGE interaction, thus blocking the signal transduction pathway ultimately leading to cellular damage (38). AGEs also provide prog-

nostic information about operative outcome and success rate of interventions in cardiovascular disease. In patients with diabetes undergoing percutaneous coronary intervention (PCI) with balloon angioplasty or bare-metal stent (BMS) implantation, elevated levels of serum AGEs were a risk factor for development of intra-stent restenosis (39). The prospective ARMYDA-AGEs Study (40) showed that in patients with diabetes on optimized glycemic control who underwent PCI with drug-eluting stent (DES) implantation, high AGEs levels in plasma were an independent predictor of intra-stent restenosis and stent lumen loss at six months. Thus, AGE levels represent a valuable marker of adverse outcome after PCI (41). Plasmatic AGE levels can predict heart failure and new cardiac events (42, 43) and proved to be better than HbA1C measurements in predicting the progression of diabetic complication (44). In patients with diabetes, with HbA1C < 6.0% and without clinically relevant complications, serum levels of AGEs were higher in comparison to a control normoglycemic cohort with comparable HbA1C and determine a prothrombotic state, which might explain the increased rate of vein graft failure after surgical myocardial revascularization (45). In fact, AGEs activated RAGE expression, inhibited PPARγ expression, enhanced intracellular ROS formation and increased neutrophil-endothelial adhesion. AGE levels were proved to be associated with poor outcome and adverse events in patients after cardiac surgery; AGEs were also related with prolonged intubations and long hospitalization in Intensive Care Unit (46). Increased serum levels of AGEs, as well as skin tissue values (47), can predict total and cardiovascular mortality in patients with diabetes during a long term follow-up (4).

2. Evidence Acquisition

Evidence acquisition process was performed on PubMed (www.ncbi.nlm.nih.gov/pubmed) and Clinical-Trials.gov. Search terms included "AGEs, advanced glycation end products, cardiovascular disease, cardiac, diabetes, drugs", with manually checked articles.

3. Results

A number of drugs had been developed to interfere with the glycation pathway. Despite most of them are solely used in preclinical settings, some are approved for human treatment. Albeit a detailed discussion of the mechanism of actions and preclinical findings of these compounds exceeds the purpose of this review, a schematic description of each anti-AGEs compound is provided in Table 1. Results of human clinical trials with inherent each compound would be described in details below and are summarized in Table 2.

Table 1. Anti-AGEs Compounds [a]

Drug	Mechanism of Anti-AGEs Activity
Aminoguanidine	Post-Amadori inhibitor by trapping dicarbonyl intermediates, NOS inhibitor
Pyridoxamine	Prevents the transformation of protein-Amadori intermediates to protein-AGE products, post-Amadori inhibitor by trapping carbonyl intermediates
Benfotiamine	Post-Amadori inhibitor by trapping dicarbonyl intermediates
ACEIs	Pre-Amadori and post-Amadori inhibitor, transition metal ion chelator
ARBs	Agonist of PPARγ
Statins	Stimulate RAGE shedding
Alagebrium (ALT-711)	Breaks carbon-carbon bonds between carbonyls ("AGE-breaker")
TZDs	Agonist of PPARγ, Reduces RAGE Expression
ALT-946 [b]	Post-Amadori inhibitor by trapping dicarbonyl intermediates, NOS inhibitor
OPB-9195 [b]	Post-Amadori inhibitor by trapping dicarbonyl intermediates, agonist of PPARγ
Tenilsetam [b]	Post-Amadori inhibitor by trapping dicarbonyl intermediates, transition metal ion chelator
LR-90 [b]	Post-Amadori inhibitor by trapping dicarbonyl intermediates, transition metal ion chelator
TM2002 [b]	Transition metal ion chelator
sRAGE [b]	Prevents AGE binding to RAGE
PEDF [b]	Serine-protease inhibitor which reduces AGE-RAGE signal transduction, activation of PPARγ signal transduction

[a] Abbreviations: ACEIs: Angiotensin Converting Enzyme Inhibitors. ARBs: Angiotensin Receptor Blockers. NOS: Nitric Oxide Synthase. TZDs: Thiazolidinediones.
[b] No human data with this agent has been published.

Table 2. Summary of Clinical Trials About Compounds Interfering With the Glycation Pathway [a]

Study	Type	Drug	Cohort	Duration of Treatment	Effect of Anti-AGEs Drug
ACTION (2004) (48)	R, DB, PC	aminoguanidine	690 T1DM	2-4 years	No beneficial effects in progression of overt nephropathy. Modest attenuation of complications of diabetes mellitus
ACTION-2 (1999) (49)	R, DB, PC, M	aminoguanidine	599 T2DM	Not Available	Unpublished data. Study discontinued due to lack of efficacy and safety concerns
Williams et al. (2007) (50)	R, DB, PC, M	pyridoxamine	212 T1/2DM	6 months	Beneficial reduction from baseline in serum creatinine
Stirban et al. (2006) (53)	O	benfotiamine	13 T2DM	3 days	Beneficial reduction in AGE levels and markers of oxidative stress
Rabbani et al. (2009) (54)	R, PC	thiamine	40 T2DM	3 months	Beneficial reduction in urinary albumin excretion
Fraser et al. (2012) (57)	R, DB, PC	benfotiamine	67 T1DM	2 years	No changes in peripheral nerve function or inflammatory markers
Alkhalaf et al. (2010) (55)	R, DB, PC	benfotiamine	82 T2DM	3 months	No changes in 24 h urinary albumin excretion or injury molecules
Alkhalaf et al. (2012) (56)	R, DB, PC	benfotiamine	82 T2DM	3 months	No changes in plasma or urinary AGEs. No changes in plasma markers of endothelial dysfunction and inflammation. No clinical benefit
Sebekova et al. (2003) (58)	PC	ramipril	29 T2DM	2 months	Reduced fluorescent AGEs. Reduction in blood pressure and proteinuria. No changes in creatinine clearance
Komiya et al. (2008) (59)	O	valsartan	15 T2DM	1 year	Reduced AGEs levels. No changes in oxidative markers. Decline in microalbumin levels in urine not statistically significant. No changes in carotid artery intima-media thickness
Ono et al. (2013) (60)	O	candesartan	25 T2DM	3 months	Reduced urinary excretion of AGEs and albumin
Saha et al. (2010) (61)	PC	candesartan	32 T2DM	3 months	Reduction in CML. Slightly increase in creatinine clearance
Scharnagl et al. (2007) (62)	R, DB, PC, M	cerivastatin	69 IGT/DM	3 months	Beneficial reduction in AGE, cholesterol, apoB and LDL levels
Cuccurullo et al. (2006) (63)	R, O	simvastatin	70 T2DM	4 months	Beneficial reduction in carotid plaque RAGE expression through diminished AGE generation. Might cause plaque stabilization by inhibiting PGE2-dependent MMP, responsible for plaque rupture
Nakamura et al. (2010) (64)	O	atorvastatin	10 CKD	1 year	Reduction from baseline in proteinuria and AGEs levels. No changes in glomerular filtration rate
Kass et al. (2001) (26)	R, DB, PC M	alagebrium	93 SH	2 months	Beneficial increment in total arterial compliance, beneficial diminished arterial pulse pressure. No effects on systemic arterial resistance, cardiac output and heart rate
Little et al. (2005) (65)	O	alagebrium	23 diastolic HF	4 months	Beneficial decrease in left ventricular mass. Beneficial increase in left ventricular diastolic filling and quality of life
Zieman et al. (2007) (66)	DB	alagebrium	13 SH	2.5 months	Beneficial increase in arterial endothelial function. Might reduce arterial stiffness and vascular remodeling
BENEFICIAL (2010) (67)	R, DB, PC	alagebrium	102 systolic HF	9 months	No changes in exercise tolerance, diastolic and systolic function, AGE accumulation, NT-pro-BNP and NYHA functional class
Oudegeest-Sander et al. (2013) (69)	R, DB, PC	alagebrium	48 sedentary life	1 year	No changes in vascular function. Lack in potentiating the effect of exercise training
Fujimoto et al. (2013) (70)	R, DB, PC	alagebrium	62 sedentary life	1 year	No changes in hemodynamic, left ventricular geometry, exercise capacity. Might have favorable effect in age-related left ventricular stiffening
Oz Gui et al. (2010) (71)	R, PC	pioglitazone	62 T2DM	3 months	Increase in sRAGE levels
Gada et al. (2013) (72)	R, PC	rosiglitazone	111 T2DM	6 months	Increase in sRAGE levels. Reduction in other 3 protective markers indicating a negative effect
PioRAGE (2014) (38)	R, PC	pioglitazone	63 T2DM	6 months	Reduced RAGE and increased sRAGE expression

[a] Abbreviations: CKD: Chronic Kidney Disease. DB: Double Blinded. DM: Diabetes Mellitus. HF: Heart Failure. IGT: Impaired Glucose Tolerance. M: Multicentric. MMP: Matrix Metalloproteinase. O: Open. PC: Placebo-Controlled. R: Randomized. SH: Systolic Hypertension.

3.1. Aminoguanidine (Pimagedine)

ACTION trial evaluated the safety and efficacy of amino-guanidine regarding the rate of progression of diabetic nephropathy. Overall, 690 patients with type-1 diabetes with known diagnosis of nephropathy and retinopathy were enrolled. After 2-4 years, aminoguanidine therapy was successful in reducing 24-hour proteinuria and in preventing the decrease in glomerular filtration rate. On the other hand, the effect on serum creatinine levels was not significant. Moreover, a minority of patients treated with aminoguanidine, in comparison with controls, experienced a progression of retinopathy. Overall, this study demonstrated that inhibiting AGEs production can result in a clinically significant attenuation of diabetes complications (48). ACTION II compared aminoguanidine with placebo on the progression of renal disease in 599 patients with type-2 diabetes and nephropathy. Side effects in high dose arm of the study, such as flu-like symptoms, hepatic abnormalities, gastrointestinal disturbances and anemia, caused an early discontinuation of this study, which failed to prove a role for aminoguanidine (49).

3.2. Pyridoxamine

Pyridoxamine reduced change from baseline in serum creatinine and urinary TGFβ1 excretion after a 6-month treatment in 212 patients with diabetes and nephropathy (50). A study reported an accelerated decline in renal function in case of vitamin B6, B9 and B12 cotherapy (51), but vitamin B6 is unlikely to be the cause (52), and thus pyridoxamine treatment seems to be safe.

3.3. Benfotiamine

Benfotiamine, proved to prevent endothelial dysfunction and oxidative stress in patients with diabetes receiving a meal rich in AGEs (53). In 40 type-2 diabetic patients with microalbuminuria, thiamine administration for three months determined a regression in urinary albumin excretion (UAE) (54). Conversely, a study performed in 2010 on 82 patients with diabetes and advanced renal disease treated with benfotiamine or placebo for three months failed to reduce UAE (55). The same group in 2012 proved that in 82 patients with type-2 diabetes, benfotiamine treatment for three months did not reduce plasma or urinary AGEs, markers of endothelial dysfunction and inflammation; hyperglycemia-induced vascular complications were not clinically improved (56). In 67 patients with diabetes and neuropathy, benfotiamine administration for two years did not significantly improve peripheral nerve function or reduced markers of inflammation (57).

3.4. Angiotensin Converting Enzyme Inhibitors

In 2003, a study enrolled 29 patients, 12 of which had diabetes and treated with ramipril, to evaluate its effect on AGEs formation and oxidative stress. After two months, ramipril reduced blood pressure, proteinuria and fluorescent AGEs, despite unchanged creatinine clearance and N (ε)-carboxy-methyl-lysine (CML) concentration (58).

3.5. Angiotensin Receptor Blockers

In 2008, 15 patients with diabetes and hypertension were treated with valsartan to study its effect on AGEs. At one year follow-up, a significant decrease in AGEs levels was demonstrated. However, there were no changes in oxidative markers and in carotid artery intima-media thickness, and the decline in urinary microalbumin levels was not statistically significant (59). Another study demonstrated that in 25 patients with diabetes and hypertension treated with candesartan for three months, urinary excretion of AGEs and albumin were reduced compared to baseline (60). In 2010, 32 patients, 11 of which diabetics with significant proteinuria, were treated with candesartan for three months, observing a reduction in CML and a slightly increase in creatinine clearance (61).

3.6. Statin

A study examined the effect of cerivastatin on serum concentration of AGEs in 69 patients with diabetes or pre-diabetes (62). After a 3-month treatment, cerivastatin improved lipids profile and decreased CML levels. Another study considered atherosclerotic plaques and the effect of statin treatment on their expression of RAGE and destabilizing genes; simvastatin was administered in 70 patients for four months before carotid endarterectomy and intraoperative samples examination concluded that simvastatin inhibits RAGE expression through a decrease in myeloperoxidase-dependent AGE production. In addition, an inhibition of matrix metalloproteases was reported, thus contributing to plaque stabilization through reduced inflammation (63). In another study on 10 patients with dyslipidemia and chronic kidney disease without diabetes treated with atorvastatin, atorvastatin treatment for one year determined a reduction in proteinuria and AGEs levels, though not affecting glomerular filtration rate (64).

3.7. ALT-711 (Alagebrium)

Alagebrium has been extensively investigated in a number of clinical trials, sponsored by Synvista Therapeutics from 2002 to 2010 (DIAMOND (NCT00043836), SAPPHIRE (NCT00045981), SILVER (NCT00045994), SPECTRA (NCT00089713), BREAK-DHF-I (NCT00662116) and BENEFICIAL (NCT00516646). However, few data had been officially published, and some of these studies had been terminated early due to financial constraints. In 2001, a pilot study enrolled 93 patients with hypertension randomized to placebo or alagebrium. After two months, patients in the treatment arm experienced a decrease in arterial pulse pressure with a concomitant increase in

vessel compliance (26). In 23 patients with diastolic heart failure, alagebrium administration for four months determined a decrease in left ventricular mass and improvements in diastolic filling (65). Another small study considered 13 patients with hypertension, treated for 10 weeks and concluded that alagebrium enhanced endothelial function and might play a role in reducing arterial remodeling (66). However, the BENEFICIAL trial (67) enrolling 102 patients with systolic heart failure, showed that alagebrium, despite being well tolerated, did not improve exercise tolerance, diastolic or systolic function, AGE accumulation, N-terminal of the prohormone brain natriuretic peptide (NT-proBNP) level or New York Heart Association (NYHA) class after 9-month treatment (68). A recent study (69) enrolled 48 healthy individuals with sedentary life, who were randomized into four groups; training + alagebrium, training + placebo, no training + alagebrium and no training + placebo. After one year of treatment, endothelial function and arterial stiffness did not change and alagebrium treatment had no independent or synergic effect on vascular function. Another study (70) randomized 62 healthy individuals into four groups in a similar way and subjects underwent heart catheterization to define hemodynamic. After one year of treatment, alagebrium had no effect on hemodynamics, left ventricular shape or exercise capacity, but improved left ventricular stiffness.

3.8. Thiazolidinediones

Thiazolidinediones, known as oral and well-tolerated drugs for diabetes, proved to have a role in anti-AGE treatment because of their PPARγ-agonist activity, which determines an increase in sRAGE expression, which is inversely associated with atherosclerosis. A study conducted in 2010 (71) on 62 patients with diabetes who received pioglitazone, rosiglitazone or placebo showed that pioglitazone but not rosiglitazone was able to significantly raise sRAGE at 12 weeks follow-up. However, another randomized placebo-controlled study conducted in 2013 (72) enrolling 111 patients with type-2 diabetes and at high risk of coronary heart disease, tested the effects of rosiglitazone after six months of treatment. Level of sRAGE were augmented, together with high-sensitivity C-reactive protein (hsCRP) indicating a protective effect on inflammation. PioRAGE trial (38) involved 63 patients with type-2 diabetes, randomly assigned to pioglitazone or glimepiride. After a follow-up of 24 weeks, pioglitazone could suppress RAGE expression and increase plasma levels of sRAGE, independently on glycaemia effect or insulin resistance index.

4. Conclusions

Considering the overall results of these studies, anti-AGEs drugs would be an attractive clinical option in the near future. The apparent lack of benefits in some trials might be related to the small sample size or the short follow-up period. In addition, there is no general agreement or evidences about the dose for each drug, which differs among various studies; this mined the possibility to perform a reliable comparison. We reliably speculate that some discordant results might have conspired against widespread use of these agents. However, considering many preclinical studies on the role of AGEs as both a marker and a cause of disease and on new compounds interfering with their effects, we might expect a forthcoming production of clinical evaluation of new anti-AGEs drugs. The most recent promising anti-AGEs agents are statins, alagebrium and thiazolidinediones even if remains unclear which patients would benefit more. Another point emerging is that AGEs measurement has still not taken a pivotal and widespread role in clinical practice. It is important for clinicians to critically appraise the value of new cardiovascular risk factors. Diabetes mellitus remains a major determinant for prognosis, but using exclusively glycaemia and glycated hemoglobin to assess the state, prognosis or outcome of patients with diabetes is not appropriate anymore. AGE levels add new information for the development and progression of cardiovascular disease in both diabetic and non-diabetic patients, because AGE accumulation occurs before than glycated hemoglobin and more closely correlates with the severity of the disease, predicting the development of cardiovascular complications. A variety of interventions against AGE accumulation, predominantly tested in preclinical contexts, appear to show beneficial effects on the development of diabetic complications and cardiovascular diseases. Findings from the current and future clinical trials may help in determining optimal therapeutic target of AGEs in cardiovascular disease.

Authors' Contributions

1- Study concept and design: Cristiano Spadaccio. 2- Acquisition of data: Antonio Nenna, Sanjeet Singh Avtaar Singh. 3- Analysis and interpretation of data: Antonio Nenna, Francesco Nappi. 4- Drafting of the manuscript: Antonio Nenna, Sanjeet Singh Avtaar Singh, Cristiano Spadaccio. 5- Critical revision of the manuscript for important intellectual content: Francesco Nappi, Fabio Di Domenico, Fraser W Sutherland. 6- Statistical analysis: Antonio Nenna. 7- Administrative, technical and material supports: Massimo Chello, Fraser W. Sutherland. 8- Study supervision: Cristiano Spadaccio, Massimo Chello.

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