Research Article

Interventional Cardiology

Novel evidence of the role of oxidative stress, its implication in the evolution of heart failure and atrial fibrillation and possible therapeutic targets. Literature review and meta-analysis

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Received date: 01-Dec-2024, Manuscript No. FMIC-24-157468;
Editor assigned: 03-Dec-2024, PreQC No. FMIC-24-157468 (PQ);
Reviewed date: 17-Dec-2024, QC No. FMIC-24-157468;
Revised date: 23-Dec-2024, Manuscript No. FMIC-24-157468 (R);
Published date: 30-Dec-2024, DOI: 10.37532/1755-5310.2024.16(6).945

Abstract

The onset, progression and manifestation of heart failure, atrial fibrillation and other cardiovascular diseases because of the oxidative stress has been recently widely described. Normal equilibrium and homeostasis between specific oxidative pathways and antioxidant production is agitated. An increase of reactive oxygen species such as Nicotinamide Adenine Dinucleotide Phosphate (NADPH) oxidase, Superoxide Dismutase (SOD), Glutathione Peroxidase (GPx), myeloperoxidase and other ROS are majorly produced, thus antioxidant capacity and its scavenging properties are decreased. Implication of disturbed ROS/antioxidant balance is the key to understand the pathophysiological effects in the onset, progression and manifestation of cardiovascular diseases. In this review we will discuss about the pathophysiological effect of elevated ROS production in heart failure and atrial fibrillation, describing also therapeutic aspects and options in case of elevated oxidative stress status.

Keywords: Oxidative stress • Heart failure • Atrial fibrillation • Antioxidants

Introduction

Worldwide leading cause of morbidity and mortality are cardiovascular diseases, becoming a major health, social and economic burden, contributing in 16% of the world's total deaths [1].

More than 4 million Europeans die every year from Cardiovascular Disease (CVD), accounting for 45% of all deaths [2], while in the US data collected from 2019 to 2020 revealed that deaths from cardiovascular diseases remain at the first place with 696,962 deaths, or 20.6% of the total death for the period 2019-2020 [3]. In North Macedonia in 2017, 11,172 people died from cardiovascular diseases with a mortality rate of 538.5 per 100,000 inhabitants. CVD account for 55.0% of total mortality and are in first place in the structure of causes of death [4].

A lot of clinical and experimental studies have shown the negative effect of inflammation in the onset of cardiovascular diseases. During inflammatory response, leukocytes and mast cells induce a "respiratory burst," releasing ROS and inflammatory mediators such as cytokines and chemokines, which, in turn, promote further Reactive Oxygen Species (ROS) release in the damaged area, contributing in the imbalance of the redox system. New data indicate that mitochondria within cardiomyocytes contribute to age-related increased ROS generation which is associated with aging-associated cardiac diseases [5].

Oxidative Stress (OS) is defined as an event where transient or lasting disruption in the oxidative/antioxidant equilibrium state [6], implicating physiological sequela within the cell and other biological compartments.

But, are ROS needless? Of course not. They are very important in physiological conditions and for the normal cell homeostasis and many components of signaling pathways appear to be susceptible to modulation by ROS participating in signal transduction systems regulating different conditions such as initiation and progression of atherosclerotic plaque, hypertrophy, fibrosis myocardial growth, proliferation or apoptosis (depending upon the OS level) and cardiomyocyte necrosis [7]. Modulation of cell signaling and signal transduction by ROS might be indirectly via formation of new signaling molecules or proteins.

Materials and Methods

Despite the enormous scientific data about the role of ROS and the associated redox mechanisms of the disease inception, evolution and progression remain elusive. Therefore, uncovering the control mechanisms of how intimate molecular regulation of the delicate balance of ROS formation occurs and opposing this process in the endothelium is a prerequisite for the discovery and implementation of novel antioxidant formula.

Objective

This review of literature aims to demonstrate the physiological and pathological effects of ROS in terms of initiation, contribution and progression of atherosclerotic plaques, heart failure and essential hypertension. We are also concentrated in showing up the evidence which stands behind rationale of antioxidant therapy and its impact on overall cardiovascular health. Although there is a lot of evidence in this topic, we consider that a lot of things are left unsaid and not properly treated.

Methodology

This literature review and meta-analysis was conducted in accordance with guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

The process of comprehensive literature research included 312 articles, from which 108 were excluded because of duplication, and 204 were excluded based on the titles or abstracts. The remaining 77 articles were further assessed by evaluating the full-text manually and two web sites also were used for its statistical importance.

When multiple RCTs were derived from the same patient cohorts, only the trial with a larger sample size and more comprehensive data were included. Since all analyses were conducted using previously published studies, ethical approval and patient consent were not required. Discrepancies in study search, selection, data extraction and quality, were resolved in accordance with a third independent reviewer, and unique statement of the three authors was respected as a final conclusion (Figure 1).

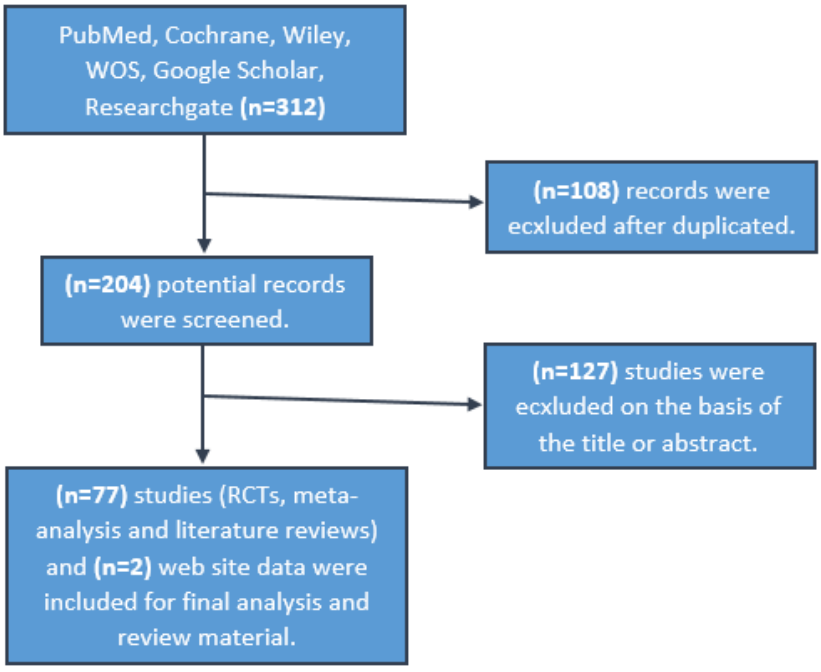

Figure 1: Meta-analysis was performed using RevMan 5 software.

Results and Discussion

Three younger investigators independently surfed through PubMed, Cochrane, Wiley, Web of Science, Google Scholar and Researchgate, 6 months in total. Terms like: Heart failure, atrial fibrillation, oxidative stress, antioxidants, randomized controlled trial and free full-text were used.

The reference lists of included studies and relevant reviews were manually searched to avoid missing relevant studies. Conference abstracts, expert opinion and case reports were not included.

Meta-analysis was performed using RevMan 5 software (version 5.4 Cochrane Collaboration, Copenhagen, Denmark), employing a random-effects model to account for potential heterogeneity among studies. Dichotomous outcomes were analyzed using Odds Ratios (OR) with 95% confidence intervals, while continuous outcomes were assessed using Mean Differences (MD) or Standardized Mean Differences (SMD). Heterogeneity was evaluated using Cochran's Q test and the I^2 statistic, guiding the choice of subgroup and sensitivity analyses. Forest plots were generated to display individual study results and the pooled effect size, providing a visual summary of findings.

Oxidative stress and heart failure

Heart failure (HF) is a condition in which the heart is unable to pump enough blood to meet the body's needs and is the leading cause of morbidity and mortality [8]. Experimental data suggest that oxidative stress and inflammation play a role in the pathogenesis of HF, and a lot of scientific research in humans is going on, aiming to get a closer insight into the impact of oxidative stress in the pathophysiology of the HF, with the ultimate goal of clarification and building new perspectives in the medical treatment and socio-economic care of heart failure patients.

Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS) are produced by mitochondria and play an important role when generated in physiological amounts, in the process of signaling functions in the healthy and homeostatic state of the healthy cardiomyocyte. Excessive amounts of ROS/RNS because of mitochondrial dysfunction is the key that opens the gates of oxidative stress, contributing in the disharmony of the heart muscle environment by damaging healthy cardiomyocytes [9]. Numerous factors that lead to mitochondrial dysfunction and respective consequences can be listed and are presented (Figure 2).

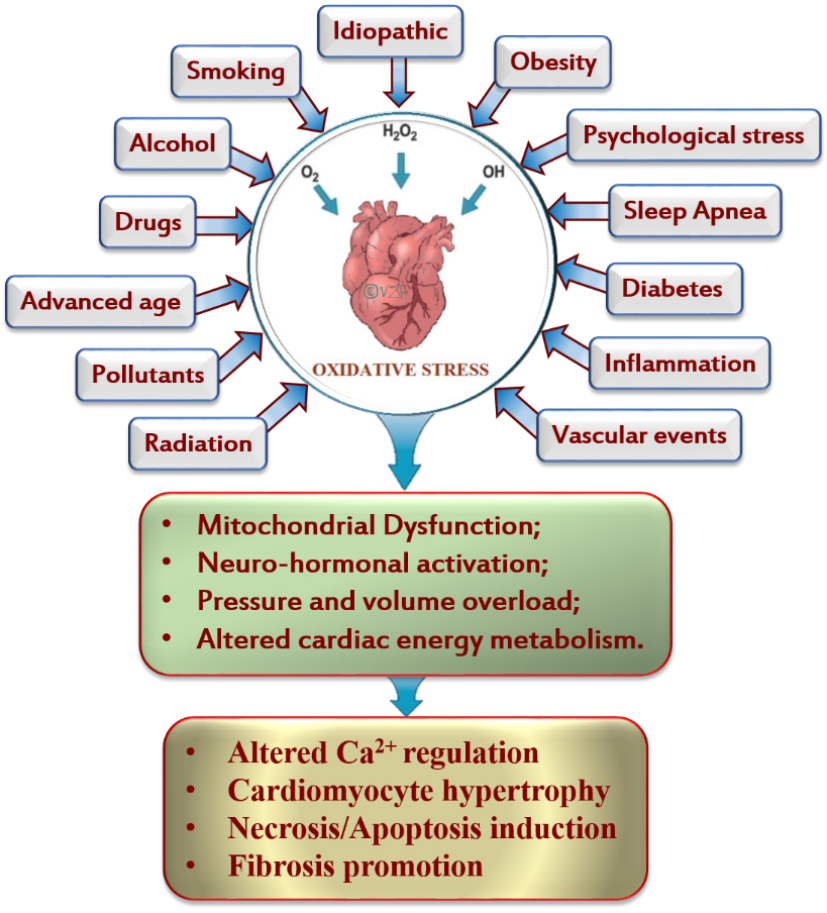

Figure 2: Factors that contribute in elevated oxidative stress status and its impact in the development of heart failure.

Whether the patient will develop Heart Failure with reduced Ejection Fraction (HFrEF) or Heart Failure with preserved Ejection Fraction (HFpEF), in a study conducted by Aimo et al., is showed that in HFrEF mitochondrial dysfunction in the myocardium, driven by increased neurohormonal stimul-ation, may be the most important source of oxidative stress [10]. In addition, the upregulation of oxidative enzymes (e.g. nicotin-amide adenine dinucleotide phos-phate oxidase) and uncoupling of nitric oxide synthase may contri-bute to the increased oxidative burden [11].

Homeostasis disorders induced by elevated oxidative stress causes cardiomyocyte damage (apoptosis/necrosis or fibrosis) and contribute into the patho-physiology of maladaptive remodeling, systolic dysfunction and occurrence of cardiac arrhythmias (through either focal triggered activity or re-entrant circuits) in patients with HFrEF [12].

In patients with HFpEF contrary to HFrEF patients, factors that can lead to chronic systemic inflammation and elevated oxidative stress status is associated with comorbidities like: diabetes, obesity, hypertension, Chronic Obstructive Pulmonary Disease (COPD), sleep apnea and other lifestyle factors that impact the quality of life in this group of patients. These factors can cause microvascular endothelial dysfunction in the myocardium, which promotes the development of cardiomyocyte hypertrophy and interstitial fibrosis in HFpEF [13].

Altered Ca^{2+} homeostasis followed by contractile dysfunction is a state which occurs when elevated ROS/RNS levels alter ryanodine receptor 2 (RyR2) activity, resulting with depletion of sarcoplasmic reticulum Ca^{2+} stores and cytoplasmic Ca^{2+} transients, leading to impairing contractile force generation [14]. ROS may also impair diastolic function through disulphide bridge formation within the cardiac specific N2B-segment of titin, a cytoskeletal protein representing the main determinant of muscle stiffness [15].

Cardiomyocyte hypertrophy is another pathophysiological change of the myocardium, mediated by elevated OS stress status which modulates several signaling pathways. NOX activity is increased during chronic pressure overload, and biomechanical stress may induce hypertrophy in cultured cardiomyocytes through ROS-dependent regulation of signaling pathways that activate extracellular signal-regulated kinases ½ [16-20]. But, in this case there are some conflicting paradox data because ROS can activate hypoxia-inducible factor 1, resulting in a paracrine secretion of Vascular Endothelial Growth Factor (VEGF) from cardiomyocytes which has in the other side protective function, essential in preserving contractile function, even though elevated OS status is followed by detrimental effect on cardiomyocytes and can impede such compartmentalization.

Cardiomyocyte apoptosis/necrosis is another fundamental and capital deterioration of cardiomyocyte life, impacted by hyper production of reactive oxygen and nitrogen species. The programmed cell death is activated by two pathways, the intrinsic and the extrinsic pathway. The intrinsic pathway is induced by B-Cell Lymphoma 2 (Bcl-2) by increasing outer membrane permeabilization, while the intrinsic pathway is induced by Tumor Necrosis Factor-α (TNF α), both pathways are modulated by ROS.

Cardiac fibrosis can be triggered by either direct heart damage or by pressure overload, involving interaction between several cytokines, cell types, growth factors and hormones, leading to matrix remodeling and collagen deposition. ROS activate Tissue Growth Factor-b (TGFb), which plays a central role in the development of fibrosis by inducing the differ-entiation of fibroblasts into myofibroblasts. Excessive collagen deposition determine a structural modification of the extracellular myocardial environment which dramatically contributes to the progression to heart failure.

From the range of analyzes that are done to determine increased levels of oxidative stress are: Isoprostanes, malondialdehyde, S-glutathionylation, oxidized phospholipids, nitrotyrosine, myeloperoxidase, oxidized low-density lipoprotein, gamma glutamyl transferase and oxidized nucleic acids (8-hydroxy-20-deoxyguanosine). Assessment of these biomarkers is relatively cheap and simple, but no reference intervals have been defined, which does not allow to measure the prevalence of oxidative stress in patients with heart failure.

Additionally, growth differentiation factor 15 is a promising predictor of outcome, while the prognostic value of other inflammatory biomarkers (such as adipokines or pentraxin-3) has not been extensively evaluated thus far.

Furthermore, evidence of the prognostic relevance of these biomarkers is currently extremely limited and further well-designed prospective randomized controlled trials need to be done to observe the real effect and impact of antioxidant therapies into the reduction of these biomarkers.

Oxidative stress and atrial fibrillation

Atrial Fibrillation (AF) is the most common sustained arrhythmia, poses significant health challenges to morbidity, mortality and healthcare costs, particularly as its prevalence rises with aging populations [21,22].

In this brief review we will explore the intricate relationship between Oxidative Stress (OS) and AF drawing on several critical studies to provide insights into pathophysiological mechanisms with a special focus on the role of ROS in:

- Electrical remodelling by shortening atrial action potential (promoting re-entrant arrhythmias);
- Structural changes in terms of atrial fibrosis (excessive collagen

deposition and fibroblast proliferation); and

- Modulated autonomic tone; offering a comprehensive understanding and potential therapeutic strategies especially antioxidant defences which play a pivotal role in AF pathogenesis [23,24].

Mitochondria are essential organelles within cells, primarly known for their role in energy production through oxidative phosphorylation. Beyond their bioenergetic functions, mitochondria are also pivotal in regulating cellular redox balance and generating ROS as byproducts of metabolic processes [25]. Dysfunctional electron transport chains within mitochondria lead to excessive ROS production, particularly in age-related AF [26]. Studies indicate that ROS generation from sources such as NADPH oxidases (NOX), mitochondria and uncoupled Nitric Oxide Synthases (uNOS) exacerbates OS by producing superoxide ($O2^{\bullet-}$) instead of Nitric Oxide (NO) leading to metabolic stress, impairing vascular function and energy deficits, thus contributing in structural abnormalities of atrial myocytes, remodelling the atrium and cause electrophysiological changes (delayed afterdepolarizations) [27,28]. Additionally, toxicised Ryanodine Receptors (RyR2) by OS results in calcium leaks and, inducing electrical remodelling by downregulating L-type calcium channels (ICaL), which shortens atrial Action Potential Duration (APD) and increases susceptibility to re-entry [29,30]. Potassium currents, such as IKur, are also attenuated by ROS-induced post-translational modifications, altering conduction velocity, changes which predispose the atria to re-entrance circuits perpetuating AF [31].

In a recent study conducted in 2024 by Pfenninger et al., were elaborated the molecular targets of ROS in AF and revealed that oxidative modifications of ion channels such as S-nitrosylation, alter channel function and conduction properties by promoting re-entrant arrhythmias [28].

ROS also activate pro-inflammatory and profibrootic pathways, notably involving Nuclear Factor-Kappa B (NF-κB) and Transforming Growth Factor-β (TGF-β) driving structural remodelling and atrial fibrosis, schematically presented in Figure 3 [32]. Also the activation of the NLRP-3 inflammasome, further links OS to inflammation in AF pathophysiology [33]. The inflammasome's activation leads to the release of interleukins IL-1β and IL-18, perpetuating the inflammatory cascade and contributing to the substrate for AF.

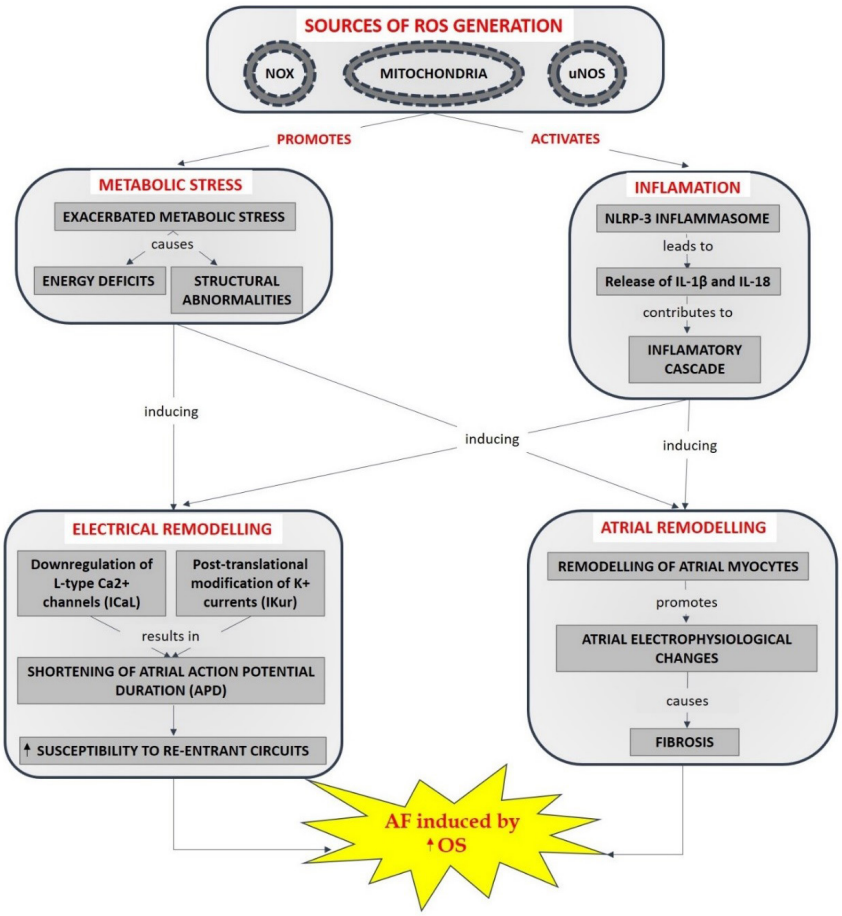

Figure 3: The interplay between OS and AF, highlighting four interconnected pathways culprit for all the consequences that lead to atrial fibrillation. **Note:** ROS: Reactive Oxygen Species; NOXL: NADPH oxidase; uNOS: Uncoupled Nitric Oxide Synthases; NLRP: Nucleotide-Binding Domain, Leucine-Rich–Containing Family, Pyrin Domain–Containing-3; IL: Interleukins.

The Autonomic Nervous System (ANS) is also blamed by intricately influencing AF pathophysiology. Abnormal autonomic innervation is associated with AF in both animal model and humans [34]. The autonomic imbalance-particularly sympathetic hyperactivity modulates atrial electrophysiology and promotes AF initiation [35]. OS exacerbates this imbalance by enhancing autonomic remodelling and increasing nerves sprouting in the atria, by secreting Nerve Growth Factor (NGF) [36]. Sympathetic neurotransmission involves norepinephrine, which interacts with adrenergic receptors on cardiomyocites, enhancing Ca^{2+} handling and promoting arrhythmogenesis. Cholinergic neurotransmission on the other hand involves acetylcholine, which activated muscarinic receptors, affecting ion channels and APD [37]. Autonomic tone can promote AF through enhanced automaticity Early and Delayed after Depolarizations (EADs, DADs). This interplay between ANS and OS suggests targeting autonomic pathways as a viable therapeutic avenue.

In clinical aspects it's an immense need that clinicians and researchers must shift focus toward understanding OS as a central driver of AF. The routine use of OS biomarker analysis in AF patients is underutilized or not used at all. OS markers such as Malondialdehyde (MDA), Glutathione Redox Potential (GRP), Carbonylated proteins, NOX2, NOX4, Hydrogen Peroxide, Nitrosyne, 8-isoprostane, Total Oxidative status [38-49]. Additionally oxidative DNA damage markers such as OHdG, have been identified in AF patients highlighting the systemic impact of oxidative stress on cellular integrity. Several biomarkers have been studied to quantify oxidative stress and its association with AF.

Notable examples include Derivatives of Reactive Oxidative Metabolites (DROMs), strongly associated with persistent AF and indicating increased oxidative damage and glutathione and cystine ratios (Eh GSH/Eh CySH), which correlate with AF severity and chronicity, while N-terminal pro-brain natriuretic peptide (NTpBNP), primarily a cardiac stress marker, is also influenced by oxidative stress and inflammation. Key biomarkers and their roles in AF are summarized in the Table 1.

By integrating OS markers into routine clinical practice and advancing therapies that counteract oxidative damage, we may unlock new pathways for preventing and managing this arrhythmia, ultimately improving patient outcomes. The clinician should appraise the potential for stratifying AF risk, tailoring patient-specific interventions and monitoring treatment efficacy.

Therapeutic aspects for coping heart failure and atrial fibrillation

HF and AF remain a complex and evolving challenge in the cardiovascular pathology, despite substantial advancements in traditional drug and device therapies. Especially these spectrum of pathologies are witnessing a trasnformative era driven by innovative treatments and emerging paradigms. Novel therapeutics agents, such as SGLT2 inhibitors and cutting edge molecular targets, are redefining standards of care, offering improved outcomes and hoper for patients. However, while there is a strong conceptual framework for antioxidant or anti-inflammatory strategies as adjunctive therapies to guideline-recommended drug and device therapy, antioxidants have been evaluated only in a few clinical trials, mostly yielding disappointing results. In this review we recapitulate current evidence on this topic in the setting of HF and AF.

Antioxidants and other therapies in HF

Extensive studies in the pre-clinical setting have shown highly prmosing results in targeting OS. As said above, the conventional antioxidant therapy highlight their limited efficacy, underscoring the need for novel approaches that focus on preventing ROS production or enhancing endogenous antioxidant defenses. In this context, enyzmes form the NADPH oxidase family, particularly those with NOX-1 or NOX-2 catalytic subunits, emerge as promising targets due to their pivotal role as major sources of ROS. Endogenous and synthetic antioxidants, such as ironchelating agents, N-acetyl-L-cysteine, apocynin, probucol, and edaravone, are useful in preventing CV injury and diseases [50]. Endogenous antioxidants in the myocardium include vitamins C and E, cysteine and the enzymes, SOD, catalase and glutathione peroxidase and in cases where events such as ischemia and hypoxia have compromised the cardiac cell's natural defense mechanisms, synthetic antioxidants have proved successful in protection against OS on reperfusion [51]. Targets for AO therapy include NADPH oxidase inhibitors such as Apocynin, which showed decreased levels of malondialdehyde and NADPH-oxidase activity induced in rat heart [52]. Edaravone, a free radical scavenger, inhibits vascular endothelial cell injury and ameliorates neuronal damage in ischemia, and provides modest cardiac protection in diabetes mellitus [53,54]. Evidence demonstrates that the optimal use of AO therapy in cardiac disease and injury is preventative and ameliorating. Avoiding smoking and maintaining a sufficient intake of fruits and vegetables, rich sources of AOs, evidently is important for CV health [55]. When needed, supplementation should be implemented. In addition to the mentioned antioxidants, many others exogenous and endogenous agents are available for cardioprotection, presented in Table 2. All this should be done because the aim is to: (1) supressing the sources of OS, (2) enhancing the body's natural antioxidant defenses, and (3) boosting antioxidant levels through supplementation with external antioxidants.

In the table above there are summarized mechanism through which various antioxidants mitigate OS, specifically in relation to HF but not only. It outlines the clinical outcomes observed with

each antioxidant, including improvements in endothelial function, reduced inflammation and decreased risk for propagating and worsening the outcomes of heart failure. The level of evidence supporting these effects is also presented.

Table 1: Biomarkers and their role in the AF.

Biomarker	Role in AF	Findings	Reference
IL-6, NF-α	Pro-inflammatory cytokines	Elevated in all AF types, linked to fibrosis	[27,33,38]
NTpBNP	Cardiac stress marker	Increased in persistent and permanent AF	[38,39]
8-OHdG	Oxidative DNA damage	Linked to AF progression and recurrence	[29,40,46]
DROMs	Reactive oxidative metabolites	Strongly associated with persistent AF	[41,42,43]
TOS	Oxidative stress index	Elevated in AF and predictive of risk	[44,45]
Oxidized Glutathione	Oxidative Stress marker	Increased AF risk	[28,47]
NOX2-derived peptides	Cellular producer of ROS	Persistent AF [20]	[28,29,45]
Malondialdehyde (MDA)	Marker of lipid peroxidation	Atrial fibrosis	[33,48]

Table 2: Role of different antioxidants in the outcome of HF.

Antioxidant	Action in Suppressing OS	Clinical Outcome	LE*	Citation
Vitamin E	Scavenges free radicals and protects cell membranes from oxidative damage, prevents LDL oxidation and reduces lipid peroxidation.	Improved cardiovascular health and reduced OS damage in specific population, consequently reducing the worsening effects of elevated OS.	B	[56]
Vitamin C	Neutralizes ROS and regenerates other antioxidants like vitamin E.	Improved immune function and response. Reduced risk for endothelial dysfunction thus contributing in the reduction of developing HF.	A	[57]
Selenium	A cofactor for GPx, reduces H2O2 and organic hydroperoxides.	Improved thyroid function by that improving the OS status and overall cardio-vascular wellbeing	C	[58]
Coenzyme Q-10	Participates in mitochondrial electron transport and scavenges free radicals.	Improved energy metabolism, reducing OS damage, contributing in improving cardiac function in HF and reduces hypertension (HTA).	B	[59]
N-Acetylcysteine (NAC)	Precursor to glutathione, scavenges free radicals, and enhances cellular antioxidant capacity.	Effective in reducing OS, protecting vascular cells, especially in patients with heart failure accompanied by respiratory and liver disorders.	B	[60]
Resveratrol	Activated antioxidant enzymes, reduces ROS, and modulates mitochondrial function, nitric oxide production and platelet aggregation.	Beside its anti-aging effects, it helps in reducing inflammation and OS in chronic HF by improving endothelial function thus reducing arterial stiffness.	B	[61]
Flavonoids	Inhibits ROS generation, chelates metal ions, quenches singlet oxygen, boosts endogenous antioxidants enzyme activity, neutralizes free radicals and reduces inflammation.	Decreased risk for HF and other cardiovascular diseases, because of reduced OS and inflammation.	C	[62, 63]
Alpha-Lipoic acid	Recycles antioxidants like Vitamin E and C, chelates metals and neutralizes free radicals in vascular tissues.	Reduced OS improved vascular endothelial health and neuropathy symptoms.	D	[64]
Astaxanthin	Quenches singlet oxygen and reduces lipid peroxidation.	Improved lipid profile, reduce OS markers and inflammation, contributing in better outcomes in HF patients	C	[65]
Polyphenols	Scavenges free radicals, reduces vascular inflammation, and improves nitric oxide bioavailability.	Lowered OS status, blood pressure and reduced cardiovascular disease risk.	D	[66]
Curcumin	Reduces ROS production, inhibits LDL oxidation, and enhances endothelial nitric oxide availability.	Reduced OS markers, risk of atherosclerosis and anti-inflammatory effect.	D	[67]
Melatonin	Scavenges free radicals, reduces lipid peroxidation, and improves mitochondrial function in heart tissue.	Protective effects against myocardial ischemia and hypertension.	C	[68]

Note: The level of evidence is modified from the Oxford Centre for Evidence-based Medicine. "The Oxford 2011 Levels of Evidence". http://www.cebm.net/index.aspx?o=5653. Grade A is based on systemic reviews of RCTs or individual RCT of good quality; Grade B is based on well-designed studies (prospective, cohort) and lower quality RCT; and Grade C is based on poorer quality studies (retrospective, case series) Grade D is based in case reports and expert opinion). *LE=Level of Evidence

Therapeutical aspects in AF in the context of raised OS status

The intricate interplay between OS and inflammation underscores the complexity of AF pathogenesis. Current antioxidant therapies have shown limited efficacy in reducing AF incidents or severity possibly due to their non-specific targeting of oxidative pathways. However, emerging strategies focusing on specific oxidative stress modulators such as NADPH oxidase inhibitors and targeted antioxidant delivery systems offer promise.

Treatment including antiarithmic drugs and catheter ablation management remains challenging due to high recurrence rates particularly in persistent AF. Increasing evidence implicates OS as a key driver of AF pathogenesis. ROS production and antioxidant defenses has emerged as a critical factor in AF development. Incorporating OS markers into routine AF management could improve patient outcomes by enabling personalized therapy.

Animal studies provide further evidence, as transgenic mice treated with mitochondrial ROS scavengers exhibit reduced AF susceptibility.

Numerous therapeutic strategies have been explored to mitigate its incidence, especially Postoperative AF (POAF), which occurs frequently after cardiac surgery and poses additional risk of complications, prolonged hospitalizations and increased healthcare costs. OS, inflammation and other pathophysiological mechanism are pivotal contributors to AF, prompting researchers to investigate targeted treatments that address these underlying factors.

In Table 3, are presented summarized findings form randomized controlled trials and meta-analyses, therapeutic agents, including antioxidants, statins, SGLT-2 inhibitors and xanthine oxidase inhibitors, offering insights into both the efficacy and limitations of these interventions.

Antioxidant therapies including mitochondrial ROS scavengers like MitoTEMPO have shown promise in reducing mitochondrial OS and preventing AF progression. Mito-TEMPO is a mitochondria-targeted superoxide dismutase mimetic with superoxide and alkyl radical scavenging properties [56-68]. NOX inhibitors which target NOX2 and NOX4 isoforms can attenuate fibrosis and electrical remodeling. N-acetylcysteine (NAC), vitamins C and E focus on mitigating OS, a well-recognized driver of atrial remodeling and electrical instability [69,70].

Pharmacological approaches including statins have demonstrated efficacy in preventing AF recurrence particularly post ablatation [71]. Atorvastatin, beyond its lipid-lowering properties, exerts anti-inflammatory and pleiotropic effects that appear beneficial in reducing the incidence of POAF, particularly in Coronary Artery Bypass Graft (CABG) patients [72-77]. The SGLT2 inhibitors, primarily used for the management of type 2 diabetes and heart failure, have shown promise in lowering AF risk, suggesting a role in addressing metabolic and hemodynamic factors associated with arrhythmogenesis. In addition to its primary uses, allopurinol has been studied for its potential cardiovascular benefits due to its antioxidant properties and ability to reduce OS. It has shown promise in conditions such as hypertension, HF and AF by decreasing OS damage and improving endothelial function, although its use in these settings is not yet standard clinical practice. Additionally neuromodulation strategies such as ganglionated plexus ablation and vagal nerve stimulation show potential in reducing ROS generation and AF triggers by addressing autonomic remodeling.

Lifestyle interventions such as weight loss dietary modifications and exercise help mitigate systemic OS and reduce AF burden [78,79].

Table 3: Summarized findings from several studies evaluating various therapeutic agents including antioxidants, anti-inflammatory agents and metabolic modulators for their potential role in reducing the incidence of AF and related complications.

Treatment	Outcome	Effect size	p-value	Notes	Citation
SGLT2 - i	Prevention of AF	OR 0.82 (95% CI: 0.72–0.93)	p=0.002	Associated with reduced risk of AF. No significant effect on stroke risk in patients with and without diabetes.	[73]
Vitamin C and E	Reduction in POAF incidence	RR: 0.154 (95% CI: 0.056 – 0.042).	p<0.05	Antioxidant properties help mitigate ischemia/reperfusion induced OS thus decreasing POAF, giving a support for their prophylactic use.	[69, 70, 72]
Relative risk reduction ~22%					
NAC	Prevention of POAF	No significant reduction (11.7% vs. 15.8%)	p=0.34	High-dose oral NAC showed no significant effect on the incidence of POAF, hospital stay, or mortality	[71, 72]
NADPH oxidase inhibitors (pioglitazone, probucol, apocynin, etc.)	Prevention of AF and oxidative stress-related remodeling	RR: 0.40 (95% CI: 0.20-0.79).	p=0.016	Early results are promising; however, patient selection and timing are critical for outcomes.	[72-75]

MitoTEMPO	Reduced mitochondrial ROS and ventricular arrhythmias	RR: 0.33 (95% CI: 0.13–0.85)	p=0.042	MitoTEMPO prevented mitochondrial ROS-induced gap junction remodeling and reduced arrhythmogenic substrate formation.	[28,76]
Atorvastatin	Prevention of POAF	RR: 0.69 (95% CI: 0.56–0.86)	p=0.001	Beneficial effect seen primarily in CABG patients. Statins reduced inflammation but did not affect AKI or MI	[72, 77]
Allopurionol	Cardiovascular outcomes (mortality and adverse events)	RR: 0.60 (95% CI: 0.33–1.11)	p>0.05	Mixed findings in secondary prevention. May benefit CABG or ACS patients but needs further trials.	[78]

Conclusion

OS plays a pivotal role in HF and AF by driving both electrical and structural remodeling of the atria and ventricles, while traditional therapies have had limited success in addressing this aspect advances in biomarker identification and targeted interventions hold promise for transforming HF and AF management. The summarized results highlight the diverse therapeutic avenues under investigation, offering a deeper understanding of the complex interplay of mechanism driving HF and AF and the potential for targeted interventions to improve patient outcomes. But, the heterogeneity of patient populations, treatment protocols and outcomes highlight the need of standardized methodologies in future research. More randomized controlled trials with larger sample sizes are necessary to validate these findings and establish clear guidelines for integrating these treatments into clinical practice.

Future research should focus on refining therapeutic approaches to mitigate OS and its downstream effects potentially reducing the burden of this pervasive pathologic states.

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