Ageing Research Reviews 69 (2021) 101363

Contents lists available at ScienceDirect

Ageing Research Reviews

journal homepage: www.elsevier.com/locate/arr

Review

The role of senescence in the pathogenesis of atrial fibrillation: A target process for health improvement and drug development

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ARTICLE INFO

Keywords:
Atrial fibrillation
Atrial fibrosis
Senescence
Ageing

ABSTRACT

Cellular senescence is a state of growth arrest that occurs after cells encounter various stresses. Senescence contributes to tumour suppression, embryonic development, and wound healing. It impacts on the pathology of various diseases by secreting inflammatory chemokines, immune modulators and other bioactive factors. These secretory biosignatures ultimately cause inflammation, tissue fibrosis, immunosenescence and many ageing-related diseases such as atrial fibrillation (AF). Because the molecular mechanisms underpinning AF development remain unclear, current treatments are suboptimal and have serious side effects. In this review, we summarize recent results describing the role of senescence in AF. We propose that senescence factors induce AF and have a causative role. Hence, targeting senescence and its secretory phenotype may attenuate AF.

1. Atrial fibrillation

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, characterized by chaotic electrical impulses firing within the left atrium of the heart, which leads to irregular contraction with the left atrium. AF is detected clinically by palpating the pulse and the pulsation is classically described as irregularly irregular. AF was first recognised in 1749, but it was not until William Einthoven invented electrocardiography in the 20th century that AF was recorded on electrocardiogram (ECG) (Lip and Beevers, 1995).

Based on the Euro Heart Survey of more than 5000 AF patients (Kirchhof et al., 2016; Nieuwlaat et al., 2005), AF can be classified into four different categories: (i) first diagnosed, (ii) paroxysmal, (iii) persistent and (iv) permanent (Table 1). AF is an unusual condition that it can affect anyone but is more prevalent as we age (Chugh et al., 2014). Some sufferers are asymptomatic, some have few symptoms, and some experience symptoms so mild that even can't notice the condition. On the other hand, some sufferers are highly symptomatic and short transient episode of atrial fibrillation, if frequent enough, can be highly debilitating. Even short transient episodes of AF can be very debilitating for these patients. It is unknown why patients range in the severity of their symptoms and others are asymptomatic.

The most widely recognised complication of AF is the development of thrombus which is felt to originate within the left atrial appendage adjacent and connected to the left atrium (Chang et al., 2012). If a portion of the thrombus breaks away, referred to as an embolus, it makes its way into the circulation often finding its way into the cerebral circulation resulting in a stroke. It is not uncommon for multiple emboli to pass into the brain causing multiple sites of injury in the brain. This explains why AF strokes tend to cause more debilitating strokes with higher rates of severe residual disability and higher mortality. While stroke prophylaxis tends to be the area most focused on in AF management, AF is frequently associated with heart failure. AF can be a complication of heart failure but can also in itself cause heart failure through poor control of the heart rate. The heart literally tires and the left ventricular function progressively declines, such that the patient develops a tachycardia induced cardiomyopathy leading to severe shortness of breathless and an inability to lie flat due to the sensation of smothering.

Although AF has been known for a century with numerous associated studies, its mechanisms remain uncertain. Treatment of AF is heterogeneous as evidenced by the wide range of antiarrhythmic medications used in real world clinical practice. Some patients respond well to their antiarrhythmic medications whereas others derive little benefit,

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https://doi.org/10.1016/j.arr.2021.101363
Received 21 November 2020; Received in revised form 24 January 2021; Accepted 12 May 2021
Available online 21 May 2021

Table 1
Classification, clinical feature and proportion of different types of AF.

AF type	Clinical feature	Proportion
First diagnosed	First diagnosed, irrespective of duration and severity	18.3%
Paroxysmal AF	Lasting 7 days or fewer	28.4%
Persistent AF	Rhythm control is achieved after 7 days	21.9%
Permanent AF	Sinus rhythm control is never established	29%

suggesting that AF may have many different endotypes and mechanisms that require a personalised medicine approach. Effective identification of endotypes and mechanisms is needed to efficiently advance our understanding of the condition, supporting diagnosis and treatment, restoring normal sinus rhythm to reduce symptom burden and to prevent complications.

1.1. AF prevalence

In 2020, AF affected 37.5 million patients worldwide, approximately 0.51% of the global population (Lippi et al., 2020). The prevalence of AF is 1–2% which rises to around 10% by the time we reach 65 years of age. Detection of AF is believed to be growing rapidly as a result of the ageing population and greater accessibility to heart monitoring equipment and is largely opportunistic. From 1990–2010, the total number of AF patients increased 4%, while the number of new diagnoses increased 32%. During this period, the recorded death rate associated with AF increased 94% (Chugh et al., 2014).

More than 7.6 million adults aged over 65 were living with AF in the European Union in 2016, and it is believed that European AF patients will reach 17.9 million by 2060 (Lippi et al., 2020). In Northern Ireland the estimated number of known atrial fibrillation patients is approximately 40,000 and there will be many more unknown asymptomatic patients.

1.2. Mechanism of atrial fibrillation

Although there are several theories that could account for AF progression, the causative mechanisms of AF are still not clear.

1.2.1. Ectopic firing theory

In 1998, Haissaguerre reported that ectopic beats originating in the pulmonary veins spontaneously initiate AF and this is accepted as the prevailing hypothesis for AF genesis (Haissaguerre et al., 1998). AF initiation was mapped using multielectrode catheters to record the electrical activities proceeding AF and atrial ectopic beats and found that 94% of ectopic beats were in the pulmonary veins. Pulmonary veins contain pacemaker cells, transition and Purkinje cells together with the fibre structure and electrical characteristics making it suitable for initiating AF (Hocini et al., 2002; Perez-Lugones et al., 2003). Around 62% AF patients showed no reoccurrence within 8 ± 6 months after the ectopic foci were ablated by radio-frequency treatment adding further support to this theory (Blaauw et al., 2002).

However, this procedure known as Pulmonary Vein Isolation (PVI) had at best modest success out to five years and almost half of the patients required at least two procedures which has a 2.2% chance of serious complications meaning that better treatments and better patient selection is required (Guhl et al., 2016). The latter is challenging when the mechanisms remain unclear.

1.2.2. AF re-entry

The multiple-wavelet theory has been proposed for AF stabilisation. In this model, wavefront fractionation propagates through atria which results in self-perpetuating daughter-wavelets. Due to the differences in the atrial refractory period, mass and conduction velocity, the total wavelets number varies. As the wavelets accumulate, AF is stabilized and sustained (Cox et al., 1991; Fuster et al., 2006).

It is further hypothesized that re-entrant rotors drive AF stabilization. Wavelets break into daughter-wavelets when wavefronts encounter some obstacles such as scars and anisotropy. However, these daughter-wavelets form into rotors after they anchor the pulmonary veins and heterogeneous atrial tissues (Vaquero et al., 2008), which could induce disorganized waves to cause AF related chaotic atrial activation (Berenfeld et al., 2002).

1.2.3. Atrial remodeling

AF causes atrial remodeling, which in turn acts as a substrate to maintain, deepen and drive AF to a more permanent status. Atrial remodeling consists of electrical remodeling and structural remodeling. Electrical remodeling happens due to ion channel activity changes. In animal models, this remodeling happens within the first few hours of AF initiation. Electrical remodeling ultimately contributes to AF development and maintenance (Corradi et al., 2008; Morillo et al., 1995; Wijffels et al., 1995).

Does electrical remodeling cause atrial remodeling or is it the other way around? We hypothesize that there may be an argument for senescence causing remodeling (discussed below in detail) which leads to AF which leads to progressive remodeling setting up a circle of left atrial modification. This supports the concept that atrial fibrillation begets atrial fibrillation. The precipitate to the initiating process may be increased left atrial pressure which most commonly arises from hypertension. Atrial structure remodeling also show architectural changes such as increased tissue fibrosis and enlarged atria size (Corradi et al., 2008) suggestive of atrial remodeling as a substrate for AF development. Further, morphological and functional changes post remodeling may ultimately contribute to development of persistent AF.

1.3. Risk factors, clinical outcomes and treatments

1.3.1. AF risk factors

Numerous risk factors have been reported for AF. Among these, ageing is the most significant. AF prevalence is seven times higher in people aged from 65 to 69 years compared to people aged from 45 to 49 years (Chugh et al., 2014). Sex was also a risk factor. Males have 1.12-fold higher risk compared to females (Lippi et al., 2020). However, the AF mortality rate between males and females remains almost the same (Chugh et al., 2014).

Cardiac conditions, including hypertension, previous heart failure and heart valve disease, are common risk factors. Diabetes (Kirchhof et al., 2016), together with factors such as smoking (Alonso et al., 2013), obesity (Wang et al., 2004), sedentary lifestyle (Alonso et al., 2013), heavy alcohol consumption (Kirchhof et al., 2016) and even excessive exercise, are accepted as non-cardiac causes. Apart from this, emerging studies show bacterial infection and virus infections such as SARS-CoV-2 may also cause AF (Gawałko et al., 2020; Ichiki et al., 2009).

1.3.2. Clinical features and treatments

Many AF patients do not show symptoms in the early stage of AF. Those that do have symptoms vary in severity with some experiencing just one symptom such as palpitations, shortness of breath, or chest pain where as others may experience a combination of these (Rienstra et al., 2012). As the disease changes from paroxysmal AF to permanent AF, patients may experience symptoms more frequently. Persistent and permanent AF are more likely to result in potential serious complications including stroke, thromboembolism, and heart failure. AF is much more likely to cause significant morbidity and can lead to a poor quality of life as opposed to mortality which is uncommon (Kirchhof et al., 2016). The risk that AF patients will develop stroke is five-fold higher than non-AF individuals and it is estimated that about 20% of strokes are attributable to AF (Association, 2016). Around 12.5% of patients die in the first month after a stroke attack and 25% die within one year. For those who survive, 30% have recurrent strokes or transient ischaemic

stroke and 50% have a disability (Association, 2016). Stroke is highly associated with ageing and the risk of stroke doubles every decade after the age of 55 (Association, 2016). Incidence of stroke in younger cohorts, especially in black and south Asian young patients, are increasing due to consumption of cigarette, alcohol and illegal drugs (Association, 2016).

The current management of AF is multifaceted and includes heart rate control, cardioversion, catheter ablation, stroke and thromboembolism prophylaxis. The mainstay of stroke prevention is anticoagulation using Warfarin but now includes Direct Oral Anticoagulants (DOACs) called Dabigatran, Rivaroxaban, Apixaban and more recently Edoxaban have taken over in many regions (Kirchhof et al., 2016). Anticoagulation drugs can prevent risk of stroke in 60% of AF patients (Hart et al., 2007), however only about half of AF patients are using these drugs according to stroke.org.uk. These treatments are accompanied with side effects for example anticoagulation drugs will cause abnormal bleeding, cardioversion may increase the risk of heart failure and stroke. Further, catheter ablation could result in cardiac tamponade and pulmonary vein stenosis (in invasive therapies). None of these treatments are fully successful in curing AF, and indeed some cause AF relapse (Kirchhof et al., 2016; Rienstra et al., 2012). A better, detailed understanding of the molecular mechanisms of AF presents an opportunity to identify novel disease endotypes and more cost-effective targeted therapeutics and enable patient stratification.

2. Cellular senescence

Cellular senescence is a state of stable and permanent growth arrest characterized by an inflammatory secretory phenotype (McCulloch et al., 2017; Rai and Adams, 2012; Van Deursen, 2014). In the 1960s, Leonard Hayflick found that human diploid cells cannot divide unlimitedly *in vitro* (being limited to approximately 50 ± 10 populations, known as "Hayflick Limit") and this phenomenon was named cellular senescence (Hayflick, 1965). Since then, theoretical and experimental studies improved our understanding of this physiological process. Senescence can be triggered by various stresses such as activated oncogenes, oxidative stress, shortening of the telomere, DNA damage and insufficient supplementation (Campisi, 2005; Herbig and Sedivy, 2006; Ramirez et al., 2001).

The onset of senescence is accompanied by changes in morphology, chromatin, transcriptome, metabolism and secretion (Herranz and Gil, 2018). Senescent cells appear enlarged in size and flattened in shape in response to cytoskeletal protein changes (Cho et al., 2004; Wang and Gundersen, 1984). Each individual chromosome condenses to form heterochromatic structures, termed senescence-associated heterochromatin foci (SAHF) (Narita et al., 2003). Other senescent hallmarks include upregulation of $p16^{INK4a}$ and $p21^{CIP1}$ and increased senescence-associated ß-galactosidase (SA-ß-Gal) activity (Caliò et al., 2015). It is thought that these changes help to maintain and deepen the senescence phenotype (Baker and Sedivy, 2013; Ivanov et al., 2013).

2.1. Effects of senescence

Senescent cells have both advantageous and detrimental effects. For example, senescence is a potent tumour suppression mechanism (Collado and Serrano, 2010), helps in wound healing (Demaria et al., 2014; Jun and Lau, 2010) and is involved in embryonic development (Muñoz-Espín et al., 2013; Storer et al., 2013). Paradoxically, naturally occurring senescent cells have been shown to contribute to tumour progression and organ dysfunction in the kidney and heart (McHugh and Gil, 2018). Long term senescence has deleterious effects by shortening lifespan (Baker et al., 2016; Muñoz-Espín et al., 2013; Storer et al., 2013), and contributing to ageing and ageing-associated diseases (Baker et al., 2008, 2011) (see Table 2 and Fig. 1). In aged rodent models, accumulation of senescent cells characterized by upregulation of p16 and p21 indicated a possible correlation between senescence and ageing

Table 2
Senescence biomarkers identified in various diseases.

Detrimental impact of cellular senescence			
Diseases	Disease sub-types	Senescence biomarker	Disease model
Cardiovascular diseases	Abdominal aortic aneurysm (Chen et al., 2016), atherosclerosis (Gorenne et al., 2006), atrial fibrillation (Hasan et al., 2019; Jesel et al., 2020), heart failure (Chimenti et al., 2003), heart rupture (Zhu et al., 2013), HFpEF (Gevaert et al., 2017), myocardial infarction (Brouilette et al., 2003), thoracic aortic aneurysm (Watson et al., 2017)	p21, MMPs, SA-ß-Gal, p16, p53, MMP-9, eNOS, telomeric shortening, CXCLs	Vascular smooth muscle cells, atrial endothelial cells, c-kit^{pot} cells, aged hearts, fibroblasts, mice, leukocyte, human ascending aortic tissue
Renal diseases	Glomerulosclerosis (Baker et al., 2016), tubulointerstitial (Sis et al., 2007)	p16, SA-ß-Gal	*ATTAC* mice, human kidney tissue
Neurodegenerative diseases	Alzheimer's (Bussian et al., 2018), Parkinson's (Chinta et al., 2018)	p16, IL-6, IL-8, MMP-3	*ATTAC*, $MAPT^{P301S}PS19$ mice, astrocytes, fibroblasts
Lung diseases	Asthma (Hadj Salem et al., 2015), bronchiectasis (Birch et al., 2016), chronic obstructive pulmonary disease (Rutten et al., 2016), idiopathic pulmonary fibrosis (Schafer et al., 2017), pneumonia (Shivshankar et al., 2011), pulmonary arterial hypertension (Noureddine et al., 2011), pulmonary emphysema (Tsuji et al., 2006)	Telomeric shortening, p21, p16, p53, SA-ß-Gal, pRb, Ki-67	*Bronchial fibroblast*, lung tissue, lymphocyte, mice, fibroblast, endothelial cells, pulmonary artery smooth muscle cells, alveolar cells
Musculoskeletal diseases	Axial spondylarthritis (Fessler et al., 2016), juvenile idiopathic arthritis (Dvergsten et al., 2013), osteoarthritis (Jeon et al., 2017), osteoporosis, rheumatoid arthritis (Schönland et al., 2003), sarcopenia (Sousa-Victor et al., 2014)	Telomeric shortening, p16, IL-6, ROS	T cells, *C57BL/6 J* mice, human articular cartilage sample, *INK-ATTAC* mice, myeloid and lymphoid cells, geriatric satellite cells
Metabolic diseases	Cachexia (Baker et al., 2016), metabolic dysfunction (Xu et al., 2015), type 2 diabetes (Sone and Kagawa, 2005)	SA-ß-Gal, p16, p53, p21, PML	*ATTAC* mice, IMR-90 cells, nutrient induced diabetic *C57BL/6 J* mice
Eye diseases	Cataracts (Fu et al., 2016), glaucomatous (Liton et al., 2005), retinal microaneurysm formation (	SA-ß-Gal	Human lens epithelial cells, donor eyes, human tissues, mice

(*continued on next page*)

Table 2 (*continued*)

Detrimental impact of cellular senescence			
Diseases	Disease sub-types	Senescence biomarker	Disease model
	López-Luppo et al., 2017)		
Genetic disorder	Down syndrome (Nawa et al., 2019), Hutchinson-Gilford Progeria syndrome (Benson et al., 2010)	ROS, SA-ß-Gal, PI3K-Akt, MMP-2	Dermal fibroblasts, iPSCs, Gene expression database
Liver diseases	Hepatocellular carcinoma (Paradis et al., 2001), liver cirrhosis (Krizhanovsky et al., 2008), non-alcoholic liver fatty diseases (Zhang et al., 2012), non-alcoholic steatohepatitis (Tomita et al., 2012)	SA-ß-Gal, Ki-67, p53, p21, p16	Liver tissue, mice

(Hudgins et al., 2018). Inactivation of p16 has been demonstrated to delay onset of age-related symptoms in sarcopenia, coronary artery disease (CAD) and osteoarthritis (Baker et al., 2008; Bussian et al., 2018; Sousa-Victor et al., 2014). Hutchinson-Gilford Progeria Syndrome (HGPS) is associated with premature senescence regulated by telomere dysfunction and DNA-damage signalling (Benson et al., 2010). Drugs that target senescent cells extend mice healthspan, lifespan and delay the onset of organ dysfunction without any notable side effects (Baker et al., 2016, 2011; Xu et al., 2018). Cellular senescence is therefore a well-known contributor to ageing and ageing related diseases.

2.2. *Senescence-associated secretory phenotype (SASP)*

Ongoing senescence results in continued secretion of bioactive molecules that may ultimately end up in the blood. Such molecules are called the senescence-associated secretory phenotype (SASP) (Campisi and Di Fagagna, 2007; Campisi, 2005; Coppé et al., 2010). SASP was first reported by Judith Campisi, when inducing senescence in fibroblasts and epithelial cells by genotoxic stress. They found that inflammatory cytokines, growth factors, immune modulators and malignancy associate factors increased *in vitro* (Coppé et al., 2008). The same phenotype was observed *in vivo* in patients receiving chemotherapy (Taschner-Mandl et al., 2016). Interestingly, SASP can both be beneficial and harmful to the organism. It is reported to be involved in wound healing and immune cell recruitment to eliminate senescent cells (Demaria et al., 2014; Velarde and Demaria, 2016). Age related accumulation of senescent cells and associated secretory molecules can cause

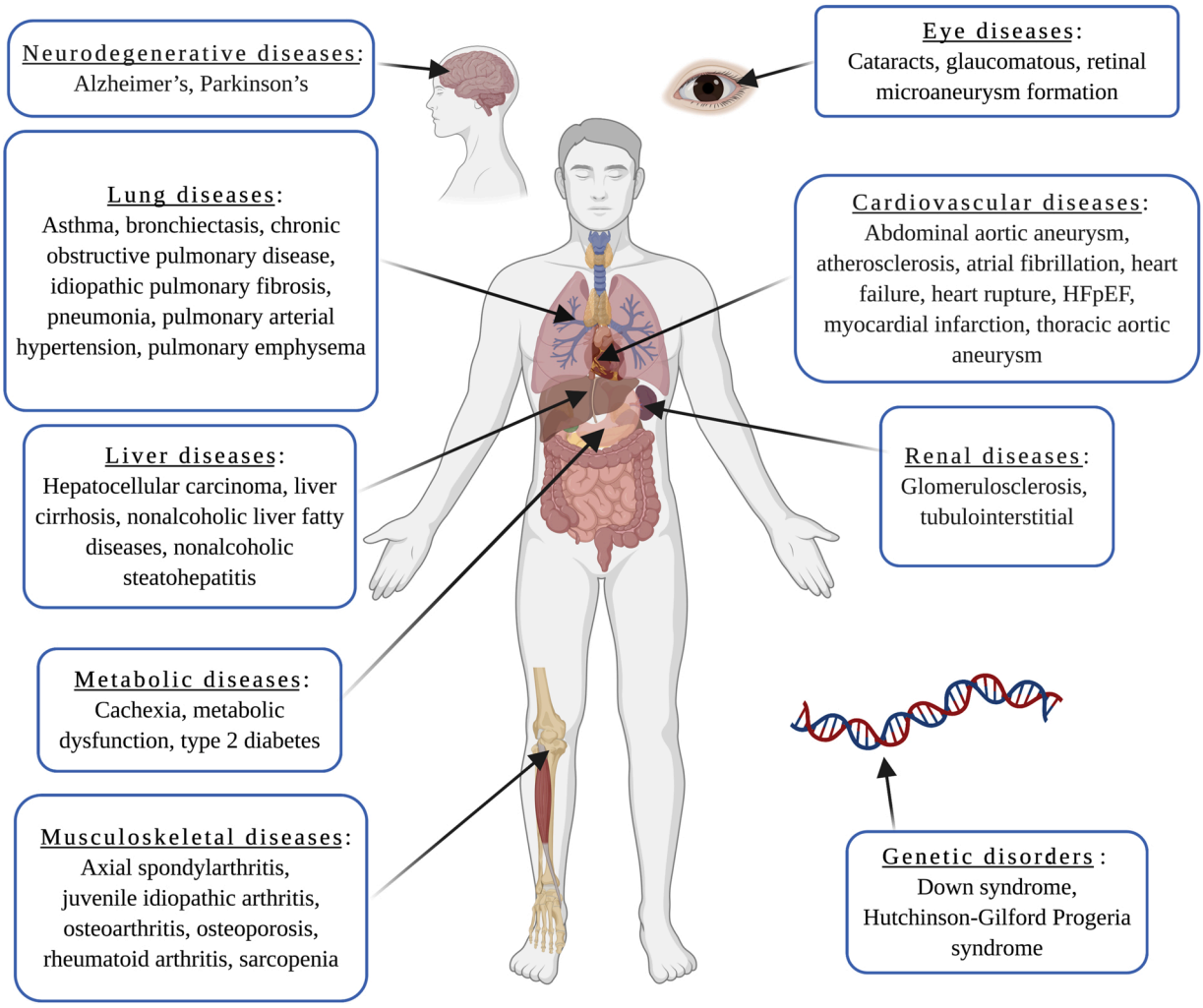

Fig. 1. Age associated diseases where senescence has been causally implicated. 37 senescence-associated diseases are classified into 9 major categories: neurodegenerative diseases, lung diseases, liver diseases, metabolic diseases, musculoskeletal diseases, eye diseases, cardiovascular diseases, renal diseases and genetic disorders.

immunosenescence, organ and tissue dysfunction (Weiskopf et al., 2009). SASP can have pathological consequences that can cause chronic diseases such as osteoarthritis and atherosclerosis (Matthews et al., 2006; Price et al., 2002). Furthermore, SASP is implicated in the development of tumours by affecting the neighbouring cells in papillary thyroid carcinoma invasions (Kim et al., 2017b). A SASP atlas containing soluble and exosome SASP factors has recently been established, in which proteomic analysis was performed for quiescent and replicative fibroblasts and epithelial cells induced by multiple triggers. Among the proteins analysed, growth differentiation factor-15 (GDF-15) and matrix metallopeptidases (MMPs) were identified as the core SASP proteins (Basisty et al., 2020). Interestingly, GDF15 has also been found to be a human ageing biomarker, identified by comparing the plasma proteome of individuals ranging from 18 to 95 years (Basisty et al., 2020; Lehallier et al., 2019). Although the precise role of GDF-15 is still not known, it may be a potential target for not only drug development but also aged disease risk prediction (Velarde et al., 2013; Wollert et al., 2017). Senescence is significantly correlated with ageing and ageing-related diseases and SASP may have the potential to predict risk and serve as a target for ageing-related diseases.

3. Interaction between atrial fibrillation and senescence

Since AF was discovered a century ago, significant efforts have been made to define it. In spite of this the precise mechanism is still unknown, with structural remodeling (Burstein and Nattel, 2008), electric remodeling (Allessie et al., 2001), autonomic remodeling (Chou and Chen, 2009) and other theories suggested to explain the aetiology of AF. Atrial fibrosis and atrial enlargement have been reported to cause atrial structure remodeling and are regarded as the basis of AF development and maintenance (Glukhov et al., 2015). Recently, AF was identified as closely correlated with senescence and emerging studies indicate that senescence plays a key role. For example, senescence triggers and mediators including oxidative stress, excessive reactive oxygen species (ROS), shortened telomere and mitochondria damage have been shown to contribute to AF progression (Lin et al., 2003; Sovari and Dudley, 2010). Furthermore, mitochondrial DNA mutations and injury caused by oxidative stress were found to be increased in AF patients (Lin et al., 2003). Analysis of blood samples from AF patients and those in normal sinus rhythm showed that AF patients have shorter telomeres (Carlquist et al., 2016). However, it is not known whether cells in the heart can cause telomere shortening in blood cells, or indeed if this is linked to the ageing process in general. The human heart contains a variety of cell types such as cardiac fibroblasts, cardiomyocytes and macrophages (Tucker et al., 2020). Cardiomyocytes do not divide, and the level of DNA damage might be low when compared to rapidly dividing cells in the circulatory system. However, they undergo ongoing transcription that results in chromatin remodeling, potentially causing DNA damage. Similarly, free radicals generated during normal physiological processes might also cause DNA damage. Finally, ongoing contraction and relaxation over decades produces mechanical stress that might trigger DNA damage.

Translational expression profiling of atrial appendages from paroxysmal/persistent AF patients (aged from 58 to 82 years old) and sinus rhythm cohorts (aged from 57 to 79 years old) has shown senescence biomarkers and prothrombotic and proinflammatory factors were elevated in AF patients compared to a sinus rhythm group (Jesel et al., 2020). These biomarkers included an increased abundances of tumour suppressor proteins p53 and p16, tissue factor, MMP-9 and decreased endothelial nitric oxide synthase (eNOS) (Matsushita et al., 2001). Interestingly, there is a positive correlation of p53 and p16 with the severity of AF, indicating these biomarkers increased as AF deepened from sinus rhythm to paroxysmal AF and persistent AF. However, eNOS was down regulated gradually, providing evidence that senescence is pathologically involved in AF (Jesel et al., 2020). Taken together, these results show that senescence may be involved in AF initiation and/or development.

3.1. Potential mechanism of senescence-induced atrial fibrillation (SIAF)

Atrial fibrosis, which is a feature of atrial structure remodeling is implicated in AF development and maintenance (Dzeshka et al., 2015; Lau et al., 2016; Spach and Boineau, 1997). Atrial fibrosis is characterized by cardiac fibroblast proliferation, excessive myofibroblast differentiation and increased extracellular matrix (ECM) production of collagen, which terminally affects the functions of myocardium (Platonov, 2017). In animal models, induction of atrial interstitial fibrosis by congestive heart failure increased the risk of developing AF (Li et al., 1999). In human subjects, a higher level of atrial fibrosis has been observed in AF patients than in sinus rhythm groups through biopsy and autopsy data (Everett IV and Olgin, 2007; Kostin et al., 2002). Furthermore, atrial fibrosis was observed in subjects who developed AF after coronary bypass surgery but not in non-AF patients (Mariscalco et al., 2006). It is hypothesized that senescence is involved in atrial fibrosis-induced AF (Batlle et al., 2015). By analysing atrial appendage samples of AF patients and sinus rhythm individuals, higher atrial fibrosis levels and shortened telomeres were observed in AF patient groups, implicating senescence in the process of atrial fibrosis and AF (Batlle et al., 2015). Renin-angiotensin system, angiotensin converting enzyme (ACE) (Iravanian and Dudley Jr, 2008), visceral adipose tissue (Abe et al., 2018), TGF-ß (Verheule et al., 2004), pro-inflammatory cytokines (Marcus et al., 2010), ECM such as collagen (Levi et al., 2020), matrix metalloproteinases (MMPs) (Li et al., 2000), connexin 43 (Thibodeau et al., 2010), mitochondrial and oxidative stress (Xie et al., 2015) are implicated in AF associated fibrosis. Interestingly, many of these proteins are also hallmarks of senescence (Lau et al., 2016; Luo et al., 2007; Sawaki et al., 2018). SASP has also been shown to be involved in fibrosis induction by promoting inflammation and disrupting tissues (Muñoz-Espín et al., 2013; Van Deursen, 2014). These results suggest understanding atrial fibrosis may be important in clarifying the role of senescence in AF (Fig. 2).

3.1.1. The role of extracellular matrix in senescence-induced atrial fibrillation

ECM comprises collagens, glycoproteins, MMPs and other ECM-associated proteins. The role of ECM is to provide a structural scaffold for cell proliferation, cell communication and to mediate signal transduction in organ and tissue interstitial matrix (Choi et al., 2011; Levi et al., 2020). ECM is associated with tissue fibrosis, development, wound healing, cancer progression (Ghosh et al., 2020) and heart diseases (Reese-Petersen et al., 2020). In particular, atrial fibrosis is known to be caused by deposition of excessive ECM. Elevated expression of collagens, MMPs, fibronectin with other ECM-associated proteins contribute to ECM-associated atrial fibrosis (Levi et al., 2020). It is possible that in the ageing heart, senescent cells secrete SASP, some of which are also part of ECM proteins including MMPs, indicating there is a crosstalk between senescence and ECM components. ECM properties and specific protein expression levels change when cells enter a senescent state, for example increasing insolubility and up-regulating collagens and fibronectins (Colige et al., 1992; Sell and Monnier, 1989). Mice engineered to express collagenase-resistant type I collagen have a senescent phenotype leading to shortened lifespan (Vafaie et al., 2014). ECM proteomic analysis comparing human senescent and young diploid fibroblasts found that several ECM proteins were differentially expressed in senescent cells (Yang et al., 2011). These studies indicate ECM may contribute to atrial fibrosis through expression of proteins such as collagen 1 and MMPs.

3.1.2. Role of Angiotensin II (Ang II) and TGF-ß/Smad in senescence-induced atrial fibrillation

Inflammation is one of the main drivers of atrial fibrosis. Senescent cells secrete interleukins and MMPs that contribute to inflammation (Rodier et al., 2009). These inflammatory markers mediate tissue

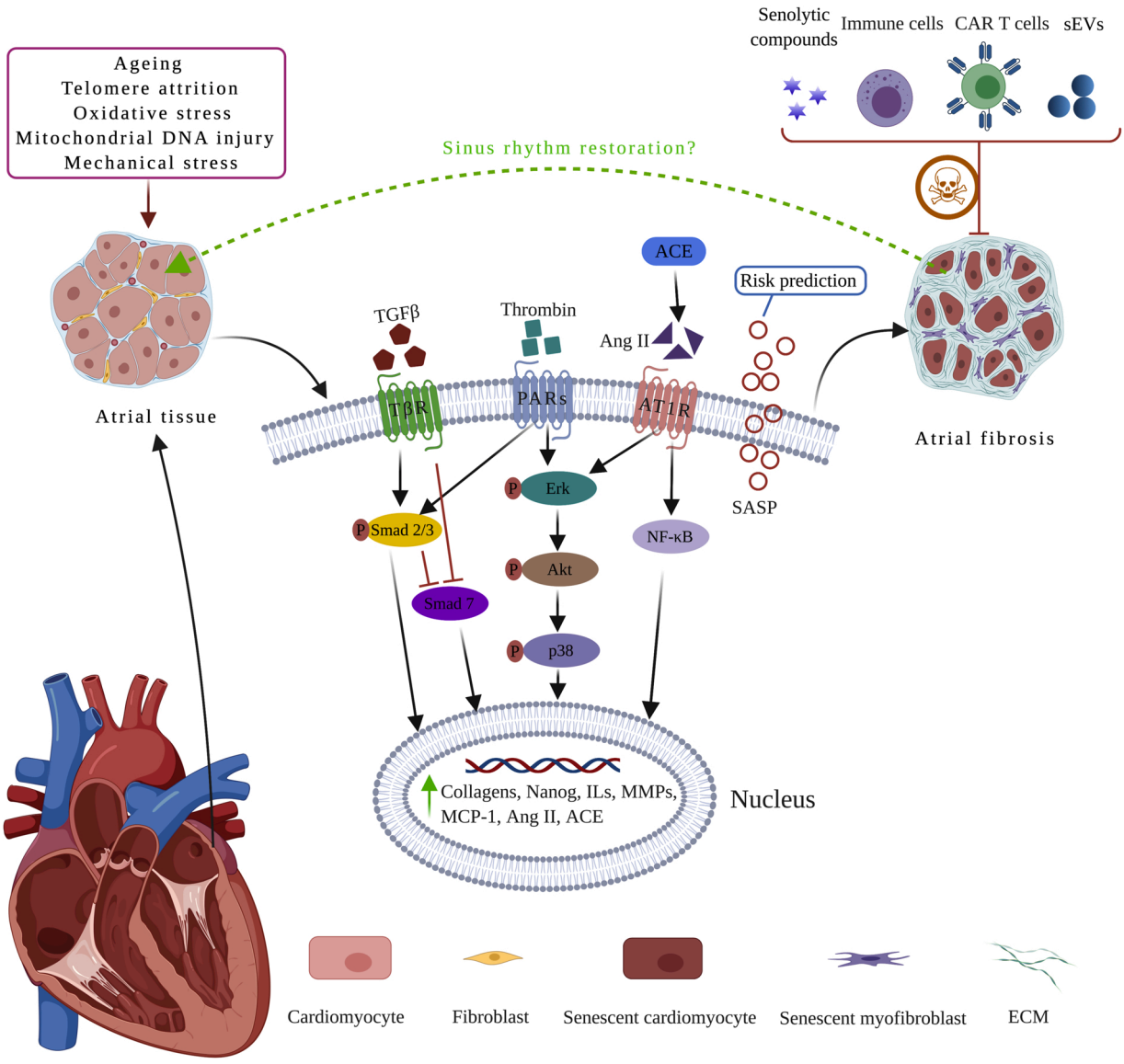

Fig. 2. Signal transduction of senescence-induced atrial fibrosis and potential diagnosis and treatment targets. Heart tissue encountering ageing, telomere attrition, oxidative stress, mitochondrial DNA injury and mechanical stress undergoes senescence. Collagens, Nanog, ILs, MMPs, MCP-1, ACE and Ang II are upregulated by thrombin and Ang II/TGF-ß pathways, which finally results in atrial fibrosis induced AF. Specific SASP factors may be exploited to develop novel AF risk prediction algorithms. Targeting senescent cardiac cells and their SASP using senolytic compounds, immune cells, CAR T cells and sEVs may attenuate AF.

fibrosis by activating the TGF-ß pathway (Lee et al., 2001). TGF-ß is known to induce senescence in hepatocellular carcinoma cells (Senturk et al., 2010) and bone marrow mesenchymal stem cells (Wu et al., 2014). TGF-ß also contributes to ageing-related disorders such as Alzheimer's disease and muscle atrophy by causing inflammation, tissue fibrosis and metabolic dysfunction (Tominaga and Suzuki, 2019). In cardiac cells and in AF mouse models, a high level of TGF-ß was accompanied with prolonged AF duration, increased tissue fibrosis, collagenous fibers, collagen synthesis and fibrotic effect associated H-proline (Li et al., 2019). Further studies in aged hearts show that fibrosis was caused by TGF-ß dependent modulation of Nanog. Nanog regulates collagen synthesis and monocyte chemoattractant protein-1 (MCP-1) transiting monocytes into myeloid fibroblasts which increase fibrosis (Cieslik et al., 2014). The TGF-ß pathway is implicated in the induction of atrial fibrosis, possibly through stem cell factors such as Nanog.

Ang II, a well-known profibrotic factor, plays a significant role in cardiac inflammation, fibroblast proliferation, cardiac contractility and finally cardiac structure remodeling through atrial fibrosis (He et al., 2011; Kim et al., 2017a). In a study investigating the potential mechanism of how Ang II exhibits its role on inflammation, HL-1 atrial cells were treated with Ang II. By transcriptional and translational analysis, it was shown that Ang II increased inflammation associated proteins and pathways such as TNFα, TGF-ß, NF-κB, ILs, ROS, cellular calcium and the MAPK/JNK pathway. Ang II type 1 receptor (AT1R), which is involved in vascular remodeling, was found to be upregulated by Ang II treatment. Whether AT1R could induce atrial inflammation still remains unclear. Addition of AT1R blocker to an atrial cell line decreased the inflammatory markers including ILs, JNK phosphorylation level, ROS, TGF-ß and NF- κB. This indicates atrial inflammation could be inhibited by targeting Ang II. In AF patients' samples, the levels of Ang II were found to correlate with inflammation (Kim et al., 2017a). In a rabbit model of AF, Ang II, AT1R, TGF-ß and Smads were found to correlate with atrial fibrosis (He et al., 2011). Ang II induces cellular senescence in vascular smooth muscle cells (VSMCs) by regulating p53 and p21, whilst concomitantly increasing inflammation. However, inhibiting the senescence pathway through inhibition of p53/p21 significantly reduced inflammation and atherosclerosis (Kunieda et al., 2006).

Atrial endothelial cells (AECs) from porcine atria display senescence hallmarks when passaged in cell culture. AECs have increased SA-ß-Gal activity, p53, p16 and p21 showing AECs were entering senescence (Hasan et al., 2018). Atrial fibrosis remodeling and inflammation was detected by MMPs, TGF-ß and by measuring local Ang II levels along with AT1R. These results indicated that atrial endothelial cellular senescence contributed to atrial inflammation, fibrosis and atrial remodeling possibly via Ang II/AT1R and TGF-ß (Hasan et al., 2018). Clinical AF samples showed that increased senescence markers were significantly associated with overexpressed collagenase I/III and TGF-ß, indicating senescence may induce atrial fibrosis (Xie et al., 2017). Ang II may contribute to AF by inducing senescence and mediating atrial fibrosis. Targeting Ang II and its receptor AT1R may therefore be attractive therapeutic option for the treatment of senescence mediated AF.

3.1.3. Role of thrombin in senescence-induced atrial fibrillation

AF is closely associated with a hypercoagulation state that causes stroke by forming blood clots. Blood coagulation, in turn, could contribute to AF progression (Spronk et al., 2017). Thrombin is widely known to play a key role in thrombogenesis, clot formation, which contributes to atrial fibrosis, atrial remodeling, and affects left atria electrical signalling together with the mechanical characteristics that finally result in AF (Chang et al., 2012; Jumeau et al., 2016; Spronk et al., 2017). It affects a variety of cells in the heart including cardiomyocytes, fibroblasts, endothelial cells and vascular smooth muscle cells. As a consequence of thrombin stimuli, protease-activated receptors (PARs) are activated, consisting of 4 members and belonging to the G-protein-coupled receptors (Jacques et al., 2000). The thrombin-PAR signalling pathway is involved in liver- (Foglia et al., 2019), lung-(Madala et al., 2012) and heart-tissue fibrosis (Walsh, 2006), inflammation, cancer, embryonic development and especially in cardiovascular diseases (Martorell et al., 2008). In isolated rat atrial fibroblasts, thrombin treatment increased phosphorylation of the PAR signal pathway proteins Akt, Erk and p38 and of the inflammatory markers IL-6, MCP-1 and MMPs (Hasan et al., 2019). These proteins are linked to senescence and promoters of atrial fibrosis, indicating that thrombin regulates senescence and fibrotic diseases. Cells treated by PAR1 agonist showed an increase of thrombin, TGF-ß, MCP-1 and H-proline (Lim et al., 2013). In mouse models of AF, levels of thrombin are increased post AF onset (Lim et al., 2013; Spronk et al., 2017). Atrial endothelial cells treated with thrombin *in vitro* were found to upregulate senescence markers such as ROS, SA-ß-gal activity, p53, p21 and p16 (Hasan et al., 2019). As a result of atrial endothelial cellular senescence, pro-fibrotic and pro-remodeling patterns emerge, which are common manifestations of AF. Results from a rat model showed that both atrial remodeling and AF episodes were improved by injecting direct thrombin inhibitors, quite possibly by targeting senescence hallmarks (Jumeau et al., 2016). Interestingly, during the thrombin induced senescence, two angiotensin related proteins, ACE and AT1R increase (Hasan et al., 2019). Thrombin induced senescence could be significantly inhibited by treating endothelial cells with losartan and perindoprilat, which is an AT1R antagonist and an ACE inhibitor, respectively (Hasan et al., 2019). These studies show that thrombin contributes to senescence and atrial fibrosis which initiates and/or maintains AF. Hence, thrombin could be a future therapeutic target for AF (Spronk et al., 2017).

3.2. Clearing senescent cells as a therapy for atrial fibrillation

It is hypothesized that clearing senescent cells may ameliorate many age associated conditions (Childs et al., 2015). Senescent cells are sometimes referred to as "Zombie cells" that resist apoptosis induced death by upregulating anti-apoptotic proteins such as Mcl1 (Demelash et al., 2015; Dikovskaya et al., 2015) and BCL-2 (Chang et al., 2016). Senescent cells can be effectively removed by pharmacological and genetically engineered strategies. Senolytic compounds (Chang et al., 2016), senolytic immune cells (Pereira et al., 2019), engineered immune cells (Amor et al., 2020), and small extracellular vesicles from young subject fibroblasts (Fafián-Labora et al., 2020) eliminated senescent cells effectively and delayed senescence-associated diseases (Bussian et al., 2018). These strategies have been very successful in cellular and murine models and have shown their effectiveness in attenuating senescence-associated symptoms (Bussian et al., 2018). No treatments have been shown to improve AF, but we suggest that there is great potential in senolytics as the role of senescence in pathogeneses of AF becomes clearer.

Senolytic compounds are a class of compounds, antibodies and peptides that preferentially eliminate senescent cells by targeting anti-apoptotic molecules such as BCL-2 and BCL-xL (Chang et al., 2016). The combination of Dasatinib and Quercetin (D & Q) was the first reported senolytic used for eliminating senescent cells. Both D & Q are anti-cancer drugs, and each used alone is not effective enough to clear senescent cells. Interestingly, the combination of D & Q showed a wide killing spectrum in senescent preadipocytes and human umbilical vein endothelial cells (HUVECs), which finally improved osteoporosis (Farr et al., 2017), hepatic steatosis, pulmonary fibrosis, cardiovascular diseases (Kim and Kim, 2019; Song et al., 2020) and prolonged lifespan in old mice (Xu et al., 2018). Inspired by the usage of D & Q, research has focussed on small molecule-compound screening for potential senotherapy. ABT-263 (Chang et al., 2016), ABT-737 (Yosef et al., 2016), FOXO4-DRI peptide (Baar et al., 2017), fiesten (Zhu et al., 2017), cardiac glycosides (CGs) (Guerrero et al., 2019; Triana-Martínez et al., 2019) and others have been reported to have broad senolytic activity. Based on the effects of these senolytic compounds, clinical trials have been initiated to investigate whether the activity is consistent in patients. First in human studies have shown that combinations of D & Q improved symptoms of idiopathic pulmonary fibrosis (Hickson et al., 2019). Data from ClinicalTrials.gov shows there are several senolytic compounds under clinical trials: D & Q targeting Alzheimer (NCT04063124), Chronic kidney disease (NCT02848131), skeletal health (combined with fisetin, NCT04313634) and fisetin targeting osteoarthritis-related articular cartilage degeneration (NCT04210986). For AF, a potential senotherapy might target senescent cardiac cells. Although there hasn't been such a specific senolytic compound for AF treatment, digoxin, currently used for AF treatment to control irregular heartbeat, was reported to have a senolytic activity (Guerrero et al., 2019; Triana-Martínez et al., 2019).

Senescence can also occur in various types of immune cells referred to as immunosenescence, which decreases immune cell numbers and weakens immune responses to infections (Aiello et al., 2019; Pereira et al., 2019). Senescent dermal fibroblast secreted SASP induces HLA-E that inhibits NK cells and $CD8^+$ T cells. Blocking the interaction between HLA-E and senescent cells activates NK cells and $CD8^+$ T cells to perform senolytic activity (Pereira et al., 2019). In murine liver, NK cells also recruit macrophages and neutrophils for senescence clearance (Xue et al., 2007). $CD4^+$ T cells, facilitated by macrophages, kill Nras-induced pre-malignant senescent hepatocytes (Kang et al., 2011). Senescent cells overexpress surface protein urokinase-type plasminogen activator receptor (uPAR). Chimeric antigen receptor (CAR) T cells preferentially kill uPAR-expressing senescent cells, an approach that may well be used in humans (Amor et al., 2020). Small extracellular vesicles (sEVs) from young subjects' fibroblasts have senolytic activity. Cells from old individuals showed decreased levels of senescent markers in response to treatment with sEVs and this effect has proved consistent in a mouse model (Fafián-Labora et al., 2020). This method represents a potential new therapeutic strategy to improve senescence-associated pathologies.

4. Conclusions

AF, as a chronic disease, is significantly correlated with ageing. Cellular senescence, one of the well-known contributors to the ageing process is believed to contribute to AF development by regulating ECM,

ANG II, TGF-ß, thrombin and other signalling pathways. Targeting these signalling pathways by means of specific senolytic compounds, immune cells, CAR T cells and sEVs that preferentially eliminate senescent cells may be a potential treatment for AF.

5. Perspectives

AF poses heavy economic, healthcare and social burdens as a result of high death rates and a low quality of life. In the western European countries, AF cost €660 m (Germany) to €3200 m (Italy) every year (Velleca et al., 2019). Further complications, secondary to AF, such as stroke, cost the European Union another €45bn annually (Velleca et al., 2019). Precise identification of AF mechanisms and better subclassification of molecular endotypes will create opportunities for better diagnostics, therapies and biomarker development that can significantly reduce the economic burden of the condition and extend human lifespan. The current gold standard method for AF diagnosis is ECG. However, ECG can not determine the self-terminated AF types that have the potential to develop into persistent AF (Matusik et al., 2019). New methods are needed to improve not only the diagnosis methods but also to improve the clinical care pathway. One way that could be effective for better diagnosis is combining the senescence markers with ECG, imaging and clinical measurements. For example, there is already research focused on stroke and embolism risk prediction using a particular SASP factor GDF-15 along with NT-proBNP (Matusik et al., 2019). High levels of GDF-15 are also associated with atheroslerotic CVD, heart failure, and all-cause mortality (Ho et al., 2018). Further, high-throughput screening of novel senolytic compounds, specific immune cells and engineered T cells that target senescent cardiac cells, and possibily sEVs could lead to development of potential treatments (Amor et al., 2020; Chang et al., 2016; Fafián-Labora et al., 2020; Pereira et al., 2019). It is still not certain that the beneficial effects are indeed due to the effective killing of senescent cells (Hickson et al., 2019) or what exact cardiac cell types could be targets of senolytics.

During the current global pandemic caused by SARS-CoV-2, coronavirus diseases 2019 (COVID-19) has posed emerging treatments and caring difficulties in AF patients. COVID-19 is reported to be associated with arrhythmia, of which AF is the most frequent. Concomitant treatments for COVID-19 patients and cancer patients may introduce cardiotoxicity to cause/worsen AF (Gatti et al., 2020). Besides, SARS-CoV-2 infection may contribute to senescence accumulation by secreting proinflammatory cytokines and chemokines (Nehme et al., 2020), which in turn weakens immune system in response to SARS-CoV-2 infection. To conclude, even though the field of senescence and AF is still emerging, it has huge economic, societal and scientific potential in the coming years.

Author agreements and contributions

All the authors have seen and approved the final version of the manuscript being submitted. All the authors warrant that the article is the authors' original work, hasn't received prior publication and isn't under consideration for publication elsewhere. GG and TSR wrote the manuscript with inputs from SW, AP, VM, SDZ and AB.

Funding

TSR acknowledges funding from PHA/HSC R&D Division (COM/5618/20) and the Western Health & Social Care Trust. The NI Centre for Stratified Medicine has been funded by a grant to AB under the EU Regional Development Fund EU Sustainable Competitiveness Programme for NI & the NI Public Health Agency. GG is recipient of Vice-Chancellor's Research Studentship from Ulster University.

Declaration of Competing Interest

The authors report no declarations of interest.

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