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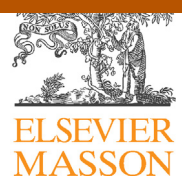

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REVIEW

New insights into symptomatic or silent atrial fibrillation complicating acute myocardial infarction

De nouvelles perspectives sur la fibrillation atriale symptomatique ou silencieuse compliquant la phase aiguë d'un infarctus du myocarde

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KEYWORDS
Silent atrial fibrillation;
Acute myocardial infarction;
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Summary Atrial fibrillation (AF) is the most frequent heart rhythm disorder in the general population and contributes not only to a major deterioration in quality of life but also to an increase in cardiovascular morbimortality. The onset of AF in the acute phase of myocardial infarction (MI) is a major event that can jeopardize the prognosis of patients in the short-, medium- and long-term, and is a powerful predictor of a poor prognosis after MI. The suspected mechanism underlying the excess mortality is the drop in coronary flow linked to the acceleration and arrhythmic nature of the left ventricular contractions, which reduce the left ventricular ejection fraction. The principal causes of AF-associated death after MI are linked to heart failure. Moreover, the excess risk of death in these heart failure patients has also

Abbreviations: ADMA, asymmetric N^G,N^G-dimethyl L-arginine; AF, atrial fibrillation; CEM, continuous ECG monitoring; ECG, electrocardiogram; LA, left atrial/atrium; LV, left ventricular/ventricle; LVEF, left ventricular ejection fraction; MI, myocardial infarction; STEMI, ST-segment elevation myocardial infarction.

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Prognosis;
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been associated with the onset of sudden death. Whatever its form, AF has a major negative effect on patient prognosis. In recent studies, symptomatic AF was associated with inhospital mortality of 17.8%, to which can be added mortality at 1 year of 18.8%. Surprisingly, silent AF also has a negative effect on the prognosis, as it is associated with an inhospital mortality rate of 10.4%, which remains high at 5.7% at 1 year. Moreover, both forms of AF are independent predictors of mortality beyond traditional risk factors. The frequency and seriousness of silent AF in the short- and long-term, which were until recently rarely studied, raises the question of systematically screening for it in the acute phase of MI. Consequently, the use of continuous ECG monitoring could be a simple, effective and inexpensive solution to improve screening for AF, even though studies are still necessary to validate this strategy. Finally, complementary studies also effect of oxidative stress and endothelial dysfunction, which seem to play a major role in triggering this rhythm disorder.

MOTS CLÉS
Fibrillation atriale silencieuse ;
Infarctus du myocarde ;
Surveillance ECG en continue ;
Pronostic ;
Asymétrique diméthylarginine

Résumé La fibrillation atriale (FA) est le plus fréquent des troubles du rythme cardiaque dans la population générale et contribue non seulement à une détérioration importante de la qualité de vie mais aussi à une augmentation de la morbi-mortalité cardiovasculaire. L'apparition de la FA dans la phase aiguë de l'infarctus du myocarde (IDM) est un événement majeur qui peut mettre en péril le pronostic des patients à court, moyen et long termes, et est un puissant facteur prédictif de mauvais pronostic après un IDM. Le mécanisme sous-jacent qui pourrait expliquer la surmortalité est la chute du débit coronaire lié à l'accélération et au caractère arythmique des contractions du ventricule gauche, qui réduisent la fraction d'éjection ventriculaire gauche. Les principales causes de décès associées à la FA après un IDM sont liées à l'insuffisance cardiaque. De plus, le sur-risque de décès chez ces patients insuffisants cardiaques est également associé à la survenue d'une mort subite par troubles du rythme ventriculaire graves. Quelle que soit sa forme, la FA a un effet négatif important sur le pronostic du patient. Dans des études récentes, la FA symptomatique a été associée à une mortalité intra-hospitalière de 17,8 %, à laquelle on peut ajouter la mortalité à 1 an de 18,8 %. De manière très intéressante, la FA silencieuse a également un effet négatif sur le pronostic des patients après un IDM, avec une mortalité intra-hospitalière de 10,4 % et qui reste élevée à un an à 5,7 %. De plus, la survenue d'une FA quelle que soit sa forme est un facteur prédictif indépendant de la mortalité au-delà de facteurs de risque traditionnels. La fréquence de survenue et l'impact pronostic à court et long termes des épisodes silencieux de FA, qui n'avaient jusqu'à été que rarement étudiés, soulèvent la question du dépistage systématique de la Fa silencieuse à la phase aiguë de l'IDM. Par conséquent, l'utilisation du monitoring en continu de l'ECG pourrait être une solution simple, efficace et peu coûteuse pour améliorer le dépistage des épisodes de FA silencieuse, même si des études sont encore nécessaires pour valider cette stratégie. Enfin, des études complémentaires semblent également prouver l'implication du stress oxydatif et de la dysfonction endothéliale, qui semblent jouer un rôle majeur dans le déclenchement de ce trouble du rythme.

Background

Atrial fibrillation (AF) is the most frequent heart rhythm disorder in the general population and contributes not only to a major deterioration in quality of life but also to an increase in cardiovascular morbimortality [1—5]; AF is a real public health problem, the effect of which is increasing with the ageing of the population. AF is present in 1—2% of the general population and affects more than 6 million Europeans; after 85 years of age, the prevalence of AF can be as high as 20%. The principal complication of AF concerns thromboembolic risk, especially stroke, which has a bleak prognosis and often serious neurological sequelae. Thus, AF affects the prognosis of patients directly, with a risk of death multiplied by 2, and an increased risk of stroke [6], hospitalization and left ventricular (LV) dysfunction.

Several factors, including age, arterial hypertension, heart failure, valvulopathy, thyroid disease and chronic obstructive pulmonary disease, promote the development and persistence of AF. In addition, myocardial ischaemia, whether acute or chronic, has been identified as one of the principal factors in the onset of AF and its persistence in the medium- and long-term [3—5,7,8].

Atrial fibrillation and myocardial infarction

Myocardial infarction (MI) is one of the major physiopathological situations that promote the onset of AF.

Epidemiology

The incidence of AF in the setting of MI has hardly changed over the past 20 years. Following the arrival of thrombolysis for the management of MI in the acute phase, the 1997 GUSTO-I study, which included 40,981 patients, found an incidence of 7.9% [26], while the 2005 OPTIMAAL study [9], in 5477 patients, reported a similar incidence of 7.2%. Our team, which conducted a study on AF after non—ST-segment elevation Min (STEMI), found an incidence of 7.6% [8]. In a recent study that evaluated the prognostic effect of AF after STEMI treated with primary angioplasty, the reported incidence was 6.4% [10]. The factors affecting the onset of AF in the acute phase of MI are now well known; those found most frequently are indicators of left ventricular (LV) dysfunction, notably Killip class IV on admission and increased heart rate on admission, particularly when it is above 100 beats per minute.

Age is a major risk factor, and is very frequently associated with the onset of AF [11—13]. Other variables, including a personal history of AF, certain cardiovascular risk factors such as hypertension or type 2 diabetes, as well as LV hypertrophy have been identified in the different studies [5]. In contrast, MI location, type of reperfusion, and the presence of ST-segment elevation do not appear to be predictors of the onset of AF [14—16]. Although the overall incidence has remained stable over time, it varies considerably from one study to another, ranging from 2.3% to 21%, because it is strongly dependent on the screening method used and the duration of screening [5].

The diagnosis of AF depends on the discovery of rhythm anomalies meeting the definition of AF according to European recommendations [17]: strictly irregular RR intervals on the surface electrocardiogram (ECG); absence of identifiable P waves, with an unidentifiable isoelectric line; atrial rhythm > 300 beats per minute or an interval between two atrial activations < 200 ms. The diagnosis of AF can be made on a 12-lead surface ECG without taking the duration into account, or on an ECG readout of at least 30 seconds [17].

The complications associated with the onset of AF do not vary according to the type of episode. Indeed, whether the AF is paroxysmal, persistent or permanent, or symptomatic or silent, it can be complicated by serious or life-threatening thromboembolic events. Two studies have shown that episodes of AF, even silent or infraclinical AF, are associated with a significantly increased risk of stroke or other thromboembolic complications, which means that systematic screening for AF is essential in any patients with ischaemic stroke [18—21]. In a study that compared different screening methods (noninvasive [3- or 7-day Holter, ECG monitor, surface ECG, etc.], invasive [implantable loop recorder] or even intracardiac recording methods [pacemaker]), the authors pointed out that the detection of AF, whether symptomatic or silent, improved with the duration of monitoring. Although there was no clear difference between the screening methods, they noted that screening by 7-day Holter was slightly superior, in that it provided continuous screening and was relatively easy to use.

Nonetheless, despite meticulous screening, there are still no recognized thresholds for AF duration or the frequency at which the thromboembolic risk becomes significant. Recommendations for the use of anticoagulants in the therapeutic management of AF, however, only take into account embolic risk factors (CHA_2DS_2-VASc score) and not AF duration or frequency [21].

Today, in routine clinical practice for the management of patients in the acute phase of MI, continuous ECG monitoring (CEM) is set up for the first 48 to 72 hours of their stay in the cardiac intensive care unit. The diagnosis of AF with a CEM apparatus is automatic; it is based on the application of algorithms incorporated in the software of the apparatus, which is able to detection a rhythm compatible with AF in only 15 cardiac cycles. The episode is considered significant when it lasts for at least 30 seconds. This screening system makes it possible to prolong the screening and determine the precise incidence of AF after MI. In addition, automatic detection also identifies infraclinical episodes. Recent studies have suggested that this type of AF is frequent after stroke and its consequences are far from innocuous.

Systematic screening for AF after MI therefore appears to be a key element in the management of patients. In recent studies, our team showed that systematic CEM could improve the efficacy of screening for episodes of AF after MI [22]. Indeed, this automated screening method revealed an incidence of AF of 21%, among which three of four were episodes of silent AF, thus identified by the CEM only.

Principal mechanisms and consequences

The onset of AF in the acute phase of MI is a major event that can jeopardize the prognosis of patients in the short-, medium- and long-term; it is a powerful predictor of a poor prognosis after MI [5,20,23—27]. In 2005, our team showed that the onset of AF was a predictor of poor prognosis in patients with non-STEMI [8]. This effect on prognosis was also reported in studies on STEMI [28,29]. This association was found whatever the type of reperfusion in the acute phase. Indeed, recent studies reported the harmful effect of AF onset in the acute phase of MI on mortality, even in patients treated with angioplasty [11,30,31]. The suspected mechanism underlying this excess mortality is the drop in coronary flow linked to the acceleration and arrhythmic nature of the LV contractions, which reduce the LV ejection fraction (LVEF). The reduced LVEF could explain the frequent episodes of heart failure following the onset of AF, found in association with increased LV telediastolic pressure and increased left atrial (LA) volume [13]. Moreover, by exacerbating LV ischaemia, AF is associated with an increased risk of severe ventricular rhythm disorders [29,30,32].

The acute phase of MI corresponds to a period of myocardial and systemic inflammation associated with elevated plasma markers [10,33,34]. This inflammatory process activates cellular growth factors and tissue repair mechanisms, leading to atrial fibrosis and remodelling, which are likely to generate the anatomical substrate favourable for the subsequent onset of AF and its persistence over time [17]. The ultrasound LA variables, particularly LA volume, indirectly reflect this remodelling. The follow-up of patients after MI

shows that those who develop new onset AF, those whose paroxysmal AF is reactivated, or even those who present with permanent AF on admission have a higher inhospital and long-term mortality rate than patients without AF after MI [5]. However, certain studies suggest that this mortality rate varies according to the type of AF.

Indeed, in the OPTIMAAL trial, the inhospital mortality rate in patients who developed new onset AF in the acute phase of MI was higher than that in patients without AF. This difference, however, was not found between patients with AF on admission and those without AF [9]. Moreover, the study by Jabre et al. provided additional details, by showing that the prognosis in patients who developed de novo AF depended on when the AF occurred. Indeed, the mortality rate in patients who developed AF beyond 30 days after MI was twice that in patients without AF after MI and greater than that in patients who developed AF between the second and thirtieth day after MI [20]. However, the early post-MI period, notably the first 48 hours, was the peak period for the onset of episodes of AF, and included 30% of such episodes. As shown above, the time to onset of AF after MI affects the prognosis. Another major element leading to excess mortality is impaired LVEF, according to data from the VALIANT study [24].

The principal causes of AF-associated death after MI are linked to heart failure [9]. Moreover, the excess risk of death in these heart failure patients has also been associated with the onset of sudden death, with an odds ratio of 1.33 (95% confidence interval 1.19—1.49; $P < 0.001$) [35].

Finally, the principal complication of AF, namely stroke, has also been studied. Three important studies showed a higher incidence of stroke after MI in patients who experienced AF in the acute phase. The analysis of data from the GUSTO-I trial showed a stroke incidence of 3.1% in patients who presented with AF in the acute phase, compared with 1.3% in patients in sinus rhythm. In this study, involving more than 40,000 patients, most of the strokes were ischaemic [36].

The onset of AF, when it occurs during the acute phase of MI, is a serious event because it increases the risk of stroke in the medium- and long-term, and is responsible for the increased mortality most often linked to heart failure and sudden death. Although numerous studies have investigated the conditions surrounding the onset of AF, the precise physiopathological mechanisms responsible for the onset of AF in the acute phase of MI are still unclear; they notably involve atrial ischaemia, increased LV telediastolic pressure and its effect on the left atrium (LA), neurohormonal phenomena and their link with atrial hyperexcitability and, finally, oxidative stress.

Implication of oxidative stress in myocardial infarction

Oxidative stress corresponds to an imbalance between the pro-oxidant and antioxidant systems. During an ischaemia/reperfusion sequence, the oxidative balance tilts in favour of the production of free radical species, such as superoxide anion [37]. An increase in oxidative stress, which is a target of choice for future therapies, could be an important mediator of atrial remodelling [38]. Indeed, studies in animal models have suggested that the oxidative stress pathway is one of the pathways via which inflammation could trigger AF. In a dog model of pacemaker-induced AF, a fall in tissue antioxidant defences (ascorbic acid) and an increase in markers of nitro-oxidative stress were observed [39]. Moreover, in a recent study in pigs subjected to rapid atrial stimulation for a week to trigger the onset of AF, the concentration of superoxide anion production in atrial tissue in the AF pigs was three times greater than that in control pigs without AF [40]. In addition, the analysis of atrial tissue from patients after a Maze operation showed oxidative-type alterations in the myofibrils in the appendages (especially the LA appendage) in these patients with chronic AF. This damage was attributed to the release of peroxynitrites and hydroxyl radicals. These free radical species lead to the formation of carbonylated proteins and nitrotyrosine, suggesting, in humans, that an oxidative process takes place in the atrial myocardium of patients with chronic AF. This study indicates that oxidative stress has a major effect on the electrophysiological and mechanical properties of atrial myocytes, resulting in remodelling that favours the development and persistence of AF.

Age is also a major risk factor of the development of AF. Age correlates with the level of oxidative stress [41], thus reinforcing the hypothesis of a link between oxidative stress and AF.

Another pathway probably implicated in the onset of AF is endothelial dysfunction. Indeed, Kim et al. showed that nitric oxide synthase decoupling was implicated in the production of superoxide anion by myocardial tissue of the atria of patients with AF [42]. This excess of free radical species causes damage to the myofibrils responsible for structural remodelling, leading to the development of AF and the subsequent risk of thrombus formation [43,44].

Among the factors likely to modulate the bioavailability of nitric oxide, certain derivatives of L-arginine, including asymmetric N^G,N^G-dimethyl L-arginine (ADMA) and its stereoisomer symmetric N^G,N'^G-dimethyl L-arginine (SDMA), have recently been proposed as new biomarkers in cardiovascular diseases [45,46]. In 1998, Usui et al. reported high circulating concentrations of ADMA in heart failure patients with permanent AF [47]. Cengel et al. also showed that ADMA concentrations in patients who developed de novo AF were higher than those in patients with chronic AF [48]. Goette et al. very recently showed a fall in ADMA concentrations after cardioversion [49]. This modification in circulating concentrations of ADMA could be a consequence of the AF, but also a cause of the onset of AF. Indeed, certain studies have shown that high ADMA concentrations were associated with a more frequent recurrence of AF after cardioversion or a radiofrequency ablation procedure [50,51]. In patients with ischaemic heart disease and AF, a high concentration of ADMA was shown to be a risk factor for cardiovascular adverse events, including ischaemic stroke or cardiovascular death. A high concentration of ADMA (> 0.55 μmol/L) is a risk factor that is independent of LA size and the CHA_2DS_2-VASc score [52].

It therefore appears that the methylated derivatives of L-arginine could potentially be implicated in the onset of AF and its effect on the prognosis of patients. In a recent study, we were able to show that the plasma concentration of ADMA was an independent predictive factor of the onset

of AF in the acute phase of MI. This study was the first to suggest that ADMA was a possible cause of AF onset, and not just a consequence of a local increase in oxidative stress linked to the loss of atrial systole and LA stretching [53].

Ultrasound left atrial size variables: value in atrial fibrillation

LA enlargement has long been known as a risk factor for the onset and persistence of AF [22,27]. Ultrasound evaluation of LA variables quickly became the reference method to determine LA enlargement in this context. Complementary studies provided evidence of the direct prognostic effect of this variable [54], by identifying LA enlargement as an independent predictor of a poor prognosis, associated with increases in all-cause mortality after MI, in the risk of stroke and in rehospitalization for cardiac decompensation in patients with heart failure [54—57]. To explain this association, it was suggested that LA enlargement was a marker of the severity and chronicity of high LA filling pressure and thus diastolic dysfunction of the left ventricle (LV) [58,59].

Different threshold values for LA enlargement, assessed according to diameter, area and volume, have been proposed by the European Association of Cardiovascular Imaging and the American Society of Echocardiography [60]. LA volume, especially when its value is indexed to body area, is a particularly robust variable for determining LA enlargement, and was validated by comparison with measurements by computed tomography or cardiac magnetic resonance imaging. LA volume appears to correlate better with cardiovascular diseases, probably because it provides a better evaluation of the sometimes asymmetrical remodelling of the left atrium [12]. These data were confirmed by a study in patients in sinus rhythm, which compared the value of LA size evaluated using either the diameter, area or volume as a predictor of a poor prognosis [61]. Our studies showed that the area of the LA indexed to body area could also be an excellent tool in routine practice to evaluate the risk of AF onset in patients in the acute phase of MI. In multivariable analysis, this variable appeared to be an independent predictor of AF, and this beyond the indexed volume [22,62]. These results can probably be explained by the accuracy of ultrasound measurements. The area in apical four-chamber and two-chamber views is measured directly by the operator, while the volume is calculated from the areas and longitudinal diameters obtained in the apical four-chamber and two-chamber views. The longitudinal diameters, however, may vary considerably depending on the view, the moment in the cardiac cycle and even the quality of the image obtained.

In our study, LA enlargement was an independent risk factor for inhospital death at 1 year after the acute phase. This major result underlines the central role of the LA in the onset of AF and in its prognostic consequences in the acute phase of MI [62].

In light of these data, it seemed interesting to evaluate LA function more precisely using more robust tools, such as speckle tracking of the LA. Indeed, this variable, which is easy to assess using current ultrasound techniques, has shown its predictive value in the maintenance of sinus rhythm after cardioversion using external electric shock [63]. Moreover, in patients after non-STEMI, the impairment of LA function evaluated by speckle tracking was significantly greater than that caused by simple enlargement evaluated by the usual variables. In addition, this impaired deformation of the LA was significantly associated with impaired LV function [64], suggesting that it could help us to understand the mechanisms leading to the onset of AF after MI.

Silent atrial fibrillation in the acute phase of myocardial infarction

AF is a frequent event in the first hours after MI, as 5% of patients present symptomatic AF. We showed for the first time that silent AF, with an incidence of 16% in the acute phase of MI, is three times more frequent than symptomatic AF.

As in symptomatic AF, old age and a history of AF are associated with a high-risk of silent AF. Moreover, the analysis of LA size variables showed for the first time that LA enlargement is an independent predictor of the onset of both symptomatic and silent AF in the acute phase of MI.

Whatever its form, AF has a major negative effect on the prognosis of patients. In our studies, symptomatic AF was associated with an inhospital mortality rate of 17.8%, to which can be added a mortality rate at 1 year of 18.8% [62]. Surprisingly, silent AF also has a negative effect on prognosis, as it is associated with an inhospital mortality rate of 10.4%, which remains high at 5.7% at 1 year [62]. Moreover, both forms of AF are independent predictors of mortality beyond traditional risk factors. The frequency and seriousness of silent AF in the short- and long-term, which were rarely studied until recently, raises the question of systematically screening for AF in the acute phase of MI, and thus, if found, its specific management. The comparative analysis of the prognosis in patients with symptomatic and silent AF showed that during the inhospital period, patients with symptomatic AF had more episodes of heart failure. In contrast, during the first year after MI, the levels of hospitalization for heart failure were similar (6.3% vs. 6.6%). In our studies, however, patients with symptomatic AF had a significantly lower LVEF at admission for MI (40% vs. 50% for symptomatic versus silent AF, respectively) [62]. To explain these apparently contradictory findings, Holter analysis 1 month after the event could make it possible to determine the risk of developing AF (paroxysmal or persistent). There is also the question of verifying the hypothesis according to which LVEF in patients who present silent AF deteriorates after they have left hospital. The role played by heart rhythm disorders in the impairment of LV function thus needs to be determined.

As we have already pointed out, given the negative effect of silent AF on prognosis, which was brought to light only recently, the question of managing silent AF arises. The initiation of anticoagulation therapy in these patients, most of whom are already taking dual antiplatelet therapy, must be discussed. Indeed, we showed that patients who present with AF are most often treated with vitamin K antagonists after discharge from hospital (27% of patients with silent AF and 50% of patients with symptomatic AF) [62]. Although

we did not evaluate the haemorrhagic risk, these data suggest that haemorrhagic events may have been implicated in the excess mortality of such patients. Our studies showed that although all-cause mortality was higher in the groups with AF, most deaths were related to cardiovascular disease. However, levels of recurrent infarction were similar in the three groups, and the statistical power was too low to analyse mortality related to stroke. In contrast, the rhythm analysis data provided by the CEM showed that the proportion of symptomatic AF patients with severe ventricular rhythm disorders (ventricular tachycardia and fibrillation) was greater than that in patients without AF (24.4% vs. 4.3%), which could explain the excess mortality.

The study of the treatments showed that, in the acute phase, when the risk of rhythm disorder is maximal, these patients were of course more likely to be treated with amiodarone and digoxin, but paradoxically were less likely to be treated with beta-blockers. This difference regarding beta-blockers was not found at discharge; it therefore does not explain the excess risk of cardiovascular death at 1 year [62].

Nonetheless, we showed that angiotensin-converting enzyme inhibitors were still underused in patients with AF [62]. It would appear interesting in the context of prospective studies to analyse the effect of atrial and ventricular remodelling on the onset of severe ventricular rhythm disorders, and the effect of treatments with angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers on these AF-related disorders. A subgroup analysis according to treatment with beta-blockers at the acute phase would make it possible to determine whether patients not treated with beta-blockers had an excess risk of death. Defining an appropriate management strategy that takes into account the specific risks of this high-risk population appears to be an important clinical challenge. This is particularly true when data relative to the LVEF are analysed in detail: impaired LVEF is a major determinant of the risk of developing AF [22,62]. The link between AF and LVEF could explain the worse prognosis in these patients. In our study, however, we showed that even in the subgroup of patients with a preserved LVEF (LVEF > 40%), silent AF was an independent predictor of death [62]. Therefore, this specific population of patients with AF are probably underidentified and undertreated, notably because the exact reasons for their poor prognosis have not yet been determined.

Conclusion

AF in the acute phase of MI is a frequent and serious event with a major effect on the prognosis of patients. In light of recent studies, it appears that no forms of AF should be ignored, and we underline in particular the importance of screening for silent AF, which appears to be the most frequent form in the acute phase of MI. The use of CEM is a simple, effective and inexpensive solution to improve screening for AF immediately, although complementary studies are still necessary to validate this strategy. Finally, complementary studies also need to be conducted to understand the pathophysiological mechanisms, especially the effect of oxidative stress and endothelial dysfunction, which seem to play a major role in triggering this rhythm disorder.

Disclosure of interest

The authors declare that they have no competing interest.

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