



# Prevention and Treatment of Acute Stroke in the Nonagenarians and Beyond: Medical and Ethical Issues

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## Abstract

*Purpose of review* As one of the fastest growing portions of the population, nonagenarians will constitute a significant percentage of the stroke patient population in the near future. Nonagenarians are nevertheless not specifically targeted by most clinical guidelines. In this review, we aimed to summarise the available evidence guiding stroke prevention and treatment in this age group.

*Recent findings* Several recent observational studies have shown that the benefits of anticoagulation for the oldest old patients with atrial fibrillation may outweigh the bleeding risk. A sub-analysis of the IST-3 trial has shown for the first time that thrombolysis treatment in acute ischaemic stroke may be beneficial and safe even in octogenarian patients and older. Several recent observational studies have assessed thrombolysis in nonagenarians. The latest of these has shown better disability outcomes without increased rates of symptomatic intracerebral haemorrhage with thrombolysis.

*Summary* Nonagenarian stroke patients may benefit from similar preventative and therapeutic strategies as their younger counterparts. A few important exceptions include primary prevention using aspirin or statins. Patient selection is nevertheless essential

given the increased adverse event rates. Patient preference should play a key role in the decision-making process. Clinical trials including more nonagenarian patients are required to yield more robust evidence.

## Introduction

In Europe alone, the population older than 90 years is expected to increase from 6.5 to 16.3 million by 2050 [1]. These demographic shifts are expected to be accompanied by concordant changes in the epidemiology of chronic diseases [2, 3]. Cerebrovascular disorders in particular exhibit such a pattern: over 20 cases in 1000 patient-years occur over the age of 85 [4], accounting for 17% of all strokes [5].

Stroke in the very old is associated with a poor prognosis: patients older than 80 years are twice more likely to die within 30 days, with a 50% increased risk of dependency [4]. Those older than 85 are 3 times more likely to die at 5 years [6]. Whilst these differences may be attributable to factors such as a decreased life expectancy, high comorbidity burden or decreased compensatory

reserve in the very elderly [7, 8], evidence suggests that older stroke patients may receive poorer care than their younger counterparts [8]. Given that the evidence for the prevention and management of stroke in the very elderly is scarce [9], clinicians may often be reluctant to offer treatments that may be perceived as 'high risk', such as anticoagulation for atrial fibrillation or thrombolysis in the setting of acute ischaemic stroke [9].

In this review, we aim to summarise the latest evidence regarding the use of preventative and curative therapies in acute stroke patients older than 90 years of age. We also highlight the ethical aspects of management in this patient group.

## Prevention

The mainstay of stroke primary prevention is the management of modifiable risk factors [10]. The INTERSTROKE study [11] evaluated the effects of modifiable risk factors on stroke incidence in 32 countries and reported that 10 risk factors are implicated in up to 90% of strokes in all ages. These risk factors include hypertension, smoking, cardiovascular disease, obesity and dyslipidaemia. Despite extensive literature regarding the management of these risk factors and the benefits of treatment [10], there is limited evidence for those over 80 years of age. The following strategies outline the current evidence in regard to these risk factors as applied to nonagenarians.

### Lifestyle modification

Physical inactivity has been shown to be associated with a 60% increase in the risk of incident stroke in patients older than 80 years [12]. Furthermore, the relationship between smoking and adverse cardiovascular events has also been confirmed in older adults [13].

The adoption of an active lifestyle along with a balanced diet and smoking cessation may be as effective for the primary prevention of stroke in the oldest old as in the general population [5, 14]. More importantly, such approaches are especially advantageous in the oldest old since they do not contribute to

increasing polypharmacy.

## Hypertension control

Hypertension is the most important risk factor for stroke [15]. Nevertheless, the management of hypertension is more complex in the oldest old patients. The classic paradigm of blood pressure control 'the lower the better' may not apply to the very elderly and frail, who may be predisposed to cognitive dysfunction, hypotension and falls [16]. Furthermore, the issue of polypharmacy is vitally important in a population especially vulnerable to the adverse effects of pharmacotherapy and drug-drug interactions [17, 18].

A few studies have reported the outcomes of antihypertensive therapy in octogenarians and above. A meta-analysis of the INDANA intervention trials [19] showed that blood pressure management reduces the stroke risk by up to 33% in those older than 80. The HYVET trial [20] showed that blood pressure reduction using indapamide ± perindopril in octogenarians reduced the risk both overall mortality and stroke incidence by 21% and 30%, respectively. It is worth noting that the blood pressure target in the HYVET study was 150/80 mmHg, slightly higher than those recommended in current guidelines for younger age groups. Nevertheless, it is important to note that these studies have limited their evidence base to the healthiest and less frail individuals by excluding those with certain comorbidities and care home residents.

Expert opinion statements regarding the management of hypertension in old and frail patients have emphasised that based on currently available evidence, hypertensive patients older than 80 years of age should be treated to a target systolic blood pressure between 130 and 150 mmHg [21, 22]. It has been recommended that therapy should always be initiated as low-dose monotherapy only after a frailty assessment [21].

## Dyslipidaemia Control

Whilst the evidence supporting the use of statins in the primary and secondary prevention of cardiovascular and cerebrovascular disease is robust [10], most studies have only provided evidence for patients with a mean age of 75 years [23, 24]. Whilst current guidelines recommend the use of statins in all patients irrespective of age, the evidence base is very scarce for the very elderly. The largest observational study to date including 8307 patients older than 85 years has concluded that statin use was not associated with any benefit in incident stroke or death in these patients [25]. Data from clinical practice suggest that the oldest old patients are nevertheless prescribed statin therapy, albeit less frequently [26].

Statin use in the very elderly may be associated with myopathy [27], sarcopenia [28] and ultimately falls and fractures. Furthermore, it has been suggested that statin use may be associated with an increased risk of incident haemorrhagic stroke in patients with a previous transient ischaemic attack or stroke [29, 30]. Despite the fact that the most recent meta-analyses have failed to support this claim in either primary or secondary stroke prevention, no age-dependent sub-analyses have been performed in these studies [31–34]. Given that age may play an important role in the statin-associated haemorrhagic stroke risk, further studies are required to elucidate this relationship for the oldest old.

Nevertheless, given the other adverse effects that may be associated with statin use in nonagenarians, it would be sensible to suggest that their usage should be discouraged in this age group.

## Antiplatelet agents

### Primary prevention

The use of aspirin in the primary prevention of cardiovascular disease remains a common practice amongst older people [35, 36], despite doubts of whether the risk-benefit ratio of aspirin therapy warrants its use [37, 38]. Given that the aspirin-associated bleeding risk increases significantly in older ages [39], this therapy should not be recommended in the very old solely for stroke primary prevention.

### Secondary prevention

It has been established that patients with stroke or transient ischaemic attack (TIA) have better outcomes with low-dose aspirin monotherapy [40]. The risk-benefit ratio in older patients is likely to be different than in younger populations, given their higher propensity to suffer haemorrhagic complications [41]. Nevertheless, in the absence of clinical trials evaluating this outcome specifically in the oldest old, it has been suggested that the benefits of aspirin secondary stroke prevention may not be age-dependent [42]. The adjunctive usage of proton pump inhibitors may be associated with a reduction in gastrointestinal haemorrhage rates and may potentially lead to more acceptable outcomes [41], but this needs to be weighed against increasing polypharmacy.

Short-term dual antiplatelet therapy (low-dose aspirin and clopidogrel within the first 21 days after stroke) has been recently proposed as a better preventative strategy than aspirin monotherapy in patients with minor strokes or TIAs [43]. The clinical trials focused mainly on younger populations, and therefore, their findings may not be necessarily applicable to the very old. A careful consideration of the risk-benefit ratio should guide the decision-making process until further clinical trial evidence emerges for secondary stroke prevention in nonagenarian patients.

## Carotid endarterectomy and stenting

The presence of carotid stenosis is a risk factor for the development of ischaemic stroke [44]. For asymptomatic patients with carotid stenosis, a comprehensive systematic review has shown that surgical endarterectomy (CEA) was associated with both lower mortality and incident ipsilateral stroke compared with best medical therapy [45]. Nevertheless, the CEA-associated morbidity and mortality were also increased compared to medical therapy [45]. Furthermore, given that recent advancements in best medical therapy may decrease the risk of ipsilateral stroke to levels comparable to CEA, most recent guidelines only offer a class IIa recommendation for CEA in patients a low perioperative risk [10]. Thus, given that nonagenarian patients are more likely to be at a higher perioperative risk and that the ACST trial failed to show a CEA-associated reduction in the stroke risk in the subgroup of patients older than 75 years of age [46], it would be advisable that aspirin and statin therapy be solely employed for stroke

prevention in nonagenarian patients with asymptomatic carotid stenosis [10].

In the case of symptomatic moderate-to-severe carotid stenosis, current guidelines recommend CEA for secondary stroke prevention, provided that the perioperative risk is less than 6% [47]. Conflicting reports exist regarding the safety of CEA in patients older than 80 years. Whilst some reports suggest that CEA was not associated with a higher perioperative risk in the very elderly compared to younger patients [48–52], others draw the opposite conclusion [53–56]. A recent meta-analysis of randomised trials has concluded that age greater than 75 years was not associated with worse CEA outcomes [57]. Nevertheless, another meta-analysis of observational studies has concluded that despite similar rates of adverse cerebrovascular events with CEA between patients older and younger than 80 years, the former were at a higher mortality risk [58•].

Carotid artery stenting (CAS) is a percutaneous alternative to CEA for carotid revascularisation. The studies evaluating the use of CAS versus CEA in the very elderly have yielded more homogenous conclusions, suggesting that CAS should be avoided in this age group due to the high perioperative stroke risk [55, 57, 58•, 59, 60, 61, 62•]. The ongoing CREST-2 trial is aiming to compare the outcomes of best medical therapy, CEA and CAS in the management of asymptomatic carotid stenosis. Subgroup analyses from CREST-2 will hopefully provide evidence on the best management strategy in the very elderly [63•]. In the meantime, appropriate medical therapy should be mainstay of treatment in those patients regardless of whether an interventional approach is also considered. Optimal patient selection for carotid revascularisation is essential in the very elderly, and adjunctive tools such as frailty scores may prove useful for this purpose [64].

## Prevention of stroke in patients with atrial fibrillation

### Oral anticoagulation

Oral anticoagulation (OAC) is the mainstay of the prevention of atrial fibrillation-related stroke [65]. Despite being at a higher risk of stroke [66], a significant proportion of older patients with atrial fibrillation (up to 60%) is either not routinely anticoagulated [67–73] or receiving suboptimal therapy compared to younger patients [67]. Older patients are more likely to have significant contraindications to anticoagulant therapy or an unacceptably high bleeding risk [65]. Nevertheless, a review of the treatment regimens of 3378 care home residents with atrial fibrillation (mean age 85 years) has shown that only 56% of those who were not anticoagulated were deemed to have clear contraindications [70]. Whilst the data regarding the quality of anticoagulation specifically in patients older than 90 years is scarce, those are even less likely to receive OAC [74•, 75]. Less dramatic differences in the quality and quantity of anticoagulation between patients older and younger than 80 years have also been reported [76, 77].

Whilst the evidence supporting the use of OAC for primary stroke prevention is robust [78], very low numbers of nonagenarians are randomised in those clinical trials, leading to an important evidence gap in this age group. Nevertheless, several observational studies [67, 68, 74•, 79•, 80] and two small clinical trials [81•, 82•] suggest that despite increased risks of both ischaemic

stroke and major haemorrhage in octogenarians and nonagenarians with AF, the efficacy of OAC not only remains superior to antiplatelet regimens, but also the benefits of OAC may exceed the risks of major haemorrhage. A further consideration specific to the elderly patients receiving OAC is the increased fall risk, which may potentially increase the bleeding risk. Nevertheless, recent evidence fails to support this hypothesis [83, 84]. Given that a patient receiving vitamin K antagonist (VKA) therapy would need to fall 295 times per year to increase their risk of haemorrhage beyond the benefits of stroke prevention, it has been suggested that a high risk of falling in itself should not constitute an absolute contraindication for OAC [85].

Furthermore, the adoption of direct OACs (DOAC) represents an important milestone in stroke prevention in this age group. The lack of monitoring requirements in DOAC treatment has led to the more extensive adoption of OAC in very old patient groups, particularly given the higher burden of comorbid dementia and cognitive decline in this group [74, 76]. Recent evidence suggests that DOACs are at least as effective as VKAs, with comparable rates of major haemorrhage [86, 87]. They currently represent a very attractive alternative for OAC in nonagenarian patients due to the ease of administration; the decreased incidence of intracranial bleeding events; comparable rates of extracranial haemorrhage with certain agents, such as apixaban, edoxaban and reduced-dose dabigatran [88]; and the emergence of specific reversal agents [89]. Furthermore, in the context of polypharmacy in older patients, DOACs may be associated with fewer, but nevertheless not ignorable, drug interactions than VKAs [86, 90]. Nevertheless, certain cautionary points need to be taken in consideration with the usage of DOACs in extreme old age. The very high prevalence of renal impairment amongst nonagenarians compared to the general population [91] proves particularly problematic in the usage of DOACs, since in this very high-risk patient subgroup, there has not been an observed reduction in the incidence of ischaemic stroke with DOAC use [92]. Furthermore, DOACs are contra-indicated in AF related to valvular heart disease, the incidence of which may be higher in nonagenarian patients [93].

Despite the scarcity of available evidence regarding the adoption of OAC in nonagenarian patients with AF, certain conclusions may be extrapolated from the rather modest body of evidence concerning those over 75–80 years. It is sensible to suggest that the benefit derived from OAC is not age-dependent and may still exceed the risks of major bleeding even in nonagenarians. This should guide the decision to offer OAC in this group, taking into account the individual patient phenotype, such as those determined to be at a high bleeding risk [65], or those with clear contraindications to OAC. Magnetic resonance imaging techniques that are able to detect the presence of cerebral microbleeds (CMB) as a marker of cerebral amyloid angiopathy may be useful in delineating patient groups in whom OAC may be associated with an unacceptably high risk of intracranial haemorrhage [94, 95]. More recently, it has been suggested that the presence of five CMBs may represent an adequate threshold for identifying such high-risk subgroups amongst ischaemic stroke patients with AF [96].

Once the decision to offer OAC has been made, a choice of between VKA or DOAC regimens should be performed on a case-by-case basis, taking into account patient preference as well as the comorbid profile. Conditions such as renal impairment, dementia and valvular aetiology of AF, along with concomitant pharmacotherapy should be considered.

## Left atrial appendage closure devices

Percutaneous left atrial appendage (LAA) closure is an emerging alternative to OAC in patients in whom OAC is either contraindicated or the risks of long-term therapy are unacceptably high. LAA closure devices have been shown to be non-inferior to VKAs for stroke prevention both in the short term [97–99] and the long term [100]. Recent evidence has shown that LAA closure devices may be suitable in patients with advanced renal dysfunction for whom OAC would either involve an unacceptable bleeding risk or would not be effective [101]. Furthermore, in AF patients with a very high comorbidity burden and in whom the OAC-related risk reduction of ischaemic stroke may not be satisfactory, the usage of LAA closure devices may improve their outcomes [102]. Nevertheless, this procedure is not without complications, as it is performed under general anaesthesia and requires peri-procedural anticoagulation as well as long-term post-procedural antiplatelet therapy [103]. Other complications include post-implantation leak or thrombosis [103]. Despite the current lack of specific evidence for LAA closure in the very elderly, such devices seem to be amenable to patient phenotypes commonly seen amongst the elderly.

## Treatment

### Intravenous thrombolysis

The adoption of thrombolytic therapy using recombinant tissue-type plasmin activator (rtPA) has represented a revolutionary milestone in the acute treatment of ischaemic stroke. Nevertheless, those agents are only licenced in the European Union for patients younger than 80 years [104]. The Third International Stroke Trial (IST-3) was the first trial to show that intravenous (IV) rtPA treatment is as beneficial and safe in patients older than 80 years as in younger patients, having included 1617 patients over the age of 80 (53% of the total number randomised) and 209 patients older than 90 years [105••, 106]. Furthermore, IST-3 patients older than 80 years who received IV rtPA had a lower 3-year post-stroke mortality than those who did not [106, 107••].

A few systematic reviews evaluating this patient group exist to date. The most recent of those concluded as part of a subgroup analysis that patients older than 80 years who received IV rtPA within 6 h had similar stroke disability and mortality outcomes as those younger than 80 years [108••]. Nevertheless, the very low proportion of such patients having been randomised in the trials included in this review (other than IST-3) led to the IST-3 being the primary driver of the results. A further meta-analysis of individual clinical trial patient data suggested that IV rtPA ischaemic stroke onset offered a favourable stroke disability outcome in both patients older and younger than 80 years [109••]. Nevertheless, there was no improvement in this outcome with IV rtPA in octogenarians if the treatment delay exceeded 3 h [109••]. The other two meta-analyses that were published before the completion of the IST-3 trial concluded that IV rtPA treatment was associated with overall less favourable outcomes in patients over 80 years of age, including higher mortality. Nevertheless, octogenarians did not have a higher incidence of symptomatic intracranial haemorrhage events in either reports [110, 111]. Both studies have concluded that the observed poorer outcomes in the over 80 group may be related to residual

confounding. Observational studies have shown that IV rtPA was associated with lower post-stroke disability rates in octogenarians [112–118]. Furthermore, the rates of post-rtPA symptomatic intracerebral haemorrhage (sICH) were similar between octogenarians and younger patients [112–115, 119–123]. Finally, it has been suggested that treatment decisions facilitated by Stroke Telemedicine in octogenarian patients receiving IV rtPA achieve similar outcomes as cases where a stroke physician is present on site [124].

The evidence concerning rtPA in the oldest old stroke patients is scarce. Given that only 209 (7%) of the participants randomised in IST-3 were older than 90 years [106], a sub-analysis of this age group has not been performed. A prospective study concluded that stroke patients older than 85 years experienced worse mortality outcomes compared to younger age groups, without a significantly increased rise in the rate of sICH [125]. Observational studies have shown that amongst patients receiving rtPA, nonagenarians had higher rates of both mortality [119, 126•] and adverse events [126•]. Other observational studies have assessed the outcomes of nonagenarian stroke patients receiving thrombolysis [127•, 128•, 129•, 130•], but have yielded contradicting results. Whilst most of those suggested that nonagenarians did not benefit from IV rtPA [128, 129, 130•], a recent study including concluded that thrombolysis was associated with a better disability outcome without a significantly increased rate of sICH in this age group [127].

Overall, whilst it seems that increasing age is associated with worse mortality outcomes with IV rtPA treatment, it may be the case that residual confounders such as the increasing comorbidity burden may be responsible for this effect. Unfortunately, the studies assessing the outcomes of nonagenarian patients receiving IV rtPA failed to yield a single conclusion regarding the benefit—risk balance, unlike in octogenarians. This is most likely due to the high risk of bias inherent from the underpowered, retrospective nature of these studies. Current evidence suggests that stroke patients older than 80 years should not be refused IV thrombolytic treatment based on age alone, although the therapeutic window in this patient group may be limited to 3 h. Unfortunately, clear recommendations cannot be made for nonagenarians at this point. Further clinical trials of IV rtPA including higher proportions of nonagenarians are required.

## Mechanical thrombectomy

Mechanical thrombectomy in conjunction with IV rtPA treatment has been shown to be associated with better long-term stroke outcomes [131, 132]. Out of the five clinical trials that included patients older than 80 years of age [133–137], four performed subgroup analyses by age. Three of them concluded that patients older than 80 years of age derive the same benefit in terms of 90-day disability from mechanical thrombectomy as younger patients [133, 135, 137]. This has been further confirmed by a subgroup analysis in a meta-analysis of individual patient data including five controlled trials [138••]. Another meta-analysis of eight observational studies including a total of 1711 patients concluded that in patients older than 80 years of age mechanical thrombectomy was as likely to be associated with recanalization as in younger patients, without an elevated risk of

sICH. Nevertheless, octogenarians had poorer 3-month outcomes [139•].

Similarly to IV rtPA, the body of evidence evaluating this treatment in nonagenarian patients is severely limited. Two retrospective studies exist, including 18 and 19 nonagenarian patients with stroke, respectively. Whilst one of them has concluded that the acute outcomes do not differ based on the age divide alone [140], the other has suggested that nonagenarian patients may have lower rates of recanalization post-thrombectomy [141]. The latter therefore suggests that certain technical difficulties may exist, such as a more complex vascular approach. Nevertheless, given that better patient selection may improve the outcomes of this procedure, it would be reasonable to suggest that acute stroke patients should not be denied mechanical thrombectomy based on age alone. Other more important factors, such as pre-stroke functional status, comorbidity burden and stroke severity should be taken into consideration when deciding on a therapeutic route in nonagenarians.

## Haemorrhagic stroke

The data regarding the epidemiology, risk factors or outcomes of haemorrhagic strokes in the very elderly are extremely limited, with no studies focusing solely on nonagenarians. However, it has been shown that the clinical characteristics of intracerebral haemorrhage may be significantly different between patients older and younger than 80 years, respectively [142–144]. Thus, very elderly patients may be more likely to have subcortical haemorrhages, higher bleed volumes [143] and intra-ventricular extension [142]. Poorer outcomes have also been reported in the very elderly [143, 144]. Despite these suggestions, it is worth noting that these results originated from small observational studies and hence may not necessarily be generalizable to other populations. In the absence of more specific and robust evidence, an individualised approach with reasonable goals should be adopted. In addition, considering the high risks of intracerebral haemorrhage associated with pre-existing CMB [94, 95, 145], patients with CMB evidence on blood-sensitive MRI should be managed more intensively, focusing particularly on primary and secondary prevention.

## Ethical considerations

Besides the medical aspects of stroke treatment in nonagenarian patients, certain ethical elements require consideration. Regardless of age, clinical decisions should be in line with the four ethical principles governing medical practice, namely, respect for autonomy, nonmaleficence, beneficence, and justice. In terms of beneficence, the growing body of evidence evaluating the management of stroke in nonagenarian patients is likely to lead to an increase in the available therapies for this age group. Clinicians should be aware of such advances and not refuse treatment inappropriately. It is also essential that clinical practice minimise iatrogenic harm: high-risk subgroups should be identified through prognostic research and caution should be exerted whenever the risk-benefit ratio may not be favourable. It is also essential to respect the wishes of the patient and ensure that the necessary information about the risk and expected outcomes of non-treatment have been appropriately communicated.

Nevertheless, given the nature of cerebrovascular events and the relatively high prevalence of dementia and cognitive impairment amongst the oldest old, communication may not be straightforward. Many nonagenarian patients presenting with a cerebrovascular event may not have the capacity to take such a complex decision. Thus, in the view of a rapidly growing nonagenarian population, healthcare providers should encourage their elderly patients to prepare for such unfortunate eventualities by completing Advance Directives.

Finally, in a very rapidly ageing population with an increasing comorbidity burden, the healthcare resources that need to be allocated to the prevention and treatment of cerebrovascular disease will also increase. According to a recent study in the UK [146], the cost of combined health and social care for stroke sufferers older than 90 years of age over 5 years after the index event varied sharply with stroke severity and was significantly higher than in younger ages. Thus, the estimated cost for a nonagenarian patient with a severe stroke would be £75,000 (\$100,000), whilst moderate and severe strokes in this age group have been estimated to cost approximately £60,000 (\$80,000) and £45,000 (\$60,000), respectively. Regardless of the estimated life expectancy of nonagenarian patients, it is likely that the healthcare costs will vary with stroke severity proportionally. Thus, efforts to prevent stroke and minimise the stroke-associated disability may be associated with an overall decrease in healthcare expenditure.

Thus, healthcare providers will need to plan resource allocation accordingly, emphasising on the importance of prompt and effective preventative and treatment strategies to minimise disability and promote independence after stroke. It is only by meeting the increased demand in acute geriatric care that fairness can be ensured when deciding the clinical management of such complex patients.

## Conclusion

Given the rapidly growing segment of population over 90 years and the age-dependent incidence of cerebrovascular disease, it is reasonable to expect that the number of nonagenarian patients suffering stroke will also increase dramatically in the coming years. Despite the relative paucity of studies evaluating stroke prevention and treatment in this patient group, recent years have seen a dramatic increase in such trials. In this review, we have assessed the relevant literature covering those topics. We have found that some primary stroke prevention therapies may still be recommended in nonagenarians, such as anticoagulation for patients with AF, careful management of hypertension and lifestyle modifications, whilst aspirin and statin therapies have not proven efficacious. In terms of acute management, we have found that intravenous thrombolysis and mechanical thrombectomy may be beneficial even in this age group, but at the cost of higher complication rates. Such treatments should be prescribed in a carefully selected nonagenarian population, taking into account other factors such as patient preference. Further research that is inclusive of this population stratum is encouraged to elucidate current gaps in evidence and to provide evidence-based recommendations for clinical practice.

## Compliance with Ethical Standards

### Conflict of Interest

The authors declare that they have no conflicts of interest.

### Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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