

Clinical Practice Guideline for the secondary prevention of stroke. Update

Short version

Clinical Practice Guidelines in the Spanish NHS
Ministry of Health

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Clinical Practice Guideline for the secondary prevention of stroke. Update

1. Introduction

This CPG addresses pharmacological treatment for the secondary prevention of ischaemic and haemorrhagic stroke in adults with atrial fibrillation, patent foramen ovale (PFO) or heart valve diseases, in both primary care and hospital settings.

The target population for this guideline is patients diagnosed with stroke or transient ischaemic attack (TIA) who are candidates for secondary prevention aimed at delaying or reducing the likelihood of stroke recurrence.

This version in English contains the following types of information:

- **Clinical questions**
- **Recommendations**
- **Rationale**
- **Complete clinical question** (link to the version in Spanish)
- **References.**

To access the full version of the CPG (as a multilayer presentation or PDF), the methods employed, material for patients, families and other caregivers, and other information in Spanish please click on the following link:

<https://portal.guiasalud.es/gpc/prevencion-secundaria-ictus-actualizacion/>

2. Antithrombotic treatment for the secondary prevention of stroke

Question:

Can apixaban 5 mg twice daily be used for the secondary prevention of stroke in patients with atrial fibrillation?

Recommendations:

WEAK RECOMMENDATION IN FAVOUR

1. After analysing the evidence available on apixaban compared to warfarin (given the lack of other comparators in the literature meeting the proposed criteria for inclusion and prioritisation), the following recommendation was made:

In adult patients with indications for secondary prevention of stroke and nonvalvular atrial fibrillation, we suggest using apixaban rather than warfarin.

Rationale

Below, we outline the rationale for one of the recommendations, highlighting the judgements of the GDG concerning the key criteria that justify the final recommendation.

The GDG considered reduction in stroke recurrence (a desirable effect) and severe bleeding (an undesirable effect) to be the most important outcomes for assessing potential benefits. Regarding stroke recurrence, it considered the reduction observed in patients treated with apixaban compared to those treated with warfarin to be significant (16 fewer cases of stroke per 1000; a relative reduction of 29%). Regarding severe bleeding, it was considered that the risk of bleeding was lower in patients treated with apixaban than those treated with warfarin (16 cases of bleeding per 1000, a relative reduction of 27%). These considerations justified a recommendation in favour of the use of apixaban.

This recommendation was additionally supported by evidence in the literature of the importance patients place on reducing stroke recurrence (rating it even higher than avoiding death). Further, health professionals considered that apixaban was easier to use given that it does not require regular monitoring and shows little interaction with foods or other drugs.

Similarly, the GDG indicated that improvements in patient quality of life observed in clinical experience with apixaban supported this weak recommendation in favour.

Complete clinical question

For full information on this question (available in Spanish), see:

<http://portal.guiasalud.es/guia-en-capas/guia-de-practica-clinica-sobre-prevencion-secundaria-de-ictus-actualizacion/#question-1>

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Question:

Can dabigatran 110 mg twice daily be used for the secondary prevention of stroke in patients with atrial fibrillation?

Recommendations:

WEAK RECOMMENDATION IN FAVOUR

After analysing the evidence available on 110 mg dabigatran compared to warfarin (given the lack of other comparators in the literature meeting the proposed criteria for inclusion and prioritisation), the following recommendation was made:

In adult patients with an indication for the secondary prevention of stroke and non-valvular atrial fibrillation, we suggest using dabigatran 110 mg twice daily rather than warfarin.

Rationale

Below, we outline the rationale for one of the recommendations, highlighting the judgements of the GDG concerning the key criteria that justify the final recommendation.

The GDG indicated that the all-cause and vascular mortality outcomes may differ significantly in favour of the intervention. It considered that the benefit of the intervention (25 fewer all-cause deaths per 1000 treated with 110 mg dabigatran, a relative reduction of 28%) was relevant and conclusive in favour of the intervention, as the confidence interval (CI) did not include the null value.

The benefits in terms of safety were favourable for dabigatran 110 mg, with a lower risk of bleeding with this treatment compared to warfarin (27 fewer cases of bleeding per 1000, a relative reduction of 33%), and the CI did not include the null value; however, regarding myocardial infarction, dabigatran 110 mg had an undesirable effect, with three more events in the intervention group than the comparator (warfarin), although the results were not conclusive given that the CI did include the null value.

The GDG considered that the risk-benefit balance was favourable for dabigatran 110 g compared to warfarin.

The magnitude of the desirable and undesirable effects in relation to all-cause mortality, vascular mortality and severe bleeding may be considered moderate (favourable for the intervention); however, evidence on the outcomes of acute myocardial infarction and stroke recurrence was inconclusive.

The GDG indicated that the weak recommendation in favour was also supported by improvements in patient clinical condition and quality of life observed in clinical experience with dabigatran 110 mg, as well as the greater ease of use, with no requirement for monitoring and only a weak interaction with foods and other drugs.

Complete clinical question

For full information on this question (available in Spanish), see:

<http://portal.guiasalud.es/guia-en-capas/guia-de-practica-clinica-sobre-prevencion-secundaria-de-ictus-actualizacion/#question-1>

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Question:

Can dabigatran 150 mg twice daily be used for the secondary prevention of stroke in patients with atrial fibrillation?

Recommendations:

WEAK RECOMMENDATION IN FAVOUR

After analysing the evidence available on dabigatran 150 mg compared to warfarin (given the lack of other comparators in the literature meeting the proposed criteria for inclusion and prioritisation) the following recommendation was made.

In adult patients with an indication for secondary prevention of stroke and non-vascular atrial fibrillation, we suggest using dabigatran 150 mg twice daily rather than warfarin.

Rationale

Below, we outline the rationale for one of the recommendations, highlighting the judgements of the GDG concerning the key criteria that justify the final recommendation.

The GDG stated that there were no significant differences in favour of or against the intervention for any of the outcomes. Nonetheless, the GDG indicated that a weak recommendation in favour was supported by improvements in patients' clinical condition and quality of life observed in clinical experience with dabigatran 150 mg, as well as the greater ease of use, with no requirement for monitoring and only a weak interaction with foods and other drugs.

The weak recommendation in favour of the intervention is the result of weighing the risk-benefit balance in favour of or against dabigatran 150 mg, very low confidence in the evidence and uncertainty concerning whether the reported effect of the intervention might differ from the true effect. The magnitude of the desirable and undesirable effects may be considered small for all the outcomes except for the reduction in acute myocardial infarction, which could be considered moderate in favour of the comparator (warfarin).

Complete clinical question

For full information on this question (available in Spanish), see:

<http://portal.guiasalud.es/guia-en-capas/guia-de-practica-clinica-sobre-prevencion-secundaria-de-ictus-actualizacion/#question-1>

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Question:

Can edoxaban 60 mg once daily be used for the secondary prevention of stroke in patients with atrial fibrillation?

Recommendations:

WEAK RECOMMENDATION IN FAVOUR

After analysing the evidence available on edoxaban compared to warfarin (given the lack of other comparators in the literature meeting the proposed criteria for inclusion and prioritisation), the following recommendation was made:

In adult patients with an indication for the secondary prevention of stroke and non-valvular atrial fibrillation, we suggest using edoxaban rather than warfarin.

Rationale

Below, we outline the rationale for one of the recommendations, highlighting the judgements of the GDG concerning the key criteria that justify the final recommendation.

The GDG considered that the cardiovascular mortality outcome (desirable effect: a reduction) provided the most important benefits. It considered that the benefit of the intervention (20 fewer deaths per 1000, a relative reduction of 21%) was significant; the benefit in terms of safety was favourable for edoxaban, with a lower risk of bleeding with this treatment than with warfarin (13 fewer cases of bleeding per 1000, a relative reduction of 16%). Nonetheless, the CI included the null value, and hence, the GDG had little confidence in the evidence, as the effect of the intervention obtained in the study might differ from the true effect.

In this comparison, results in terms of stroke recurrence supported the intervention (9 fewer cases of stroke per 1000), although the CI did include the null value. The recommendation was also influenced by some studies having described patients preferring a reduction in stroke recurrence over improvements in other outcomes (even death).

The magnitude of the desirable and undesirable effects may be considered small.

The GDG had very low confidence in the estimate of the effect, especially because of the risk of bias and imprecision in the results, and hence, the risk-benefit balance was not clear and showed only weak support for benefits.

Nonetheless, the GDG indicated that a weak recommendation in favour was supported by improvements in patients' clinical condition and quality of life observed in clinical experience with edoxaban.

The conditional recommendation in favour of the intervention was reached after assessing the risk-benefit balance of using edoxaban rather than warfarin for the secondary prevention of stroke. In this assessment, it was considered that the balance would be positive (beneficial), although with a very low level of confidence in the available evidence, the expected effect possibly differing from the true effect (in the real world).

For the aforementioned reasons, the recommendation is weakly in favour of the intervention (edoxaban) over the comparator (warfarin).

Complete clinical question

For full information on this question (available in Spanish), see:

<http://portal.guiasalud.es/guia-en-capas/guia-de-practica-clinica-sobre-prevencion-secundaria-de-ictus-actualizacion/#question-1>

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Question:

Can rivaroxaban 15-20 mg once daily be used in patients with atrial fibrillation for the secondary prevention of stroke?

Recommendations:

WEAK RECOMMENDATION IN FAVOUR

After analysing the evidence available on rivaroxaban compared to warfarin (given the lack of other comparators available such as acenocoumarol), the following recommendation was made:

In adult patients with an indication for the secondary prevention of stroke and non-valvular atrial fibrillation, we suggest using rivaroxaban rather than warfarin.

Key clinical considerations: the usual warnings and precautions for use listed in the summary of product characteristics were identified and special emphasis was placed on the need to check for adequate kidney function. There was insufficient evidence to make recommendations by subgroup, although there could be differences by sex and age.

Rationale

Below, we outline the rationale for one of the recommendations, highlighting the judgements of the GDG concerning the key criteria that justify the final recommendation.

The majority opinion in the GDG was that, in general, treatment with rivaroxaban has similar effects to that of treatment with warfarin for the secondary prevention of stroke in terms of the variables included in the analysis with the GRADE Evidence to Decision (EtD) framework and evidence profiles or tables. It was considered relevant to analyse certain variables associated

with severe bleeding in patients with a history of stroke which had not previously been included. These variables were fatal bleeding (which could be considered “major bleeding”) and extracranial bleeding. In the case of the former, a relative risk (RR) of 0.98 (95% CI: 0.80–1.20) was observed with 44 cases per 1000 treated with rivaroxaban and 45 cases per 1000 treated with warfarin. For this reason, the GDG concluded that it could suggest treatment with rivaroxaban rather than warfarin in patients with a risk of bleeding (the majority of patients).

Regarding the other variables, compared to warfarin, rivaroxaban for the secondary prevention of stroke had similar absolute effects (per 1000 patients treated, rivaroxaban being associated with 1 fewer case of stroke [95% CI: 9 fewer to 10 more strokes], 2 fewer cases of all-cause mortality [95% CI: 13 fewer to 10 more deaths], the same stroke-related mortality [95% CI: 3 fewer to 2 more] and 1 fewer case of vascular mortality [95% CI: 10 fewer to 10 more deaths]) and similar adverse effects (rivaroxaban being associated with 1 fewer case of severe bleeding [95% CI: 9 fewer to 10 more cases], 2 more cases of myocardial infarction [95% CI: 3 fewer to 9 more cases, and the same risk of systemic embolism). It should be highlighted that the assessment carried out by the methodology working group for this guideline considered that the studies included had limitations as a result of the risk of bias or imprecision while the GDG indicated that improvements in patients’ clinical condition and quality of life in clinical experience with this treatment supported the weak recommendation in favour.

Complete clinical question

For full information on this question (available in Spanish), see:

<http://portal.guiasalud.es/guia-en-capas/guia-de-practica-clinica-sobre-prevencion-secundaria-de-ictus-actualizacion/#question-1>

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3. Patent foramen ovale, stroke and antithrombotic treatment

Question:

Can PFO closure plus antiplatelets be used instead of anticoagulation for the secondary prevention of stroke in adult patients with PFO?

Recommendations:

WEAK RECOMMENDATION IN FAVOUR

After analysing the evidence available regarding PFO plus antiplatelet therapy instead of anticoagulation for the secondary prevention of stroke, the following recommendation was made (given the lack of individual comparators in the literature meeting the proposed criteria for inclusion and prioritisation):

In patients under 60 years old with cryptogenic stroke or TIA (both embolic in nature), we suggest using PFO closure plus antiplatelet therapy instead of anticoagulation for the secondary prevention of stroke.

Rationale

Below, we outline the rationale for one of the recommendations, highlighting the judgements of the GDG concerning the key criteria that justify the final recommendation.

The experts considered that opting for PFO closure followed by antiplatelet therapy instead of the use of anticoagulation treatment may have little or no impact on stroke recurrence (1.6% of events in 5 years) and would probably reduce the occurrence of major bleeding (2.0% of events in 5 years). Further, they considered that it may have little or no impact on rates of all-cause mortality, TIA, and systemic embolism.

The results observed in terms of absolute values showed that PFO closure plus antiplatelet therapy was associated with 20 fewer episodes of major bleeding per 1000 patients treated with anticoagulation (95% CI: 27 fewer to 2 more episodes). The odds ratio was 0.26 (95% CI: 0.07 – 0.82). For other key variables (TIA, all-cause mortality, and systemic embolism), the absolute values all had confidence intervals that included the null value, and hence, no statistically significant differences were observed between the treatments.

Therefore, the GDG considered that PFO closure plus antiplatelet therapy reduced the risk of major bleeding compared to anticoagulation, although there would not be significant benefits in terms of reduction in the risk of stroke or TIA.

The weak recommendation in favour of the intervention or suggestion to perform PFO closure followed by antiplatelet therapy in the context of the Spanish National Health System was the result of the balance of the health effects likely favouring the intervention, taking into account the values and preferences of patients, who rated all the variables as critical and manifested their preference for stroke prevention over other variables, and also considering it to be a relevant issue that anticoagulant therapy needs monitoring.

Regarding the outcomes of stroke recurrence and all-cause mortality, the confidence in the evidence was rated as low, and therefore, the effect observed in the study is likely to be substantially different from the true effect. For the outcomes of severe bleeding, TIA, and systemic embolism, the confidence in the evidence was considered moderate.

Complete clinical question

For full information on this question (available in Spanish), see:

<http://portal.guiasalud.es/guia-en-capas/guia-de-practica-clinica-sobre-prevencion-secundaria-de-ictus-actualizacion/#question-2>

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Question:

Can PFO closure plus antiplatelet therapy be used instead of antiplatelet therapy alone for the secondary prevention of stroke in adult patients with PFO?

Recommendations:

WEAK RECOMMENDATION IN FAVOUR

After analysing the evidence available on PFO closure plus antiplatelet therapy compared to antiplatelets alone for the secondary prevention of stroke in adult patients with PFO, the following recommendation was made:

We suggest using closure of PFO plus antiplatelet therapy instead of antiplatelet therapy alone in patients under 60 years of age with stroke or cryptogenic TIA (both embolic in nature) in whom the most plausible cause of these events is the PFO.

Rationale

Below, we outline the rationale for one of the recommendations, highlighting the judgements of the GDG concerning the key criteria that justify the final recommendation.

The weak recommendation for the intervention (PFO closure followed by antiplatelet therapy) in the context of the Spanish National Health Service was the result of weighing the health effects (it being considered that the balance was in favour of the intervention) as well as the values and preferences of patients (who preferred prevention of stroke over prevention of other complications).

A reference study (Mir et al. 2018) found that PFO closure plus antiplatelet therapy was associated with an 8.7% reduction in the risk of stroke recurrence after 3.8 years, and with a 0.6% increase in all-cause mortality and a 0.6% decrease in TIA over the 3.8 years of follow-up⁵⁸. Regarding adverse events, fewer cases of severe bleeding (0.7%) and systemic embolism (0.1%) were observed in patients treated with PFO closure plus antiplatelet therapy, over the 3.8-year follow-up. The confidence in the results observed (available evidence) was considered moderate, in favour of the intervention (PFO closure plus antiplatelet therapy), although limited due to the occurrence of serious intervention-related adverse events. In general, it was considered that although the use of a closure device would be associated with higher costs, this would be compensated for in the long term by a reduction in the rate of recurrence. Closure of PFO plus antiplatelet therapy seems feasible and would probably be accepted by the target population due to a reduction in the risk of stroke recurrence.

Complete clinical question

For full information on this question (available in Spanish), see:

<http://portal.guiasalud.es/guia-en-capas/guia-de-practica-clinica-sobre-prevencion-secundaria-de-ictus-actualizacion/#question-2>

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Question:

Can anticoagulant therapy be used instead of antiplatelet therapy for the secondary prevention of stroke in adult patients with PFO?

Recommendations:

WEAK RECOMMENDATION IN FAVOUR

After analysing the evidence available on anticoagulant compared to antiplatelet therapy for the secondary prevention of stroke in adult patients with PFO, the following recommendation was made:

In patients opting for medical treatment alone, without PFO closure, we suggest either antiplatelet or anticoagulation therapy, given that the result of the comparison indicates that the two types of treatment have similar effects.

Rationale

Below, we outline the rationale for one of the recommendations, highlighting the judgements of the GDG concerning the key criteria that justify the final recommendation.

In patients with cryptogenic stroke and PFO, no differences were found between the use of anticoagulation and antiplatelet therapy in terms of desirable effects (reduction in the risk of stroke and TIA) or in the occurrence of adverse effects (bleeding or major bleeding), and hence, there was no basis for recommending anticoagulation over antiplatelet therapy. Further, it was observed that there was probably little or no difference in the rates of mortality, TIA or systemic embolism (evidence of moderate/low quality).

The low confidence in the evidence and variability in the values and preferences of patients reduce the confidence in the results.

Complete clinical question

For full information on this question (available in Spanish), see:

<http://portal.guiasalud.es/guia-en-capas/guia-de-practica-clinica-sobre-prevencion-secundaria-de-ictus-actualizacion/#question-2>

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4. Heart valve disease, stroke and antithrombotic treatment

Question:

Can oral anticoagulants be used instead of antiplatelets for the secondary prevention of stroke in adult patients with mitral valve prolapse?

Recommendations:

WEAK RECOMMENDATION AGAINST

After analysing the evidence available on oral anticoagulants vs antiplatelets for the secondary prevention of stroke in patients with mitral valve prolapse, the following recommendation was made:

We suggest not using anticoagulants instead of antiplatelets in adult patients with mitral valve prolapse with an indication for secondary prevention of stroke.

Rationale

Below, we outline the rationale for one of the recommendations, highlighting the judgements of the GDG concerning the key criteria that justify the final recommendation.

The GDG considered that there was uncertainty given the lack of evidence regarding the benefits of the intervention considered in the question posed.

The GDG did not know the magnitude of the desirable or undesirable effects as no studies were found that analysed the proposed comparator.

Complete clinical question

For full information on this question (available in Spanish), see:

<https://portal.guiasalud.es/guia-en-capas/guia-de-practica-clinica-sobre-prevencion-secundaria-de-ictus-actualizacion/#question-3>

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Question:

Can direct oral anticoagulants be used instead of oral vitamin K antagonists for the secondary prevention of stroke in adult patients with mitral stenosis?

Recommendations:

WEAK RECOMMENDATION AGAINST

After analysing the evidence available on direct oral anticoagulants (DOACs) compared to vitamin K antagonists for the secondary prevention of stroke in patients with mitral stenosis, the following recommendation was made:

In adult patients with moderate-to-severe mitral stenosis with an indication for secondary prevention of stroke, we suggest not using DOACs instead of vitamin K antagonists.

Rationale

Below, we outline the rationale for one of the recommendations, highlighting the judgements of the GDG concerning the key criteria that justify the final recommendation.

The GDG considered that there was uncertainty given the lack of evidence regarding the benefits of the intervention considered in the question posed.

It did not know the magnitude of the desirable or undesirable effects as no studies were found that analysed the proposed comparator.

There was consensus in the GDG to not include mild mitral stenosis in the recommendation, given that these patients were included in an RCT that analysed the efficacy of DOACs^{31,44,67,68}.

Complete clinical question

For full information on this question (available in Spanish), see:

<http://portal.guiasalud.es/guia-en-capas/guia-de-practica-clinica-sobre-prevencion-secundaria-de-ictus-actualizacion/#question-3>

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Question:

Can direct oral anticoagulants be used instead of oral vitamin K antagonists for the secondary prevention of stroke in adult patients with a prosthetic heart valve?

Recommendations:

WEAK RECOMMENDATION AGAINST

After analysing the evidence available on DOACs compared to vitamin K antagonists for the secondary prevention of stroke in patients with a prosthetic heart valve, the following recommendation was made:

In adult patients with a prosthetic heart valve with an indication for secondary prevention of stroke, we suggest not using DOACs instead of vitamin K antagonists.

Rationale

Below, we outline the rationale for one of the recommendations, highlighting the judgements of the GDG concerning the key criteria that justify the final recommendation.

The GDG considered that there was uncertainty given the lack of evidence regarding the benefits of the intervention considered in the question posed.

It did not know the magnitude of the desirable or undesirable effects as no studies were found that analysed the proposed comparator.

Complete clinical question

For full information on this question (available in Spanish), see:

<http://portal.guiasalud.es/guia-en-capas/guia-de-practica-clinica-sobre-prevencion-secundaria-de-ictus-actualizacion/#question-3>

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5. Therapeutic approach for patients with intracerebral haemorrhage during antithrombotic treatment

Question:

What therapeutic approach should be taken in patients with intracerebral haemorrhage during antithrombotic treatment?

Recommendation:

WEAK RECOMMENDATION AGAINST

After analysing the evidence available on survivors of stroke on antithrombotic treatment for secondary prevention with haemorrhage, we recommend conducting **research**. The identification of this area of uncertainty reveals a clear need for patients, health professionals and health systems.

Rationale

No studies assessing the research question have been found, mainly due to the exclusion of the target population from clinical trials. In general, randomised trials reported have excluded patients with a history of haemorrhage, and therefore, it is not possible to assess the risk/benefit balance of antiplatelet and anticoagulant therapy for the secondary prevention of stroke, despite the interest in having and need for standardised treatment regimens for this type of patient⁷⁵.

Three relevant publications were found that identified the clinical uncertainty associated with patients under antithrombotic treatment (antiplatelets or anticoagulants) who developed haemorrhage, although none of them met the inclusion and exclusion criteria set^{74,75,77}. The 2019 RESTART study included patients on therapy for the prevention of occlusive vascular disease in whom this therapy was withdrawn after they experienced intracerebral haemorrhage. That study excluded patients with a history of ischaemic stroke (haemorrhagic transformation of stroke), and therefore, did not include the target population of this guideline.

Secondly, in the case of the 2017 systematic review by Perry et al., the analysis included patients with intracerebral haemorrhage on heparin, and hence, their data could not be used to provide an answer to the question posed⁷⁵.

Thirdly, the 2017 systematic review and meta-analysis of retrospective studies by Murthy et al. included patients with a previous stroke and other disorders but disaggregated data were not reported. Although these authors carried out sensitivity analyses for various factors, they did not include the population with a history of stroke in the analyses, and hence, it was not possible to extract data to provide an answer to the question posed.

Regarding the clinical practice guidelines identified, we should highlight those of the European Society of Cardiology (ESC) recently published in collaboration with the European Heart Rhythm Association (EHRA). These guidelines state that the recommendation in patients with atrial fibrillation with a high risk of ischaemic stroke to (re) start treatment with DOACs rather than use vitamin K antagonists (in patients who meet the criteria for this medication) should be considered in consultation with the neurologist (stroke expert) after the onset of intracranial haemorrhage whether related to trauma or with a spontaneous acute onset (including subdural, subarachnoid, and intracerebral haemorrhage) for careful consideration of the risks and benefits⁷⁸.

The existence of recent guidelines addressing this topic and lack of scientific evidence make it clear that this issue is relevant and there is a major need for and interest in making practice guidelines available.

Complete clinical question

For full information on this question (available in Spanish), see:

<http://portal.guiasalud.es/guia-en-capas/guia-de-practica-clinica-sobre-prevencion-secundaria-de-ictus-actualizacion/#question-4>

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