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EMA/CHMP/341511/2014
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on 'Guideline on clinical investigation of medicinal products for prevention of stroke and systemic embolic events in patients with non-valvular atrial fibrillation' (EMA/CHMP/341363/2014)

Stakeholder no.	Name of organisation or individual
1	Robert G. Hart, M.D. McMaster University / Population Health Research Institute
2	Jean-Pierre Baeyens European Union Geriatric Medicine Society (EUGMS) representative
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1. General comments - overview

<table>
<tr><th>Stakeholder no.</th><th>General comment (if any)</th><th>Outcome (if applicable)</th></tr>
<tr><td>1.</td><td>
Comment 1: The document does not explicitly address the issue of “double-counting” of intracerebral hemorrhages (termed “hemorrhagic strokes” in the recent phase III trial publications. These events are included in the primary outcome of all strokes, and then counted again as major bleeds as intracranial hemorrhages. Among warfarin-assigned patients in recent atrial fibrillation studies, intracerebral hemorrhages account for about 15% of major hemorrhages (see table, below).

This double-counting has been consistently part of the recent NOAC trials and the tradition may be difficult to change at this point. Nevertheless, this is confusing and should be explicitly mentioned and address in the EMA/CHMP document, in my view.

Table: Fraction of major hemorrhages due to intracranial hemorrhage in recent (published between 2003 and 2013) studies of vitamin K antagonists in atrial fibrillation patients.^
<table>
<tr><th>Study</th><th>Number of anticoagulated patients (mean age)</th><th>Number (annualized rate) of major hemorrhages^</th><th>Fraction due to intracranial hemorrhage (n)</th></tr>
<tr><td>SPORTIF III (2003)(1)</td><td>1703 (70 yrs)</td><td>50 (2.2%/yr)</td><td>22% (11)</td></tr>
<tr><td>SPORTIF V (2005)(2)</td><td>1962 (72 yrs)</td><td>93 (3.4%/yr)</td><td>10% (9)</td></tr>
<tr><td>BAFTA (2007)(3)</td><td>488 (82 yrs)</td><td>25 (1.9%/yr)</td><td>32% (8)</td></tr>
<tr><td>ATRIA (2007)(4)</td><td>9217 (NR)</td><td>170 (1.1%/yr)</td><td>42% (72)</td></tr>
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It is agreed that there has been a double-counting of hemorrhagic strokes in recent trials with direct oral anticoagulants.

In fact, the last amendment of the guideline has been intended to exclude haemorrhagic stroke from the main efficacy outcome, as we consider this component a safety endpoint, instead of an efficacy endpoint. It is also agreed that current wording is somewhat confusing. The following amendment has been included in section 5.1 “Primary efficacy description” to reinforce that intracranial haemorrhages should not be a part of the primary efficacy outcome:

“Intracranial haemorrhages ~~Subdural or epidural haematoma are not considered as strokes and~~ (i.e.: hemorrhagic stroke/intracerebral hemorrhage, subdural or epidural hematoma/hemorrhage, or subarachnoid hemorrhage) should not be part of the primary efficacy outcome and should be primarily assessed as safety endpoint (major bleedings).”
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RE-LY (2009)(5)	6022 (72 yrs)	397 (3.4%/yr)	26% (87)
ROCKET AF (2011)(6)	7125# (73 yrs)	386 (3.4%/yr)	22% (84)
J-ROCKET (2011)(7)	639 (71 yrs)	30 (3.6%/yr)	33% (10)
ARISTOTLE (2011)(8)	9081 (70 yrs)	462 (3.1%/yr)	26% (122)
ENGAGE AF (2013)(9)	7036 (72 yrs)	524 (3.4%/yr)	25% (132)
Pooled	-	2137	25% (535)

NR = not reported; yrs = years.

^ Studies with target INR range of 2-3. Criteria for major hemorrhage are that used in the study and vary, but all include intracranial bleeding and subdural hematoma.

+"Safety population".

*Number of subdural hematomas estimated by subtracting intracerebral hemorrhages from total intracranial hemorrhages.(8)

References

1. Olsson SB, Executive Steering Committee on behalf of the SPORTIF III Investigators. Stroke prevention with the oral direct thrombin inhibitor ximelagatran compared with warfarin in patients with non-valvular atrial fibrillationi: randomized controlled trial. *Lancet* 2003; 362: 1691-8.

2. SPORTIF Executive Steering Committee for the SPORTIF V Investigators. Ximelagatran vs. warfarin for stroke prevention in patients with nonvalvular atrial fibrillation. *JAMA* 2005; 293: 690-8.

3. Mant J, Hobbs FD, Fletcher K, Roalfe A, Fitzmaurice D, Lip GYH, et al. on behalf of the BAFTA investigators and the Midland Research Practices Network. Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial. *Lancet*

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	2007; 370: 493-503. 4. Fang MC, Go As, Chang Y, Hylek EM, Henault LE, Jensvold NG, Singer DE. Death and disability from warfarin-associated intracranial and extracranial hemorrhages. *Am J Med* 2007; 120: 700-5. 5. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009; 361, 1139-51. 6. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011; 365: 883-91. 7. Hori M, Matsumoto M, Tanahashi N, Momomura S, Uchiyama S, Goto S et al. Rivaroxaban vs. warfarin in Japanese patients with atrial fibrillation. *Circ J* 2012: 76: 2104-11. 8. Granger CB, Alexander JH, McMurray JJV, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011; 365; 981-92. 9. Giugliano RP, Ruff CT, Braunwald E, et al. for the ENGAGE AF-TIMI 48 Investigators. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2013; doi:10.1056/NEJMoa1310907.	
1	**Comment 2:** The new oral anticoagulant agents have been referred to collectively as the “novel oral anticoagulants”, but the first results of phase III trials testing an oral direct thrombin inhibitor were published a decade ago,(SPORTIF III in *Lancet* 2003) and it is time for “novel” to be replaced. What distinguishes these agents from vitamin K antagonists is that they directly interact with their coagulation protein target, and direct-acting oral anticoagulant (DOACs) seems as good a replacement as any.	The comment is endorsed. The term “new” has been replaced by “direct oral” in subsection “Choice of control group”. Other references to “new” in the guideline have been applied to the drugs under clinical investigation, and therefore, the term “new” remains valid in these cases.
1	**Comment 3:** About 25% of major hemorrhages occurring in elderly	The comment is agreed.

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	patients during warfarin anticoagulation are intracranial, and most of these bleeds (about 75%) are either fatal or result in severe residual disability.(1) In contrast, major extracranial hemorrhage uncommonly results in death or permanent disability.(1) Almost 90% of deaths from warfarin-associated bleeding are due to intracranial bleeding.(1) The health consequences of intracranial hemorrhage are so different from those of extracranial major hemorrhage that it begs the question whether these two sites of bleeding should be grouped together as "major hemorrhage" when reporting the results of randomized trials of antithrombotic therapies. ***References*** 1. Fang MC, Go AS, Chang Y, et al. Death and disability from warfarin-associated intracranial and extracranial hemorrhages. *Am J Med* 2007: 120: 700-5.	The following paragraph has been added at the end of the subsection "major bleeding": "*Major intracranial bleedings (hemorrhagic stroke/intracerebral hemorrhage, subdural or epidural hematoma/hemorrhage, or subarachnoid hemorrhage) comprise an important part of all major bleedings reported in this indication, and are associated to a higher risk of death or disability than major extracranial bleedings. Therefore, major bleedings should also be described by localisation (e.g.: intracranial and extra-cranial, separately) and outcome (e.g.: resulting in death; resulting in disability; recovered without sequels).* "
1	**Comment 4:** The major phase III randomized trials have reported renal function using the out-of-date Cockcroft Gault equation for estimating creatinine clearance. Many clinical laboratories automatically provide an estimate glomerular filtration rate (eGFR) calculated by the more accurate CKD-EPI equation (1) or the MDRD (3)equation. Estimated creatinine clearance is clinically useless (and not identical to the eGFR). Data regarding renal function must always be presented using eGFR and not estimated creatinine clearance (of historical interest only).(2) ***References*** 1. Levey AS, Stevens LA, Schmid CH, Zhang Y, Castro AF, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J for the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration): A new equation to estimate	The comment is partially endorsed. While it is accepted that accurate methods should be used to calculate GFR, as stated in the EMA guideline on the evaluation of the pharmacokinetics of medicinal products in patients with impaired renal function (CHMP/EWP/225/02), indirect methods for estimating GFR, like creatinine clearance, although less accurate, may be acceptable. As it is not in the scope of the guideline to enter into discussion in how the GFR has to be measured, we have made the following amendment in the wording: We have replaced "creatinine clearance" by "renal function

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	glomerular filtration rate. Ann Intern Med 2009; 150: 604-12. 2. Stevens LA, Coresh J, Greene T, Levey AS. Assessing kidney function--measured and estimated glomerular filtration rate. N Engl J Med 2006; 354: 2473-83. 3. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Rot D. A more accurate method to estimate glomerular filtration rate from serum creatinine: anew prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 1999; 130: 461-70.	subgroups" in the "Statistical considerations" subsection.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
557	2	**Comment 1:** ”older” is non-specific and not correct. Stroke incidence is increasing exponentially with aging! We have to focus on the oldest “frail” older persons!! Proposed change (if any): “Frail Oldest older persons”	We have included the requested term “frail oldest older persons in section 8.3 “Special populations: *“Generating clinical data in older (≥75) and **frail** old**est** **older persons** (≥85 years) patients with high comorbidity is a matter of utmost importance, as they will represent an important part of the target population in standard practise.”*
Line 553 and followings	3	**Comment 1:** This is a well written and exhaustive guideline, with several useful recommendations. We would like EMA experts to consider one more recommendation. We believe it is important to recommend to include, in Phase III clinical trials, an adequate percentage of women. No recommendation is given on this peculiar aspect	We thank for the comments. However, a specific mention to women in the “special populations” subsection has not been included due to the following reasons: a) Section 6.1 “study population” already includes a general statement about the need for adequate representativeness of the population to be included in clinical trials. *“Inclusion and exclusion criteria in clinical trials should ensure adequate representativeness of the population studied across the entire clinical development, in reference to the population who will be treated with the new drug in standard clinical practice, while keeping the necessary assay sensitivity of individual studies.* b) In addition, women comprises about 40-45% of the population included in contemporary SPAF trials (Gomez-Outes et al, Thrombosis. 2013; 640723). This percentage is quite comparable to the 50% of AF patients that are women in standard clinical practice (Joppi et al. Eur J Intern Med.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			2013;24:318-23). The main concern about special populations is the under-representation of elderly patients above 75 years, which accounts for 31-40% of all patients included in phase III SPAF trials (Gomez-Outes et al, Thrombosis. 2013; 640723) compared with 65% of patients with AF in standard practice that are above 75 years (Joppi et al. Eur J Intern Med. 2013;24:318-23). Therefore, in the “special populations” subsection, we have focused on the appropriate representation of elderly patients.