Heparin bridging therapy and bleeding events in octogenarian inpatients with atrial fibrillation starting anticoagulation: results of an ancillary study.

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Heparin Bridging Therapy and bleeding events in octogenarians inpatients with atrial fibrillation starting anticoagulation: Results of an ancillary study

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To the Editor:

The prevalence of atrial fibrillation (AF) rises with advancing age reaching almost 10% in octogenarians[1]. Progress in medicine leads physicians to prescribe more Vitamin K antagonists (VKA) in octogenarians according to Evidence-Based Clinical Practice Guidelines[2,3,4]. The guidelines are however unclear regarding the need for heparin bridging therapy (HBT) at the initiation of VKA in patient without indication for immediate cardioversion. Indeed, the American College of Cardiology (ACC), the American Heart Association (AHA) and the European Society of Cardiology (ESC)[2,4] give no specific recommendation. The American College of Chest Physicians (ACCP)[3] specifies that "stable patients with AF can be anticoagulated on an outpatient basis with VKAs alone" but adds that "For particularly worrisome patients, physicians may be more comfortable with a heparin/warfarin bridging regimen". Who are the "particularly worrisome" patients? Should HBT be prescribed in octogenarians with high risk for thromboembolism and low risk for bleeding, as assessed by scores?

This article reports the results of an ancillary study from a pharmacokinetic and pharmacodynamic study on fluindione in French octogenarian inpatients. This ancillary study aimed to characterize the rate of HBT use in octogenarians starting AF-related anticoagulation during an acute care stay and to describe the thrombotic and bleeding events occurring during this stay.

METHOD:

The multicenter, prospective PREPA study was conducted between September 2005 and September 2007 in 6 medical and 1 surgical (cardiac) acute-care units at 3 French university-affiliated hospitals. The objective of the PREPA study was to model the pharmacokinetic and pharmacodynamic components of the response to fluindione in octogenarians inpatients starting fluindione (VKA-naive patients or after a 15-day wash-out) regardless of indication

(AF,venous thrombo-embolism, valvular prosthesis). Consecutive patients were included and physicians managed drugs according to routine clinical practice, without any algorithm. Therefore this study reflects real life practice of HBT. For this ancillary study, analyses were restricted to patients who were newly prescribed VKA for AF. Exclusion criteria were: fluindione absolute contraindications, contraindicated comedication, inability to give informed consent, inclusion in another trial of therapeutic evaluation and expected length of stay <3 days. Patients were followed until their discharge from the study unit or during the subsequent 30 days after the inclusion. Causes for premature withdrawal from the study were death, consent withdrawal or prescription of Vitamin K and/or Prothrombin complex concentrates. All bleeding and embolic events occurring during the follow-up were collected. Bleeding was considered severe if it required stopping VKA and/or additional procedure and/or treatment. Scores for thrombo-embolism and bleeding risks, as described in the 2010 ESC guidelines[4], were retrospectively assessed in patients with bleeding events.

RESULTS

Among the 132 included patients, 69 patients were newly prescribed VKA for AF. These patients were mostly females (N=44, 64%) and had a mean age of 86 ± 4 years. 20 (29%) patients were in post-operative care after cardiac surgery. The mean Charlson comorbidity index was 6.7 ± 2.4 and the patients had 8 ± 3 daily comedications at inclusion. Heparin or its derivatives were prescribed as a bridge therapy in 59 (85.5%) of these patients. None had an indication of cardioversion. General attrition rate during PREPA study was high, with a short length of stay: 49.2% of the included patients remained in the study at D7, 56.2% in the subgroup of AF-patients new to VKA. No thrombotic event occurred in the 69 VKA-naive AF patients during the study follow-up, whether they received HBT or not. Eight of these patients (11.6%) experienced bleeding (cf table1). All of them were considered to be at high risk of thrombo-embolism according to the CHA(2)DS(2)-VASc[4] score and at low-risk of bleeding

according to the HAS-BLED bleeding risk score[4] .Bleeding was severe in 5 patients (7.2%), with one related death. These severe bleedings occurred in the first 4 days and were always associated to HBT: in 3 cases, an heparin over-dosage was observed despite a correct heparin initial dose, in 1 case the INR was above the target range simultaneously to intercurrent infectious disease and the last occurred in a patient with a triple antithrombotic therapy and a very unstable health status. No thrombopenia was observed in the patients with a bleeding event.

DISCUSSION

This study showed a high rate (85.5%) of HBT use in octogenarians with AF starting VKA in acute-care units. The rate of bleeding events occurring in these patients during the first week of the fluindione initiation was very high (11.6%), especially the rate of severe bleeding (7.2%).

Inception cohorts[5,6] have established that bleeding risk is increased in AF octogenarians (especially in the first 90 days). The incidence of bleedings ranges from 1.9 to 13.1/100 person-years, but this estimate is subject to selection and methodological biases[7,8]. These cohorts included outpatients or mixed populations, the VKA (warfarin) was managed by anticoagulation clinics and the rate of heparin bridging therapy was not specified. The rate of bleeding in our small cohort is particularly worrying. It may be explained by the studied population (very old patients with unstable clinical status) with VKA (fluindione) managed by hospital clinicians without algorithm. The high rate of HBT may also have contributed to these bleedings, at least in 3 patients with an anti-Xa activity above the upper therapeutic range. However, heparin was not contra indicated in our population, according to the scores assessing risks of bleedings and of thrombotic events (cf table 1).It is surprising that the HAS-BLED score, which has the best predictive value of several bleeding risk stratification schemas[9], concluded wrongly to a low risk for bleeding (maximum risk of 1.88 bleeds per 100

patient years) in our patients with bleeding. The retrospective assessment of the score may have underestimated some items, notably alcohol use and labile INR. Above all, this score, which is based on almost 4,000 out and inpatients in the EuroHeart Survey on AF (mean Age 66+/-13 years) followed during one year for major bleeding, probably does not adapt well to octogenarian inpatients starting anticoagulation.

Our study has important limits due to its ancillary feature. First, the number and characteristics of the eligible non included patients were not recorded, precluding assessment of the sample representativity. Second, the high attrition rate could have induced an underestimation of bleeding and thrombotic events, especially those occurring after discharge. Nevertheless, our study underlines (i) the inappropriateness of the HAS-BLED score to predict individual risk of bleeding in octogenarian inpatients so that "known risk factors for increased risk of bleeding should be taken into account on an individual basis when starting anticoagulation"[11] and (ii) the need for future well-designed studies to provide relevant evidence to make recommendations for HBT administration in octogenarians inpatients with AF.

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Honoraria		X		X		X		X		X		X		X		X		X
Speaker Forum		X		X		X		X		X		X		X		X		X
Consultant		X		X		X		X		X		X		X		X		X
Stocks		X		X		X		X		X		X		X		X		X
Royalties		X		X		X		X		X		X		X		X		X
Expert Testimony		X		X		X		X		X		X		X		X		X

Board Member		X		X		X		X		X		X		X		X		X
Patents		X		X		X		X		X		X		X		X		X
Personal Relationship		X		X		X		X		X		X		X		X		X
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Employment or Affiliation		X		X		X												
Grants/Funds		X		X		X												
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Speaker Forum		X		X		X												
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Royalties		X		X		X												
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Table 1 : Bleeding events during the PREPA study (severe bleedings in grey)

Type of AF and AF-related symptoms (EHRA score)[4]	Age	Sex	Surgery	CHA_2DS_2VASc score and risk stratification*	HAS-BLED bleeding risk scoreand risk stratification†	Type of bleeding event	a) VKA stop b) additionnal treatment c) additional investigations	Date of bleeding ††	INR> 3§	HBT	AntiXa or PTT > therapeutic target §	Comments
First diagnosed AF Dyspnea (EHRA 4)	83	M	No	4 = High risk	2= low risk	Abdominal wall haematoma (9X6cm) with anemia (7.8g/dl))	a) Yes b) Blood transfusion + Vitamin K c) Abdominal echography	D4	Yes 3,37	Yes LMWH	No	Infectious event with prescription of Telithromycin respectively at D0 and D1 Fluindione dose was decreased from 15 to 10mg at D2
First diagnosed AF Dyspnea (EHRA 4)	88	M	No	4 = High risk	2= low risk	Hemorrhagic shock on digestive hemorrhage with anemia (5 g/dl)	a) Yes b) Blood transfusion + Gelofusine c) UGE	D2	No 1.45	Yes LMWH	No	Severe infectious disease before fluindione start with increased CRP (68), low serum albumin (28g/l) and prescription of Lévofloxacine (D-10 to D0) and amoxicillin clavulanic acid (D-8 to D0). Aspirin was stopped at D-1
Permanent AF No symptom (EHRA 1)	85	M	No	4 = High risk	2= low risk	Psoas Haematoma	a) Yes b) No c) TDM	D4	No 1.45	Yes UFH	Yes	Initial dose of HBT adjusted to clearance and weight (moderate renal failure at admission) No acute failure during the stay
First diagnosed AF Dyspnea (EHRA 4)	88	F	No	4 = High risk	2= low risk	Ankle haematoma	a) Yes b) Yes c) No	D3	No 1.44	Yes Calcium heparin	Yes	
First diagnosed AF No symptom (EHRA 1)	85	F	No	4 = High risk	1= low risk	Hemorrhagic shock with death	a) Yes b) Yes c) No	D2	No 1.39	Yes LMWH	Yes	Documented acute renal failure at D3 (no renal failure at admission)
First diagnosed AF Dyspnea (EHRA 3)	92	F	No	4 = High risk	2= low risk	Epistaxis	a) No b) No c) No	D6	No 2.68	Yes LMWH	No	Documented acute renal failure at D4 (moderate renal failure at admission)
Persistent AF No symptom (EHRA 1)	82	F	Yes: Aortic valve remplacement	5= High risk	2= low risk	Rectum haemorrhage	a) No b) No c) No	D8	No 2.61	No	NA	
Paroxysmal AF >48h feeling of faintness (EHRA 4)	83	F	No	3 = High risk	1= low risk	Rectum haemorrhage	a) No b) No c) No	D3	No 2.82	No	NA	

*items of CHA2DS2VASc score : **'major' risk factors** weigthed two points are "Previous stroke/ transient ischaemic attack.or systemic embolism" and "Age > 75 years", **Clinically relevant non-major' risk factors weighted one point are : "**Heart failure or moderate to severe Left Ventricular systolic dysfunction (e.g. < 40%)" and "Hypertension" and" Diabetes mellitus" and "Female sex" and " Age 65–74 years" and "Vascular disease"

† items of HAS-BLED score :Hypertension defined as systolic blood pressure >160 mmHg (1 point), presence of chronic dialysis or renal transplantation or serum creatinine ≥200 µmol/L (1 point), Abnormal liver function defined by chronic hepatic disease (e.g. cirrhosis) or biochemical evidence of significant hepatic derangement (e.g. bilirubin

.2 x upper limit of normal, in association with aspartate aminotransferase/alanine aminotransferase/alkaline phosphatase .3 x upper limit normal, etc. (one point), stroke (one point), previous bleeding history and/or predisposition to bleeding, e.g. bleeding diathesis, anaemia,(one point) labile INRs (one point- this item was systematically weighted zero in our study), age>65 years (one point), concomitant use of drug (antithrombotic agents, non-steroidal anti-inflammatory drugs etc) (one point) or alcohol (one point)

[† †] D0=Day of fluindione initiation

[§]the day of the bleeding event

AF= Atrial Fibrillation ; CRP= C-Reactive Protein ; EHRA =European Heart Rhythm Association ; HBT= Heparin Bridging Therapy ; HTA = Hypertension ; LMWH=Low-Molecule-Weight Heparin ; NA = Non adapted item ; PTT= Partial Thromboplastin Time ; TDM= Tomodensitometry ; UGE= Upper Gastrointestinal Endoscopy ; UFH= Unfractionned Heparin ; VKA= Vitamin K antagonist