once-daily Lixiana® edoxaban

What to Consider when It Comes to AF in the Elderly?

Higher Bleeding Risk[1]

For those ≥ 75 years:

- **3-Fold** Major Bleeding
- **4-Fold** ICH

vs. < 65 years

Increased Risk of Falls*,[2]

- **30%** p = 0.023 — Major Bleeding
- **67%** p = 0.013 — Life-Threatening Bleeding
- **45%** p < 0.001 — All-Cause Death

Need of Dose Adjustment

- All available DOACs are partly renally excreted[3,4]
- Not all low-dose DOACs have sufficient data from RCTs[4]

Polypharmacy

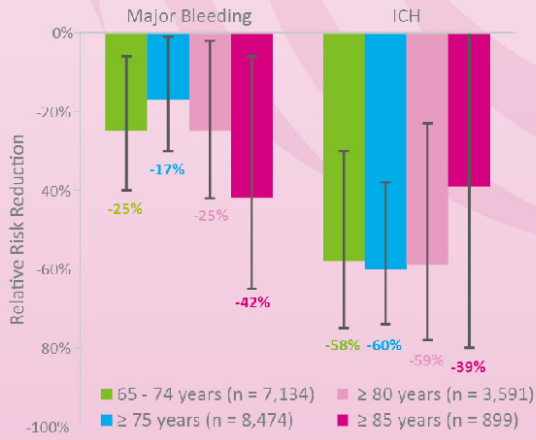
- Potential for drug interactions between a DOAC and concomitant medications[5]

LIXIANA®: Full Wealth of Data Supporting Use in the Elderly

LIXIANA® was well-tested in the elderly (≥ 65 years‡) and the very elderly (≥ 80 years & ≥ 85 years)[1]

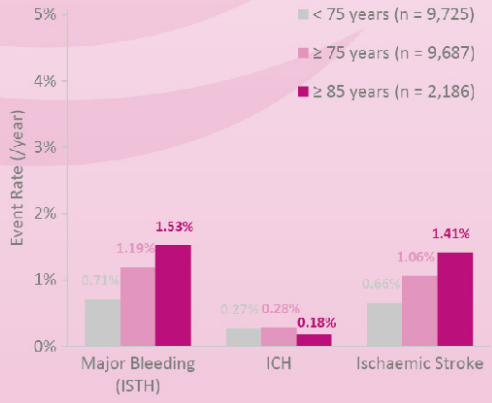
Evidence from ENGAGE AF-TIMI 48

Significant Major Bleeding and ICH Risk Reductions versus Warfarin†,[1]



Evidence from Global Real-World Study

Generally Low Rates of Major Bleeding (incl. ICH) and Ischaemic Stroke[6]



* Categorised as those fulfilling any of the following 8 criteria at randomization: 1) prior history of falls; 2) lower extremity weakness; 3) poor balance; 4) cognitive impairment; 5) orthostatic hypotension; 6) use of psychotropic drugs; 7) severe arthritis; or 8) dizziness.[2]

† In age groups from "65 - 74 years" to "≥ 85 years" for major bleeding and from "65 - 74 years" to "≥ 80 years" for ICH.[1]

‡ The elderly were defined as those ≥ 75 years of age in Kato ET, et al. (2016).[1]

Study design:
ENGAGE AF-TIMI 48 was a double-blind, double-dummy, randomised controlled trial of patients (≥ 21 years old) with AF and a $CHADS_2$ score ≥ 2. Patients (n = 21,105) were randomised (1:1:1) to receive either high-dose LIXIANA® (60 mg), low-dose LIXIANA® (30 mg) or warfarin (dose-adjusted to INR of 2.0 - 3.0) for a median follow-up period of 2.8 years. Dose was halved in patients in both LIXIANA® arms if any of the following was present: 1) CrCl 30 - 50 mL/min, 2) body weight ≤ 60 kg, or 3) concomitant use of verapamil, quinidine or dronedarone. The primary efficacy end point was the time to the first adjudicated stroke (ischaemic or haemorrhagic) or systemic embolic event.[7]
Global ETNA-AF is a multinational, prospective, noninterventional program encompassing several regional noninterventional observational studies to collect data on patient characteristics and routine clinical care outcomes in LIXIANA® -treated patients. A total of 26,100 patients with AF was targeted to enrol in Global ETNA-AF, with data from medical records consolidated up to 2 years after enrolment. Primary outcomes for ETNA-AF include bleeding events, drug-related adverse events and cardiovascular and all-cause mortality.[8,9]

Saving Frail Patients from Bleeding Events with LIXIANA®

In patients at increased risk of falls*, 1 bleeding event can be prevented in every…

ICH	NNT = 57	Life-Threatening Bleeding	NNT = 71

patients treated with LIXIANA® instead of warfarin†,2

LIXIANA® Provided Greater Protection with Consistent Efficacy in Patients Requiring Dose Reduction[9]

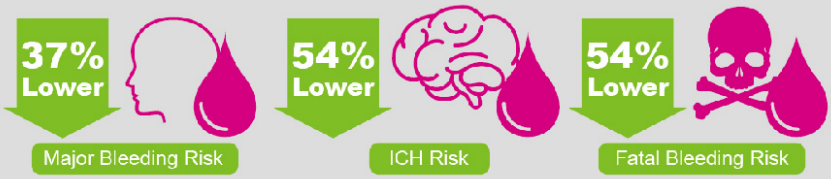
For patients with any 1 of the following:[10]

- **B**ody weight ≤ 60 kg
- **C**rCl 15 - 50 mL/min
- **D**rug concomitantly used: ciclosporin, dronedarone, erythromycin, ketoconazole

Dose Reduction to **30 mg QD** is Recommended[10]

Dose Reduction while on LIXIANA®‡

In ENGAGE AF-TIMI 48, 25.4% of patients in the LIXIANA® arms required dose reduction,[9] and 30.7% of those aged ≥ 65 years met dose reduction criteria at randomisation[1]



Compared with warfarin§,9

Think of LIXIANA® when offering anticoagulant to your elderly AF patients

- The only DOAC with data of patients ≥ 85 years[1]
- Significant bleeding risk reduction in elderly patients and in those at increased fall risk[1,2]
- The only DOAC with pivotal trial designed to include dynamic dose adjustments[9]
- Once daily with or without food[10] and with low propensity for CYP-mediated drug interactions[11]

* Categorised as those fulfilling any of the following 8 criteria at randomization: 1) prior history of falls; 2) lower extremity weakness; 3) poor balance; 4) cognitive impairment; 5) orthostatic hypotension; 6) use of psychotropic drugs; 7) severe arthritis; or 8) dizziness.[2]

† In the arm receiving standard dose LIXIANA® (60 mg QD, or 30 mg QD if either CrCl 30 - 50 mL/min, body weight ≤ 60 kg or with concomitant use of verapamil, quinidine or dronedarone) in ENGAGE AF-TIMI 48.[2]

‡ In ENGAGE AF-TIMI 48, 60% of dose reductions was performed due to CrCl 30 - 50 mL/min and 31% due to body weight ≤ 60 kg.[9]

§ In the arm receiving standard dose LIXIANA® (60 mg QD, or 30 mg QD if either CrCl 30 - 50 mL/min, body weight ≤ 60 kg or with concomitant use of potent P-glycoprotein inhibitors) in ENGAGE AF-TIMI 48.[9]

AF = atrial fibrillation. CrCl = creatinine clearance. CYP = cytochromes P450. DOAC = direct oral anticoagulant. ICH = intracranial haemorrhage. INR = international normalised ratio. ISTH = International Society on Thrombosis and Hemostasis. NNT = number needed to treat. QD = once daily. RCT = randomised controlled trial.

References: **1.** Katz ET, Giugliano RP, Ruff CT, et al. J Am Heart Assoc. 2016;5:e003432. **2.** Steffel J, Giugliano RP, Braunwald E, et al. J Am Coll Cardiol. 2016;68:1169-1178. **3.** Shroff GR. J Am Coll Cardiol. 2017;70:2733-2734. **4.** Steffel J, Verhamme P, Potpara TS, et al.; ESC Scientific Document Group. Eur Heart J. 2018;39:1330-1393. **5.** Kim IS, Kim HJ, Yu HT, et al. J Cardiol. 2019;73:515-521. **6.** Wang CC, Kim YH, Brueggenjuergen B, et al. ESC Congress 2019; 2019 Aug 31-Sep 4; Paris (France). Poster P4788. **7.** Giugliano RP, Ruff CT, Braunwald E, et al.; ENGAGE AF-TIMI 48 Investigators. N Engl J Med. 2013;369:2093-2104. **8.** De Caterina R, Agnelli G, Laeis P, et al. Clin Cardiol. 2019;42:1147-1154. **9.** Ruff CT, Giugliano RP, Braunwald E, et al. Lancet. 2015;385:2288-2295. **10.** LIXIANA® (edoxaban) package insert. Hong Kong; 2016 Sep.**11.** Poulakos M, Walker JN, Baig U, et al. Am J Health Syst Pharm. 2017;74:117-129.

LIXIANA® 60 mg/30 mg/15 mg film-coated tablets.
Each film coated tablet contains 60 mg/30 mg/15 mg edoxaban (as tosilate). List of excipients: Mannitol (E421), Pregelatinised starch, Crospovidone, Hydroxypropylcellulose, Magnesium stearate (E470b), Hypromellose (E464), Macrogol 8000, Titanium dioxide (E171), Talc, Carnauba wax, Iron oxide yellow (E172), Iron oxide red (E172). Therapeutic Indications: Prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation (NVAF) with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack (TIA); 60 mg LIXIANA® once daily. Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults: 60 mg LIXIANA® once daily following initial use of parenteral anticoagulant for at least 5 days. For NVAF and VTE 30 mg LIXIANA® once daily in patients with moderate or severe renal impairment (CrCl 15 - 50 mL/min), body weight ≤ 60 kg or concomitant use of P-glycoprotein (p-gp) inhibitors ciclosporin, dronedarone, erythromycin, or ketoconazole. Contraindications: Hypersensitivity to the active substance or any of the excipients; clinically significant active bleeding. Hepatic disease associated with coagulopathy and clinically relevant bleeding risk; Lesion or condition, if considered to be a significant risk for major bleeding. This may include current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities; Uncontrolled severe hypertension; Concomitant treatment with any other anticoagulants e.g. unfractionated heparin (UFH), low molecular weight heparins (enoxaparin, dalteparin, etc.), heparin derivatives (fondaparinux, etc.), oral anticoagulants (warfarin, dabigatran etexilate, rivaroxaban, apixaban, etc.) except under specific circumstances of switching oral anticoagulant therapy or when UFH is given at doses necessary to maintain an open central venous or arterial catheter; Pregnancy and breast-feeding. Undesirable effects: Common: anaemia; epistaxis; lower GI haemorrhage; upper GI haemorrhage; oral/pharyngeal haemorrhage; nausea; blood bilirubin increased; gamma-glutamyl transferase increased; cutaneous soft tissue haemorrhage; rash; pruritus; macroscopic haematuria/urethral haemorrhage; vaginal haemorrhage; puncture site haemorrhage; liver function test abnormal. Uncommon: hypersensitivity; intracranial haemorrhage (ICH); conjunctival/scleral haemorrhage; Intraocular haemorrhage; other haemorrhage; haemoptysis; blood alkaline phosphatase increased; transaminases increased; aspartate aminotransferase increased; urticaria; surgical site haemorrhage. Rare: anaphylactic reaction; allergic oedema; subarachnoid haemorrhage; pericardial haemorrhage; retroperitoneal haemorrhage; Intramuscular haemorrhage (no compartment syndrome); Intra-articular haemorrhage; subdural haemorrhage; procedural haemorrhage.
Please refer to Package Insert before prescribing. Daiichi Sankyo Hong Kong Limited

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Daiichi-Sankyo

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