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Interstitial Lung Disease With Non–Vitamin K Oral Anticoagulants—A Clinical Concern?

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The landscape of atrial fibrillation (AF) management has changed considerably over the past decade, and the worldwide transition from warfarin to non–vitamin K oral anticoagulants (NOACs) has been almost fully achieved.[1] Notwithstanding the well-established advantages of NOACs over warfarin in AF, including a consistent and clinically relevant reduced risk of intracranial bleeding, postmarketing surveillance remains pivotal to characterize their comparative safety, especially with regard to rare but unpredictable nonbleeding adverse events.

In this context, the timely retrospective nationwide cohort study by Chan et al[2] tested the hypothesis that NOACs are associated with increased risk of incident interstitial lung disease (ILD) in patients with nonvalvular AF without a preexisting lung disease, an emerging safety issue, especially in the current COVID-19 era. Using the Taiwan National Health Insurance Research Database, a recognized claims archive covering 99% of the population in Taiwan, Chan et al[2] implemented an intention-to-treat design and applied a propensity score stabilized weighting method to balance more than 30 covariates across groups, including comorbidities and baseline medications. Several subgroup and sensitivity analyses were also performed to handle the measurable and unmeasurable confounders, including the use of falsification outcomes, use of a cause-specific hazard model, and restriction to new users or to a rigid idiopathic pulmonary fibrosis definition.

During a follow-up of at least 2 years, factor Xa (FXa) inhibitors (as a class and individual drugs), but not dabigatran, were associated with a higher risk of incident ILD compared with warfarin (0.29 vs 0.17 per 100 patient-years), with an absolute risk increase of 0.12 (95% CI, 0.08-0.17). Among patients who were treated with anti–FXa drugs and diagnosed with ILD during the follow-up period, approximately 9% received antifibrotic agents and 69% received immunosuppressant agents. These findings were consistent across subgroup and sensitivity analyses, with patients who were at the highest risk of incident ILD receiving cotreatment of FXa inhibitors with amiodarone (0.38 vs 0.26 per 100 patient-years).

This population-based study by Chan et al[2] has the key merit of assessing a previous pharmacovigilance signal to confirm (or refute) the drug-related hypothesis.[3] When examining adverse reactions to NOACs from spontaneous reporting systems, an undeclared overlooked bias might exist, with potential implications for results: compared with the old-fashioned warfarin, drug-related complications associated with NOACs are likely to be more easily reported in the interest of postmarketing surveillance and detection of rare adverse effects. Moreover, channeling bias (the propensity to preferentially prescribe NOACs in frail patients with risk factors for adverse events) is a real threat in pharmacovigilance. The study by Chan et al[2] supported the existence of a genuine pharmacovigilance signal (ie, a real adverse drug reaction) and, for the first time, corroborated the association between FXa inhibitors and ILD.

The association of ILD with NOACs mirrors the recent debate on the potential risk of drug-induced liver toxicity (DILI). By definition, ILD and DILI are idiosyncratic; the mechanistic basis, primum movens, host-, patient- and drug-related risk factors are still incompletely characterized, especially for ILD, making our understanding, prediction, and prevention in clinical practice unsatisfactory. Moreover, these adverse events were underestimated in clinical phases (no imbalances were noted with regard to lung events in pivotal trials of NOACs) and only emerged during postmarketing use. A striking difference exists: the pharmacovigilance signal of DILI[4] was not

confirmed by 2 different retrospective cohort studies,[5,6] thus allaying the concern about the hepatotoxic effect potential of NOACs.

What are the resulting clinical and research implications? Because of the inherent limitations of analytical observational research, an association does not mean causation.[7] The Taiwan National Health Insurance Research Database cannot capture smoking as a crucial covariate, and channeling bias (and unmeasurable confounders) cannot be ruled out with certainty, as demonstrated by the higher risk found in the subgroup of patients with CHA_2DS_2-VASc and HAS-BLED scores of 3 or higher. Therefore, this first important piece of clinical evidence cannot stand alone when selecting a given oral anticoagulant; the overall risk-benefit profile of NOACs remains unaffected. The (small) absolute difference in rates of ILD between the FXa inhibitors and warfarin groups (0.12 per 100 patient-years each) was much lower than the corresponding absolute reduction in thromboembolism and major bleeding (0.78 per 100 patient-years each) and even lower than previous estimates on DILI (0.73 per 100 person-years).[5]

Therefore, the welcome contribution by Chan et al[2] should not be viewed as an alarm but rather as an alert for clinicians, including general practitioners, hospitals, and specialized physicians. Recommending the close monitoring of lung function in patients who were treated with NOACs is not justified, and any regulatory measure cannot be envisioned other than an update of the summaries of product characteristics. However, patients should be instructed to timely communicate early respiratory signs and symptoms to their clinicians, who should remain vigilant for adverse lung effects, especially in patients receiving anti–FXa agents and concomitant amiodarone. It is also important to report suspicious cases (with detailed clinical, laboratory, and imaging data) to the national pharmacovigilance services to improve our understanding of ILD and identify biomarkers.

A multidisciplinary multimodal research should be encouraged to address unsettled issues, such as the mechanistic basis (fibrotic vs inflammatory pathogenesis, including the potential contribution of alveolar bleeding), reversibility after discontinuation, the role of genetics and population susceptibilities (eg, Asian race and ethnicity), ILD phenotypes (including radiopathological patterns). The study by Chan et al[2] has confirmed, once more, the value of clinical evidence for timely safety assessment of medications and has challenged the common view that rare events with low background rate are unlikely to be captured in administrative databases. Additional observational studies are warranted, especially in different contexts, such as the European scenario, to verify the generalizability of the findings. We in the research community should promote and support proper design, conduct, reporting, and interpretation of clinical evidence within the spectrum of observational research,[7] including nationwide registries, industry-sponsored drug-based or disease-based registries, hospital cohorts, claims databases, and spontaneous reporting systems, to inform safer use of NOACs.

ARTICLE INFORMATION

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REFERENCES

1. Grymonprez M, Simoens C, Steurbaut S, De Backer TL, Lahousse L. Worldwide trends in oral anticoagulant use in patients with atrial fibrillation from 2010 to 2018: a systematic review and meta-analysis. *Europace*. 2022;24(6):887-898. doi:10.1093/europace/euab303

2. Chan YH, Chao TF, Chen SW, et al. Development of interstitial lung disease among patients with atrial fibrillation receiving oral anticoagulants in Taiwan. *JAMA Netw Open*. 2022;5(11):e2243307. doi:10.1001/jamanetworkopen.2022.43307

3. Raschi E, Fusaroli M, Diemberger I, Poluzzi E. Direct oral anticoagulants and interstitial lung disease: emerging clues from pharmacovigilance. *Drug Saf*. 2020;43(11):1191-1194. doi:10.1007/s40264-020-00990-9

4. Raschi E, Poluzzi E, Koci A, et al. Liver injury with novel oral anticoagulants: assessing post-marketing reports in the US Food and Drug Administration adverse event reporting system. *Br J Clin Pharmacol*. 2015;80(2):285-293. doi:10.1111/bcp.12611

5. Alonso A, MacLehose RF, Chen LY, et al. Prospective study of oral anticoagulants and risk of liver injury in patients with atrial fibrillation. *Heart*. 2017;103(11):834-839. doi:10.1136/heartjnl-2016-310586

6. Douros A, Azoulay L, Yin H, Suissa S, Renoux C. Non-vitamin K antagonist oral anticoagulants and risk of serious liver injury. *J Am Coll Cardiol*. 2018;71(10):1105-1113. doi:10.1016/j.jacc.2018.01.009

7. Torp-Pedersen C, Goette A, Nielsen PB, et al; External Reviewers. 'Real-world' observational studies in arrhythmia research: data sources, methodology, and interpretation. A position document from European Heart Rhythm Association (EHRA), endorsed by Heart Rhythm Society (HRS), Asia-Pacific HRS (APHRS), and Latin America HRS (LAHRS). *Europace*. 2020;22(5):831-832. doi:10.1093/europace/euz210