# Gastrointestinal bleeding risk following concomitant treatment with oral glucocorticoids in patients with atrial fibrillation on direct-acting oral anticoagulants

A. Holt[1], P. Blanche[2], B. Zareini[1], P.V. Rasmussen[1], J.E. Strange[1], D. Rajan[1], M.H. Jensen[1], M. El-Sheikh[1], A.M. Schjerning[3], M. Schou[1], G.H. Gislason[1], C. Torp-Pedersen[4], P. McGettigan[5], M.K. Lamberts[1]

*[1]Herlev and Gentofte Hospital, Department of Cardiovascular Research, Copenhagen, Denmark; [2]University of Copenhagen, Section of Biostatistics, Copenhagen, Denmark; [3]Zealand University Hospital, Department of Cardiology, Roskilde, Denmark; [4]Nordsjaellands Hospital, Department of Clinical Research, Hilleroed, Denmark; [5]William Harvey Research Institute, Department of Pharmacology, London, United Kingdom*

**Funding Acknowledgement:** Type of funding sources: Foundation. Main funding source(s): Ib Mogens Kristiansens Almene FondandHelsefonden

**Background:** Oral glucocorticoids and direct-acting oral anticoagulants (DOAC) have both been associated with a risk of gastrointestinal (GI) bleeding. However, drug safety, especially regarding the risk of bleeding, in relation to concomitant treatment with oral glucocorticoids and DOACs is insufficiently explored.

**Purpose:** We aimed to investigate the short-term risk of GI bleeding in patients with atrial fibrillation (AF) following concomitant treatment with DOACs and oral glucocorticoids.

**Methods:** Register-based, retrospective and nationwide Danish study including patients with AF and on DOAC treatment during 2012–2018. Patients were defined as exposed to oral glucocorticoids from the date of a redeemed prescription and 60 days forward. We associated concomitant treatment with GI bleeding and reported hazard ratios (HR) via a nested case-control design and standardized 60-day absolute risk adjusted for comorbidities using a cohort design. In both analyses, exposed were compared to non-exposed controls matched on age, sex, calendar year, follow-up time and DOAC agent.

**Results:** We included 98,376 patients (age [interquartile range]: 75 [68–82], 44% females) with AF on DOAC treatment. The use of oral glucocorticoids among included patients was widespread with 16% redeeming at least one prescription within three years, 4% redeeming at least five (Figure 1A). Lung disease was the most frequent indication (Figure 1B). Concomitant treatment with DOACs and oral glucocorticoids was associated with an increased incidence of GI bleeding (total n=4,946) compared with only DOAC treatment, including a dose-response trend (<20mg daily dose, HR [95% confidence interval (CI)]: 1.64 [1.38–1.95]; ≥20mg daily dose, HR [95% CI]: 2.29 [1.90–2.77]). Likewise, the standardized 60-day absolute risk of GI bleeding from first oral glucocorticoid exposure was increased compared with non-exposed (Figure 2).

**Conclusion:** Caution should be exercised when prescribing even short-term oral glucocorticoid treatment for DOAC treated patients, most notably in high doses and for patients with elevated bleeding risk.

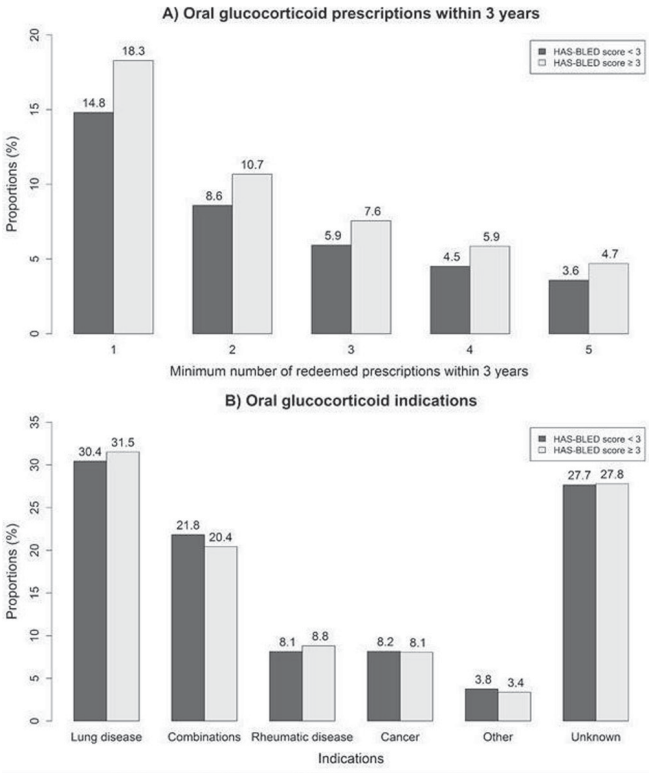


**Figure 1:** Oral glucocorticoid use and indications, according to HAS-BLED score

**A:** Average number of oral glucocorticoid prescriptions redeemed within the first three years from inclusion 60 days after initiation of direct-acting oral anticoagulants.

**B:** Indication for oral glucocorticoid prescription pertaining to the first redeemed prescription during follow-up

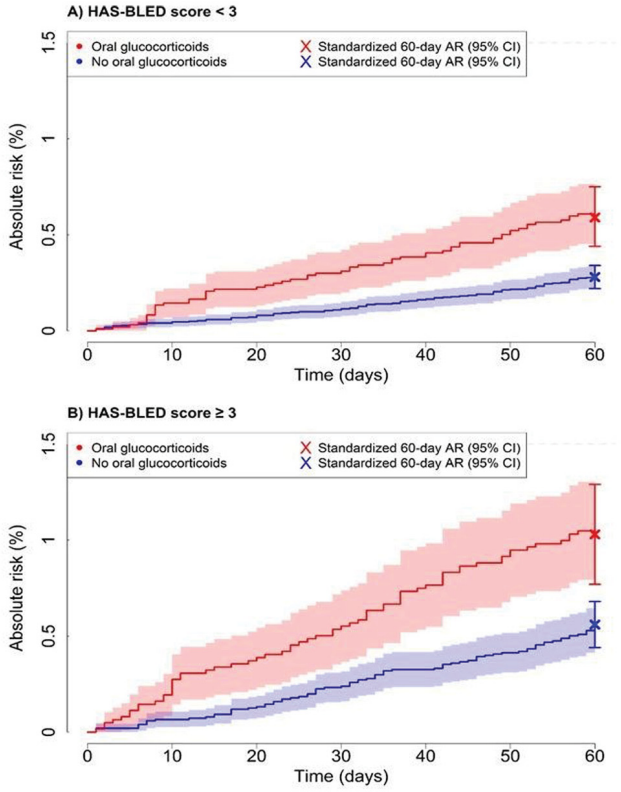


**Figure 2:** Crude and standardized 60-day absolute risk of gastrointestinal bleeding following a redeemed oral glucocorticoid prescription (exposed) compared with non-exposed, stratified by HAS-BLED score
AR = Absolute risk, CI = Confidence interval

Curves are unadjusted 60-day absolute risk of gastrointestinal bleeding
X indicates the standardized 60-day absolute risk with 95% confidence intervals adjusted for modified HAS-BLED score, cancer and educational level.