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Objectives: Although polypharmacy is an accepted proxy for multimorbidity, there has been limited attention for risk stratification among polypharmacy patients, especially in the elderly. We used the number of drug classes prescribed to determine the extent of co-morbidity and the risk of adverse outcome.

Methods: Prospective study among elderly patients (≥75 years) with polypharmacy (≥5 drugs) using a vitamin K antagonist (VKA) for AF. The reference group used VKA and cardiovascular drugs only, the other groups used 1, 2 or ≥3 additional drug classes (defined by the Anatomical Therapeutic Chemical [ATC] classification system).

Measurements: Charlson Comorbidity Index and cumulative comorbidity count; 3-year clinical follow-up.

Results: Median age and CHA\textsubscript{2}-DS\textsubscript{2}-VASc score (n=1,430) were 81 years (IQR 78–85) and 5 (IQR 4–6). Across groups, there was a significant increase in hierarchical and cumulative comorbidity counts. Patients with ≥3 additional drug classes had a higher risk of major bleeding (aHR 3.17, 95% CI [1.24–8.05]) than the reference group. The aHRs of all-cause mortality for the groups with 1, 2 or ≥3 additional drug classes were 2.25 (95% CI [1.27–3.96]); 3.04 (95% CI [1.75–5.29]) and 3.88 (95% CI [2.23–6.76]), respectively.

Conclusion: In this AF cohort of elderly patients with polypharmacy, ATC drug class counts are associated with comorbidity burden and adverse outcome. These findings support the concept of risk stratification among the heterogeneous group of patients.