Drug-drug interactions (DDIs) in elderly patients can induce severe adverse drug reactions (ADRs) leading to admission to emergency department (ED). The aim of the present study was to determine the frequency and characteristics of potential DDIs among elderly patients presenting at ED, and to assess which potential DDIs can result in clinical signs and symptoms consistent with the reason for ED admission. The present analysis evaluated data collected during the ANCESTRAL-ED study. This retrospective study is based on the evaluation of ADRs, DDIs and appropriate drug prescription in elderly patients (≥65 years) admitted to the ED of Pisa University Hospital (Italy) between May 2012 and May 2014. 'Potential' DDIs were assessed using Thomson Micromedex®, and classified on the basis of their clinical relevance (contraindicated, major, moderate, minor). Each ED admission (discharge diagnosis) consistent with the signs and symptoms expected for a potential DDI was classified as an 'actual' DDI. Throughout the study period, 3,005 ED admissions (1,899 patients, 58% females, mean age: 80.3 years) were recorded. An overall number of 16,662 drugs were evaluated and the mean number of drugs for patient was 5.1±3.4. Acetylsalicylic acid (ASA), furosemide and pantoprazole were the most frequently used medications. The overall number of potential DDIs was 7,451 (41 contraindicated; 2,000 major; 5,208 moderate; 197 minor and 5 not defined), and they were detected in 1,899 (63%) patients. The drug combination expected to result in the most frequently recorded DDI was ASA plus furosemide (decreased diuretic and antihypertensive efficacy of furosemide), reported in 324 cases (4%). Overall, 301 DDIs were found to be consistent with ED admission in 194 patients (representing 10.22% of patients with potential DDIs and 6.46% of the overall number of patients included in the cohort). Allopurinol in combination with warfarin (bleeding) was the most frequently reported actual DDI (6 cases), followed by levothyroxine+warfarin (bleeding, 5 cases), ASA+amlodipine (gastrointestinal hemorrhage and/or antagonism of hypotensive effect, 5 cases) and ASA+furosemide (5 cases). More than half of elderly patients admitted to ED presented at least a potential DDI among the drugs taken at the time of admission. Notably, only 4% of potential DDIs accounted for an event actually related to ED admission. Educational efforts and the consequent awareness of prescribers about the risk of potential DDIs in the elderly would help to prevent actual DDIs and improve the patient care. A close monitoring of ADRs due to DDIs should be implemented by large observational studies.