A systematic overview of Potentially Inappropriate Medications (PIMs) with risk of Major Adverse Cardiac and Cerebrovascular Events (MACCE)

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**Background** Aside with population ageing, often polypharmacy emerges. At least one drug in a polypharmacy elder may be inappropriate and lead to the occurrence of Adverse Drug Reactions (ADRs). Inappropriate prescribing tools have been developed, but information on MACCE is scarce.

**Purpose** The goals of this project are: (a) to study the PIMs associated with MACCE risk of occurrence described in inappropriate prescribing tools; and (b) to quantify the number of PIMs associated with MACCE risk of occurrence.

**Method** A systematic review was undertaken (PubMed, Medline and Google Scholar; 1991-2017) using the PICO method. Titles and abstracts were reviewed and eligibility criteria applied. The list of outcomes described was reduced to those affecting the cardio and cerebrovascular system. Criteria were organized in drugs that should be avoided in the elderly and drug-disease interactions. Intra-class correlation (ICC) coefficient was calculated, considering the different tools as raters for this analysis (IBM SPSS v.24.0). Finally, outcomes were classified into MACCE (e.g. stroke, myocardial infarction and exacerbation of heart failure) and Cardiac and Cerebrovascular Adverse Events (CCAE).

**Findings** The literature search enabled the identification of 644 papers, from which 24 were retained. A total of 935 PIM and 331 drug-disease interaction were initially considered. After excluding irrelevant outcomes and duplicates, 13 PIMs and 21 drug-disease interactions were retained. A mean of 3.7 (SD=3.0) PIMs with MACCE risk of occurrence were reported per tool, ranging from 1 to 11 PIMs. Stroke (n=7; 53.8%) was the most frequently described MACCE and was associated with the exposure to: antipsychotics, COX-II inhibitors, estrogen, nicardipine, nifedipine (non-sustained release) and venlafaxine. Heart failure (n=4; 30.8%), myocardial infarction (n=4; 30.8%) were also described to a lower extent. NSAIDs were associated with all the events described. Exacerbation of heart failure was the only drug-disease interaction described in these tools. NSAIDs, calcium channel blockers (e.g. verapamil and diltiazem), nifedipine (non-sustained release) and disopyramide were the most frequently described PIMs associated with this last outcome. A low relative agreement between tools was obtained [0.234; 95%CI: 0.121 ? 0.784].

**Conclusion** Inappropriate prescribing tools focus on minor adverse events and poorly describe the potential of these PIMs to cause major negative outcomes (MACCE). Future work will focus on choosing a particular PIM to use as a case-study and quantify the risk of MACCE occurrence after drug exposure in real world patients.