SECURE

Secondary prEvention of CardiovascUlaR disease in the Elderly trial

Deliverable 6.2:
SECURE recommendations

Grant Agreement number: 633765 H2020-PHC-17-2014-two-stage

Start date of project: 1 May 2015 Duration: 80 months

Lead beneficiary of this deliverable: LSHTM / CNIC

Dissemination Level : **Public** Document type: Report

Due date of deliverable: 31/12/2021 Actual submission date: 16/09/2022

Description: Recommendations of the investigators after the analysis of results

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Glossary

Abbreviation/ acronym	**Description**
CV	Cardiovascular
CVD	Cardiovascular Disease
FDC	Fixed Dose Combination
LMICs	Low and Middle Income Countries
SoC	Standard of Care

1. Executive Summary

A polypill strategy including antiplatelet, lipid lowering and blood lowering treatments has been proposed as a simple approach to reduce cardiovascular morbidity and mortality. SECURE aimed to assess the effectiveness and safety of a three component polypill including aspirin 100mgs, atorvastatin 20mg or 40mgs, and ramipril 2.5 mgs, 5mgs or 10mgs, as compared to usual care in reducing major adverse cardiovascular events in elderly post myocardial infarction patients.

SECURE is the first trial testing the efficacy of a fixed dose combination (FDC) polypill for secondary cardiovascular prevention in the elderly population (≥ 65 years old). The main objective is to evaluate the potential benefit of the FDC as a component of a cost-effective, globally available and comprehensive treatment strategy for secondary prevention of cardiovascular events as compared to standard therapy (the three components of the polypill given separately). As part of the secondary endpoints, SECURE compares the effect of both strategies on adherence and intermediate measures of risk factor control. Importantly, it also measures the pharmacoeconomic impact of the FDC intervention as well as regional differences in all outcomes. The project involves subjects from Spain, Italy, France, Germany, Hungary, Poland and Czech Republic.

SECURE is a randomized, un-blinded, controlled, 2-group, parallel, multinational trial which includes 2499 patients over 65 post MI from Spain, Italy, France, Germany, Poland, Czech Republic and Hungary. The primary end point is to assess the efficacy of a polypill (including aspirin[100mg], Ramipril [2.5-5-10mgs], atorvastatin [20-40mgs] – a total of six different formulations) with taking several drugs separately (usual care according to the local clinical practices at each participating country) in secondary prevention of cardiovascular events (incidence of the first occurrence of any component of the following composite endpoint, as adjudicated by the Clinical Events Committee: death from cardiovascular causes, nonfatal myocardial infarction, stroke, and urgent revascularization not resulting in death). The median follow up has been 36 months.

In this trial we have shown that **Polypill treatment is an effective approach in secondary prevention in the elderly.** In particular, we demonstrated that **the use of a cardiovascular polypill as a substitution approach, namely to use the polypill in patients already taking cardio protective drugs for secondary prevention, should be an integral part of the preventive strategy to reduce mortality and morbidity worldwide**.

2. Description of Results

While Cardiovascular diseases (CVD) are the main cause of death worldwide, they are responsible for half of all deaths in Europe. The overall ageing of the European population and improving survival of patients with coronary heart disease has created a large population of older adults eligible for secondary prevention. Despite the established efficacy of cardiovascular medications, suboptimal adherence reduces their effectiveness and is the primary reason for suboptimal clinical benefit.

CVD is responsible for a remarkable reduction in quality of life and life expectancy and also imposes huge costs on health systems in different countries.

The results of the SECURE trial will have profound impact on secondary cardiovascular prevention in the elderly population in different EU countries as it provides:

- The proof of concept of the efficacy and cost-effectiveness of an FDC polypill for secondary CVD prevention and treatment over traditional therapies.
- Understanding the impact of a polypill strategy on adherence to CVD treatment.
- Recommendations on how to address major challenges related to effective secondary CVD prevention: adherence, risk factor control, access to treatment and health care utilisation and costs related to the aforementioned.

Measuring and comparing the effect of both strategies on health care resource utilisation and costs will help design more efficient interventions tailored to meet the specific challenges of secondary prevention in different European countries.

The SECURE consortium partners consider that the present study is necessary in order to effectively tackle the CVD epidemic that is taking place worldwide. The demographic changes taking place in Europe will mean that ever increasing numbers of people will live longer and that an increasing proportion of this elderly population will be subject to secondary CV prevention. Currently we have access to very effective pharmacologic and non-pharmacologic interventions for CV prevention in Europe, but their efficacy on the control of the disease growth is limited, mainly due to non-adherence. Moreover, health care costs have continued to rise throughout Europe. Importantly, these demographic changes are mirrored in most of the rest of the world. Hence, the extrapolation of the data and application of the potential benefit of the polypill in LMICs (Low and Middle Income Countries) could have an impact on sparing millions of lives.

In the SECURE trial, a treatment strategy for secondary prevention with a polypill containing aspirin 100 mg, atorvastatin 20 or 40 mg, and ramipril 2.5, 5, or 10 mg in patients with a recent MI resulted in a lower risk of major adverse cardiovascular events (MACE), as compared with a usual care strategy of individual medications based on current European Society of Cardiology guidelines. The results were consistent irrespective of country, age, sex, diabetes, chronic kidney disease, or prior revascularization. The results of SECURE are broadly applicable to the general population, especially considering that the average age at first MI is 65.6 years for males and 72.0 years for females and the significant prevalence of diabetes mellitus, chronic kidney disease, and previous coronary artery disease. The risk reductions observed in the polypill strategy may be explained partly by increased adherence.

A total of 2499 patients were randomized with a median follow up of 36 months. The primary outcome occurred in 118 (9.5%) participants in the polypill strategy group compared with 156 (12.7%) in the usual care group (hazard ratio, 0.76; 95% CI 0.60 to 0.96, p=0.02). The key secondary outcome occurred in 101 participants (8.2%) in the polypill group and in 144 participants (11.7%) in the usual care group (hazard ratio 0.70; 95% CI, 0.54 to 0.90). The results were consistent across prespecified subgroups. Patients randomized to the polypill arm showed higher levels of adherence compared with usual care. Adverse events were similar between the polypill group and the usual care group.

The results of the trial have been presented at the “Late-Breaking Trial” session of the European Society of Cardiology (ESC) Congress. In addition, the main paper containing the main results of the trial has been published in one of the most prestigious journal of the field, the New England Journal of Medicine (Polypill Strategy in Secondary Cardiovascular Prevention. New England Journal of

Medicine August 26, 2022; DOI:10.1056/NEJMoa2208275 https://www.nejm.org/doi/full/10.1056/NEJMoa2208275?query=featured_home). Thus, the dissemination of those results will be simultaneously in the congress and the journal. In addition, we will expand our dissemination strategy to cover primary healthcare physicians, patients and general public via targeted interaction with different stakeholders through professional colleges, patient groups, newspapers, etc. In addition, we will release by the partners webpage all the information about the results and disseminate it in lay language through general newspapers.

3. Conclusion

The findings and conclusions obtained in SECURE allow the drafting of clinical guidelines and recommendations that will provide useful guidance and will serve as a reference framework for all stakeholders involved. Furthermore, SECURE provides necessary data to address the critical issue of secondary prevention of CV disease in LMICs, where a FDC polypill strategy could prove useful to address several problems that limit the effectiveness of secondary prevention strategies: inadequate health policies, poor availability, and lack of affordable medication.

In the present trial, a treatment strategy based on a polypill containing aspirin, atorvastatin, and ramipril, led to reductions in recurrent cardiovascular events following MI in elderly patients. The use of a cardiovascular polypill as a substitution approach, namely, to use the polypill in patients destined to take cardiovascular drugs effective in secondary prevention, could be an integral part of a preventive strategy. **The rational is straightforward: by simplifying treatment complexity, improving availability and efficiency, the polypill might serve as a widely applicable strategy to improve accessibility to treatment, adherence and ultimately decrease the risk of recurrent disease and death at a global scale.**