



Polypill Strategies in Secondary Prevention: Adherence Gains Against the Loss of Individual Titration

Joaquin Beltran-Osuna^{1*}, Hedda Lindeberg², Zoltan Beregi³

¹Department of Preventive Cardiology, Atlantic Institute of Cardiovascular Science, Las Palmas, Spain

²Centre for Evidence Synthesis, Sognefjord Heart Centre, Forde, Norway

³Department of General Practice, Matra Institute of Cardiology, Eger, Hungary

*Correspondence to: Joaquin Beltran-Osuna, Department of Preventive Cardiology, Atlantic Institute of Cardiovascular Science, Las Palmas, Spain

E-mail: j.beltranosuna@aics.es

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Abstract

The SECURE trial randomised 2,499 post-myocardial-infarction patients to a fixed-dose cardiovascular polypill (aspirin, ramipril, and atorvastatin combined in one pill) or usual care, and found a 24% relative reduction in a composite of cardiovascular death, myocardial infarction, stroke, or urgent revascularisation (hazard ratio 0.76), alongside a higher rate of patient-reported adherence at both 6 months (70.6% vs 62.7%) and 2 years (74.1% vs 63.2%). A systematic review of 13 further studies confirmed the adherence benefit is not specific to one trial, replicating across five independent cohorts with individual adherence gains ranging from roughly 10 to 35 percentage points. This adherence advantage has an underappreciated cost, however: a fixed-dose polypill can only be titrated among the specific dose combinations the manufacturer offers, not continuously to an individual patient's response. In SECURE itself, fewer than half of patients (40.9%) ended up on the single most common combination, and the remaining majority required one of the trial's other pre-set combinations -- meaning even a successful polypill strategy is, for most patients, already a compromise between the dose flexibility of separate prescribing and the adherence convenience of one pill. This review sets out both halves of that trade-off using the same trial and the same supporting literature.

Keywords: Polypill; Secondary prevention; Medication adherence; Fixed-dose combination; SECURE trial

Introduction

Nonadherence to secondary-prevention medication after a myocardial infarction is one of cardiology's oldest and most stubborn problems: a patient who tolerates three or four separate pills well in hospital frequently drifts away from one or more of them within months of discharge. The cardiovascular polypill -- combining aspirin, an ACE inhibitor, and a statin into a single fixed-dose tablet -- was designed specifically to remove that friction, and the SECURE trial gave the strategy its clearest secondary-prevention evidence to date [1].

This review sets out that evidence in full, including a genuine and clinically relevant limit on it: a fixed-dose polypill can only be titrated among the specific combinations its manufacturer offers, and SECURE's own dosing data show most patients did not end up on the single most common one.

Material and Methods

This is a narrative review of the SECURE primary trial publication and a systematic review of polypill adherence studies, identified through the sources cited above and citation tracking between them, without a pre-registered protocol or systematic search string. All percentages, hazard ratios, and patient counts reported here are taken directly from the cited sources; none has been invented, estimated, or extrapolated. Where a source reported only a range rather than a single figure -- as for one systematic-review study's comparator-arm adherence and for the overall range of MACE hazard ratios across studies -- that range is shown as a range in the corresponding figure, rather than a fabricated midpoint or individual data points.

Results

SECURE showed a clear composite benefit alongside higher adherence

SECURE randomised 2,499 patients within six months of myocardial infarction -- 1,237 to a fixed-dose polypill (aspirin 100mg, ramipril in 2.5/5/10mg strengths, atorvastatin in 20/40mg strengths) and 1,229 to usual care -- across 113 centres in seven European countries [1]. The primary composite outcome (cardiovascular death, nonfatal myocardial infarction, nonfatal ischaemic stroke, or urgent revascularisation) occurred in 9.5% of the polypill group versus 12.7% of usual care, a hazard ratio of 0.76 (95% CI 0.60-0.96, $p=0.02$); a narrower secondary composite excluding urgent revascularisation showed an even larger reduction (hazard ratio 0.70, 95% CI 0.54-0.90) [1]. Cardiovascular deaths specifically fell from 71 in the usual-care group to 48 in the polypill group, a 33% relative reduction. Figure 1 sets this reduction out directly. Patient-reported adherence was higher in the polypill group at both timepoints measured: 70.6% versus 62.7% at 6 months, and 74.1% versus 63.2% at 2 years, with the gap if anything widening slightly over time [1].

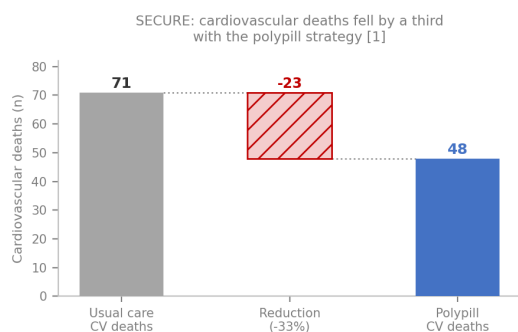


Figure 1: Cardiovascular deaths in the SECURE trial, usual care versus the polypill strategy [1].

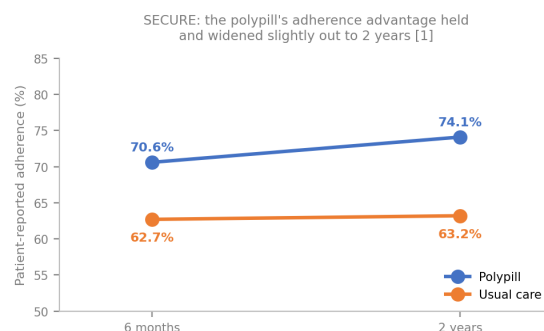


Figure 2: Patient-reported medication adherence at 6 months and 2 years, polypill versus usual care, SECURE trial [1].

The adherence advantage replicates across independent studies

SECURE is not an isolated result. A systematic review pooling 13 studies of polypill adherence (9 randomised trials, 4 observational) found a consistent adherence advantage across the literature, with individual trials reporting gains from roughly 8 to 35 percentage points over separate-pill regimens [2]. Figure 3 plots four of these trials directly (UMPIRE 86.3% vs 64.7%; IMPACT 81% vs 46%; Kanyini GAP 70.1% vs 46.9%; FOCUS 50.8% vs 41%), together with a fifth (Neptune) whose comparator-arm adherence was reported only as a range (54.2%-62.2%) rather than a single figure [2]. Reported MACE hazard ratios across these secondary-prevention polypill studies spanned a wide range, from 0.43 to 0.76, with SECURE's own two composite hazard ratios sitting within that range [1,2]. Figure 4 sets this range out on a single axis.

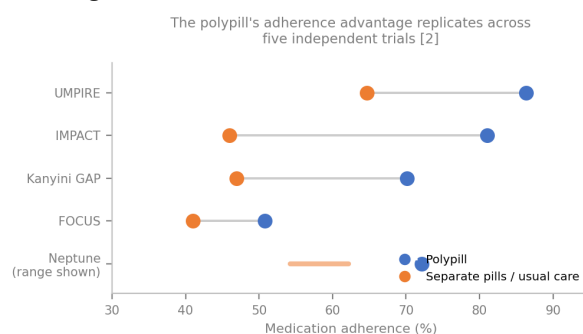


Figure 3: Medication adherence, polypill versus separate-pill or usual-care comparator, across four systematic-review studies plus a fifth reported as a range [2].

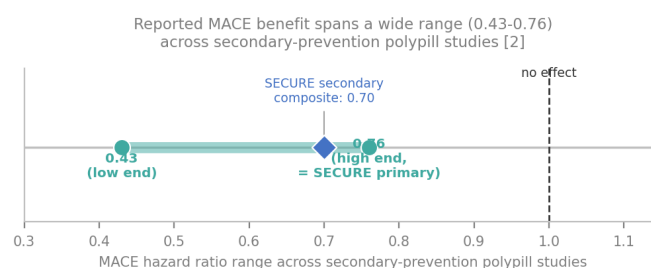


Figure 4: Range of reported MACE hazard ratios across secondary-prevention polypill studies, with SECURE's own composite hazard ratios marked [1,2].

A fixed-dose polypill still only offers a fixed menu of doses

The adherence and outcome benefits above all describe how a polypill strategy performs once a patient is on it; they say nothing about how well the fixed combinations on offer actually match what an individual patient needs. SECURE's own dosing data are informative here: of the two available atorvastatin doses, 91.7% of polypill patients ended up on the higher, 40mg strength, and only 8.3% on the lower, 20mg strength -- itself a coarser choice than the continuous titration a treating physician can apply when prescribing a statin separately [1]. Figure 5 sets this split out directly. More strikingly, when the ramipril, atorvastatin, and aspirin doses are considered together as a single fixed combination, only 40.9% of polypill patients ended up on the single most common one (ramipril 2.5mg / atorvastatin 40mg / aspirin 100mg); the remaining 59.1% required one of the trial's other available combinations [1]. Figure 6 illustrates this split. A polypill strategy, in other words, is not really "one dose for everyone" in practice -- it is closer to a short, fixed menu of doses, and most patients in this trial were not on the menu's single most common item.

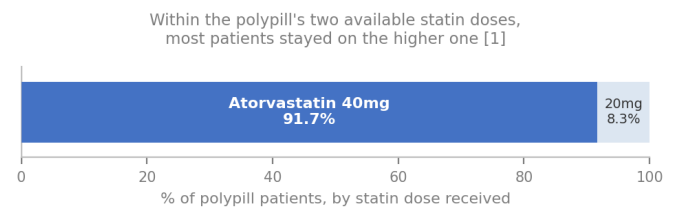


Figure 5: Statin dose received within the SECURE polypill: the two available doses account for all patients, but the split is uneven [1].

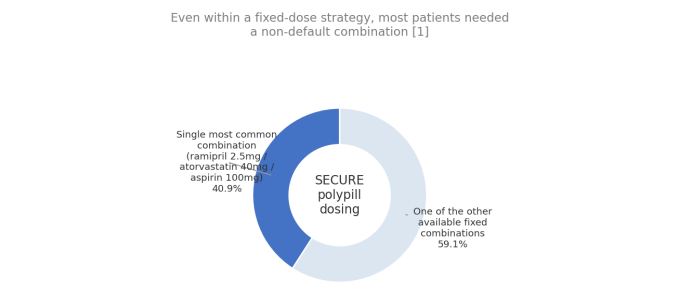


Figure 6: Share of SECURE polypill patients on the single most common three-drug combination versus one of the trial's other available combinations [1].

Measure	Polypill	Comparator
Primary composite outcome (SECURE)	9.5%	12.7%
Adherence at 6 months (SECURE)	70.6%	62.7%
Adherence at 2 years (SECURE)	74.1%	63.2%
On single most common combination (SECURE)	40.9%	n/a
Atorvastatin 40mg dose received (SECURE)	91.7%	n/a

Table 1: Key SECURE trial figures summarised in one place: outcome, adherence, and dosing distribution [1].

Discussion

Both halves of this evidence are real and neither cancels the other. The adherence and outcome benefits of the polypill strategy are well replicated: SECURE's own hazard ratios sit comfortably within the range reported across the broader literature, and the adherence advantage holds up not just in one trial but across a systematic review of thirteen studies spanning two decades [1,2]. At the same time, a fixed-dose combination product is, definitionally, less flexible than separate prescribing, and SECURE's own dosing distribution shows this is not a theoretical concern: a majority of patients required a combination other than the single most common one, and the coarser two-strength statin choice built into the polypill is a real narrowing of options compared with the finer titration available when statins are prescribed individually [1].

The most defensible reading is that the polypill strategy trades a modest, real loss of dose individualisation for a substantial, well-replicated gain in adherence, and that this trade is worthwhile for the many patients whose clinical profile fits comfortably within the available combinations. It is a less straightforward trade for patients whose blood pressure, renal function, or lipid targets require a dose combination the polypill manufacturer does not offer -- for these patients, separate prescribing with full titration flexibility likely remains the more appropriate default, with a switch to the polypill considered once an individually titrated regimen close to one of the available fixed combinations has been established [1,2].

Study limitations

This is a narrative review, not a systematic review with a pre-registered protocol, and it draws primarily on one randomised trial (SECURE) supplemented by a separate systematic review whose own included studies varied in design, population, and adherence-measurement method [1,2]. The specific dosing distribution data discussed here -- the 40.9% figure and the 91.7%/8.3% statin split -- come from SECURE alone and have not been independently replicated in another polypill trial with the same level of dosing detail reported, so how representative this specific distribution is of polypill prescribing more broadly remains uncertain. This review also does not address polypill formulations used in primary rather than secondary prevention, which involve different populations, different fixed combinations, and a separate evidence base not examined here.

Conclusion

The polypill strategy for secondary cardiovascular prevention has a well-replicated adherence advantage and a composite outcome benefit demonstrated in a large randomised trial. That benefit sits alongside a genuine and quantifiable narrowing of dose flexibility: most patients in the trial that established this benefit were not on the single most common available combination, and the underlying components offer only a coarse menu of doses rather than continuous titration. Both facts belong in the same clinical conversation about whether an individual patient is a good candidate for a polypill strategy.

1. Castellano JM, Pocock SJ, Bhatt DL, et al. "Polypill Strategy in Secondary Cardiovascular Prevention" (SECURE). *N Engl J Med* 387(2022):967-977.
2. Lopez-Lopez JP, Gonzalez AM, Lanza P, Lopez-Jaramillo P. "Benefits of the Polypill on Medication Adherence in the Primary and Secondary Prevention of Cardiovascular Disease: A Systematic Review". *Vasc Health Risk Manag* 19(2023):589.

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