

**Supplementary Appendix: The International Polycap Study (TIPS-3): design, baseline characteristics and challenges in conduct**

**Sample size and study power calculations to determine the effect of the Polycap compared to placebo:**

Originally, the trial was planned to randomize 5000 study participants and follow them for a mean of 5 years, which would have >80% power for a 35% reduction, >90% power for a 40% reduction in composite CV events at 5 years (supplemental table 1). The sample size calculation was based on an estimated yearly event rate of 1% for major CVD events in the placebo group; non-adherence rates in the intervention arm of 8% in the first year, an additional 3% in the second year, and an additional 2% per year for subsequent years for each active therapy (17% at 5 years); drop-in rates of 2% per year (10% over 5 year; and rates of lost to follow-up of < 2 % at 5 years. We have set the two-sided alpha at 0.05.

**SUPPLEMENTARY TABLE 1: ORIGINAL SAMPLE SIZE CALCULATIONS ASSUMING TWO YEARS OF RECRUITMENT, PLUS FOUR YEARS OF FOLLOW-UP (MEAN FOLLOW-UP OF 5 YEARS) WITH AN 18% DROPOUT RATE, AND A 10% DROP IN RATE.**

Risk Reduction (%)	Control Event Rate (CV death, MI, stroke, heart failure, revascularization, resuscitated cardiac arrest)	Power (%)	
		80	90
35	1.0%/year	4224	5654
40	1.0%/year	3132	4194
50	1.0%/year	1876	2512

The trial has enrolled 5713 participants, and assumptions were revised based on the trial experiences to date. The following modifications were made to estimate study power: a total trial period of approximately 8 years, control event rate of 1.2% to 1.3% per year (assuming a treatment effect exists with an overall event rate of 1.1% observed so far), drop-out rate of 29% at 8 years, drop in rate of 8% at 8 years (instead of 17% and 10% respectively), and loss to follow up of 2% at 8 years. Based on these modifications, the study will still have >80% power for a 35% reduction, >90% power for a 40% reduction in composite CV events (supplemental table 2).

**SUPPLEMENTARY TABLE 2: REVISED SAMPLE SIZE CALCULATIONS BASED ON TRIAL PERFORMANCE AT THE END OF THE ENROLLMENT PHASE:**

<b>Risk Reduction (%)</b>	<b>Control Event Rate (CV death, MI, stroke, heart failure, revascularization, resuscitated cardiac arrest)</b>	<b>Power (%)</b>
35	1.2%/year	83.7
	1.3%/year	86.6
40	1.2%/year	92.5
	1.3%/year	94.4

**Statistical considerations for interim analyses:**

An independent Data Safety and Monitoring Board (DSMB) will review all data on safety and efficacy at regular intervals (every 6 months). Three formal interim analyses are planned, equally spaced with respect to accumulating number of events. If the interim analyses show clear benefit, the DSMB may recommend early trial termination. A conservative stopping rule approach will be recommended and will be formalized in conjunction with the DSMB at their first meeting. A suggested guideline for early termination for efficacy is a reduction of 4 standard deviations (corresponding to a p value of 0.00006) in the primary outcomes at the first and second looks, or

3 standard deviations (corresponding to a p value of 0.0027) at the third look. Conversely, a 3 standard deviation excess in the primary study outcomes with treatment at the first two looks and 2 standard deviations excess at the third look would be considered evidence for harm. The monitoring boundaries should remain crossed at 2 successive analyses at least 3 months apart to ensure that temporary variations in the effect sizes do not lead to early termination. Given these extremely conservative monitoring boundaries and the limited number of formal interim analyses, the type I error rate adjustment for the final analysis will be negligible ( $<0.00001$ ). If the study is discontinued for one component, the trial will continue evaluating the other components.

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