

TIPS

Background

- CVD is a global problem.
- Association between risk factors (BP, lipids) and CVD is continuous and extends into the “normal” range.
- Average levels of risk factors are likely abnormal in all individuals in most **urban** settings.
- A polypill that can be given to all individuals > 50 years has been theorized to reduce CVD > 80 %.
- However, it is not known whether a polypill can be formulated to reduce risk factors and CVD substantially in the average individuals?
- Will it be well tolerated?

TIPS: Primary Objectives

Whether the Polycap:

1. is equivalent in reducing BP when compared with its components containing 3 BP lowering drugs (HCTZ, Atenolol, ramipril) at low doses with and without ASA
2. is equivalent in reducing HR vs Atenolol
3. is equivalent in modifying lipids vs. simvastatin alone
4. is equivalent in suppressing urine thromboxane B2 vs ASA alone
5. has similar adverse event rates vs. its components

TIPS: Study Design

- Randomized and double blind
- Polycap(n=400) vs. 8 other formulations (n=200 each)
- 12 weeks of active treatment
- 4 week wash out
- Impact on BP, HR, lipids, urine thromboxane B2
- Safety and tolerability.
- Parallel PK study.

TIPS: Components of each Groups vs Polycap

Antiplatelet	ASA	100 mg/d
Statin	Simvastatin	20 mg/d
ACE-Inhibitors	Ramipril	5 mg/d
Beta-blocker	Atenolol	50 mg/d
Diuretic	Hydrochlorothiazide	12.5 mg/d
Polycap	All of the above	

TIPS: Composition of the eight comparator groups

ASP:	Aspirin	100 mg
T:	Thiazide	12.5 mg
T + R:	Thiazide (12.5mg)	Ramipril (5 mg)
T + At:	Thiazide (12.5mg)	Atenolol (50 mg)
R + At:	Ramipril (5mg)	Atenolol (50 mg)
T + R + At:	Thiazide (5mg)	Ramipril (5 mg) Atenolol (50 mg)
T + R + At + ASA:	Above + ASA	100 mg
S	Simvastatin	20 mg

TIPS: Organization

50 Centers in India

Indian Coordinating Center
St. John's Medical College,
Bangalore

International Coordinating Center
Population Health Research Institute
HHS and McMaster University, Hamilton, Canada

Sponsor: Cadila Pharma, Ahmedabad, India

TIPS: Target Population

Inclusion Criteria:

- Age 45 to 80 years
- At least one CV risk factor (**DM** on one oral drug / diet)
- Hypertension (SBP > 140 ≤ 159 syst; DBP > 90 ≤ 100 Hg, but treated)
- Informed consent

Exclusion Criteria:

- On study meds and cannot be stopped
- 2 or more BP lowering meds
- LDL > 3.1 mmol/L
- Abnormal renal function (Cr . 2.0mg/dl on K+ 5.5 meq/L)
- Previous CVD or CHF

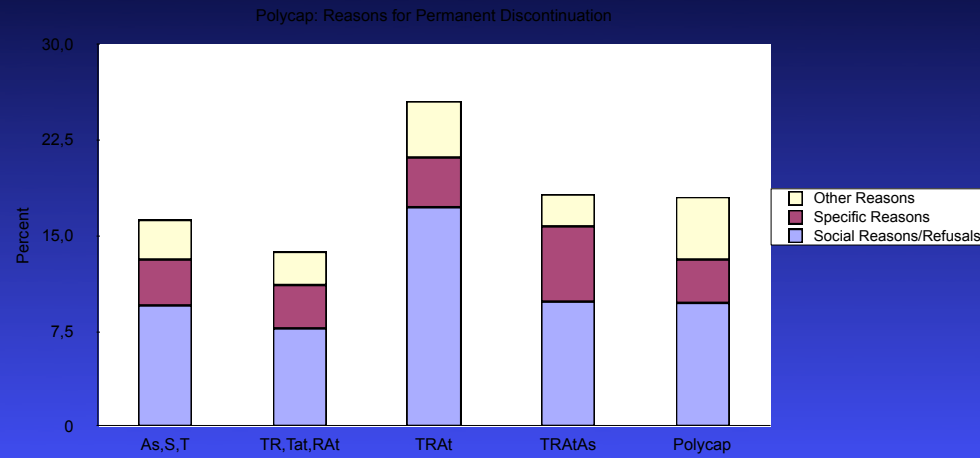
TIPS: Selected Baseline Characteristics

Characteristics	Overall
N=	2053
Age	54.0 (7.9)
BMI	26.3 (4.5)
Heart rate (beats/min)	80.1 (10.7)
Diabetes	33.9%
Current Smoker	13.4%
Females	43.9%
Calcium Channel Blockers	21.7%

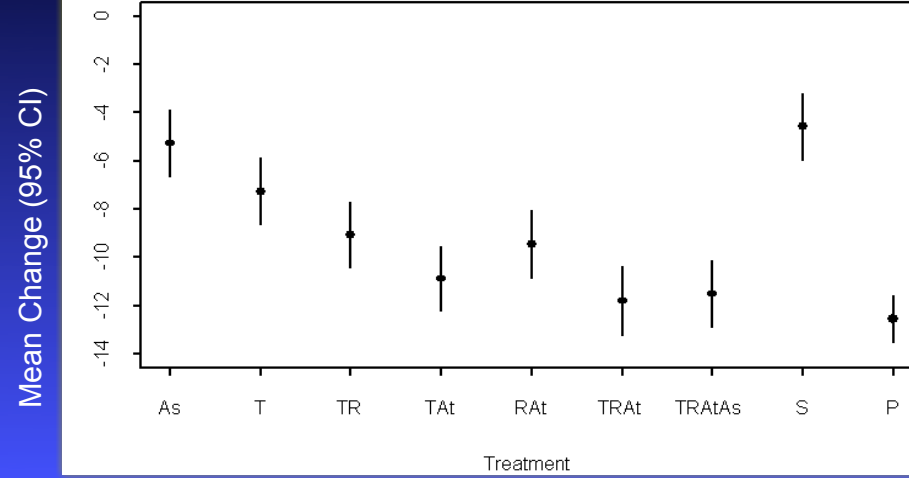
TIPS: Selected Baseline Characteristics

Characteristics	Overall
N=	2053
Systolic BP (mmHg)	134.4 (12.3)
Diastolic BP (mmHg)	85.0 (8.1)
Total Cholesterol (mmol/d)	4.7 (0.9)
LDL (mmol/L)	3.0 (0.8)
HDL (mmol/L)	1.1 (0.3)
Triglycerides (mmol/L)	1.9 (1.2)
ApoB	0.9 (0.2)
ApoA	1.2 (0.2)

TIPS: Reasons for Permanent Discontinuation of Study Drug



TIPS: SBP (mm Hg)



Mean Changes in BP (95% CI) vs 0 Drugs

	Reductions mmHg	
1 BP lowering	-2.2	-1.3
2 BP lowering	-4.7	-3.6
3 BP lowering	-6.9	-5.0
Polycap	-7.4	-5.6

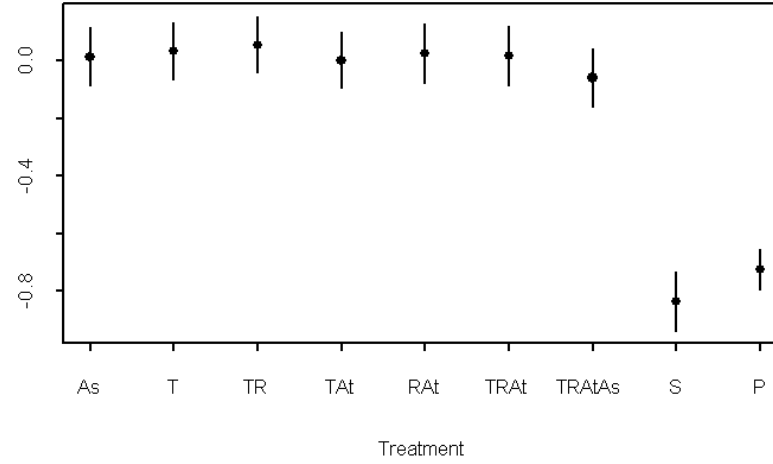
Impact of Atenolol arms vs Polycap on Heart Rate

	Reduction in	CI	P
Polycap	-7.0	(-6.3 to -7.7)	0.001
Other Atenolol	-7.0	(-6.2 to 7.9)	0.001
Non Atenolol	0.0	(-0.84 to 0.84)	0.99

Polycap/Other atenolol vs non-atenolol arms $<<0.0001$

LDL (mmol/L)

Mean Change (95% CI)



Impact on LDL & ApoB

	Mean	CI	%
Simvastatin :	-0.83 mmol	-0.94 to -0.74	27.7%
Polycap :	-0.70 mmol	-0.78 to -0.64	23.3%
Differences:	-0.13 mmol	(-0.25 to -0.01)	4.4%

Differences vs both simvastatin arms compared to non-statin $p < 0.001$

LDL change with Polycap vs Simvastatin $p = 0.04$

Parallel impact on ApoB: Simv: -0.21 mmol/L vs Polycap : -0.18 mmol/L
(Diff of 0.03 mmol; $p = 0.06$).

Impact on Triglycerides

	Mean	CI	%
Simvastatin :	-0.37	(-0.22 to -0.51)	-19.5
Polycap :	-0.17	(-0.06 to -0.28)	-9.5
Differences:	0.20 mmol/L	-0.03 to 0.36	-10

Differences vs both simvastatin arms $p < 0.001$

Trig change with Polycap vs Simvastatin $p = 0.02$

No impact on HDL or ApoA1

TIPS: Impact of BP lowering drugs and simvastatin on urinary thromboxane B2 (ng/mmol of Cr)

	Mean	CI	P*
Thiazide	+39.7	(-26 to	0.24
Th +	-33.7	(-96 to +29)	0.29
Th +	-32.8	(-95 to +29)	0.30
Ram + Aten	-123	(-192 to -55)	P=0.001
Th + At + Ramipril]	-1.1	(-71 to -69)	0.97
Th + At + Ramipril + ASA]	-389	(-458 to 321)	p<0.001
Simvastatin	-85	(-150 to -20)	p=0.01

TIPS: Impact of Various Treatments on Urinary Thromboxane B2

	Mean	CI	
ASA alone	-388.0	(-453 to	} P < 0.001 vs baseline
3 BP lowering	-389.2	(-457 to -321)	
Polycap	-322.3	(-369 to	

Estimated reductions in CHD/Stroke of a Polycap in Those With Average Risk Factor Levels

		% Relative Reduction		
		Reduction in Risk Factors	CHD	Stroke
LDL-C (mmol/L)	Est (Simv 20)	0.80	27%	8%
DBP (mmHg)	Est (3, ½ dose)	5.7	24%	33%
Platelet function	Est (ASA 100 mg)	Similar	32%*	16%
Combined	Est	-	62%	48%

*RCTs suggest a smaller benefit

TIPS: Conclusions

In those with average risk factor levels,

1. The Polycap is similar to the added effects of each of its 3 BP lowering components. There is greater BP lowering with incremental components. ASA does not interfere with the BP lowering effects.
2. The Polycap reduces LDL to a slightly lower extent compared to simvastatin alone
3. The Polycap lowers thromboxane B2 to a similar extent as aspirin alone.
4. The Polycap is well tolerated.
5. The Polycap could potentially reduce CVD risk by about half.