

# The Indian Polycap Study (TIPS) study design and results

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S Yusuf, P Pais, D Xavier et al. ACC, LBCT and Lancet, March 2009



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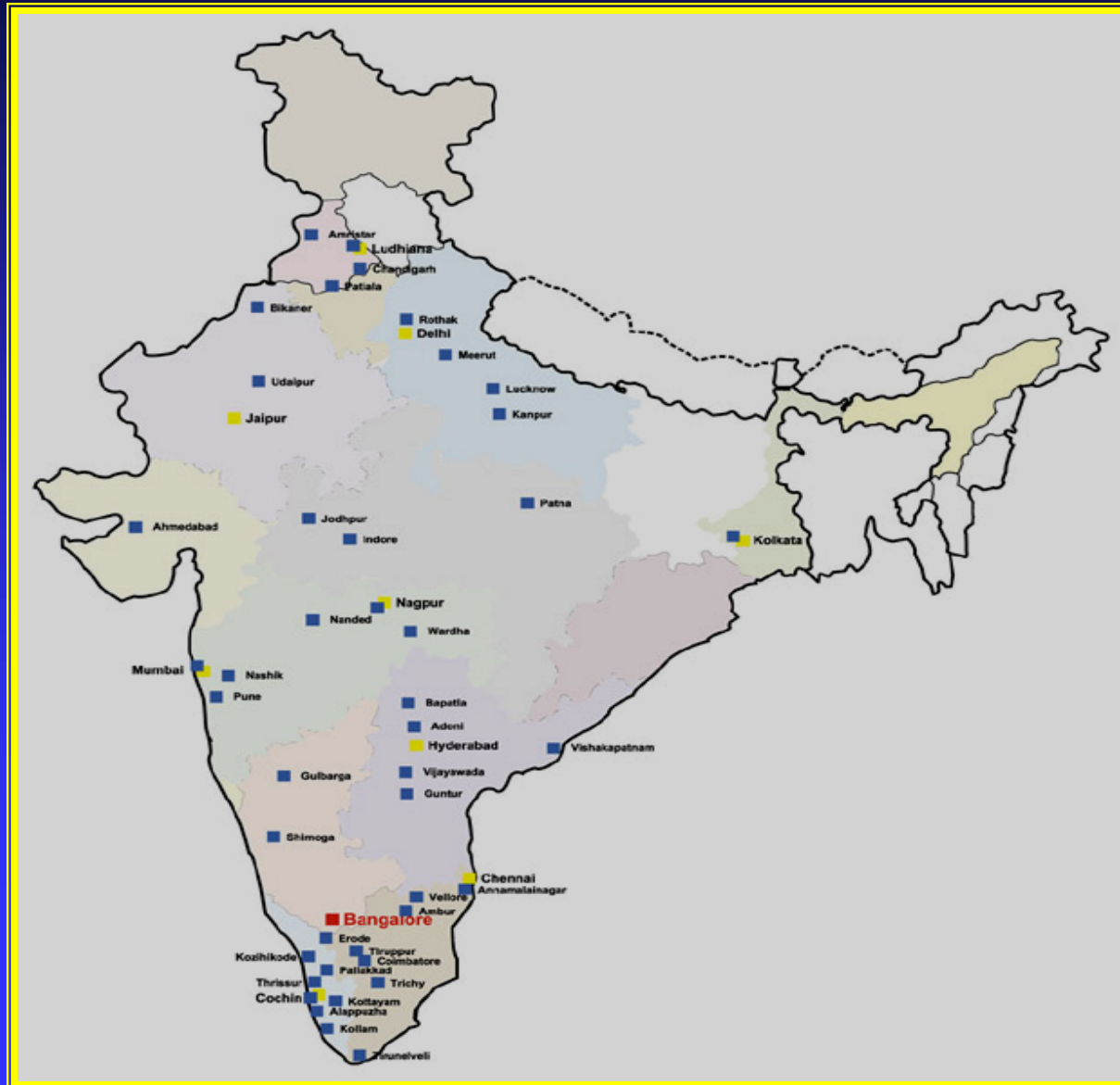
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# Over 160 Sites in >50 cities in India



# St. John's Research Institute

## CVD research

### – CVD epidemiology [28,500]

- ICMR-National C-C in AMI [2,600]
- INTERHEART [950] [Lancet-04-07]
- CREATE ACS Registry [~20,500] [Lancet-08]
- INTERSTROKE\* [550 → → 5,000]

### – Large Clinical Trials

(164 institutions, 60 cities >24,000)

- CREATE, 8,060, [JAMA-04, AHJ-04]
- POISE, 777 [Lancet-08]
- PRoFESS, 1,620, [NEJM-08]
- OASIS 5, 544 [NEJM-06]
- TIMACS, 29 [AHA'08]
- OASIS 6, 1,450 [JAMA-07]
- CURRENT, 1802+
- VITATOPS, 1450+
- RELY, 650
- POLYCAP, 2053 [ACC'09, Lancet'09\*]

- AVVEROES,\* 190+
- ARISTOTLE,\* 450+
- HOPE-3,\* 2,000
- MARS\* 400
- ASPIRE,\* 400
- RECREATE,\* 250
- RELY AF Registry,\* 750
- OASIS-8,\* 500

- In 2009 Obs Epi studies and Trials to be initiated [~40,000]
  - VISION, 8,000
  - APPRAISE - 2000
  - APOLLO - 2000
- Oventions-NHLBI projects
  - Stroke registry - 10,500
  - SPREAD - 800
  - Primary prevention, 15,000

\*ONGOING STUDIES

# TIPS: Questions we asked

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1. Can we formulate a Polycap with 5 or 6 drugs?
2. How will it act when given to individuals at low or average risk?
3. Will it be well tolerated?
4. Can it reduce risk factors and CVD substantially?

# TIPS: Components of the 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

# TIPS: Composition of the eight comparator groups

1) ASP:	Aspirin (100 mg)		
2) T:	Thiazide (12.5 mg)		
3) T + R:	Thiazide (12.5mg)	Ramipril (5mg)	
4) T + At:	Thiazide (12.5mg)	Atenolol (50mg)	
5) R + At:	Ramipril (5mg)	Atenolol (50 mg)	
6) T + R + At:	Thiazide (5mg)	Ramipril (5 mg)	Atenolol (50 mg)
7) T+R+At+ASA:	Above (6) + ASA100 mg		
8) S	Simvastatin 20 mg		

# TIPS: Study Design

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- Randomized and double blind
- Polycap vs. 8 other formulations
- Superiority and inferiority comparisons
- Active treatment for 12 weeks
- Wash out for 4 weeks
- Impact on BP, HR, lipids, urine thromboxane B2
- Safety and tolerability.
- Parallel PK study.

# Combinations and comparisons

Composition of comparators	Type of comparison
Thiazide 12.5mg + Ramipril 5mg + Atenolol 50mg	Non-inferiority (BP)
Thiazide 12.5mg + Ramipril 5mg + Atenolol 50mg + Aspirin 100mg	Non-inferiority (BP, Platelet inhibition)
Aspirin 100mg	Non-inferiority (Platelet inhibition )
Simvastatin 20mg	Non-inferiority (lipid lowering)
Hydrochlorothiazide 12.5mg	Superiority (BP)
Thiazide12.5mg+Ramipril 5mg	Superiority (BP)
Thiazide12.5mg +Atenolol 50 mg	Superiority (BP)
Ramipril 5 mg + Atenolol 50 mg	Superiority (BP)

# TIPS: Primary Objectives

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Whether the Polycap is equivalent :

1. in reducing BP when compared with its components containing 3 BP lowering drugs (HCTZ, Atenolol, ramipril)
2. in reducing HR when compared with Atenolol
3. in modifying lipids when compared with simvastatin alone
4. in suppressing urine thromboxane B2 vs ASA alone
5. in its rates of adverse event when compared with its equivalent components

# TIPS: Secondary Objectives

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- Whether Polycap is superior in reducing BP compared to its components containing
  - One BP lowering drug (thiazide) or
  - Two BP lowering drugs
    - HCTZ + Ramipril
    - HCTZ + Atenolol
    - Ramipril + Atenolol

# Power for Non-Inferiority Comparisons for the Key Outcomes

Outcomes	Comparison of Treatment Arms	Non-Inferiority Margin (SD)	1-sided type 1 error	Power
BP: Diastolic BP	P vs TRAt or TRAtAs	2 (6) mm Hg	0.025	94%
Lipids (LDL chol)	P vs S	0.155 (0.46) mmol/L	0.025	97%
Antiplatelet therapy (Urinary Thromboxane B2)	P vs TRAtAs	60 (181)	0.025	96%

# TIPS: Statistical methods

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- Intention to treat.
- All post- rand variables utilized by a repeated measures approach.
- Results are baseline and “control” group subtracted.
- When 12 week BP, HR or lipids were missing, we used earlier measures resulting in 96% BP data and 91% lipid data.

# TIPS: Organization

53 Centers in India

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graph TD; A[53 Centers in India] --> B[Indian Coordinating Center  
St. John's Medical College and  
Research Institute,  
Bangalore]; B --> C[International Coordinating Center  
Population Health Research Institute  
HHS and McMaster University,  
Hamilton, Canada];
```

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HHS and McMaster University,  
Hamilton, Canada

# TIPS: Target Population

## Inclusion Criteria:

- Age 45 to 80 years
- At least one CV risk factor
  - Hypertension (SBP  $> 140 \leq 159$ ; DBP  $> 90 \leq 100$ Hg, but treated)
  - Diabetes mellitus (on one oral drug / diet)
  - Smoker  $> 5$  years
  - Raised WHR
  - Abnormal lipids (LDL 130-175mg/dl)
- Informed consent

## Exclusion Criteria:

- On study meds and cannot be stopped
- 2 or more BP lowering meds
- LDL  $> 175$ mg/dl
- Abnormal renal function (Cr  $> 2.0$ mg/dl or K $^{+}$   $> 5.5$  mEq/L)
- Previous CVD or CHF

# TIPS: Study Flow

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## Screening

(stabilization and baseline assessments)

↓ 3 weeks

**Randomization** (BP, HR, urine, lipids)

↓ 7 to 10 days (BP, HR)

↓ 4 weeks (BP, HR)

↓ 8 weeks (BP, HR)

↓ 12 weeks (BP, HR, urine, lipids)

**Washout** ↓ 16 weeks (BP, HR)

# Flow Chart of the Study and Data Completeness

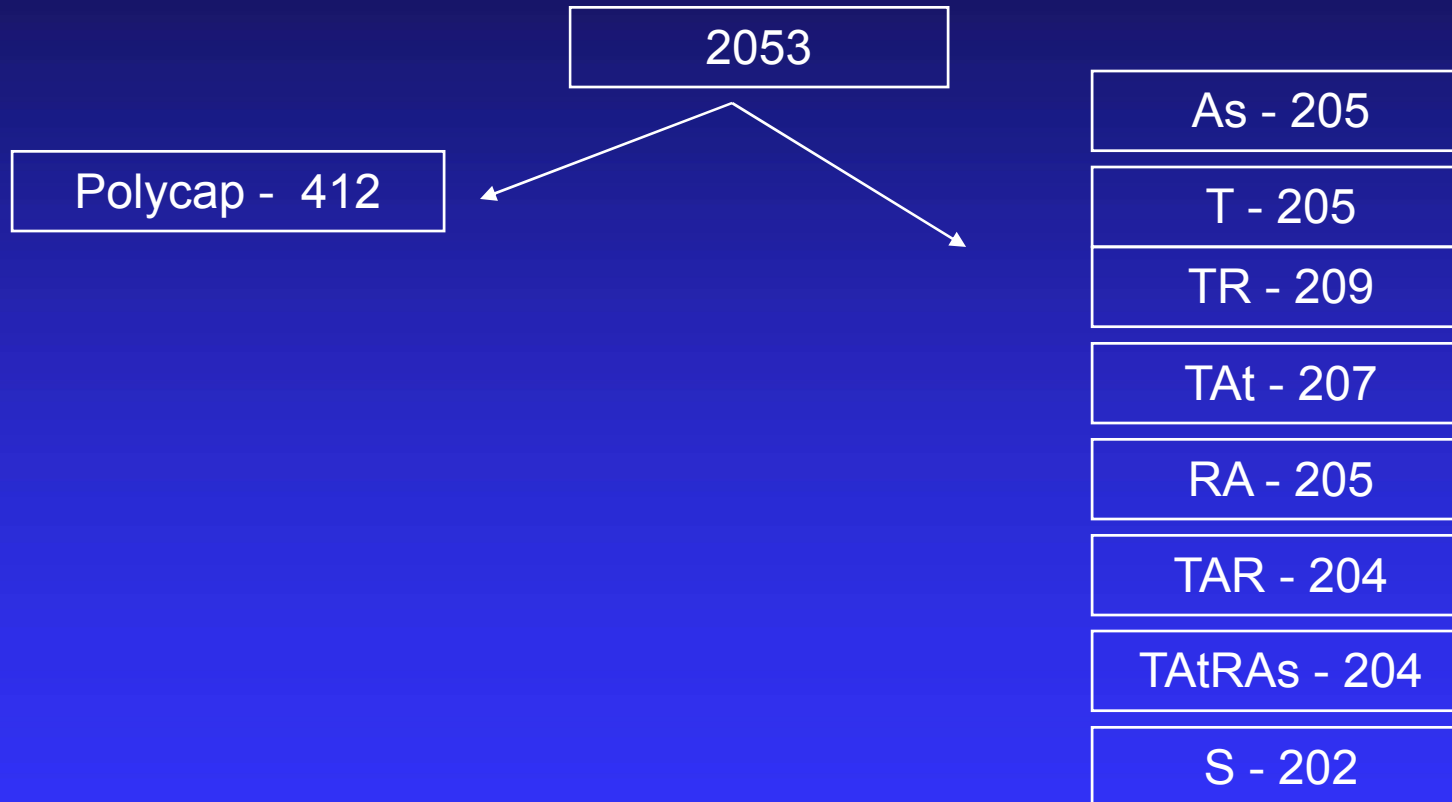
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No. randomized	=	2053
No. final visit	=	86%
No. with post rand HR/BP	=	96%
No with post rand lipids at anytime	=	91% (81%)*

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\*At scheduled end

# Final treatment allocation



# Inclusion criteria

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Total patients randomized	2053
HTN	1297(63.2)
Type-2 DM	696(33.9)
Current smoker>5yrs	240(11.7)
High WHR	1501(73.1)
Abnormal lipids	676(32.9)

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# 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)

# Selected safety parameters (%)

	Ov	As	T	TR	TAt	RA	TRA	TR AtAs	S	P
Dizziness	4.5	4.9	3.9	1.9	2.9	5.4	5.4	5.4	2.5	6.3
Cough	3.8	1.5	3.4	7.2	0.5	3.9	3.9	5.9	1.0	5.3
Fatigue	1.8	1.0	2.0	1.4	1.9	2.0	3.4	0.5	2.0	1.7
Bradycardia	0.2	0	0	0	1.0	0	0.5	0.5	0	0.2
Cr>50% Rnd	8.3	9.3	6.8	7.7	9.7	7.3	7.4	10.3	7.9	8.5
Potasm>5.5	5.3	5.9	4.4	5.3	4.8	5.9	7.4	6.9	3.5	4.4
SGPT>2 ULN	1.0	0.5	0.5	3.3	1.9	1.0	0	0.5	1.5	0.5

# Reasons for drug discontinuations

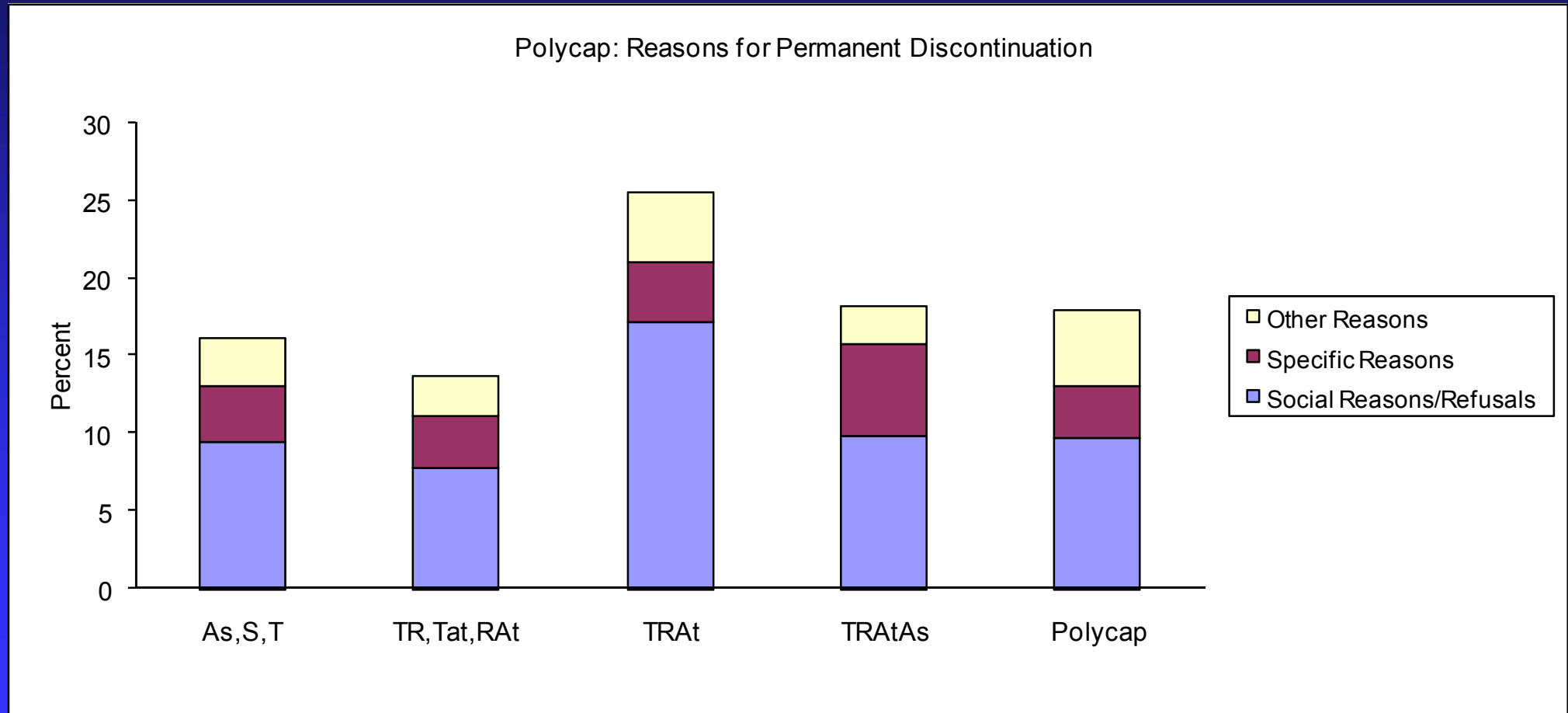
## Temporary or Permanent (%)

	Ov	As	T	TR	TAt	RAt	TRA	TR AtAs	S	P
Soc/ refused	21.8	22.9	22.0	21.5	16.4	22.0	27.0	24.5	23.8	19.2
Dizz/ HoT	3.4	2.9	3.4	1.0	1.9	4.4	4.4	4.4	3.0	4.4
Gastr/ dysp	1.4	1.5	1.0	2.4	1.0	1.5	1.0	1.5	1.5	1.2
Hyperkalem	0.2	0	0	0	0	0.5	0.5	0.5	0	0.2
Cough	0.9	0.5	0.5	2.4	0	1.0	0.5	1.5	0	1.5
Drug intol (other)	0.5	0.5	0.5	1.0	0	0.5	0	1.5	0	0.5
Bradycard	0.2	0	0	0	0.5	0.5	0	0.5	0	0.5
Other	6.3	6.8	4.9	4.8	6.3	7.8	7.8	7.4	3.5	7.0
Total	29.8	28.3	28.0	27.8	24.2	31.2	35.8	33.8	28.2	29.9

## Reasons for permanent drug discontinuation (%)

	Ov	As	T	TR	TAt	RAt	TR <sub>A</sub>	TR <sub>AtAs</sub>	S	P
Soc/ refused	9.8	10.7	8.3	6.7	4.8	11.7	17.2	9.8	9.4	9.7
Dizz/ HoT	2.2	1.5	3.4	0.5	1.0	3.4	2.9	2.9	2.0	2.4
Gastr/ dysp	0.7	1.5	1.0	1.9	0.5	0.5	0	1.0	0.5	0.2
Hyperkalem	0.1	0	0	0	0	0.5	0.5	0	0	0.2
Cough	0.4	0.5	0.5	1.0	0	0.5	0.5	1.0	0	0.2
Drug intol (other)	0.4	0.5	0.5	0.5	0	0.5	0	1.5	0	0.2
Bradycardia	0.2	0	0	0	0.5	0.5	0	0.5	0	0.2
Other	3.4	4.4	2.4	1.0	3.4	3.4	4.4	2.5	2.5	4.9
Total	14.8	14.6	13.7	10.0	9.7	17.6	22.5	15.2	12.4	16.0

# TIPS: Reasons for Permanent Discontinuation of Study Drug



# Open label meds by drug group (%)

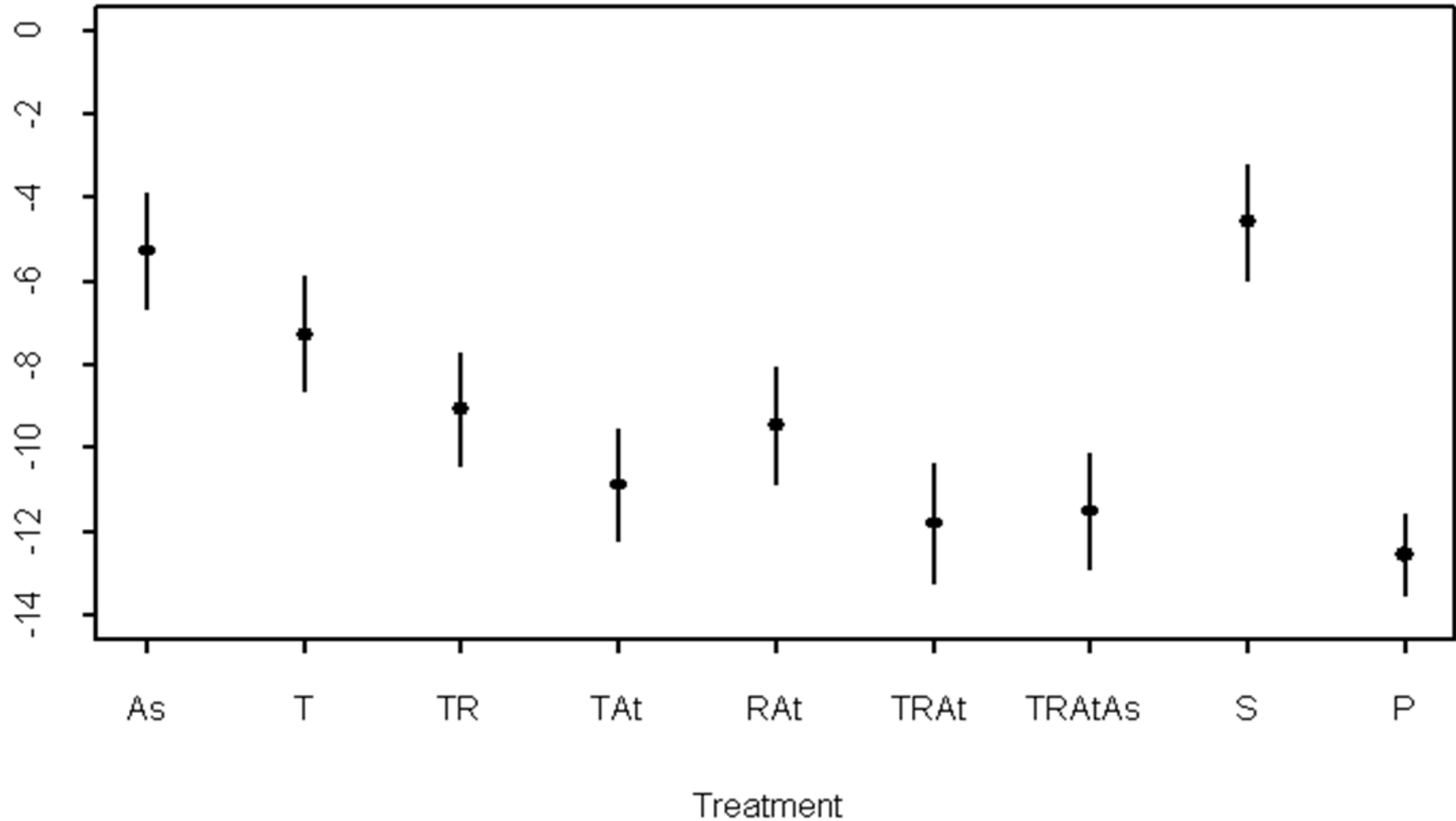
	Ov	As	T	TR	TAt	RAt	TRA	TR AtAs	S	P
Any med	2.1	2.4	0.5	1.4	2.4	1.0	3.4	2.9	0.5	3.2
ASA	0	0	0	0	0	0	0	0	0	0.2
Diur	0.5	0.5	0	0.5	0.5	0.5	0.5	1.0	0.5	0.7
Beta bloc	0.7	2.0	0.5	0.5	0.5	0.5	0.5	1.5	0.5	0.5
ACE-I	0.7	0	0	0.5	1.0	0	2.0	0.5	0.5	1.2
Statin	0.8	1.5	0	0	1.4	0	1.5	1.0	0.5	1.0

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

	Reductions (mmHg)	
	SYS	DIA
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

# TIPS: SBP (mm Hg)

Mean Change (95% CI)



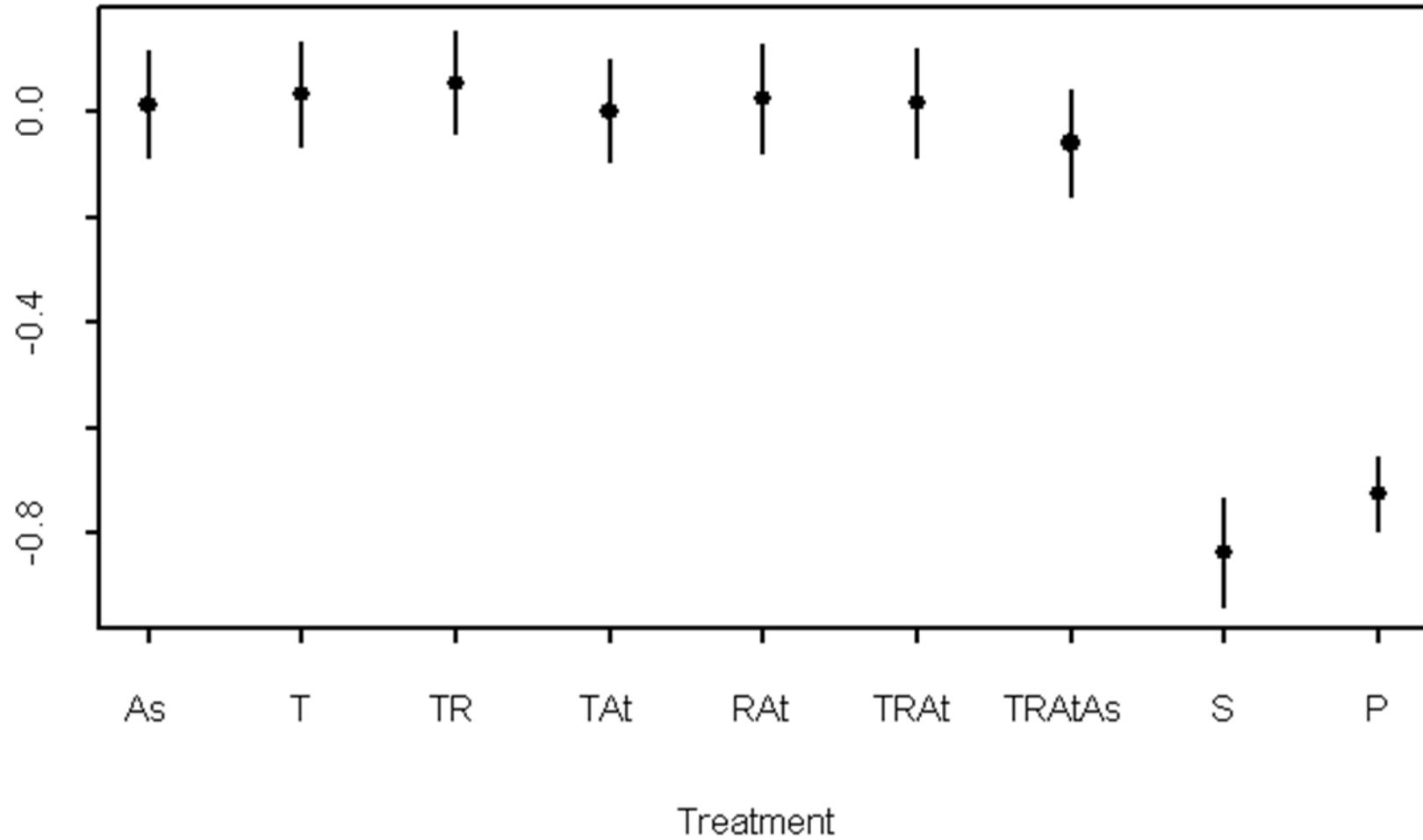
# Impact of Atenolol arms vs Polycap on Heart Rate

	Reduction in HR	CI	P
Polycap	-7.0	(-6.3 to -7.7)	0.001
Other Atenolol arms	-7.0	(-6.2 to 7.9)	0.001
Non Atenolol arms	0.0	(-0.84 to 0.85)	0.99

Polycap/Other atenolol vs non-atenolol arms  $\ll 0.0001$

# LDL (mmol/L)

Mean Change (95% CI)



# Impact on LDL

	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;  $p = 0.06$ ).

# TIPS: Impact of Various Treatments on Urinary Thromboxane B2

	Mean	CI	
ASA alone	-388.0	(-453 to -322)	P <0.001 vs baseline
3 BP lowering drugs + ASA	-389.2	(-457 to -321)	
Polycap	-322.3	(-369 to 276)	

# 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, 1/2 dose)	5.7	24%	33%
Platelet function	Est (ASA 100 mg)	Similar	32%*	16%
Combined	Est	-	<b>62%</b>	<b>48%</b>

\*RCTs suggest a smaller benefit

# TIPS: Limitations

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1. A relatively high rate (19%) of non-completion of the full scheduled treatment and follow up
2. Largely overcome by using measures obtained at earlier time points.
  - BP and HR available in 96%
  - Lipids available in 91%

However, urinary thromboxane B2 is only available in 1490 (73%) at baseline and 1185 (58%) at study end

3. Study conducted only in India

# TIPS: Strengths

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- 9 Arms
  - Ability to understand impact of specific components of Polycap
- Comprehensive evaluation of
  - Safety (glucose, SGPT, clinical) and
  - Efficacy (BP, HR, lipids, TBx2)
- Provides substantial information for the development of a clinically useful Polycap

# TIPS: Conclusions

In those with average risk factor levels,

- 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.
- The Polycap reduces LDL to a slightly lower extent compared to simvastatin alone
- The Polycap lowers thromboxane B2 to a similar extent as aspirin alone.
- There are no significant drug-drug interactions
- The Polycap is well tolerated.
- The Polycap could potentially reduce CVD risk by about half.

**Thank you**

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