The Indian Polycap Study 1 & 2 (TIPS 1 & 2) and The International Polycap Study 3 & 4 (TIPS 3 & 4)

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Outline

1. Design and results: TIPS-1 & TIPS-2
2. PK study
3. Design and update of TIPS-3
4. Design of TIPS-4

The Indian Polycap Study (TIPS): Questions we asked in 2005

1. Can we formulate a Polypill 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: Primary Objectives

Whether the Polycap is similar:

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: Study Design

- Randomized, double blind, partial factorial
- Polycap vs. 8 other formulations
- Superiority and inferiority comparisons
- Active treatment for 12 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: Organization

TIPS: subjects

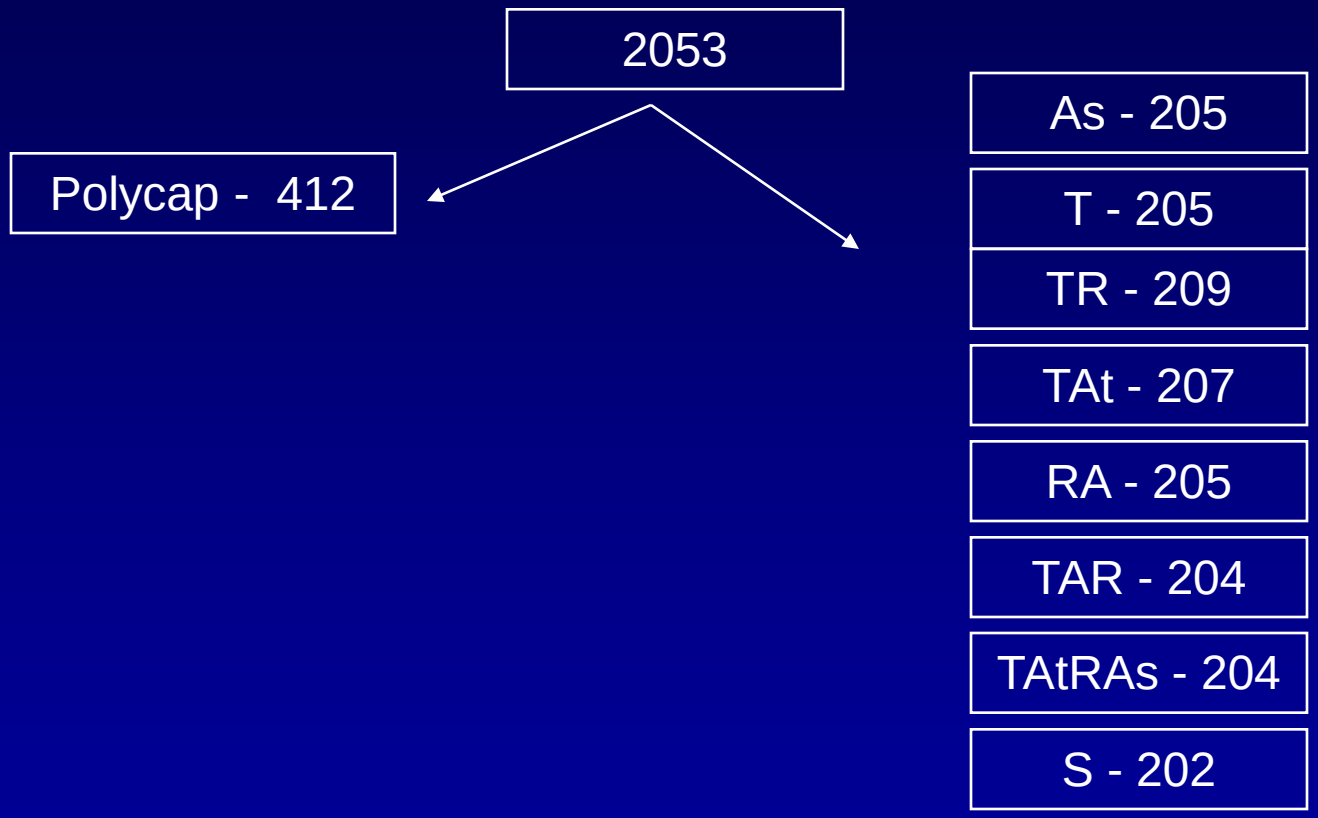
Inclusion Criteria:

- Age 45 to 80 years
- At least one CV risk factor
  - Hypertension (SBP > 140 ≤ 159; DBP > 90 ≤ 100Hg, 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 >175mg/dl
- Abnormal renal function (Cr>2.0mg/dl or K+>5.5 mEq/L)
- Previous CVD or CHF

Final treatment allocation



Yusuf S, Pais P, Xavier D et al. Lancet 2009

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

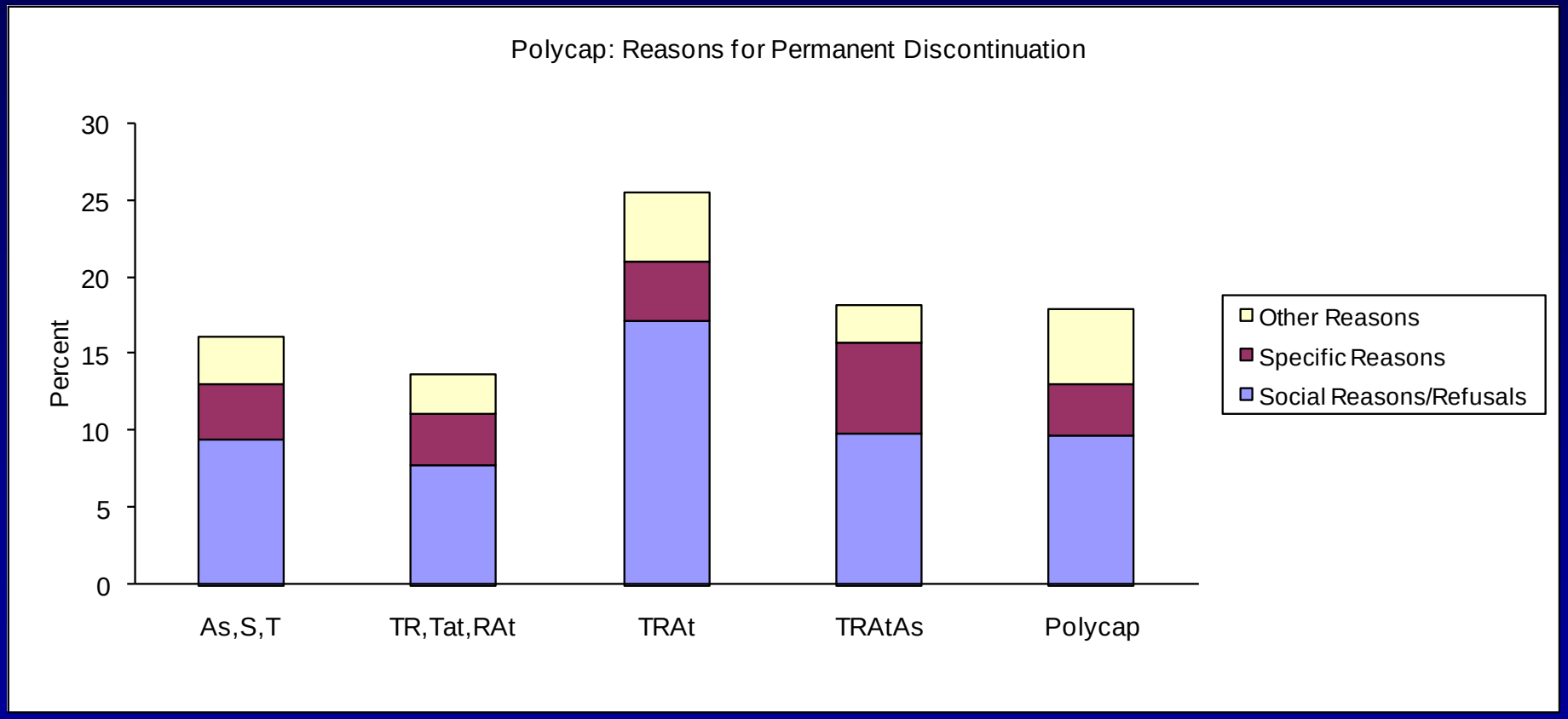
Characteristics	Overall
N	2053
Systolic BP (mmHg)	134.4 (12.3)
Diastolic BP (mmHg)	85.0 (8.1)
Total Cholesterol (mmol/d)	4.7 (0.9)
LDL (mmol/L)	3.0 (0.8)
HDL (mmol/L)	1.1 (0.3)
Triglycerides (mmol/L)	1.9 (1.2)
ApoB	0.9 (0.2)
ApoA	1.2 (0.2)

Selected safety parameters (%)

	Ov	As	T	TR	TAt	RA	TR A	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

Yusuf S, Pais P, Xavier D et al. Lancet 2009

TIPS: Reasons for Permanent Discontinuation of Study Drug



Mean Changes in BP (95% CI) vs no BP lowering 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

Yusuf S, Pais P, Xavier D et al. Lancet 2009

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 <<0.0001

Yusuf S, Pais P, Xavier D et al. Lancet 2009

Impact on LDL

	Mean redn	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; $p=0.06$).

Yusuf S, Pais P, Xavier D et al. Lancet 2009

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

			% Relative Reduction	
		Reduction in RF	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

Yusuf S, Pais P, Xavier D et al. Lancet 2009

TIPS-1: 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
- Polycap is well tolerated.
- Polycap could potentially reduce CVD risk by about **half**.

Yusuf S, Pais P, Xavier D et al. Lancet 2009

PHARMACOKINETIC STUDY

- Polycap vs single drug: 5 arms
- Normal healthy volunteers - 195
- PK parameters: Cmax, AUC; 80-125%
- Findings
  - Safe
  - No PK drug-drug interactions
  - BA preserved

A Patel et al, Am J CV Drugs, 2010

Polycap in secondary & high risk prevention

With full doses

Indian Polycap Study-2 (TIPS-2)

- In patients with stable CVD or elevated risk factors

  To evaluate two doses of Polycap, compared to a single dose

TIPS-2 patients and FU

- 518 eligible patients randomized to
- Single dose low strength Polycap plus placebo, or
- Two doses low strength Polycap
- Study medications for 8 weeks,

Characteristics of Participants

	SINGLE DOSE POLYCAP (N=261)	DOUBLE DOSE POLYCAP (N=257)
	Mean (SD)	
Age (years)	57.7 (9.5)	57.3 (9.1)
BMI (kg/m^2)	25.6 (4.6)	25.4 (4.7)

Characteristics of Participants

	SINGLE DOSE POLYCAP (N=261)	DOUBLE DOSE POLYCAP (N=257)
	Mean (SD)	
Pre-Run-in		
Systolic BP (mmHg)	143.8 (13.84)	144.3 (13.54)
Diastolic BP (mgHg)	86.8 (7.74)	87.8 (7.69)
Heart rate (beats/min)	78.1 (10.54)	78.9 (11.16)
Total cholesterol (mmol/L)	4.2 (1.1)	4.1 (1.1)
LDL cholesterol (mmol/L)	2.40 (0.9)	2.32 (0.9)
HDL cholesterol (mmol/L)	1.03 (0.30)	0.99 (0.25)
Triglycerides (mmol/L)	1.73 (1.05)	1.82 (1.44)

Characteristics of Participants

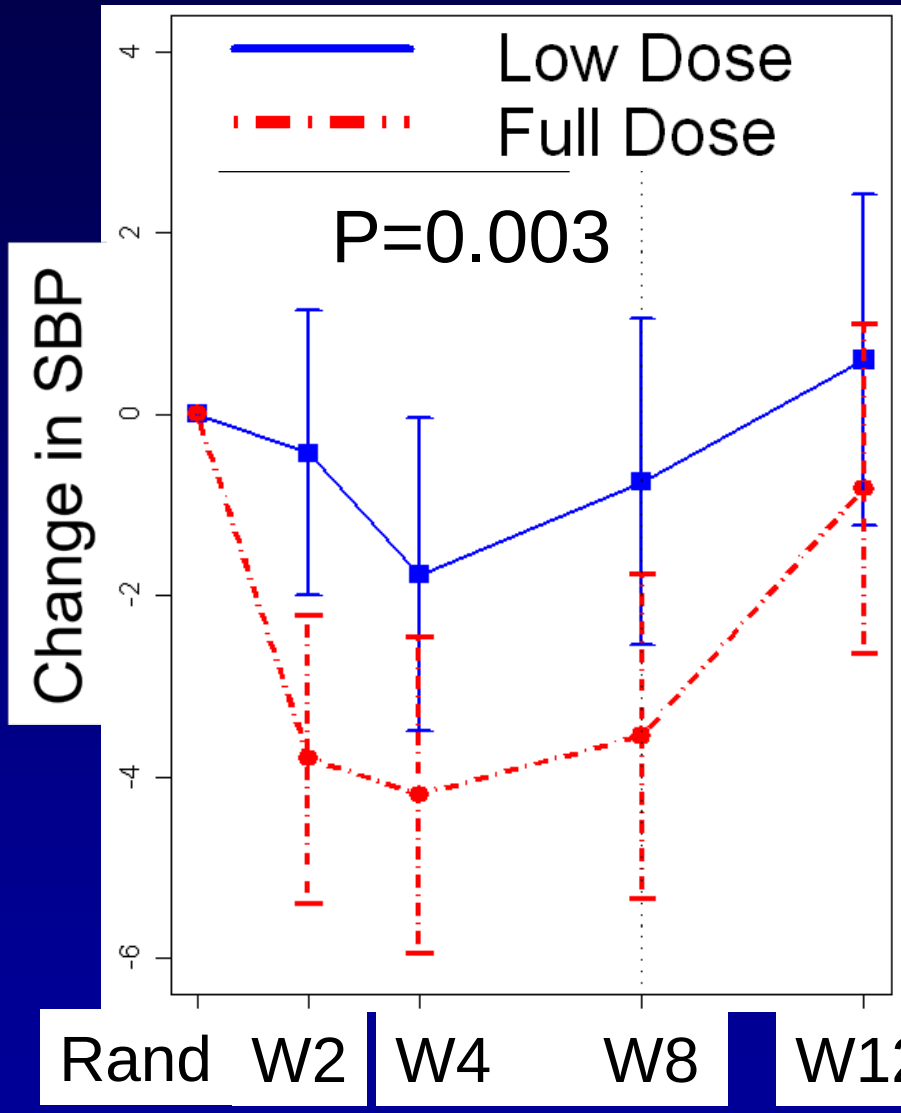
	SINGLE DOSE POLYCAP (N=261)	DOUBLE DOSE POLYCAP (N=257)
	No. (%)	
Randomization		
Diabetes	105 (40.2)	107 (41.6)
Current smoker	14(5.4)	15(5.8)
Men	153 (58.6)	154 (59.9)
CHD	145(55.6)	142(55.3)
Stroke/cerebrovascular disease	31 (11.9)	34 (13.2)
Peripheral artery disease	5 (1.9)	4 (1.6)

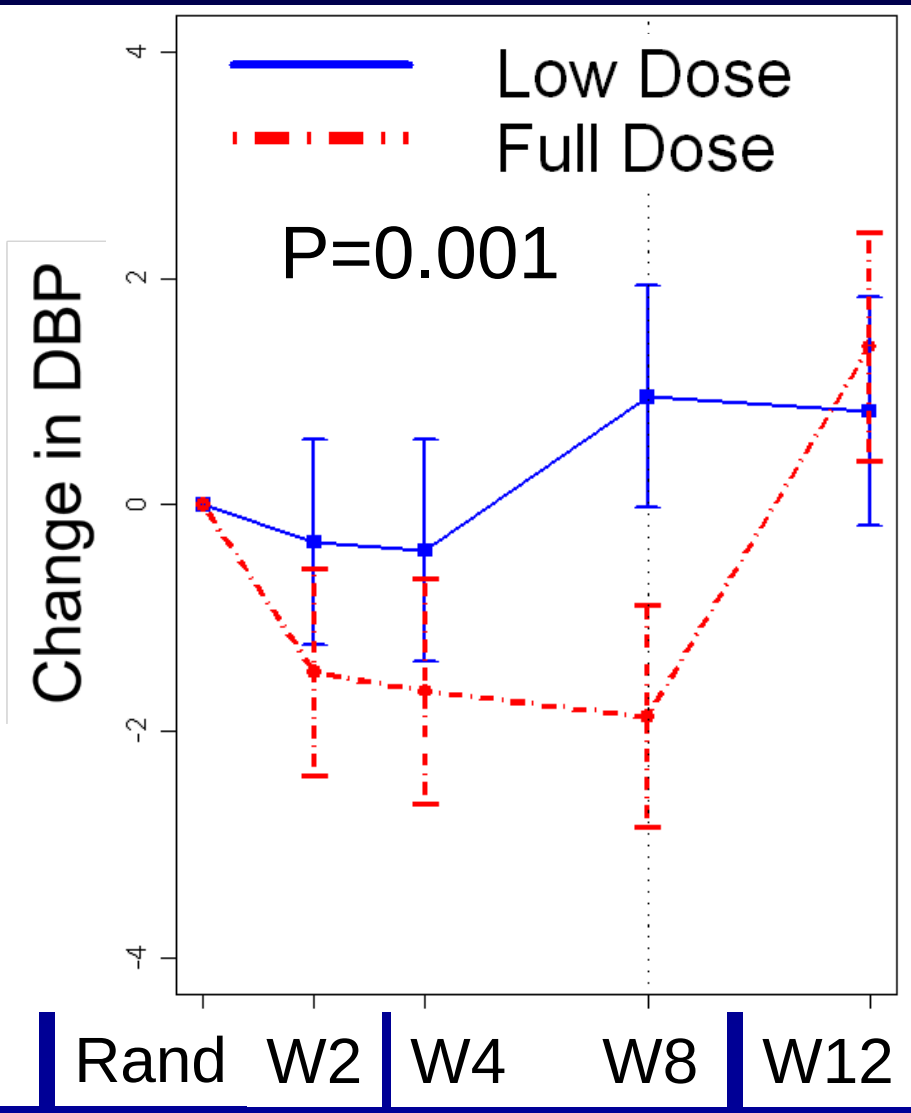
Yusuf, Pais, Sigamani, Xavier, Circulation Res 2012

Characteristics of Participants

	SINGLE DOSE POLYCAP (N=261)	DOUBLE DOSE POLYCAP (N=257)
	No. (%)	
Drugs Prior to Run-in		
Diuretics	88 (33.7)	86 (33.5)
ACE-inhibitors	122 (46.7)	134 (52.1)
Angiotensin receptor blockers	92 (35.2)	70 (27.2)
Beta-blockers	121 (46.4)	128 (49.8)
Calcium channel blockers	73(28.0)	63(24.5)
Aspirin	162 (62.1)	163 (63.4)
Statins	155 (59.4)	160 (62.3)
Drugs at Randomization		
Calcium channel blockers	42 (16.1)	30 (11.7)
Alpha blocker	5 (1.9)	3 (1.2)
Oral hypoglycemic drug	124 (47.5)	140 (54.5)
Insulin	31 (11.9)	32 (12.5)

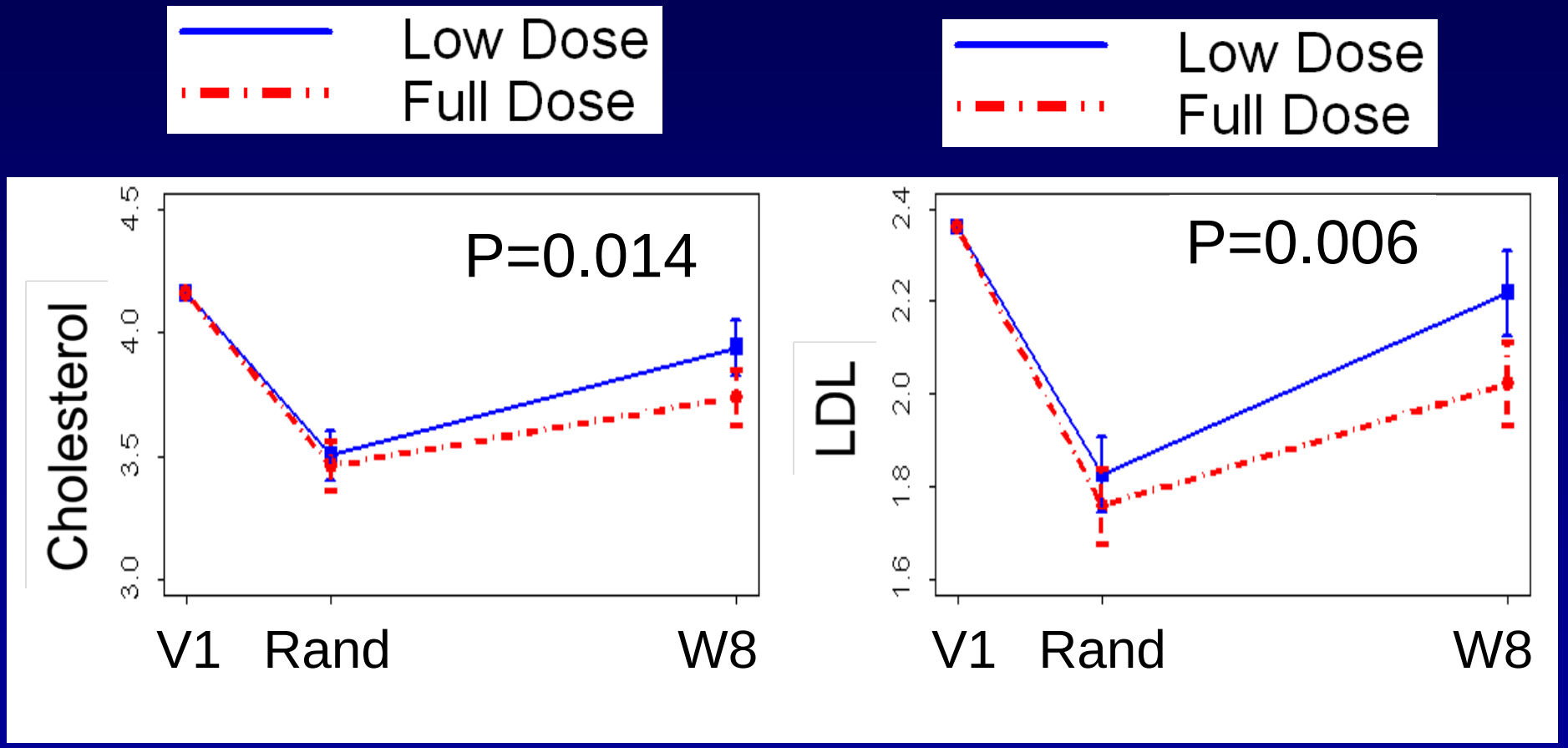
TIPS-2 BP: mean change and 95% CI





† adjusted for baseline value

Mean levels of Lipids from run-in



† adjusted for baseline value

Reasons for study drug discontinuation after randomization

	Temporary or Permanent Discontinuation	
	N (%)	
	Single Dose	Double Dose
No. randomized	261	257
No. discontinued	31 (11.9%)	36 (14.0%)
Cough	9 (3.4%)	5 (1.9%)
Dizziness	6 (2.3%)	6 (2.3%)
Gastritis/dyspepsia*	1 (0.4%)	9 (3.5%)
Increased K^+/Cr	1 (0.4%)	2 (0.8%)
Surgery	1 (0.4%)	1 (0.4%)
Other	14 (5.4%)	15 (5.8%)
* P <0.05		

Reasons for study drug discontinuation after randomization

	Permanent Discontinuation	
	N (%)	
	Single Dose	Double Dose
No. randomized	261	257
No. discontinued	18 (6.9%)	20 (7.8%)
Cough	5 (1.9%)	3 (1.2%)
Dizziness	4 (1.5%)	3 (1.2%)
Gastritis/dyspepsia*	1 (0.4%)	7 (2.7%)
Increased K^+/Cr	1 (0.4%)	2 (0.8%)
Surgery	0 (0%)	0 (0%)
Other	7 (2.7%)	5 (1.9%)
* P <0.05		

TIPS-2 Conclusions and Implications

- Double dose Polycap reduces
  - BP and LDL-C levels to a significantly greater extent compared to the low dose, with similar tolerability
  - double dose Polycap should lead to a proportionately larger clinical benefit
- These results, translate into
  - 50% to 60% relative risk reduction in major CVD when administered long term

TIPS-3
The International Polycap Study

A randomized double-blind placebo-controlled trial for the evaluation of a polycap, low dose aspirin and vitamin D supplementation in primary prevention

Funded by the Wellcome Trust and Cadila Pharma

Background

- To evaluate the impact of
  - Full dose Polycap, without aspirin on long term hard clinical end points in,
    - Moderate or high risk individuals without CVD, and
    - A wider range of populations
- TIPS-1 and 2 helped to identify
  - Optimal dose of Polycap and
  - Demonstrated tolerability

TIPS-3 DESIGN

- Randomized, double blind, International
- Long term clinical events study
- 2 x 2 x 2 factorial design

TIPS-3: Primary Objectives

1. **Polycap:** whether the Polycap reduces risk of the composite outcome of major CVD (CV death, non-fatal stroke, non-fatal MI), plus heart failure, resuscitated cardiac arrest, or revascularization with evidence of ischemia)
2. **Aspirin:** whether aspirin reduces the risk of composite outcome of CV events (CV death, MI or stroke), and cancers.
3. **Vitamin D:** whether vitamin D reduces the risk of fractures

compared to placebo at 5 years of follow-up.

Study Population

- Men ≥ 55 and women ≥ 60 years with:
  - an INTERHEART risk score of ≥ 10,
  - no known vascular disease and
  - no clear clinical indication or contraindication for statin, beta blocker, ACE inhibitor, diuretic, aspirin, clopidogrel or higher doses of vitamin D (>400 IU/day); in the judgment of the physician.

Trial Organization

- Central Coordination
  - Population Health Research Institute
- Sponsors:
  - Wellcome Trust & Cadila Pharma

	India	China	Philippines
Centers (100)	30-40	30-40	10
Participants (5000)	2000	2250	750
Others: (75-100 Centers) Canada, S Africa, Tanz, Arg, Brazil, Malys			2,000 or 3,000

TIPS-3 Global Status

- India
  - Run in 134 and randomized 45 patients from 14 centers
- Philippines
  - Run in 8 randomized 0 patients from 1 centers
- China
  - Will take few more months for regulatory approvals
- Canada
  - Obtained an independent grant
- Other countries
  - Brazil, Argentina, Columbia, Chile, USA, Malaysia
  - Applied for grants; planning procedures

The International Polycap Study - TIPS 4 - in Hypertension

A randomized trial evaluating the effects of different combinations of blood pressure lowering agents, with and without statins

Goals:

- To assess the incremental BP lowering by full doses of

  - two 3-BP lowering drugs compared to

  - three 2-BP lowering drugs combinations.

- To assess the impact of adding a statin on lipids to the BP lowering drug combinations.

Trial Design

- Randomized double blind factorial design consisting of
  - a main trial of BP lowering
    - Clinic BP primary outcome measure
  - an ABPM substudy,
    - subset of participants main trial,
    - 24 hr BP as the primary outcome.

Primary Objectives:

- To compare BP lowering effects of
  - 3 drug combination arms (n=350)

  versus

  - 2 drug combination arms (n=525).
- To assess whether statins
  - simvastatin or atorvastatin affect the BP lowering

Inclusion criteria:

- Men or women aged 30 years or older,
- With SBP 150 to 180 mmHg

Study Drugs

- 2 drug combinations:
    1. HCTZ (25mg) + Amlodipine (10 mg)
    2. HCTZ (25 mg) + Atenolol (100 mg)
    3. HCTZ (25 mg) + Ramipril (10 mg)
- 3 drug combinations:
    1. Low doses:
        - HCTZ 12.5 mg + rami 5 mg + aten 50 mg or Amlodipine 5mg
    2. Full doses:
        - HCTZ 25 mg + ramipril 10 mg + atenolol 100 mg or Amlodipine 10mg
- Simvastatin 40 mg
- Atorvastatin 20 mg

Study duration

- 2 weeks run in
- 8 weeks treatment

Study update

- India, Canada, Italy
- Being submitted for regulatory

Summary: TIPS 1,2,3 & 4

1. Systematic approach since 2005
   - Evaluate different aspects of combination pharmacotherapy
   - In primary and secondary prevention of CVD
2. TIPS-1 & TIPS-2
   - Completed
   - Demonstrated tolerability and efficacy
3. TIPS-3
   - Ongoing, large, international, clinical events trial
   - Primary prevention
4. TIPS-4
   - To start in 3 months