



Polypill for CVD prevention

Status and future plans

Apr 20th, 2010

OxHA meeting, Delhi

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Outline

1. Context
2. Polypill concept
3. Completed studies
4. Answers available
5. Ongoing studies
6. Potential global impact

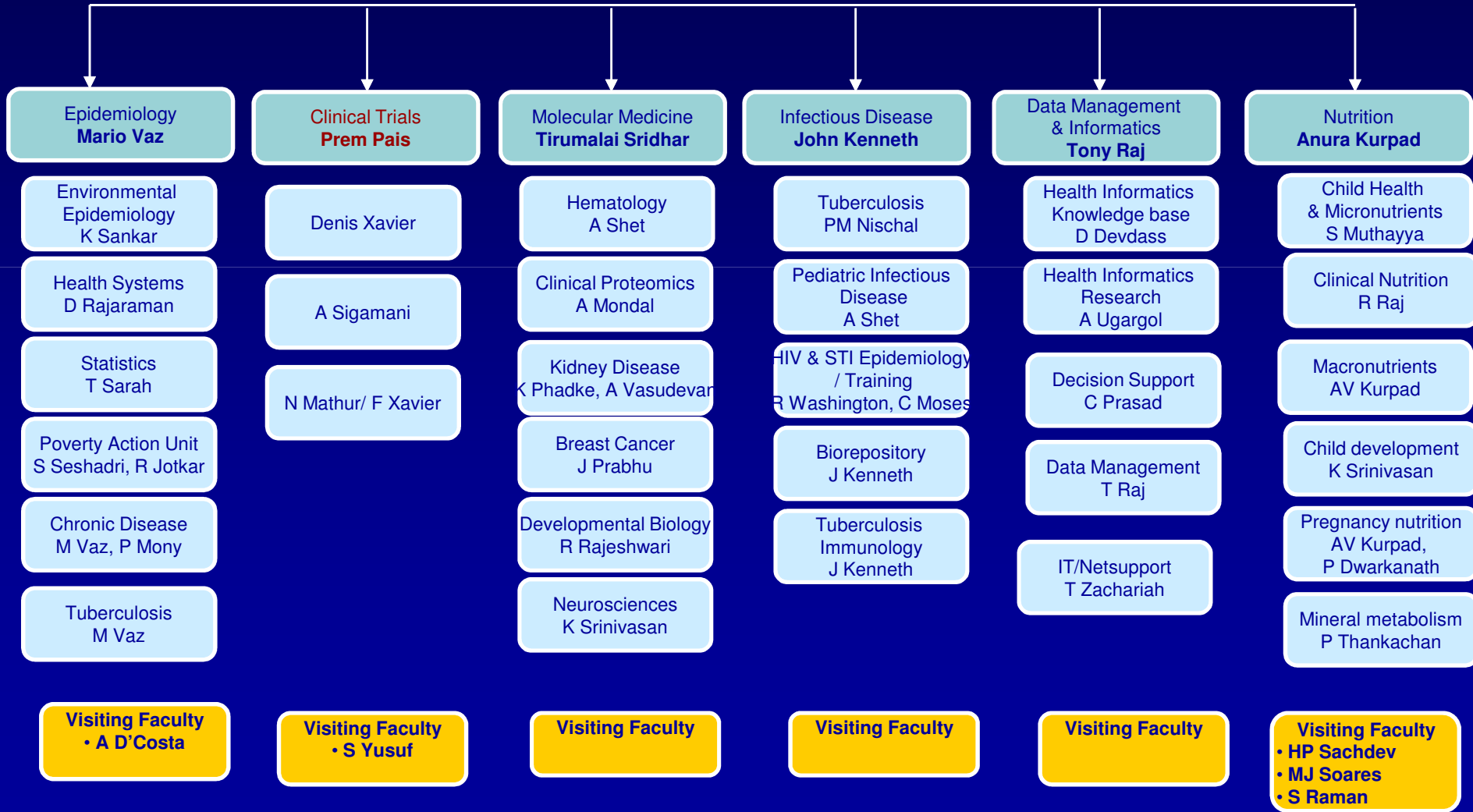
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SJRI: CVD studies

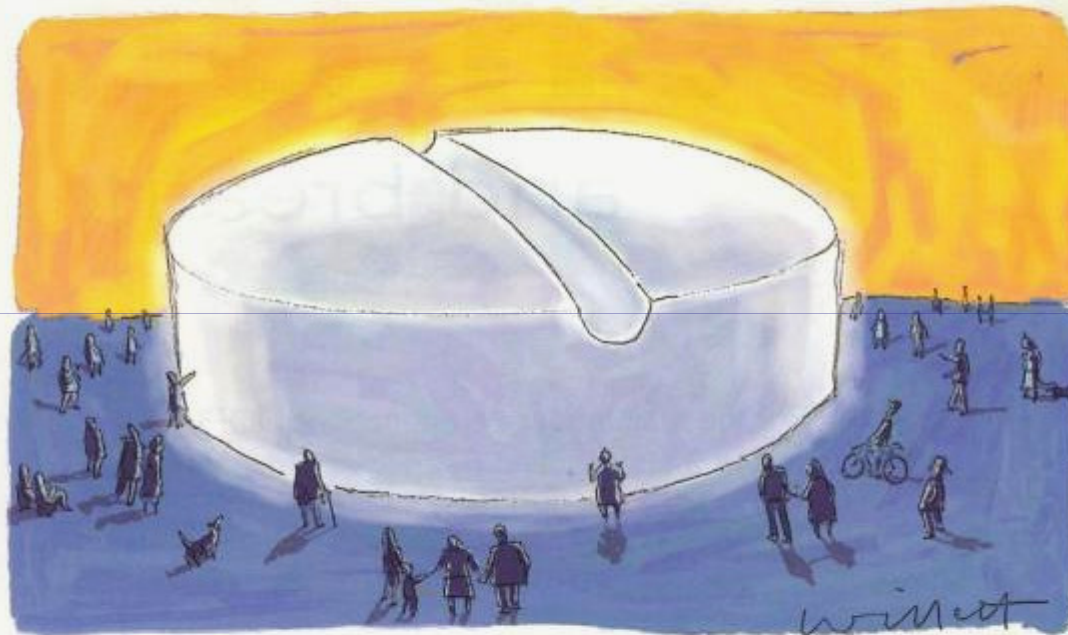
Designed / coordinated since 1999

- **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 [1500 → → 4,000]
- **Large Clinical Trials**
(170+ institutions, 60 cities >25,000)
 - CREATE, 8,060, [JAMA-04, AHJ-04]
 - POISE, 777 [Lancet-08]
 - PRoFESS, 1,620, [NEJM-08]
 - OASIS 5, 544 [NEJM-06]
 - OASIS 6, 1,450 [JAMA-07]
 - CURRENT, 2300+ [completed]
 - VITATOPS, 1450+ [completed]
 - RELY, 650 [NEJM - 09]
 - POLYCAP, 2053 [ACC'09, Lancet'09]
 - AVVEROES, 190+
 - ARISTOTLE, 450+
 - HOPE-3, 2,000
 - MARS – 400 [completed]
 - ASPIRE, 400
 - RECREATE, 250
 - OASIS-8, 500
 - RELY AF Registry, 1,500
- **In 2010 Obs Epi studies and Trials to be initiated [~50,000]**
- **NHLBI- UH projects**
 - INSPIRE - 10,500 (pilot)
 - SPREAD - 800
 - PREPARE - 15,000
 - **Wellcome Trust Polypill trial**
 - 2500 (5,000)
 - ASSURE - 800
 - APOLLO - 2000
 - VISION - 8,000 (pilot)
 - MACE – 10,000
 - PEGASUS - 600
 - APPRAISE - 1000

28 June 2003

BMJ

28 June
2003



A pill to prevent 80% of heart attacks

Polypill would contain a statin, three antihypertensives, folic acid, and aspirin pp1407, 1419, 1423, 1427

Risk reductions with the Polypill

Risk Factor	Component	Approximate risk factor reduction	Reduction in risk	
			IHD	Stroke
LDL cholesterol	Statin	1.8 mmol/L	61%	17%
	e.g. simvastatin 40mg/day atorvastatin 10mg/day			
Blood pressure	Half standard dose of 3 from:	10.7 mm Hg diastolic	46%	63%
	– Thiazide – β -blocker – ACE-inhibitor or ARB – Calcium channel blocker (CCB)			
Serum homocysteine	Folic acid (0.8mg/day)	3 μ mol/L	16%	24%
Platelet aggregation	Aspirin (75mg/day)	–	32%	16%
Combined effect			88%	80%

POTENTIAL BENEFITS - POLYPILL

1. Large benefits possible, with few side effects.
2. Lower Costs * (Packaging, handling, distribution, prescription, fewer physician visits).
3. Better Adherence* (Physician/Subject/guidelines).
4. Low medication errors*
5. Improved access & equity* (provide polypill through existing non-physician medical personnel).
6. Impact globally.

* Experiences in HIV, tuberculosis and malaria.

Target population and the strategy

- Target population
 - Virtually all with vascular disease
 - High risk primary prevention ($>1\%/yr$ risk)
 - Sub-clinical disease (abnormal ABI, ECG markers, DM, microalbuminuria)
 - over 55 yrs + 3 risk factors (eg metabolic syndrome)
 - in those - benefits outweigh the risks by at least 4 or 5 fold.
- The “polypill” strategy
 - Not a replacement
 - But complementary to lifestyle changes

The Indian Polycap Study (TIPS): Questions we asked

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
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Statin	Simvastatin	20 mg/d
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ACE-Inhibitors	Ramipril	5 mg/d
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Beta-blocker	Atenolol	50 mg/d
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Diuretic	Hydrochlorothiazide	12.5 mg/d
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Yusuf S, Pais P, Xavier D et al. Lancet 2009

TIPS: Primary Objectives

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

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

TIPS: Study Design

- 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.

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

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)

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%

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

TIPS: Organization

53 Centers in India



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

Sponsor:
Cadila Pharma, India

Central lab:
SRL, Mumbai



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

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

TIPS: subjects

Inclusion Criteria:

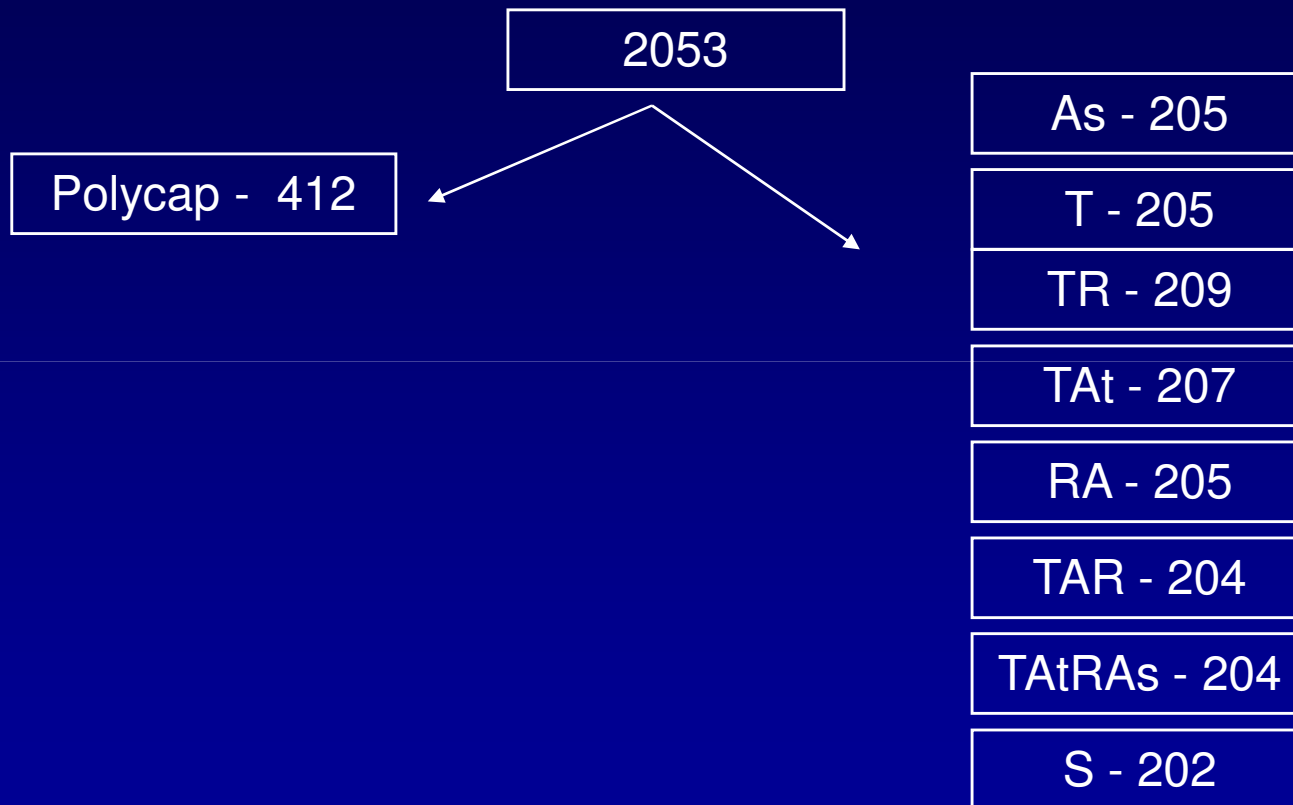
- Age 45 to 80 years
- At least one CV risk factor
 - Hypertension (SBP $> 140 \leq 159$; DBP $> 90 \leq 100$ Hg, but treated)
 - Diabetes mellitus (on one oral drug / diet)
 - Smoker > 5 years
 - Raised WHR
 - Abnormal lipids (LDL 130-175mg/dl)
- Informed consent

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

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

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

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

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

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)	

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 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

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

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**.

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

Challenges with the polypill

- Getting the 'buy-in' of
 - Medical professionals
 - Primary vs secondary prevention
 - Risk factors as a continuum; any reduction is beneficial
 - Autonomy issues - prescription and dose titration
 - Patients (more open)
 - Cost, ease
- Positioning lifestyle interventions
 - False sense of security?
- Economic issues
 - Complex
 - Patients, Pharma, Government and Insurance Cos.

Status in India

- Polycap
 - Approved for marketing in India to ‘reduce CV risk’
 - Regulatory questions: ?indication
- Efforts to reach
 - Medical community
 - ‘Patients’
 - Care givers
 - Policy makers

Next steps

- Need definitive data from large studies on
 - Adherence,
 - Tolerability in larger populations,
 - Efficacy on reducing clinical outcomes
- Wellcome Trust Polypill trial
 - Large clinical events trial on 5000 patients (5-7 years)
 - To start in 2010

Criteria - Wellcome Trust strategic translation award RFP

1. Primary prevention
2. Study leads to approval in India
3. Study conducted according to EMEA standards (GCP-ICH)
4. PI primarily based in India
5. Study solely or substantially conducted in India (but other countries allowed)
6. Polypill is affordable

Large Trial for Primary Prevention.

- **Question:**

- In those at moderate risk (1 to 1.5 %/yr) and no vasc disease,
- does the polycap lead to a large reduction in CVD safely and cost effectively in addition to practical lifestyle advice?

- **Design:**

- 5000 people randomized to receive 4 component polycap without ASA (low /hi dose) vs placebo for 5 yrs
- India and China.(possibly +3000 from S.America/Africa)
- High power to detect 40 to 50% RRR

Timelines

- Final Contracts being signed
- Trial initiation - Q-1 2011
- Recruitment - 2 years
- Follow up - 5 years
- Completion - 2016

POLYPILL TRIALS

Name/ N	Sponsor/ location	Components	Outcomes	Status
TIPS 2053. Prm	Cadila, PHRI, St. John's, India	ASA, sim, aten, HCT, rami	CV risk, safety	Completed Lancet 2009
Polypill 200, prm	Wake Forest, Sri Lanka Furberg, Mendis	-	CV risk, adherence	Ongoing
Tehran/ U Birmingham 475, Prm	Iran Malekzedah/ Marshall	ASA, HCT, enalapril, atorvastatin	Reduce BP, Cholesterol	Completed, Iran
UMPIRE 2000, Sec	Europe, India Thom, Poulter, Prabhakaran	ASA, simva, lisono +/-aten, HCT	2 year Adher, BP, Chol	To start, end Jan 2013
TIPS-K 500 Sec	Cadila, PHRI, St. John's, India	Higher dose polycap +/- K	RF redn, tolerability	Recruiting End, Aug 2010

Conclusions

- Polypill
 - Potential to make an important global impact in the prevention of CVD
- Demonstrated
 - Feasibility, tolerability and physiological benefits
- Ongoing studies: Impact on
 - Clinical outcomes and adherence,
 - Uptake and economic
- Beyond studies
 - Public health issues
 - Engage Governments and World Bodies

Thank you