Comparison of Risk Factor Reduction and Tolerability of a Full-Dose Polypill (With Potassium) Versus Low-Dose Polypill (Polycap) in Individuals at High Risk of Cardiovascular Diseases

The Second Indian Polycap Study (TIPS-2) Investigators

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Background—A daily single capsule (polycap) of 3 blood pressure (BP) lowering drugs (hydrochlorothiazide, 12.5 mg; atenolol, 50 mg; ramipril, 5 mg) at low doses, simvastatin (20 mg), and aspirin (100 mg) has been demonstrated to be well tolerated and to reduce BP and low-density lipoprotein cholesterol. We examined the incremental effects of 2 (full dose) plus K⁺ supplementation versus single polycap (low dose) on risk factors and tolerability.

Methods and Results—After a run-in period, 518 individuals with previous vascular disease or diabetes mellitus from 27 centers in India were randomly assigned to a single-dose polycap or to 2 capsules of the polycap plus K⁺ supplementation for 8 weeks. The effects on BP, heart rate (HR), serum lipids, serum and urinary K⁺, and tolerability were assessed using an intention-to-treat analysis. The full-dose polycap (plus K⁺ supplementation) reduced BP by a further 2.8 mm Hg systolic and 1.7 mm Hg diastolic, compared with that observed with the low-dose polycap (P=0.003; P=0.001), but there were no differences in HR (0.1 bpm). The differences in total and low-density lipoprotein cholesterol between the full-dose and low-dose polycap was 7.2 mg/dL (P=0.014) and 6.6 mg/dL (P=0.006), respectively, but there were no differences in high-density lipoprotein cholesterol or triglycerides. The rates of discontinuation of the study drug after randomization were similar in the 2 groups (6.0% low dose versus 7.8% full dose).

Conclusions—The full-dose polycap (plus K⁺ supplementation) reduces BP and low-density lipoprotein cholesterol to a greater extent compared with the low dose, with similar tolerability. Therefore, the full-dose polycap should potentially lead to larger benefits.

Clinical Trial Registration—URL: http://www.ctri.nic.in. Unique identifier: CTRI/2010/091/000054.

(Key Words: risk factors • blood pressure • lipids • cardiovascular disease)

A

Aspirin, β-blockers, statins, and angiotensin-converting enzyme inhibitors reduce myocardial infarction, stroke, and cardiovascular death in secondary prevention. It was proposed that a combination of these 4 drugs could reduce the risk of cardiovascular disease (CVD) by 75% in secondary prevention, and that a combination of 6 drugs (3 blood pressure [BP] lowering drugs at half doses, aspirin, a statin, and folic acid) could reduce CVD in all individuals older than 55 years by 80%. This hypothesis became popularly known as the polypill concept. Of these components, folic acid does not reduce CVD, and so current research has focused on the other components.

The advantages of such a fixed dose combination include improved compliance, reduced side effects, and cost savings. In the first major clinical trial of the polypill reported in 2009, the Indian Polycap Study (TIPS) demonstrated that a combination of 5 drugs at low doses (aspirin, 100 mg; atenolol, 50 mg; ramipril, 5 mg; thiazide, 12.5 mg; simvastatin, 20 mg) was well tolerated and reduced risk factors so that about a halving of CVD was projected. This is substantially lower than previous theoretical estimates. Similar results have also been reported with another polypill preparation. However, if a higher strength of the polypill is more effective in lowering risk factors, or has benefits through additional mechanisms, then larger...
WHAT IS KNOWN?

- Reducing cardiovascular risk factors, including blood pressure and cholesterol, remains a critically important strategy for reducing the global burden of cardiovascular disease.
- A polypill combining generic hydrochlorothiazide (12.5 mg), atenolol (50 mg), ramipril (5 mg), simvastatin (20 mg), and aspirin (100 mg) has been shown to reduce blood pressure and cholesterol in patients with vascular disease.

WHAT THIS ARTICLE ADDS

- A randomized trial of providing 2 polypills to 257 subjects, along with potassium supplementation (30 mEq), resulted in further blood pressure reduction (mean systolic reduction of 2.8 mm Hg and diastolic reduction of 1.7 mm Hg; 95% CI, −0.17 to −2.8 mm Hg) and low-density lipoprotein cholesterol (adjusted difference, −7.2 mg/dL; 95% CI, −1.5 to −12.9 mg/dL), compared with a single polypill provided to 261 subjects.
- No significant difference in heart rate, high-density lipoprotein, or triglycerides was observed.
- The polypill regimens were similarly tolerated with 11.9% and 14% of the low- and high-dose groups stopping the study medication for some period during the 8 weeks of medication exposure.

Methods

Study Design and Population

Between April 1, 2010, and September 18, 2010, 725 patients, who were 40 years or older with a seated BP of 120/80 mm Hg on 2 consecutive occasions (or BP ≥120/80 mm Hg on antihypertensive drugs) and vascular disease or high-risk diabetes mellitus (HbA1c <7.5%, with microalbuminuria or BP >140/90 mm Hg), were eligible. Patients with known intolerance to, or a clear indication for any of the study drugs, planned or recent coronary intervention or surgery, renal dysfunction (serum creatinine >2 mg/dL [176.8 µmol/L] or serum K >5.0 mEq/L or estimated glomerular filtration rate <45 mL/min/1.73 m²), or inability to attend follow-up visits were excluded. All individuals provided written informed consent and then entered a run-in phase where they initially received 1 capsule of the low-dose polypill (acetylsalicylic acid or aspirin, 100 mg; simvastatin, 20 mg; atenolol, 50 mg; ramipril, 5 mg; hydrochlorothiazide, 12.5 mg) for 10 days, followed by 2 capsules of the polypill (full strength) for another 10 days (n = 645). Of these 645 individuals, 518 entered the randomized phase of the trial comparing low-dose polypill versus full-dose polypill plus potassium (Figure 1).

Patients were recruited from 27 clinical centers in India. The coordinating centers were located at the Division of Clinical Trials, St. John’s Research Institute, Bangalore, India, and at the Population Health Research Institute, Hamilton Health Sciences and McMaster University, Canada. The protocol was approved by the respective ethics committee or research ethics boards and regulatory authorities.

Procedures

A total of 518 patients were randomized (using a central computerized system) to receive 2 capsules (full dose) of the low-dose polypill, each containing simvastatin 20 mg, ramipril 5 mg, atenolol 50 mg, hydrochlorothiazide 12.5 mg, and aspirin 100 mg, or one polypill plus equivalent placebo. Patients were instructed to take both capsules together and at the same time every day. Those allocated to potassium received 30 mEq/L once daily supplements in an open fashion; the original design was to randomize patients using a 2 × 2 factorial design. However, because of an error in programming, all participants randomized to the full-dose polypill also received K+, whereas nobody in the low-dose polypill group received K+ (see online-only Data Supplement). This error in programming in randomization was discovered only at the end of the study, and so all investigators at the sites or the coordinating centers were unaware of this during the conduct of the study, thereby maintaining the study blind. Given that the polypill dose comparison were placebo controlled and double blind, whereas the K+ supplementation was open, investigators ascribed adverse events to each component separately based on their judgment.

HR, sitting BP in the right arm (using an automated instrument with an average of 2 readings after 5 minutes and 7 minutes of rest), tolerability, and compliance were assessed at each visit (screening, first post-run-in visit, second run-in visit, at the randomization visit; 2 weeks ± 6 days, 4 weeks ± 6 days, 8 weeks ± 6 days postrandomization, and at 4 weeks ± 6 days of washout). Advice on healthy lifestyles was provided at each visit, and the quality of diet was assessed at randomization and at 8 weeks. Lipid levels, serum creatinine, potassium, and liver function tests were done at the initial visit, randomization, and at 8 weeks postrandomization. Serum creatinine was also assessed at 2 weeks postrandomization. Fasting blood glucose, urinary microalbuminuria, urinary, and serum K+ were obtained at screening and at 8 weeks postrandomization.

Lipids were measured in a central laboratory on fasting blood samples. Low-density lipoprotein (LDL)-cholesterol was measured with a direct enzymatic photometer (Roche Hitachi 912 analyzer with LDL cholesterol second-generation kits; Roche Diagnostics, Mannheim, Germany). The coefficient of variation of the assay was <4% with a measurement range of 0.1 to 14.5 mmol/L (3.5-561 mg/dL) and an analytic sensitivity of 0.08 mmol/L (3 mg/dL).

Sample Size, Power, and Statistical Analyses

Using information from the TIPS-1 study, we estimated that 500 patients randomized equally to 2 groups would provide 90% power to detect differences of 2.4 mm Hg in diastolic BP, 3.4 mm Hg in systolic BP, and 9.7 mg/dL in LDL cholesterol.

Comparisons of the impact on BP, HR, and lipids were based on an intention-to-treat approach using the randomization values (at which time participants were on full-dose polypill) as the baseline measure (as the most sensitive analysis of the subsequent differences between the 2 doses). A repeated measures model (incorporating the BP values...
at 2, 4, and 8 weeks) with an analysis of variance was used. One-way analysis of covariance was used to compare changes in lipid values between baseline and week 8. All P values are 2-sided and baseline-adjusted changes (mean ± 95% CI) are provided in the tables and figures. Data on BP were available at 8 weeks in 93% and on lipids on 92% of individuals. The consistency of the results was assessed in these prespecified subgroups: those with an HbA1c above or below 7.0 at baseline, those equal to/above and below an LDL level of 70 mg/dL, and elevated BP (≥140 mm Hg) versus normal BP measured at randomization.

Role of the Funding Source
The study was funded by Cadila Pharmaceuticals, Ahmedabad, India, who manufacture the polycap. Representatives of the sponsor of the study were members of the Steering Committee who designed the trial, but they had no role in data collection, analysis, interpretation, or writing this article. Dr Yusuf, Afzal, and Dr Pais had full access to the data and take responsibility for the manuscript and the decision to submit for publication.

Results
Figure 1 shows the trial profile, and Table 1 provides details of baseline characteristics.

Prerandomization Run-In Period
Seven hundred twenty-five individuals entered the first phase of run-in (ie, a single dose of polycap for 10±5 days; Table 2). At the end of this period, 80 individuals did not enter the second phase of run-in (11%). Of the 645 who completed phase I, 518 were randomized and 127 were not.

Postrandomization Tolerance and Adherence
Of the 261 patients randomized to the low dose of polycap, 18 (6.9%) stopped the study medication permanently after randomization compared with 20 (7.8%) with the full dose (Table 3). In addition, 13 and 16 patients, respectively, temporarily stopped study medications, so that 31 (11.9%) in the low dose and 36 (14.0%) in the full dose stopped study medication for some time after randomization. There was no difference in stopping the study medications for any specific reason (Table 3), except for dyspepsia (1 versus 7; low versus full dose; P=0.04). Twenty-seven (10.5%) of those receiving K+ supplements permanently discontinued this (11 for dyspepsia; 4 for elevated creatinine or K+; 12 for other reasons). The rates of specific adverse events (including dizziness) leading to discontinuation were not higher in those with initial BP<130 mm Hg.

Changes in Systolic BP
From the initial pre–run-in value of 144.0 mm Hg, the systolic BP decreased to 130.5 at randomization (–13.5 mm Hg). After randomization, systolic BP decreased to 126.6 mm Hg with the full dose compared with 129.4 with the low dose (adjusted difference, –2.8 mm Hg; CI, –4.70 to –1.0; P=0.003) (Figure 2).
Changes in Diastolic BP
From the initial mean pre–run-in value of 87.3 mm Hg, the diastolic BP decreased to 78.6 mm Hg at randomization (–8.7 mm Hg). After randomization, the diastolic BP averaged 77.0 mm Hg with the double dose compared with 78.7 mm Hg with the low dose (adjusted difference, –1.7 mm Hg; 95% CI, –2.8 to –0.7; \( P = 0.001 \)).

Changes in HR
HR decreased by –8.2 bpm during the run-in, with little difference postrandomization (adjusted difference, 0.1 bpm; 95% CI, –1.0 to 1.2; \( P = 0.87 \); Figure 3).

Changes in Lipids
LDL cholesterol was 91.1 mg/dL at the pre–run-in visit (note 60.8% were receiving lipid lowering drugs prior to randomization; Figure 4). LDL decreased by 21.9 mg/dL at the end of run-in. At week 8, compared with the randomization levels (Figure 4), the LDL cholesterol had increased by 16.6 mg/dL with the low dose compared with 10.0 mg/dL with the full dose (adjusted difference, –6.6 mg/dL; CI, –11.3 to –1.9; \( P =0.006 \)). The differences in total cholesterol paralleled the changes in LDL (adjusted difference from randomization, –7.2 mg/dL; 95% CI, –12.9 to –1.5; \( P = 0.014 \)). There were no significant changes in high-density lipoprotein or triglycerides.

Potassium and Creatinine
The serum K\(^+\) levels at pre–run-in and randomization were both 4.3 mEq/L. There was a significantly higher level of serum K\(^+\) with the double-dose polycap (plus K\(^+\)) at 2 weeks (4.2 versus 4.4 mEq/L; mean difference, 0.2; 95% CI, 0.1–0.3; \( P < 0.001 \)), but not at 8 weeks (4.3 versus 4.4 mEq/L; mean difference, 0.1; CI, –0.03 to 0.1; \( P =0.20 \)). Serum creatinine was 1.0 mg/dL at the pre–run-in visit and increased during run-in (0.1 mg/dL) to 1.03 at randomization. After randomization, there was little difference in creatinine values at 2 weeks (1.0 versus 1.0 mg/dL; difference, 0.03 mg/dL; \( P=0.15 \)) or at 8 weeks (0.96 versus 0.99 mg/dL; difference, 0.03; \( P=0.12 \)).
Urinary Potassium, Sodium, Creatinine, or Microalbuminuria

Urinary potassium was 52.9 mEq/L prior to run-in. At 8 weeks, there was little change with the single dose (−0.7 mEq/L) compared with an increase of +6.9 mEq/L with the double dose plus K+ (difference, +7.6 mEq/L; CI, 1.6 to +13.6; \(P=0.013\)). There was no impact of the treatments on urinary sodium, creatine, or microalbuminuria; data not shown.

Subgroups

Figures 5 and 6 demonstrate the results in prespecified subgroups on the comparative effects of full-dose polycap plus K+ versus low-dose polycap and indicate no statistically significant evidence of differential effects across subgroups.

Discussion

The TIPS-2 study extends the findings of the first TIPS study, which demonstrated that a polycap consisting of a combination of 3 BP lowering drugs, with simvastatin and aspirin, all given at low doses in a single capsule (polycap), was well tolerated. In TIPS-1, compared with groups not using BP or lipid lowering drugs, the low-dose polycap reduced systolic BP by 7.4 mm Hg and diastolic BP by 5.6 mm Hg, LDL by 27.0 mg/dL, and HR by 7.0 beats/min, in individuals with initial average lipids (total cholesterol of 181.5 mg/dL and LDL of 115.8 mg/dL) and BP of 134.4/85.0 mm Hg. These reductions in risk factors with a low daily dose of the polycap (along with aspirin at 100 mg/day) would be theoretically expected to reduce the risk of coronary heart disease (CHD) by 62% and stroke by 48%. In the TIPS-2 study, we evaluated whether twice the dose of the polycap would be well tolerated and provide further reductions in risk factors. Seventy percent of the participants in TIPS-2 had previous CVD. They had a baseline BP and total cholesterol that were lower than TIPS-1 at randomization (134.4 mm Hg systolic in TIPS-1 versus 130.5 mm Hg in TIPS-2 and 180.3 mg/dL in TIPS-1 versus 134.4 mg/dL in TIPS-2, respectively).

Because TIPS-2 was also assessing the feasibility of a large-scale long-term trial, we wanted to ensure that patients who were likely to be adherent would be included. In TIPS-1, about 15% of patients discontinued blinded medication (which was similar with the polycap compared with its individual components), but only about one third of the discontinuation were for drug-specific adverse effects and two thirds were for non-specific effects. To minimize early dropouts because of both

<table>
<thead>
<tr>
<th>Temporary or Permanent Discontinuation</th>
<th>Permanent Discontinuation</th>
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<tbody>
<tr>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Low Dose</td>
<td>Full Dose</td>
</tr>
<tr>
<td>No. randomized</td>
<td>261</td>
</tr>
<tr>
<td>No. discontinued</td>
<td>31 (11.9)</td>
</tr>
<tr>
<td>Cough</td>
<td>9 (3.4)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>6 (2.3)</td>
</tr>
<tr>
<td>Gastritis/dyspepsia</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Increased K+/Cr</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Surgery</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Other</td>
<td>14 (5.4)</td>
</tr>
</tbody>
</table>

K+ indicates potassium; Cr, creatinine.

*\(P=0.01\); **\(P=0.04\).

Figure 2. Mean blood pressure by visits from run-in (V1), during run-in (V2), at randomization (first vertical line), and at weeks 2, 4, and 8 (W8) (second vertical line) after wash out. Data are represented as mean (95% CI). V indicates prerandomization visits; W, postrandomization visit; W12, visit at 12 weeks after study drug withdrawal; SBP, systolic blood pressure; and DBP, diastolic blood pressure.
lack of interest of the participants and early adverse events, in TIPS-2 we included two 10-day run-in periods where the polycap was given initially at the low dose (used in TIPS-1), and then at the full dose (ie, twice the dose used in TIPS-2). About 28.6% of patients discontinued participation during this phase, but the vast majority (>75%) were unrelated to any drug-specific effects. The rates of discontinuation for study drug-related side effects were similar in the first phase (when low-dose polycap was used) and the second phase (when full-dose polycap was used; 4.3% versus 3.1% for a total of 7.4%), and these rates should be added to the rates of discontinuation for specific reasons observed after randomization (total of around 14%–15%). The rates of discontinuation for non-specific reasons was also similar in the 2 phases (4.4% versus 6.7%). These data, although not derived from randomized parallel comparisons, indicate that the full dose of the polycap is likely to be well tolerated, which is supported by the results of the randomized, parallel group double-blind phase of the study. However, the rates of discontinuation for dyspepsia were greater in higher dose compared with lower dose, and this adverse effect is likely because of gastrointestinal effects of the higher dose of aspirin (200 versus 100 mg/day). If aspirin is used at low doses in the polycap, its tolerance is likely to be enhanced.

The higher dose of the polycap (plus K+ supplement) reduced BP by a further 2.8/1.7 mm Hg (compared with the
Figure 5. Changes in LDL in predefined subgroups. LDL indicates low-density lipoprotein; SBP, systolic blood pressure.

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>N</th>
<th>Mean value at rand (mg/dL)</th>
<th>Full Dose Mean(95%CI)</th>
<th>Low Dose Mean(95%CI)</th>
<th>Difference(95%CI)</th>
<th>P</th>
<th>P for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>452</td>
<td>68.0</td>
<td>16.6(13.3-19.9)</td>
<td>10.0(6.7-13.3)</td>
<td>-6.6(-11.3-1.9)</td>
<td>0.006</td>
<td>-</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>LDL &gt;=70mg/dL</td>
<td>181</td>
<td>93.2</td>
<td>3.9(-1.3-9.0)</td>
<td>-2.9(-8.4-2.6)</td>
<td>-6.8(-14.3-0.7)</td>
<td>0.076</td>
<td>0.97</td>
</tr>
<tr>
<td>LDL &lt;70mg/dL</td>
<td>271</td>
<td>51.1</td>
<td>25.0(20.6-29.4)</td>
<td>18.7(14.6-22.8)</td>
<td>-6.3(-12.3-0.3)</td>
<td>0.039</td>
<td>-</td>
</tr>
<tr>
<td>SBP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP &gt;=140mmHg</td>
<td>115</td>
<td>69.1</td>
<td>15.6(8.8-22.4)</td>
<td>8.3(2.0-14.6)</td>
<td>-7.3(-16.7-2.1)</td>
<td>0.128</td>
<td>0.70</td>
</tr>
<tr>
<td>SBP &lt;140mmHg</td>
<td>337</td>
<td>67.6</td>
<td>17.3(13.5-21.1)</td>
<td>10.2(6.3-14.1)</td>
<td>-7.1(-12.6-1.6)</td>
<td>0.012</td>
<td>-</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>185</td>
<td>64.1</td>
<td>21.1(15.2-26.9)</td>
<td>13.0(7.3-18.7)</td>
<td>-8.1(-16.2-0.1)</td>
<td>0.053</td>
<td>0.62</td>
</tr>
<tr>
<td>No diabetes</td>
<td>267</td>
<td>70.7</td>
<td>13.6(9.6-17.6)</td>
<td>7.8(3.8-11.8)</td>
<td>-5.8(-11.4-0.1)</td>
<td>0.047</td>
<td>-</td>
</tr>
</tbody>
</table>

Figure 6. Changes in SBP in predefined subgroups. LDL indicates low-density lipoprotein; SBP, systolic blood pressure.

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>N</th>
<th>Mean value at rand (mmHg)</th>
<th>Full Dose Mean(95%CI)</th>
<th>Low Dose Mean(95%CI)</th>
<th>Difference(95%CI)</th>
<th>P</th>
<th>P for Interaction</th>
</tr>
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<tbody>
<tr>
<td>Overall</td>
<td>518</td>
<td>130.5</td>
<td>-3.8(-5.1-2.4)</td>
<td>-0.9(-2.3-0.4)</td>
<td>-2.8(-4.7-1.0)</td>
<td>0.003</td>
<td>-</td>
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<tr>
<td>LDL cholesterol</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL &gt;=70mg/dL</td>
<td>210</td>
<td>131.7</td>
<td>-3.0(-5.1-0.9)</td>
<td>-1.3(-3.3-0.7)</td>
<td>-1.7(-4.6-1.2)</td>
<td>0.256</td>
<td>0.41</td>
</tr>
<tr>
<td>LDL &lt;70mg/dL</td>
<td>292</td>
<td>129.5</td>
<td>-3.8(-5.6-2.1)</td>
<td>-0.6(-2.3-1.2)</td>
<td>-3.3(-5.8-0.8)</td>
<td>0.010</td>
<td>-</td>
</tr>
<tr>
<td>SBP</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>SBP &gt;=140mmHg</td>
<td>142</td>
<td>149.3</td>
<td>-3.5(-6.5-0.4)</td>
<td>-1.6(-4.6-1.4)</td>
<td>-1.9(-5.5-1.6)</td>
<td>0.293</td>
<td>0.55</td>
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<tr>
<td>SBP &lt;140mmHg</td>
<td>376</td>
<td>123.4</td>
<td>-3.9(-5.6-2.2)</td>
<td>-0.7(-2.4-1.0)</td>
<td>-3.2(-5.4-1.0)</td>
<td>0.005</td>
<td>-</td>
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<tr>
<td>Diabetes</td>
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<tr>
<td>Diabetes</td>
<td>212</td>
<td>130.6</td>
<td>-1.7(-3.7-0.3)</td>
<td>2.5(0.5-4.5)</td>
<td>-4.2(-7.0-1.4)</td>
<td>0.004</td>
<td>0.22</td>
</tr>
<tr>
<td>No diabetes</td>
<td>306</td>
<td>130.4</td>
<td>-5.2(-6.9-3.5)</td>
<td>-3.3(-5.0-1.7)</td>
<td>-1.9(-4.3-0.5)</td>
<td>0.119</td>
<td>-</td>
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</table>
7.4/5.6 mm Hg reductions observed in TIPS-1 with the lower dose) and LDL by a further 6.6 mg/dL (compared with the 27.0 mg/dL reduction with low-dose polycap in TIPS-1), but lead to no further reductions in HR. The incremental reductions in BP and LDL with the higher dose of the polycap compared with the low-dose polycap was about 25%. Therefore, the greater risk factor reductions with the full-dose polycap compared with the low-dose polycap can be theoretically expected to reduce the risk of CHD and stroke to a greater extent (Table 4). Therefore, the combined theoretical effects of a full dose of the polycap without aspirin due solely to reductions in BP lowering and LDL cholesterol would be expected to be about a 60% relative reductions in CHD and stroke (Table 4). These theoretical estimates are lower than the estimates of Wald and Law and indicate that combined pharmacotherapy, even at full doses, is unlikely to be as effective as previously suggested.

In secondary prevention, the addition of aspirin to the polycap would be expected to further reduce CHD and stroke, so that the overall effects of a full dose of the polycap that includes aspirin would be expected to reduce CHD by about 75% and stroke by about 65%. In secondary prevention, each component of the polycap given at full doses has been demonstrated to reduce clinical events, and so a demonstration of its tolerability (as in TIPS-2) is sufficient for its use in such patients. Indeed, the majority of individuals in TIPS-2 had previous CVD. By contrast, such individuals were excluded from the first TIPS study. Whether or not a polycap can reduce CHD and stroke to a substantial extent (eg, a relative risk reduction by half or two thirds) in primary prevention among those with average risk factors is unproven and requires a large long-term trial.

There remains a controversy as to the role of aspirin in primary prevention. Although aspirin reduces CHD, it increases the risk of major bleeds. It is important to recognize that the majority of individuals entering the primary prevention trials were physicians or other health workers who are at lower risk of CVD than the average population. Therefore, given the modest absolute reduction in CHD in the low-risk people enrolled in the previous trials of primary prevention, the benefits may have been offset by increased bleeding. However, substantial BP lowering with the polycap may mitigate the higher small absolute risk of intracranial hemorrhage with aspirin, and the use of low doses in an enteric-coated formulation (<100 mg versus 325 mg/day) may minimize gastrointestinal bleeding. Further, the recent data on cancer prevention with the long-term use of aspirin (for >5 years) are intriguing. Therefore, a trial in individuals at moderately elevated risk but without vascular disease using the polycap (without ASA) is worth conducting, but with the effects of low daily doses of ASA being reevaluated (using a factorial design) as the benefit-risk balance (especially if cancers are prevented and bleeding is minimized) may be more favorable.

Our study has some limitations. The major limitation is that a programming error changed the allocation of K+ supplementation from a 2x2 factorial design to an allocation that paralleled the 2 doses of the polycap. Despite an open design, only 5.2% of patients discontinued K+ supplements, and so it appears to be well tolerated. K+ supplementation does not affect lipids or HR and so, comparisons of the 2 doses of the polycap on these outcomes are secure. Although consumption of foods high in potassium may have a small impact on BP, recent trials of K+ supplementation have indicated little or no impact on BP. In TIPS-2 there was only a small, but significant, increase in serum potassium at 2 weeks (by 0.17 mEq/L), but the impact on BP lowering at this time was not significant. Conversely, at 8 weeks, there was little impact on serum potassium (difference, 0.06 mEq/L), but the reduction in

| Table 4. Projected Theoretical Relative Risk Reductions in CVD of the Two Strengths of the Polycap Using the Approach of Wald and Law But Based on Data From TIPS-1 and TIPS-2 |
|---------------------------------|------------------|------------------|
|                                 | Low-Dose Polycap (Based on TIPS-1) | Full-Dose Polycap (Based on Differences Between Full vs Low Dose Plus Data From TIPS-1) |
| Reduction in Risk Factors       | Projected Reductions | Reduction in Risk Factors | Projected Reductions |
| LDL cholesterol, mg/dL         | CHD, % Stroke, %     | CHD, % Stroke, %         |
| –27.0                          | 27 8                | –33.6                    | 33 10                |
| Diastolic BP, mm Hg             | 24 33               | –7.3                     | 32 43                |
| Combined effects of lowering LDL cholesterol and BP | 44 33 | NA 54 49 |
| Aspirin*                       | 32 16               | NA 32 16                 |
| Combined effects of lowering LDL cholesterol, BP, and antiplatelet agents (eg, for secondary prevention) | 62 48 | 69 57 |

TIPS-1 indicates the Indian Polycap Study-1; LDL, low-density lipoprotein; BP, blood pressure; CHD, coronary heart disease; and CVD, cardiovascular disease.

The methods used by Wald and Law to estimate benefits has been used to first calculate the risk reductions in CHD and stroke based on the TIPS-1 results with low-dose polycap. The incremental reductions in LDL cholesterol and in diastolic BP observed in TIPS-2 with full dose compared with low dose are used to estimate the treatment benefits with the double-dose polycap. The estimates of Wald and Law are based on prolonged treatments, whereas even in trials of 5 years of treatment, the mean time from randomization to the occurrence of an event is about half of this (ie, 2.5 years). So, the observed benefits in trials of 5 years of treatment will likely be somewhat lower (perhaps about three fourths of the above estimates). Therefore, trials of a full-dose polycap could reasonably be expected to reduce CVD by 50% to 60% in trials of 5 years duration.

*As projected by Wald and Law, which is higher than that observed in the antithrombotic trialists meta-analyses.
BP was clear and statistically significant. Additionally, there is evidence that potassium supplementation has no influence on BP in patients who are concurrently receiving potassium lowering diuretics such as thiazides. These data suggest that it is unlikely that the K+ supplementation used in TIPS-2 materially impacted the BP difference between low-dose and full-dose polycap, but this possibility cannot be totally excluded. This programming error is unlikely to affect our data on tolerability of the polycap, and therefore, a formulation of full doses of 3 BP lowering agents and 40 mg of simvastatin should be considered for evaluation in future trials and for use in secondary prevention (along with low doses of aspirin).

In conclusion, a full dose of the polycap (plus K+ supplements) is as well tolerated as a low dose and reduces risk factors by a further 25% to 30%. Therefore, the full-dose polycap would be expected to reduce CVD risk by about 50% to 60% in primary prevention, but this requires confirmation in large, long-term trials.

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Comparison of Risk Factor Reduction and Tolerability of a Full-Dose Polypill (With Potassium) Versus Low-Dose Polypill (Polycap) in Individuals at High Risk of Cardiovascular Diseases: The Second Indian Polycap Study (TIPS-2) Investigators
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**Roles and Responsibilities:**

All members of the writing group designed the trial, oversaw its conduct, were involved in the analysis and interpretation of the data. S. Yusuf wrote the first draft of the paper and all other members provided feedback and comments. R. Afzal and P. Gao managed the database and performed all the analysis.
Notes on Error in Randomization Schedule in the TIPS-2 trial

The TIPS-2 trial was a 2x2 factorial design of the polycap used at a higher dose versus polycap at a lower dose; and potassium supplementation versus no potassium. Trial participants were intended to be randomized to one of four factorial cells: polycap higher dose and potassium, polycap higher dose and no potassium, polycap lower dose and potassium, and polycap lower dose and no potassium.

An error occurred in generating the randomization schedule for this study and, as a result, only two of the four factorial cells were implemented. We identified three sources of this error. First, a decision was made to generate this randomization schedule at the level of the margin rather than for the four factorial cells, producing two separate schedules for the poly-pill and potassium interventions. Second, the same random key was used for both schedules, producing identical lists, that when put together randomized participants only to the combination of polycap higher dose and potassium or polycap lower dose and no potassium. There was a review process for these randomization schedules, but each was checked independently and one could detect the error when both lists were combined. Finally, there was no interim review of treatment allocations during this study, so that the error remained undetected for the entire duration of the trial.

In reviewing this error and analyzing its root causes, we have identified and implemented new quality assurance procedures to prevent this from happening again. Our improved process for the generation and validation of randomization schedules included the following:
1. Randomization schedules for factorial designs are generated and tested at the level of the factorial cells, not at the margin.

2. The check list for review of all randomization schedules instructs the reviewer to ensure that all random keys used are unique.

3. Requirement for mandatory and early checks of the implementation of the randomization schedules for all trials, even if no DSMB exists for that study. All trials will have the randomized allocations examined early in the trial and throughout its recruitment phase. These processes and checks will ensure that the randomization schedule is being followed as planned and that the appropriate allocation ratio is being implemented in the study. We are committed to learning from our errors and improving our processes to consistently achieve high quality randomized controlled trials. Hopefully, others can learn from our failings and adopt similar quality assurance procedures in producing randomization schedules for their trials.