Cardiovascular Combination Pharmacotherapy Global Summit, 2014

from concept to reality

Major Trials in Progress

HOPE 3, HOPE 4, TIPS 3

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Disclosure Statement of Financial Interest

I, Koon K. Teo, DO NOT have a financial interest/arrangement or affiliation with any healthcare related companies that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation.

Other Major Trials

- **HOPE 3**: 12,700, factorial of comb BP lowering +/- statin, intermediate risk. Results 2016.
- **TIPS 3**: 5000 high risk primary prevention (90% Stage 1 hypertension , 50% dysglycemics). Results 2019-20
- **HOPE 4**: Strategy of global risk reduction in high risk primary/secondary using NPHW+ polypill + lifestyle advice + treatment supporter vs usual care. Pilot of 2000/full scale of 10,000

HOPE 3: Rationale

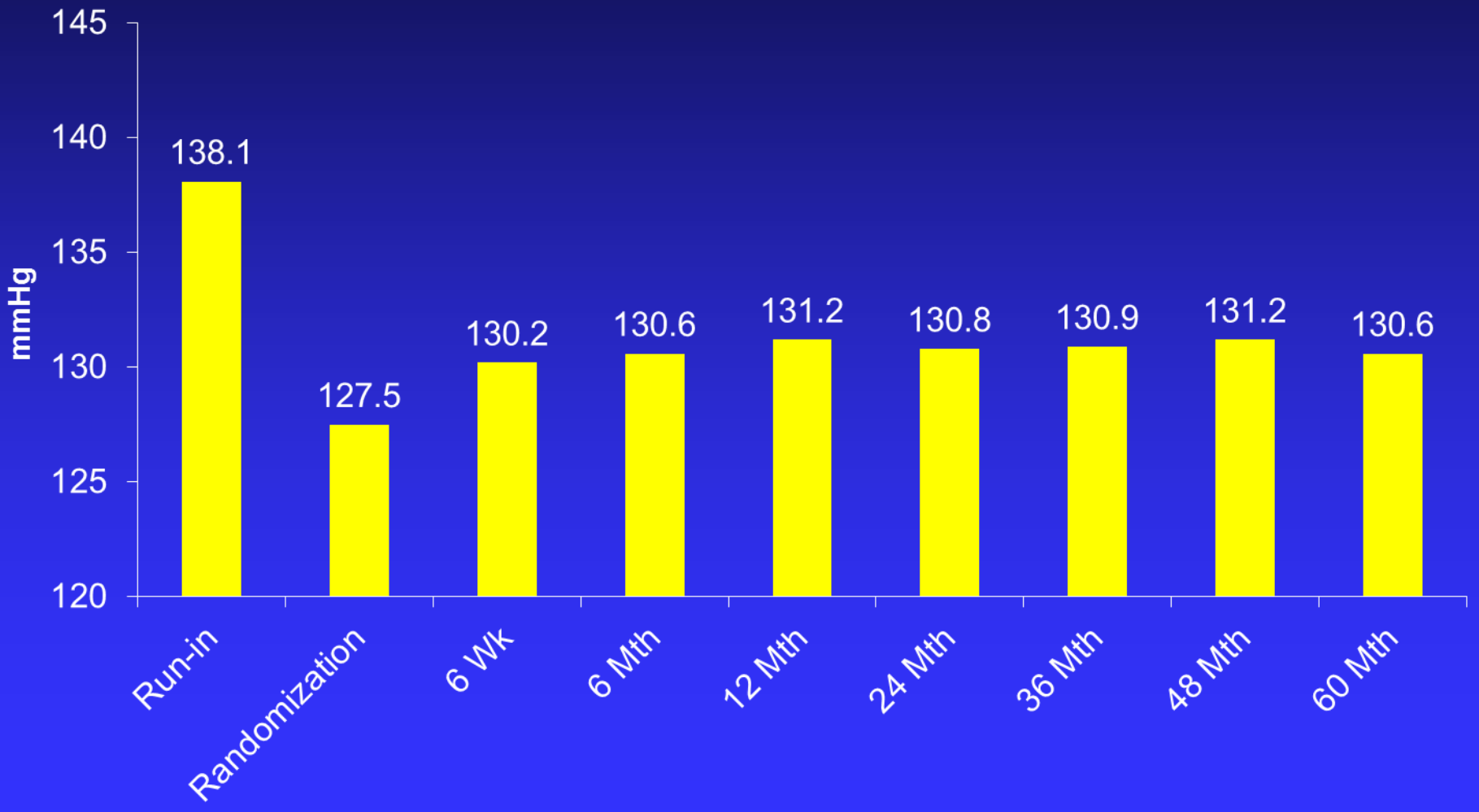
- HOPE-3 tests a novel approach to CV prevention
- Lowering both BP and LDL significantly will together lead to a 50 to 60% RRR in CVD (Mini-polypill)
- Main entry criteria are the uncertainty principle, moderate risk (age +one or more risk factors)
- Multiple ethnic groups, so globally applicable
- Range of vascular outcomes

HOPE 3

- Lipid modification (LDL lowering) with rosuvastatin 10 mg/day.
- BP lowering with combined candesartan 16 mg/HCT 12.5 mg daily.
- Combined lipid modification (rosuvastatin 10 mg/day) & BP lowering (candesartan 16 mg/HCT 12.5 mg/day).

- 12,705 people at average risk without CVD
- ~ 19 countries, 176 centres
- Average duration of follow-up: 5 years
- 2x2 factorial design
    - Rosuvastatin 10 mg/day vs. placebo
    - Candesartan/HCT 16/12.5 mg/day vs. placebo
- Active run-in; lifestyle advice

HOPE 3 -Systolic BP Over Time



Limitations of Usual Approaches to Hypertension and other CV Risk Factors

- Lack of systematic approaches to screening and identifying those with HT or CVD, left to busy clinician, lack of time
- Complex cumbersome algorithm to initiate and follow up treatment
- Use individual drugs of moderate effect separately in stepwise fashion delays effective control
- Little attention to concomitant risk factors
- No systematic efforts to
  - (1) enhance adherence, and
  - (2) monitor physician or health system performance

HOPE 4: What are we doing about the poor detection & treatment of hypertension ?

- Starting countries:
  - Malaysia and Columbia, both UMIC,
  - high prevalence of HT
  - marked increases of HT and CVD risk factors in last 2 decades
  - existence of detailed data from PURE
  - existence of local infrastructure to build project on
  - political will and keenness shown at high levels of government to implement programs to control CVD
- Plan to expand project to 10 other similar countries

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No systematic approach to screening and identifying HT or CVD

- Trained Non Physician Health Worker (NPHW) to systematically approach and identify those with HT and/or existing CVD or are at high/moderate risk of CVD in a population

Complex algorithms to initiate cumbersome drug treatment & Use of individual drugs to lower BP: moderately effective and stepwise approach delays BP control

- **NPHW to identify appropriate individuals** and initiate and titrate treatment under supervision of physician following a simple plan of starting and follow up
- A polypill to simplify treatment and ensure BP under control

Little attention for concomitant risk factors / global CVD risk

- NPHW to screen for other CVD risk factors (e.g. using Non-Lab based INTERHEART Risk Score) to identify at risk subjects, in addition to HT at initial contact
- Polypill with statin for lipid lowering and aspirin for antiplatelet therapy

No systematic efforts to enhance/maintain adherence to treatment

- Cannot afford time or costs of travel to visit physicians
  - NPHW to visit individuals and provide meds at home
- Cost of drugs
  - Polypill available at low costs and affordable to people with low income
- Poor adherence due to forgetfulness etc
  - Innovative approaches such as “patient supporter” and regular phone reminders

No systematic efforts to monitor physician or health system performance

- focused knowledge translation efforts as incentives for physicians
- Periodic measurement of outcomes between intervention and control groups

Next Steps

- ***Address Question***: Can a community based strategy of screening and treatment with a polypill by NPHW in high & moderate risk individuals reduce CVD risk by 40% within 6 yrs?
- ***Setting***: 190 communities (10,000 people) in Columbia, Argentina, S Africa, Tanzania, Rwanda, India, Malaysia, Philippines & Canada.
- ***Intervention:*** Systematic screening for prevalent CVD, hypertension & diabetes .Communities randomized to active intervention (NPHW based polycap + LS advice) or usual care.

The International Polycap Study (TIPS)-3

A randomized double-blind placebo-controlled trial for the evaluation of a ***Polycap, low dose Aspirin*** and ***Vitamin D*** in primary prevention

TIPS-3 Primary Objectives and Outcomes

To determine whether

1. **Polycap** reduces CVD events* compared to placebo at 5 years

   **major CVD (CV death, non-fatal stroke, non-fatal MI), heart failure, resuscitated cardiac arrest, or revascularization with evidence of ischemia)*

2. **aspirin** reduces CV events and cancers compared to its placebo at 5 years .
3. **vitamin D** reduces fractures compared to its placebo at 5 years.

TIPS 3: Study Design

- 2x2x2 factorial design
- 5,000 participants worldwide
- ~145 centres, 10 countries

- Study Phases
  - Recruitment: 2-3 years (June 2012-Sep 2015)
  - Follow-up: At least 5 year (June 2015-2019)
  - Results: 2020

Inclusion Criteria

1. Men aged ≥ 55 years and women aged ≥ 60 years
2. INTERHEART risk score of 10 or greater:

TIPS-3 **Participant Eligibility Worksheet**

Participant ID# ☐☐☐ ☐☐☐☐ *Centre #* *Participant #* **Initials** ☐☐☐ *F/M/L*

Please complete and store locally in participant file.

A. INCLUSION CRITERIA

If NO to any of the criteria below, participant is NOT eligible for the TIPS 3 trial

1. Man aged ≥ 55 years or woman aged ≥ 60 years ☐ *No* ☐ *Yes*
2. INTERHEART risk score ≥10 ☐ *No* ☐ *Yes*
3. Provision of informed consent ☐ *No* ☐ *Yes*

Exclusion Criteria

- Clear clinical indication or contraindication, preference for or intolerance to statin, beta blocker, ACE inhibitor, diuretic, aspirin or clopidogrel
- Peptic ulcer, frequent dyspepsia or bleeding
- Known vascular disease
- SBP < 120 mm Hg at run-in
- Symptomatic hypotension during run-in
- Chronic liver disease or abnormal liver function
- Renal impairment pre/post run-in

Progress

- Countries: India, Philippines, Canada
- Other countries in the process of starting
- Current recruitment (as of April 28th, 2014): Run-in 1951, randomized 1483