



THE GEORGE INSTITUTE  
*for International Health*



Sydney, AUSTRALIA | Beijing, CHINA | Hyderabad, INDIA | London, UK



*Affiliated with the University of Sydney*

# Polypill trials

Anthony Rodgers  
The George Institute

# 3 main research areas

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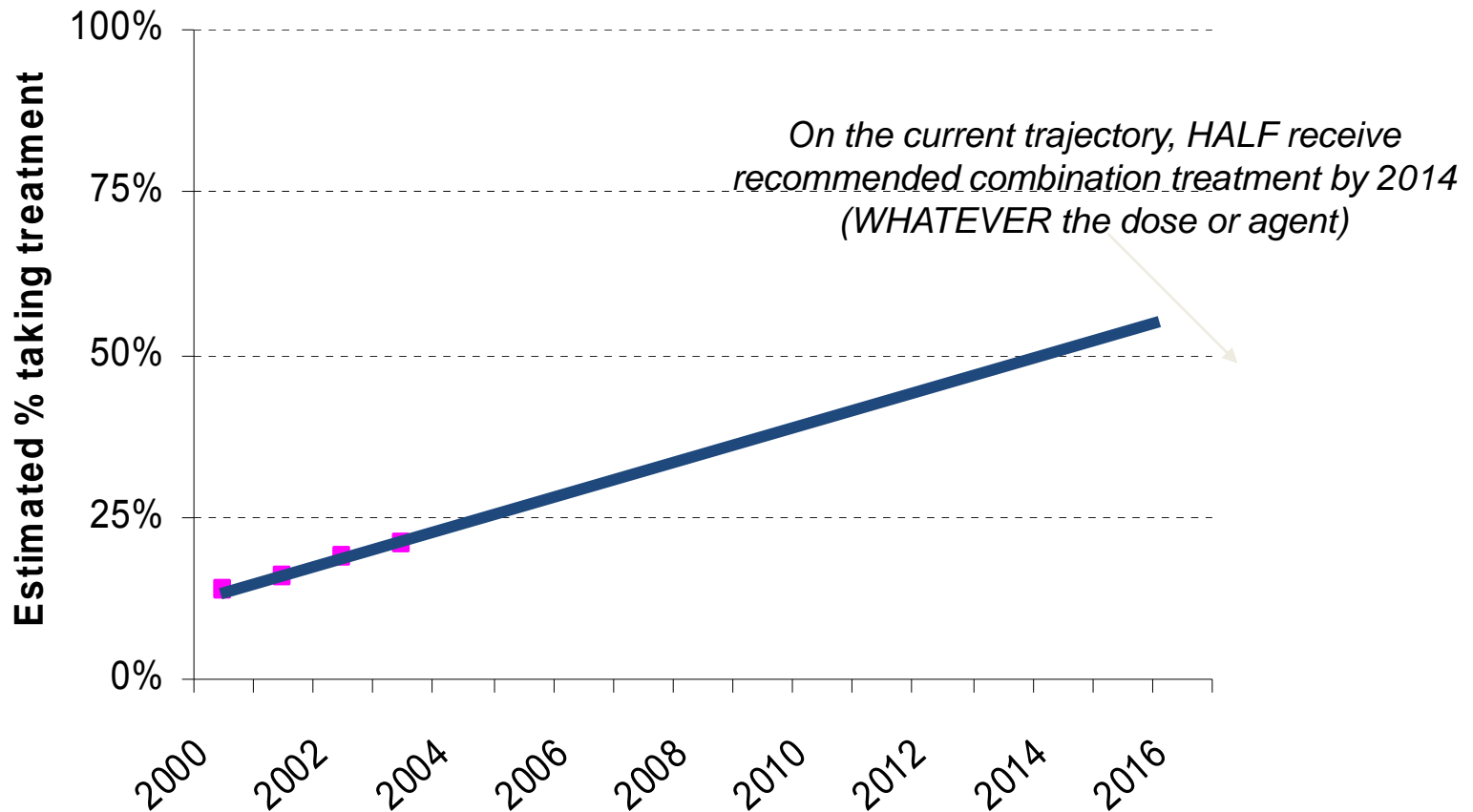
- Established indications / secondary prevention: does the polypill help adherence? is it worth the reduced flexibility in tailoring?
- Primary prevention: are benefits greater than side effects in people at raised risk?
- Unimodal vs multimodal care: eg. would it be better to treat high risk hypertensives with a polypill?

# People with established vascular disease “low hanging fruit”

- Almost half cardiovascular events occur in the ~5-8% of people who have had a symptomatic event:
  - clear consensus that medicines indicated
  - relatively easily identified
  - highest risk
  - most motivation
  - enormous treatment gaps:
    - >90% in LMICs
    - 50-80% in HICs
- For LMICs, enormous issues of affordability and availability

LMICs= low and middle income countries; HICs = high income countries

# Example treatment gaps: New Zealanders with established vascular disease taking BP, cholesterol *and* antiplatelet therapy



# Established indications trials

- Patients with clear indications (coronary disease, cerebrovascular disease etc) for treatment with all polypill components
- Randomise to polypill-based vs usual care

“do any improvements in access and adherence outweigh the issues posed by reduced tailoring”

- Outcomes: BP, lipids, adherence
- Four trials starting 2009 in NZ, Australia, Europe, India (each n=6-1000)
- Funded: HRC in NZ, NHMRC in Australia, EU FP7 for Europe and India

# Primary prevention trial

- Polypill vs placebo in people with 7.5% to 15% risk of a cardiovascular event over the next 5 years
- Eligible if in target risk range and no indication or contraindication for treatment with polypill components
- Primary outcome: Major cardiovascular events (myocardial infarction, stroke or cardiovascular death)
- 5,000 patients followed for average of 3.5 years
- >90% power to detect 40% reduction in primary outcome

# International Steering Committee

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- Anthony Rodgers (PI), Bruce Neal (Australia)
- Otavio Berwanger (Brazil)
- Z Chen, Y Wu (China)
- K Srinath Reddy, D Prabhakaran, Anushka Patel (India)
- Natasha Rafter, Rod Jackson (New Zealand)
- Simon Thom & Neil Poulter (UK)
- Richard Grimm & Jim Neaton (US)



# Funding

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- The Wellcome Trust
- The British Heart Foundation
- The National Health and Medical Research Council (Australia)
- The Health Research Council (New Zealand)

# Baseline data on first 104 patients randomised in pilot study

Male	75%
Age	63 years sd 8
Smoker	33%
SBP	137 sd 7 mmHg
DBP	81 sd 9 mmHg
Total cholesterol	5.8 sd 0.9 mmol/l
HDL	1.3 sd 0.4 mmol/l
LDL	3.9 sd 0.8 mmol/l
5 year CVD risk	11.8% SD 5.8%

# Principles of selecting target group

1. Benefits reasonably expected to outweigh side effects
  2. Easily identified
- Other considerations:
    - get regulatory approval and get this product on the market!
    - appropriate placebo control, to show full effects
  - We suggest this is most likely to be people with 5 year CV risk of  $>7.5$  to 15%

# Focus on global risk intervention in patients at high risk of CVD

“the terms primary/secondary prevention have yielded their place for a more comprehensive strategy aimed at treating patients at high risk of CVD.....Current therapeutic strategies are aimed at identifying global CVD risk in an individual and treating all risk factors. Global risk intervention, rather than single risk modification is the standard of care..”

# Reflections

# The polypill: a poster child for market failure?

- A product that is likely to:
  - halve CVD risk
  - be highly affordable
  - have huge public interest
  - have relatively rapid and inexpensive R&D (£5-10M rather than £100Ms)
- But, progress has been glacial - now 8 years since WHO-Wellcome Cambridge meeting and 6 years since BMJ polypill papers

# Reasons for the delay

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- Technical challenges
- Professional groups, patch protection and perfectionism
- Regulatory hurdles
- But, major issue is *market failure*

# Market failure

- Still, the vast amount of medicine R&D is directed to new chemical or biological entities, because system rewards that most
- Generics players permitted to copy exactly ie. no innovation
- Huge gap in innovation using established medicines
  - public funding agencies not filling R&D gap
  - private sector not yet oriented/incentivised sufficiently
  - major health funders not providing “market pull”



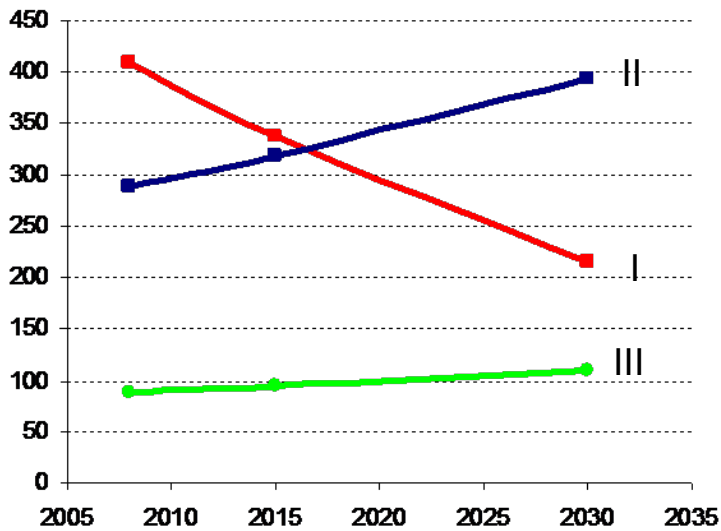
# Conclusions

# CVD preventive medicines

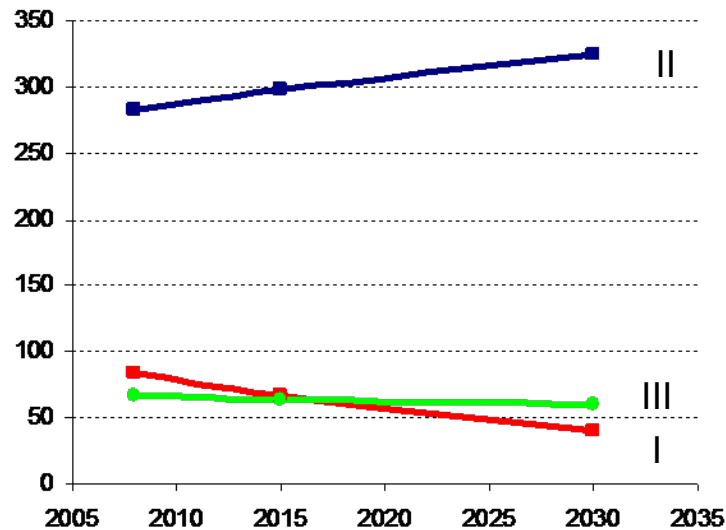
## – the importance of the next 20 years

- Huge unrealised potential from existing effective medicines to blunt the NCD increase in the next two decades, but needs:
  - affordable, scalable adaptations like the polypill
  - integration in to relevant models of care
  - policy responses to R&D gap and market failure
- Familiar problem, but stakes much higher and costs of delays now far greater than ever

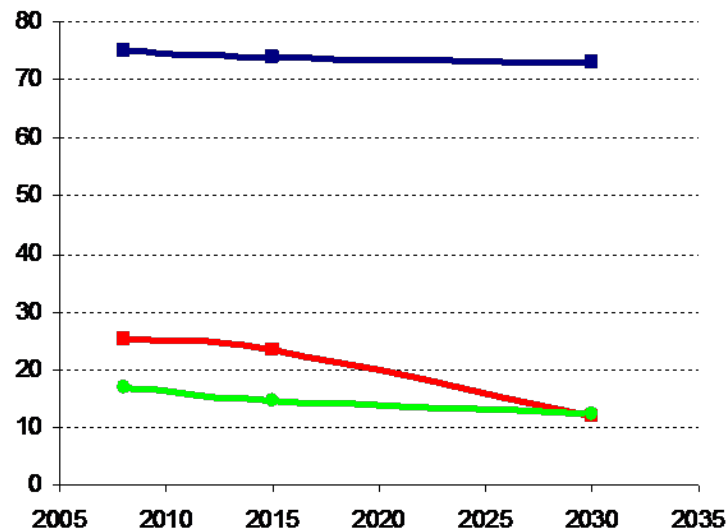
**Low income**  
Current pop<sup>n</sup>: 2.6bn



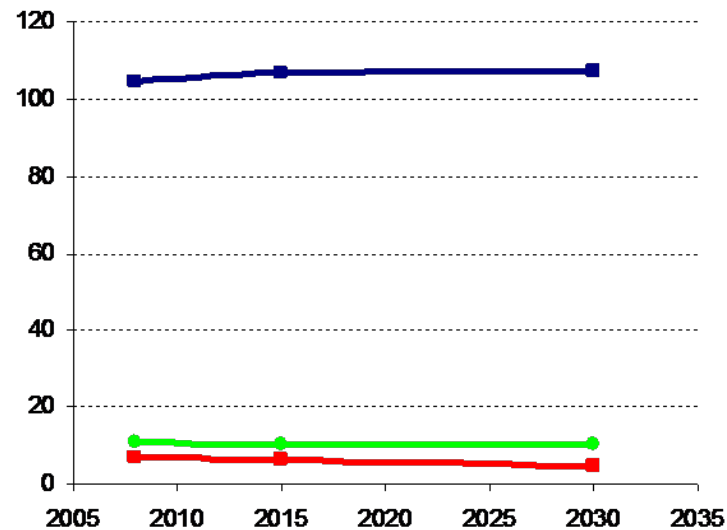
**Lower middle income**  
Current pop<sup>n</sup>: 2.5bn



**Upper middle income**  
Current pop<sup>n</sup>: 0.5bn



**High income**  
Current pop<sup>n</sup>: 1.0bn



No. predicted lost healthy life years

■ Group I  
■ Group II  
■ Group III

Source: [WHO](#), The global burden of disease: 2004 update.



# Evidence gap

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- Unprecedented body of evidence on effectiveness of statins, BP lowering and low-dose aspirin
- Little direct evidence on effects of practicable, scale-able strategies

# CVD preventive medicines

## – the last 40 years

- 1970s to 90s
  - establishment of effectiveness of antiplatelet therapy, statins and main BP lowering drugs
- 1990s to current:
  - little or no benefits of 'next big thing' - new BP lowering agents, HRT, HDL-raising, intensive glucose lowering, drug-coated stents, new antiplatelet agents, heart rate lowering, etc
  - glacial progress in increasing uptake of effective medicines
  - steady increase in lives lost from CVD, especially in developing countries

# Making a major impact on chronic diseases in low and middle income countries

- Major WHO analysis “Preventing chronic diseases: a vital investment” published in *The Lancet* in 2007
  - Goal of a 2% per year reduction in chronic disease mortality rates for low and middle income countries
    - core vascular medicines (the components of this polypill)
    - reduced salt intake
    - increased tobacco taxation
  - Increased access to core vascular medicines would by itself meet three-quarters of the WHO goal
  - Findings concur with other analyses by WHO, The World Bank, The Disease Control Priorities Project and others
- Could together reach this goal cost-effectively

# The causes of cardiovascular disease

- Main causes known for many decades
- Blood pressure, dyslipidaemia and tobacco cause over 70% of CVD (WHR2002)
- 9 risk factors cause over 90% of CVD (INTERHEART)



# Getting a medicine on the market vs appropriate use of the medicine

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# Evidence to date: long-term trials

Agents	No. trials	No. patients
Statins	>60	>100,000
Blood pressure lowering	>60	>200,000
Low-dose aspirin	7	90,000

# Potential for the polypill: access and long-term adherence in people with vascular disease

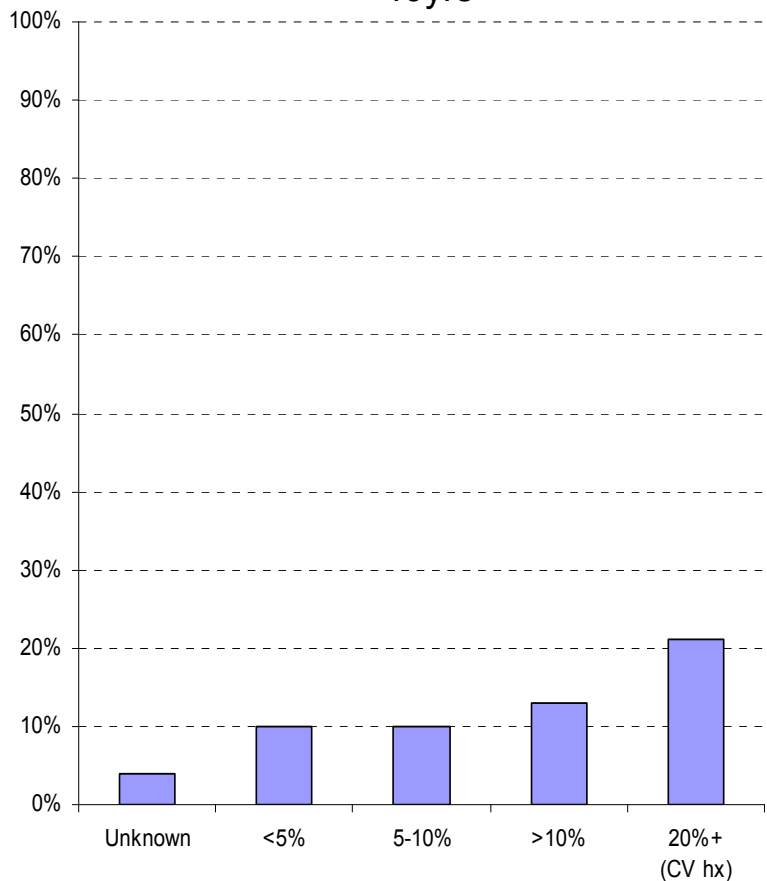
# Main rationale: unmet need, even among those with clear indications

- Resource-rich countries:
  - <50% receive 'core' CV medicines long-term
  - large inequities in access
- Economically developing countries:
  - <5% have access
  - CV disease rates large and growing

# Prescription of blood pressure and cholesterol lowering therapy according to absolute cardiovascular risk level

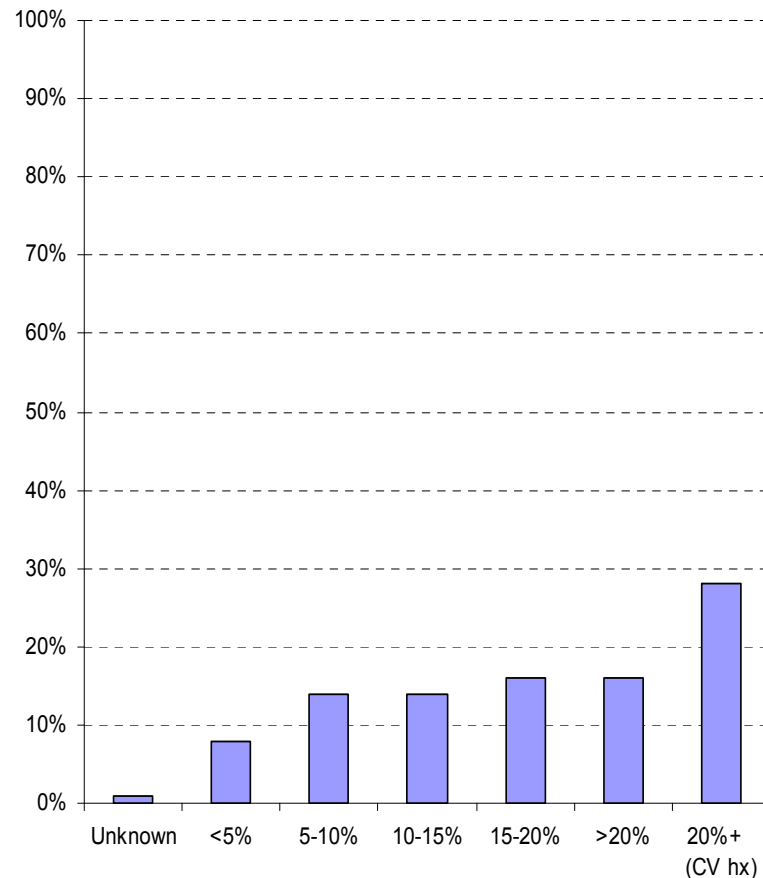
## USA

USA, NHANES 1999 – 2000: people aged > 40yrs\*



## NZ

NZ primary care 2000: men>45 women>55 \*\*



•VanderHoorn S, personal communication,

•\*\* Rafter et al NZMJ 2005

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- The most common dose of statin after a heart attack?

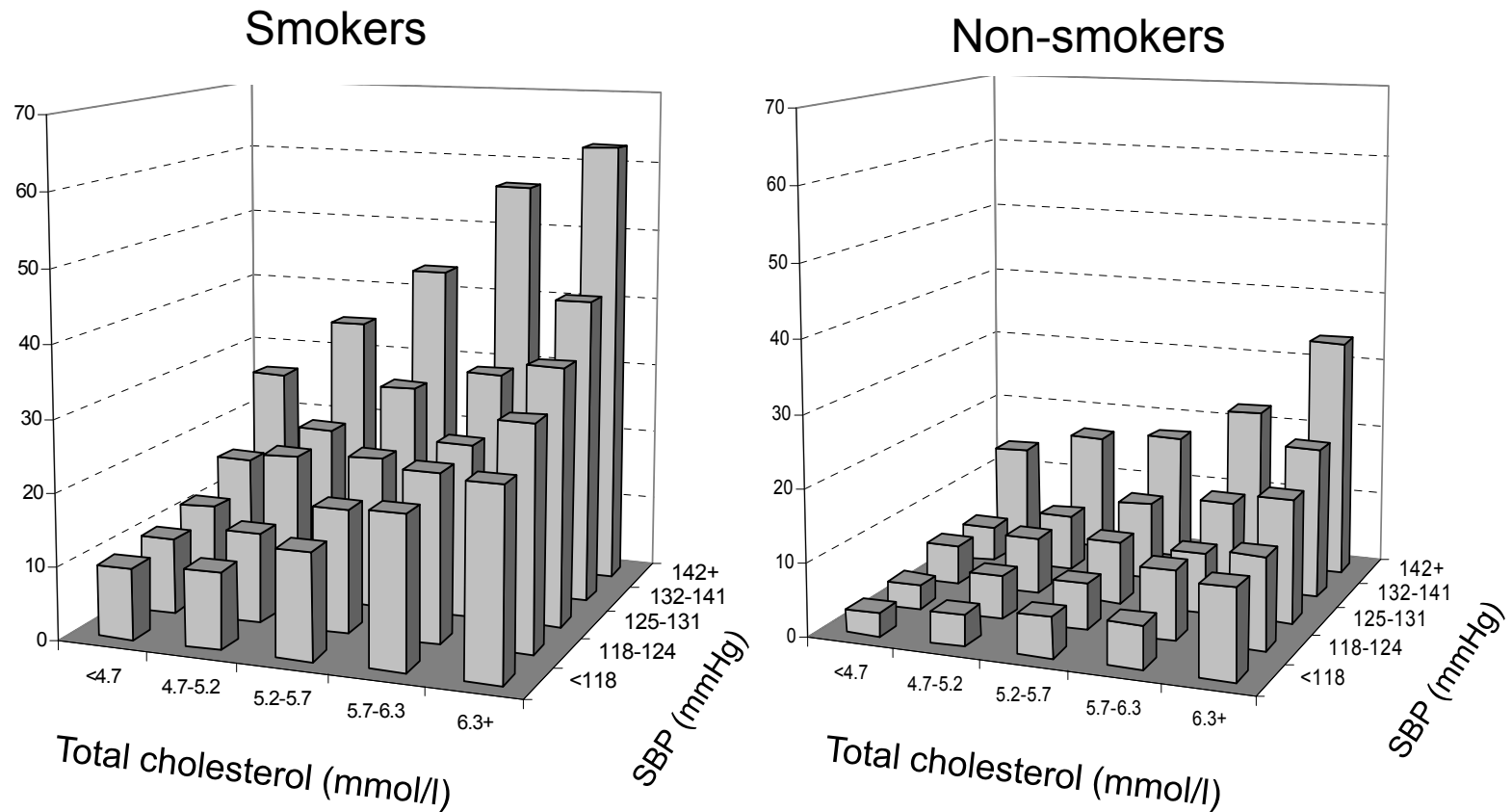
0mg

- The most common type of ACE inhibitor after a heart attack?

nothingpril

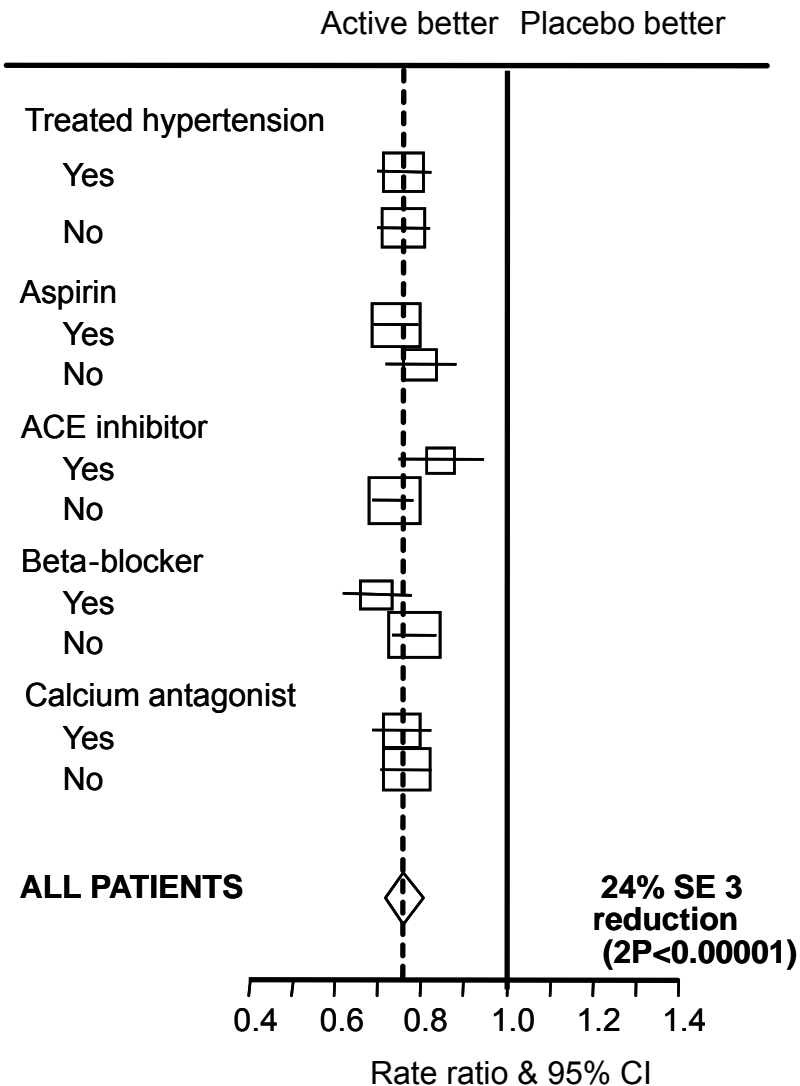
# Potential for the polypill: primary prevention in those at high risk

# Joint effects of blood pressure, cholesterol and smoking on coronary heart disease risk in the MRFIT Screenees Cohort

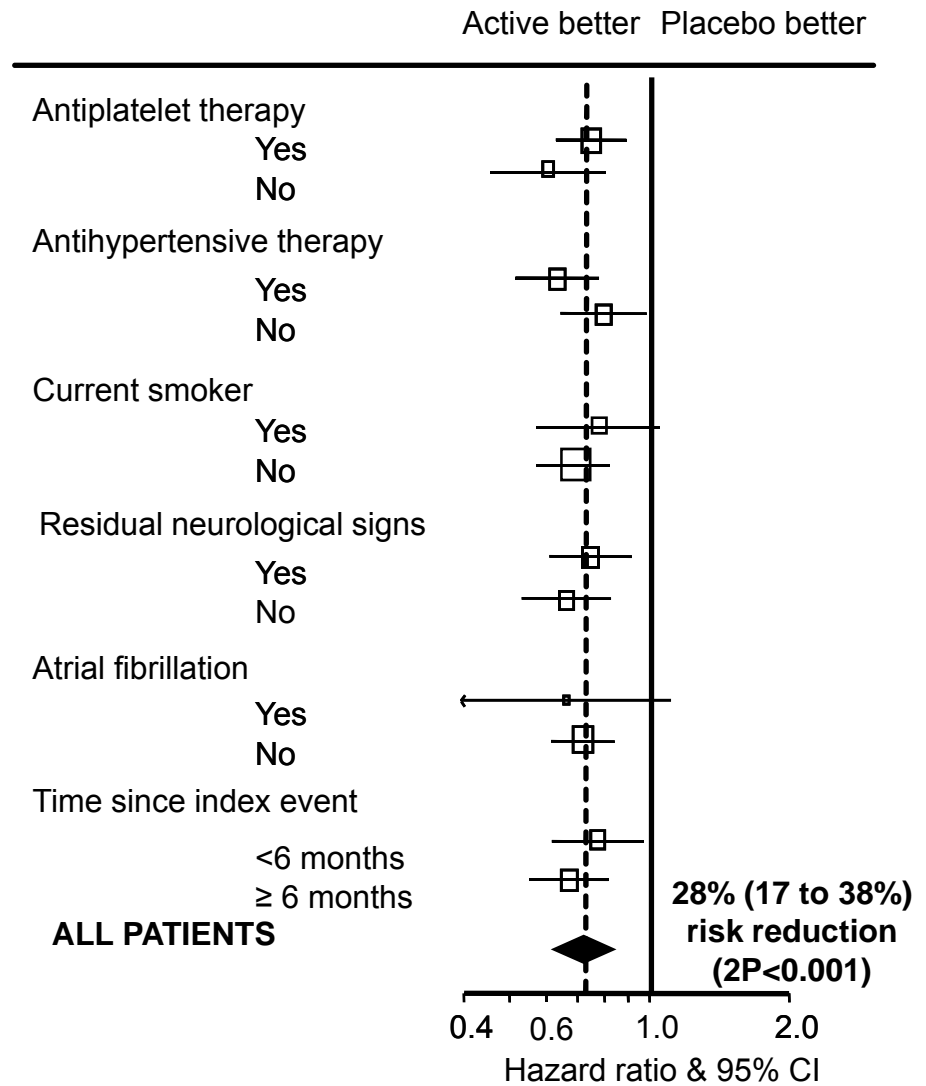




## Reduction of vascular events with statin therapy in the Heart Protection Study

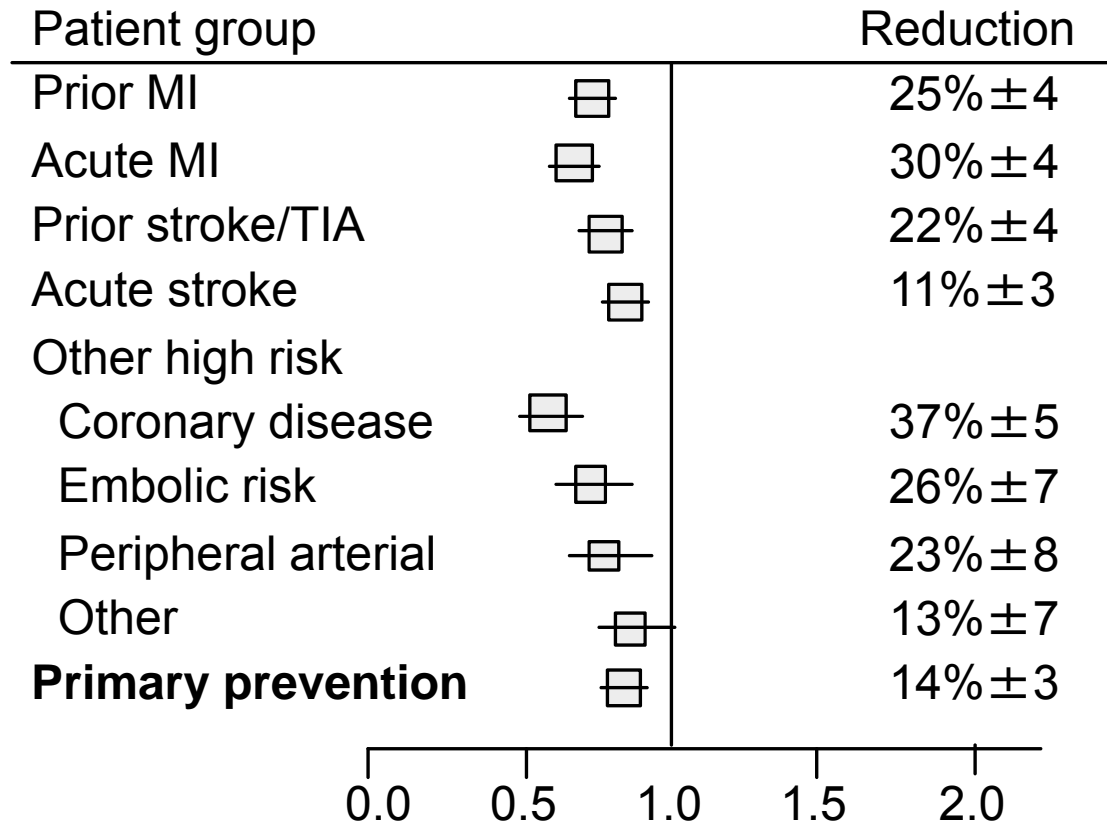


## Reduction of stroke with blood pressure lowering in the PROGRESS study

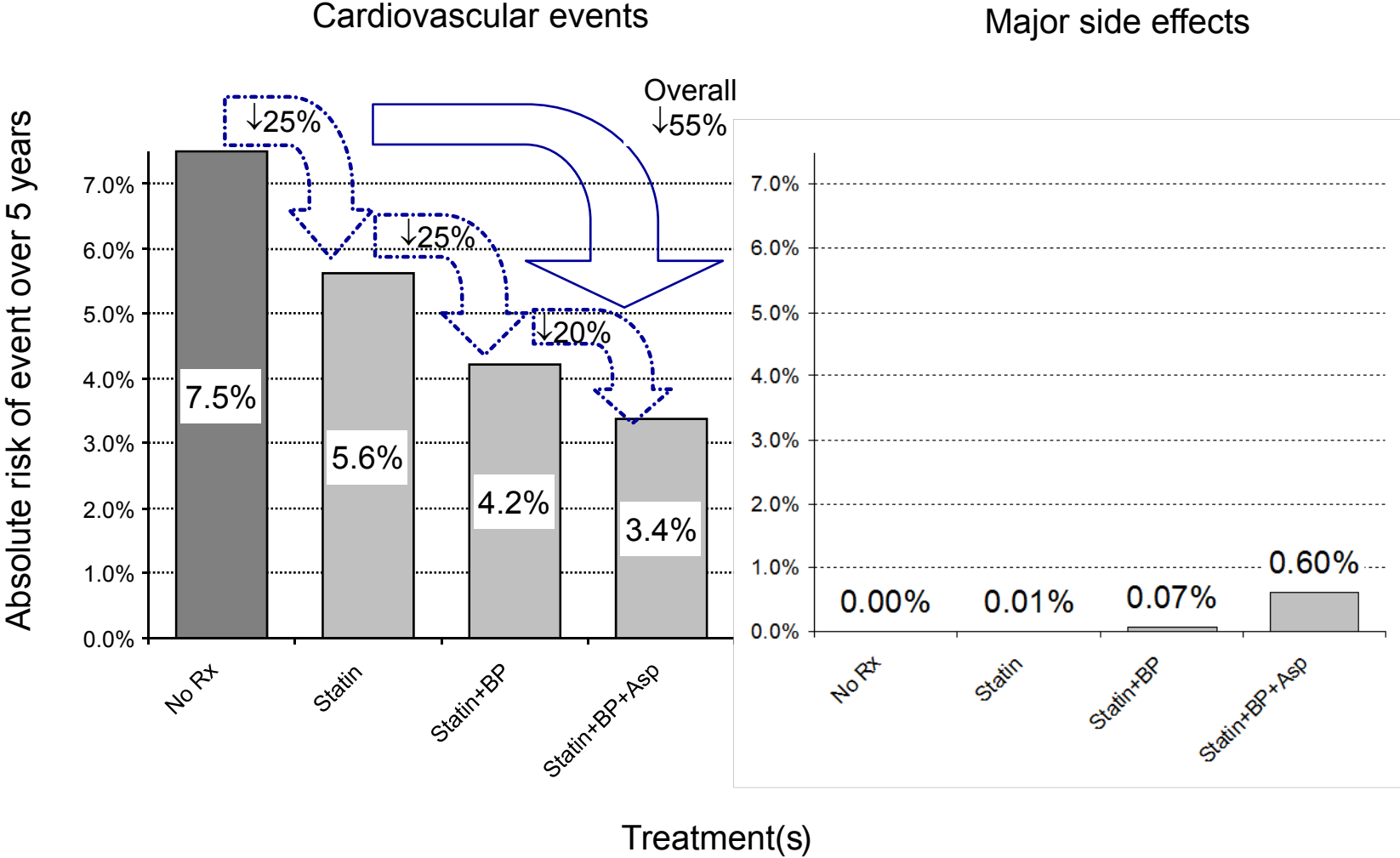


# Reduction in vascular events with antiplatelet therapy

Antithrombotic Treatment Trialists Collaboration and  
updated meta-analysis of low-dose aspirin primary prevention trials

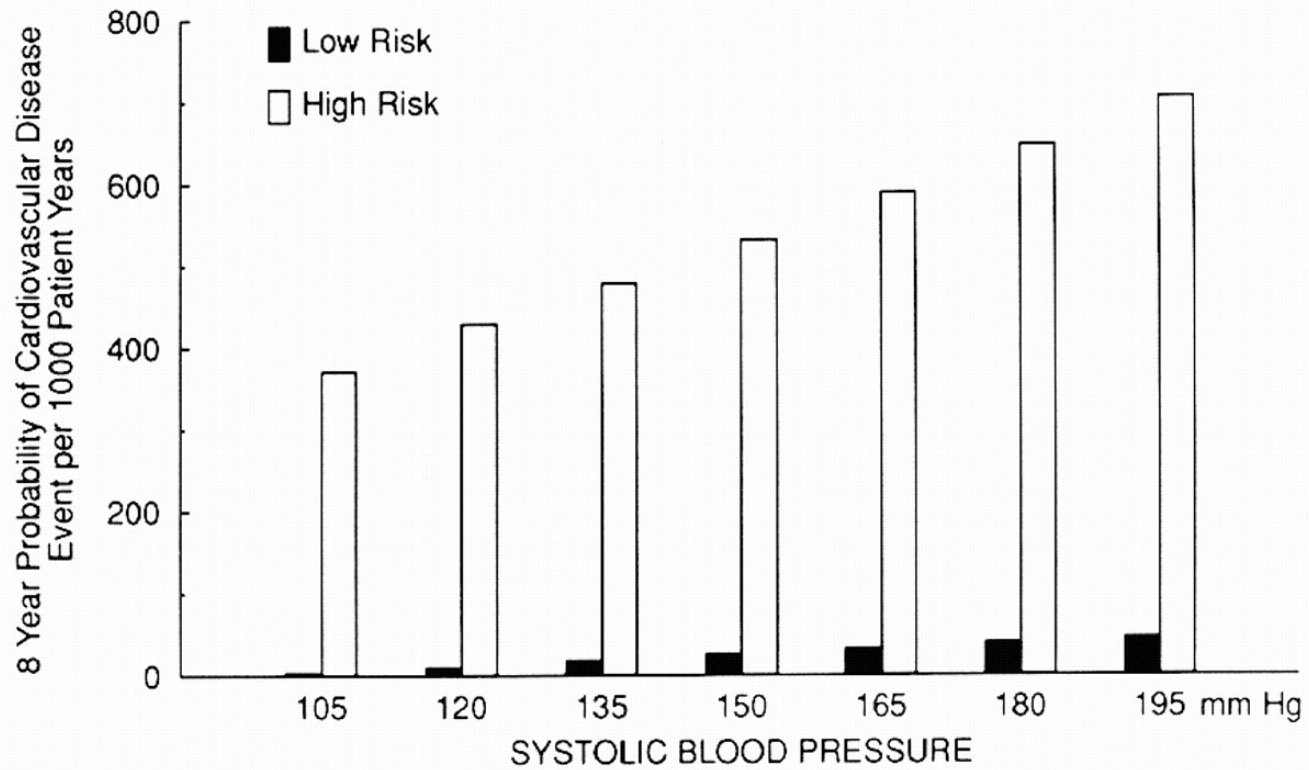


# Estimated absolute risks of major clinical events over a 5 year period



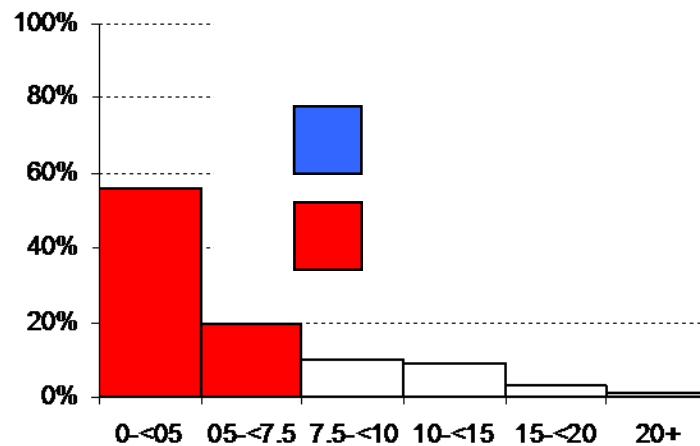
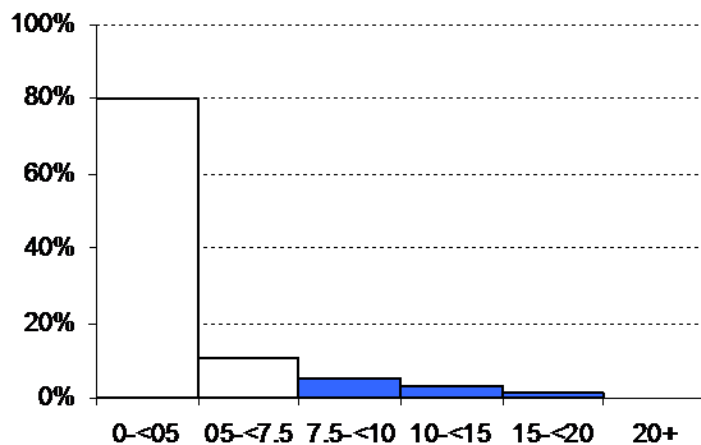
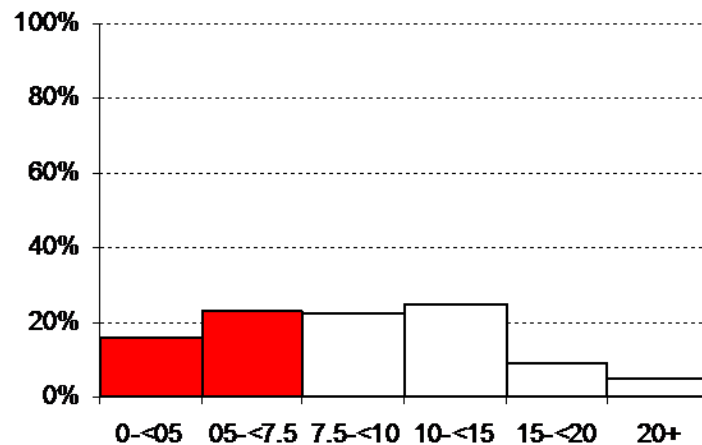
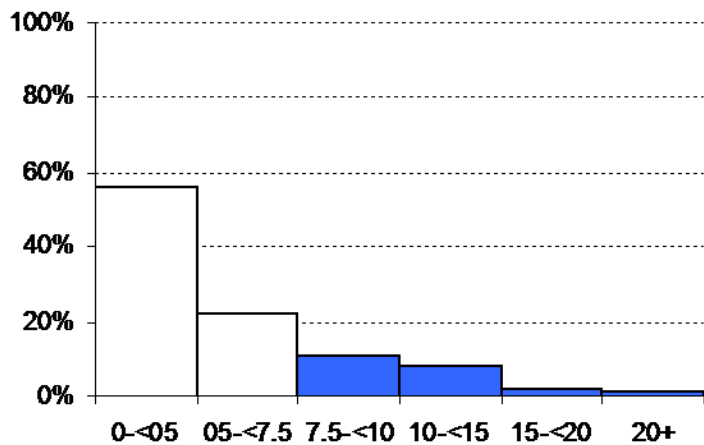
# Alternative target groups

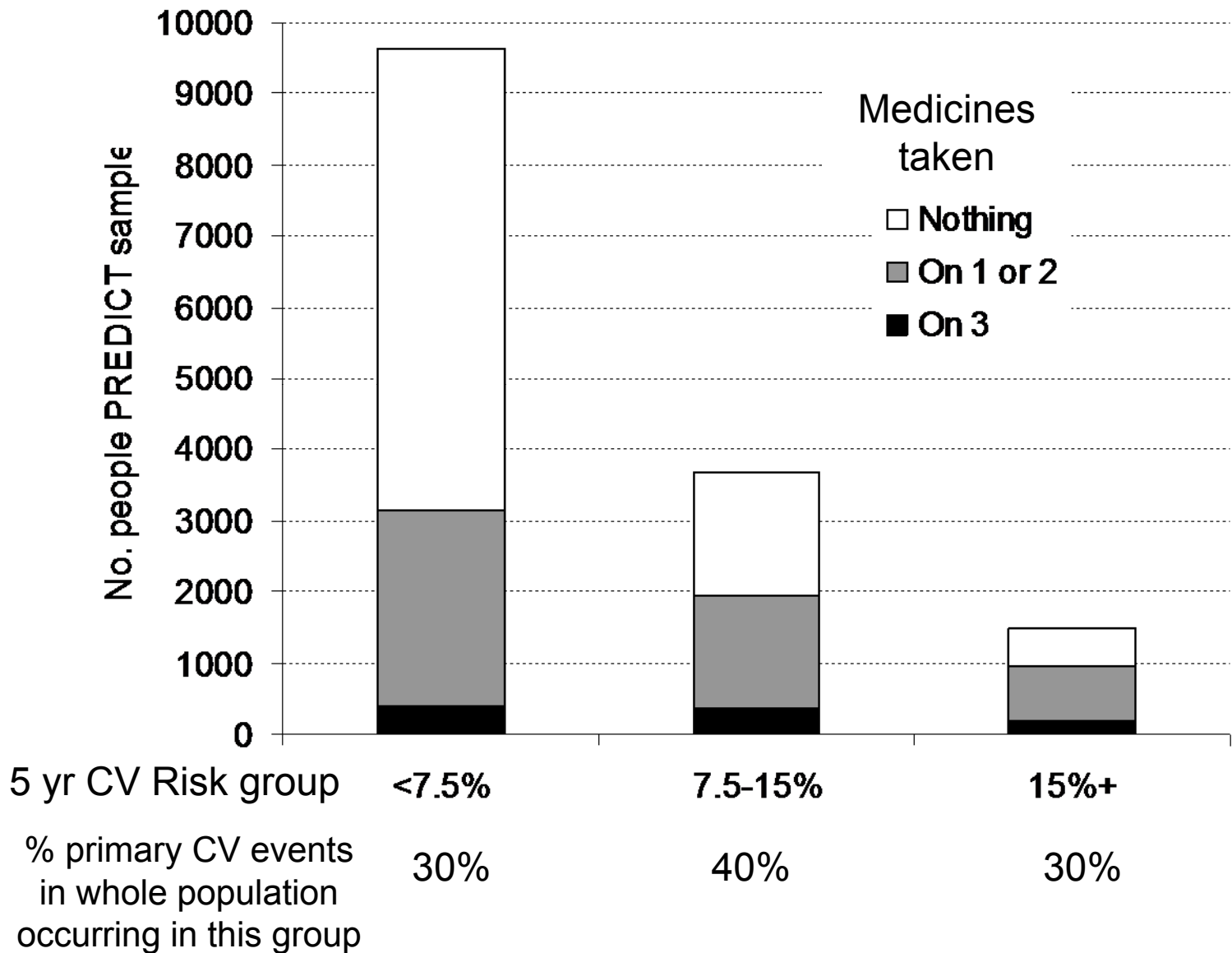
- EMEA note alternative possible risk functions (eg. SCORE) and need to justify risk group
- Others have recommended single factor cut-offs (eg. “hypertension”) or age over 55 years, but we propose:
  - miss many high risk people
  - overtreat many low risk people
  - treating everyone over a certain age is not practical



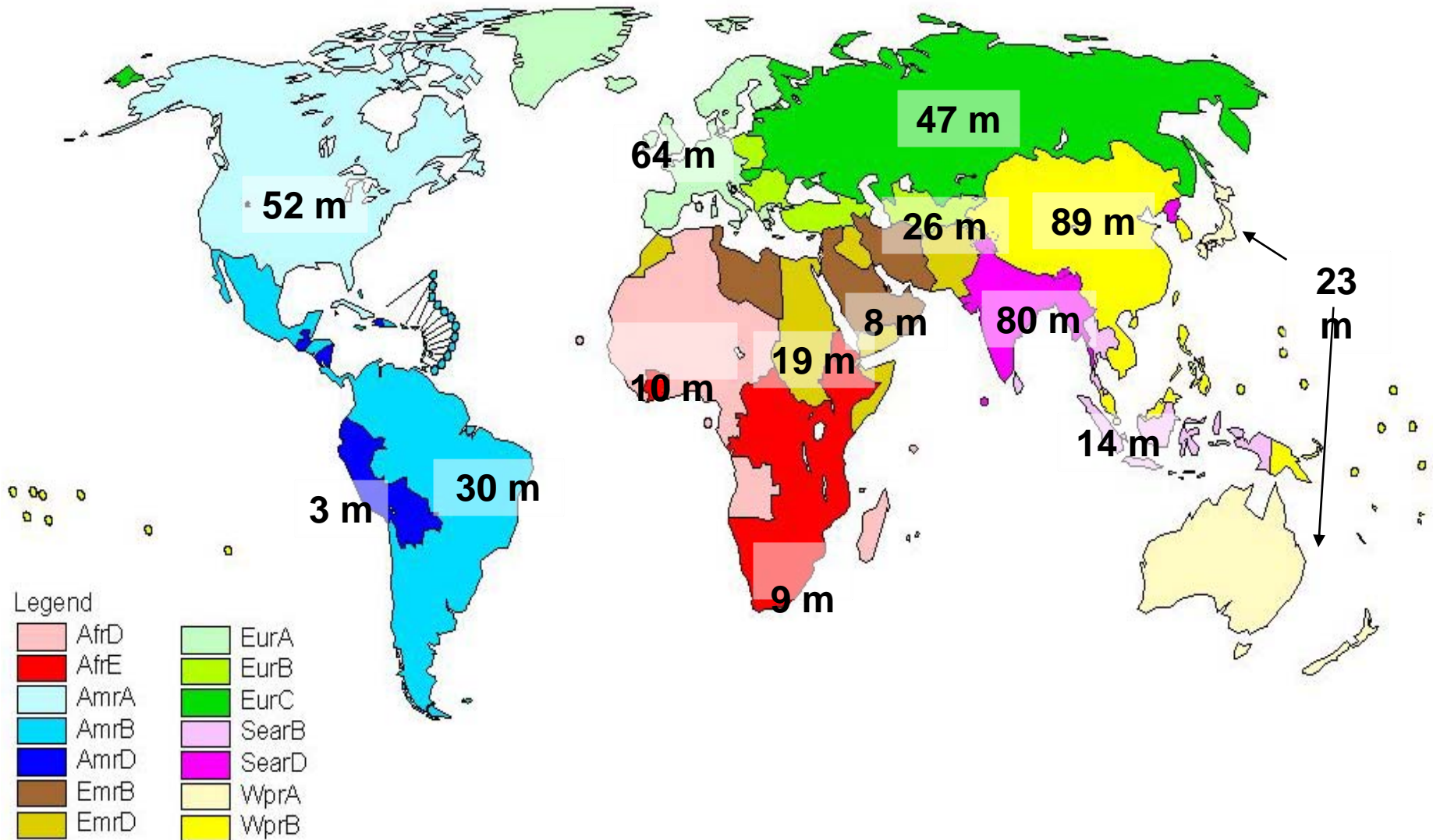
*High Risk: left ventricular hypertrophy, cigarette smoker, glucose intolerance, cholesterol = 8.02 mmol/L. From Alderman 1993*

## 45-54yrs – none treated



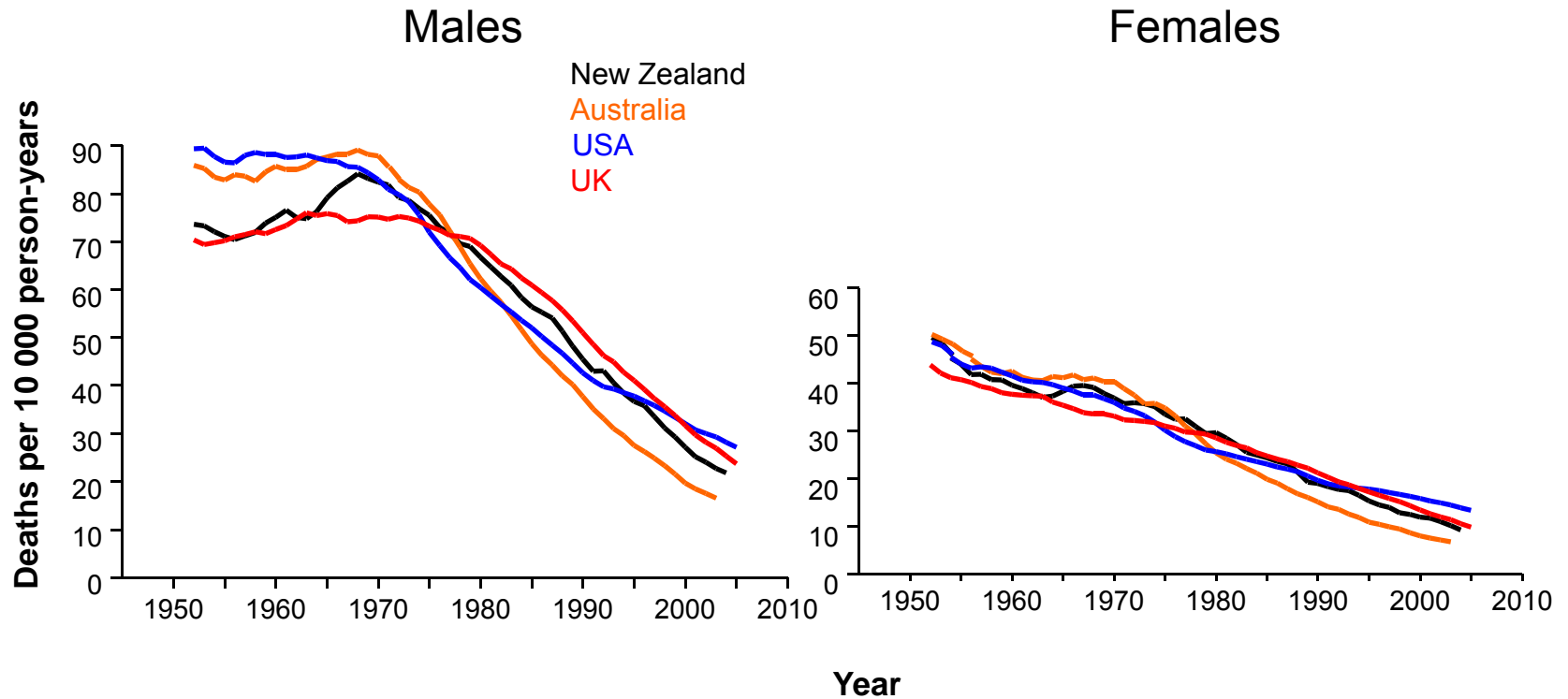


# Estimated number of people with previous cardiovascular disease or at over 7.5% risk in next 5 years, by WHO region

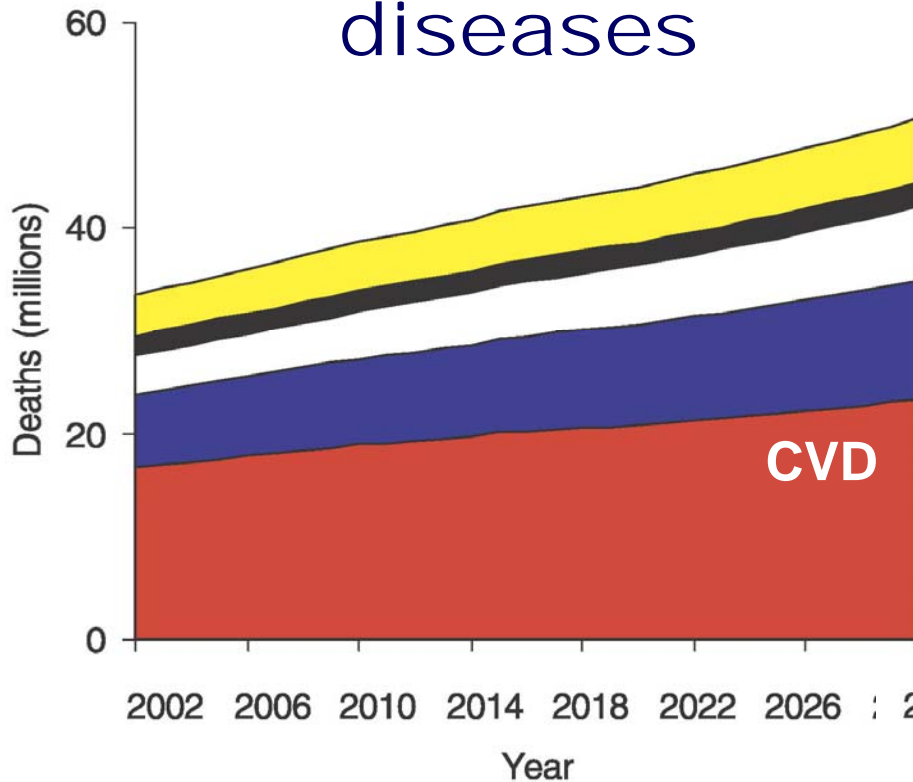




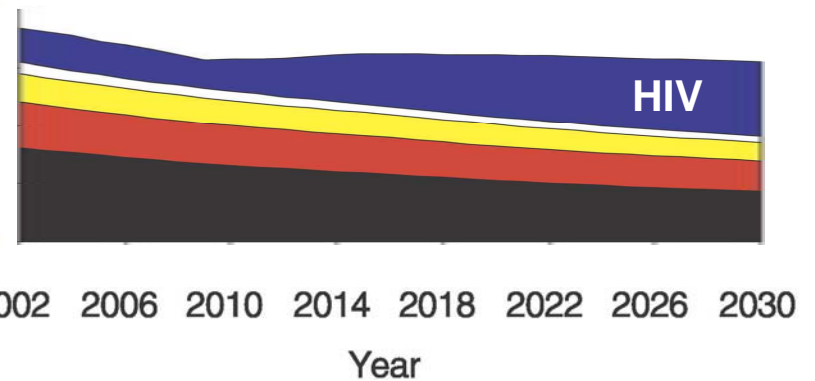
# Cardiovascular deaths 1950-2005, 35-69yr olds



## Chronic diseases

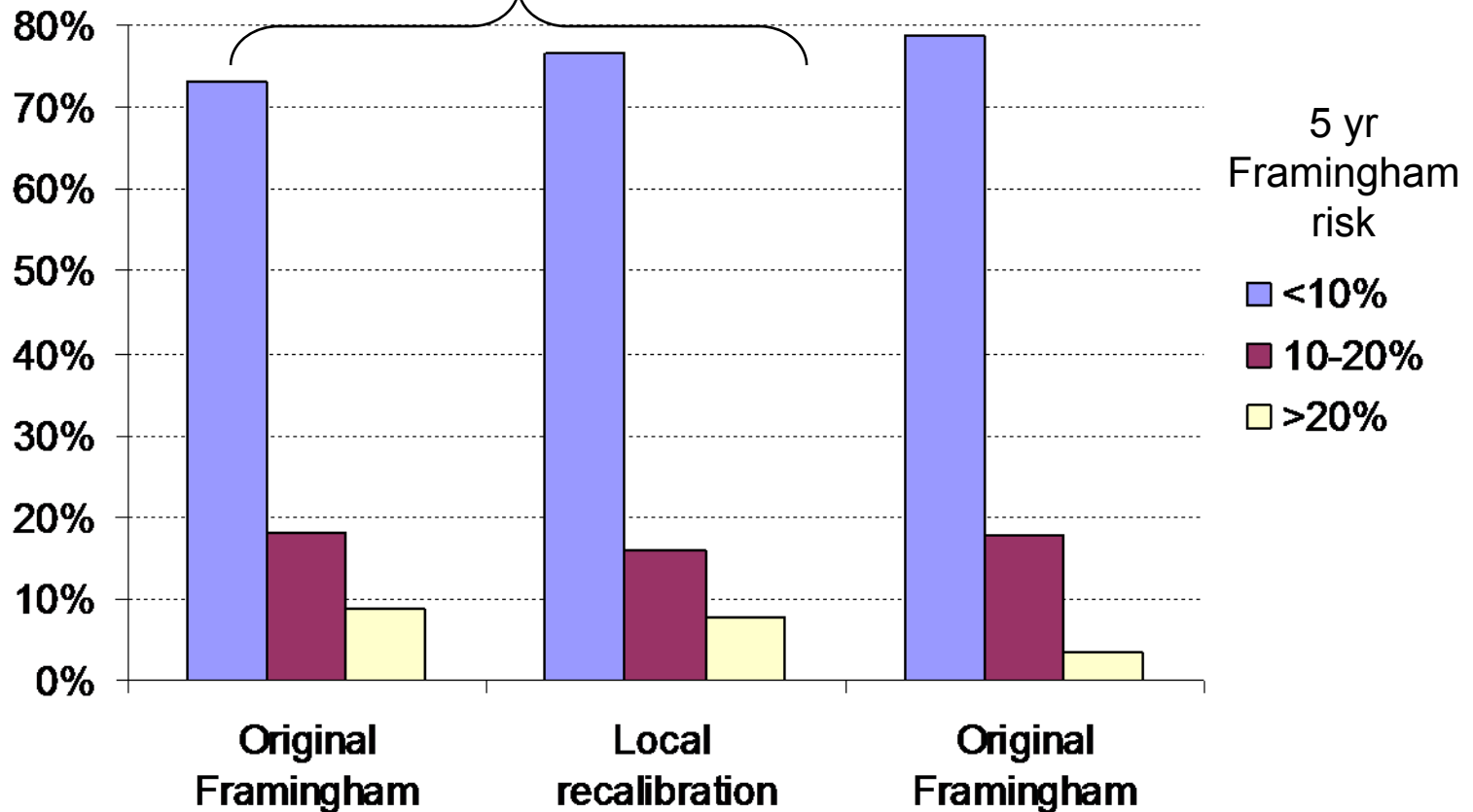


## Communicable diseases



# Proportion of population in different risk groups in rural Andhra Pradesh, India and urban Auckland, New Zealand

At least as many people at raised risk in Andhra Pradesh, and local calibration makes little difference



## Andhra Pradesh Rural Health Initiative

Stratified random sample of 4535 adults 30 years and over drawn from 20 villages in rural Andhra Pradesh. Chow et al, in press 2008

## NZ Primary care population

41,000 people screened for cardiovascular disease in Auckland general practises (99% over 30 yrs). S Wells, personal communication

# History of the polypill

- General concept conceived independently by several people in late 1990s and earlier eg “aspolol”
- WHO-Wellcome Trust meeting, Cambridge 2001
- Salim Yusuf Lancet editorial 2002
- Dr Reddy’s public-private partnership in 2003
- “Polypill” term coined by publication of BMJ papers in 2003

# Wald and Law papers 2003

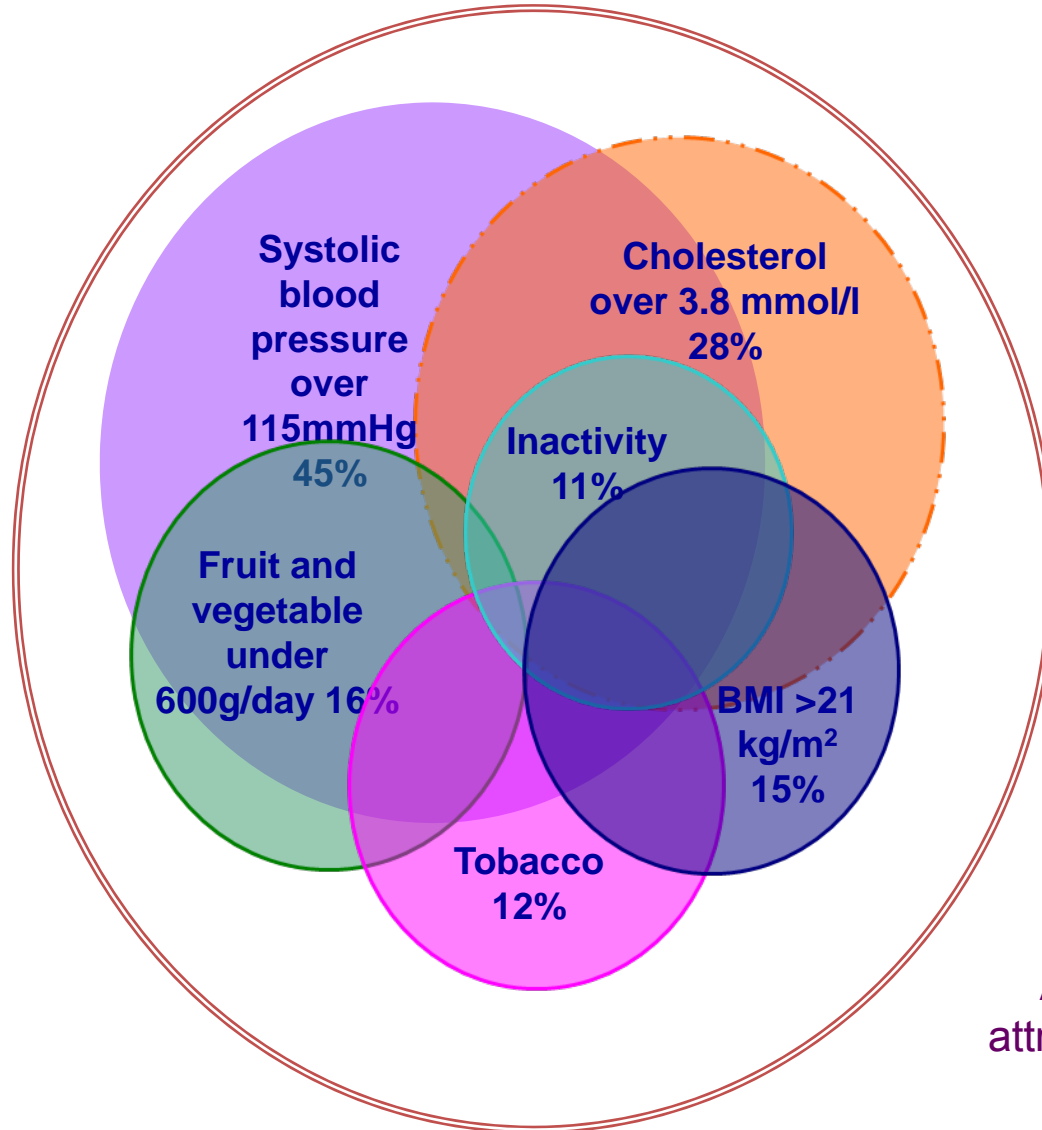
- What was not new?
  - combination of BP drugs, statin and aspirin
  - treat people with vascular disease
  - claim of 70%+ risk reductions
- What was new?
  - superb synthesis of evidence
  - ~~3 BP agents at half standard dose & folic acid~~
  - treat everyone over 55 years

!!!!!!!

# Other “polypills”

- Long history of fixed dose combinations (FDCs) in CVD (especially hypertension) and other areas of medicine
- Most Western adults take “multivitamins” regularly
- Half way polypills – caduet®, aspirin&pravastatin packaged together
- 3-4 drugs FDCs in tuberculosis and HIV/AIDS

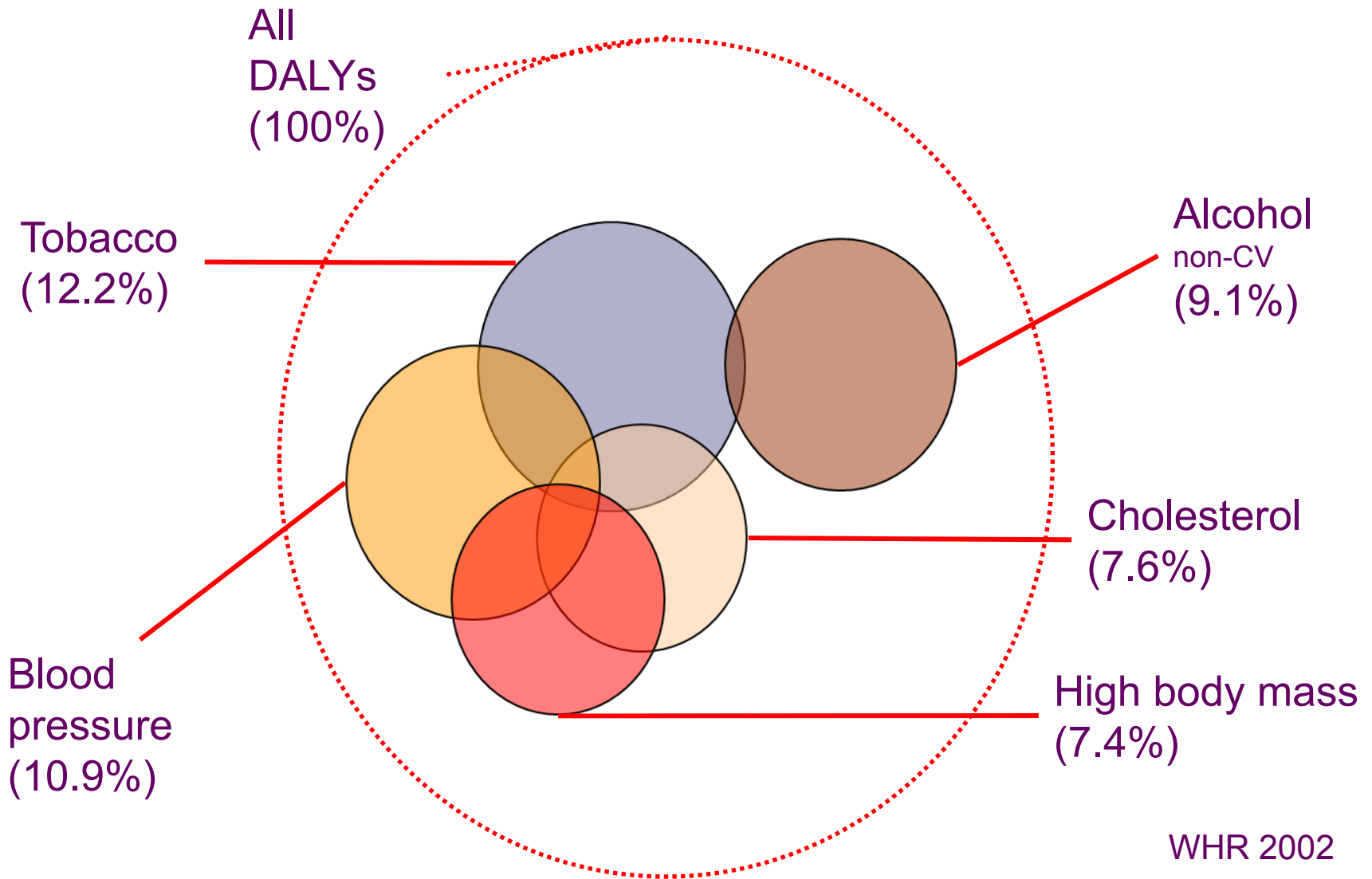
# Global cardiovascular disease burden due to 6 major risk factors



WHR 2002

Area proportional to attributable global DALYs

# Proportion of all lost healthy life years in developed countries





# RHP components

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- Lisinopril 10 mg
- HCTZ 12.5 mg
- Simvastatin 20 mg
- Aspirin 75 mg