Principles of Combination Polypharmacy: CVD 2º Prevention

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CVD 2º Prevention

- Strong evidence demonstrating benefit of ASA, β-blockers, and statins following a CVD event
  - ASA: 15% RRR for death *ATC 2002*
  - β-blockers: 23% RRR for death *Freemantle 1999*
  - Lipid-lowering therapy: 27% RRR for death *CTT 2010*

- Quitting smoking results in risk similar to non-smokers within 2-5 years
- Cardiac rehabilitation ↓ recurrent events by up to 26%
- Variable benefits of dietary modification

Estimated Costs of 5 Priority Interventions

	Interventions	Cost per person per year		
		China	India	Russia
Tobacco	FCTC	0.14	0.16	0.49
Dietary salt	Mass-media, voluntary action by food industry	0.05	0.06	0.16
Obesity, unhealthy diet and physical inactivity	Mass-media, food taxes, subsidies, labeling and marketing restriction	0.43	0.35	1.18
Harmful alcohol intake	Tax, advertising bans, restricted access	0.07	0.05	0.52
Cardiovascular risk reduction	**Combination of drugs, polypharmacy**	**1.02**	**0.9**	**1.73**
Total cost per person		**1.72**	**1.52**	**4.08**

Lancet 2011: doi:10.1016/S0140-6736(11)60393-0

Cost-Effectiveness of CVD Prevention

Region	Secondary prevention	Primary prevention		
		AR > 25%	AR > 15%	AR > 5%
East Asia and Pacific	336	890	923	1214
East Europe and central Asia	362	858	905	1207
Latin America and Caribbean	388	881	930	1219
Middle East and north Africa	341	872	930	1221
South Asia	306	746	790	1039
Sub-Saharan Africa	312	771	846	1145

[a]Abbreviation: AR: absolute risk; QALY, quality-adjusted life year.

Potential in secondary prevention and high risk primary prevention

Dabhadkar et al, ARPH 2011

Evidence-based therapy (EBT) at community level: PURE (Yusuf S, et al. *Lancet* 2011)

- Community-based cohort study in 17 countries
  - 628 urban and rural communities
  - N= 153,966 individuals
  - 7,850 self-reported cases of CHD or stroke

- ~14-25% overall use of EBT (statins at lowest)
- ~3-10 % received EBT in low-income countries
- Zero drugs:
  - 80% in low income
  - 69% in low-middle income

Economic status was most important predictor

If CVD 2^{o} prevention is so beneficial, then why is it not followed widely?

- *Physician/Health care delivery level*
- *Patient level*
- *Health system and country level*

Physician/Health Care Delivery Level: Categories of Suboptimal Care

Omission: Failure to use therapies that are proven to be beneficial

Commission: Inappropriate or incorrect use of treatment strategies, dose, or procedures

Examples of omission and commission: recent example from Kerala

European Heart Journal
doi:10.1093/eurheartj/ehs219

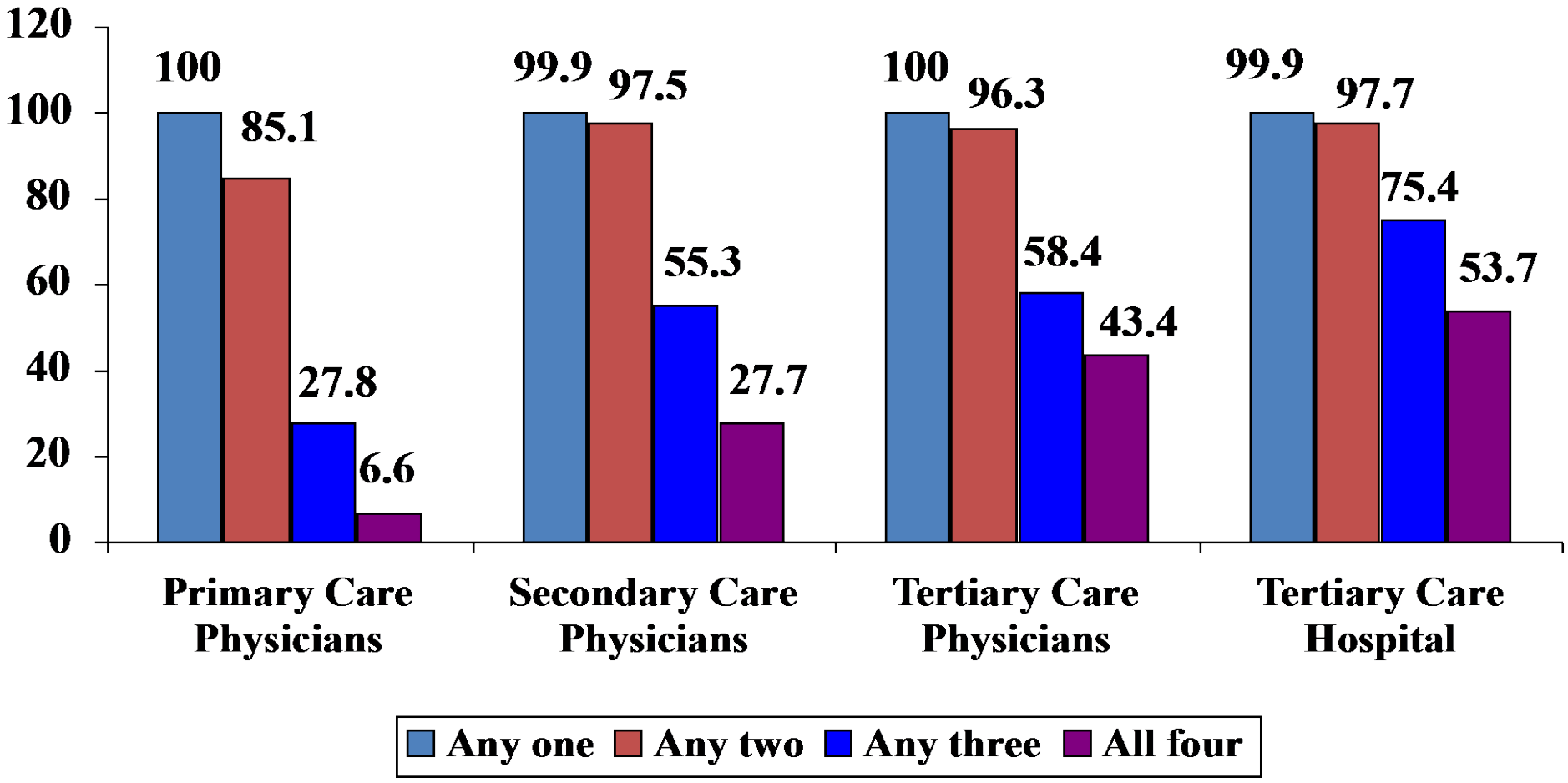
CLINICAL RESEARCH

Presentation, management, and outcomes of 25 748 acute coronary syndrome admissions in Kerala, India: results from the Kerala ACS Registry

Padinhare Purayil Mohanan[1*], Rony Mathew[2], Sadasivan Harikrishnan[3], Mangalath Narayanan Krishnan[4], Geevar Zachariah[5], Jhony Joseph[6], Koshy Eapen[7], Mathew Abraham[8], Jaideep Menon[9], Manoj Thomas[10], Sonny Jacob[11], Mark D. Huffman[12], and Dorairaj Prabhakaran[13,14], on behalf of the Kerala ACS Registry Investigators

- Sub-optimal discharge medications (<80%)
- Nitrates (75%) more common than β-blockers (63%) at d/c
- Inadequate and inappropriate use of thrombolysis (NSTEMI [18%] and unstable angina [11%])

Low Use of Multiple Therapies for 2º Prevention at Different Levels of Care



Sharma K, Gupta R, Agarwal A, et al. *Vasc Health Risk Manag* 2009;5:1007.

Patient Level: Adherence

- Poor adherence to treatment
  - Under-recognized since adherence is infrequently assessed by physicians (and under-reported by patients?)

- 40% of ~45 million US patients treated with BP and lipid lowering agents do not adhere to treatment

  (PricewaterhouseCoopers online 2008 – Pharma 2020:The vision)

- Reasons for poor adherence:
  - Costs
  - Clinical factors, including side effects
  - Complexity of treatment
  - Poor medical literacy
  - Psychological and psychiatric disorders

Sub-optimal Adherence to CVD 2º Prevention in CAD: Duke Experience

Medicine	Self-reported adherence (%)	*Consistent adherence (%)
ASA	83	71
β-blockers	61	44
Lipid lowering agent	63	46
ASA+ β-blocker	54	36
ASA+ β-blocker + lipid lowering agent	39	21
ACE-I (HF)	51	39
ACE-I (no HF)	39	20

* At more than 2 consecutive follow-up surveys over 6±12 months

Newby LK et al., *Circulation* 2006;113:203-12

Health System/Country Level: Barriers

Barriers to 2^{o} CVD prevention at PHCs in Himachal Pradesh:

- Competing priorities –
  - CD vs. NCD vs. MCH
- Uneven distribution of health care (across state/region)
- Emphasis on curative care over preventive services
- Insufficient & inadequately trained human resources
- Lack of infrastructure: drugs, diagnostics, etc.
- Lack of standard clinical practice guidelines, especially to aid in task-shifting

Inequity, Access, Availability and Distribution

Medecins Sans Frontieres

- 15% of world's population consumes >90% of world's drugs
- Shandong prov. China – metformin 500mg (generic) = 8.2x more expensive than international standard;

  1 month Rx = ~10.8 days wages
- Tajikistan – HCTZ 25mg (generic) = 33.5x more expensive

  1 month Rx = ~1 month wages

https://www2.essex.ac.uk/human_rights_centre/rth/
Grover A & Citro B. Lancet 2011; 37: 976-7
Gelders S. et al. Price, availability & affordability: an international comparison of chronic disease medicines.
WHO: http://mednet3.who.int/medprices/

(Potential) Limitations of Fixed Dose Combination Therapy

"How will I be able to evaluate my patients' side effects of the individual medications?"

- Possibly overstated given distinctions across drugs
  - Bleeding vs. mylagias vs. orthostasis vs. cough

"I need to titrate the doses of my patients' drugs."

- Limited role dose escalation/de-escalation for most patients
  - Low dose aspirin and high-dose statin preferred for 2^{o} prev.

- Likely does not require cardiologist, nor even physician

"What about clopidogrel for my post-MI patients?"

Potential Solutions

Physician/health care delivery level

- Improving quality of care: avoiding errors of omission and commission
  - Quality improvement programs
  - Fixed dose combination Rx

Patient level

- Improving adherence: fixed dose combination Rx

Health system/country level

- Improving access:
  - *Care*: Universal health coverage (Mexico, Brazil, India?)
  - *Drugs*: Fixed dose combination Rx

Innovative approaches:

- Local/traditional approaches in improving 2^{o} CVD prevention
- Task shifting (nurses, physician assistants, et al.)
- Leveraging technology (IT, mHealth, gaming technologies)

CVD 2º Prevention: Efficacy to Effectiveness to Efficiency and Beyond

Physician level: improving practice pattern

- Integrating 2º prevention into primary health care
- Improved referral and follow-up care through vascular/secondary prevention clinics

Patient level: enabling uptake and optimizing adherence

- Simpler regimens, utilizing technology-based reminders
- Support systems for easier access

Health care system/country level:

- Health system strengthening, including human resources
- Improving access to primary and secondary care
- Improving access, affordability to essential medicines

Monitoring and evaluation of interventions at all levels

Principles of CVD 2º Prevention: Take Home Points

2º CVD prevention is **effective** and cost-effective but is widely **underutilized** due to physician, patient, and country level barriers.

Fixed dose combination therapy could simplify and improve access to essential medicines for 2º CVD prevention across all 3 levels.

- *Theoretical arguments against fixed dose combination therapy do not appear compelling at this time*

Additional improvements at all levels are needed to improve effectiveness of 2º CVD prevention.

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