

**MULTI-LEVEL COMMUNITY INTERVENTIONS FOR PRIMARY STROKE PREVENTION:
A CONCEPTUAL APPROACH BY THE WORLD STROKE ORGANIZATION**

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ABSTRACT

The increasing burden of stroke and dementia emphasises the need for new, well-tolerated and cost-effective primary prevention strategies that can reduce the risks of stroke and dementia worldwide, and specifically in low and middle-income countries (LMICs).

This paper outlines conceptual frameworks of three primary stroke prevention strategies: (a) the 'polypill' strategy; (b) a 'population-wide' strategy; and (c) a 'motivational population-wide' strategy.

a) A polypill containing generic low-dose ingredients of blood pressure and lipid lowering medications (e.g. candesartan 16 mg, amlodipine 2.5 mg and rosuvastatin 10 mg) seems a safe and cost-effective approach for primary prevention of stroke and dementia.

b) A population-wide strategy reducing cardiovascular risk factors in the whole population, regardless of the level of risk is the most effective primary prevention strategy. A motivational population-wide strategy for the modification of health behaviours (e.g. smoking, diet, physical activity) should be based on the principles of cognitive behavioural therapy. Mobile technologies, such as smartphones, offer an ideal interface for behavioural interventions (e.g. Stroke Riskometer app) even in LMICs.

c) Community health workers (CHWs) can improve the maintenance of lifestyle changes as well as the adherence to medication, especially in resource poor areas. An adequate training of CHWs is a key point.

Conclusion: An effective primary stroke prevention strategy on a global scale should integrate pharmacological (polypill) and lifestyle modifications (motivational population-wide strategy) interventions. Side effects of such an integrative approach are expected to be minimal and the benefits among individuals at low-to-moderate risk of stroke could be significant. In the future pragmatic field trials will provide more evidence.

Stroke and dementia/cognitive impairment are the second most common causes of death and disability in the world.¹⁻⁴ In 2016, there were approximately 124 million people living with stroke and dementia worldwide, and every year stroke and dementia affect about 13.7 million and 7.8 million people, respectively.^{1,2} The commonest outcome of cerebrovascular disease is not stroke, but cognitive impairment.⁵ Given the reciprocal links and shared risk factors between cerebrovascular disease and dementia, interventions to prevent stroke should be beneficial to prevent dementia.⁶ Over the last three decades stroke incidence and mortality rates in the world have decreased, however the absolute number of people affected by stroke, died from or remained disabled from stroke as well as the absolute number of people with dementia has increased in all countries of the world.^{1,2} Moreover, globally since 2010 there has been an increase in stroke and dementia mortality and disability-adjusted life-years lost (DALYs) and stroke has become a disease primarily of working-age people (almost 60% of people affected by stroke in 2016 were people under 70 years of age) and since 1990 there has been a large and ongoing increase in stroke incidence rates in people aged 15 to 49 years.³

The increased burden of stroke and dementia across all countries in the world provides strong evidence that currently used primary stroke and dementia prevention strategies are not sufficiently effective.⁷ These inefficiencies are further highlighted by the significant sex and ethnic disparities in stroke⁸ and globally observed increases in the prevalence of many risk factors (including type 2 diabetes mellitus and various lifestyle factors).^{7,9} Due to ongoing ageing of the population, population growth and a trend towards increasing prevalence of many important risk factors for stroke and dementia, the burden of stroke and dementia is likely to continue to increase^{1,2} unless cost-effective primary stroke/dementia preventative strategies are found and implemented.^{7,9}

The huge and increasing burden of stroke, dementia and other non-communicable diseases (NCDs) has led to the historical 2011 United Nations resolution¹⁰ followed by the WHO Global Action plan¹¹ calling upon all governments to give primary prevention of non-communicable diseases, including stroke and dementia, the highest priority. Mandatory and voluntary global targets were set, up to the year 2030, but the progress to date is unsatisfactory.¹² There is a pressing need to identify new, well-tolerated and affordable strategies for the majority of people that will reliably reduce the risks of stroke and dementia/cognitive decline across all countries in the world.^{9,13} This paper outlines conceptual frameworks of three promising primary stroke prevention strategies to be pragmatically tested in large field trials: (a) the 'polypill' strategy; (b) a 'population-wide' strategy; and (c) a 'motivational population-wide' strategy.

Polypill strategy

A polypill strategy for primary prevention of cardiovascular disease (CVD) was first introduced by Drs Wald and Law in 2003 to reduce CVD by more than 80%.¹⁴ In previous polypill RCTs primarily for secondary CVD prevention, this approach has yielded largely improved adherence to the medications (compared to usual multi-pill approach) as well as sizeable reductions in SBP (between 9.9 and 17.9 mmHg reduction) and low-density lipoprotein cholesterol (LDL-cholesterol)^{15,16} but caused haemorrhagic side effects in about 1 in 6 people due to the presence of aspirin as part of the polypill.^{15,17} In addition, cost-effectiveness analysis showed that most health gain in such polypill trials is achieved by the polypill without aspirin and a statin dose corresponding to the recommended standard dose.¹⁸ To maximize the treatment effect on stroke prevention while reducing the possibility of adverse effects, it seems reasonable for the new polypill to contain the following generic low-dose ingredients: candesartan 16 mg, amlodipine 2.5 mg and rosuvastatin 10 mg. There is evidence from the large STELLAR trial that lipid-lowering effects of rosuvastatin 10 mg are comparable to the effects of simvastatin 80 mg, atorvastatin 40 mg, and superior to 40 mg of pravastatin.¹⁹ Elevated blood pressure and dyslipidaemia are well-established risk factors for stroke and dementia (including cognitive impairment).^{3,20,21} In the recent HOPE-3 trial, a combination of rosuvastatin (10 mg per day), candesartan (16 mg per day), and hydrochlorothiazide (12.5 mg per day) reduced CVD events by 29% over 5.6 years in adults at moderate risk of CVD.²² Due to well-known side effects of hydrochlorothiazide^{23,24} such as hyponatremia, hypokalemia and dysglycemia, it seems reasonable to replace it with a calcium channel blocker (e.g. amlodipine 2.5 mg). It was shown that calcium channel blockers not only reduce blood pressure level but also reduce the risk of dementia²⁵ and blood pressure variability,²⁶ a well-known independent risk factor for stroke.²⁷ A combination of amlodipine with an angiotensin II receptor blocker (e.g. candesartan) was shown to be particularly beneficial in reducing CVD events.²⁸ The increased risk of CVD, including stroke, is not restricted to those with “hypertension” or “hypercholesterolemia”, but is continuous down to at least a blood pressure of 115/75mmHg and total cholesterol level of 135 mg/dL (4.0 mmol/l).^{29,30} There is now clear evidence that blood pressure lowering medications and statins reduce the risk of stroke and cognitive decline.^{20,31-35} The use of a combination of blood pressure and lipid lowering medications is proven to be generally safe even in people with average or below-average systolic blood pressure and cholesterol levels³⁶ and, in low dosages such as in the polypill, as an adjunct therapy to other blood pressure and lipid lowering medications.^{37,38} However, there is considerable uncertainty about whether these benefits extend to primary prevention among people without or with borderline hypertension or dyslipidaemia. In addition, it has been argued that prescribing a single pill, without lifestyle

changes, to prevent CVD is pointless and could lead to excessive medicalisation³⁹ and neglect of lifestyle risk factors.⁴⁰

Population-wide strategy

A population-wide strategy for primary prevention of CVD was first introduced by Geoffrey Rose in 1981.⁴¹ By reducing exposure to CVD risk factors (such as smoking cessation, salt and sugar reduction, physical inactivity etc.) in the whole population, regardless of the level of CVD risk, this is undoubtedly the most effective primary prevention strategy not only for stroke and dementia but also for other NDCs that share common risk factors. The WHO has recommended that governments consider the implementation of the “WHO best buy” interventions⁴² that include some evidence-based, cost-effective, feasible population-wide primary stroke prevention interventions. Despite these recommendations, opposition from industry and the requirements for legislative/regulatory changes have made this strategy very challenging to implement on a national level,⁷ especially in LMIC.⁴³ A recently introduced WHO technical package for CVD management in primary health care via team-based care and healthy-lifestyle counselling⁴⁴ offers an opportunity to enhance primary stroke, dementia and CVD prevention strategy in community low-resource settings.

Motivational population-wide strategy

A motivational population-wide strategy for primary stroke prevention was first introduced by Feigin and Norrving in 2014.⁴⁵ Lifestyle risk factors, such as poor diet, low physical activity, overweight and smoking, account for over 70% of the stroke burden worldwide.³ Importantly, there is evidence that modifying unhealthy behaviours (e.g. smoking, poor diet, physical inactivity) is feasible, improves health outcomes, and also reduces stroke, cognitive decline and dementia risk and healthcare costs.^{20,31,46-48} The critical identified elements of effective behavioural interventions are based on principles of cognitive behavioural therapy, including behavioural motivation, goal-setting and empowering.⁴⁴ However, to be widely available such interventions must be affordable and easily accessible. Widely used mobile technologies, such as smartphones, offer an ideal interface for behavioural interventions to the majority of people, even in low and middle-income countries (LMICs). AUT University has developed⁴⁹ and validated⁵⁰ the novel, not-for-profit Stroke Riskometer app. It uses individual data on demographic, health and lifestyle factors to derive a person’s validated absolute and relative risk of stroke.^{49,50} The app then provides, saves and tracks an individual’s risk self-management information (with goal-setting options and push notifications as a prompt to users to take action to achieve their goals), thereby empowering users to act on this potentially life-

saving information. This provides an opportunity to combine both population-wide and high-risk prevention strategies, thus opening up a new paradigm for primary prevention of stroke, dementia and other major NCDs.^{13,45} Data from the recent pilot RCT on Stroke Riskometer app indicate motivational value and potential efficacy of this novel mobile intervention to improve lifestyle risk factors as well as acceptability of this lifestyle intervention.^{51,52}

Smartphone apps can serve as an educational tool to assess the CVD risk, improve health education, and modify lifestyle behaviours. Unfortunately, the adherence to healthy behaviour is often poor. The involvement of community health workers (CHWs) can be an additional powerful opportunity to advance primary stroke prevention strategies, especially in resource poor areas, by increasing recruitment, minimizing drop-outs, and by improving the maintenance of lifestyle changes as well as the adherence to medications.

CHWs are trained individuals embedded in the community with limited or no formal medical education who provide a broad range of patient oriented health services. Their main roles in primary care are clinical services, community and social resource connections, and health education and coaching.⁵³ By sharing life experiences, culture, ethnicity, language and socio-economic status, they can provide peer support and more effectively link communities to the health and social services systems.⁵³⁻⁵⁵ Despite the heterogeneity of CHW programs and the often-low quality of studies, there is growing evidence that CHWs can improve health outcomes.⁵⁵⁻⁵⁸ Programmes involving CHWs have shown to be particularly successful to reduce inequities in access to health care in settings with shortage of health professionals.^{53,55,58} Factors central to effective CHWs programs were community embeddedness, supportive supervision, continuous education, and adequate logistical support and supplies.⁵⁵

While the majority of programs involving CHWs focus on maternal-child health and HIV, a number of studies showed that CHWs can successfully play a role in primary prevention programs for NCDs.⁵⁶ Compared to standard care CHWs programmes for NCDs prevention in LMICs were successful to increase smoking cessation and decrease blood pressure and blood sugar levels.⁵⁶ Similarly, community-based primary prevention programs to improve cardio-metabolic risk in non-urban communities were more effective than non-community based programs in improving blood pressure, BMI and lipids.⁵⁷ Furthermore, a review of 9 studies showed that interventions involving CHWs for CVD prevention were also cost effective.⁵⁹ However, no trial has addressed CHWs for the primary prevention of stroke and dementia/cognitive decline.

An adequate training is a key point to empower CHWs to fulfil their role; this training should include technical competency as well as social skills.⁵⁵ This training for stroke prevention

and cognitive decline could be based on the HEARTS technical package for cardiovascular disease management in primary health care which includes a module with practical material and strategies for primary health care trainers on healthy-lifestyle counselling.⁴⁴

Integrative approach

For a primary prevention strategy targeted at stroke and dementia to be most effective on a global scale it should include both pharmacological (such as a polypill containing blood pressure and lipid lowering medications) and lifestyle modification (such as motivational population-wide strategies) interventions.^{7,60} Ideally, any primary stroke and dementia prevention interventions should include a population-wide strategy for primary prevention of CVD (such as the “WHO best buy” interventions),⁴² which could be enhanced by the WHO technical package for CVD management in primary health care.⁴⁴ In 2015, the World Stroke Organization, Alzheimer's Disease International, the Alzheimer's Society UK, Public Health England, the American Heart/Stroke Association, the Alzheimer's Association, and 16 other international, regional, and national organizations endorsed a proclamation on stroke and potentially preventable dementias, calling for their joint prevention.⁶¹

There is evidence of a reduced risk of stroke and mild cognitive impairment following reductions in blood pressure^{62,63} and cholesterol^{64,65} and lifestyle modifications,^{31,66-68} including eHealth interventions^{69,70} in middle-aged individuals (i.e., those aged 50 to 70) at high risk of CVD. Collectively, existing data provide evidence that the new polypill (a three-component pill containing candesartan 16 mg, amlodipine 2.5 mg and rosuvastatin 10 mg) with lifestyle modification via the Stroke Riskometer app may provide a more effective means to prevent stroke than either approach individually (Figure). Its applicability across a large and varied population will also enhance generalizability.⁷¹ These interventions also have the potential to reduce the risks of other major non-communicable diseases (NCDs), including cognitive decline, ischemic heart disease and type 2 diabetes mellitus.

Expected global impact and future directions “cut stroke in half”

The net benefits of combined treatment with blood pressure lowering, statin and lifestyle modification could be substantial, since each intervention can work in an independent and additive manner. The potential impact of controlling risk factors for the burden of stroke and cognitive decline is substantial, as it has also been estimated that about 90% of stroke is attributable to ten modifiable risk factors including hypertension, obesity, hyperlipidaemia, smoking and diabetes,^{3,8} and it has been estimated that about 35% of dementia is

attributable to a combination of nine modifiable risk factors including midlife hypertension and obesity, later life smoking, physical inactivity, and diabetes.²⁰ Based on extrapolation from previous trials, a more than halving of cardiovascular risk (including stroke) would be expected. This is likely to exceed a two-thirds reduction after the first two years, once the full effects of the component medications and lifestyle modification accrue. Moreover, these treatments are generally affordable (estimated at a dollar a week) and safe given the low-dose combinations of blood pressure lowering agents and statins. Adverse effects are expected to be minimal and would be vastly outweighed by the net benefits among individuals at low-to-moderate risk of stroke and dementia. In the absence of robust evidence for the benefits, safety, and cost-effectiveness of this approach, large randomized controlled trials with clinically meaningful endpoints demonstrating efficacy for the reduction of stroke and dementia are urgently required.^{72,73}

References

1. GBD 2016 Stroke Collaborators. Global, regional, and national burden of stroke, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol* 2019; 18:439-458.
2. GBD 2016 Dementia Collaborators. Global, regional, and national burden of Alzheimer's disease and other dementias, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol* 2019; 18:88-106.
3. Feigin VL, Roth GA, Naghavi M, et al. Global burden of stroke and risk factors in 188 countries, during 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet Neurol* 2016; 15:913-924.
4. The shared burden of stroke and dementia. *Lancet Neurol* 2016; 15:891.
5. Kalaria RN. Cerebrovascular disease and mechanisms of cognitive impairment: Evidence from clinicopathological studies in humans. *Stroke* 2012 ;43:2526-2534.
6. Hachinski V. Stoop to conquer: preventing stroke and dementia together. *Lancet* 2017; 389:1518.
7. Feigin VL, Norrving B, George MG, et al. Prevention of stroke: a strategic global imperative. *Nat Rev Neurol* 2016; 12:501-512.
8. O'Donnell MJ, Chin SL, Rangarajan S, et al. Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): a case-control study. *Lancet* 2016; 388:761-775.
9. Feigin VL. Primary stroke prevention needs overhaul. *Int J Stroke* 2017; 12:5-6.
10. United Nations General Assembly. Resolution adopted by the General Assembly: 66/2: Political Declaration of the High-level Meeting of the General Assembly on the

Prevention and Control of Non-communicable Diseases. Adopted September 19, 2011, Published January 24, 2012 ed2012.

11. World Health Organization. Global action plan for the prevention and control of noncommunicable diseases 2013-2020. WHO, Geneva
http://www.who.int/nmh/events/ncd_action_plan/en/ 2013.
12. United Nations General Assembly, Seventy-second session. Progress on the prevention and control of non-communicable diseases. Report of the Secretary-General. 21 December 2017. A/72/662
https://ncdalliance.org/sites/default/files/resource_files/UNSG%20Report%20on%20NCDs%20December%202017%20A.72.662%20SG%20report.pdf Accessed on 9 March 2018.
13. Feigin VL, Norrving B, Mensah GA. Primary prevention of cardiovascular disease through population-wide motivational strategies: insights from using smartphones in stroke prevention. *BMJ Global Health* 2017; 2:e000306.
14. Wald NJ, Law MR. A strategy to reduce cardiovascular disease by more than 80%. *BMJ* 2003; 326:1419-1419.
15. Cimmaruta D, Lombardi N, Borghi C, et al. Polypill, hypertension and medication adherence: The solution strategy? *Int J Cardiol* 2018; 252:181-186.
16. Wald DS, Morris JK, Wald NJ. Randomized polypill crossover trial in people aged 50 and over. *PLoS One* 2012; 7:e41297.
17. PILL Collaborative Group, Rodgers A, Patel A, et al. An international randomised placebo-controlled trial of a four-component combination pill ("polypill") in people with raised cardiovascular risk. *PLoS One* 2011; 6:e19857.
18. van Gils PF, Over EA, Hamberg-van Reenen HH, et al. The polypill in the primary prevention of cardiovascular disease: Cost-effectiveness in the Dutch population. *BMJ Open* 2011; 1:e000363.
19. McKenney JM, Jones PH, Adamczyk MA, et al. Comparison of the efficacy of rosuvastatin versus atorvastatin, simvastatin, and pravastatin in achieving lipid goals: Results from the STELLAR trial. *Curr Med Res Opin* 2003; 19:689-98.
20. Livingston G, Sommerlad A, Orgeta V, et al. Dementia prevention, intervention, and care. *Lancet* 2017; 390:2673-2734.
21. Bellou V, Belbasis L, Tzoulaki I, et al. Systematic evaluation of the associations between environmental risk factors and dementia: An umbrella review of systematic reviews and meta-analyses. *Alzheimers Dement* 2017; 13:406-418.
22. Yusuf S, Lonn E, Pais P, et al. Blood-pressure and cholesterol lowering in persons without cardiovascular disease. *New Engl J Med* 2016; 374:2032-2043.

23. Vongpatanasin W. Hydrochlorothiazide is not the most useful nor versatile thiazide diuretic. *Curr Opin Cardiol* 2015; 30:361-365.
24. Messerli FH, Bangalore S. Half a century of hydrochlorothiazide: Facts, fads, fiction, and follies. *Am J Med* 2011; 124:896-899.
25. Forette F, Seux ML, Staessen JA, et al. Prevention of dementia in randomised double-blind placebo-controlled Systolic Hypertension in Europe (Syst-Eur) trial. *Lancet* 1998;352:1347-51.
26. Kollias A, Stergiou GS, Kyriakoulis KG, et al. Treating Visit-to-Visit Blood Pressure Variability to Improve Prognosis: Is Amlodipine the Drug of Choice? *Hypertension* 2017;70: 862-866.
27. Wang J, Shi X, Ma C, et al. Visit-to-visit blood pressure variability is a risk factor for all-cause mortality and cardiovascular disease: A systematic review and meta-analysis. *J Hypertens* 2017;35:10-17.
28. Koyanagi R, Hagiwara N, Yamaguchi J, et al. Efficacy of the combination of amlodipine and candesartan in hypertensive patients with coronary artery disease: a subanalysis of the HIJ-CREATE study. *J Cardiol* 2013; 62:217-223.
29. Forouzanfar MH, Liu P, Roth GA, et al. Global burden of hypertension and systolic blood pressure of at least 110 to 115mmHg, 1990-2015. *JAMA* 2017; 317:165-182.
30. Farzadfar F, Finucane MM, Danaei G, et al. National, regional, and global trends in serum total cholesterol since 1980: systematic analysis of health examination surveys and epidemiological studies with 321 country-years and 3.0 million participants. *Lancet* 2011; 377:578-86.
31. Ngandu T, Lehtisalo J, Solomon A, et al. A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): A randomised controlled trial. *The Lancet* 2015; 385:2255-2263.
32. Meschia JF, Bushnell C, Boden-Albala B, et al. Guidelines for the primary prevention of stroke: A statement for healthcare professionals from the American heart association/American stroke association. *Stroke* 2014; 45:3754-3832.
33. Song Y, Nie H, Xu Y, Zhang L, Wu Y. Association of statin use with risk of dementia: A meta-analysis of prospective cohort studies. *Geriatr Gerontol Int* 2013; 13:817-824.
34. Beckett NS, Peters R, Fletcher AE, et al. Treatment of hypertension in patients 80 years of age or older. *New Engl J Med* 2008; 358:1887-1898.
35. Peters R, Beckett N, Forette F, et al. Incident dementia and blood pressure lowering in the Hypertension in the Very Elderly Trial cognitive function assessment (HYVET-COG): a double-blind, placebo controlled trial. *Lancet Neurol* 2008; 7:683-689.

36. Sever PS, Dahlöf B, Poulter NR, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial - Lipid Lowering Arm (ASCOT-LLA): A multicentre randomised controlled trial. *Drugs* 2004; 64:43-60.
37. Webster R, Rodgers A. Polypill: Progress and Challenges to Global Use—Update on the Trials and Policy Implementation. *Curr Cardiol Rep* 2015;17:121.
38. Elley CR, Gupta AK, Webster R, et al. The Efficacy and Tolerability of 'Polypills': Meta-Analysis of Randomised Controlled Trials. *PLoS One* 2012; 7:e52145.
39. Costantino G, Ceriani E, Rusconi AM, et al. Prevention of cardiovascular disease with a polypill. *Lancet* 2007; 369:185-186.
40. Selak V, Bullen C, Stepien S, et al. Do polypills lead to neglect of lifestyle risk factors? Findings from an individual participant data meta-analysis among 3140 patients at high risk of cardiovascular disease. *Eur J Prev Cardiol* 2016; 23:1393-1400.
41. Rose G. Strategy of prevention: lessons from cardiovascular disease. *Br Med J (Clin Res Ed)*. 1981; 282:1847-51.
42. From Burden to “Best Buys”: Reducing the Economic Impact of Non-Communicable Diseases in Low- and Middle-Income Countries. World Health Organization, World Economic Forum and the Harvard School of Public Health. World Economic Forum, Geneva, Switzerland 2011
http://www.who.int/nmh/publications/best_buys_summary.pdf Accessed 11 September 2018.
43. Allen LN, Pullar J, Wickramasinghe K, et al. Are WHO “best buys” for non-communicable diseases effective in low-income and lower-middle-income countries? A systematic review. *Lancet Global Health* 2017; 5:S17.
44. World Health Organization. (2018). Technical package for cardiovascular disease management in primary health care: healthy-lifestyle counselling. World Health Organization. <http://www.who.int/iris/handle/10665/260422>. License: CC BY-NC-SA 3.0 IGO.
45. Feigin VL, Norrving B. A new paradigm for primary prevention strategy in people with elevated risk of stroke. *Int J Stroke* 2014; 9:624-626.
46. Spring B, Ockene JK, Gidding SS, et al. Better population health through behavior change in adults: A call to action. *Circulation* 2013; 128:2169-2176.
47. Teuschl Y, Matz K, Firlinger B, et al. Preventive effects of multiple domain interventions on lifestyle and risk factor changes in stroke survivors: Evidence from a two-year randomized trial. *Int J stroke* 2017; 12:976-984.

48. Matz K, Teuschl Y, Firlinger B, et al. Multidomain Lifestyle Interventions for the Prevention of Cognitive Decline After Ischemic Stroke: Randomized Trial. *Stroke* 2015;46: 2874-2880.
49. Feigin VL, Krishnamurthi R, Bhattacharjee R, et al. New Strategy to Reduce the Global Burden of Stroke. *Stroke* 2015; 46:1740-1747.
50. Parmar P, Krishnamurthi R, Ikram MA, et al. The Stroke Riskometer(TM) App: validation of a data collection tool and stroke risk predictor. *Int J Stroke* 2015;10:231-244.
51. Krishnamurthi R, Bhattacharjee R, Parmar P, et al. Effectiveness of the Stroke Riskometer App for Primary Stroke Prevention: A Pilot RCT. Final Program of the International Stroke Conference in Los Angeles, USA 23-26 January 2018. Late-Breaking News Science Abstracts of the International Stroke Conference 24 January 2018 2018;Presentation Number LBP18:page 85.
52. Krishnamurthi R, Barker-Collo S, A. T, et al. Mobile technology for primary stroke prevention: a proof-of-concept pilot randomised controlled trial - a brief report. *Stroke* 2018; 50:196-198.
53. Hartzler AL, Tuzzio L, Hsu C, et al. Roles and Functions of Community Health Workers in Primary Care. *Ann Fam Med* 2018; 16:240-245.
54. Bhutta ZA, Lassi ZS, Pariyo G, et al. WHO Global Health Workforce Alliance. Global Experience of Community Health Workers for Delivery of Health Related Millennium Development Goals: A Systematic Review, Country Case Studies, and Recommendations for Integration into National Health Systems. Geneva: 2010.
55. Scott K, Beckham SW, Gross M, et al. What do we know about community-based health worker programs? A systematic review of existing reviews on community health workers. *Hum Resour Health* 2018; 16:39.
56. Jeet G, Thakur JS, Prinja S, et al. Community health workers for non-communicable diseases prevention and control in developing countries: Evidence and implications. *PLoS One* 2017; 12:e0180640.
57. Rodrigues AL, Ball J, Ski C, et al. A systematic review and meta-analysis of primary prevention programmes to improve cardio-metabolic risk in non-urban communities. *Prev Med* 2016; 87:22-34.
58. Perry HB, Zulliger R, Rogers MM. Community health workers in low-, middle-, and high-income countries: an overview of their history, recent evolution, and current effectiveness. *Annu Rev Public Health* 2014; 35:399-421.
59. Jacob V, Chattopadhyay SK, Hopkins DP, et al. Economics of Community Health Workers for Chronic Disease: Findings From Community Guide Systematic Reviews. *Am J Prev Med* 2019; 56:e95-e106.

60. Feigin VL, Krishnamurthi R. Stroke is largely preventable across the globe: where to next? *Lancet* 2016; 388:733-4.
61. Hachinski V. Stroke and Potentially Preventable Dementias Proclamation. *Stroke* 2015; 46:3039-3040.
62. Gaciong Z, Siński M, Lewandowski J. Blood pressure control and primary prevention of stroke: Summary of the recent clinical trial data and meta-analyses. *Curr Hypertens Rep* 2013; 15:559-574.
63. Goldstein FC, Levey AI, Steenland NK. High blood pressure and cognitive decline in mild cognitive impairment. *J Am Geriatr Soc* 2013; 61:67-73.
64. O'Regan C, Wu P, Arora P, et al. Statin Therapy in Stroke Prevention: A Meta-analysis Involving 121,000 Patients. *Am J Med* 2008; 121:24-33.
65. Chu CS, Tseng PT, Stubbs B, et al. Use of statins and the risk of dementia and mild cognitive impairment: A systematic review and meta-analysis. *Sci Rep* 2018; 8:5804.
66. Larsson SC, Akesson A, Wolk A. Primary prevention of stroke by a healthy lifestyle in a high-risk group. *Neurology* 2015; 84:2224-2228.
67. Tikik K, Sookthai D, Monni S, et al. Primary preventive potential for stroke by avoidance of major lifestyle risk factors: The European prospective investigation into cancer and nutrition-heidelberg cohort. *Stroke* 2014; 45:2041-2046.
68. Lutsep HL. Medical and lifestyle interventions, not procedures, should be the primary focus in stroke prevention. *Expert Rev Neurother* 2013; 13:877-878.
69. Spassova L, Vittore D, Droste DW, et al. Randomised controlled trial to evaluate the efficacy and usability of a computerised phone-based lifestyle coaching system for primary and secondary prevention of stroke. *BMC Neurol* 2016;16:22.
70. Aalbers T, Qin L, Baars MA et al. Changing behavioral lifestyle risk factors related to cognitive decline in later life using a self-motivated ehealth intervention in Dutch adults. *J Med Internet Res* 2016;18:e171.
71. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults. Hypertension 2017;DOI: 10.1016/j.jacc.2017.11.006.
72. López-Jaramillo P, González-Gómez S, Zarate-Bernal D, et al. Polypill: an affordable strategy for cardiovascular disease prevention in low–medium-income countries. *Ther Adv Cardiovasc Dis* 2018; 12:169-174.
73. Brainin M, Feigin V, Martins S, et al. Cut stroke in half: Polypill for primary prevention in stroke. *Int J Stroke* 2018; 13:633-647.

Box: Actions for Primary Prevention in Stroke

- Given the immense and increasing burden of stroke and dementia - especially in low- to middle-income countries (LMIC) - **cost-effective primary stroke preventative strategies** have to be found and implemented worldwide. Such strategies may include population-specific prevention or governmental-based strategies (e.g. via taxation) that address unhealthy behavior.
- Risk factor interventions and medications have to be **affordable and easily accessible**
- Given the reciprocal links between **cerebrovascular disease and dementia**, interventions to prevent stroke should go hand-in-hand with interventions to prevent dementia
- A **population-wide strategy**, independent of stroke risk, is the most effective primary prevention strategy and does also target other non-communicable diseases that share common risk factors with stroke.
- A **polypill strategy** containing generic low-dose ingredients of blood pressure lowering medications and statins to reduce the risk of stroke and cognitive decline (e.g. candesartan 16 mg, amlodipine 2.5 mg and rosuvastatin calcium 10 mg) is a safe approach to improve adherence to medications and has been shown to lower systolic blood pressure as well as low-density lipoprotein cholesterol.
- A motivational population-wide strategy should target **modification of lifestyle** (poor diet, smoking, physical activity). Critical elements of effective behavioral interventions are based on principles of cognitive behavioral therapy, including behavioral motivation, goal-setting and empowering. Education should include self-efficacy, basic understanding of stroke, its risk factors and measures required for prevention. Interventions have to be population-specific and culturally adapted.
- **Mobile health technologies** (e.g. smartphone apps), electronic health tools and social media should be included for risk factors screening and serve as interface for behavioral interventions because they are accessible to the majority of people, even in LMICs.
- **Community health workers** should be involved as link between communities and the health and social services systems. Especially in resource poor areas they can reduce inequities in access to health care and serve as peer support thereby improving lifestyle changes, adherence to medication as well as health outcomes. The WHO technical package for CVD management in primary health care offers practical tools for team-based care and teaching material for trainers in healthy-lifestyle counselling.
- **Clinical field trials** including an initiative for a large randomized controlled trial have to be carried out to test the efficacy and cost-effectiveness of an integrative approach of these primary prevention strategies.

Figure. Multi-level interventions of community health workers, polypill, and e-Health applications to reduce stroke incidence by 50%.

