# *Selected Summaries*

## Polypill for primary prevention in individuals with intermediate risk for cardiovascular disease

Yusuf S, Joseph P, Dans A, Gao P, Teo K, Xavier D, López-Jaramillo P, Yusoff K, Santoso A, Gamra H, Talukder S, Christou C, Girish P, Yeates K, Xavier F, Dagenais G, Rocha C, McCready T, Tyrwhitt J, Bosch J, Pais P, for the International Polycap Study 3 Investigators. (The Population Health Research Institute, McMaster University and Hamilton Health Sciences, Hamilton, Ontario, Queen's University, Kingston, Ontario, and Université Laval Institut Universitaire de Cardiologie et de Pneumologie de Québec, Quebec—all in Canada; the University of the Philippines, Manila; St John's Medical College, Bengaluru, India; Fundación Oftalmológica de Santander, Universidad de Santander, Bucaramanga, Colombia; Universiti Teknologi MARA Selayang, Selangor, and UCSI University, Cheras, Kuala Lumpur—both in Malaysia; Universitas Indonesia, National Cardiovascular Center, Jakarta; Fattouma Bourguiba Hospital and University of Monastir, Monastir, Tunisia; and Eminence, Dhaka, Bangladesh.) Polypill with or without aspirin in persons without cardiovascular disease. *N Engl J Med* 2021;**384:**216–28.

SUMMARY

Polypill, comprising multiple cardioprotective medications, has been proposed to lower cardiovascular disease (CVD) among intermediate-to-high risk individuals. The International Polycap Study 3 (TIPS-3) was a randomized factorial design placebo-controlled trial done to study the impact of polypill and aspirin individually and in combination. The polypill comprised 40 mg of simvastatin, 100 mg of atenolol, 25 mg of hydrochlorothiazide and 10 mg of ramipril. Aspirin was administered at a dose of 75 mg per day. Patients without CVD having intermediate risk for CVD based on the INTERHEART risk score were included in the trial. Follow-up was at 6 weeks, at 3, 6, 9 and 12 months and every 6 months after that till the end of the trial. A total of 5713 participants underwent randomization between 30 July 2012 and 12 August 2017. Almost half the patients were from India. The mean age of the participants was 64 years, and approximately half of them were women. The mean follow-up was for 4.6 years. Discontinuation of polypill and aspirin was roughly 40%, much more than the anticipated 20% in the study design. The reasons were due to side-effects and more commonly related to administrative barriers to drug distribution and then the Covid-19 pandemic. In the polypill arm, major cardiovascular events plus heart failure, resuscitated cardiac arrest and arterial revascularization (primary outcome) occurred in 4.4% of individuals compared to 5.5% in the placebo group (hazard ratio 0.79; 95% confidence interval [CI] 0.63–1.00). Death from cardiovascular causes, myocardial infarction or stroke (primary outcome for aspirin arm) occurred in 4.1% in the aspirin group and 4.7% in the placebo group (hazard ratio 0.86; 95% CI 0.67–1.10). The primary outcome for the polypill plus aspirin group (major cardiovascular events plus heart failure, resuscitated cardiac arrest or arterial revascularization) occurred in 4.1% of individuals compared to 5.8% in the double-placebo group (hazard ratio 0.69; 95% CI 0.50–0.97). Thus, polypill plus aspirin led to a 31% lower relative risk of cardiovascular events with discontinuation rates due to side-effects similar to the placebo arm.

COMMENT

The prevalence of CVD worldwide is estimated to be 422.7 million, and it causes approximately 18 million deaths per year, most of which are in low- and middle-income countries.[1,2] In India, too, CVD is the leading cause of mortality. This is due to the high cardiovascular risk burden and poor control of these risk factors.[3] Polypill is proposed as an important strategy to reduce CVD risk and improve management of hypertension and dyslipidaemia. This was postulated more than 15 years ago with the hope that it would reduce cardiovascular events by more than 80%.[4] However, to date, its uptake in clinical practice remains low—one of the reasons being inadequate evidence of its benefit. The TIPS-3 trial helps bridge that gap with proof for primary prevention. Among other studies with polypill, the UMPIRE trial, which included 2004 participants with CVD or high risk for CVD, showed significant improvement in adherence and marginal improvement in blood pressure and low-density lipoprotein-cholesterol control with the use of polypill.[5] The other long-term polypill study, The PolyIran study included 6838 participants from Iran and followed them up for 5 years.[6] The study used hydrochlorothiazide 12.5 mg, aspirin 81 mg, atorvastatin 20 mg and enalapril 5 mg or valsartan 40 mg (in those who developed cough). Akin to TIPS-3, it showed that once-daily polypills reduced the risk of major cardiovascular events in both those with and without CVD. The effect was more pronounced in participants with high adherence to the polypill.

Thus, the cumulative evidence for clinical benefit of polypill has built up with the TIPS-3 study and should help improve the uptake of this strategy as a CVD prevention therapy. However, additional factors that seem to limit the uptake of polypill include lack of scope of drug titration, discontinuation of all medicines in case of intolerance to any one and low acceptability among physicians.[7] These barriers may be largely overcome by expanding the menu with multiple polypills with different agents at varied dosages. The polypill used in TIPS-3 included high doses of atenolol, thiazide and statin—all diabetogenic agents[8] and thus an unsuitable polypill for Indians, who are prone to diabetes. The vibrant pharmaceutical industry in India makes it possible to have diverse polypills tailored to various needs. This needs to be encouraged through its wider use by physicians and the initiation of its use by government health centres. The polypill distribution through government health centres would benefit millions of those with CVD and its risk factors and help economise costs with bulk purchase.

Control of risk factors and improvement in lifestyle factors such as cessation of tobacco use, enhanced physical activity and healthy diet have been shown to reduce CVD mortality by over two-thirds in the western world.[9] The time is ripe to implement the same in India to help reduce the burgeoning CVD risk. Polypill may be one of the useful tools in this battle.

*Conflicts of interest.* None declared

REFERENCES

1 Roth GA, Johnson C, Abajobir A, Abd-Allah F, Abera SF, Abyu G, *et al*. Global, regional, and national burden of cardiovascular diseases for 10 causes, 1990 to 2015. *J Am Coll Cardiol* 2017;**70:**1–25.
2 Murray CJ, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C, *et al*. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: A systematic analysis for the global burden of disease study 2010. *Lancet* 2012;**380:**2197–223.
3 India State-Level Disease Burden Initiative CVD Collaborators. The changing patterns of cardiovascular diseases and their risk factors in the states of India: The global burden of disease study 1990–2016. *Lancet Glob Health* 2018;**6:**e1339–51.
4 Wald NJ, Law MR. A strategy to reduce cardiovascular disease by more than 80%. *BMJ* 2003;**326:**1419.
5 Thom S, Poulter N, Field J, Patel A, Prabhakaran D, Stanton A, *et al*. Effects of a fixed-dose combination strategy on adherence and risk factors in patients with or at high risk of CVD: The UMPIRE randomized clinical trial. *JAMA* 2013;**310:**918–29.
6 Roshandel G, Khoshnia M, Poustchi H, Hemming K, Kamangar F, Gharavi A, *et al*. Effectiveness of polypill for primary and secondary prevention of cardiovascular diseases (PolyIran): A pragmatic, cluster-randomised trial. *Lancet* 2019;**394:**672–83.
7 Roy A, Naik N, Srinath Reddy K. Strengths and limitations of using the polypill in cardiovascular prevention. *Curr Cardiol Rep* 2017;**19:**45.
8 Grodzinsky A, Arnold SV, Jacob D, Draznin B, Kosiborod M. The impact of cardio-vascular drugs on glycemic control: A review. *Endocr Pract* 2017;**23:**363–71.
9 Unal B, Critchley JA, Capewell S. Explaining the decline in coronary heart disease mortality in England and Wales between 1981 and 2000. *Circulation* 2004; **109:**1101–7.

SATYAVIR YADAV
AMBUJ ROY
*Department of Cardiology*
*All India Institute of Medical Sciences*
*New Delhi*
*India*
*drambujroy@gmail.com*

## Antenatal dexamethasone for early preterm birth in low-resource countries

Oladapo OT, Vogel JP, Piaggio G, Nguyen M-H, Althabe F, Gülmezoglu AM, Bahl R, Rao SPN, De Costa A, Gupta S, Baqui AH, Khanam R, Shahidullah M, Chowdhury SB, Ahmed S, Begum N, Roy AD, Shahed MA, Jaben IA, Yasmin F, Rahman MM, Ara A, Khatoon S, Ara G, Akter S, Akhter N, Dey PR, Sabur MA, Azad MT, Choudhury SF, Matin MA, Goudar SS, Dhaded SM, Metgud MC, Pujar YV, Somannavar MS, Vernekar SS, Herekar VR, Bidri SR, Mathapati SS, Patil PG, Patil MM, Gudadinni MR, Bijapure HR, Mallapur AA, Katageri GM, Chikkamath SB, Yelamali BC, Pol RR, Misra SS, Das L, Nanda S, Nayak RB, Singh B, Qureshi Z, Were F, Osoti A, Gwako G, Laving A, Kinuthia J, Mohamed H, Aliyan N, Barassa A, Kibaru E, Mbuga M, Thuranira L, Githua NJ, Lusweti B, Ayede AI, Falade AG, Adesina OA, Agunloye AM, Iyiola OO, Sanni W, Ejinkeonye IK, Idris HA, Okoli V, Irinyenikan TA, Olubosede OA, Bello O, Omololu OM, Olutekunbi OA, Akintan AL, Owa OO, Oluwafemi RO, Eniowo IP, Fabamwo AO, Disu EA, Agbara JO, Adejuyigbe EA, Kuti O, Anyabolu HC, Awowole IO, Fehintola AO, Kuti BP, Isah AD, Olateju EK, Abiodun O, Dedeke OF, Akinkunmi FB, Oyeneyin L, Adesiyun O, Raji HO, Ande ABA, Okonkwo I, Ariff S, Soofi SB, Sheikh L, Zulfiqar S, Omer S, Sikandar R, Sheikh S, Giordano D, Gamerro H, Carroli G, Carvalho J, Neilson J, Molyneux E, Yunis K, Mugerwa K, Chellani HK. (Department of Maternal, Newborn, Child, Adolescent Health and Ageing, World Health Organization, Geneva, Switzerland; Johns Hopkins Bloomberg School of Public Health, Baltimore, USA; Bangabandhu Sheikh Mujib Medical University, Projahnmo Research Foundation, Institute of Child and Mother Health, Center for Woman and Child Health, and Enam Medical College and Hospital, Dhaka, and Sylhet Muhammad Ataul Gani Osmani Medical College Hospital, Jalalabad Ragib–Rabeya Medical College Hospital, and Sylhet Women's Medical College Hospital, Sylhet—both in Bangladesh; KLE Academy of Higher Education and Research, Jawaharlal Nehru Medical College, Belagavi, Shri B.M. Patil Medical College, Vijayapura, S. Nijalingappa Medical College, Bagalkot, Srirama Chandra Bhanja Medical College, Cuttack, and Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi—all in India; University of Nairobi and Kenyatta National Hospital, Nairobi, Coast Provincial General Hospital, Mombasa, Nakuru Level 5 Hospital, Nakuru, Kiambu Level 5 Hospital, Kiambu, and Thika Level 5 Hospital, Thika—all in Kenya; the College of Medicine, University of Ibadan, and University College Hospital, Ibadan, Kubwa General Hospital, Kubwa, Nyanya General Hospital, Nyanya, State Specialist Hospital and Mother and Child Hospital, Akure, Lagos Island Maternity Hospital, and Lagos State University Teaching Hospital, Lagos, Obafemi Awolowo University, Ile-Ife, University of Abuja, Abuja, Sacred Heart Hospital, Abeokuta, Mother and Child Hospital, Ondo, University of Ilorin, Ilorin, and University of Benin, Benin City—all in Nigeria; Aga Khan University, Karachi, Sheikh Zayed Medical College and Hospital, Rahim Yar Khan, and Liaquat University Hospital, Hyderabad—all in Pakistan; Centro Rosarino de Estudios Perinatales, Rosario, Argentina; Statistika Consultoria, Campinas, Brazil; University of Liverpool, Liverpool, United Kingdom; College of Medicine, University of Malawi, Blantyre; American University of Beirut, Beirut, Lebanon; and the Makerere University College of Health Sciences, Kampala, Uganda.) Antenatal dexamethasone for early preterm birth in low-resource countries. *N Engl J Med* 2020;**383:**2514–25.

SUMMARY

The WHO Antenatal Corticosteroids for Improving Outcomes in preterm Newborns (ACTION-I) trial is a randomized study that investigated the safety and efficacy of antenatal steroid, dexamethasone, among women at risk of preterm birth in low- and middle-income countries (LMICs). A total of 2852 women between 26 weeks 0 days and 33 weeks 6 days of gestation from 29 secondary- and tertiary-level hospitals across five LMICs—Bangladesh, India, Kenya, Nigeria and Pakistan—were randomized to receive intramuscular dexamethasone at a dose of 6 mg every 12 hours for four doses or an identical placebo if preterm birth was expected in the next 48 hours. Eligible women were assessed by obstetric care providers and gestational age was confirmed using ultrasonographic examination performed in early gestation or at presentation. Women with clinical signs of severe infection, major congenital foetal anomalies and those with previous use or contraindication to systemic glucocorticoids were excluded from the study. One repeat course (identical to initial