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A:CARE CONGRESS 2024

Non-adherence without borders: Cross-continent perspectives and local realities

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NON-ADHERENCE WITHOUT BORDERS Clinician's point of view

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I received speaker honorarium from Abbott, AstraZeneca, Boehringer Ingelheim, Sanofi, GSK, Amgen, Bayer, Daiichi.

ASCVD is a chronic progressive disease

Appropriate treatment and risk factor control are crucial Cardiovascular events Time

ASCVD: Atherosclerotic cardiovascular disease

Visseren FLJ, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J. 2021 Sep 7;42(34):3227-3337 ; 2. Steinl DC and Kaufmann BA. Ultrasound Imaging for Risk Assessment in Atherosclerosis. Int. J. Mol. Sci. 2015, 16, 9749-9769



Appropriate treatment and risk factor control reduce CV events

Specific treatment

- Antiplatelets
- Coronary revascularization
- GDMT for HF

Risk factor control

- Diabetes
 - Hypertension
- Dyslipidemia
- Smoking
- **Obesity**
- Physical inactivity

CV: Cardiovascular ; GDMT : Guideline-directed medical therapy; HF: Heart failure.

Visseren FLJ, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J. 2021 Sep 7;42(34):3227-3337.

Guidelines recommend for risk factors control



1. Mancia G, et al. 2023 ESH Guidelines for the management of arterial hypertension. J of Hypertension 2023, Diabetes Care 2024;47(Suppl. 1):S158–S178 ; 2. Virani SS, et al. 2023 AHA/ACC/ACCP/ASPC/NLA/PCNA Guideline for the Management of Patients With Chronic Coronary Disease: A Report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. Circulation. 2023;148(9):e9-119 ; 3. Mach F. et al, ESC Scientific Document Group , 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk: The Task Force for the management of dyslipidaemias of the European Acterosciety (EAS), European Heart Journal. 2020;41(1): 111–188 ; 4. ElSayed N. et al, on behalf of the American Diabetes Association 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes Care. 2023;46(Suppl 1):S140-S157.

Real world study demonstrated the suboptimal management of ASCVD risk factors

Core-Thailand registry: cohort of Thai patients with high ASCVD risk (9390 patients) including patients with established ASCVD and patients with multiple risk factors



ASCVD: Atherosclerotic cardiovascular disease; BP: Blood pressure; DBP: Diastolic blood pressure; EAD: Established atherosclerotic disease; HbA1c: Hemoglobin A1c; MRF: Multiple risk factors; SBP: Systolic blood pressure. Phrommintikul A, et al. Management of atherosclerosis risk factors for patients at high cardiovascular risk in real-world practice: a multicenter study. Singapore Med J. 2017;58(9):535-542.

Real world study demonstrated the suboptimal management of ASCVD risk factors in coronary artery disease

CORE-Thailand Registry: Cohort of Thai patients with high ASCVD risk (9390 patients) including patients with established ASCVD and patients with multiple risk factors

EUROASPIRE V: A cross-sectional ESC-EORP survey at 131 centers in 81 regions in 27 countries in patients (<80 years) with CV events or interventions



ASCVD: Atherosclerotic cardiovascular disease; BP: Blood pressure; DBP: Diastolic blood pressure; HbA1c: Hemoglobin A1c; SBP: Systolic blood pressure.

1. Phrommintikul A, et al. Management of atherosclerosis risk factors for patients at high cardiovascular risk in real-world practice: a multicenter study. Singapore Med J. 2017;58(9):535-542 ; 2. De backer et al. Management of dyslipidaemia in patients with coronary heart disease: Results from the ESC-EORP EUROASPIRE V survey in 27 countries. Atherosclerosis. 2019;285:135-146

Factors associated with suboptimal treatment



Świątoniowska et al. Psychosocial determinants of treatment adherence in patients with type 2 diabetes-a review. Diabetes, Metabolic Syndrome and Obesity. 2021: 2701-2715.

Persistence to cardiovascular medicines significantly declines following initiation

Using Australian national dispensing

Adults (\geq 18years) initiating antihypertensives, statins, oral anticoagulants, or antiplatelets in 2018.



De Oliveira Costa J, et al. Persistence and Adherence to Cardiovascular Medicines in Australia. Journal of the American Heart Association. 2023;12(13):e030264.

Poor adherence is dose-dependently associated with significantly increased risk of cardiovascular events and all-cause mortality in patients with CAD

Countries involved: Canada, China, Finland, France, Israel, Italy, UK and USA



Dose–response relationship (linear and nonlinear) of cardiovascular medication adherence and cardiovascular events. The solid line and the dashed lines represent the estimated relative risk and the 95% confidence interval, respectively.

CAD: coronary arterial disease; CV: Cardiovascular disease.

Chen C et al. Adherence with cardiovascular medications and the outcomes in patients with coronary arterial disease: "Real-world" evidence. Clin Cardiol. 2022;45(12):1220-1228.

Impact of medication adherence on long term CV outcomes and cost

Adherence levels and MACE (Hospitalizations per 100 patient-years)

Non

Partially

Fully

- Database of a large health insurer for patients hospitalized for MI or with atherosclerotic disease in USA
- Proportion of days covered (PDC) for statin and ACE inhibitors
- · Outcome: Composite of all-cause death, MI, stroke, or coronary revascularization

Adherent	Adherent	Adherent							
				Post-MI C	ohort (Per Patier	ıt Per Year)	ATH Col	10rt (Per Patient P	er Year)
<40%	40-79%	≥80%		Non- adherent	Partially Adherent	Fully Adherent	Non- adherent	Partially Adherent	Fully Adherent
^{18.1} / 17.2			MI	\$844.46	\$774.09	\$404.64	\$396.03	\$297.02	\$181.51
			Stroke	\$178.49	\$133.87	\$89.24	\$168.62	\$116.74	\$77.82
12.	.8		Revascularization	\$3,375.21	\$3,070.50	\$2,531.41	\$1,863.60	\$1,353.33	\$1,064.91
	10.9	0	Angina and CV atherosclerosis	\$1,432.86	\$1,527.12	\$1,093.50	\$1,772.64	\$1,236.72	\$865.71
	MI Atheroscler	.9	All-cause ED visits	\$256.97	\$219.56	\$182.64	\$181.65	\$132.43	\$109.29
			Cardiac-related ED visits	\$14.77	\$12.80	\$13.29	\$10.34	\$6.89	\$4.92
			Outpatient visits to cardiologist	\$639.38	\$657.47	\$645.19	\$411.83	\$423.24	\$424.32
Post-MI		clerosis	Outpatient visits to cardiologist with CV testing	\$558.76	\$553.16	\$576.67	\$446.69	\$436.41	\$446.69

Bansilal S et al. Assessing the Impact of Medication Adherence on Long-Term Cardiovascular Outcomes. J Am Coll Cardiol. 2016;68(8):789-801.

Factors associated with low adherence to medications



1. Wilhelmsen NC, Eriksson T. Medication adherence interventions and outcomes: an overview of systematic reviews. European Journal of Hospital Pharmacy 2019;26:187-192 ; 2. Simon ST, et al. Medication adherence in cardiovascular medicine. BMJ. 2021;374:n1493.

Medication adherence and cardiovascular disease

- Effective treatment and risk factor management are crucial for preventing cardiovascular events.
- Adherence to prescribed medical therapies is a key determinant of successful risk factor control.
- Low medication adherence is linked to unfavorable cardiovascular outcomes and increased healthcare costs.
- Tackling the multifactorial causes of low adherence is essential for improving patient outcomes.







NON-ADHERENCE WITHOUT BORDERS Clinical and economic benefits of improving medication adherence

Prof. Nathorn Chaiyakunapruk Professor, College of Pharmacy, University of Utah, Salt Lake City, United States

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Background

Why medication adherence is important

Expectation vs. Reality

- Drugs will NOT show the same efficacy as in randomized clinical trial
- "Drugs don't work in patients who don't take them" by Charles Everett Koop, MD

How much & where does it matter?

Low adherence rate (<taking medication less than 80%) was reported to be less than 50% in Low and Middle Income Countries¹

What can we do?

- Pharmacist service, text message or alerting
 - Digital therapeutics

Etc.

Background

Why health economic study is important

Non-adherence underrecognized

Need to demonstrate both clinical and economic impact of improved adherence

Important information for clinicians and policy makers

Research question

What is the potential benefit of improving adherence in secondary cardiovascular diseases patients in Mexico, Thailand, and China

• These countries are representative middle income country in each geographic region, Latin America, Southeast Asia, and East Asia

Method*

Objective

To estimate benefit of improving adherence during **lifetime** using **health** economic model simulation

Can we do a clinical trial?

• Impossible to perform **lifetime** clinical trial

Impossible to have comparator arm for poor medication adherence

Simulation



CVD: Cardiovascular disease

*Full text is not yet published, only the manuscript is being presented.

Method

Overview

Health economic model simulation to estimate benefit of improving adherence during **lifetime** time horizon

Optimal adherence scenario

 Expected outcomes of lipid-lowering agents from model simulation using input from meta-analysis of RCTs and retrospective studies^{1,2}

Status quo scenario

O Current level of adherence

Mexico³ Thailand⁴ China² 50% 53% 19%

RCT: Randomized controlled trial;

1. Chaiyasothi T, et al. Effects of Non-statin Lipid-Modifying Agents on Cardiovascular Morbidity and Mortality Among Statin-Treated Patients: A Systematic Review and Network Meta-Analysis. Front Pharmacol. 2019;10:547. 2. Zhao B, et al. Adherence to statins and its impact on clinical outcomes: a retrospective population-based study in China. BMC Cardiovasc Disord. 2020;20:282 3. Morales-Villegas EC, et al. Management of hypertension and dyslipidemia in Mexico: Evidence, gaps, and approach. Arch Cardiol Mex. 2023;93:077-087. 4. Woodham N, et al. Medication adherence and associated factors among elderly hypertension patients with uncontrolled blood pressure in rural area, Northeast Thailand. Journal of Health Research. 2018;32:10.

Method

Outcomes



Result

Key findings

Result of base-case analysis from 1,000 patients in each country

Outcomes	Mexico	Thailand	China
Cardiovascular events averted			
Non-fatal CVEs	22.07	21.36	38.49
Fatal CVEs	17.91	12.67	24.47
Total CVEs	41.54	34.05	62.96
Incremental effectiveness	0.60 LY	0.59 QALYs	0.93 QALYs
Incremental direct medical costs			
Disease management cost	\$226.67	\$23.74	\$271.96
Non-fatal CVE cost	-\$401.78	-\$226.78	-\$523.05
Fatal CVE cost	-\$223.98	-\$86.63	-\$300.80
Incremental direct non-medical costs	\$2.71	\$102.66	\$9.72
Incremental indirect costs	-\$15.74	-\$31.93	-\$148.66
Incremental costs from healthcare system perspective	-\$399.09	-\$289.67	-\$551.90
Incremental costs from societal perspectives	-\$412.12	-\$218.95	-\$690.84

CVE: cardiovascular events; LY: Life Year; QALY: Quality-adjusted life year

Result

Threshold analysis

Result of threshold analyses from a societal perspective

Item	Mexico	Thailand	China
Willingness-to-pay threshold	\$11,091/LY	\$4,688/QALY	\$18,207/QALY
Direct medical costs			
Prevented CVE-related costs	\$625.76	\$313.42	\$823.85
Incremental disease management costs due to increased life years	\$226.67	\$23.74	\$271.96
Incremental direct non-medical costs	\$2.71	\$102.66	\$9.72
Incremental indirect costs	-\$13.03	-\$31.93	-\$148.66
Lifetime permissible expense for optimal adherence for cost saving	\$412.12	\$218.95	\$690.84
Annual permissible expense for optimal adherence for cost saving	\$32.58	\$14.72	\$57.75
Lifetime permissible expense for optimal adherence for cost-effectiveness	\$7,124.15	\$3,421.91	\$17,706.21
Annual permissible expense for optimal adherence for cost-effectiveness	\$563.18	\$230.00	\$1,480.02

CVE: cardiovascular events

Discussion

Key take away

Projected cost savings associated with optimal adherence were highlighted:

- This study shows consistent results with **not only cost saving but improved health outcomes** in three countries from three different geographic regions
 - Our analyses rely on several network meta-analyses to ensure **generalizability**
 - Our analyses are validated by key stakeholders to ensure **relevancy**

Most cost savings comes from prevented cardiovascular event

• The healthcare system has been suffered from **preventable** medical costs due to **poor medication adherence**

Our model provide **a platform of health economic study** on medication adherence, which allow to estimate cost-effectiveness of newly developed adherence improving interventions such as **digital applications**

Conclusion

Improving medication adherence to optimal levels in CVD patients requiring lipidlowering therapy is not only cost-saving but averting cardiovascular events and increasing life-years and quality-adjusted life years in Mexico, Thailand, and China from both societal and healthcare perspectives.

2 Our findings advocate for the consideration of strategies by national healthcare systems to improve optimal adherence (e.g., digital technologies or programs leading to behavior changes) in these countries.







NON-ADHERENCE WITHOUT BORDERS Policy maker's point of view

Dr. Miguel Angel Díaz Aguilera National Center for Preventive Programs and Disease Control, Mexico City, Mexico

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Cardiovascular diseases

Have collectively remained the leading causes of death worldwide and substantially contribute to loss of health and excess health system costs¹.



Hyperlipidemia increase the risks of heart disease and stroke; globally, a third of ischemic heart disease is due to high cholesterol².

Overall, hyperlipidemia was attributable to cause 2.6 million deaths and 29.7 million DALYS in 2019².



In 2008, the global prevalence of raised total cholesterol among adults was 39% (37% for males & 40% for females)².

Burden of comorbidities in hyperlipidemia, prevalence

1951 1951	Diabetes ³⁻⁷	16-36%
Ŗ	Hypertension ^{4-5,7}	62-98%
63	Heart failure ^{5,7-8}	4–21%

CKD4-7

1. Vaduganathan M, et al. The Global Burden ofCardiovascular Diseases and Risk. JACC. 2022;80(25): 2361-2371. 2. World Health Organization. Raised cholesterol, available at: https://www.who.int/data/gho/indicatormetadata-registry/imr-details/3236#:~:text=Raised%20cholesterol%20levels%20increase%20the,or%202%25%20of%20total%20DALYS. (consulted August 25th, 2024) 3. Bruckert E, et al. Proportion of High-Risk/Very High-Risk Patients in Europe with Low-Density Lipoprotein Cholesterol at Target According to European Guidelines: A Systematic Review Adv Ther. 2020; 37(5):1724-1736 ; 4. Steen DL, et al. Retrospective examination of lipidlowering treatment patterns in a real-world high-risk cohort in the UK in 2014: comparison with the National Institute for Health and Care Excellence (NICE) 2014 lipid modification guidelines. BMJ Open 2017;7:e013255 ; 5. Fox KM, et al. Treatment patterns and low-density lipoprotein cholesterol (LDL-C) goal attainment among patients receiving high- or moderate-intensity statins. Clin Res Cardiol. 2018; 107(5): 380–88 ; 6. Vallejo-Vaz AJ, et al. Associations between lower levels of low-density lipoprotein cholesterol and cardiovascular events in very high-risk patients: Pooled analysis of nine ODYSSEY trials of alirocumab versus control Atherosclerosis. 2019;288:85-9 ; 7. Lindh M, et al. Cardiovascular event rates in a high atherosclerotic cardiovascular disease risk population: estimates from Swedish population-based register data. Eur Heart J Qual Care Clin Outcomes. 2019;5(3):225-32 ; 8. Rashid M, et al. Impact of co-morbid burden on mortality in patients with coronary heart disease, heart failure, and cerebrovascular accident: a systematic review and meta-analysis Eur Heart J Qual Care Clin Outcomes. 2017; 3(1):20-36

3-24%

Poor/no adherence to medications

Despite numerous medical advances and new drug launches, the **management of various chronic diseases has not improved**, driven primarily by lack of adherence to treatments. Affects approximately half of the patient population, leading to severe health complications, premature deaths, and an increased use of healthcare services.

The three most prevalent chronic conditions – diabetes, hypertension, and hyperlipidemia – stand out regarding the magnitude of avoidable health complications, mortality, and healthcare costs.

Broad reasons behind these low rates of adherence to chronic disease medications

- The problem of poor/no adherence has rarely been explicitly included in national health policy agendas.
- Interventions tend to attribute the problem exclusively to patients, while the evidence suggests that health/social-care organization characteristics – in particular, the quality of patient-provider interaction, procedures for refilling prescriptions, or out-of-pocket costs – are lead drivers.
- Patients with chronic conditions frequently feel left out of the decision about their therapy and are inclined to rebuff.

Khan, R. and K. Socha-Dietrich. Investing in medication adherence improves health outcomes and health system efficiency: Adherence to medicines for diabetes, hypertension, and hyperlipidaemia. OECD Health Working Papers. 2018 No. 105, OECD Publishing.

Medication adherence initiatives identified from the survey responses – Organisation for Economic Co-operation and Development (OECD) countries

Country	Routine monitoring of adherence at a national level	Studies assessing non- adherence rates, drivers and impact on health outcomes and costs	Interventions to promote adherence		
Australia	No	Yes	PDI, DTI		
Belgium	No	Yes	No		
Canada	No	Yes	PDI		
Czech Rep.	No	No	No		
Estonia	No	Not reported	Not reported		
France	No	Yes	PDI		
Hungary	No	Yes	PDI		
Iceland	No	No	No		
Israel	Not at a national level, but at physician level	Yes	PDI, DTI		
Japan	No	Yes	PDI		
Korea	No	Yes	No		
Latvia	No	No	No		
Norway	No	Yes	DTI, PDI		
Poland	No	Work-in-progress	IC (PDI is planned)		
Portugal	No	Yes	IC		
Slovenia	Not at a national level, but at physician level	Yes	PDI		
Sweden	Yes	Not reported	Not reported		
Switzerland	No	No	PDI		
Turkey	Not at a national level, but at physician level	Yes	PDI		
United Kingdom	No	Yes	PDI, IC, DTI		
United States	Not at national level, but at Centre for Medicare and Medicaid level	Yes	PDI, IC, DTI		

Key: PDI - Provider delivered intervention with financial incentives for the providers. **IC** -Public information/education campaigns targeting patients **DTI** - Data & technology infrastructure.

Current spend of health & potential benefits of improving adherence in CVD patients

Country	Current Health Expenditure pe (Current US\$)¹	Government Healt capita (Curr	er Out of po	Out of pocket Health Expenditure per capita (Current US\$) ¹				
China	\$671 (5.38% GPD)	\$363 (2.92		\$231 (34.3% CHE)				
Mexico	\$611 (6.08% GPD)		\$304 (3.05		\$253 (41.3% CHE)			
Thailand	nailand \$364 (5.16% GPD)		\$671 (5.38% GPD)			\$33 (9.04% CHE)		
This study shows that patients who achieve optimal adherence can prevent CVD episodes ²		1	Incremental effectiveness per patient ²		Cost savings per patient with optimal adherence ²			
63 in China	4034in Mexicoin Thailand	0.60 life-y in Mexi	ears 0.59 QALYs in co Thailand	0.93 QALYs in China	\$700 for China	\$412 for Mexico	\$316 for Thailand	

The most relevant benefit of improving medication adherence in CVD patients was the improvement in health outcomes in all 3 countries, in addition to the cost savings obtained

GPD: Gross domestic product; CHE: Current health expenditure

The values shown on this slide reflect the speaker's interpretation of the data published in the references: 1. World Health Organization Global Health Expenditure database (https://apps.who.int/nha/database/country_profile/Index/en). The data was retrieved on August 06, 2024 ; 2. Cho JY, et al. Projected Cost Savings with Optimal Medication Adherence in Cardiovascular Disease Patients Requiring Lipid Lowering Therapy: a Multi-National Economic Evaluation Study. JAHA 2024. Manuscript in Press

Adherence as a health public policy



A recent OECD report points to the fact that medication adherence is a measure of quality and effectiveness of the entire healthcare system



In such a case, **all policymakers should direct their attention towards it**



If **adherence leads to savings of payer organizations**, they have clear incentives to improve it

Hence, the communities, which directly and indirectly benefit from adherence, should use their power to make all these stakeholders truly involved in bettering adherence

Khan, R. and K. Socha-Dietrich. Investing in medication adherence improves health outcomes and health system efficiency: Adherence to medicines for diabetes, hypertension, and hyperlipidaemia. OECD Health Working Papers. 2018 No. 105, OECD Publishing.

Non-adherence factors related to the healthcare system or equipment

No national or local programs have been created to eliminate or reduce barriers of therapeutic adherence, since the medical guidelines for treating chronic diseases are based mainly on pharmacological treatments, controlled diet and recommendations on a healthy lifestyle¹

The consequence of not addressing these diseases in a comprehensive manner is an increase in the prevalence of these diseases, affecting those who suffer from it with a poor quality of life and premature death¹

- Health centers with inadequate infrastructure and deficient resources²
- Underpaid and overworked health personnel leading to short consultations lacking in quality and warmth²
- Inadequately trained health personnel lack of knowledge about adherence and effective interventions to improve adherence²

Lack of adherence has been shown to be associated with an increase in number of hospitalizations among patients, which has an impact on the increased cost of health care resources, as well as on health care personnel burnout.

1. Reyes RM. Therapeutic adherence in patients with chronic non-communicable diseases: diabetes, hypertension and obesity. Medicina y Etica. 2021;32(4): 923-945 ; 2. Ortega Cerda, et al. Therapeutic adherence: a health care problem. Acta méd. Grupo Ángeles. 2018;16(3):226-232.

Innovative medication adherence solutions

Technological innovation offer a multitude of options to enhance medication adherence

In particular, fast digitization of the healthcare sector creates fertile grounds for assessing and modifying suboptimal drug taking

Solutions targeting medication adherence directly Solutions targeting medication adherence indirectly Innovative drug design Telemedicine / remote consultation options 1. 1. Smart inhalers, injectors and drug packaging **Electronic prescriptions** 2. 2. Data via mobile applications for (self)monitoring Automatized prescription renewal systems 3 3. Multidose drug packaging, weekly or monthly pill organizers Decision support systems for prescribers 4. 4. Smart drug organizers and dispensers Online pharmacies and home delivery of prescription drugs 5. 5. (solution not universally supported due to varying legislation Wearable sensors 6. across countries). Automatized appointment reminding systems Big Data repositories collecting prescribing and dispensing data 6. Mobile/online applications 8.

Mobile apps can help, remind and monitor medication intake and are useful in addressing unintentional non-adherence.

Mobile/online application with gamification

10. E-Prescribing software solutions

11. Incentivizing healthcare providers

9.

Adherence & health apps

The phenomenon of apps has burst into the world of medicine, changing the paradigm of healthcare as a whole, as they allow sharing experiences in the environment that most concerns human beings, their own health, through a smartphone or tablet device

Apps are on the way to becoming an essential element in **patient empowerment** and **habit modification**, offering great potential for modifying behaviors that result in health benefits, such as promoting and controlling physical activity, diet, smoking cessation, etc.

• Furthermore, **apps have many potential uses in the doctorpatient relationship**, since they facilitate communication and the management of diseases, especially chronic diseases.

Lee Ventola. Mobile Devices and Apps for Health Care Professionals: Uses and Benefits. P&T. 2014;39(5):357-364 ;



Conclusion

1

Despite availability of effective tools, **adherence levels remain low**, and relevant evidence-based interventions are underused and this **leads to serious health and economic repercussions**

2

There is an **urgent need to change the paradigm of the healthcare**, putting adherence high enough in national agendas 3

Technical innovations may help that, provided that all the stakeholders get involved in creating an environment that will support and enhance adherence

Conclusion

4

Health apps contribute to the paradigm shift of the new medicine, which is undoubtedly aimed at empowerment of the patient, optimizing treatment and monitoring of their disease, improving compliance with all recommendations, pharmacological or nonpharmacological

5

Adherence to treatment is a key health behavior in people with chronic **diseases**, so increasing the effectiveness of adherence interventions may have a far greater impact on public health than any specific improvement in medical treatments

6

Improving adherence has the potential to **abysmally decrease costs and significantly improve the clinical condition of patients**





NON-ADHERENCE WITHOUT BORDERS: CROSS-CONTINENT PERSPECTIVES AND LOCAL REALITIES

Discussion and Q&A

Ass. Prof. Arintaya Phrommintikul

Cardiologist, Chiang Mai University, Chiang Mai, Thailand **Prof. Nathorn Chaiyakunapruk** Professor, College of Pharmacy,University of Utah, Salt Lake City, United States **Dr. Miguel Angel Díaz Aguilera** National Center for Preventive Programs and Disease Control, Mexico City, Mexico

