Impact of the Polypill Approach in the Efficacy and Safety of Trinomia®: Post-marketing Pharmacovigilance Data After 3-years

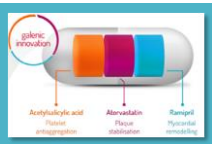
9th International Conference and Exhibition on Pharmacovigilance & Drug Safety
July 17-18, 2017 Munich, Germany

Jorge González Borroto, PhD.
Senior Toxicologist/Pharmacovigilance Officer
Pharmacovigilance Department / Scientific Area
Ferrer Internacional S.A., Barcelona, Spain

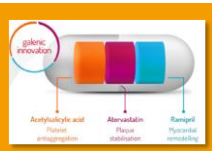
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OBJECTIVES OF THE PRESENTATION

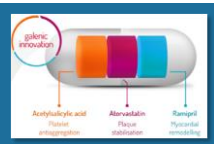


REVIEW OF IMPORTANT DATA RELATED WITH THE DRUG DEVELOPMENT PROCESS



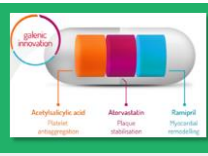
DATA OF EPIDEMIOLOGY CARDIOVASCULAR DISEASE (CVD)

COST FOR HEALTHCARE SYSTEMS



POLYPILL-CONCEPT:

TRINOMIA EFFICACY IN ADHERENCE FOR MANAGEMENT OF CVD



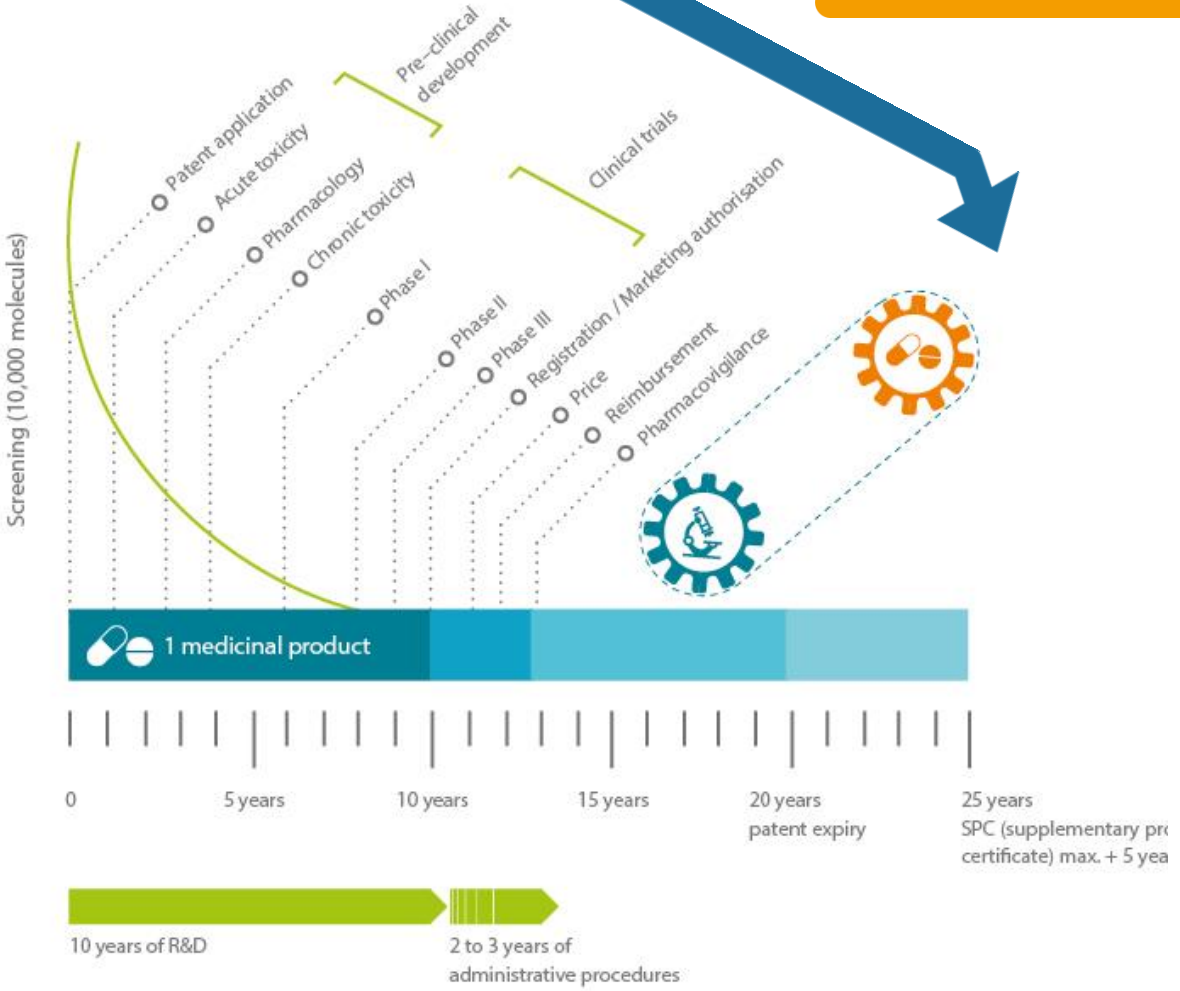
PHARMACOVIGILANCE SAFETY DATA OF TRINOMIA AFTER THREE YEARS IN THE MARKET

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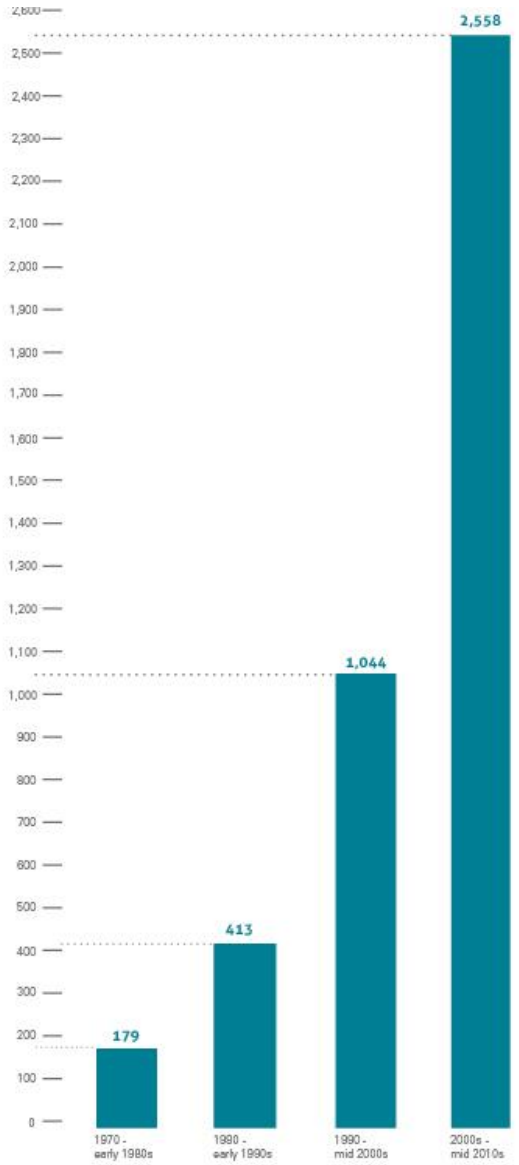
DRUG DEVELOPMENT PROCESS

HIGH TIME CONSUMING

HIGH COST



Estimated full cost of bringing a new chemical or biological entity to market ($ Million, year 2013 $)

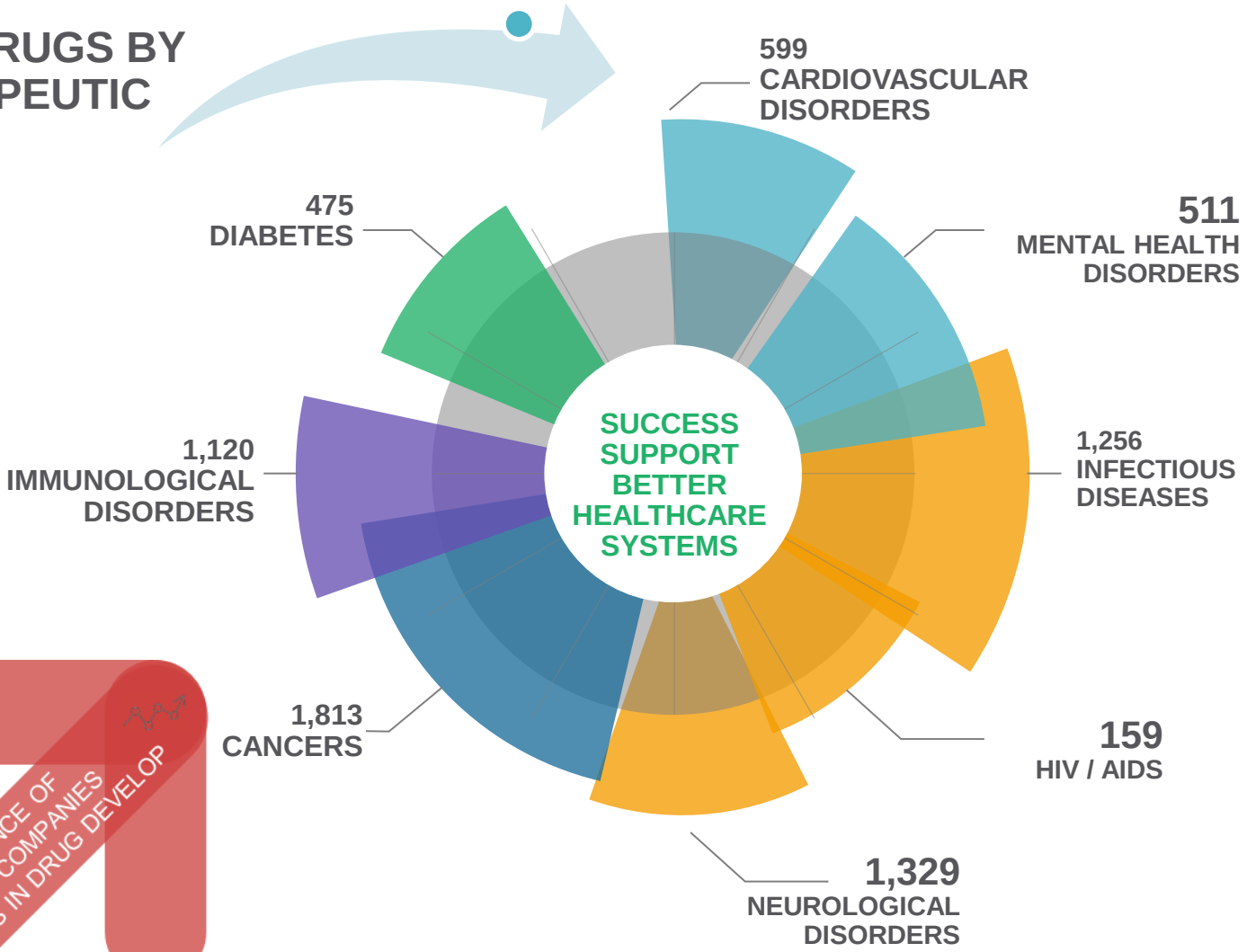


EFPIA-website:
Source: Joseph A. DiMasi, Henry G. Grabowski, Ronald W. Hansen, Innovation in the pharmaceutical industry: New estimates of R&D costs, Journal of Health Economics, 47 (2016), 20-33

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With over 7000 medicines in Development, the exciting new wave of medical innovation will play a key role in addressing the challenges faced by patients and healthcare systems

NEW DRUGS BY THERAPEUTIC AREAS



RELEVANCE OF PHARMA COMPANIES STRATEGIES IN DRUG DEVELOP

Source: SCRIP – EFPIA-website

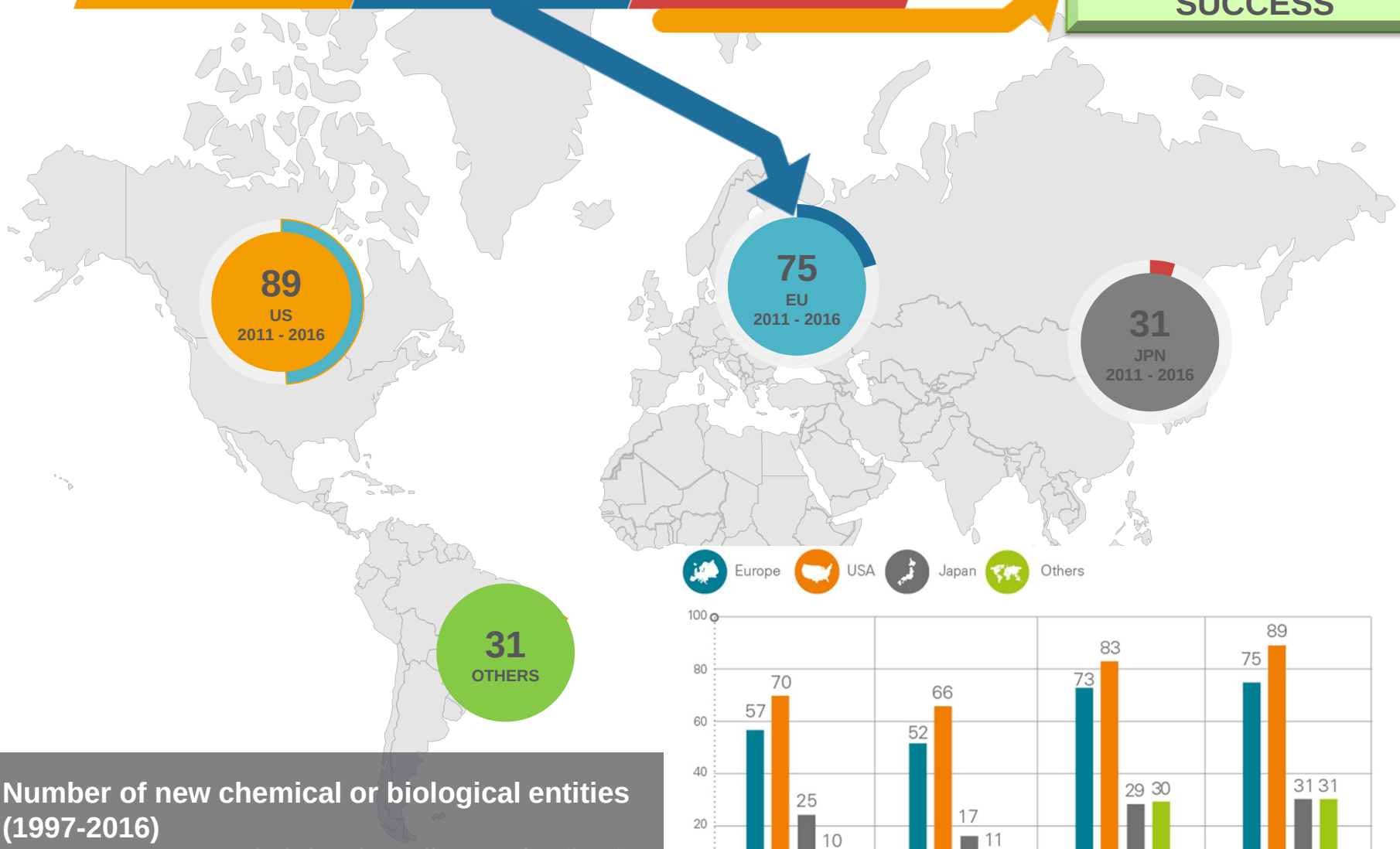
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DRUG DEVELOPMENT PROCESS

HIGH TIME CONSUMING

HIGH COST

PHAMA COMPANIES NEED THE BETTER STRATEGY FOR SUCCESS



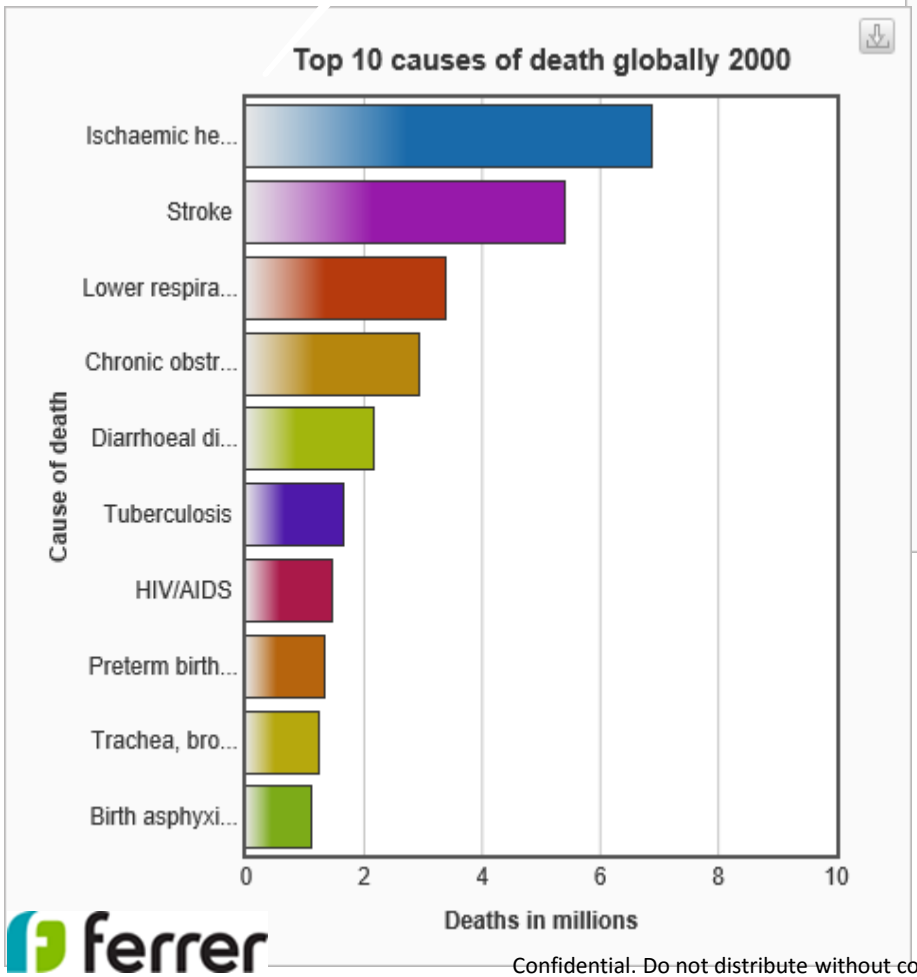
Number of new chemical or biological entities (1997-2016)

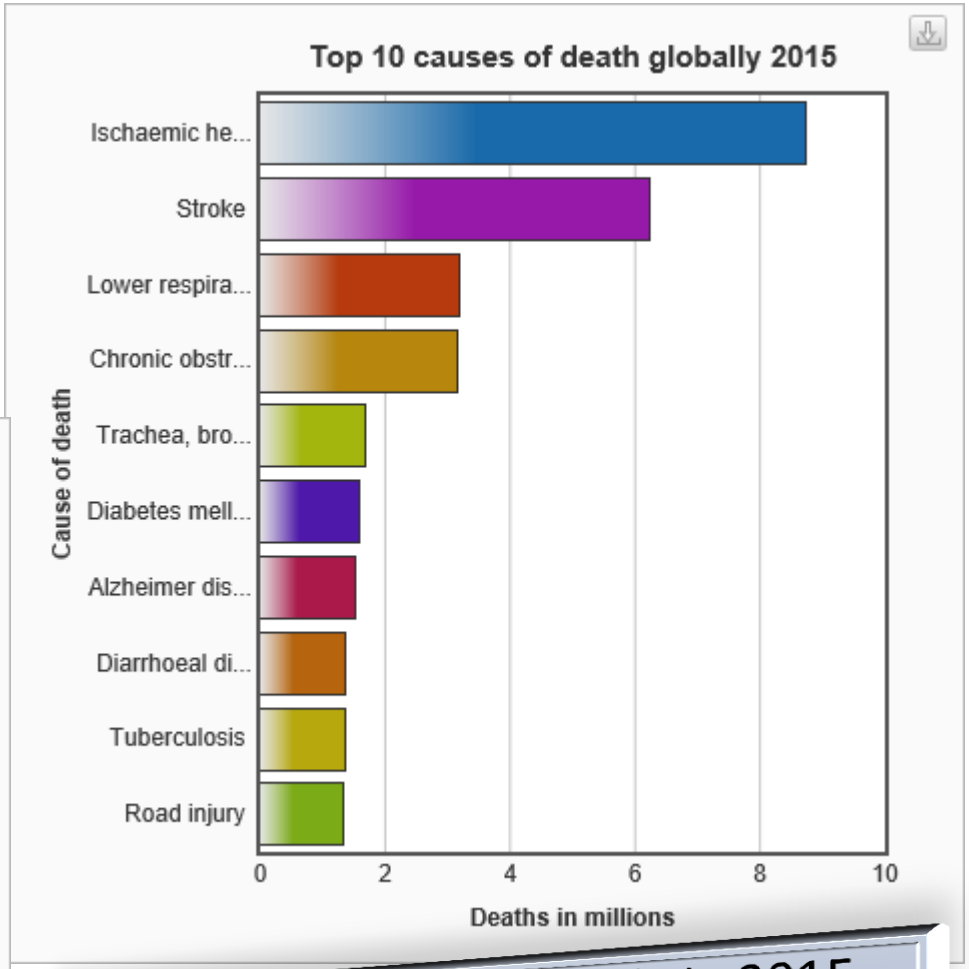
Source: SCRIP - EFPIA calculations (according to nationality of mother company)

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Healthcare Systems
Needs Efficacy to cover
Patients requirements in several therapeutic areas

Progress in 15-years



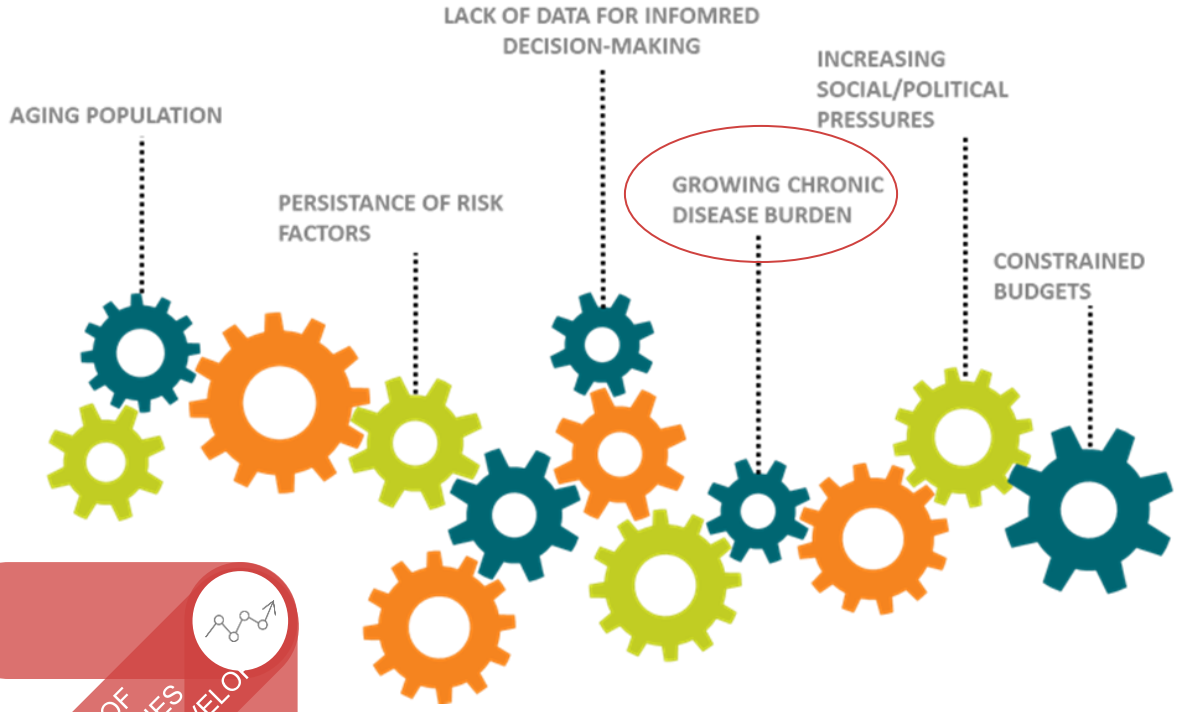


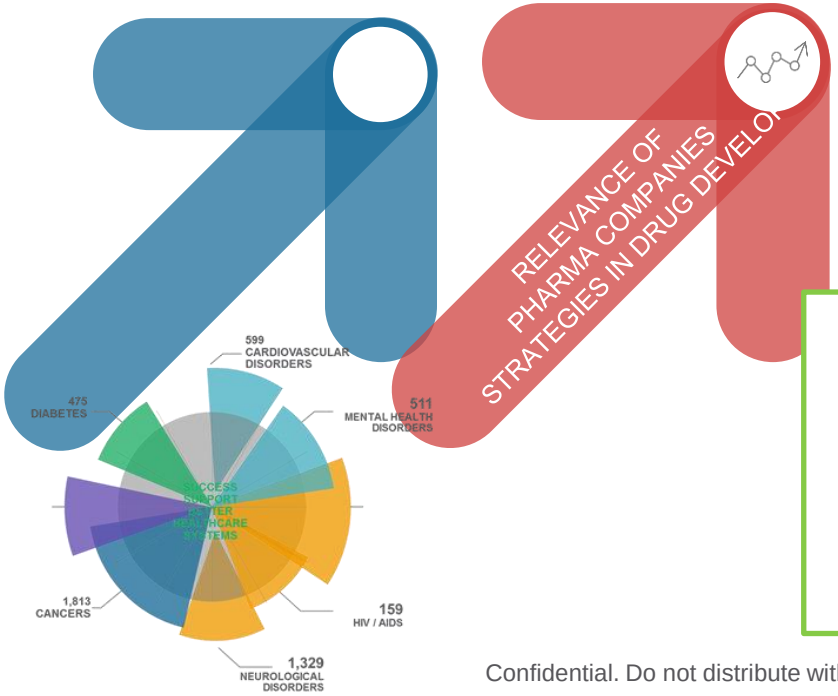
Of the 56.4 million deaths worldwide in 2015, more than half (54%) were due to the top 10 causes. **Ischaemic heart disease and stroke** are the world's biggest killers, accounting for a combined **15 million deaths** in 2015.

Source: *World Health Organization (media center-Jan 2017)*

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Healthcare systems face significant challenges in expanding access to healthcare while managing constrained budgets





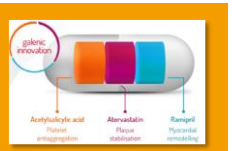
PHARMA COMPANIES HAVE GREAT RELEVANCE / RESPONSIBILITIES TO SUPPORT BETTER HEALTHCARE SYSTEMS

SUCCESSFUL STRATEGIES IN DRUG DEVELOPMENT ARE HIGHLY REQUIRED

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OBJECTIVES OF THE PRESENTATION



DATA OF EPIDEMIOLOGY CARDIOVASCULAR DISEASE (CVD)

COST FOR HEALTHCARE SYSTEMS

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EPIDEMIOLOGY DATA OF CARDIOVASCULAR DISEASES

CVDs ARE THE MAIN CAUSES OF DEATH WORLDWIDE

Of 56.4 million deaths worldwide in 2015

15 Milions CVDs



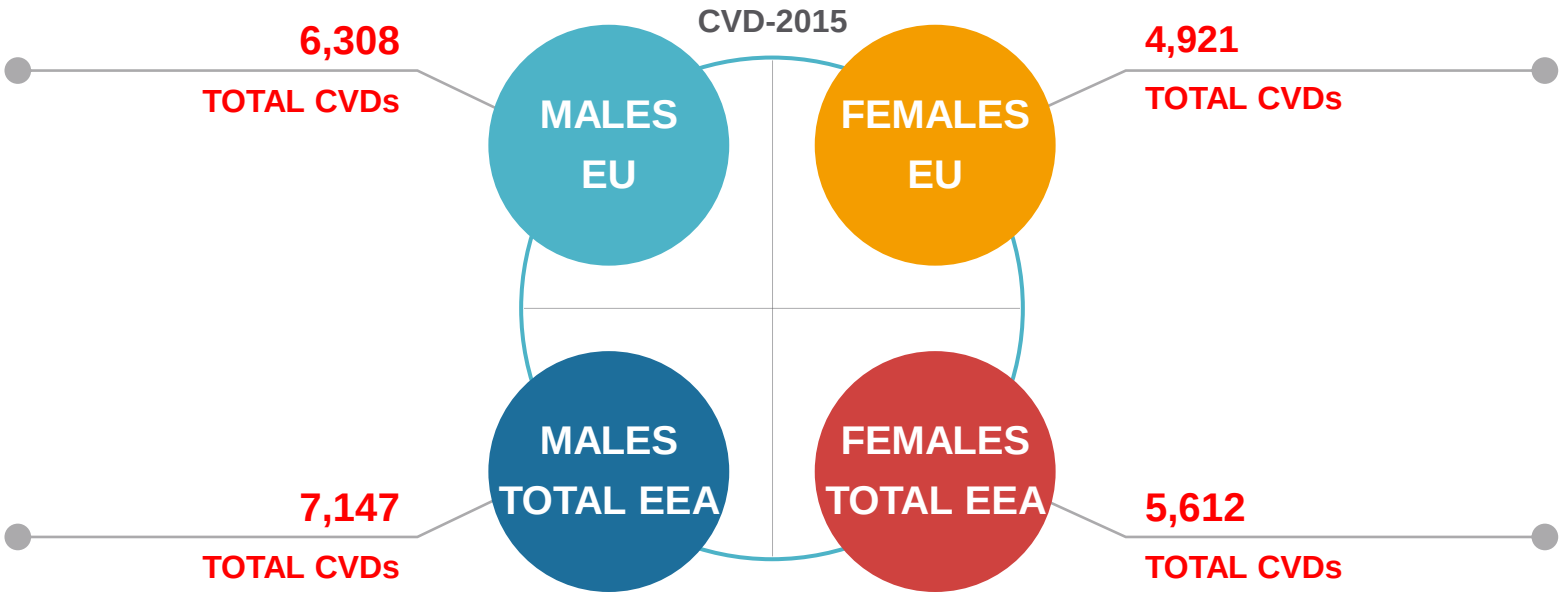
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Castellano JM et al. J Am Coll Cardiol. 2014 Aug 12;64(6):613-621

Prevalence Rates of Cardiovascular Diseases, by sex, 2015, Europe

Ischaemic heart disease, Stroke, Peripheral Vascular Disease, Other CVD, Atrial Fibrillation

Age-standardised prevalence rate per 100,000



Incidence and prevalence are significant:

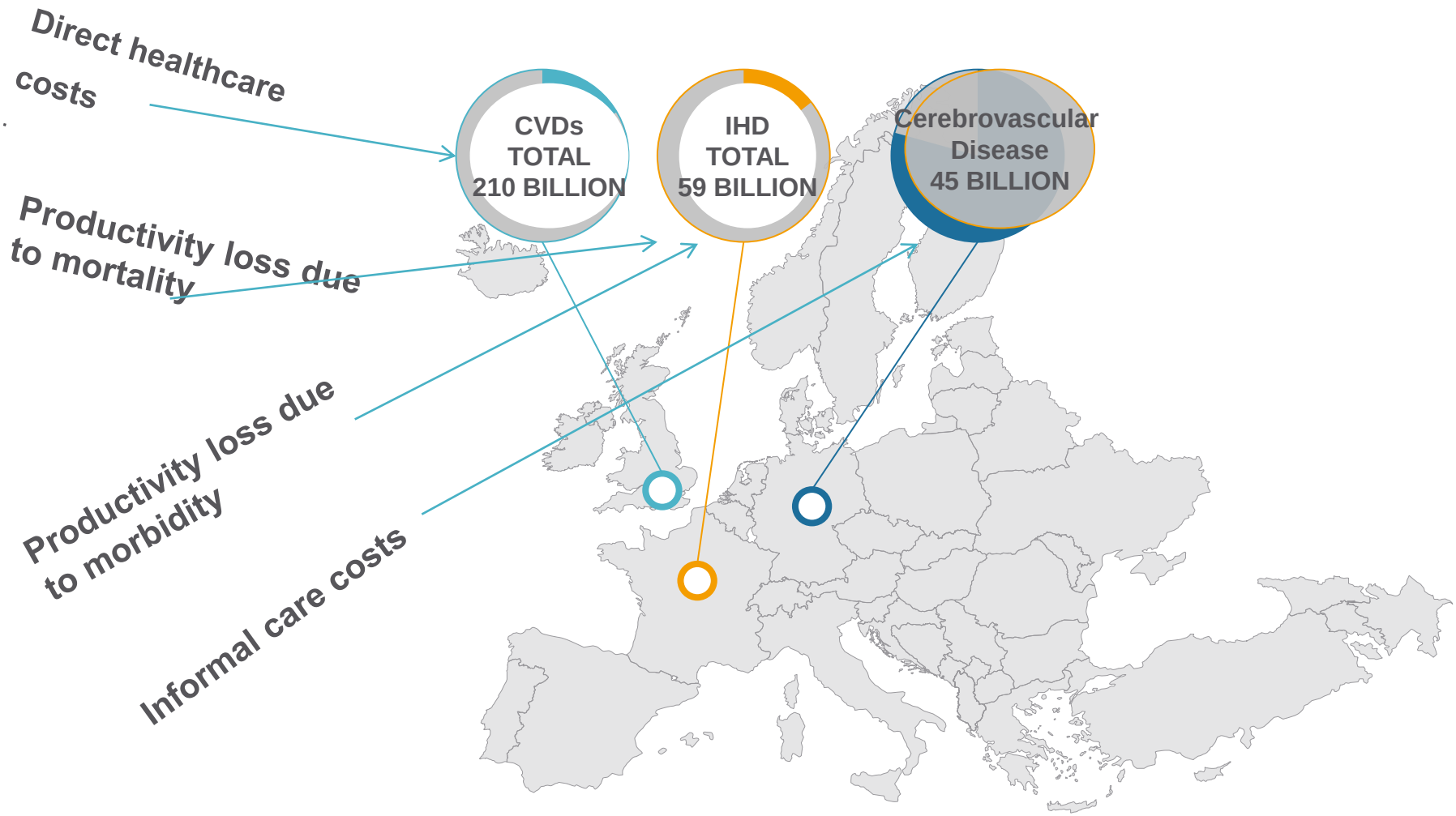
- **More than 6 million new cases of CVD in the EU**
- **More than 11 million in Europe as a whole**,
- **With almost 49 million people living with the disease in the EU,**
- **The cost to the EU economies is high at €210 billion a year.**

Source: EUROPEAN HEART NETWORK: European Cardiovascular Disease Statistics 2017

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Total cost of CVD, IHD and cerebrovascular diseases, 2015, EU



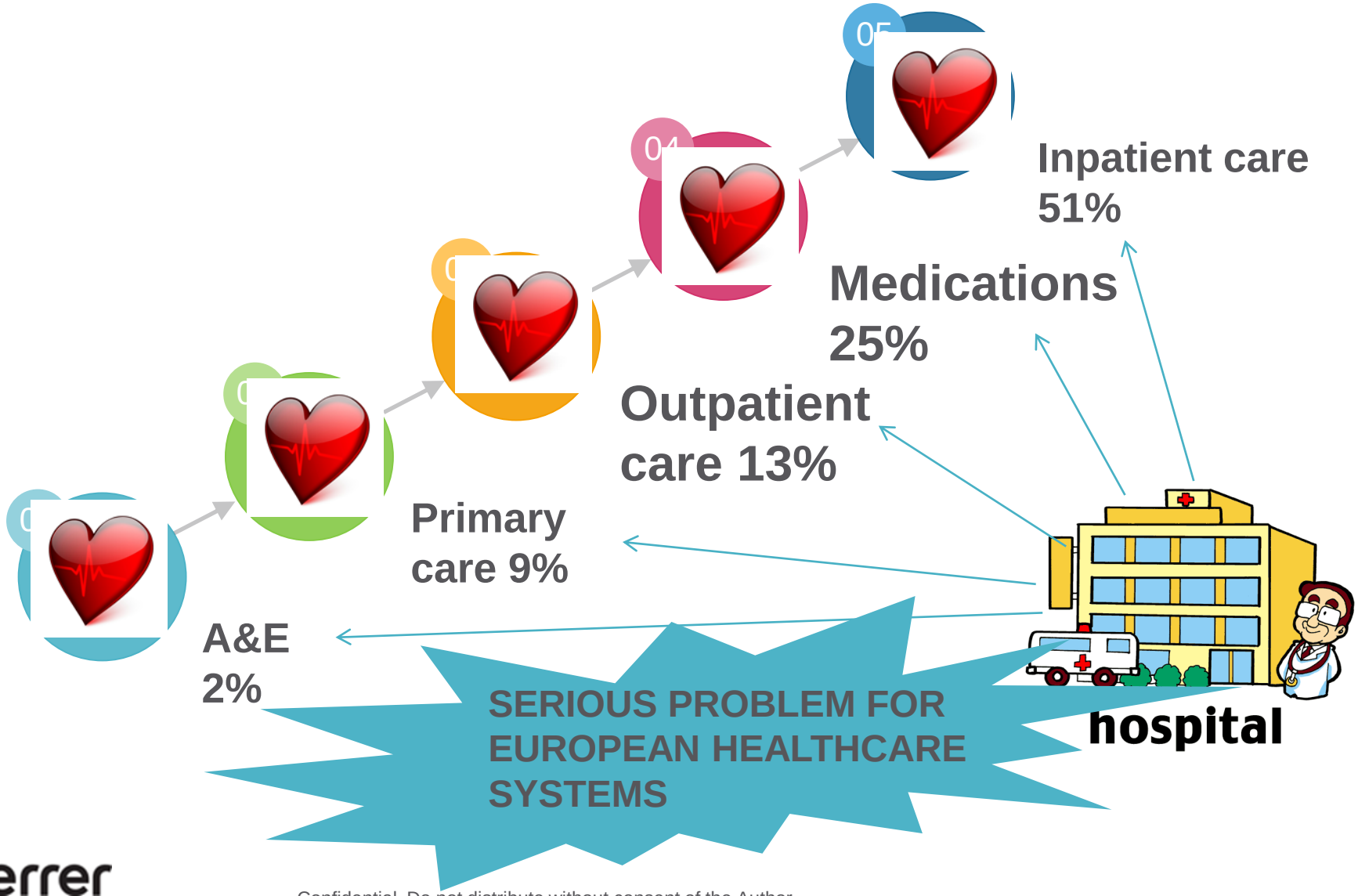
HIGH COST FOR EUROPEAN ECONOMY

Source: EUROPEAN HEART NETWORK: European Cardiovascular Disease Statistics 2017

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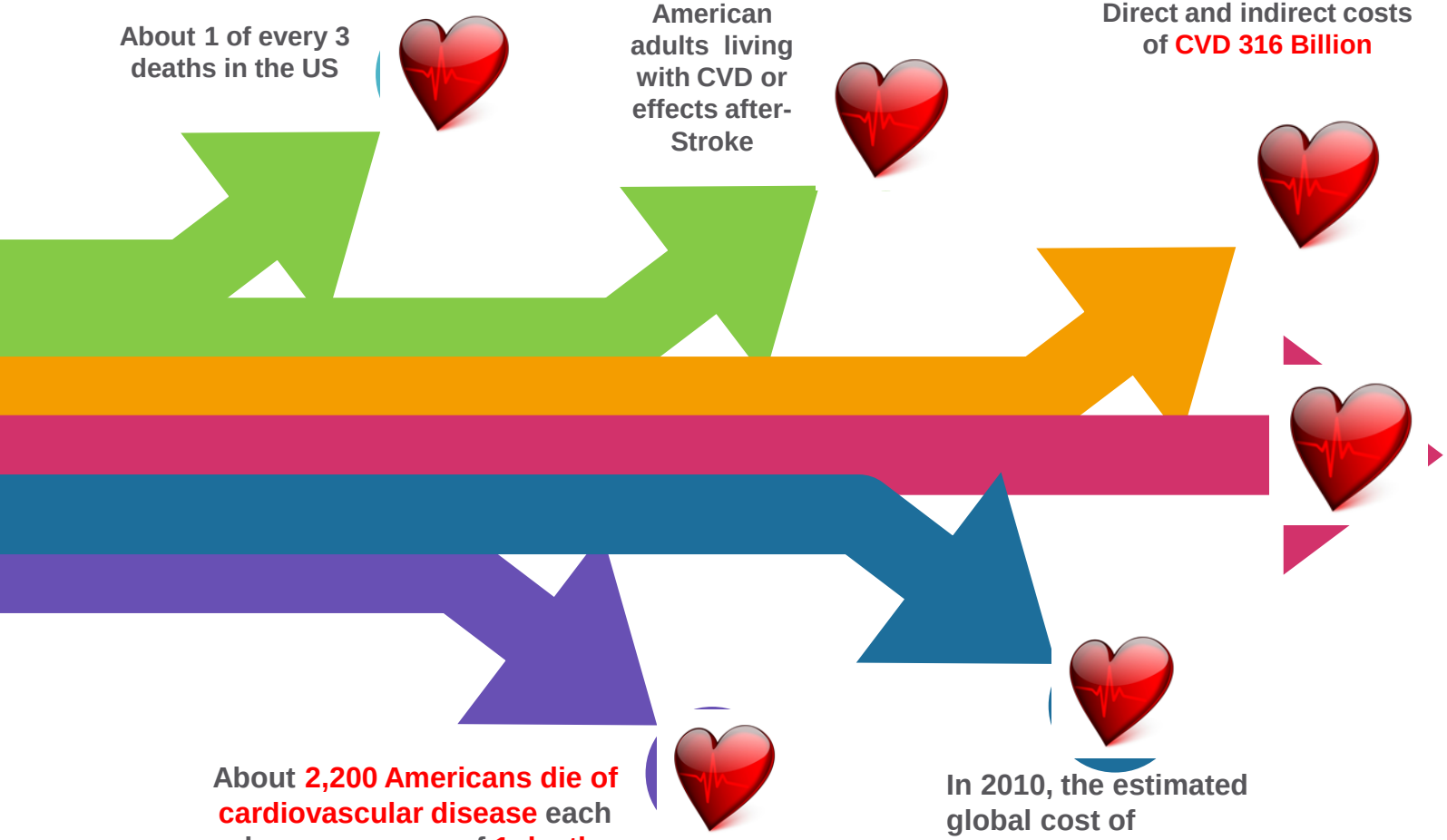
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Percentage of total Healthcare Expenditure on CVD in the EU, 2015, by resource use category



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Heart Disease and Stroke Statistics 2017 USA



CVDs **801,000 deaths** in the US

About 1 of every 3 deaths in the US

92.1 million American adults living with CVD or effects after-Stroke

Direct and indirect costs of **CVD 316 Billion**

CVDs: claim more lives each year than all forms of cancer and Chronic Lower Respiratory Disease combined

About **2,200 Americans die of cardiovascular disease** each day, an average of **1 death every 40 seconds.**

In 2010, the estimated global cost of cardiovascular disease was $863 billion, and it is **estimated to rise to $1044 billion by 2030**

Source: Heart disease and stroke statistics—2017 update: a report from the American Heart Association [published online ahead of print January 25, 2017]. *Circulation*. doi: 10.1161/CIR.0000000000000485

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The World Heart Federation Goal

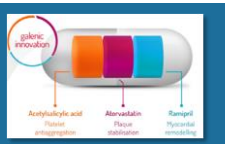
PHARMA COMPANIES WILL PLAY A RELEVANT ROLE



WORLD HEART FEDERATION®

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OBJECTIVES OF THE PRESENTATION



POLYPILL-CONCEPT:

TRINOMIA EFFICACY IN ADHERENCE FOR MANAGEMENT OF CVD

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Polypill Concept: Public-Private Project CNIC & Ferrer Internacional

trinomia
acetylsalicylic acid • atorvastatin • ramipril

National Center of Cardiovascular Research (Madrid)



WORLD HEART FEDERATION

To prevent cardiovascular disease and promote health

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Spanish Pharmaceutical Company (Barcelona)



Trinomia®: Treatment of choice for secondary cardiovascular prevention in very high risk patients*

3 Therapeutic aproaches in one single pill

Increase in adherence/ reduction of polymedication
-Improve adherence to clinical guidelines
-Increase patient´s adherence

A higher number of patients protected
-A better potential risk factor control**
-Potential reduction in morbi-mortality**

Increase the efficiency of the health systems
-Cost-effecteness
-Patient´s preference**

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*Including patients at secondary prevention and in primary prevention such as; subclinical atherosclerosis, diabetics with target organ damage or with 1 risk factor, CKD or SCORE> 10% or Pooled Cohort Risk Equation (PCE) ≥7,5%. ** Ongoing trials

Characteristics of the CNIC-FS-FERRER Polypill (Trinomia®)

trinomia
acetylsalicylic acid • atorvastatin • ramipril

Hard gelatin 0 size capsule containing inmediate release pills:

- Aspirin (100 mg)
- Statin (atorvastatin 20 or 40 mg
- ACE inhibitor (ramipril 2,5 mg; 5mg or 10 mg)

New Galenic innovation-technology that allows avoiding chemico-physical incompatibilities between ingredients inside the capsule.

TRINOMIA®: REPRESENT AN ADVANTAGE FOR PATIENTS ADHERENCE

Trinomia ® presentations:

- Trinomia® 100 /20,40 /2,5
- Trinomia® 100 /20, 40 /5
- Trinomia® 100 /20,40 /10

Trinomia® should be taken orally as a single capsule per day, preferably after a meal.

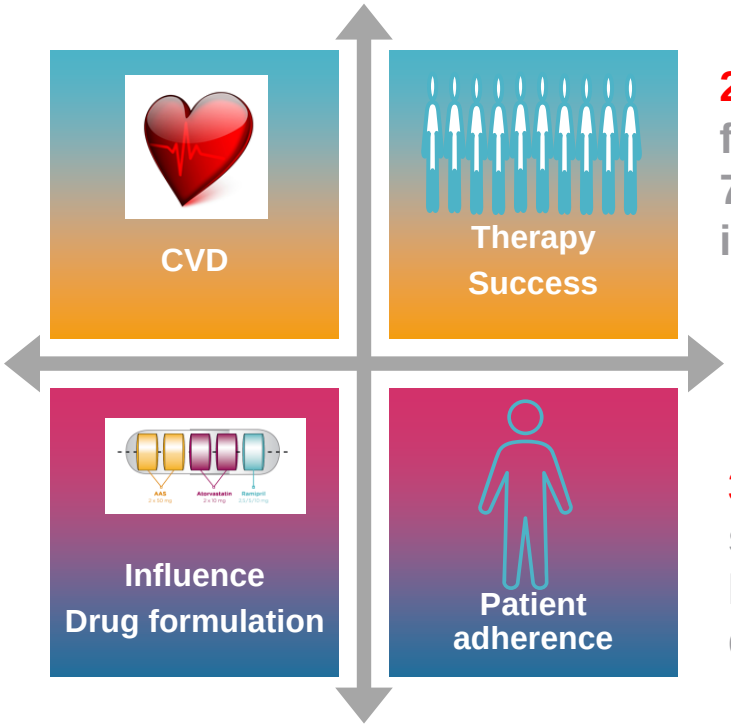
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Polymedicated Patients always take their Medication ??

20% of chronic patients do not initiate the prescribed treatment.
50% of patients leave the medication after 6 months

Importance of Treatment Adherence



24% of patients do not follow the treatment 7 days after a Myocardial infarction

12% of patients stop treatment of the 3 drugs within the first month after discharge

34% of patients stop treatment of at least **1 drug** the first day after discharge

In CVDs Patients Treatment Adherence: IS A KEY FACTOR

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Jackevicius CA et al. Circulation. 2008;117:1028–1036

ADVANTAGES OF TREATMENT ADHERENCE IN CVDs

Only **60%** of the included patients were **good adherents***

Good Adherence to CV Medication led to:

- **20% reduction of CVD risk**
- **35% reduction of all-cause mortality**

Study promoted by the ESC with almost 2.000.000 patients included

Importance of Treatment Adherence

9,1% of all events derived from poor adherence in patients prescribed with cardiovascular medications.

Metanalysis of 44 prospective studies, comprising 1,978,919 non-overlapping participants with CVD: 135,627 CVD events, 94,126 cases of all-cause mortality.

***Good adherence: ≥80% taking medication.**

Chowdhury et al. Eur Heart J 2013

Most important new information

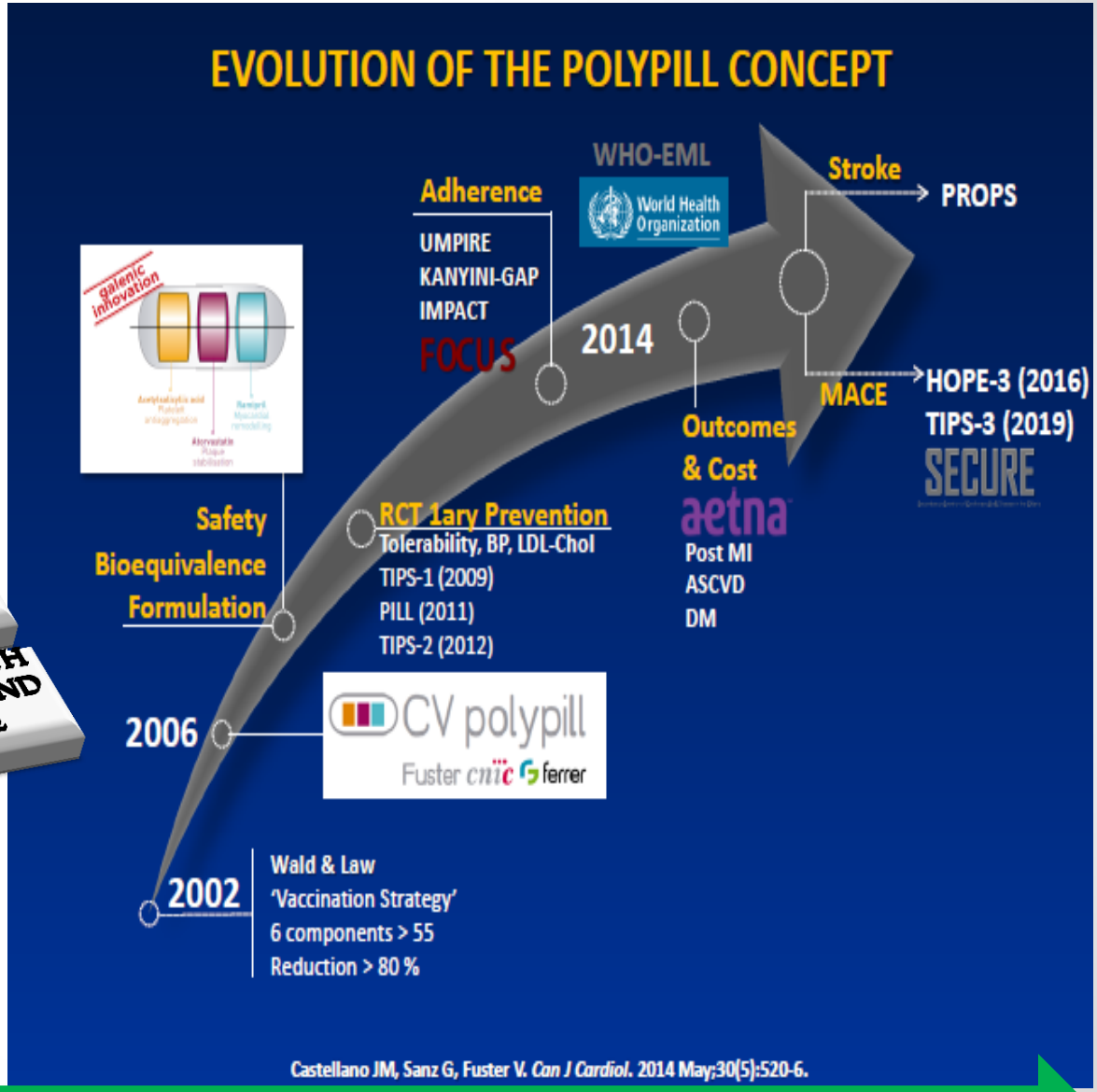
- Evidence suggests that reducing dosage demands is the most effective single approach to enhancing medication adherence.

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TRINOMIA: Drug Formulation Influence in Efficacy and Safety





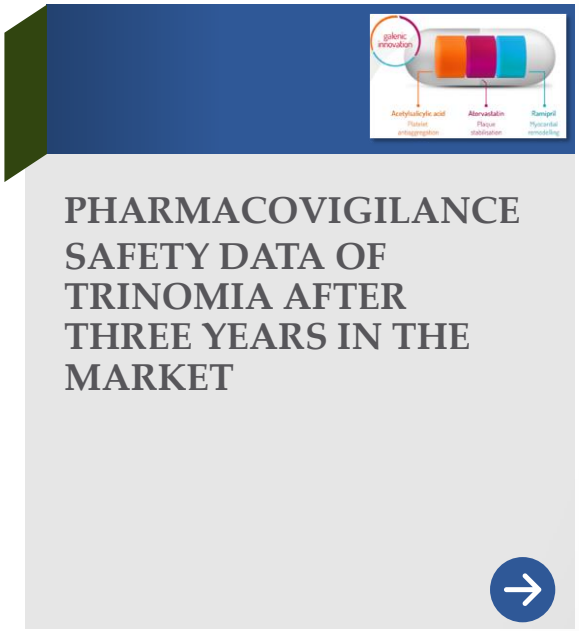
Castellano JM, Sanz G, Fuster V. *Can J Cardiol*. 2014 May;30(5):520-6.

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TRINOMIA: VALUABLE ALTERNATIVE FOR ADHERENCE IN CVDs

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OBJECTIVES OF THE PRESENTATION



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Indication in the EU countries

Trinomia® is indicated for the secondary prevention of cardiovascular accidents as substitution therapy in adult patients adequatelly controlled with the monocomponents given concomitantly at equivalent therapeutical doses.

The three active ingredients of the combination have:

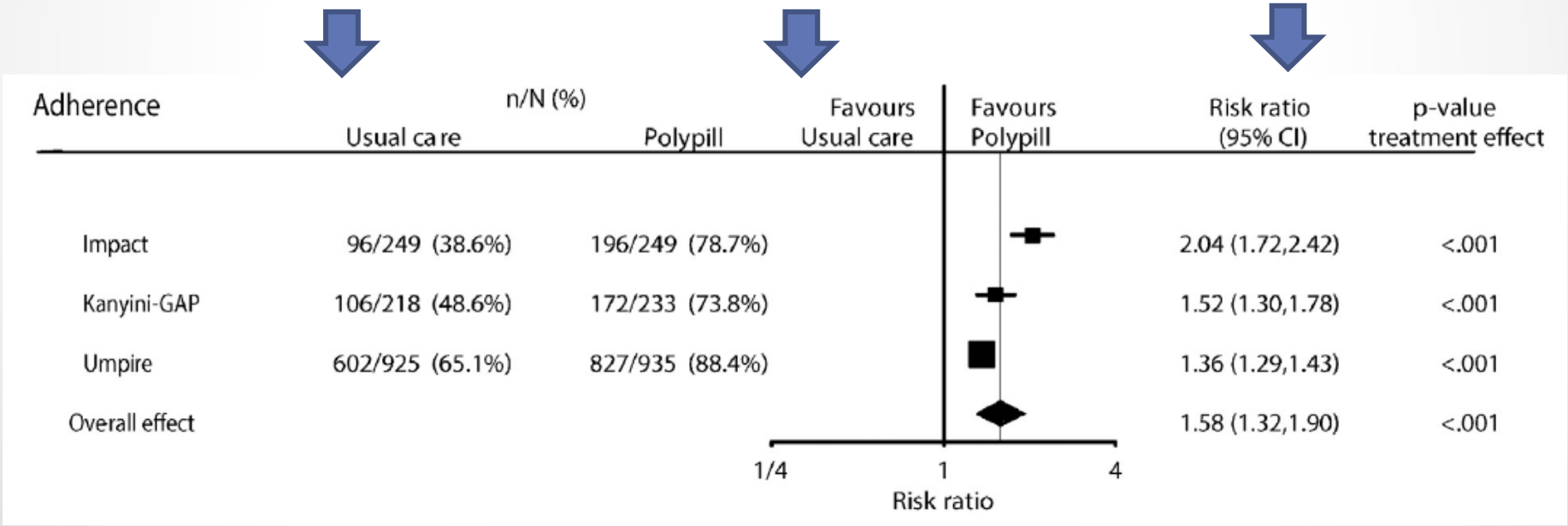
- Marketing Authorisation in UE countries, USA and other big markets.
- Wide and longterm worldwide experience in clinical practice as a free combination.
- Wellknown risk/benefit ratio.
- Evidence based efficacy and safety in secondary cardiovascular prevention.
- Currently recommended as concommitant therapy in secondary cardiovascular prevention. (ESC and AHA Guidelines)

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Polypill and Adherence

SPACE Collaboration Meta-analysis

- Available data from **3140 patients** with **established CV disease or very high risk** randomised within 3 trials (UMPIRE, Kanyini Gap, IMPACT) to CV Polypill vs. Usual Care.
- Median follow-up overall was 15 months (inter-quartile range: 12 to 21).
- Intervention and control groups were similar at baseline



Global effect: **58% Increase of Adherence** (RR 1.58 (1.32-1.90; p<0,01)

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Webster R et al., Int J of Cardiol. 2016;205:147-156

Polypill Treatment and Safety

SPACE Collaboration Meta-analysis

Serious adverse event	Polypill n (%)	Usual care n (%)
Any cause	360 (23%)	316 (20%) p = 0.07
Renal and urinary disorders	106 (6.8%)	83 (5.3%)
Cardiac disorders	87 (5.5%)	74 (4.7%)
Infections and infestations	75 (4.8%)	62 (4.0%)
Gastrointestinal disorders	35 (2.2%)	31 (2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	34 (2.2%)	
Nervous system disorders	32 (2.0%)	
Vascular disorders*	35 (2.2%)	
Injury, poisoning and procedural complications	29 (1.9%)	(1.4%)
Musculoskeletal and connective tissue disorders	26 (1.7%)	25 (1.6%)
Investigations	20 (1.3%)	17 (1.1%)
General disorders and administration site conditions	16 (1.0%)	16 (1.0%)
Respiratory, thoracic and mediastinal disorders	15 (1.0%	14 (0.9%)
Metabolism and nutrition disorders	15 (	9 (0.6%)
Reproductive system and breast disorders*		17 (1.1%)
Hepatobiliary disorders		4 (0.3%)
Eye disorders	%)	1 (0.1%)
Skin and subcutaneous tissue disorders	(0.2%)	4 (0.3%)
Surgical and medical procedures	4 (0.3%)	2 (0.1%)
Blood and lymphatic system disorders	5 (0.3%)	0 (0.0%)
Psychiatric disorders	1 (0.1%)	4 (0.3%)
Endocrine disorders	3 (0.2%)	1 (0.1%)
Immune system disorders	1 (0.1%)	1 (0.1%)
Congenital, familial and genetic disorders	0 (0.0%)	1 (0.1%)
Ear and labyrinth disorders	1 (0.1%)	0 (0.0%)
Social circumstances	0 (0.1%)	1 (0.1%)

* $p < 0.05$.

Polypill Safety Profile Similar to Standard Therapy

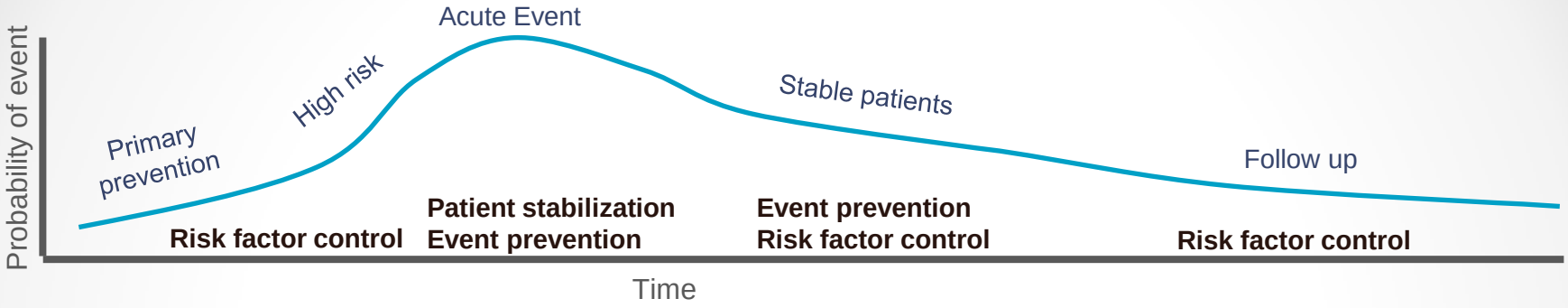
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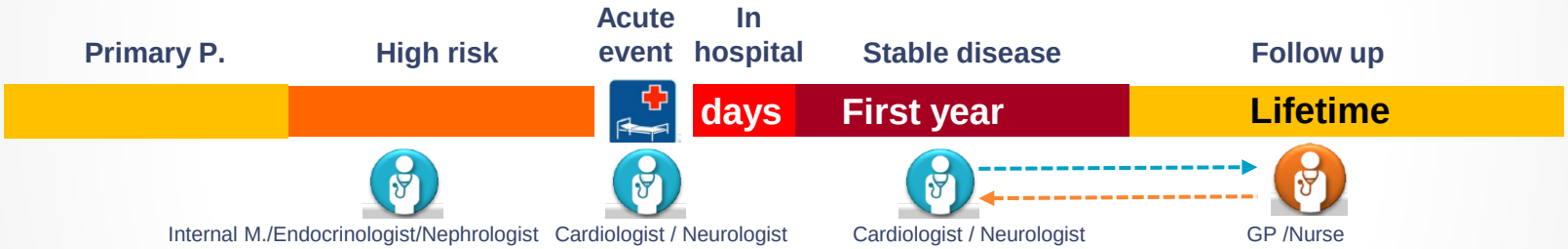
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Webster R et al., Int J of Cardiol. 2016;205:147-156

The AURA Program in Perspective.

Present ad Future Actions with TRINOMIA





VULCANO
RF control

FOCUS
Adherence

SECURE
Event prevention elderly

APOLO
RF control (secondary prevention)

SORASE
Registry

SATURNO
Clinical practice

AURORA
Patient´s preference

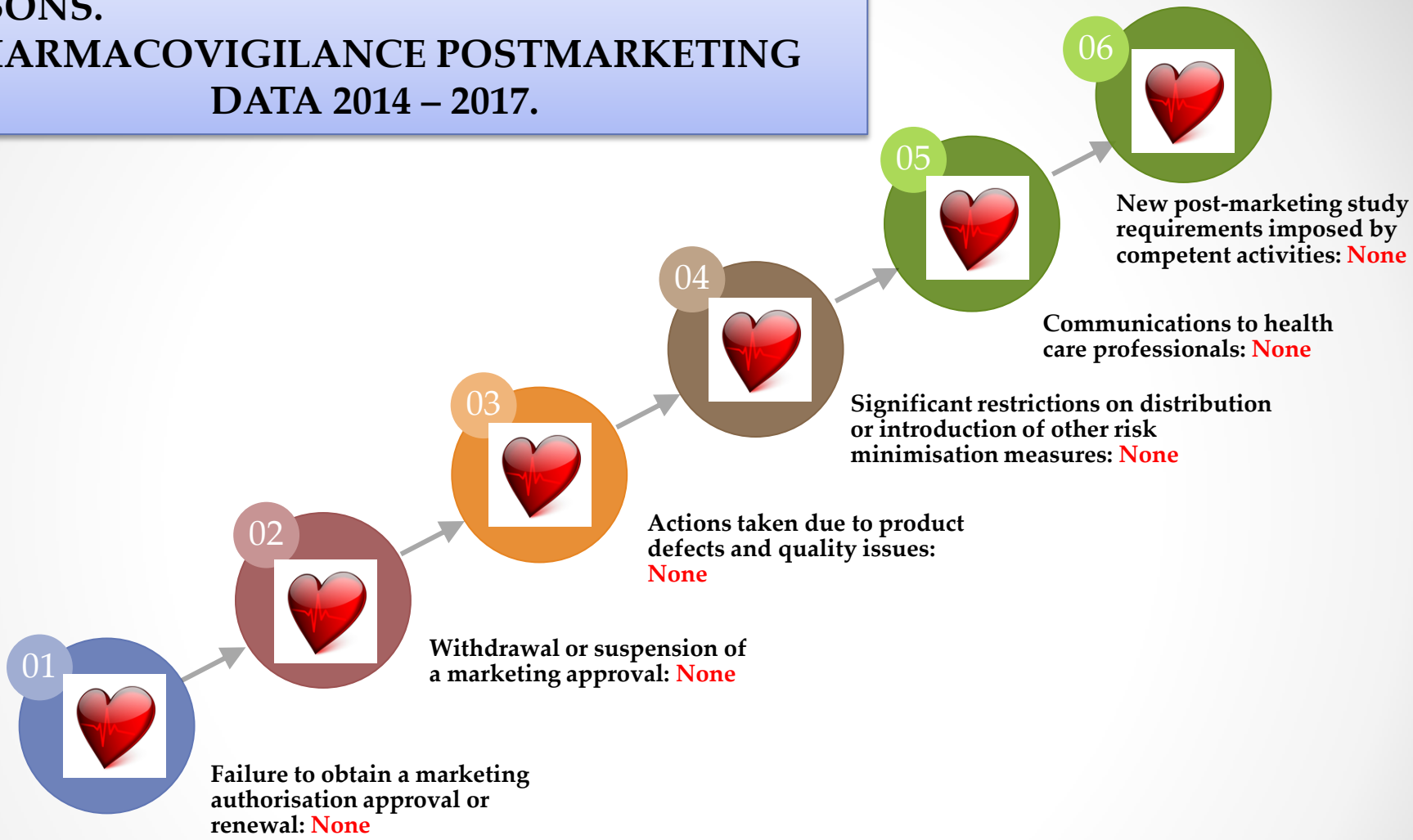
TRINOMIA:
Good Safety Profile in CVD prevention

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Finished *On going*

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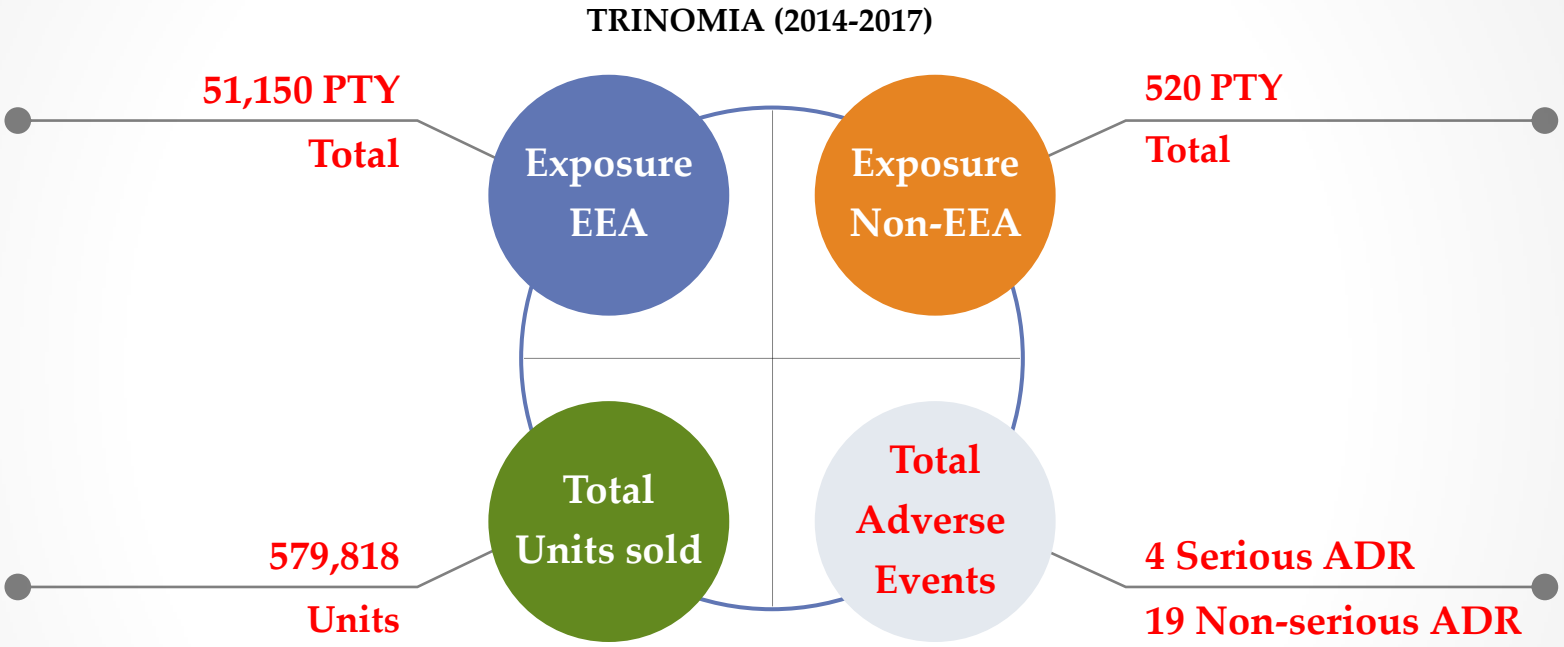
TRINOMIA: ACTIONS TAKEN FOR SAFETY REASONS.
PHARMACOVIGILANCE POSTMARKETING DATA 2014 – 2017.



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TRINOMIA: PHARMACOVIGILANCE POSTMARKETING DATA 2014 – 2017

Postmarketing Exposure: Patient Treatment-Year (PTY)
Postmarketing Data of Adverse Events

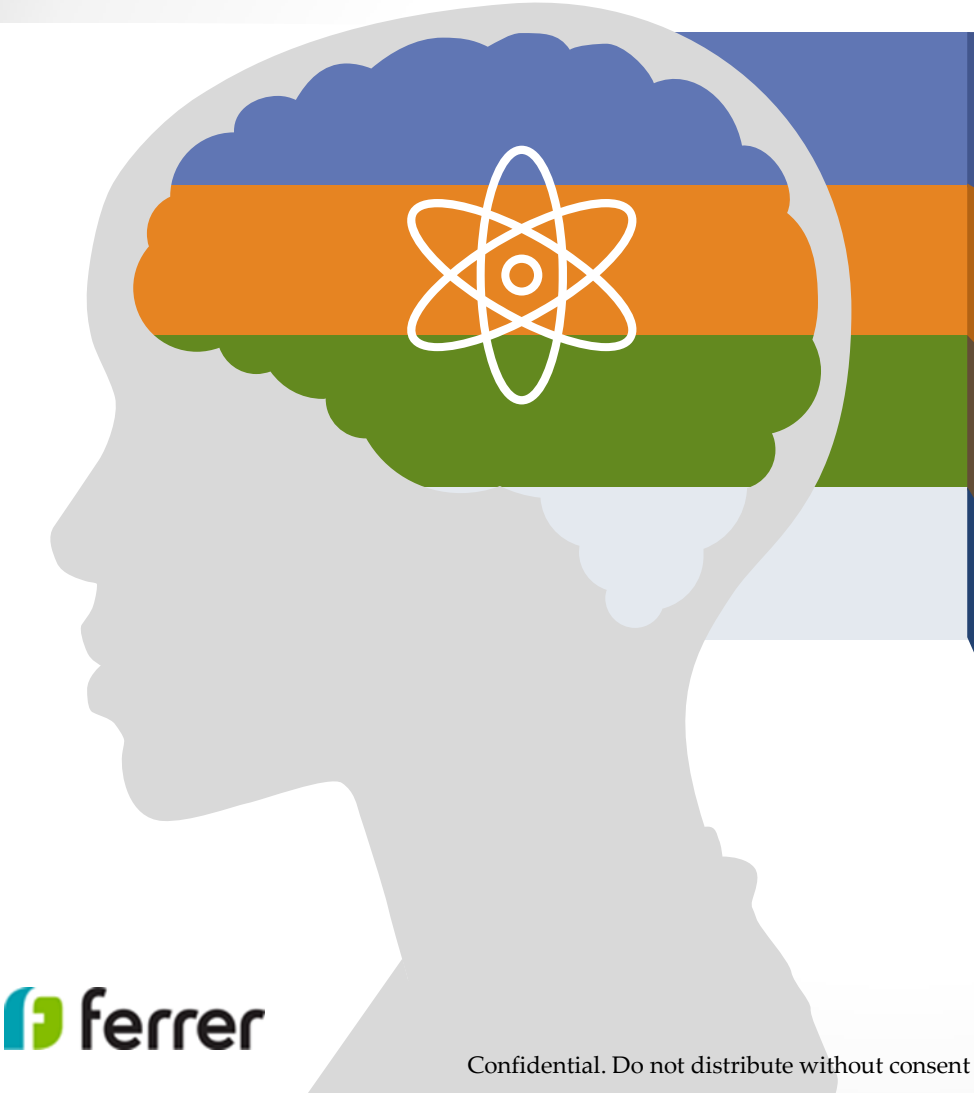


TRINOMIA SAFETY PROFILE DATA:

- The benefits outweigh the risks for the patients
- The medicinal product is considered a valuable therapeutical-alternative for the approved indication to prevent CVDs

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MAIN CONCLUSIONS



01 Drug Development Process is High time Consuming and have High Cost

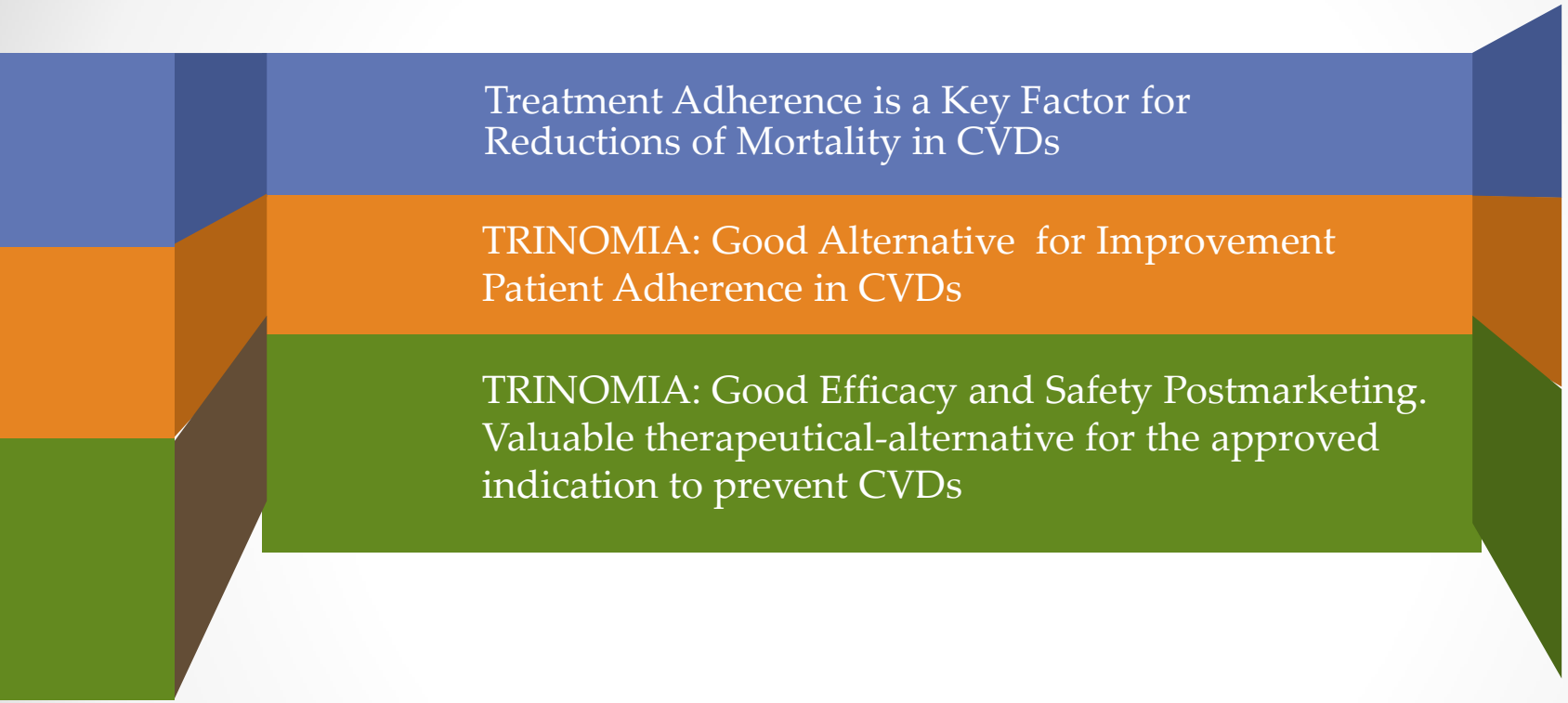
02 Healthcare Systems are Seriously Affected by Chronic Pathologies

03 Pharma Companies Play a Central Role to Improve Healthcare Systems

04 CVDs is the leading global cause of death, 17.3 million deaths per year in 2013, a number that is expected to grow to more than 23.6 million by 2030.

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THANKS FOR ATTENTION





- **Ferrer Internacional S.A. Staff-Pharmacovigilance Department**
- **Dr. José Emilio Ruiz Olivar, Medical Advisor, Ferrer Internacional S.A. Scientific Area, Ferrer Internacional S.A.**
- **Partners of Ferrer Internacional S.A.:** MINISTERIO DE SANIDAD Y CONSUMO, cnic

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