



Aspirin to Reduce Risk of Initial Vascular Events

Aspirin to Reduce Risk of Initial Vascular Events: The ARRIVE Study

Bayer HealthCare Press Conference

Messe Wien Congress Centre

Industry Press Conference Room

Monday, 3 September 2007, 14:00-15:00 CEST



ARRIVE™

Aspirin to Reduce Risk of Initial Vascular Events

Announcing ARRIVE: A Landmark Clinical Trial

Wes Cetnarowski, M.D.

Senior Vice President, Bayer HealthCare
Global Research & Development

Bayer announces the ARRIVE trial

- ▶ The largest trial ever to evaluate Aspirin for preventing initial cardiovascular and cerebrovascular events in moderate risk patients
- ▶ ARRIVE will expand the already existing, strong body of evidence supporting the use of Aspirin for primary prevention of cardiovascular and cerebrovascular events
- ▶ Benefits of broader, appropriate use of Aspirin
 - Significantly impact the global burden of cardiovascular disease
 - Improve public health and reduce the related costs
- ▶ ARRIVE reinforces Bayer's strong commitment to work with the scientific community to advance the science of Aspirin

ARRIVE will supplement the body of evidence

- ▶ Clinical trials supporting the use of Aspirin for primary prevention of cardiovascular events:
 1. British Doctor's Trial (BDT)
 2. Physicians' Health Study (PHS)
 3. Primary Prevention Project (PPP)
 4. Hypertension Optimal Treatment Trial (HOT)
 5. Thrombosis Prevention Trial (TPT)
 6. Women's Health Study (WHS)

+

- 7. **Aspirin to Reduce Risk of Initial Vascular Events (ARRIVE)**

Agenda

▶ Dr. J. Michael Gaziano

- Brigham & Women's Hospital, VA Healthcare System, Harvard Medical School, Boston, MA, USA
- *Advancing the Science of Aspirin in CVD Prevention: The ARRIVE Study*

▶ Prof. Dr. med. Harald Darius

- Kardiologie & Konservative Intensivmedizin, Vivantes Klinikum Neukölln, Berlin, Germany
- *Primary Prevention and the Way Forward: Advancing Identification of the At-Risk Patient*

▶ Prof. Luis M. Ruilope

- 12 de Octubre Hospital, Complutense University, Madrid, Spain
- *Aspirin Underutilization: The Facts and the Socioeconomic Impact*



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Advancing the Science of Aspirin in CVD Prevention

Aspirin to Reduce Risk of Initial Vascular Events: The ARRIVE Study

J. Michael Gaziano, M.D., M.P.H

Brigham & Women's Hospital

VA Boston Healthcare System

Harvard Medical School

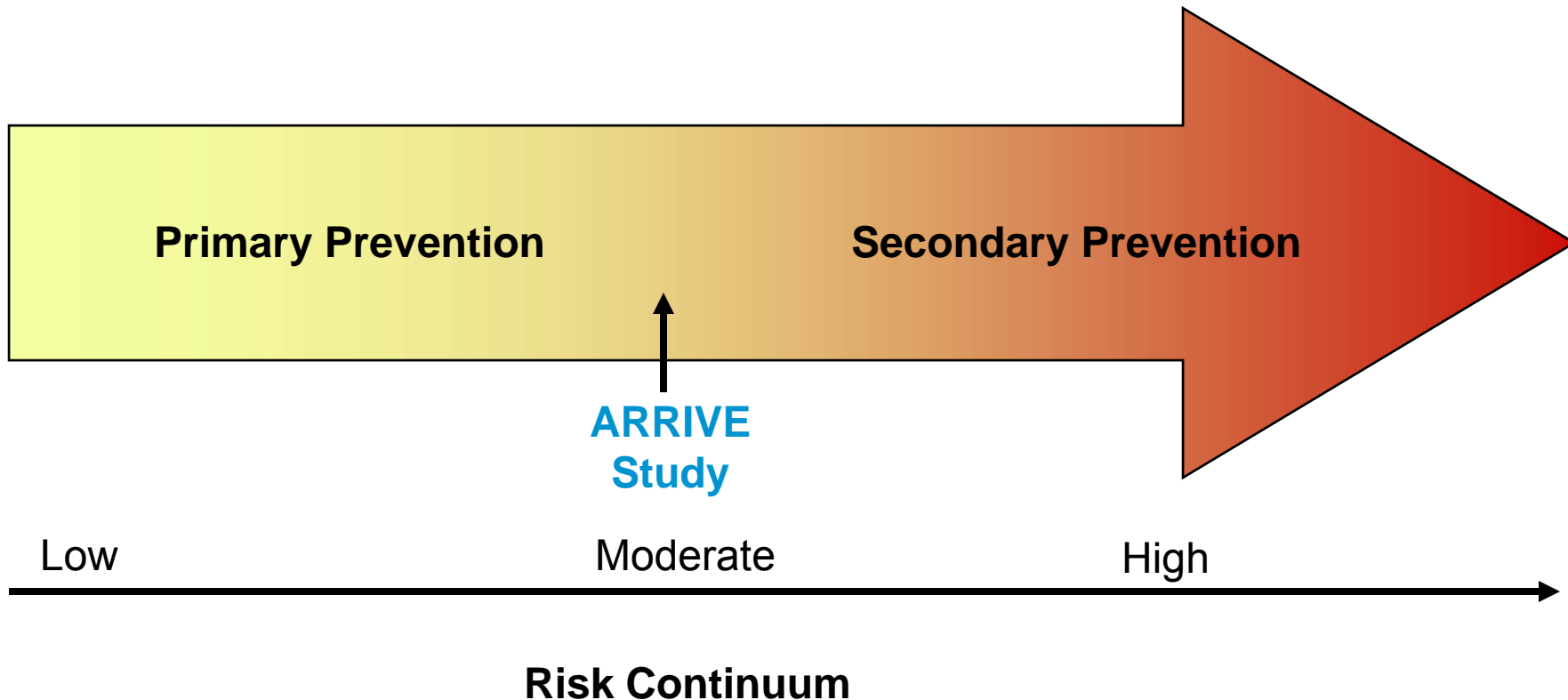
Boston, MA, USA



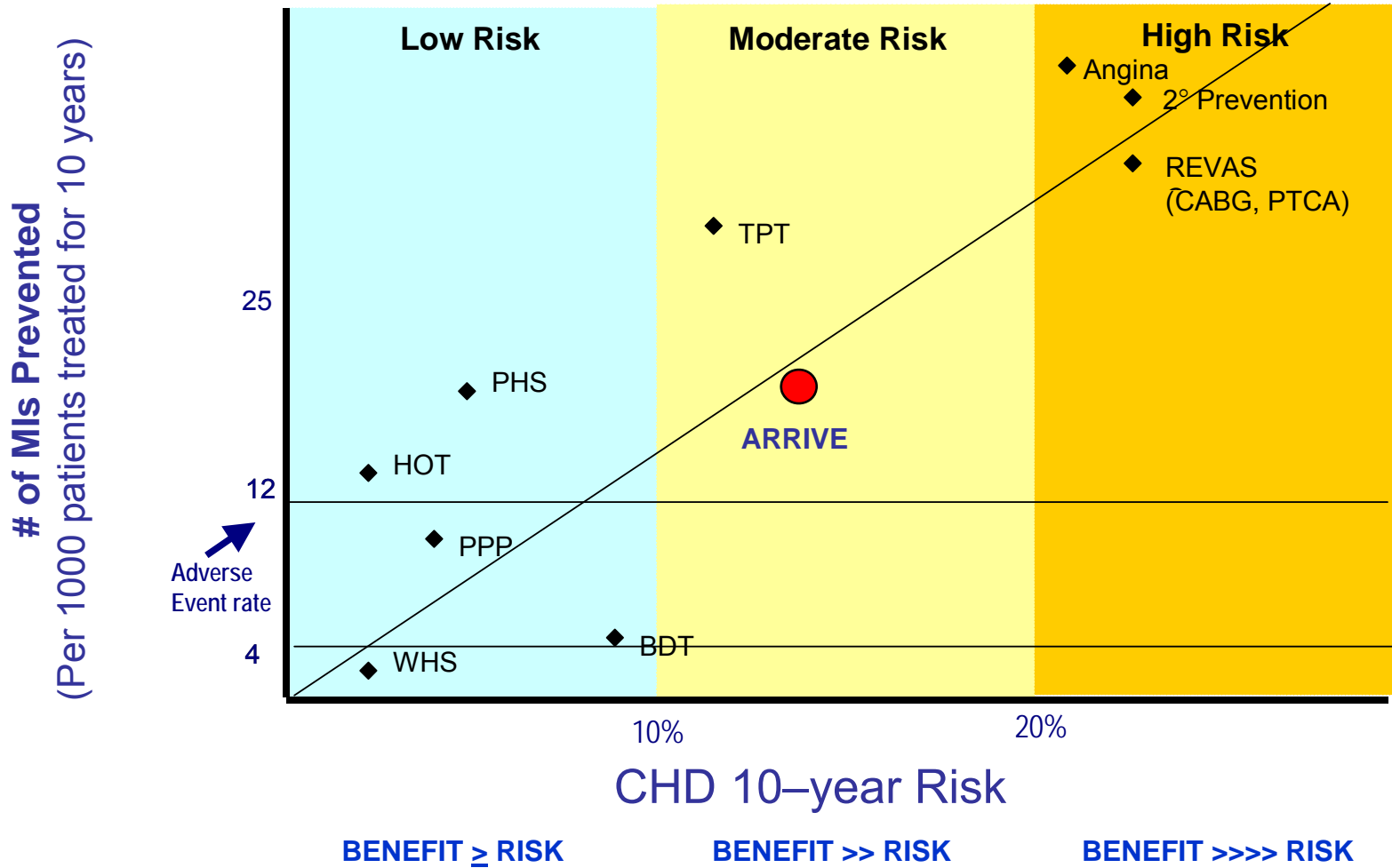
Aspirin Reduces Risk of Primary and Secondary Cardiovascular Events

- ▶ Worldwide indications for secondary prevention of stroke and MI
- ▶ Indicated in 36 countries around the world for use in primary prevention
- ▶ Multiple organizations endorse Aspirin use in primary and secondary prevention:
 - World Health Organization, NIH, European Society of Cardiology, International Diabetes Federation
 - American Heart Association, American Stroke Association, U.S. Preventive Task Force, American Diabetes Association

ARRIVE will help define those who may benefit most from Aspirin therapy



Coronary Heart Disease Risk Continuum



The ARRIVE Study

- ▶ **Initial** occurrence of non-fatal MI, non-fatal stroke, and cardiovascular death in patients at moderate CVD risk treated with Aspirin or placebo
- ▶ Conducted as a multi-national, double-blind, randomized, placebo-controlled study
- ▶ Includes innovative, new international risk calculation method that models overall risk for the composite study endpoint of CHD, plus stroke, plus cardiovascular death
 - Establishes entry criteria to identify patients at moderate risk who may benefit most from preventative therapies

General Study Parameters

- ▶ **Sample Size:** N=12,000 patients (6,000 per group) enrolled to obtain at least 1,488 adjudicated events over approximately 5 years
 - The largest trial to be conducted in a moderate risk population
- ▶ **Duration of Study:** Event Driven — approximately 5 years
- ▶ **Study Locations:** International across five countries:

Germany



UK



USA



Italy

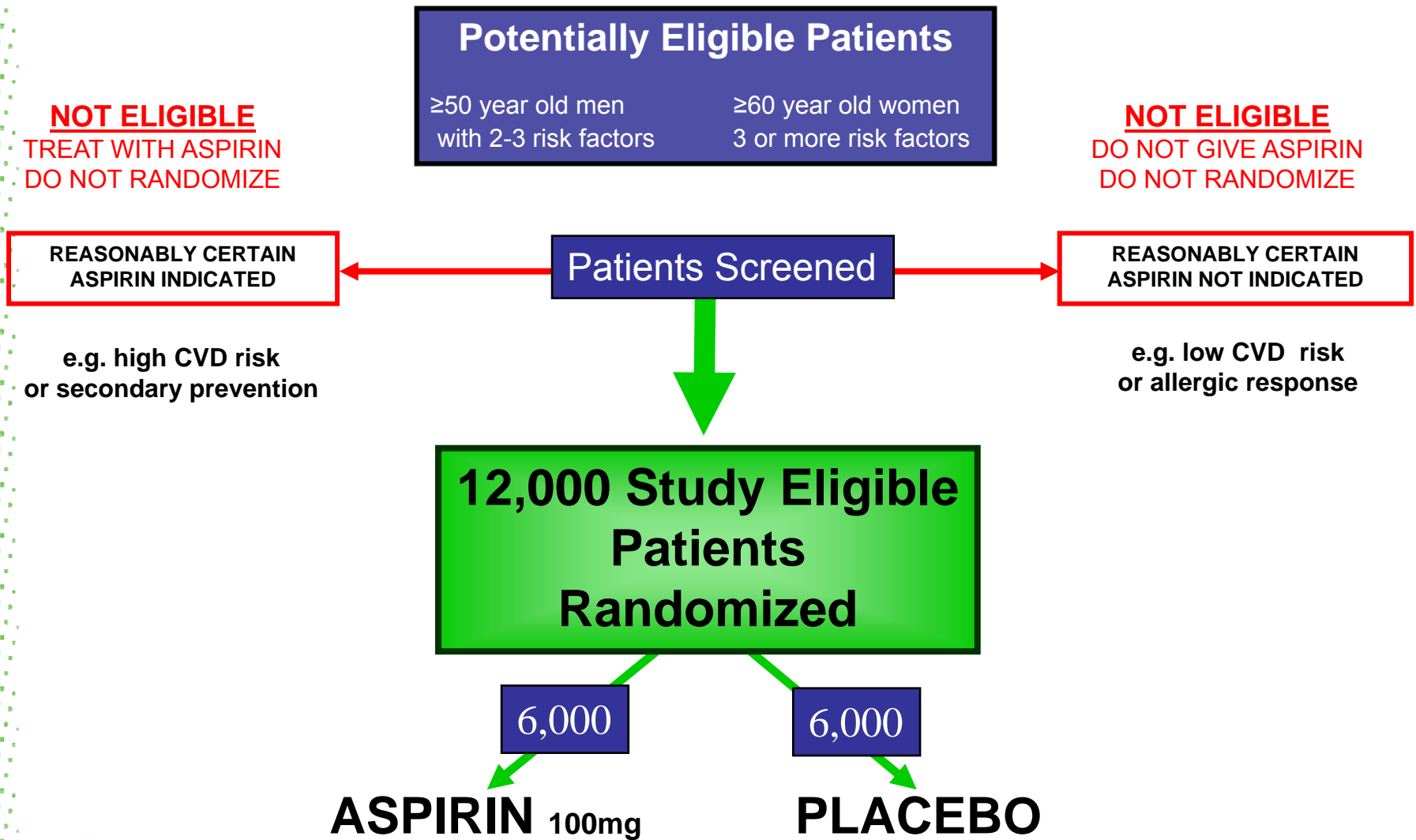


Spain



- ▶ **Gender Distribution:** 70% male / 30% female
- ▶ **Primary Efficacy Endpoint:** Time to first occurrence of the composite outcome of MI, stroke, or cardiovascular death

ARRIVE Trial Design



Study Oversight – Executive Committee

J. Michael Gaziano, MD, MPH, Chairman (USA) Cardiology and Epidemiology

Carlos Brotons, MD, MPH, PhD (Spain)

General Practice Leader

Claudio Cricelli, MD (Italy)

General Practice Leader

Harald Darius, MD (Germany)

Cardiology

Philip B. Gorelick, MD, MPH, FACP (USA)

Neurology and Epidemiology

George Howard, DrPH (USA)

Biostatistics and Epidemiology

Thomas A. Pearson, MD, MPH, PhD (USA)

Cardiology and Epidemiology

Peter M. Rothwell, MD, PhD, FRCP (UK)

Neurology and Epidemiology

Luis M. Ruilope, MD (Spain)

Internal Medicine and Hypertension

Gianni Tognoni, MD (Italy)

Pharmacology and Epidemiology

Value of ARRIVE

- ▶ As a large, well-defined primary prevention trial done specifically in a population at moderate risk of suffering a cardiovascular event, and on an international basis, ARRIVE will:
 - Increase understanding of the benefits of Aspirin
 - Expand the already existing, strong body of evidence supporting the use of Aspirin for primary prevention of CVD events
 - Improved understanding and identification of at-risk patients most likely to benefit from primary prevention with Aspirin
 - New data will prompt scientific publications and media coverage
 - » **Increased awareness among medical professionals can help address Aspirin underutilization and positively impact global cardiovascular health**



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Primary Prevention and the Way Forward: Advancing Identification of the At-Risk Patient

Harald Darius, M.D.

Kardiologie & Konservative Intensivmedizin

Vivantes Klinikum Neukölln

Berlin, Germany

Aspirin Prevents Primary Cardiovascular and Cerebrovascular Events

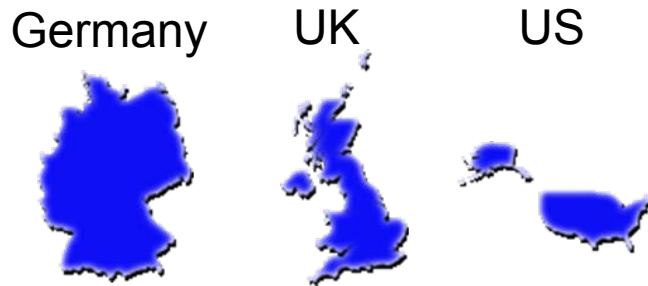
- ▶ Past meta-analyses have shown that Aspirin reduces risk of a first heart attack up to 32%, and combined risk of heart attack, stroke, and vascular death by 15%
- ▶ Six large primary prevention trials have demonstrated effects of Aspirin on preventing cardiovascular events
 - BDT: 42% reduction in TIAs
 - PHS: 44% reduction in risk of first MI
 - PPP: 44% decrease in risk of CVD deaths
 - HOT: 36% reduction in MIs, 15% reduction in major CVD events
 - TPT: 32% reduction in non fatal MI
 - WHS: 17% decrease in risk of stroke
- ▶ Recent meta-analysis of these six trials reinforce these results
 - Significant reductions in risk of non-fatal MI (25%), total coronary events (23%), and total CVD events (15%)
 - Strong trend toward reduction in risk for all-cause mortality (6.5%)

ARRIVE Patient Eligibility Criteria

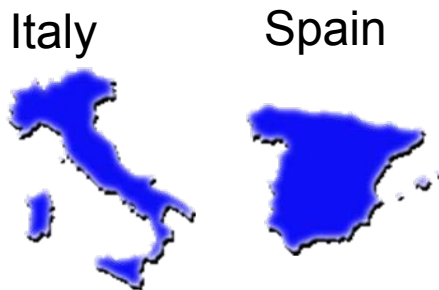
- ▶ Goal: Enroll patients at moderate risk for coronary heart disease and overall cardiovascular disease events as follows:
 - CVD: 20-30% 10-year risk, or
 - CHD: 10-20% 10-year risk
- ▶ No previous history of cardiovascular events
- ▶ No history of gastric/duodenal ulcers or GI bleeding
 - Chronic/frequent use of NSAIDs or COX-2 inhibitors not allowed

Highlights of Moderate Risk Modeling/ Protocol Design

High Risk Countries



Low Risk Countries



The Issue:

- ▶ Study in 5 countries with variable risk
- ▶ No global risk calculator available on the primary endpoint: time to the first CardioVascular Disease (CVD) event
- ▶ CVD = CHD + Stroke + CV death
- ▶ Stand-alone risk calculators available for components of the primary, but different according to the region of study — and no modeling for CHD in low risk countries

Highlights of Moderate Risk Modeling/ Protocol Design

High Risk Countries



Low Risk Countries



The Solution:

- ▶ Reviewed the literature and available public resources
- ▶ With guidance from the Executive Committee, we devised a method of using publicly available risk calculators for the components of the primary endpoint (CHD, Stroke and CV Death)
- ▶ A lot of number crunching and conversion factors to account for high and low risk countries
- ▶ New more focused inclusion criteria for the study
- ▶ *Methodology was reviewed by key Health Authorities (BfArM, AEMPS, FDA).*

Innovative Risk Calculation Methodology

- ▶ ARRIVE utilizes an innovative international risk calculation methodology to establish entry criteria for moderate risk
- ▶ Combines elements of 4 existing risk calculator methods:
 - CHD
 - » PROCAM — European-based risk calculator
 - » Framingham — US-based risk calculator
 - Stroke
 - » Framingham — US-based risk calculator
 - Cardiovascular Death
 - » Modeled from SCORE charts (pooling project of EU cohort studies)
- ▶ Risk Factor Criteria:
 - Men must be at least 50 years old and have 2 or 3 CVD risk factors (being 60 or older counts as a risk factor)
 - Women must be aged 60 years and have 3 or more CVD risk factors

CVD Risk Factors

- ▶ Elevated total cholesterol, or LDL cholesterol
 - >200 mg/dL (total), >130 mg/dL (LDL) for men
 - >240 mg/dL (total), >160 mg/dL (LDL) for women
- ▶ HDL <40 mg/dL
- ▶ Any cigarette smoking in last 12 months
 - Note: Cannot be only additional risk factor for men ≥ 60
- ▶ Elevated BP (Systolic >140 at screening)
- ▶ Currently on medication to treat high blood pressure
- ▶ Positive family history of early coronary heart disease
 - 1st degree relative (father, mother, brother, sister, son, daughter)

Overall CHD, Stroke and Cardiovascular Death

Risk Estimates by Age and Gender (All Countries)

	Mean 10-Year Risk %			
	CHD (PROCAM and Framingham)	STROKE (Framingham)	CV DEATH (SCORE)	TOTAL (CVD)
High risk countries	15.8%	9.1%	5.1%	30.0%
Low risk countries	8.5%	9.1%	2.75%	20.3%
Overall	12.9% ¹	9.1%	4.1%	26.1% ²

Risk Calculation Methodology

- ▶ Bayer working to evolve and refine this methodology used in ARRIVE
- ▶ Provide a tool for practitioners around the world for use in routine practice
- ▶ A simple robust method for predicting CVD risk will help broaden appropriate use of Aspirin

Expected ARRIVE Results

- ▶ Reinforce results from landmark Aspirin trials and meta-analyses of these trials
- ▶ Similar cardiovascular protective effects
- ▶ Favorable benefit-to-risk ratio



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Aspirin Underutilization: The Facts and the Socioeconomic Impact

Luis M. Ruilope, M.D.

12 de Octubre Hospital

Complutense University

Madrid, Spain

Aspirin Evidence Outlined

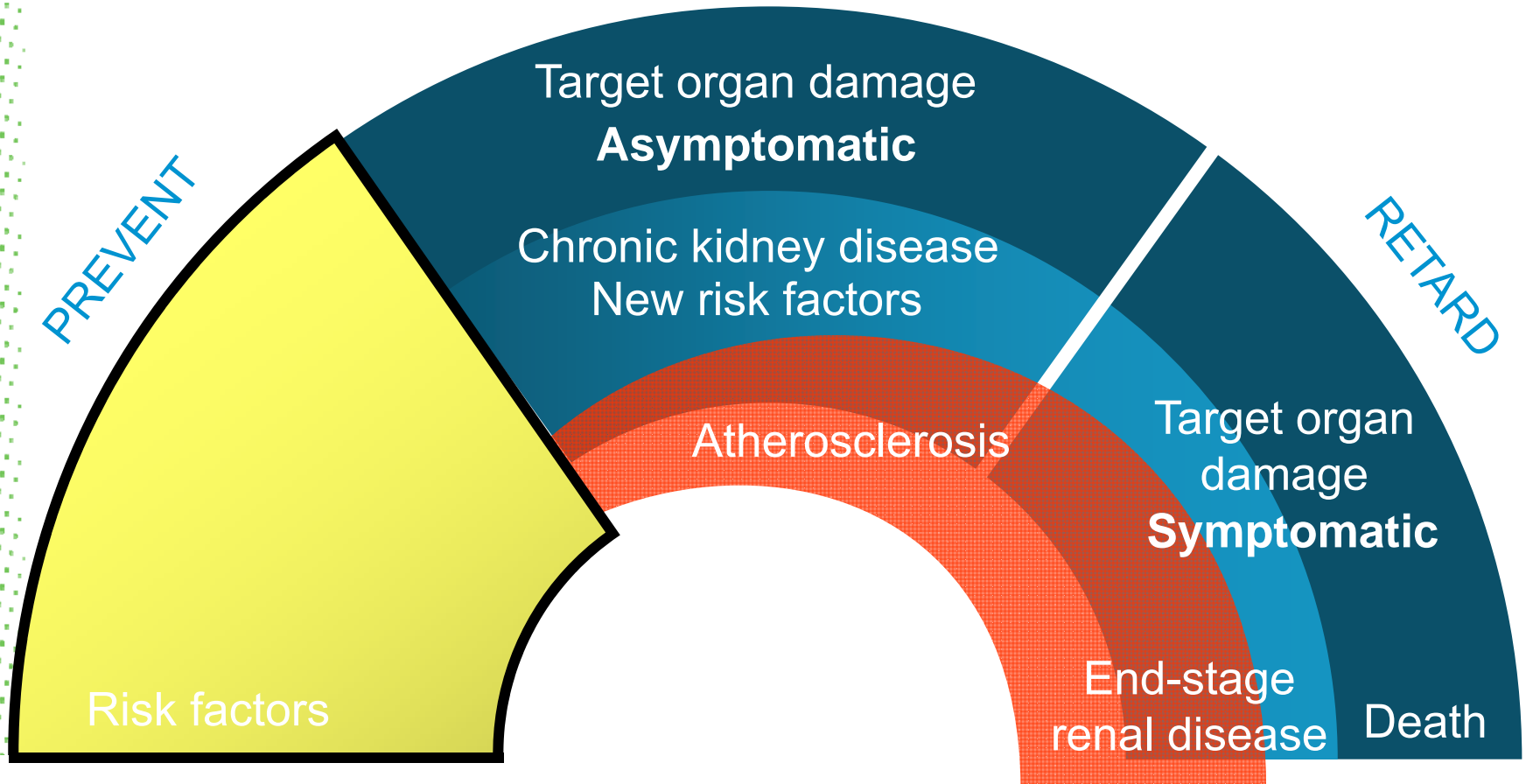
- ▶ Much of the world recognizes at least one, if not more, of the evidence-based findings regarding the potential of Aspirin:
 - Reduced risk of first heart attack by 32%
 - Reduced risk of vascular death by 15%
 - Reduced risk of death from acute heart attack by up to 23% (if administered when heart attack is suspected, and for 30 days after)
 - Reduced risk of stroke in women who have suffered a transient ischemic attack
 - Reduced risk of a second or recurrent stroke

Aspirin's Potential to Positively Affect Cardiovascular Health

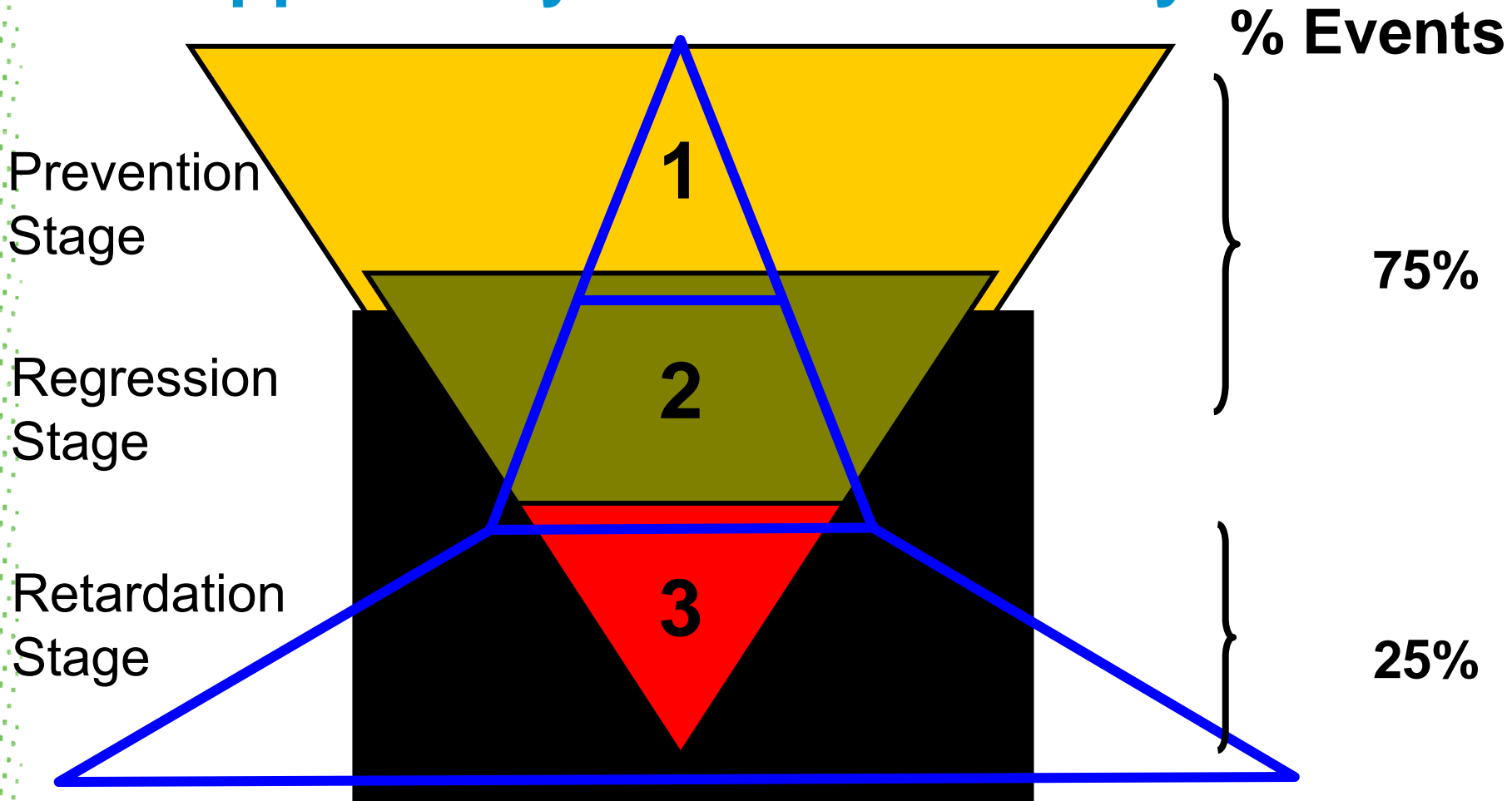
- ▶ Existing evidence demonstrates the significant potential for Aspirin to prevent cardiovascular events
- ▶ Aspirin only costs pennies per day
- ▶ Cost-utility analyses demonstrate overall value
 - For example: 2006 study in Spain
 - » Average net savings of €797 over 10 years in patients with 15% CHD risk
- ▶ However, significant underutilization has been reported/observed
 - Only ~7– 55% of patients at moderate to high risk are regularly using Aspirin

Cardio-renal Risk Continuum

REGRESS



The Opportunity to Intervene Early



COST



ASPIRINCARDIO®



The Public Health Impact of Cardiovascular Disease

- ▶ Cardiovascular disease has no geographic, gender or socioeconomic boundaries
- ▶ By 2020 cardiovascular disease will become the leading cause of death and disability worldwide
 - Currently represents the leading cause of death, accounting for **17.5 million, or 30%** of all deaths
 - CVD causes **nearly half of all deaths in Europe**
 - In the U.S. nearly 700,000 people will have a first heart attack this year, and 500,000 more will have a recurrent attack
 - CVD has become the **leading cause of death in many Asian countries**
 - In 2001, CVD accounted for **31% of deaths in Latin America**, expected to rise to **38% by 2020**



The Public Health Impact of Cardiovascular Disease

- ▶ Associated costs are staggering ... some examples:
 - In Europe, projected costs associated with CVD are huge; estimated at **€169 billion in the EU in 2006**
 - **In the U.S.** estimated direct and indirect costs in 2004 for CVD were **\$368.4 billion**
 - **In Canada, \$18 billion annually**
- ▶ At least 20 million people survive heart attacks and strokes every year
 - Many require continuing costly care, and are at high risk for recurrences and death

Increased Aspirin Utilization = Improved Outcomes

- ▶ For only pennies a day, broader Aspirin use in appropriate patients may help prevent tens of thousands of initial CVD events and save untold financial resources
 - Aspirin is more economical and potentially more cost effective than other available prescription agents in preventing CVD events in appropriate patients
 - Daily Aspirin could possibly prevent 25% of major CVD events in low- and middle-income nations
- ▶ New studies continue to bolster the preventive benefit of Aspirin
 - A recently released report funded by the U.S. Centers for Disease Control and others, reports **in the U.S. alone an additional 45,000 lives could be saved annually if 90% of at-risk adults took Aspirin regularly**
 - Follows on 2006 report where **Aspirin counseling was ranked the number one preventive health service** to improve public health
- ▶ **ARRIVE provides an additional important opportunity to gather data and educate professionals and consumers about the value of Aspirin in preventing CVD events**



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Summary and Conclusions

- ▶ ARRIVE will expand the already existing, strong body of evidence supporting use of Aspirin for primary prevention of CVD events
- ▶ ARRIVE creates additional opportunities to communicate the positive benefits of Aspirin and address the problem of underutilization
- ▶ The appropriate use of Aspirin in patients at moderate risk can have a significant public health and health economic impact worldwide



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Thank You.

Questions?



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