

# Clinical & Research Genomics

*Washington DC VA Medical Center*

**Jack H. Lichy, M.D., Ph.D.**



Veterans Health Administration

**Research  
Development**

Improving Veterans' Lives → [www.research.va.gov](http://www.research.va.gov)

# What is Genomic Medicine?

- DNA & RNA Testing:
  - *Personalized Medicine*
- An Accepted Standard of Care
- Applications
  - Sensitivity to Adverse Drug Reactions
  - Inherited Diseases & Syndromes
  - Cancer Diagnosis
  - Infectious Disease

# Clinical & Research Genomics Core

## *The Concept*

The same technologies used for clinically required DNA testing in the *clinical* laboratory are made available to support *research* in a single core laboratory facility.

# Clinical & Research Genomics Core

## *Organization*

- Clinical Laboratory directly meeting requirements of Veterans Healthcare
- CLIA Certified Laboratory for Research
- Collaborative
- Translational

# Clinical & Research Genomics Core

## *Support*

- Start-up Grant from Office of Research and Development
- Clinical testing supported by clinical funds
- Research supported by grant funds

# Clinical & Research Genomics Core

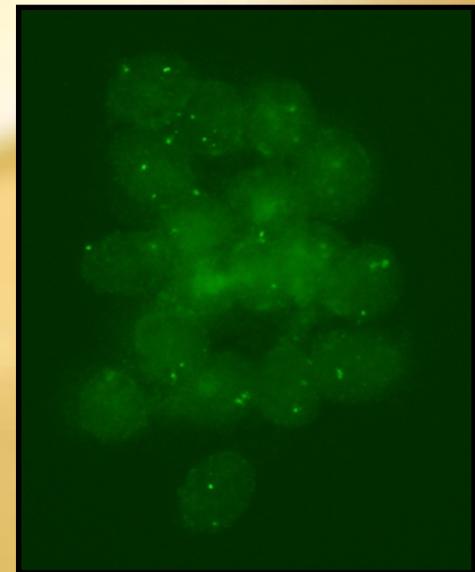
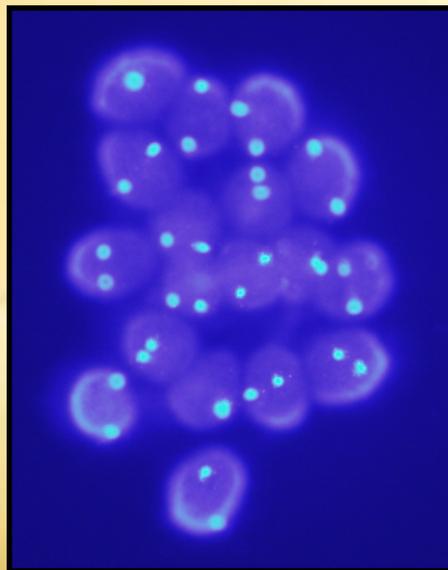
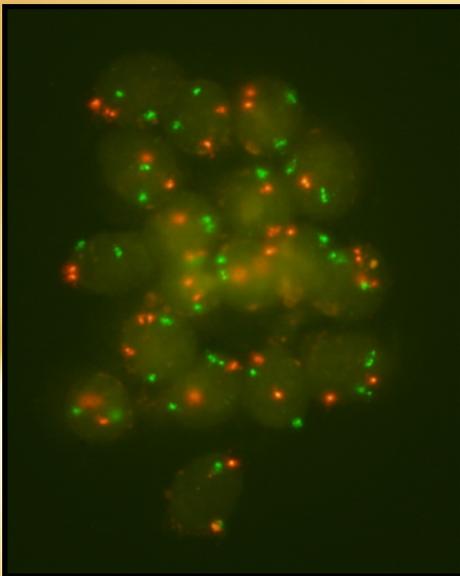
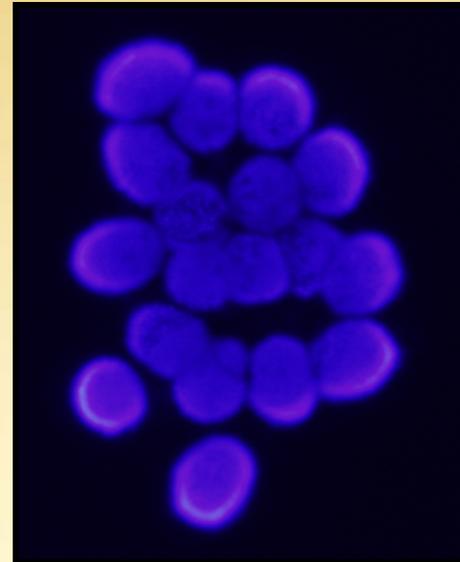
## *Technologies*

- FISH: Fluorescent *in situ* Hybridization
- PCR, DNA Sequencing
- Genotyping by Microarray Hybridization

# Current Testing Capabilities

## Urovysion:

A sensitive method for diagnosis of bladder cancer and early detection of recurrences.



# Current Testing Capabilities

- Predicting Optimum Drug Dosage
  - Cytochrome P450's:
    - CYP 2C9, 2D6, 2C19, 3A4, 3A5
  - Others:
    - VKORC1, UGT1A1



***“HERE’S MY SEQUENCE . . .”***

# Current Testing Capabilities

- Prediction of Tumor Response to Therapy
  - *K-ras* Mutation Detection
  - Microsatellite Instability
- Diagnosis of leukemia and lymphoma
  - Gene Rearrangement Assays
- Risk factors for coagulation disorders
  - Factor V Leiden
  - Prothrombin G20210A

# The Research Core

- Collaborative efforts to support a wide variety of research projects.
- Examples:
  - Evaluating Clinical Utility of Genetic Testing in Warfarin Dosing
  - Pharmacogenomic assay validation
  - Neurotransmitter expression in PTSD model
  - Testing genomic markers of risk for mental health disorders

# Example: Warfarin Dosing

- Too Little → Thrombosis
- Too Much → Bleeding
- Complications cause 43,000 ED visits/year in USA.
- Wide variation in dose requirements



# Warfarin Dosing: Clinical & Research Challenges

## Clinical:

- Implement genetic testing data into Warfarin dosing decisions.

## Research:

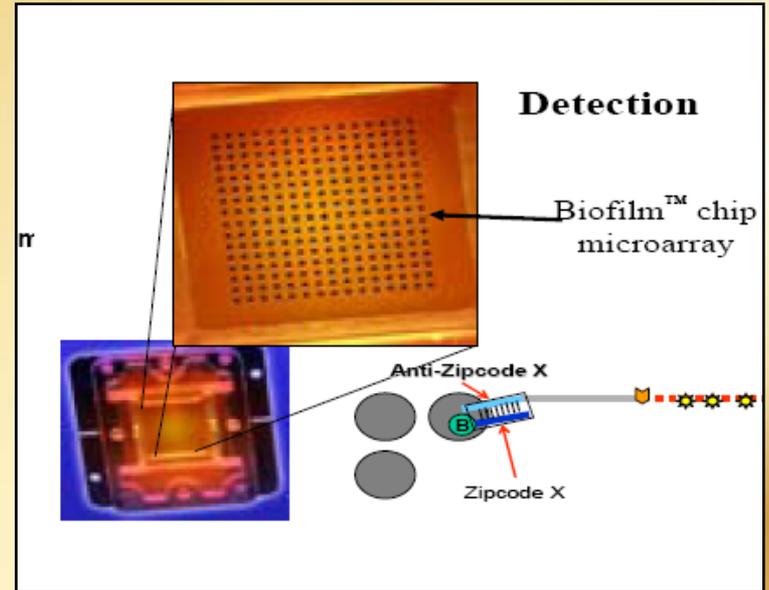
- Does genetic testing reduce the incidence of adverse reactions?
- Are there genetic markers of adverse reactions specific for minority populations?

# Warfarin: Collaborations

- Clinical Staff
- Pharmacy
- ACOS Research
- ACOS Informatics
- Anticoagulation Research Lab

# Warfarin: Accomplishments

- Assay Development
  - 3 well established markers
  - 11 markers seen in minority groups
- Educational Activities
- Software evaluations
  - Incorporating genetic data into dosing
  - Interface with Electronic Medical Record
- Research Collaboration



# Benefits to Veterans

- Tests already in use to support cancer diagnostics, clotting risk, Warfarin sensitivity.
- Reduced costs for clinical tests
- Fewer days in the hospital
- Fewer serious adverse drug reactions
- More effective cancer treatments
- Disease Prevention: Knowing the risk



# **HIV RESEARCH: Improving Veterans' Lives**

*Washington VA Medical Center  
Washington DC • April 30, 2009*

**Melissa M. Turner, MSW**



Veterans Health Administration

**Research  
Development**

Improving Veterans' Lives → [www.research.va.gov](http://www.research.va.gov)

# HIV Research: Improving Veterans' Lives

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- A Veteran Participating in HIV Research
  - 42-year old man who presents to the AEC with swollen lymph nodes, fever and fatigue and is offered HIV testing
  - After receiving positive test results in Yellow Team he is escorted to ID Clinic and provided crisis management and further medical assessment
  - His primary care is transferred to ID and during a regular visit, he is invited to participate in a randomized treatment trial for antiretroviral naïve volunteers
  - He declines, but he is introduced to research team members and the informed consent process, and learns how research is integrated in and complementary to HIV primary care

# HIV Research: Improving Veterans' Lives

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- Patient declines participation in the randomized trial but accepts an invitation to attend a meeting of the ID Clinic research advisory board
- Patient's interest in clinical trials increases as he learns more about treatment regimens, protocol development, informed consent, volunteer recruitment and retention strategies, and opportunities for veterans to collaborate with scientists in the VA protocol development process
- When an observational, non-interventional trial becomes available at the site, he joins the study
- Over time, patient's interest in HIV science propels him to become a leader of the ID Clinic research advisory board and a prominent HIV treatment activist in multiple networks in DC and the nation

# Veterans Living with HIV

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- Largest single provider of direct HIV care in the United States
  - Approximately 23,000 true unique patients with HIV infection
- 

Washington VA Medical Center / Total Patients in Care 2008 939

Gender	
Male	910
Female	32

Age	
0 – 13	0
14-17 yrs	0
18 – 49 yrs	392
50 – 59 yrs	377
>= 60 yrs	170

Race	
White	93
Black	693
Latino	12
Asian	1
Other	109

Source of Infection	
Injection Drug	178
Heterosexual	452
Same Sex	250
Mother-Infant	0
Other	23

# Type of HIV Research

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- Research is an integral part of the VA's efforts to improve the diagnosis, treatment and prevention of HIV infection
- HIV Treatment Research
- Optimizing clinical management of HIV/AIDS, including co-infections and other HIV-related conditions

# Major Collaborations

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- VA Cooperative Studies
- Centers for Disease Control
  - Tuberculosis Trials Consortium
- National Institutes of Health
  - Community Programs for Clinical Research on AIDS (CPCRA)
  - International Network for Strategic Initiatives in Global HIV Trials (INSIGHT)
  - HIV Prevention Trials Network (HPTN)
  - AIDS Clinical Trials Group (ACTG)
- Partnerships with Pharmaceutical Companies

Weather

Tuesday: Mostly sunny.  
High 48, Low 24.  
Wednesday: Mostly sunny.  
High 47, Low 23.

Section B1

# The Washington Post

DISTRICT  
FINAL

10/20

TUESDAY, FEBRUARY 7, 2006

## NIH Warns AIDS Patients Against Stopping

### Therapy

*Study Finds People Who Forgo Continuous Treatment More Likely to Develop Other Illnesses or Die*

By DAVID BROWN

*Washington Post Staff Writer*

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People infected with the AIDS virus who periodically interrupt their drug treatment run a higher risk of falling ill and dying of both AIDS and other diseases compared with people who stay on the medicines.

That is the conclusion of the largest and most expensive AIDS treatment study ever conducted....

## Liver-Related Deaths in Persons Infected With the Human Immunodeficiency Virus

*The D:A:D Study*

*The Data Collection on Adverse Events of Anti-HIV Drugs Study Group\**

## Mortality in the Highly Active Antiretroviral Therapy Era *Changing Causes of Death and Disease in the HIV Outpatient Study*

*Frank J. Palella, Jr., MD,\* Rose K. Baker, MA,† Anne C. Moorman, BSN, MPH,‡ Joan S. Chmiel, PhD,\* Kathleen C. Wood, BSN,† John T. Brooks, MD,‡ Scott D. Holmberg, MD, MPH,‡ and HIV Outpatient Study Investigators*

## Grade 4 Events Are as Important as AIDS Events in the Era of HAART

*Ronald B. Reisler, MD, MPH, Cong Han, PhD, William J. Burman, MD, Ellen M. Tedaldi, MD, and James D. Neaton, PhD*

## Causes of death among human immunodeficiency virus (HIV)-infected adults in the era of potent antiretroviral therapy: emerging role of hepatitis and cancers, persistent role of AIDS

*Charlotte Lewden,<sup>1</sup> Dominique Salmon,<sup>2</sup> Philippe Morlat,<sup>1,3</sup> Sÿbille BÉvillacqua,<sup>4</sup> Eric Jouglu,<sup>5</sup> Fabrice Bonnet,<sup>1,3</sup> Laurence HÉripret,<sup>6</sup> Dominique Costagliola,<sup>7,8</sup> Thierry May,<sup>4</sup> Geneviève ChÉne,<sup>1</sup> and the Mortality 2000 study group*

## Is there evidence for an increase in the death rate from liver-related disease in patients with HIV?

*Amanda Mocroft<sup>a</sup>, Vincent Soriano<sup>b</sup>, Jurgen Rockstroh<sup>c</sup>, Peter Reiss<sup>d</sup>, Ole Kirk<sup>e</sup>, Stephane de Wit<sup>f</sup>, Jose Gatell<sup>g</sup>, Bonaventura Clotet<sup>h</sup>, Andre Jens D. Lundgren<sup>e</sup> for the EuroSIDA Study Group\**

## Highly Active Antiretroviral Therapy and Incidence of Cancer in Human Immunodeficiency Virus-Infected Adults

*International Collaboration on HIV and Cancer*

## Effective therapy has altered the spectrum of cause-specific mortality following HIV seroconversion

*CASCADE Collaboration\**

## Highly active antiretroviral therapy and the incidence of HIV-1-associated nephropathy: a 12-year cohort study

*Gregory M. Lucas<sup>a</sup>, Joseph A. Eustace<sup>a</sup>, Stephen Sozio<sup>a</sup>, Evelyn K. Mentari<sup>a</sup>, Kofi A. Appiah<sup>b</sup> and Richard D. Moore<sup>a</sup>*

## Class of Antiretroviral Drugs and the Risk of Myocardial Infarction

*The DAD Study Group\**

# How HIV Research Improves Veterans' Lives

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- ~~Death Sentence~~ → Survival
- ~~Despair~~ → Hope/Optimism
- Quantity and Quality of life
- Thriving
  - Achieving sobriety
  - Acquiring housing
  - Pursuing higher education/training/career advancement
  - Maintaining stronger Relationships
  - Addressing other health issues (smoking, obesity, etc)
  - Pursuing dreams, aspirations and a future

# How HIV Research Improves Veterans' Lives

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- Altruism
- Mental Health - "a state of well-being in which the individual realizes his or her own abilities, can cope with the normal stresses of life, can work productively and fruitfully, and is able to make a contribution to his or her community"
- High Acceptance of Research Participation/Repeat Volunteers
- Enhances primary care
- Advocacy

# How HIV Research Shapes Healthcare Delivery

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- Expanded treatment options
- Increasing complexity
- Outpatient management
- Shorter hospitalizations
- Development of a chronic disease management paradigm for lifelong care of HIV infection

# Impact on International Scope and Next Steps

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- Emphasis on earlier intervention
- Improve early detection of HIV infection
- Expand and simplify HIV testing
- Prevention education programs associated with relevant VA programs: drug treatment programs, homeless programs, counseling programs, domiciliary facilities, STD programs and primary care clinics

# **HIV Research: Improving Veterans' Lives**

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Many, many thanks to our  
nation's veterans for  
volunteering to participate in  
HIV research studies

# Control of Hypertension and Seasonal Variation

*Location*

*Washington DC • April 30, 2009*

**Ross Fletcher M.D.**



Veterans Health Administration

**Research  
Development**

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# Control of Hypertension and Seasonal Variation in a Large VA Study 2000 - 2007

## VA Research: Improving Veterans' Lives



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Demo Patient 1  
000-00-0001 001/01/1901 (00) AEC Feb  
Provider: C

Last 100 Signed Notes

- New Note in Progress
  - Mar 02,04 AEC NURSING TRIAGE I
- All signed notes
  - Mar 01,04 AEC-FOCUS/MINOR (992
  - Feb 27,04 SPEECH PATHOLOGY PM
  - Feb 26,04 CONSENT FOR ANESTHI
  - Feb 26,04 OPERATIVE NOTE, RED
  - Feb 26,04 OPERATIVE NOTE, RED
  - Feb 25,04 OPERATIVE NOTE, AEC I
  - Feb 25,04 OPERATIVE NOTE, AEC I
  - Feb 25,04 OPERATIVE NOTE, UROI
  - Feb 25,04 OPERATIVE NOTE, UROI
  - Feb 24,04 OPERATIVE NOTE, AEC I
  - Feb 23,04 Preventive Medicine Scree
  - Feb 19,04 TATTOO/PIGMENTED LE

Templates

Reminders

- PROSTATE CANCER SCREENING EDUCA
- PTSD Screen
- Tetanus Diptheria (TD-Adult)
- ALCOHOL ABUSE SCREENING (AUDIT-C)
- INFLUENZA IMMUNIZATION
- Weight and Nutrition Screen
- Diabetes-Hemoglobin A1C
- Diabetic Foot Exam
- MST Screening
- MDD SCREEN FOR <60
- PPD Results
- Suicidal Risk Assessment (Annual)
- HTN Assess for Elevated BP>140/90**
- Not Applicable
- All Evaluated

Encounter

Cover Sheet Problems Meds Orders Notes

The most recent recorded BP was elevated. Satisfying this reminder requires addressing medication issues and/or education issues.  
(\* Indicates a required field)

The patient's last recorded BP is:

152/94 (03/01/2004 15:01)

Repeat BP

142/84

**Progress Note  
Reminder Screen**

INTERVENTIONS

- Medications Adjusted
- Medication changes not warranted - BP usually controlled
- Medications changes not warranted based on comorbid illness/life expectancy/other
- Refuses Medication Adjustment

EDUCATION

- Lifestyle Education for Hypertension done today (includes exercise and nutrition education)
- Lifestyle Modifications Recommended - specific interventions
- Adherence to Therapy Education
- No Education Warranted (based on comorbidities/life expectancy/other)
- Incorrect diagnosis of hypertension

Clear Clinical Maint Visit Info < Back Next > Finish Cancel

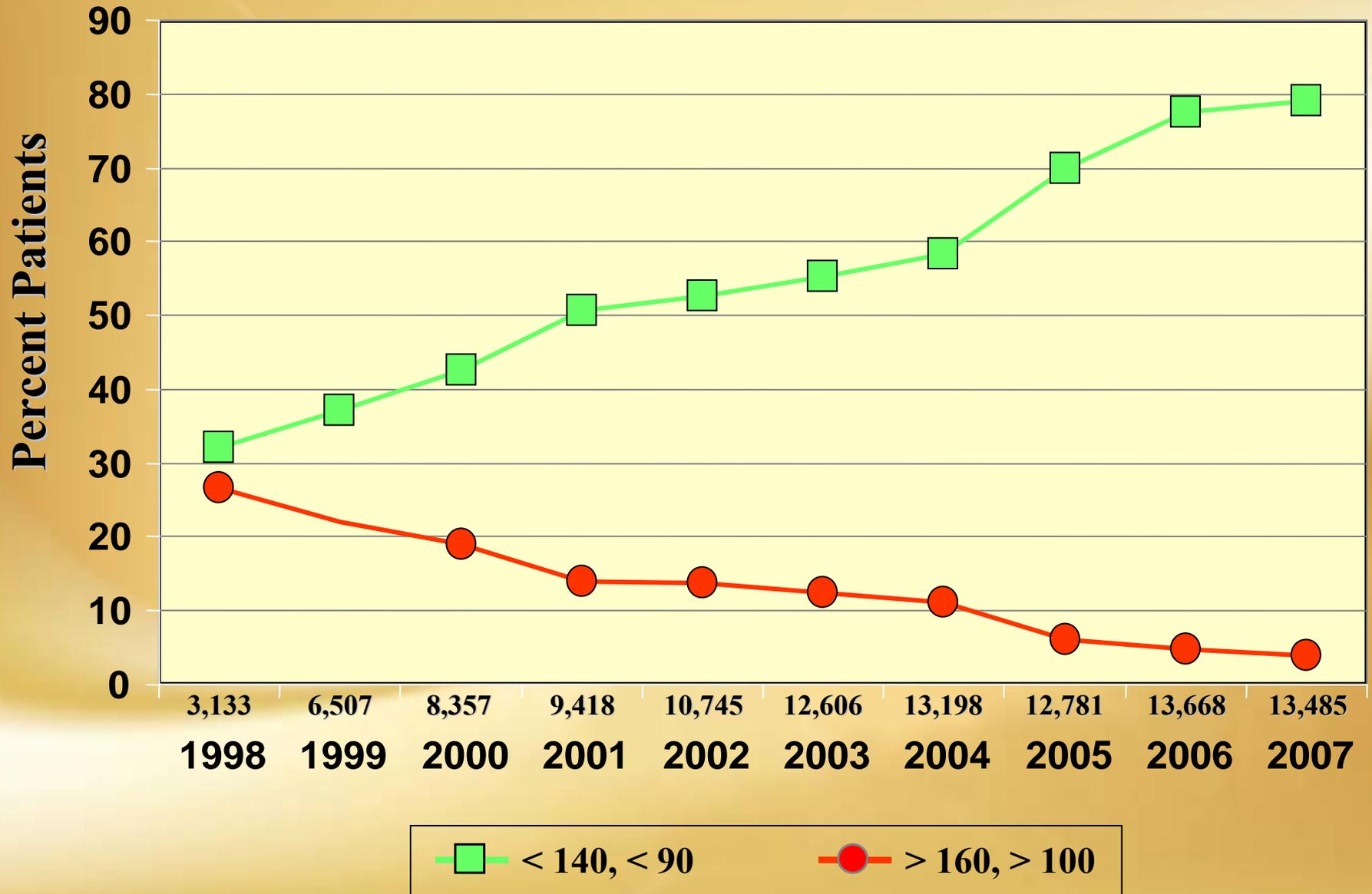
**HTN Assess for Elevated BP>140/90:**  
**Repeat BP**  
**142/84**  
**The patient's blood pressure is usually adequately controlled. No medication changes are indicated at this time.**  
**The patient was educated on the role of weight control, low salt diet and a heart healthy diet in the control of blood pressure.**  
**The importance of regular aerobic exercise 30 minutes at least**

Patient Educations: HTN Lifestyle Modifications  
Health Factors: HTN MED CHANGES NOT NEEDED  
Blood Press. 142/84 Feb 13,2004 11:31

Postings  
CA  
sing Inform Change...

# Improving Hypertensives

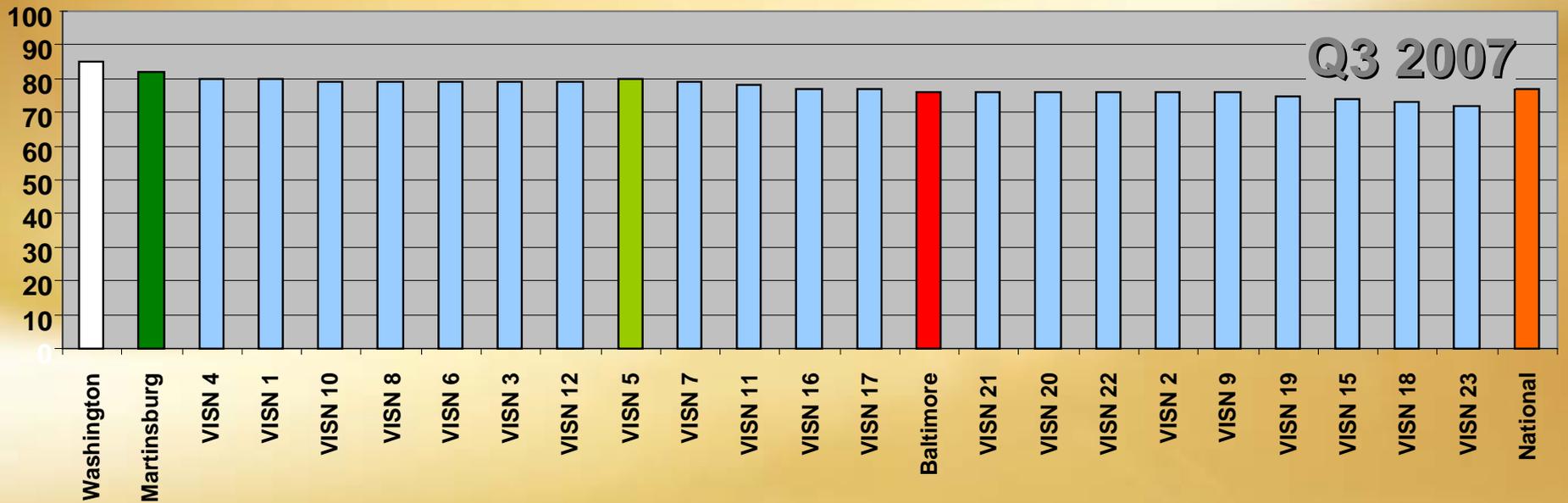
## Washington, DC VAMC



# **Systematic Response in Hypertensive Patients**

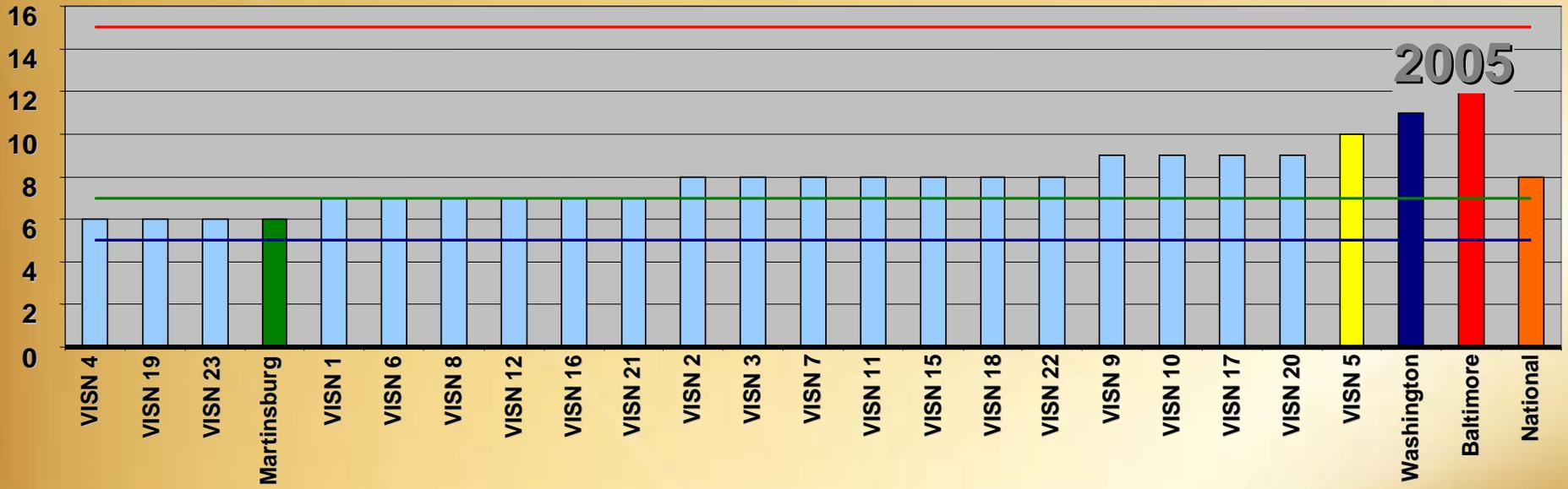
- **Reminder Due should be addressed in all clinics.**
- **Elevated Blood pressure should be repeated two or three times. The lowest one counts.**
- **Treatment change should follow continued elevations.**
- **Remeasure BP in nurse run or other clinics in less than 2 weeks.**
- **Increase the availability of subspecialty clinics for those who have continued elevations.**

# HTN BP $\leq$ 140 / 90 2005 – Q3 2007

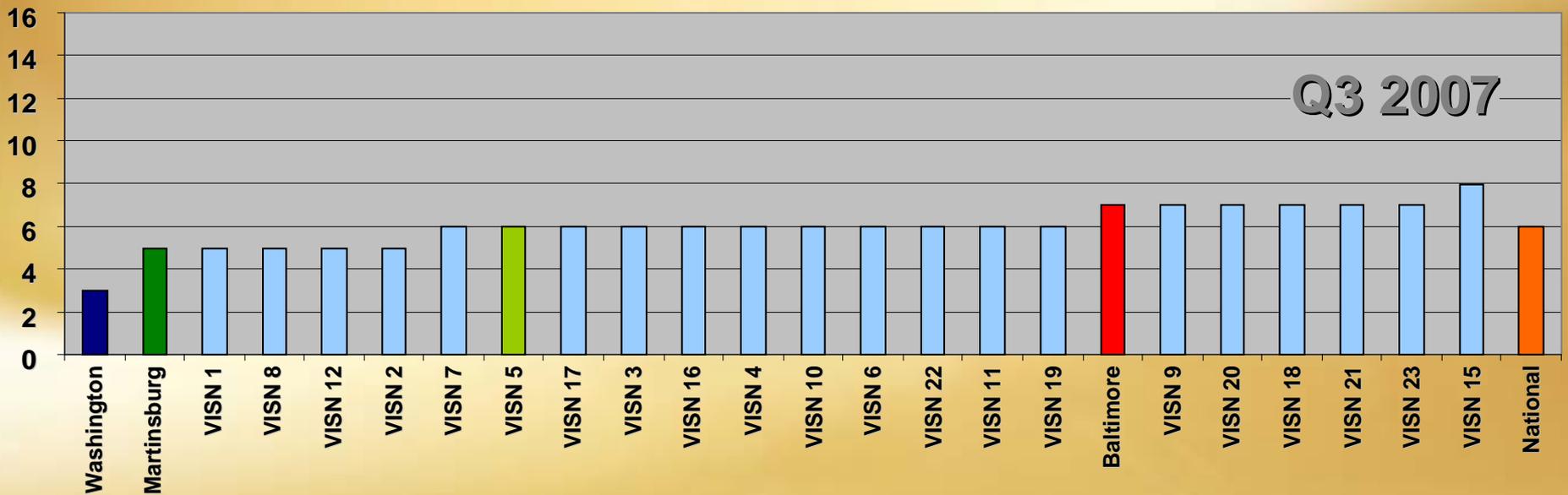


# HTN BP > 160 / 100 2005 – Q3 2007

2005



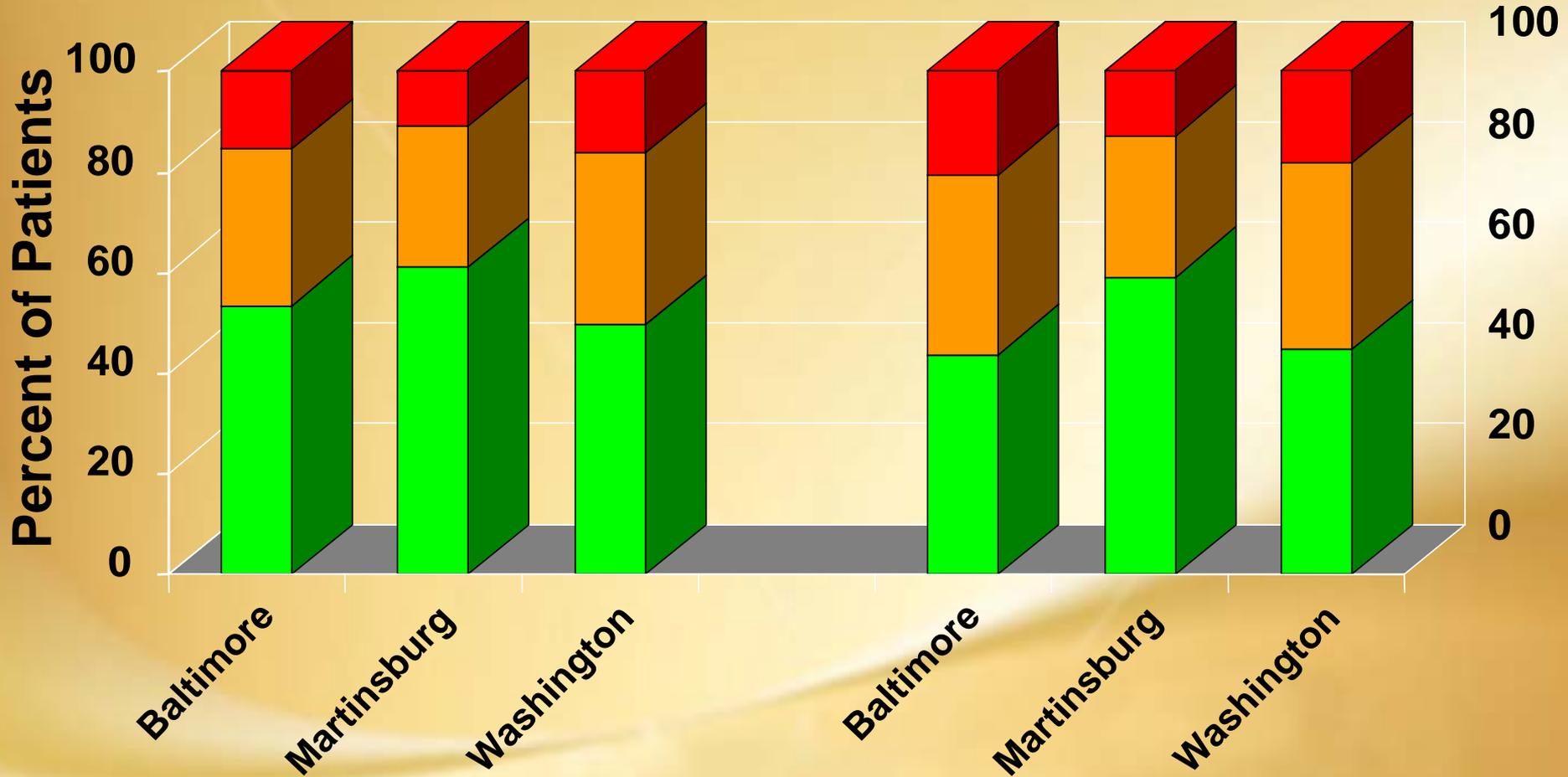
Q3 2007



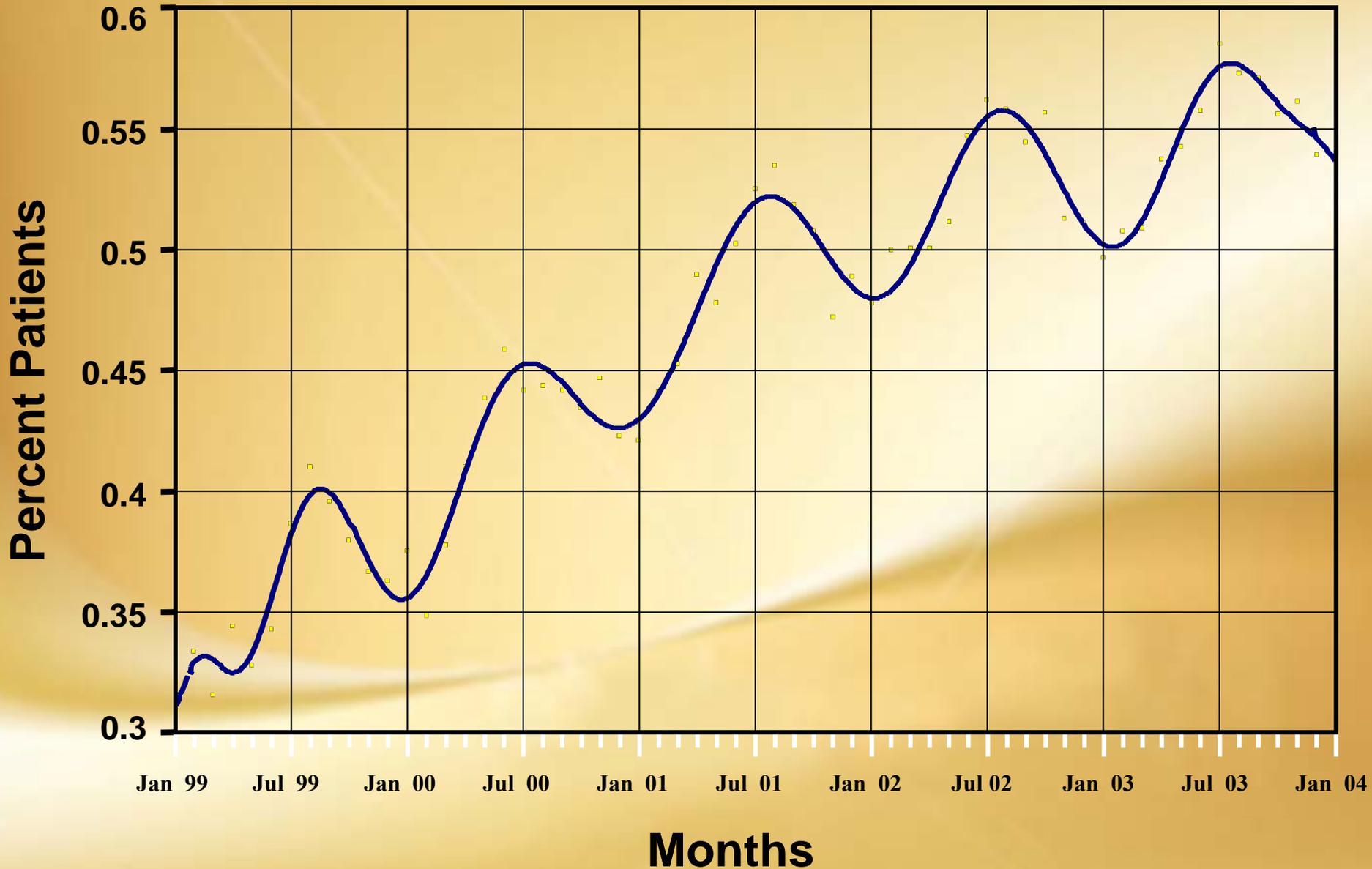
# Analysis at 4 month Interval

September 20, 2001

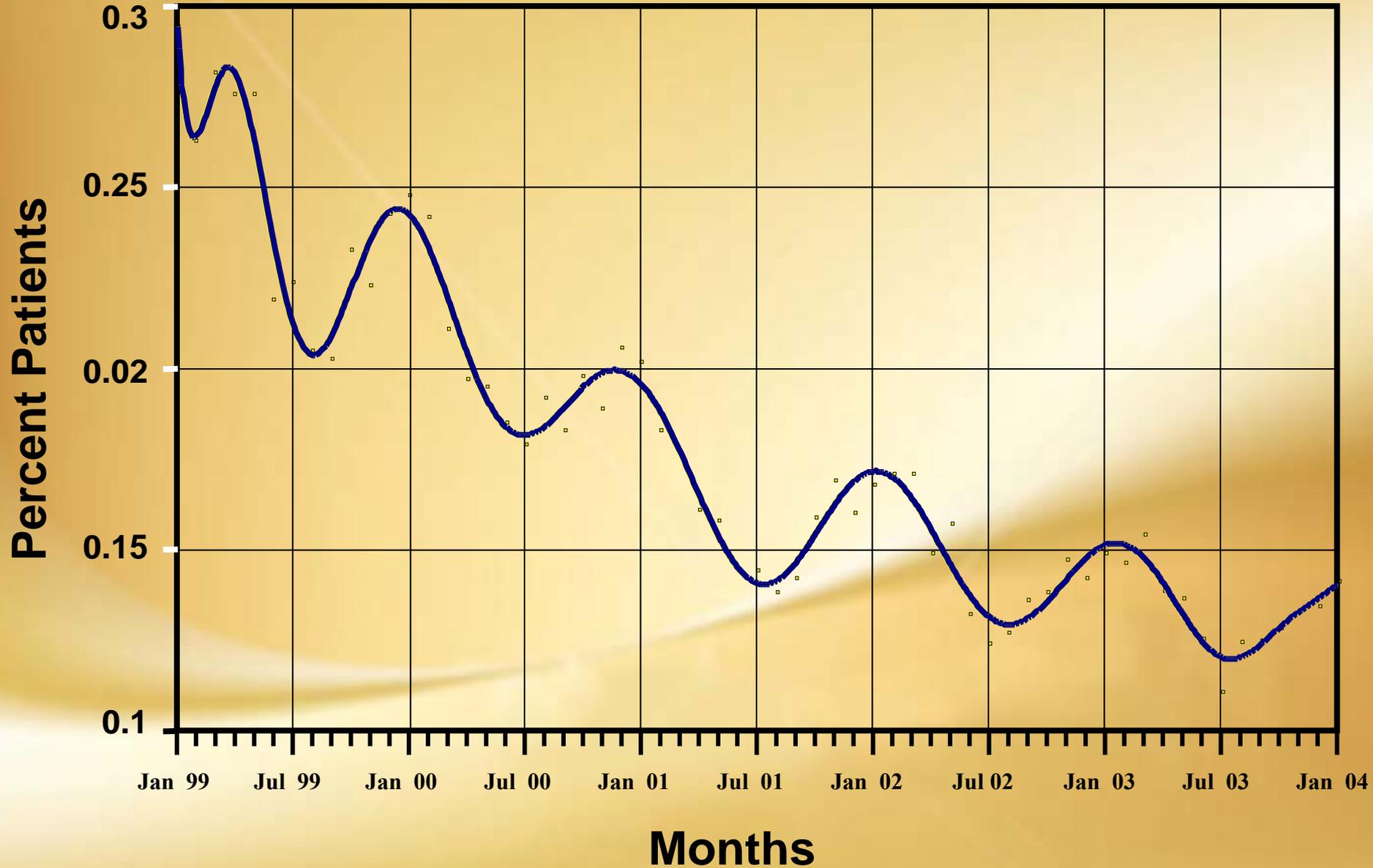
January 3, 2002



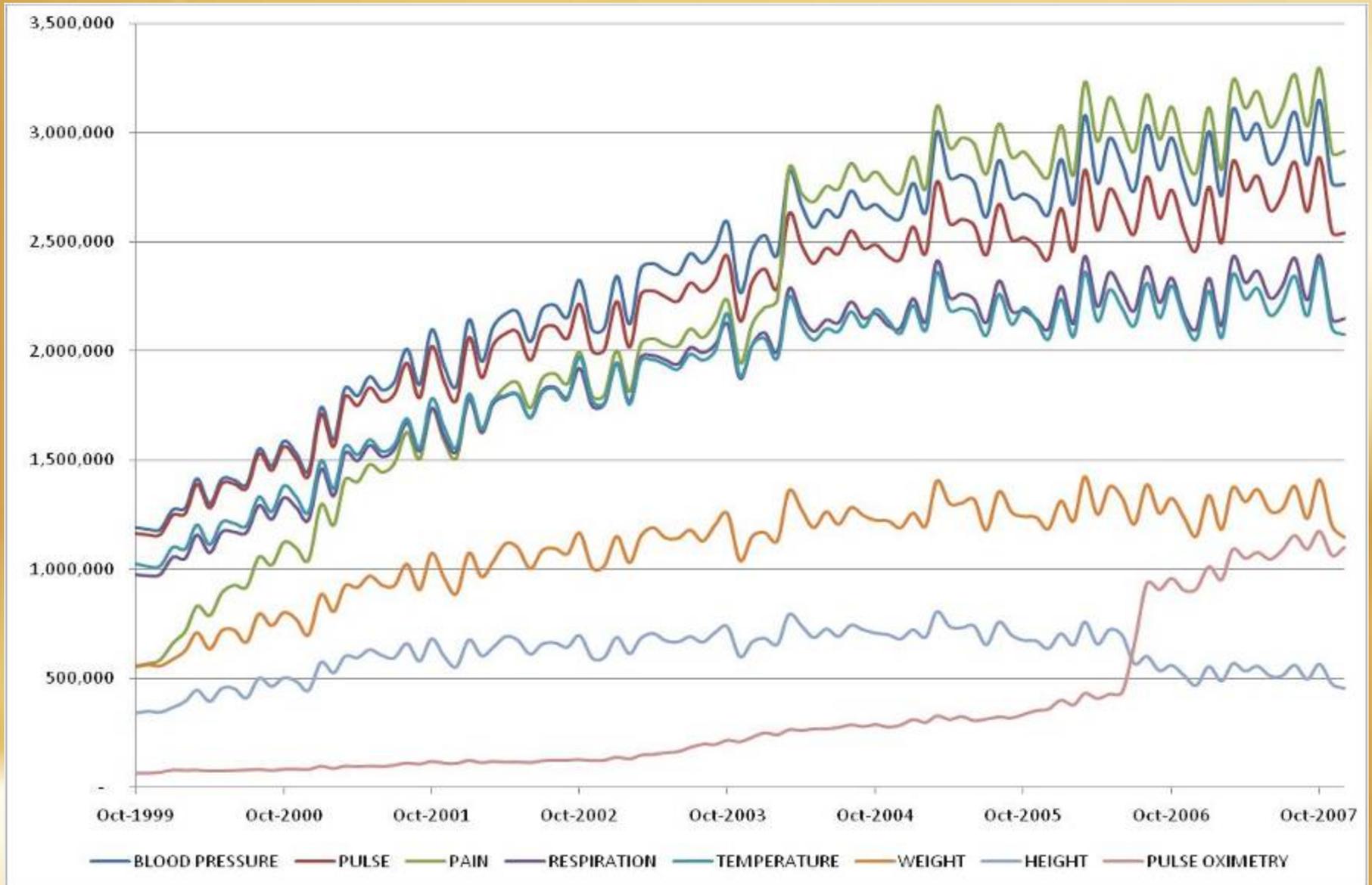
# Hypertensive Patients Returning to $< 140 / < 90$



# Hypertensive Patients with BP > 160 > 100



# VistA/HDR: Vital Sign History



● Anchorage, AK

Los Angeles, CA

● Honolulu, HI



Portland, OR

Fargo, ND

Minneapolis, MN

Chicago, IL

Philadelphia, PA

Washington, DC

Boston, MA

New York, NY

Baltimore, MD

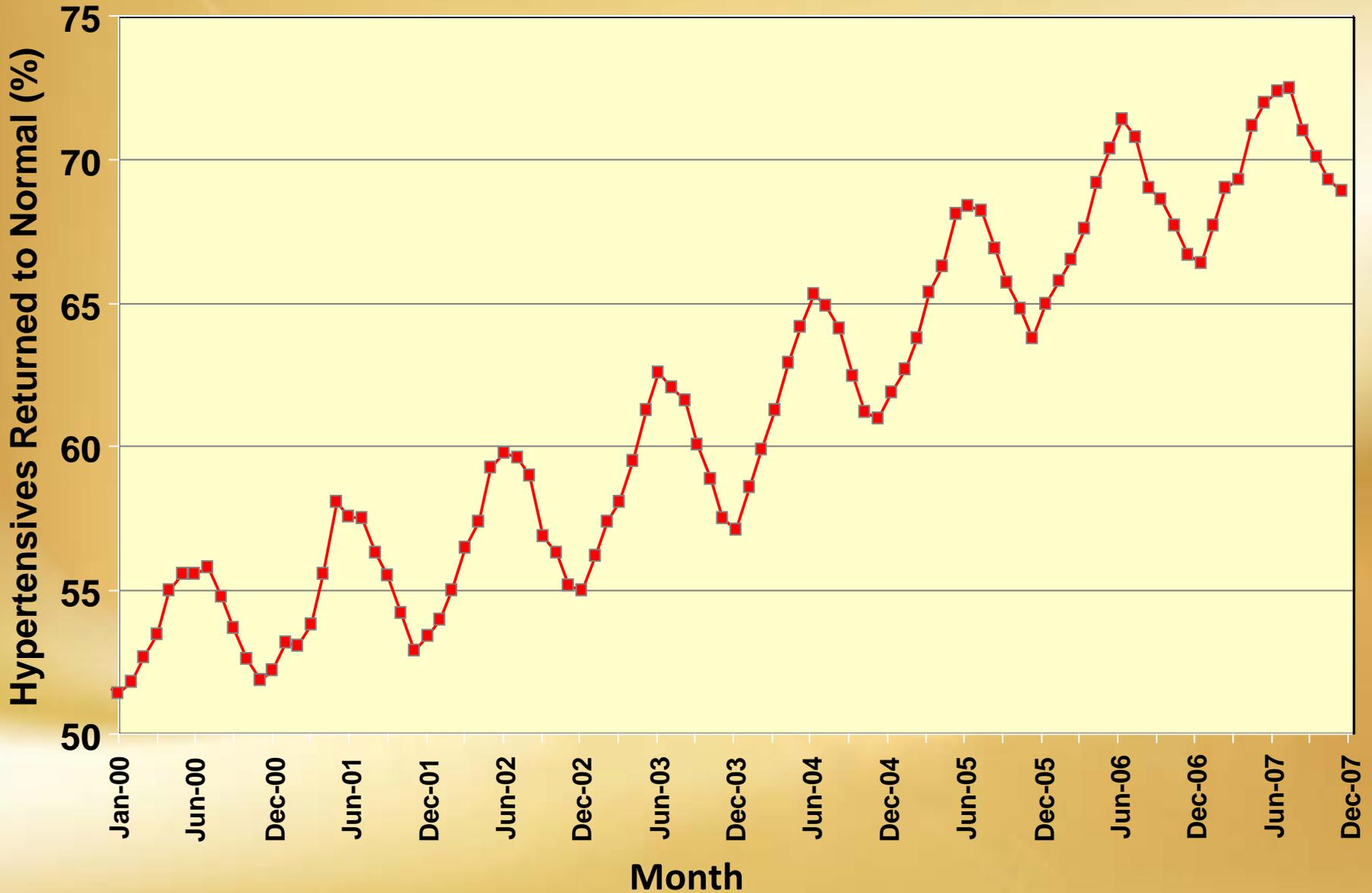
Houston, TX

Miami, FL

San Juan, PR

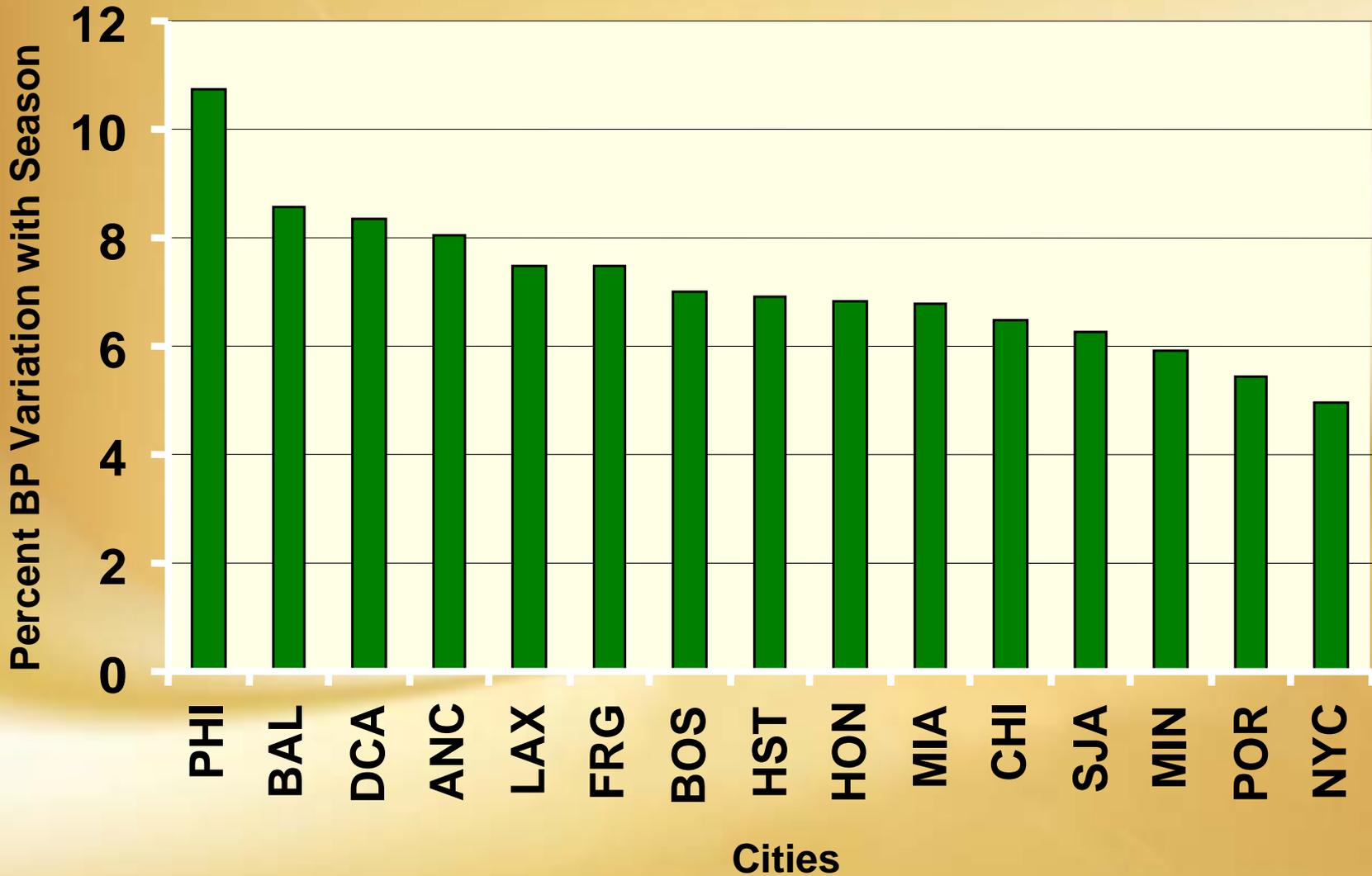
# Controlling Hypertension Showing Seasonal Variation

## 15 Cities – 522,264 patients



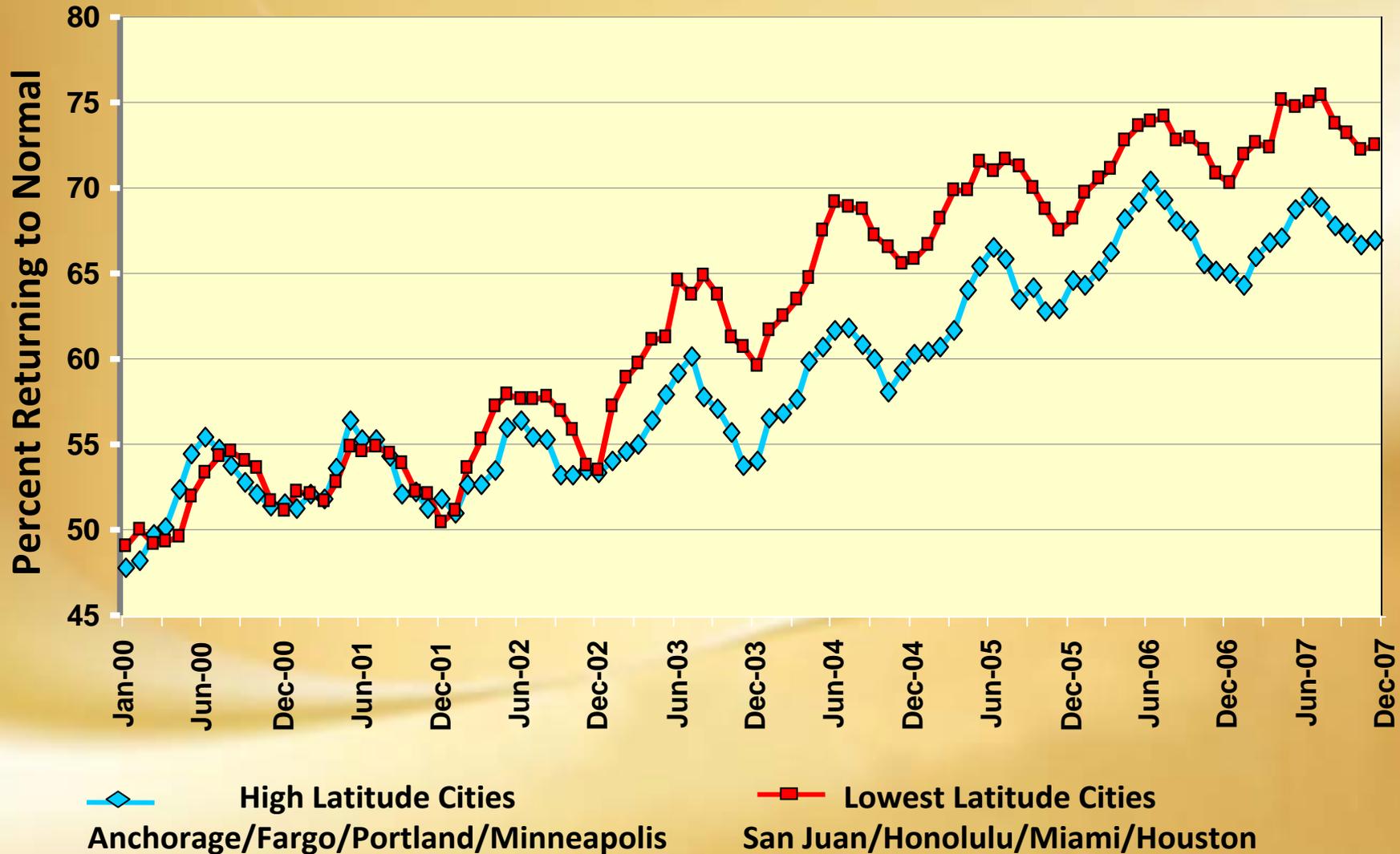
# Hypertensives Returning to Normal

## Season Effect by City Rank



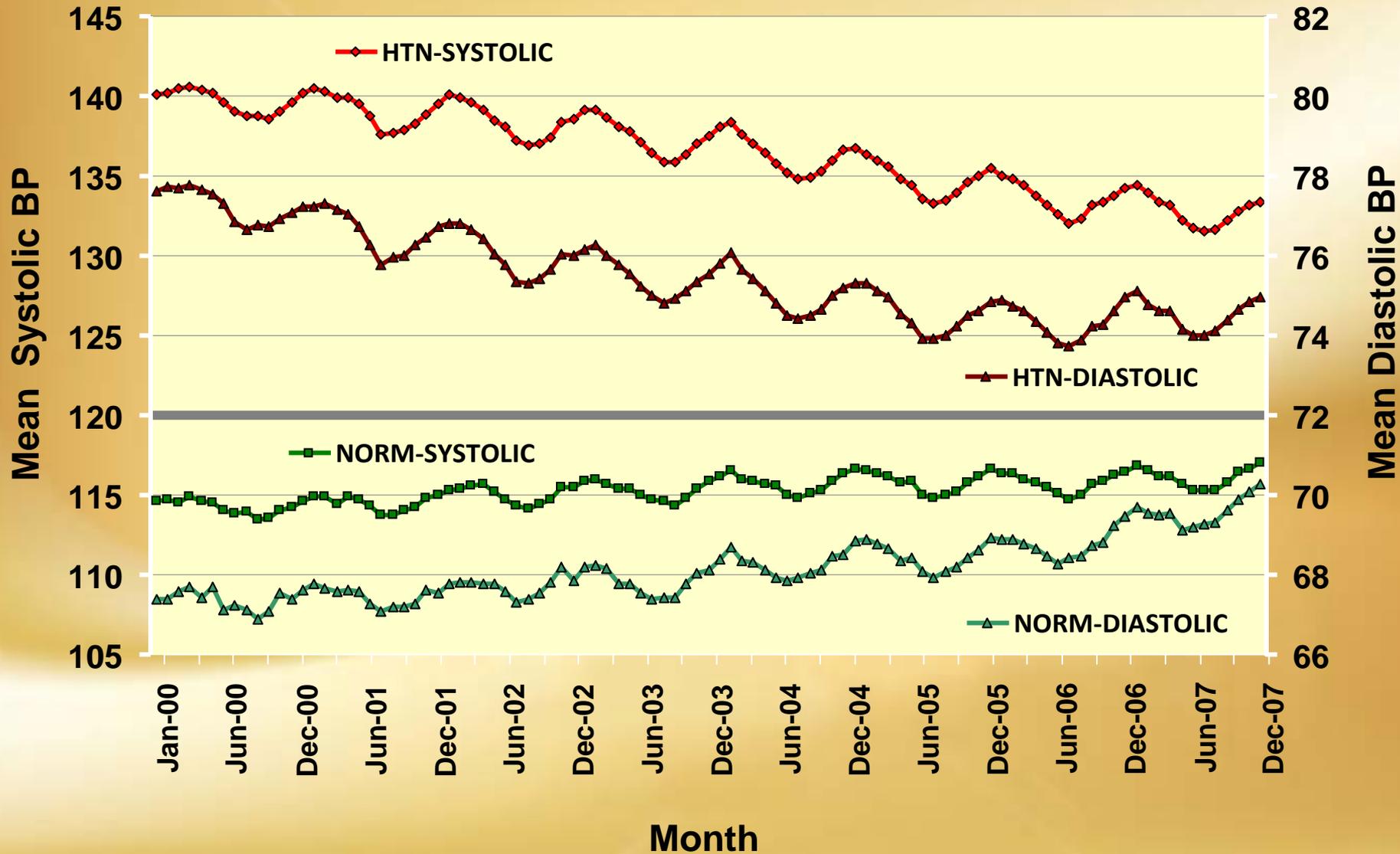
# Latitude and Seasonal Variation

## 4 Cities with the Highest vs. 4 with the Lowest Latitude



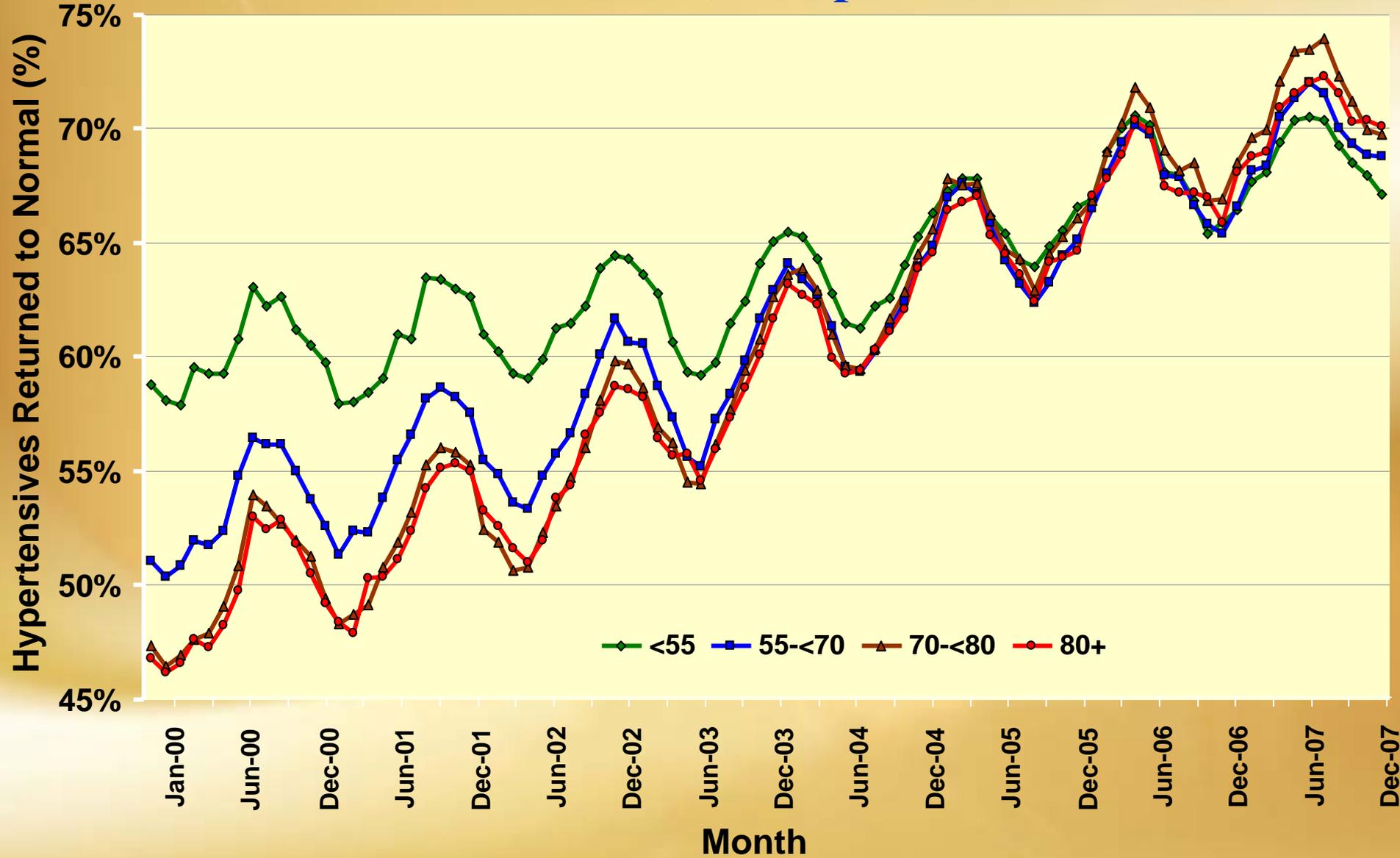
# BP Seasonal Variation

## Hypertensives vs. Normotensives



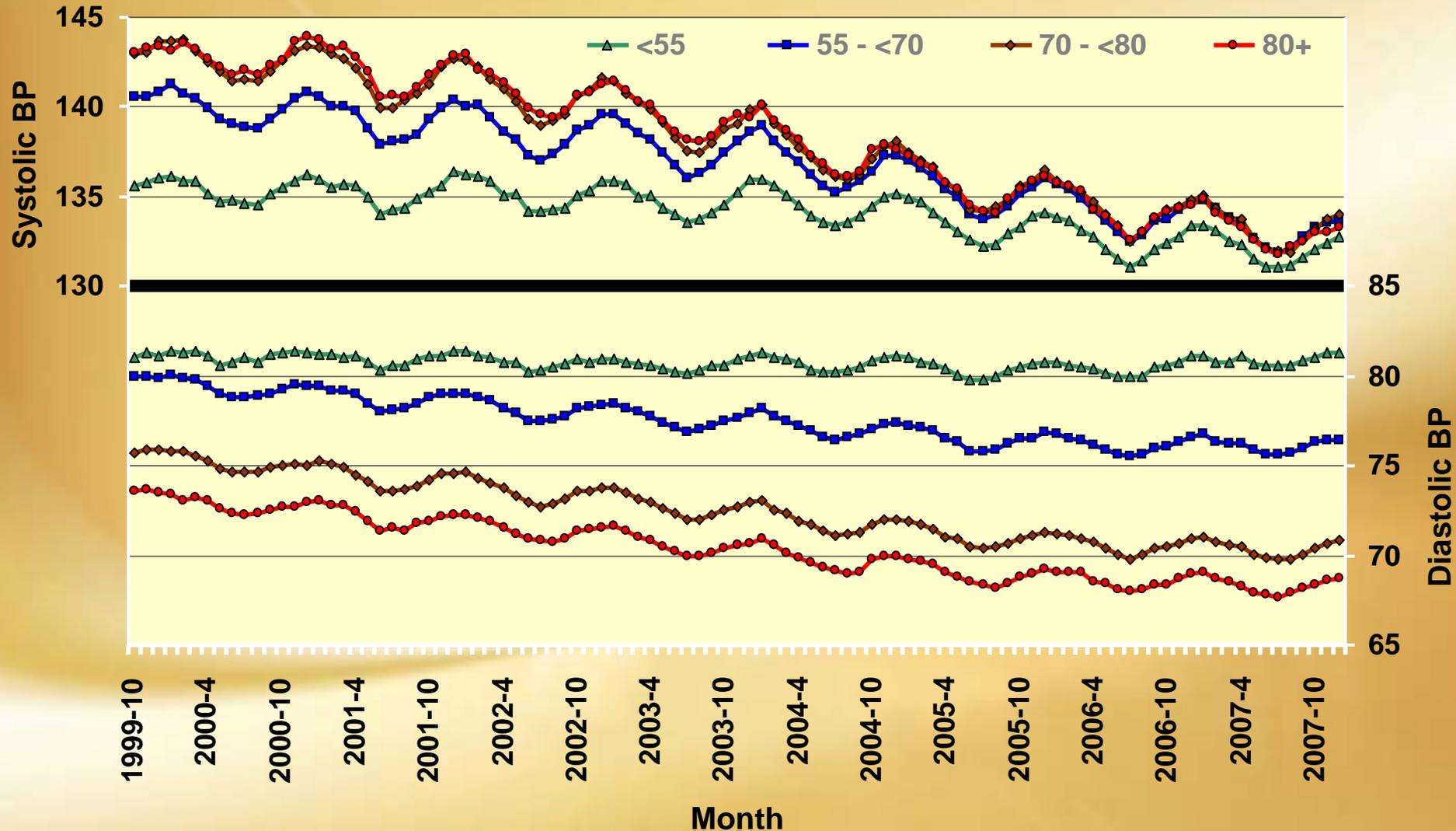
# Controlling Hypertension by Age

15 Cities – 522,264 patients

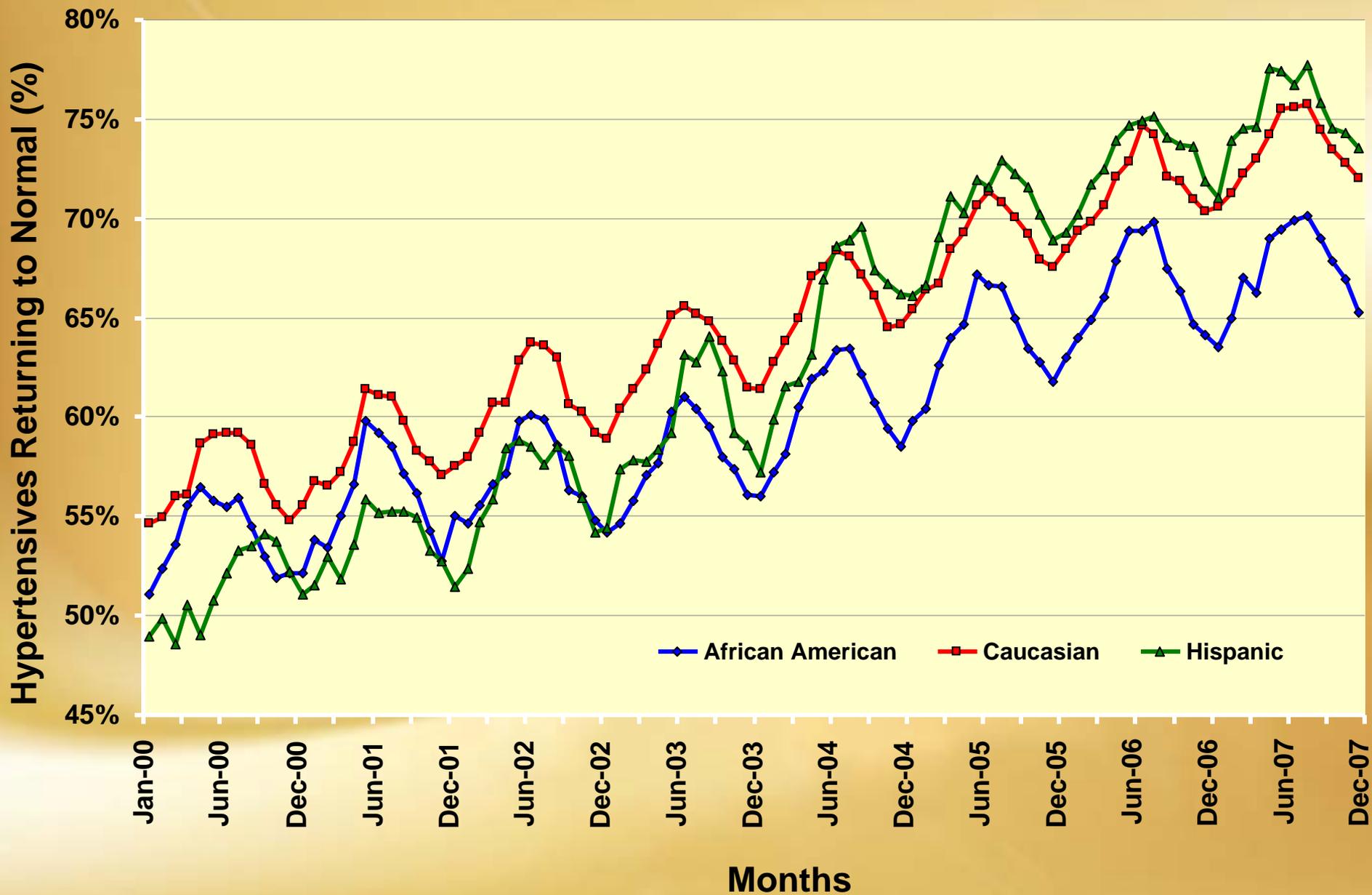


# Systolic and Diastolic BP by Age

## 15 Cities – 522,264 hypertensive patients

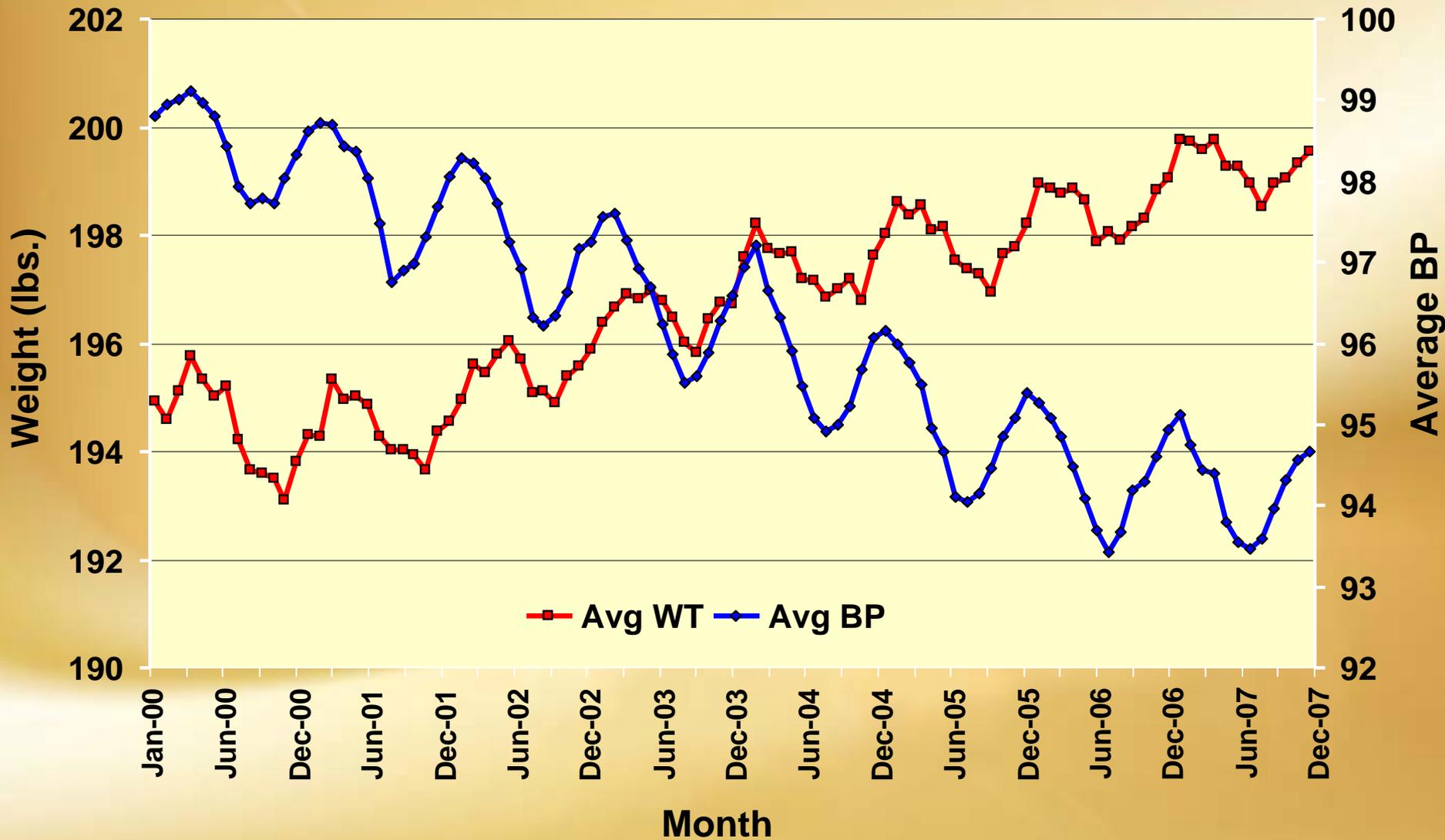


# Controlling Hypertension by Race



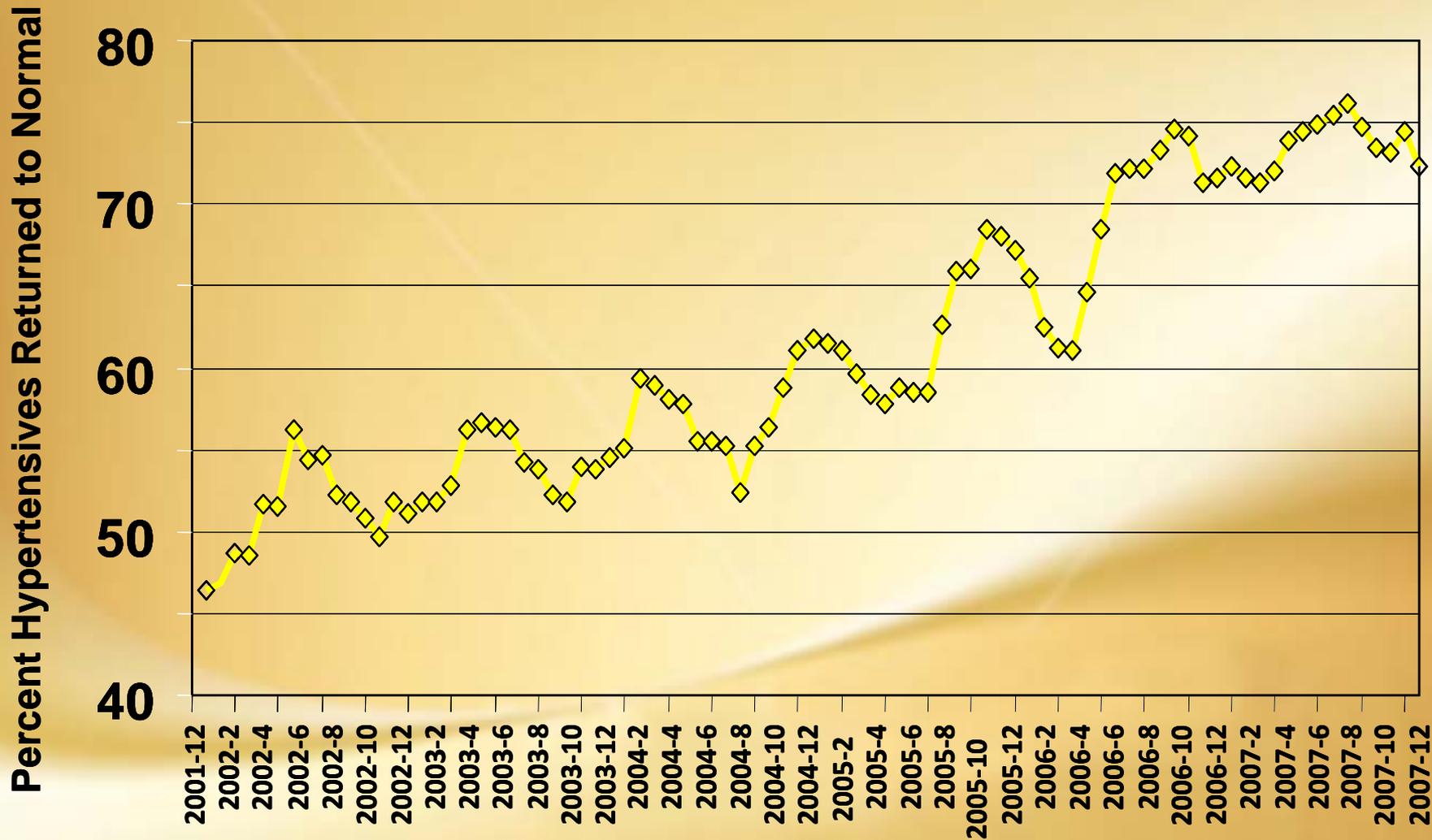
# Seasonal Variation in Weight

15 Cities – 522,264 hypertensive patients



# HTN Showing Improved Winter Treatment

## Washington, DC



# VA Research: Improving Veterans' Lives



Veterans Health Administration  
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Improving Veterans' Lives → [www.research.va.gov](http://www.research.va.gov)

# **Fitness Lowers Mortality in Veterans with Type 2 Diabetes**

**Peter Kokkinos, PhD**

***Veterans Affairs Medical Center  
Washington DC • May 1, 2009***



Veterans Health Administration

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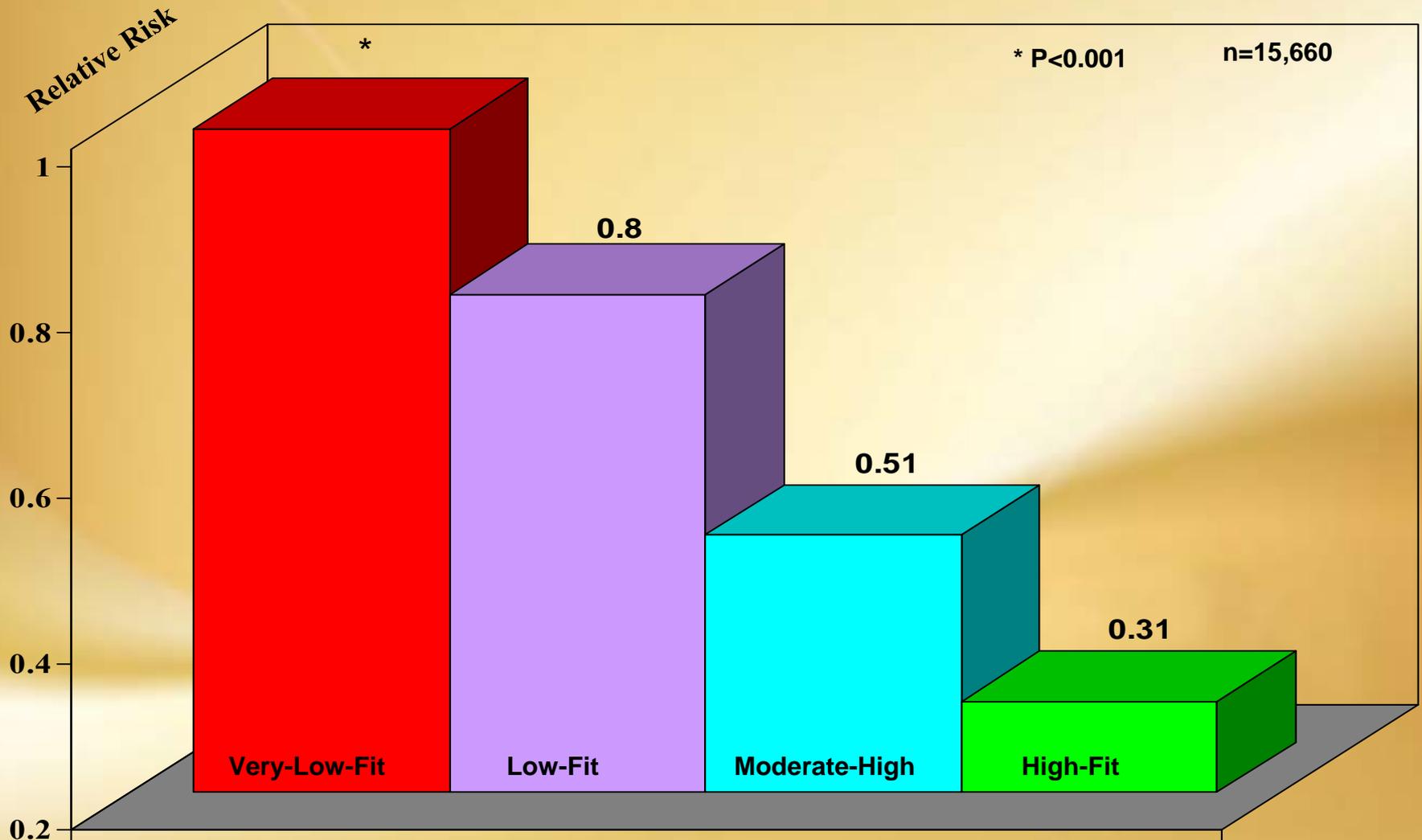
# **Special Thanks to All Veterans for Making this study possible!**

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- Dr. Jon Myers** Palo Alto VAMC
- Dr. Eric Nysten** DC VAMC
- Dr. Marc Blackman** DC VAMC
- Dr. Charles Faselis** DC VAMC
- Dr. Steven Singh** DC VAMC

# Fitness and All-Cause Mortality in Veterans

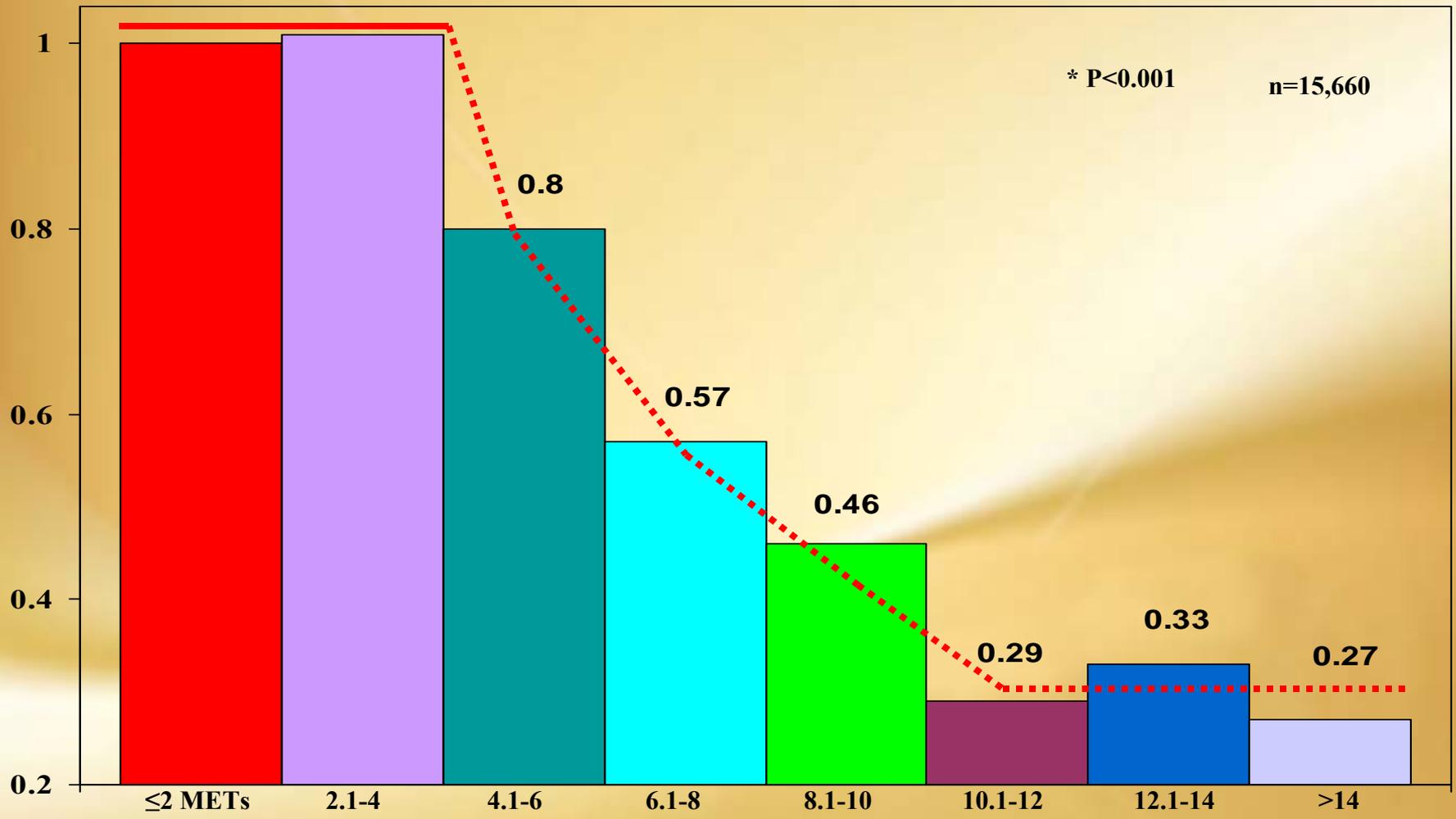
Kokkinos et al. Circulation 2008; 117:614-622



# Fitness Levels and Mortality

Kokkinos et al. Circulation 2008; 117:614-622

Relative Risk

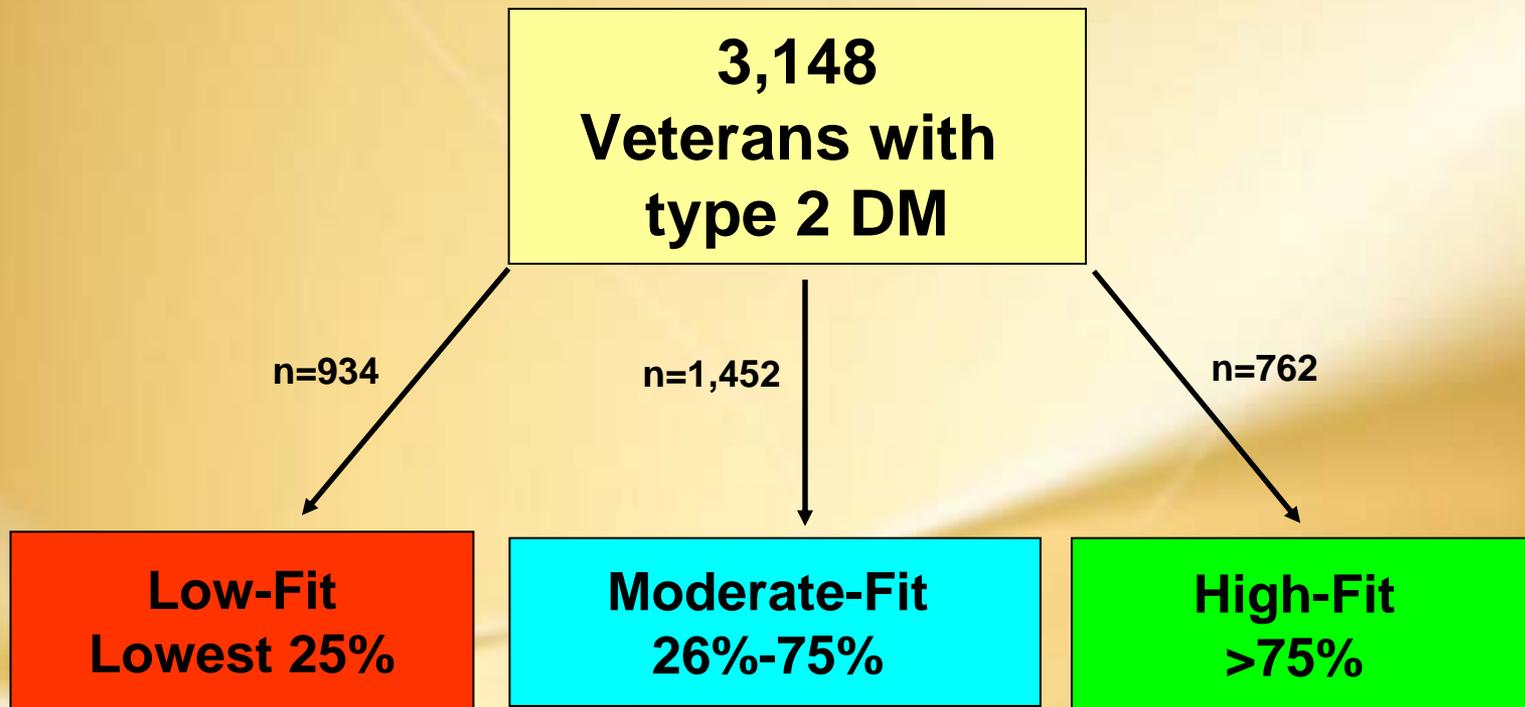


# Questions

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- **Does fitness reduce mortality risk (improve survival) in veterans with DM?**
- **Is fitness effective if DM co-exists with other risk factors?**
- **Is it effective in both young and older diabetics?**
- **Are the health benefits similar for African-Americans and Caucasians?**

# Fitness Categories are Based on Peak Exercise Time Achieved on the Treadmill Using a Standardized Protocol.



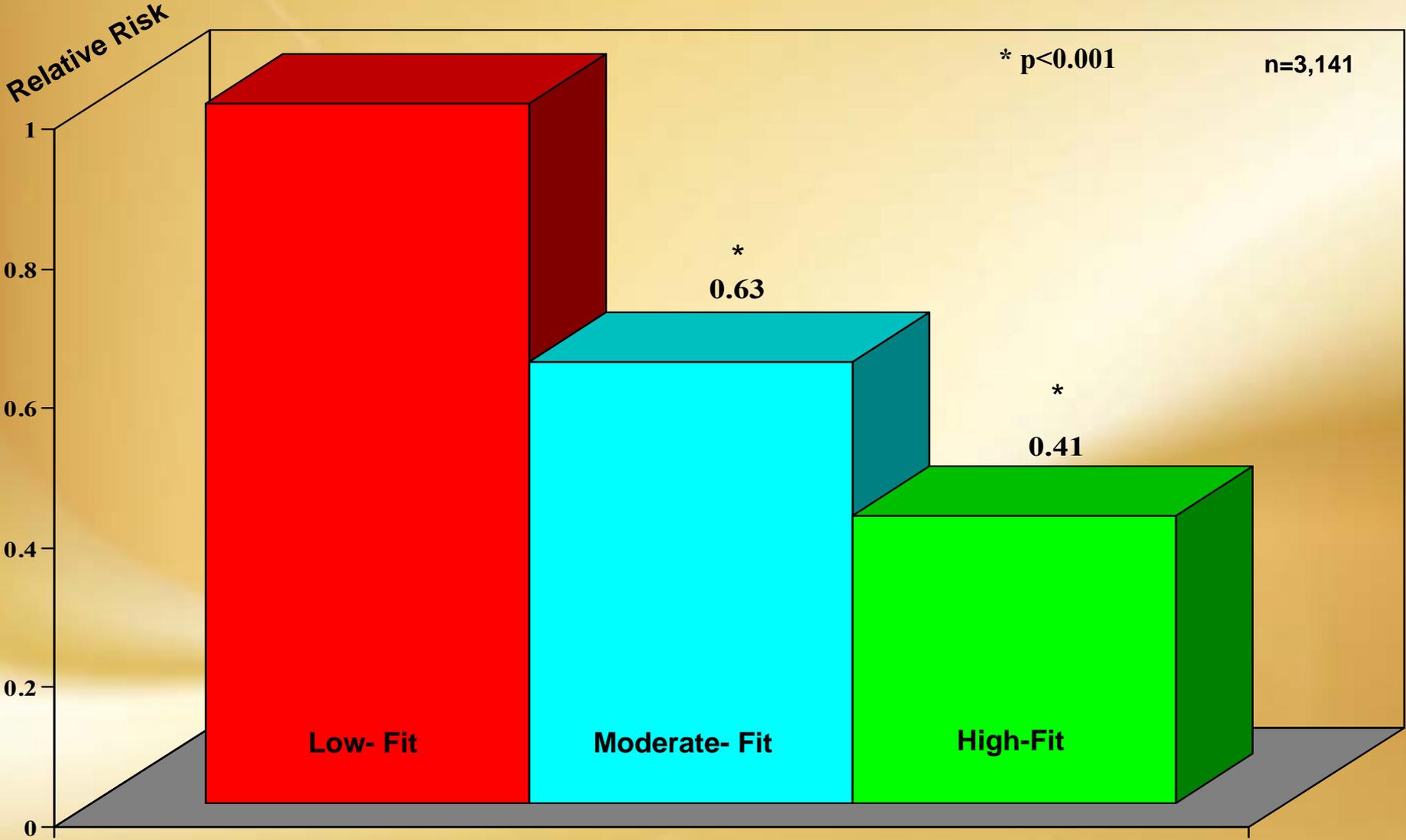
# Question 1

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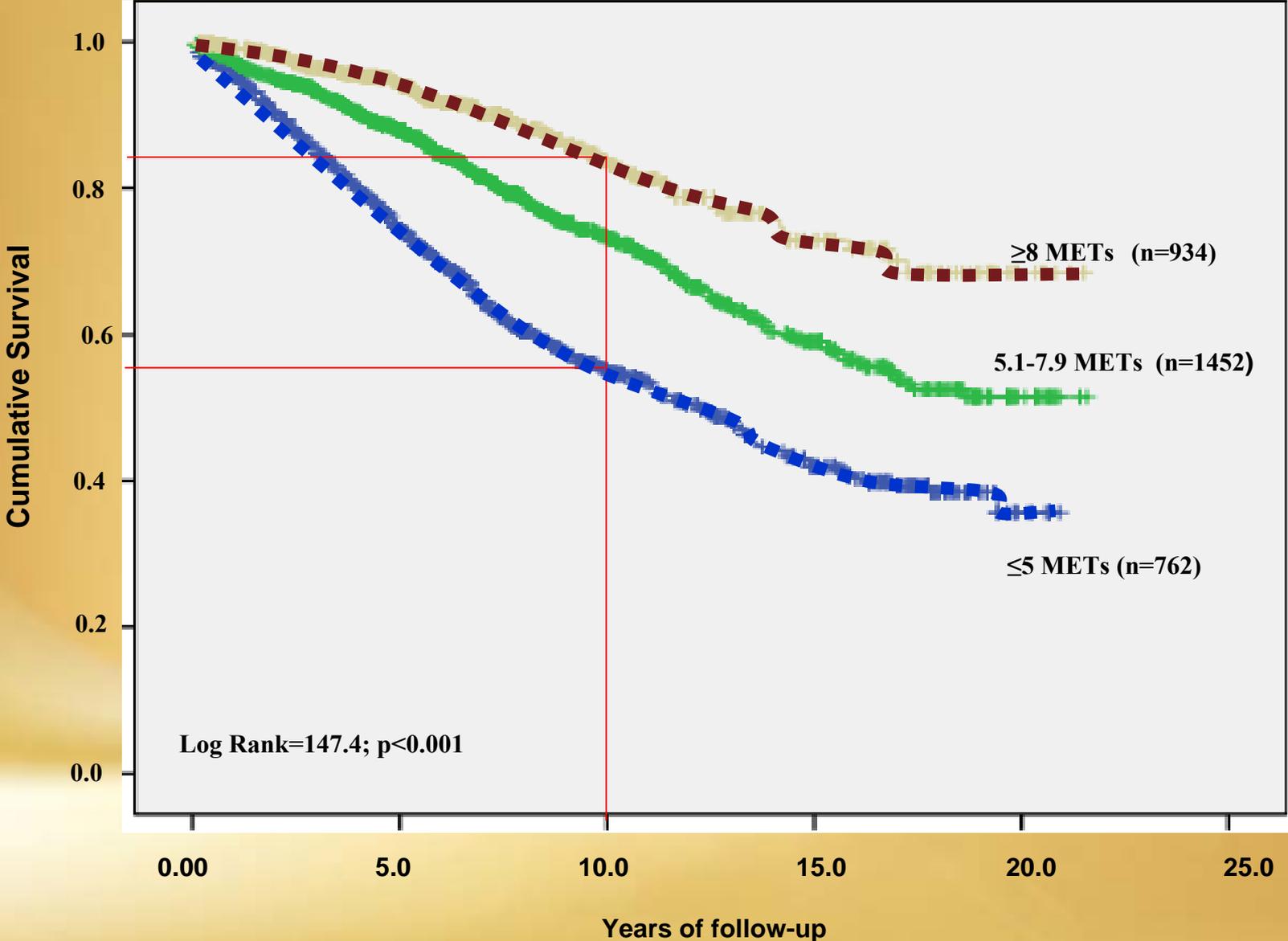
**Does fitness reduce mortality risk (improve survival) in veterans with DM?**

# Exercise Capacity and Mortality in Diabetics

Kokkinos P, et al. Diabetes Care 2009



# Survival According in Diabetic Veterans According to Fitness

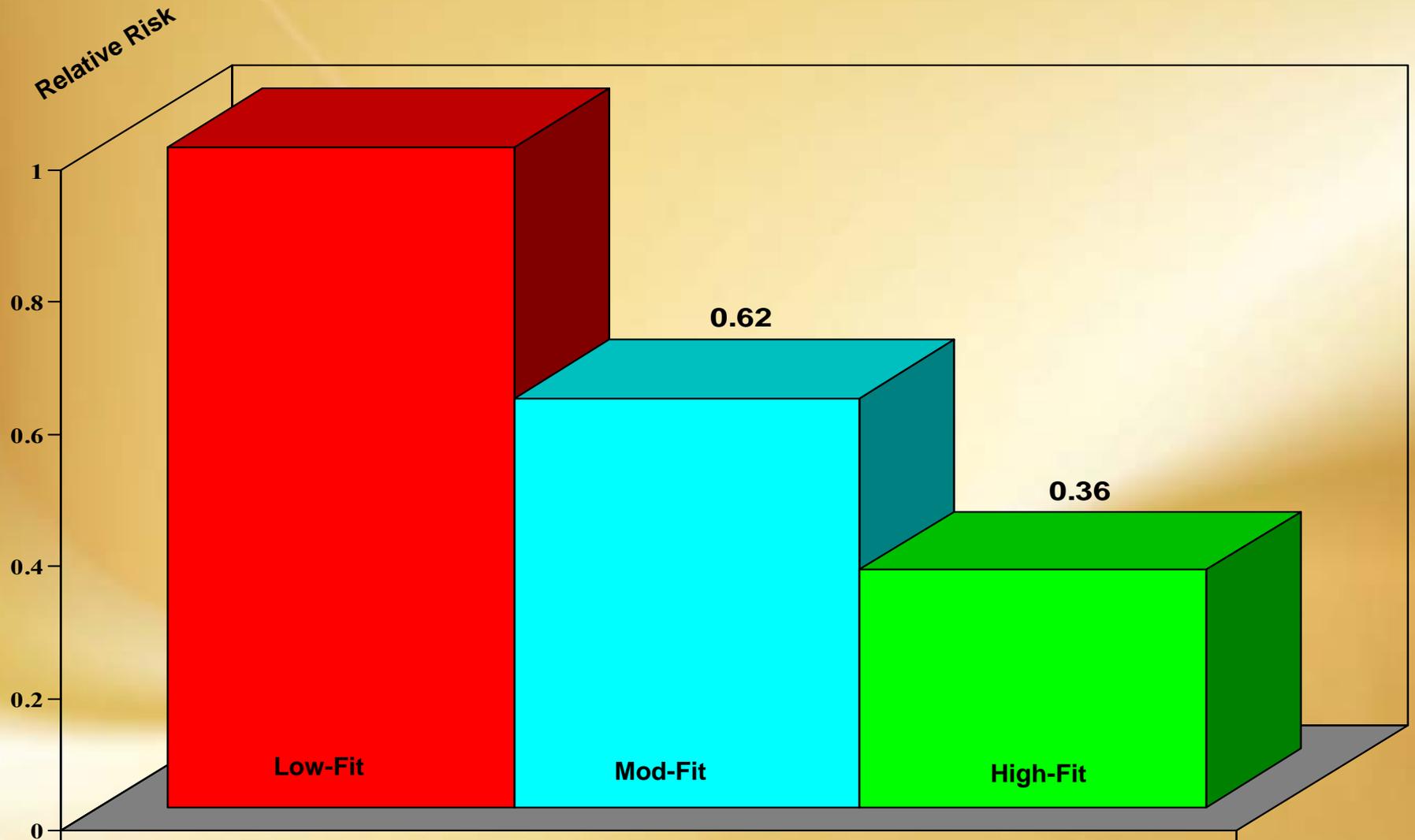


# Question 2

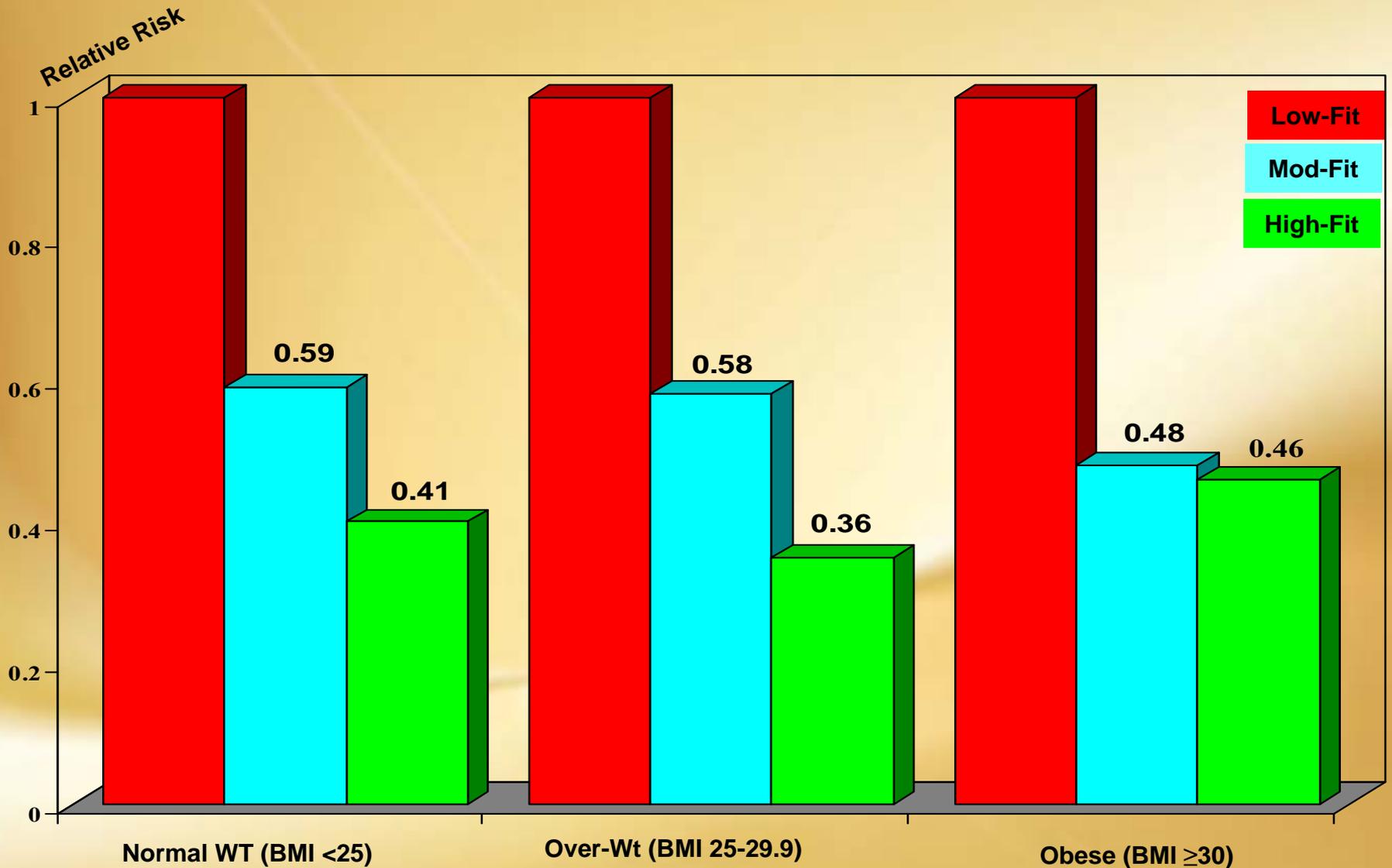
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**Is fitness effective if DM  
co-exists with other  
risk factors?**

# Fitness and Mortality in Diabetics with Hypertension



# Mortality in Diabetics According to Fitness and Fatness

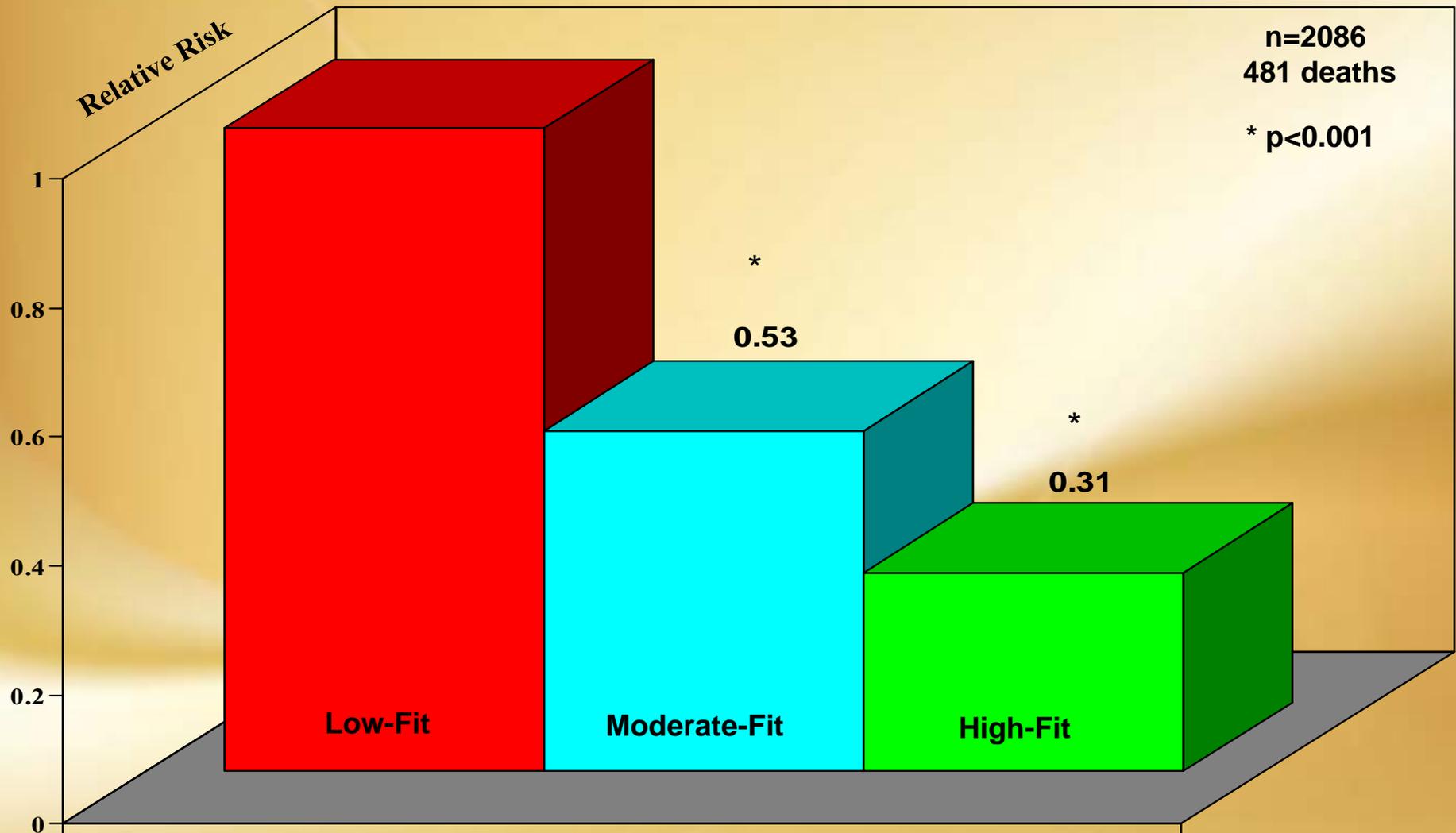


# Question 3

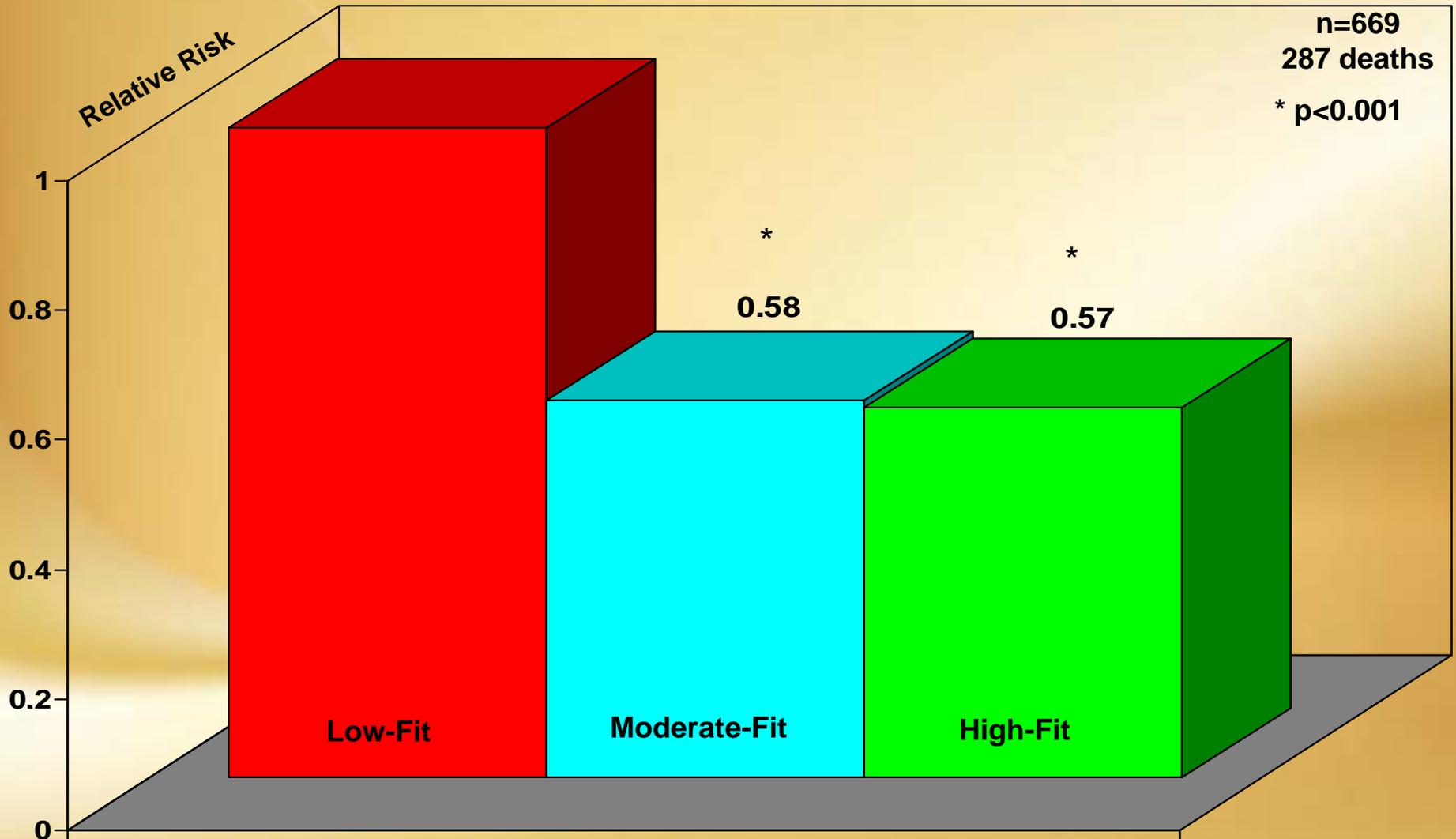
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**Is fitness effective in both young and older diabetics?**

# Fitness and Mortality in Diabetics 50-69 Years of Age



# Fitness and Mortality in Diabetics 70 Years and Older



# Question 4

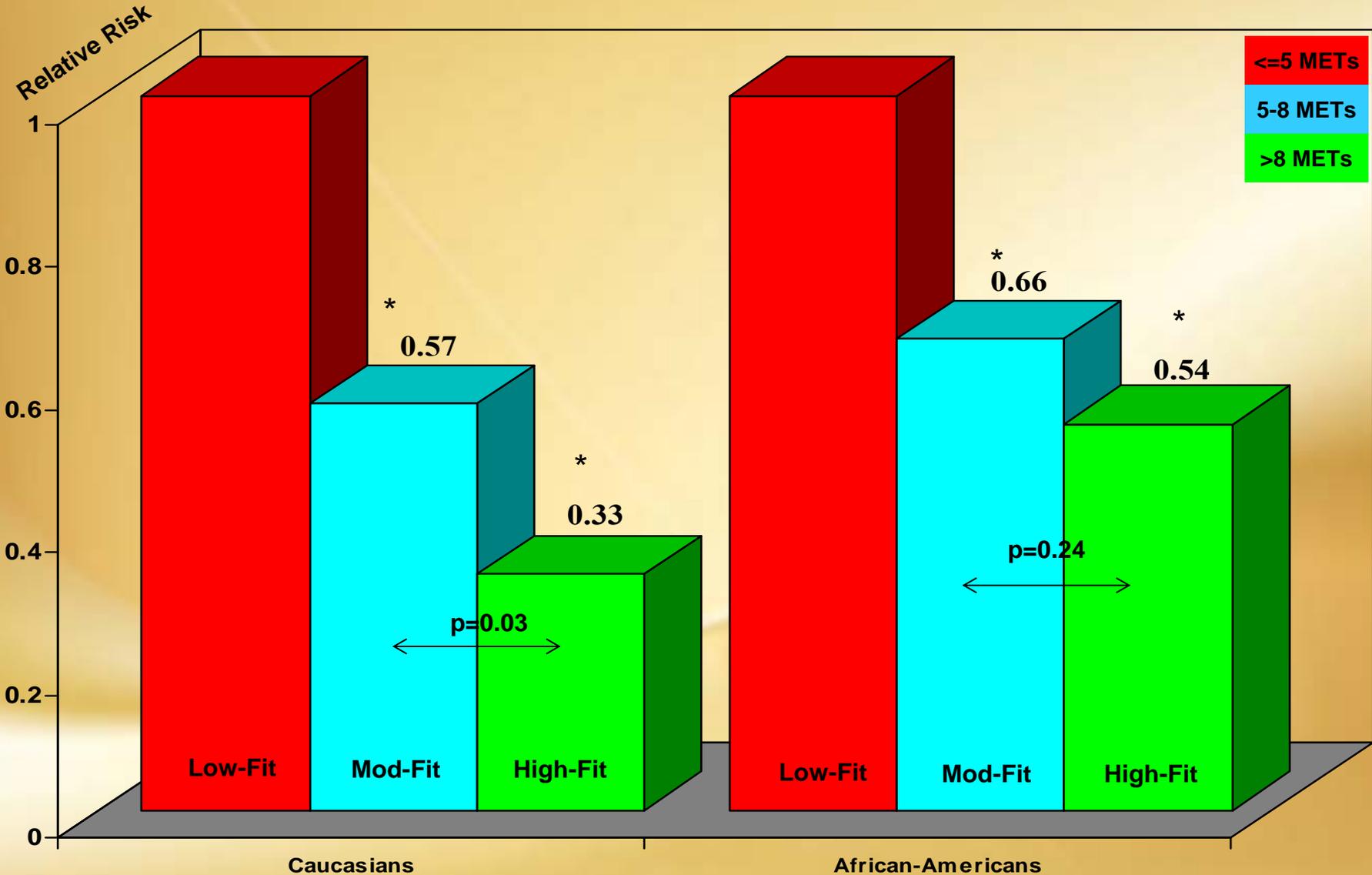
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An intriguing finding of some studies is that African-American diabetics exhibit significantly lower exercise capacity than do Caucasian diabetics.

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**Does fitness have similar beneficial effects for African-Americans and Caucasians?**

# Fitness and Mortality in Veterans with Type 2 Diabetes



# What does it Take to become Moderate to High-Fit?

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**Low-Fit**

**Moderate-Fit**

**High-Fit**

**20-40 min of Brisk walk/jog most days of the Week**

# Summary of Our Findings

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- **Increased fitness is associated with reduced risk of mortality for all diabetics regardless of age, risk factors or race.**
- **Mortality rates were lower by at least 40% and up to 70% in some cases, for Moderate and High-Fit diabetic veterans**
- **The risk was reduced by 17% for every one unit increase in the level of fitness.**

# VA Research: Improving Veterans' Lives



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# Thank You!