DIABETES AND CARDIAC SAFETY: KNOWLEDGE GAPS

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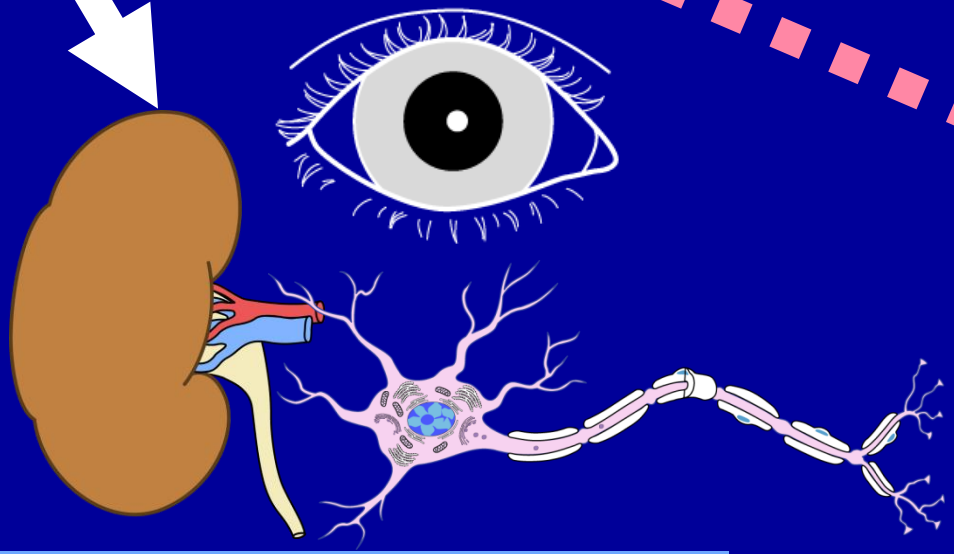
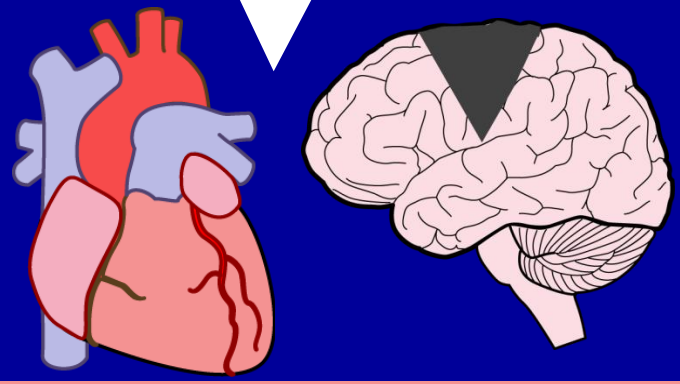
TYPE 2 DIABETES MELLITUS (T2DM) IS TWO DISTINCT DISEASES

T2DM

Chronic Hyperglycemia

Hypertension
Dyslipidemia
Obesity
Endothelial dysfn
Insulin Resistance
Inflammation



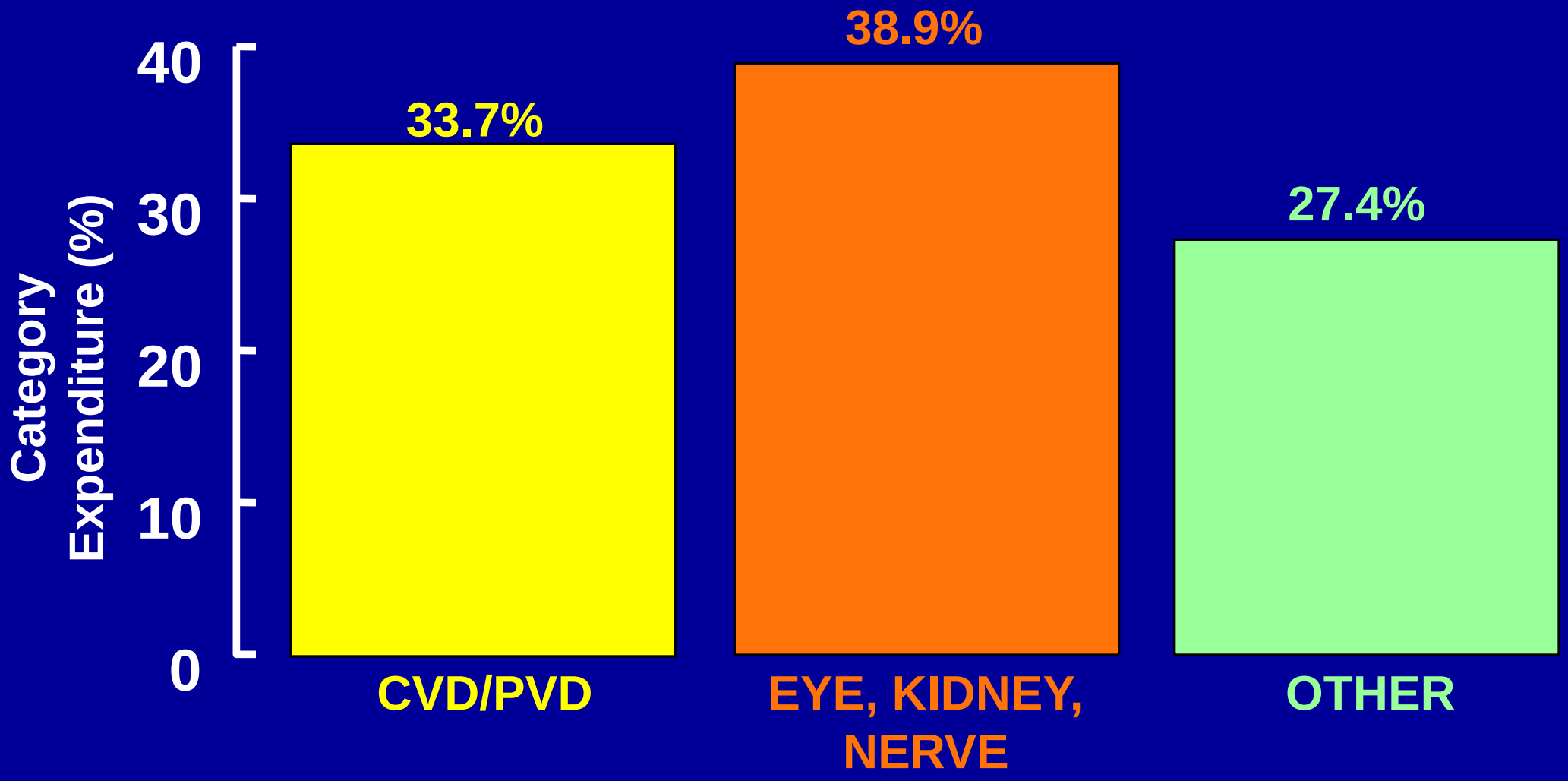


MICROVASCULATURE

MACROVASCULATURE

2007 ECONOMIC COST ($175 billion) OF DIABETES IN U.S. BY CATEGORY

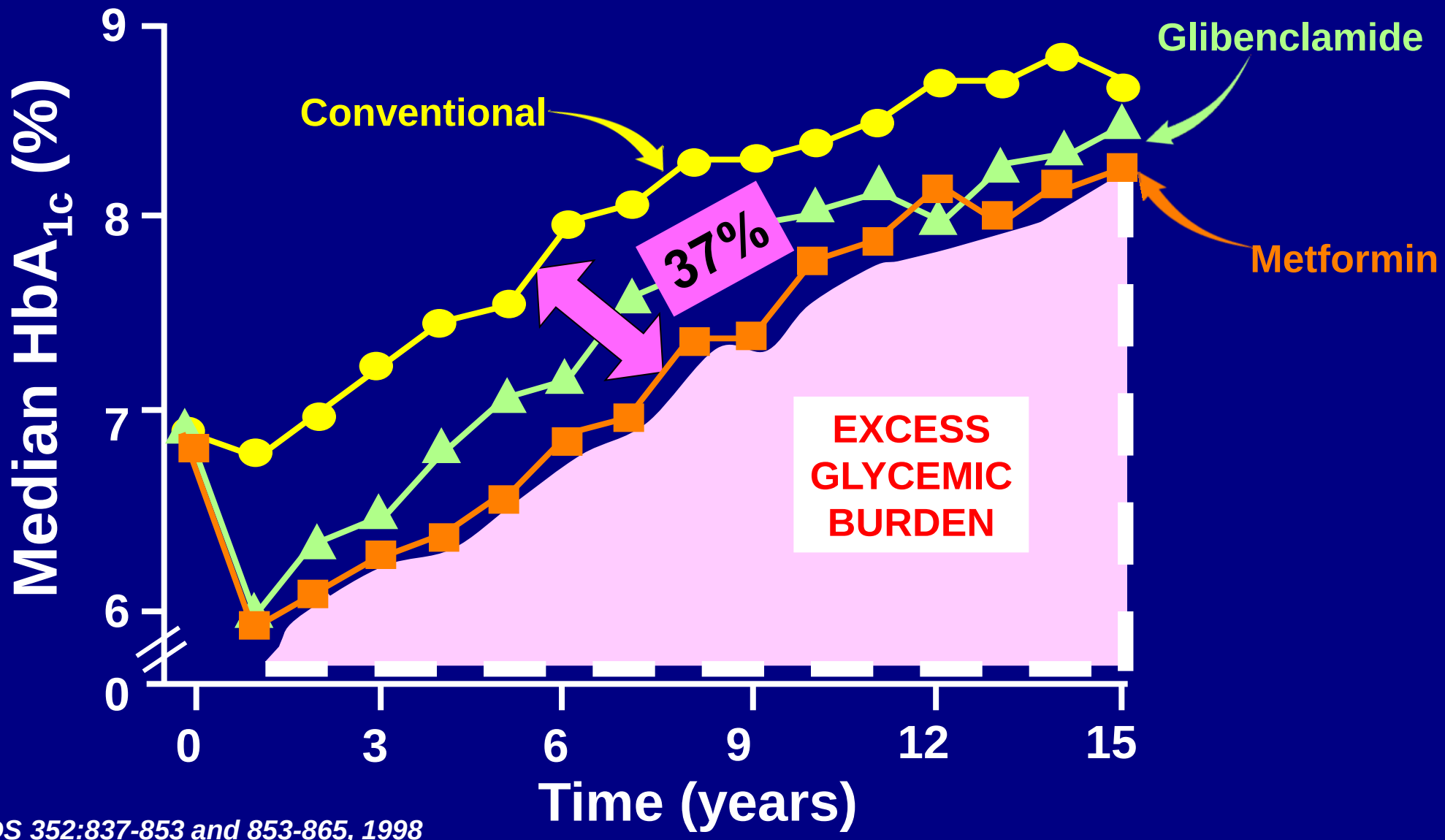
ADA, Diabetes Care 31:596-615,2008



MICROVASCULAR COMPLICATIONS

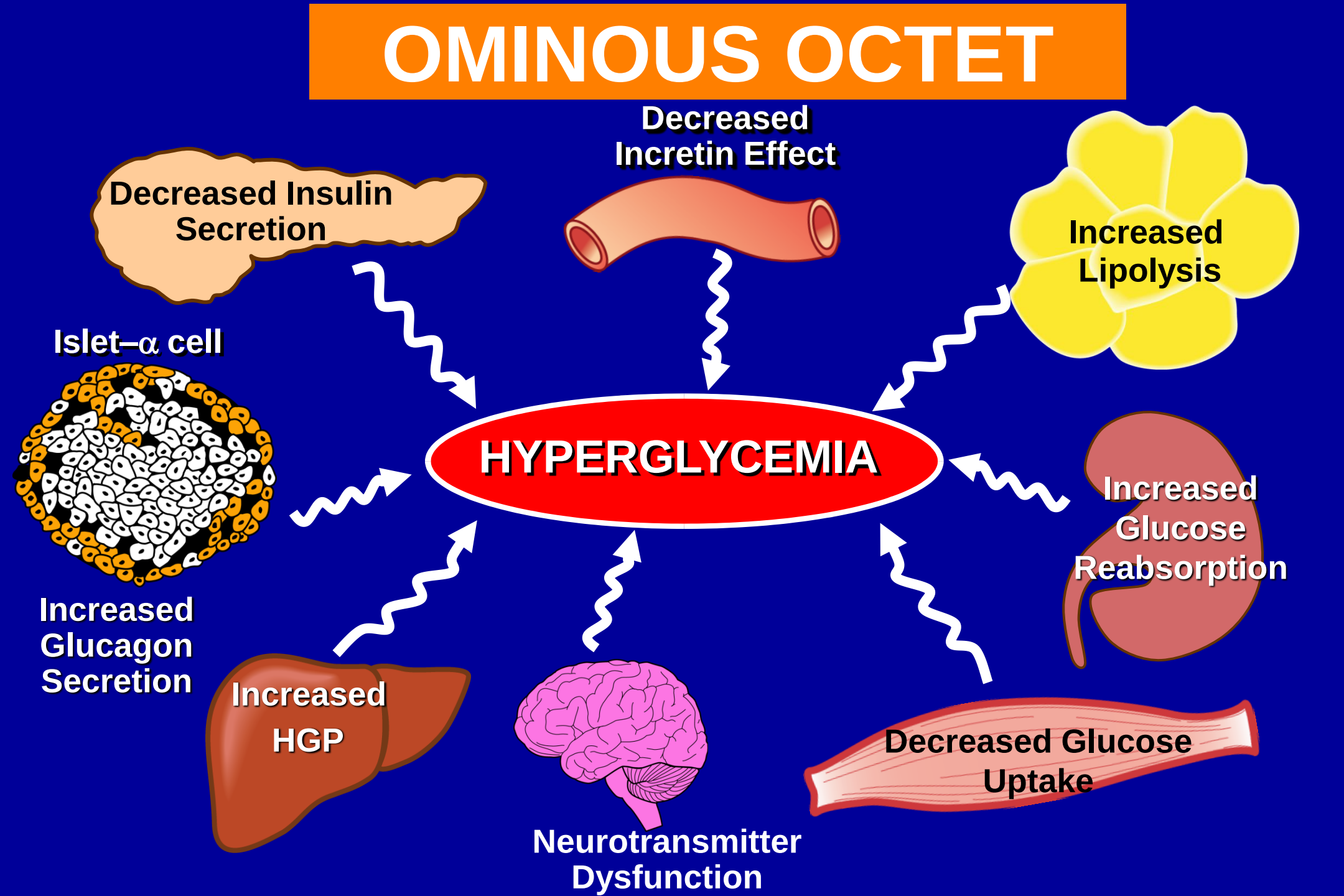
There is no cost that can be assigned to the morbidity and suffering associated with blindness, dialysis, and neuropathy

UKPDS: Effect of SU & Metformin Rx on HbA_{1c}



UKPDS 352:837-853 and 853-865, 1998

OMINOUS OCTET



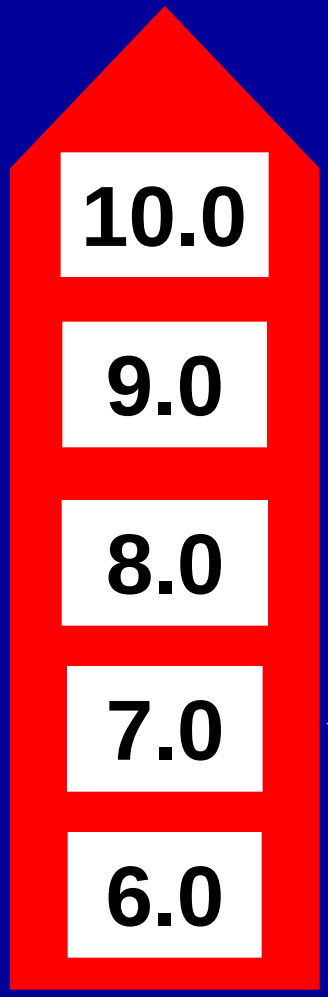
CLINICAL AND THERAPEUTIC IMPLICATIONS

- We need novel and more efficacious medications that correct known pathophysiologic disturbances present in T2DM.

- Multiple medications used in combination will be required to reverse the multiple and diverse pathogenic abnormalities present in T2DM.

DIABETES REPORT CARD: A1C GOALS ARE UNMET IN MOST T2DM PATIENTS

1. Saydah, et al. JAMA 291:335, 2004.
2. Koro, et al. Diabetes Care 27:17, 2007.
5. Cheung et al, AJM 122:443, 2009.
6. Resnick et al, Diabetes Care 29:531, 2006
7. AACE, State of Diabetes in America, 2006
8. Hoerger et al, Diabetes Care 31:81, 2008.
9. Grant et al, Diabetes Care 30:807, 2005.
10. NCQA, www.neca.com



12.4% have A_{1C} > 10%[1]

20.2% have A_{1C} > 9%[1]

37.2% have A_{1C} > 8%[1]

63% of patients with type 2 diabetes have A_{1C} > 7.0%

ADA target (< 7%)[3]

AACE /EASD target (≤ 6.5%)[4]

Upper limit of normal (6.0%)[3]

3. ADA. Diabetes Care 26(suppl 1):S33-S50, 2003.
4. ACE. Endocr Prac 15:540-59, 2009.

NATIONAL COMMITTEE FOR QUALITY ASSURANCE (NCQA)

The State of Health Care Quality: October 22, 2009

POOR DIABETES CONTROL
(HbA1c > 9.0%)
is present in 29 - 45% of T2DM patients in
COMMERCIAL, MEDICAID, and MEDICARE HEALTH PLANS
based upon 2009 HEDIS

www.ncqa.com

FDA GUIDELINES, DECEMBER 2008

PHASE 3 Upper bound of 2-sided 95% CI for cardiovascular HR <1.8

IMPACT – Requires data on >120 events

REALITY: Using MACE (CV mortality, MI, stroke) with annual incidence of 1.5% (traditional population), this would require ~8,000 patient years

FDA GUIDELINES, DECEMBER 2008

PHASE 3 Upper bound of 2-sided 95% CI for cardiovascular HR <1.3

IMPACT – Requires data on 600-700 events

REALITY: Using MACE (other endpoints uncertain) with annual incidence of 2-3% (high risk population), this would require ~20,000 patient years

CV outcome trials may be relevant to elderly patients with type 2 diabetes, but they do not address therapy in the growing number of younger patients, who are less likely to experience CV events and in whom a lifetime of exposure to hyperglycemia is likely to increase the risk for microvascular complications

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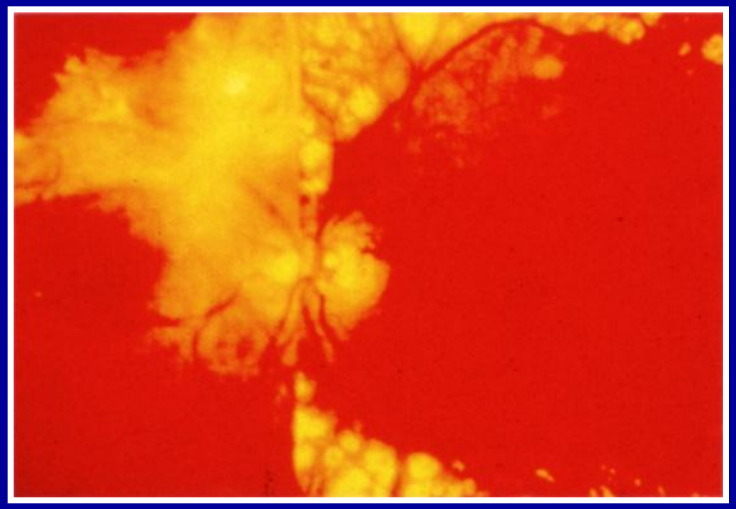
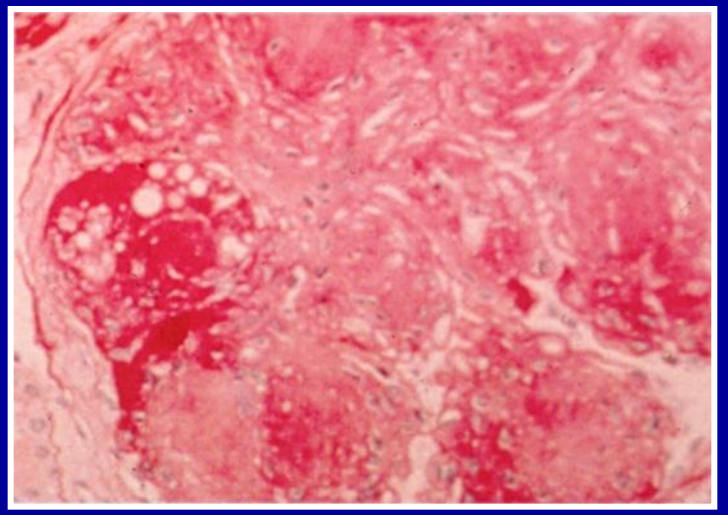
DRUG DISCOVERY SHOULD NOT BE ABANDONED JUST BECAUSE MEDICATIONS HAVE A NEUTRAL EFFECT ON CV OUTCOMES OR CVRFs

- The concentration on risks of heart attack/stroke may miss important benefits in prevention of blindness or renal failure.



- The recruitment into trials of individuals with pre-existing heart disease (or high risk of developing it) may obscure other benefits or problems. It also raises ethical concerns.



SAFETY IS OF PARAMOUNT IMPORTANCE

- **Recent discussions by the FDA have focused on cardiovascular safety, and for new antidiabetic agents a cardiovascular outcome trial is required.**
- **However, the only absolutely safe drug policy would be not to prescribe any medications whatsoever.**
- **Then, there would be no drug safety problems, and patients simply would die from their diabetes and associated complications.**

RISK OF REGULATIONS

- By mandating CV outcome trials, the cost of drug development will increase by ~300 million per drug, and only very large pharmaceutical companies will be able to afford this.
- The increased cost of drug development will, of necessity, be passed onto the patient, making the medication(s) unaffordable.
- Some pharmaceutical companies already have decreased their metabolic pipeline and/or are getting out of the diabetes business. This will reduce discovery efforts for novel antidiabetic medications
- The recruitment into trials of individuals with pre-existing heart disease (or high risk of developing it) may obscure other benefits or problems. It also raises ethical concerns.

CONCERNS ABOUT THE CURRENT FDA GUIDELINES FOR CARDIOVASCULAR SAFETY

- When should the cardiovascular outcome trials be performed? Before approval? After approval? During the approval process?
- What is an appropriate CV signal for a CV outcome trial?
- What is the appropriate population for a CV outcome trial? Elderly? Prior CV event? Renal disease?
- Requirements for CV safety trial can change without sufficient time for pharmaceutical companies to respond.
- Much of the information from these CV outcome trials can not be included in the label.

CARDIOVASCULAR STUDY SAFETY DESIGN: ALTERNATIVE APPROACHES

(1) Combine Phase 3 with Phase 4 study

(2) Graded approval based upon surrogate CVRFs with subsequent removal of restrictions

- (i) biomarkers, i.e. A1c, lipids, BP, other
- (ii) carotid IMT, plaque volume (or equivalent)
- (iii) large CV safety trial

(3) Real life CV safety trial using national electronic record data base