Dal rischio al danno cardio e cerebrovascolare (il valore dell'epidemiologia clinica)

Giorgio Sesti

Università "Magna Graecia" di Catanzaro

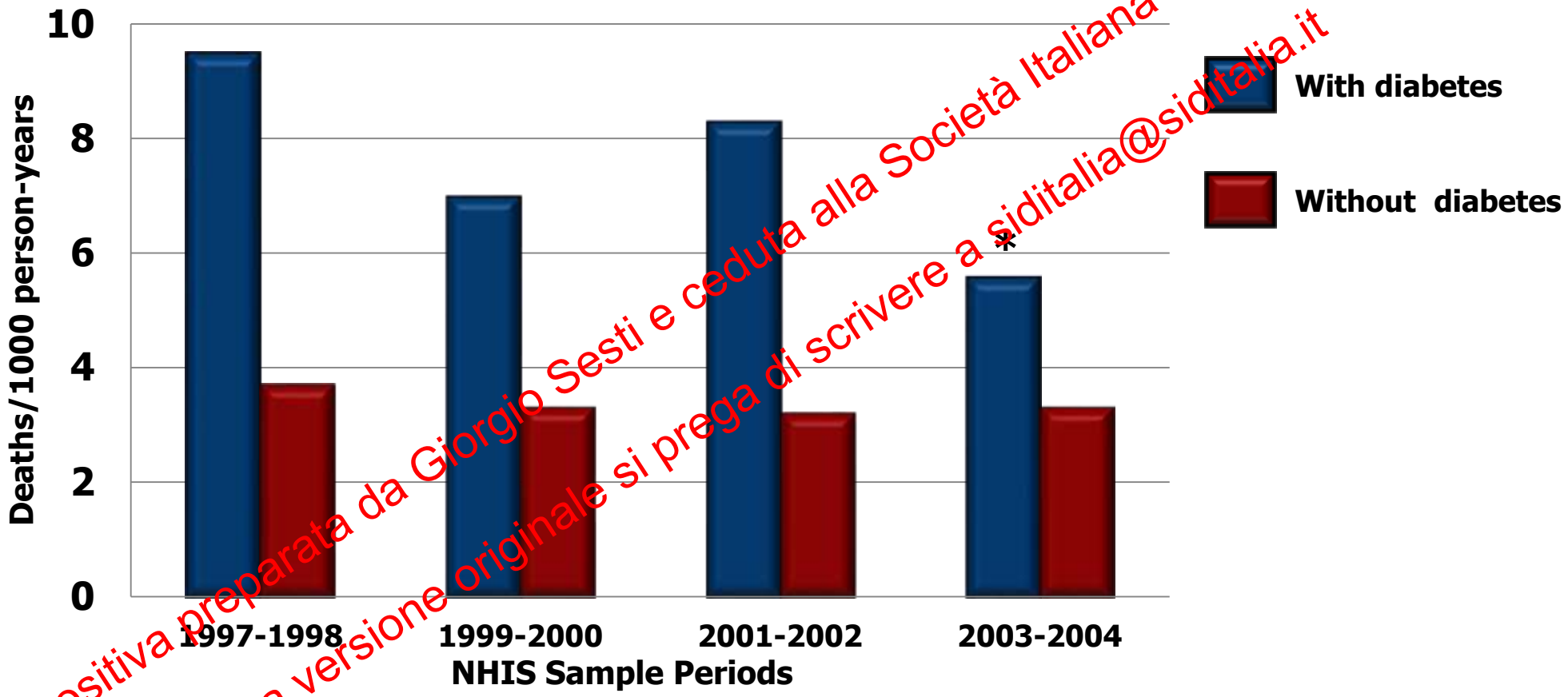
Potenziali conflitti di interesse

Il Prof Giorgio Sesti dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

Novo Nordisk, MSD, Boehringer-Ingelheim, Lilly, Janssen, AstraZeneca, Novartis e Takeda per attività di Relatore ad eventi.

Novo Nordisk, Intarcia, Boehringer-Ingelheim, Lilly, MSD, Servier, AstraZeneca e Janssen per attività di Consulenza.

CVD mortality rate among people with and without diabetes: the National Health Interview Survey (NHIS) (242,383 adults >18 years)



*Rate difference between 1997/1998 and 2003/2004, –4.0; *P* < 0.001 for trend

Gregg et al., Diabetes Care 35: 1252—1257, 2012

The Bradford Hill criteria

1. **Strength (effect size)**
2. **Consistency (reproducibility)**
3. **Specificity**
4. **Temporality**
5. **Biological gradient**
6. **Plausibility**
7. **Coherence**
8. **Experiment**
9. **Analogy**

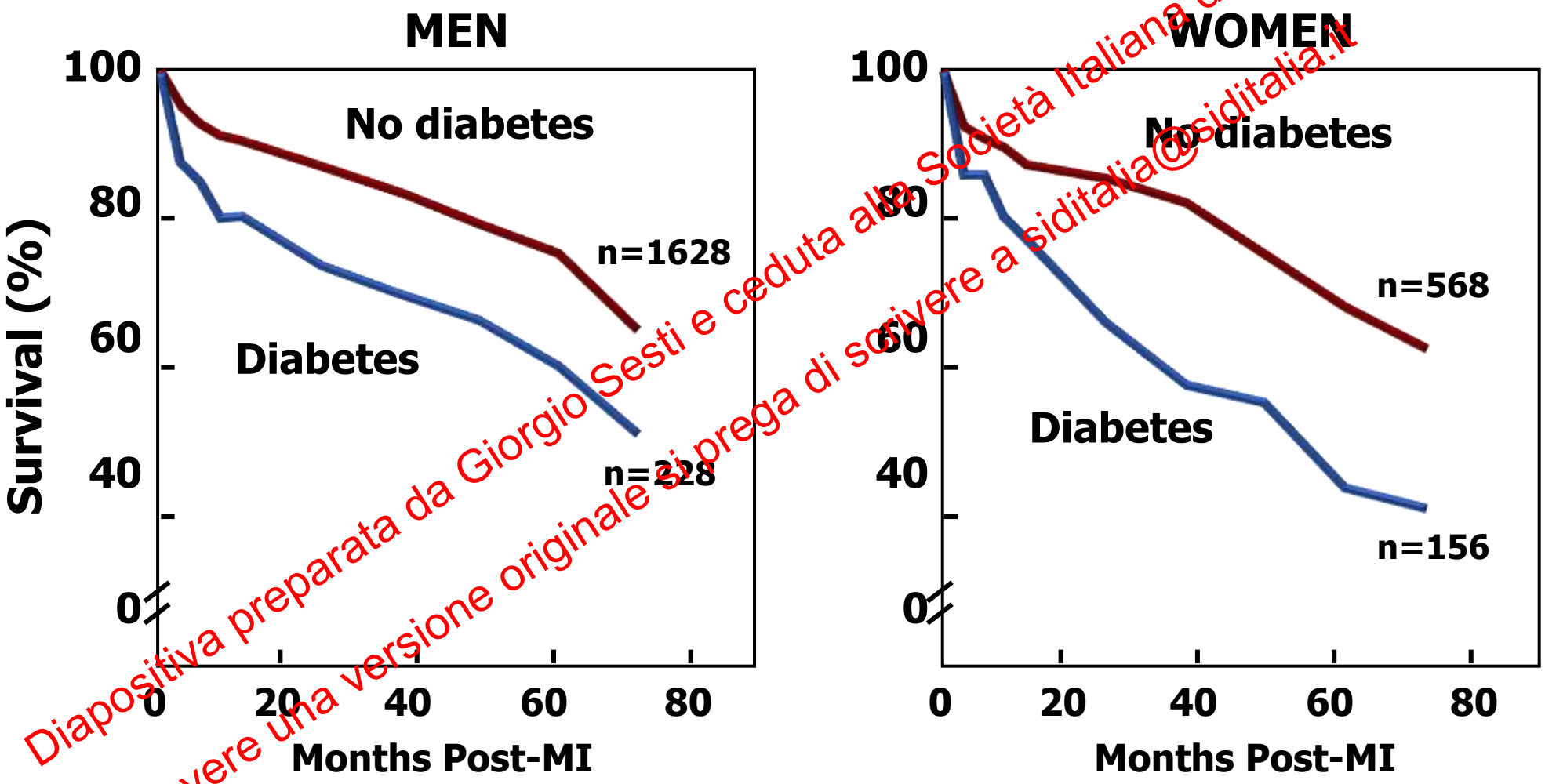
Bradford Hill A Proceedings of the Royal Society of Medicine 58: 295–300, 1965

The Bradford Hill criteria

1. **Strength (effect size): A small association does not mean that there is not a causal effect, though the larger the association, the more likely that it is causal.**
2. **Consistency (reproducibility)**
3. **Specificity**
4. **Temporality**
5. **Biological gradient**
6. **Plausibility**
7. **Coherence**
8. **Experiment**
9. **Analogy**

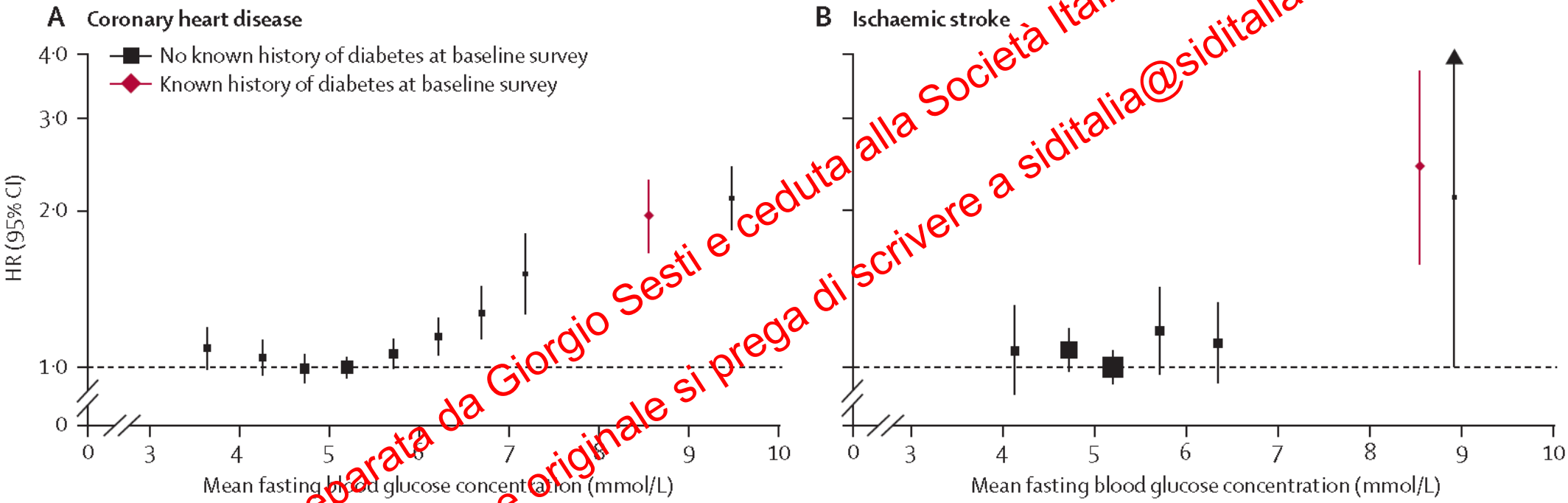
Bradford Hill A Proceedings of the Royal Society of Medicine 58: 295–300, 1965

Survival Post-MI in Diabetic and Nondiabetic Men and Women: Minnesota Heart Survey



Sprafka JM et al. Diabetes Care 14:537-543, 1991

Hazard ratios (HRs) for coronary heart disease and ischaemic stroke by baseline fasting blood glucose concentration: a cohort study in 1,921,260 individuals in England



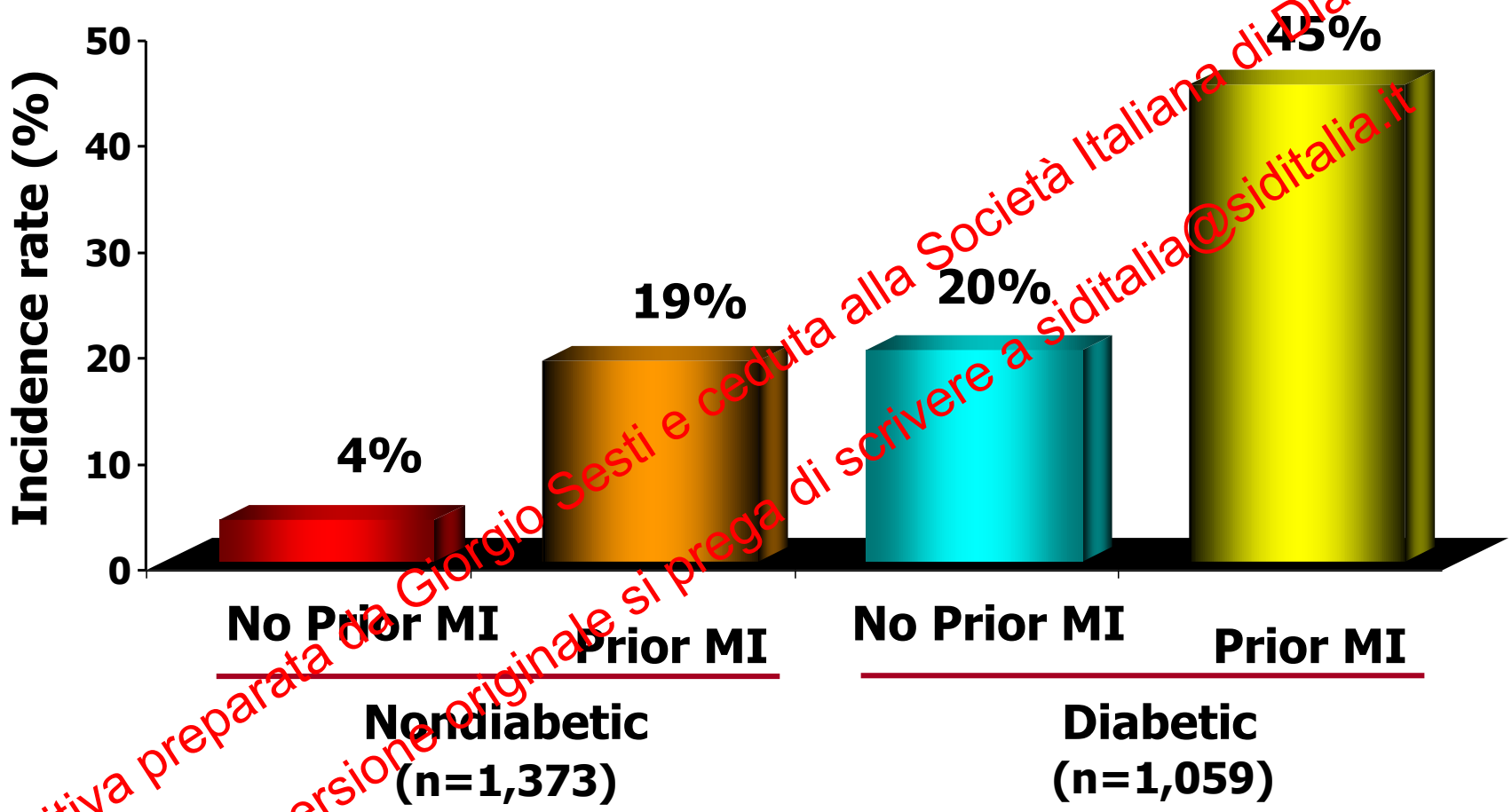
Dinesh Shah A et al. Lancet Diabetes Endocrinol 3: 105–13, 2015

The Bradford Hill criteria

1. Strength (effect size)
2. **Consistency (reproducibility): Consistent findings observed by different persons in different places with different samples strengthens the likelihood of an effect.**
3. Specificity
4. Temporality
5. Biological gradient
6. Plausibility
7. Coherence
8. Experiment
9. Analogy

Bradford Hill A Proceedings of the Royal Society of Medicine 58: 295–300, 1965

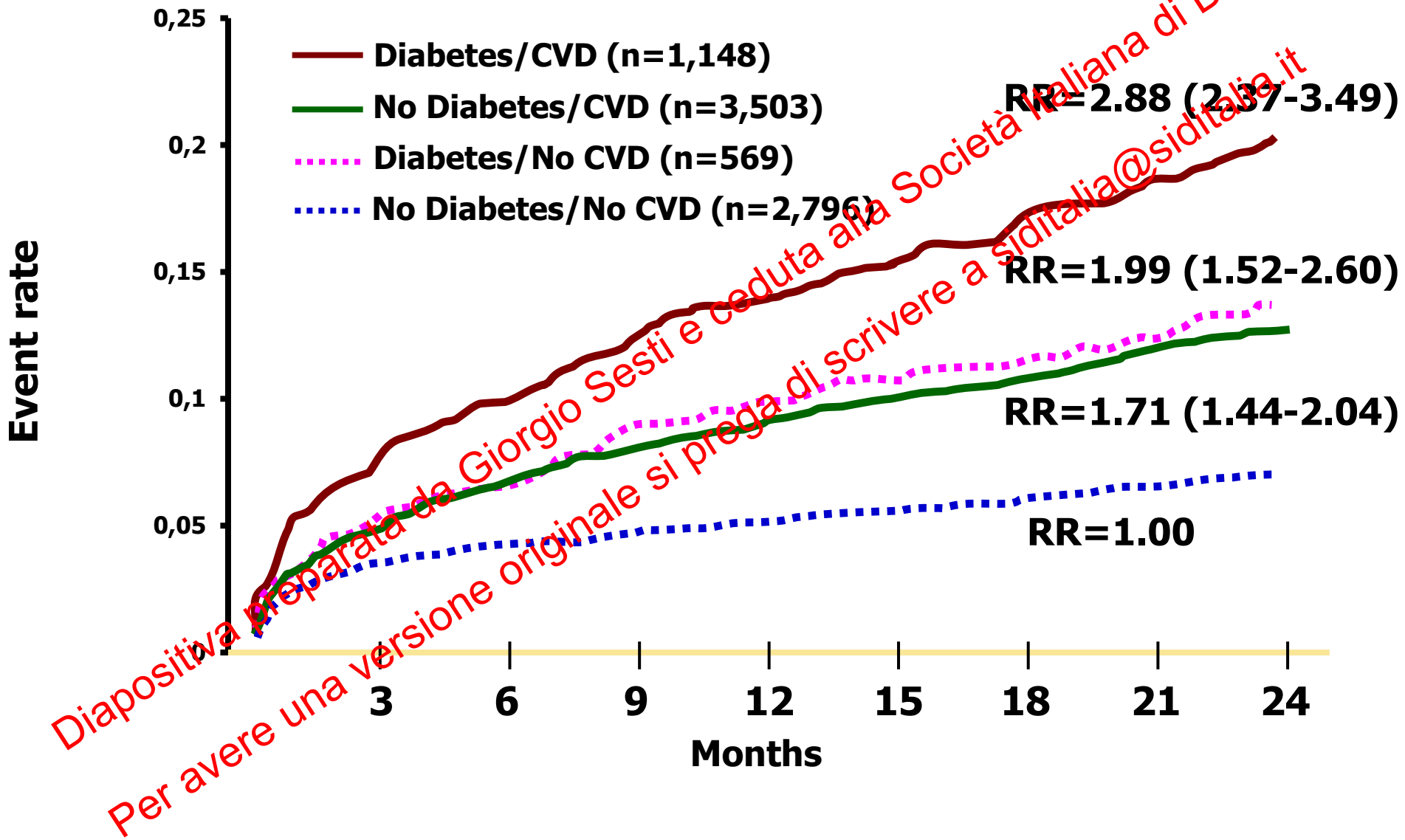
7-Year Incidence of Fatal and Nonfatal MI



P<0.001 for prior MI vs. no prior MI and for diabetes vs. no diabetes

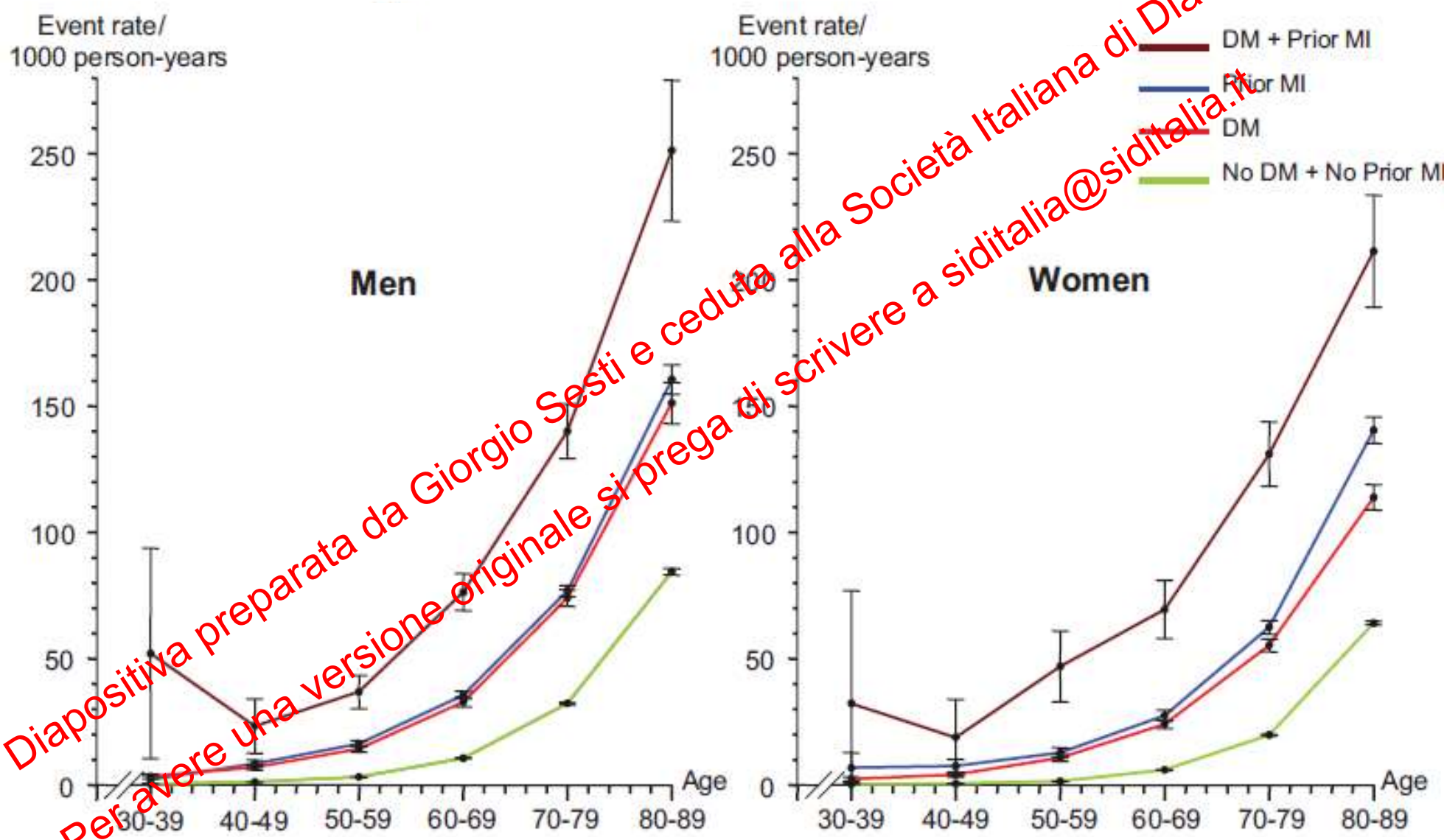
Haffner SM, et al. N Eng J Med 339:229-234, 1998

Organization to Assess Strategies for Ischemic Syndromes (OASIS) Study
Mortality by Diabetes and CVD Status



Malmberg K, et al. Circulation 102:1014-1019, 2000

Cardiovascular mortality in relation to diabetes mellitus and a prior MI: A Danish Population Study of 3.3 Million People



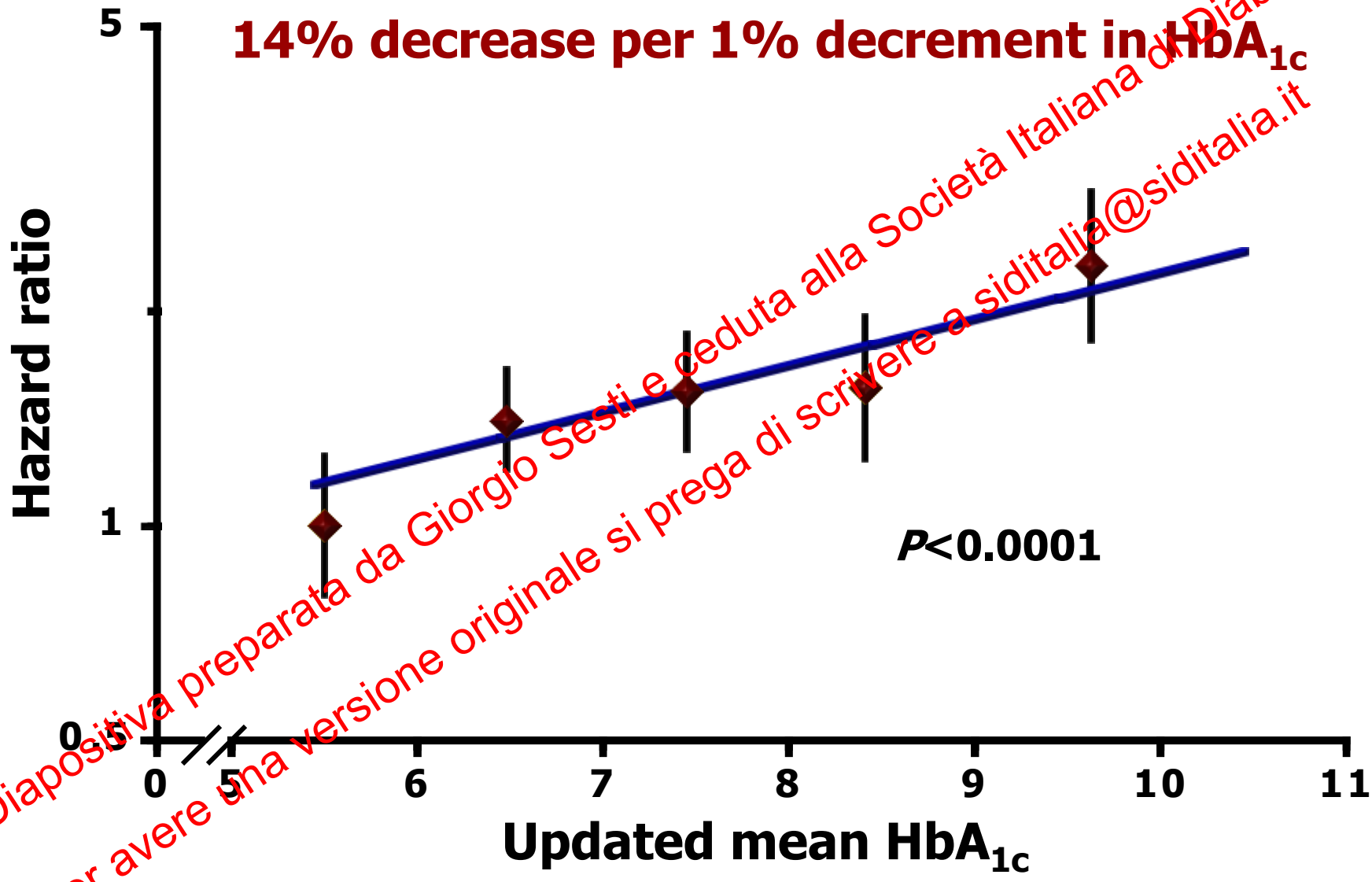
Schramm et al. Circulation 117:1945-54, 2008

The Bradford Hill criteria

1. Strength (effect size)
2. Consistency (reproducibility)
3. **Specificity: The more specific an association between a factor and an effect is, the bigger the probability of a causal relationship.**
4. Temporality
5. Biological gradient
6. Plausibility
7. Coherence
8. Experiment
9. Analogy

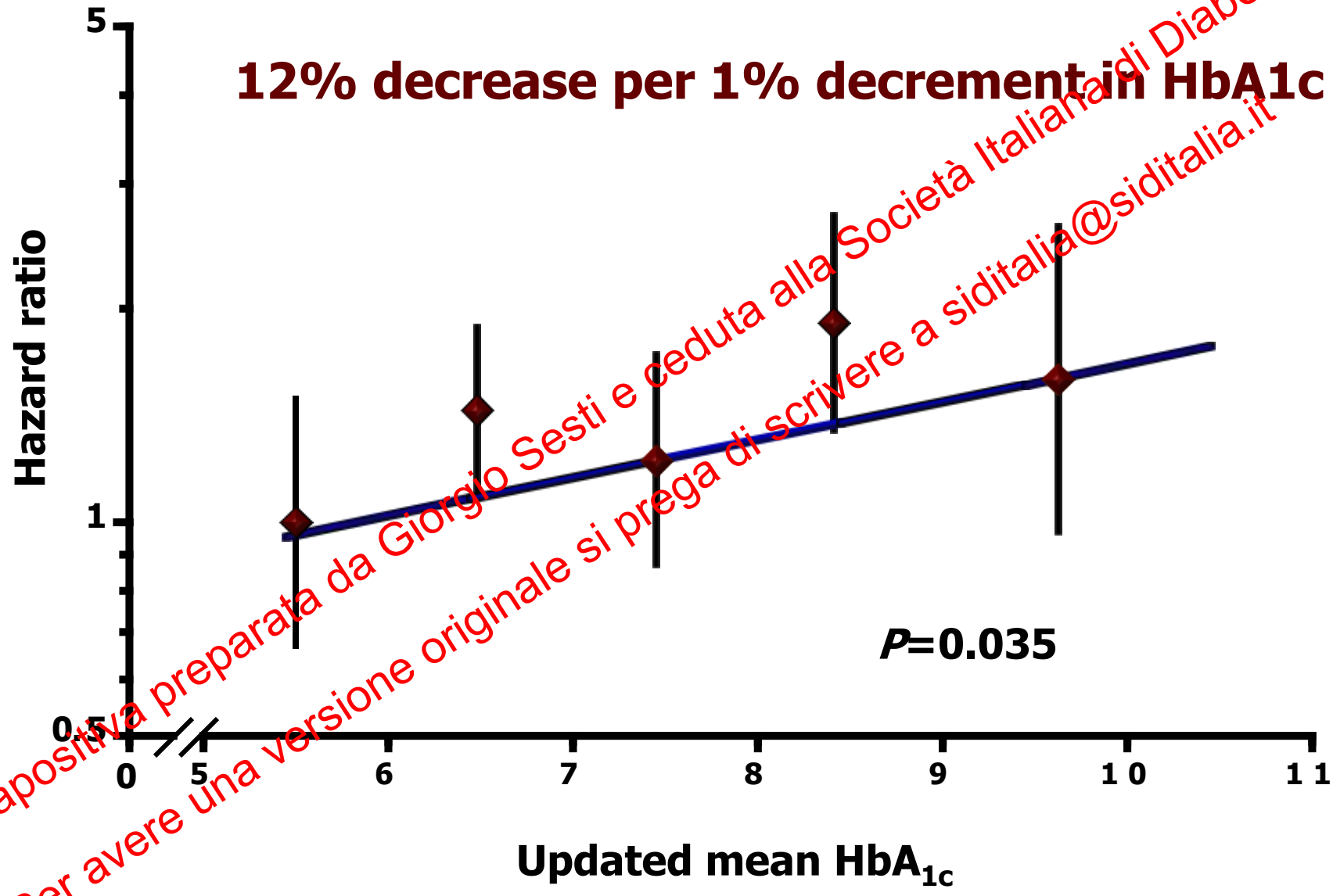
Bradford Hill A Proceedings of the Royal Society of Medicine 58: 295–300, 1965

UKPDS 35 - Fatal and Non-Fatal Myocardial Infarction



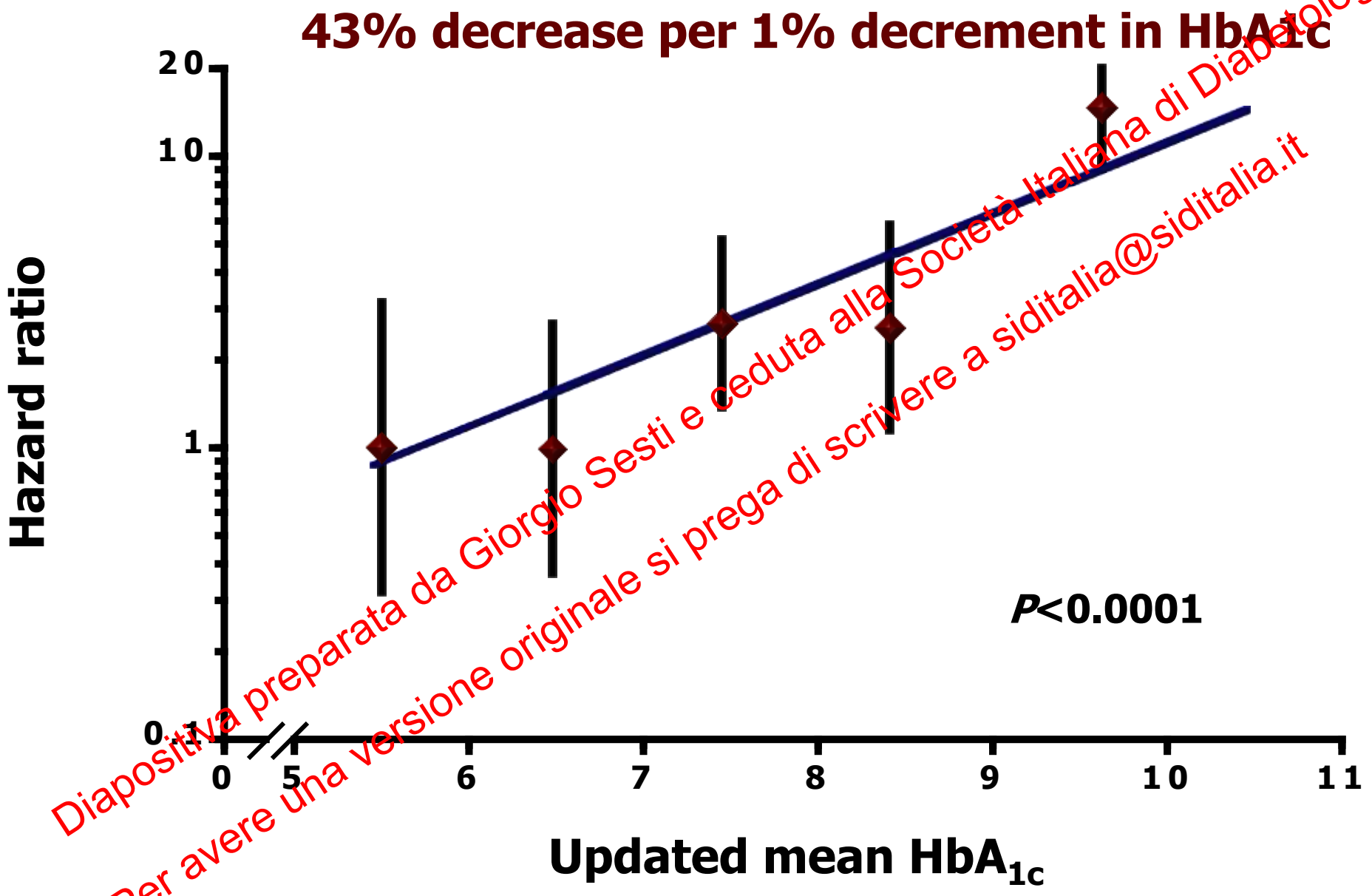
Stratton IM, et al. UKPDS 35. BMJ 321: 405-412, 2000

UKPDS 35 - Fatal and Non-Fatal Stroke



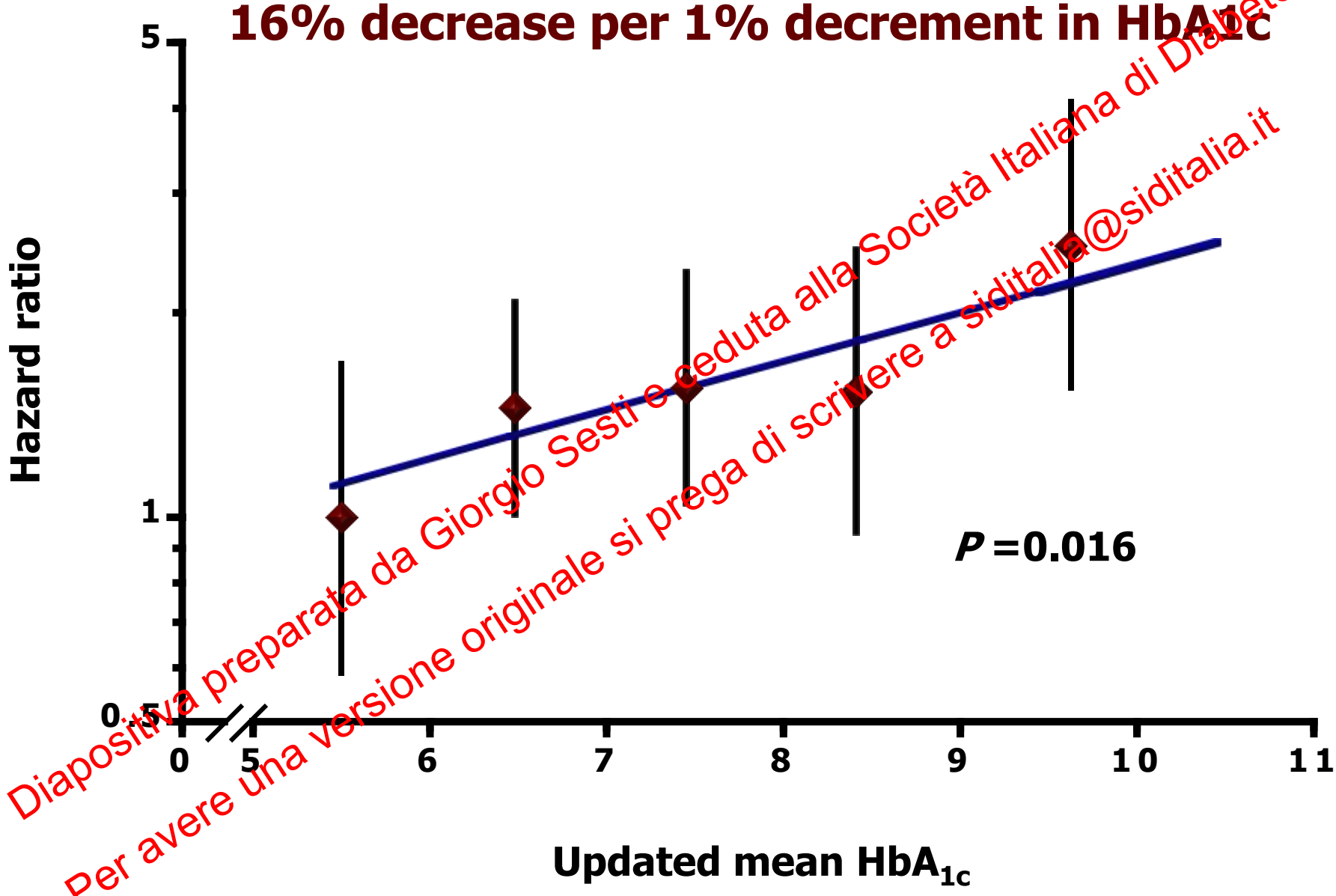
Stratton IM, et al. UKPDS 35. BMJ 321: 405-412, 2000

UKPDS 35 - Amputation or Death from Peripheral Vascular Disease



Stratton IM, et al. UKPDS 35. BMJ 321: 405-412, 2000

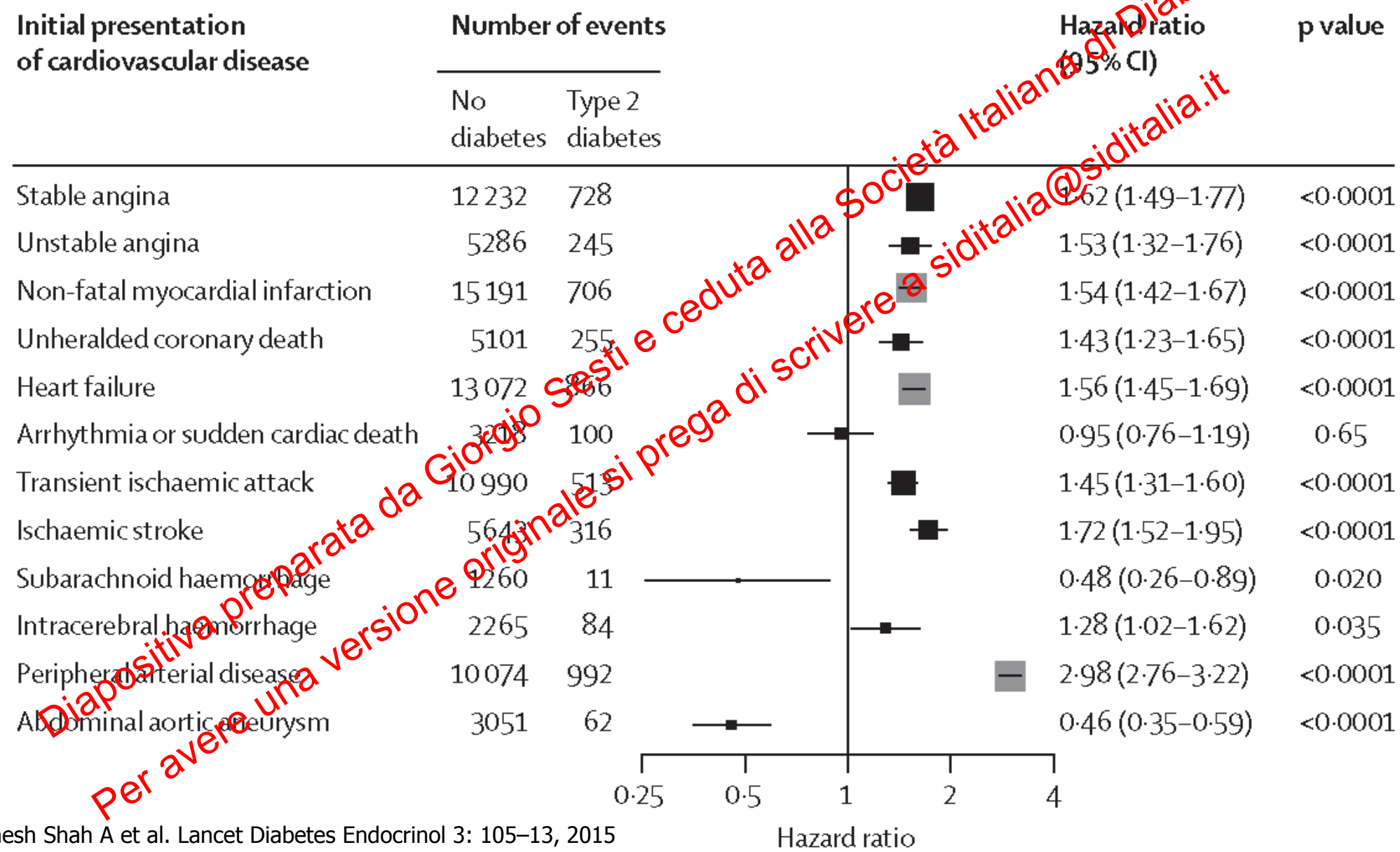
UKPDS 35 - Heart Failure



Stratton IM, et al. UKPDS 35. BMJ 321: 405-412, 2000

Association of type 2 diabetes with 12 CVD in patients aged ≥30 years: a cohort study in 1,9 millions individuals

HRs for different initial presentations of CVD associated with T2DM, adjusted for age, sex, BMI, deprivation, HDL cholesterol, total cholesterol, systolic blood pressure, smoking status, and statin and antihypertensive drug



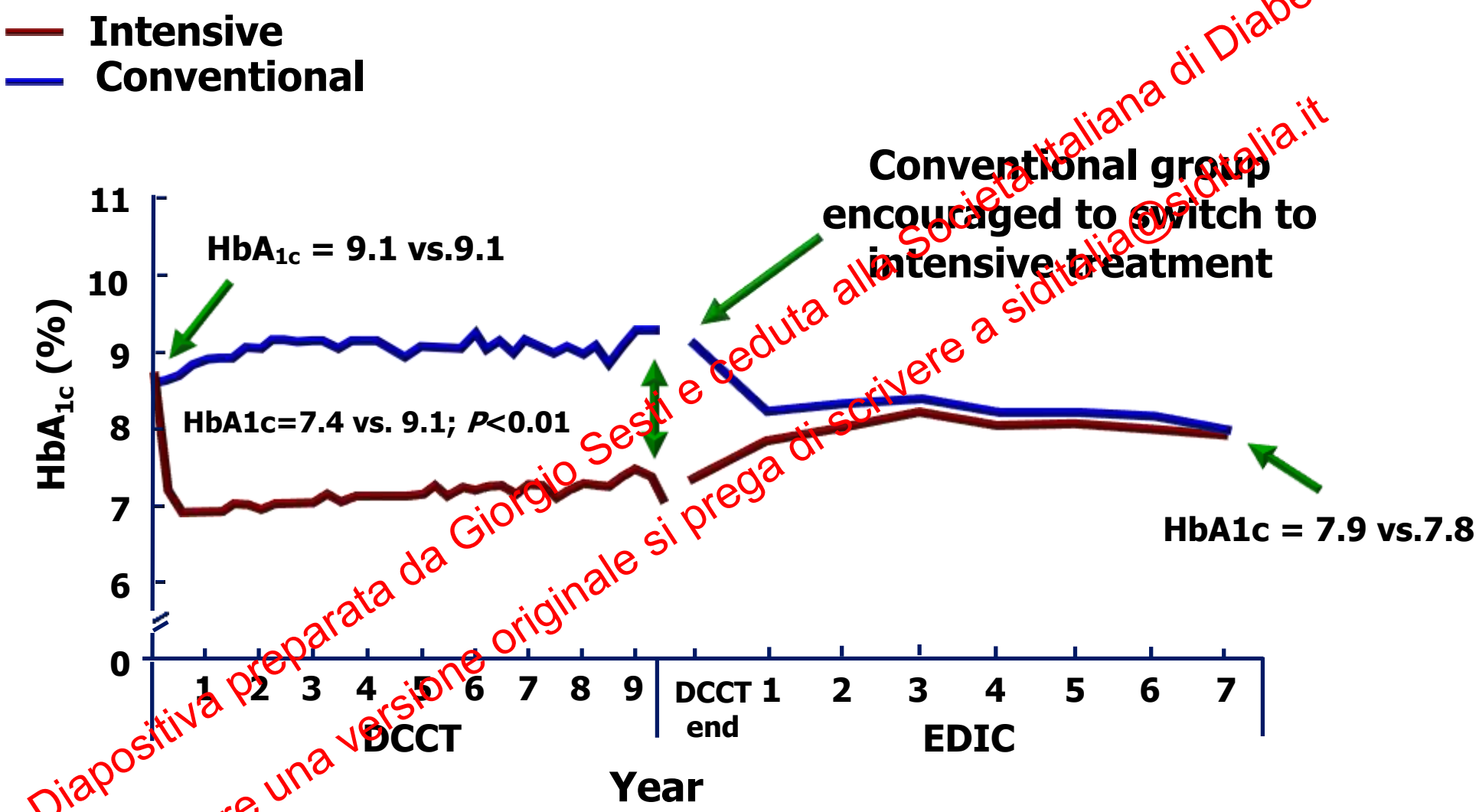
Dinesh Shah A et al. Lancet Diabetes Endocrinol 3: 105–13, 2015

The Bradford Hill criteria

1. Strength (effect size)
2. Consistency (reproducibility)
3. Specificity
4. **Temporality: The effect has to occur after the cause**
5. Biological gradient
6. Plausibility
7. Coherence
8. Experiment
9. Analogy

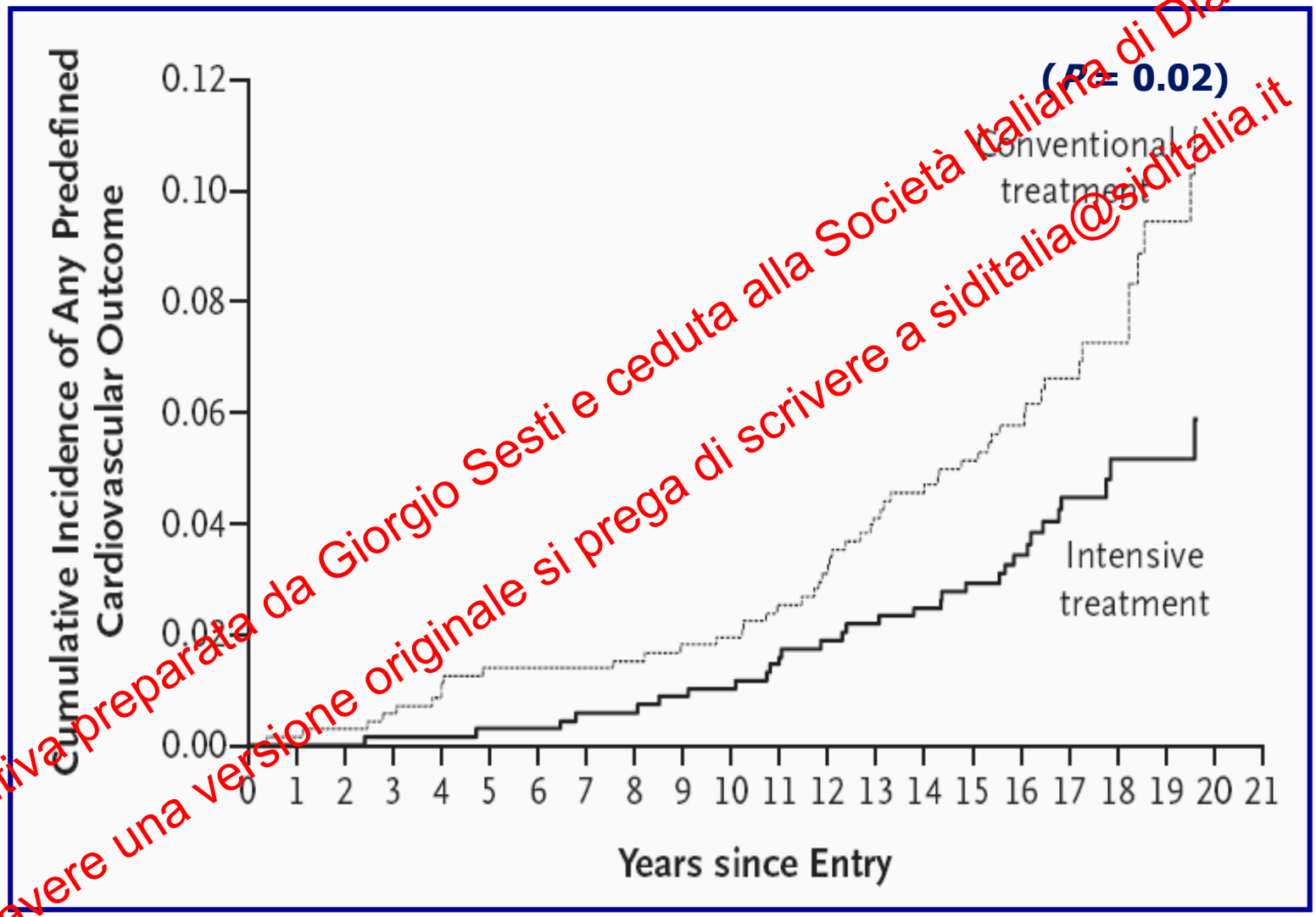
Bradford Hill A Proceedings of the Royal Society of Medicine 58: 295–300, 1965

DCCT-EDIC: intensive treatment significantly reduces and maintains HbA_{1c}



N Engl J Med 353:2643-2653, 2005

DCCT-EDIC: intensive treatment is associated with a 42% reduction in risk of CVD as compared with conventional treatment



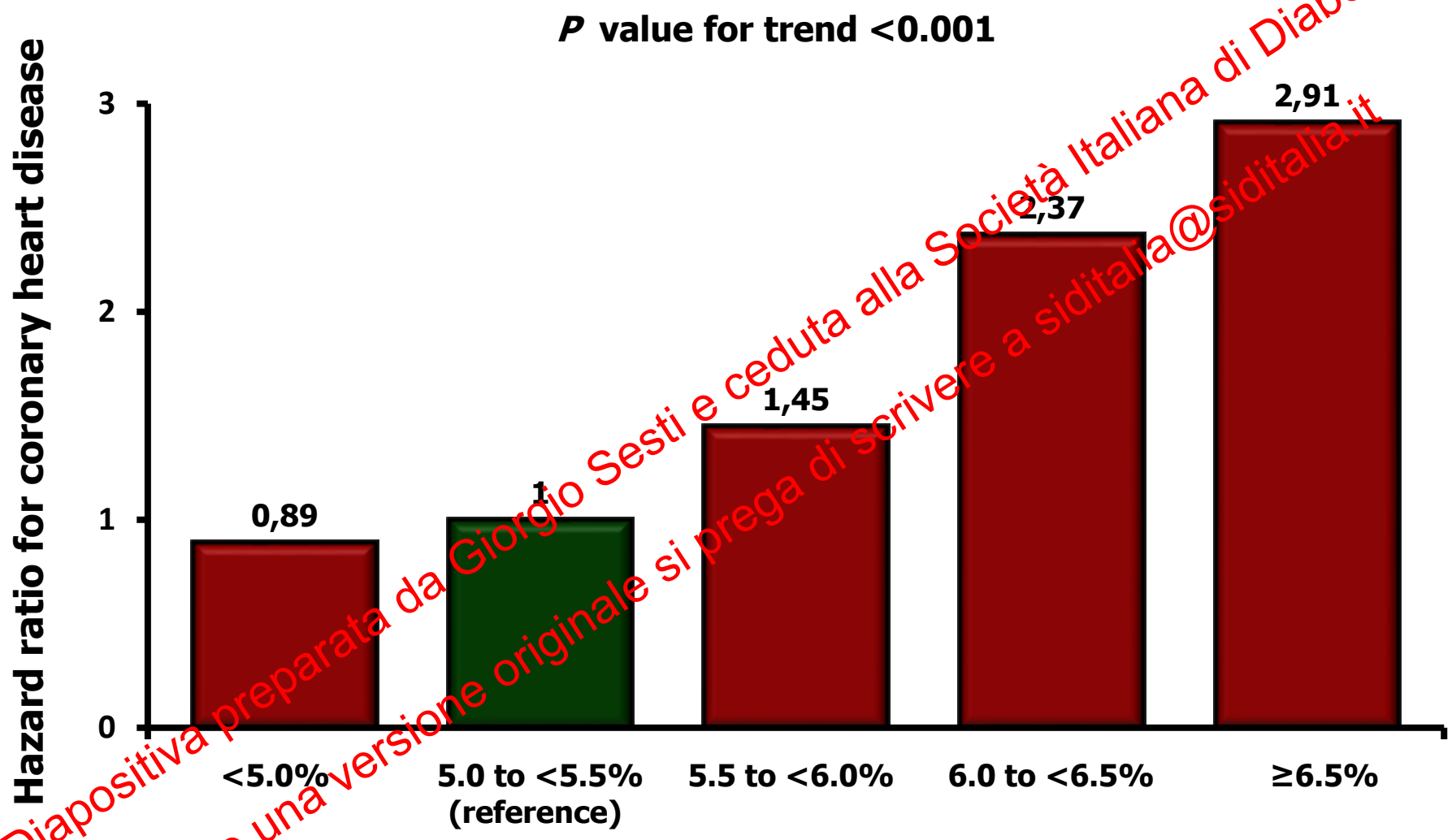
N Engl J Med 353:2643-2653, 2005

The Bradford Hill criteria

1. Strength (effect size)
2. Consistency (reproducibility)
3. Specificity
4. Temporality
5. **Biological gradient: Greater exposure should generally lead to greater incidence of the effect.**
6. Plausibility
7. Coherence
8. Experiment
9. Analogy

Bradford Hill A Proceedings of the Royal Society of Medicine 58: 295–300, 1965

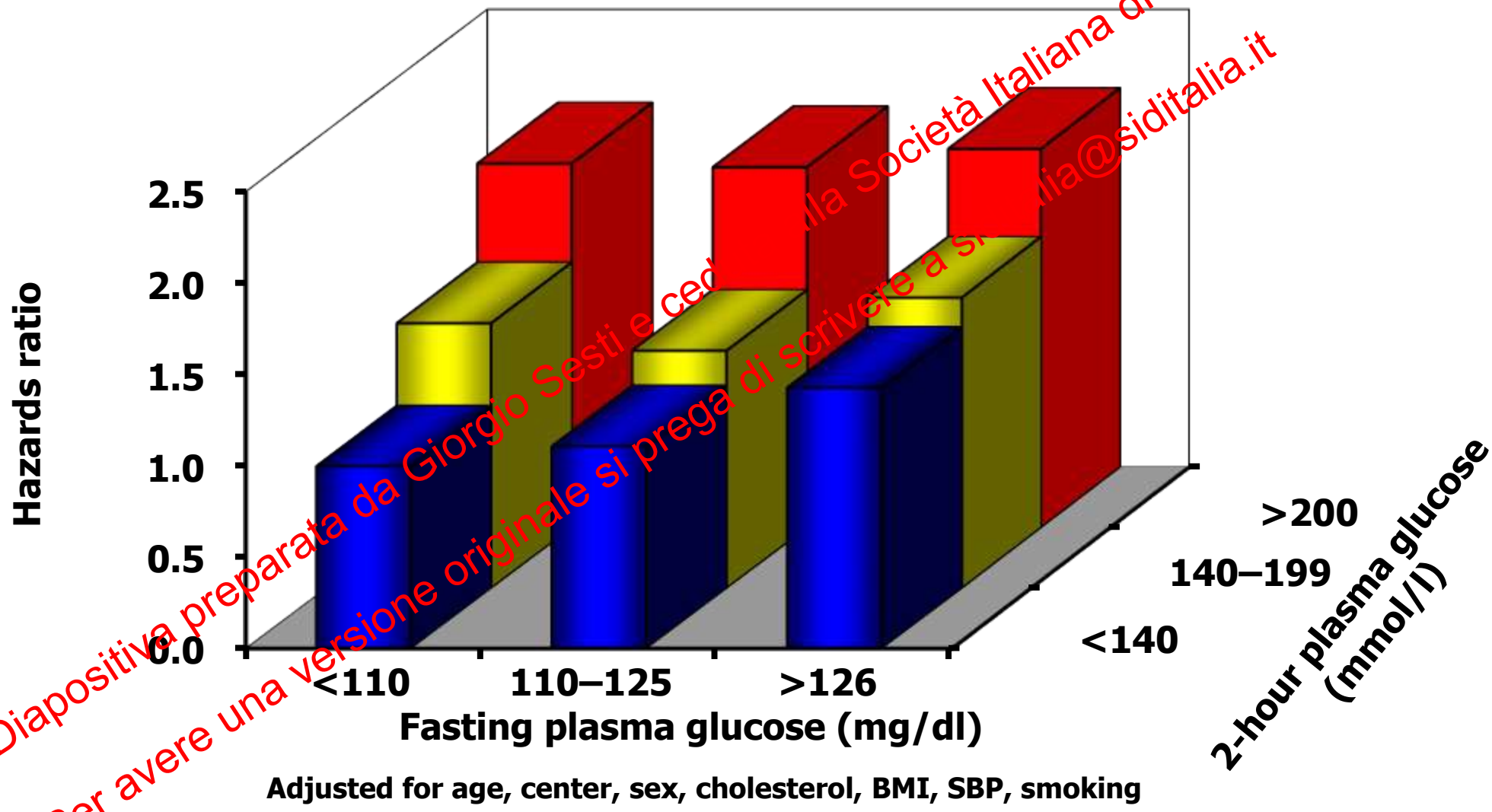
Hazard Ratios for coronary heart disease in the Atherosclerosis Risk in Communities (ARIC) population during the 15-Year study period according to HbA1c category at baseline



Model was adjusted for age, sex, and race

Selvin E. et al. N Engl J Med 362:800-11, 2010

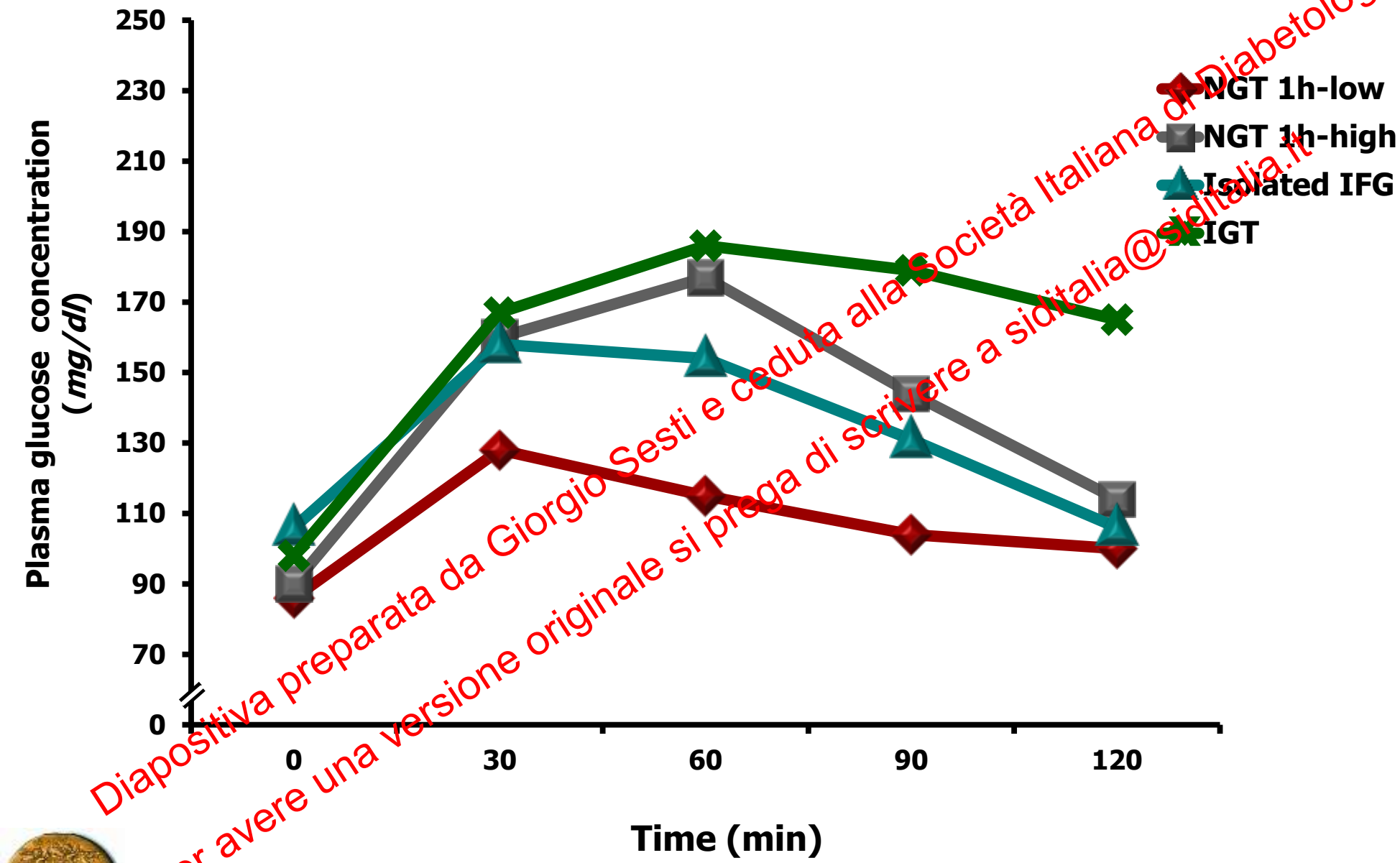
Relative Risk of mortality in a population of 25.364 subjects without known diabetes according to fasting plasma glucose and 2h post-OGTT (DECODE)



Adjusted for age, center, sex, cholesterol, BMI, SBP, smoking

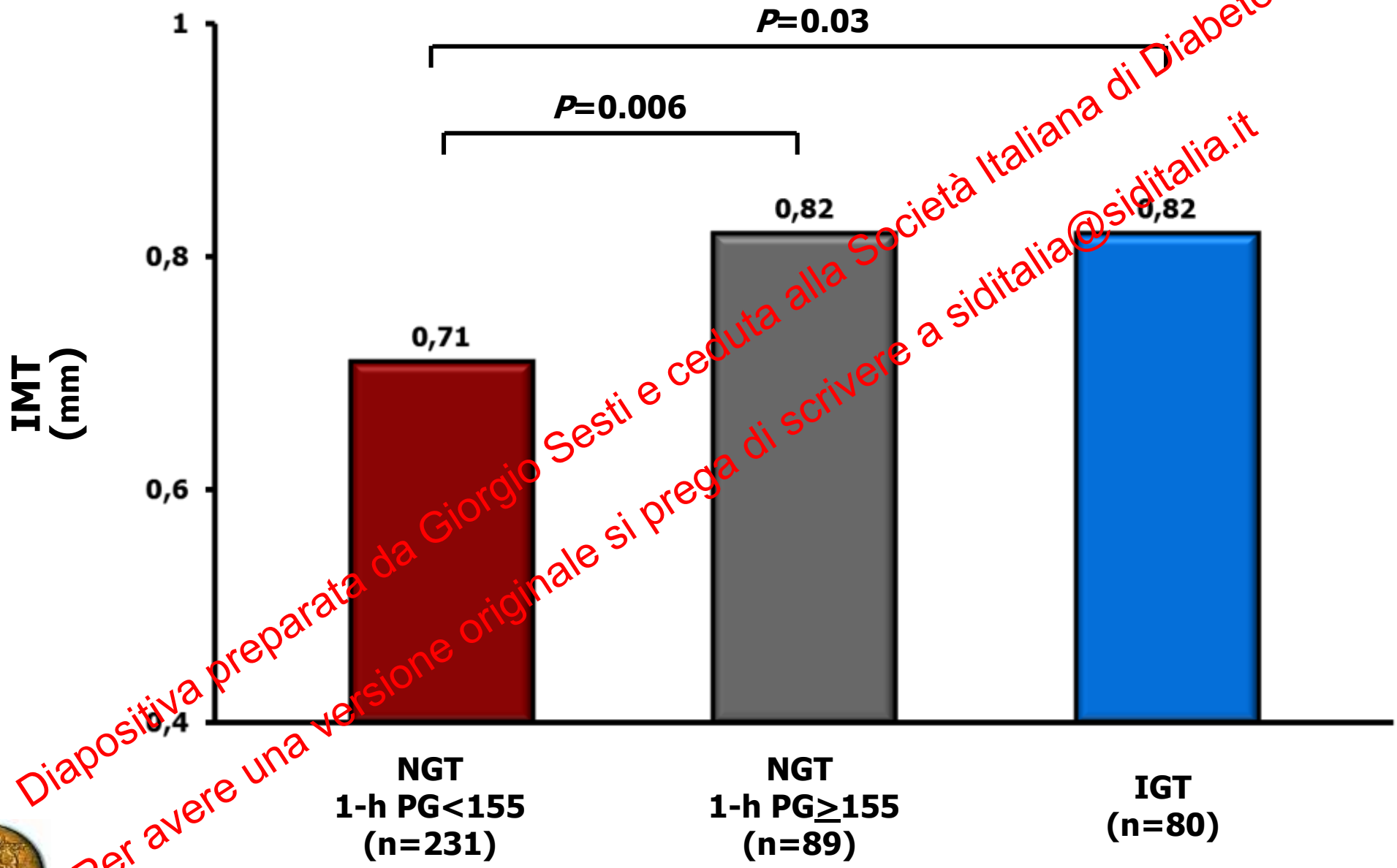
DECODE Study Group. Lancet 354: 617-621, 1999

Plasma glucose levels during OGTT in subjects with NGT 1h-low, NGT 1h-high, isolated IFG and IGT



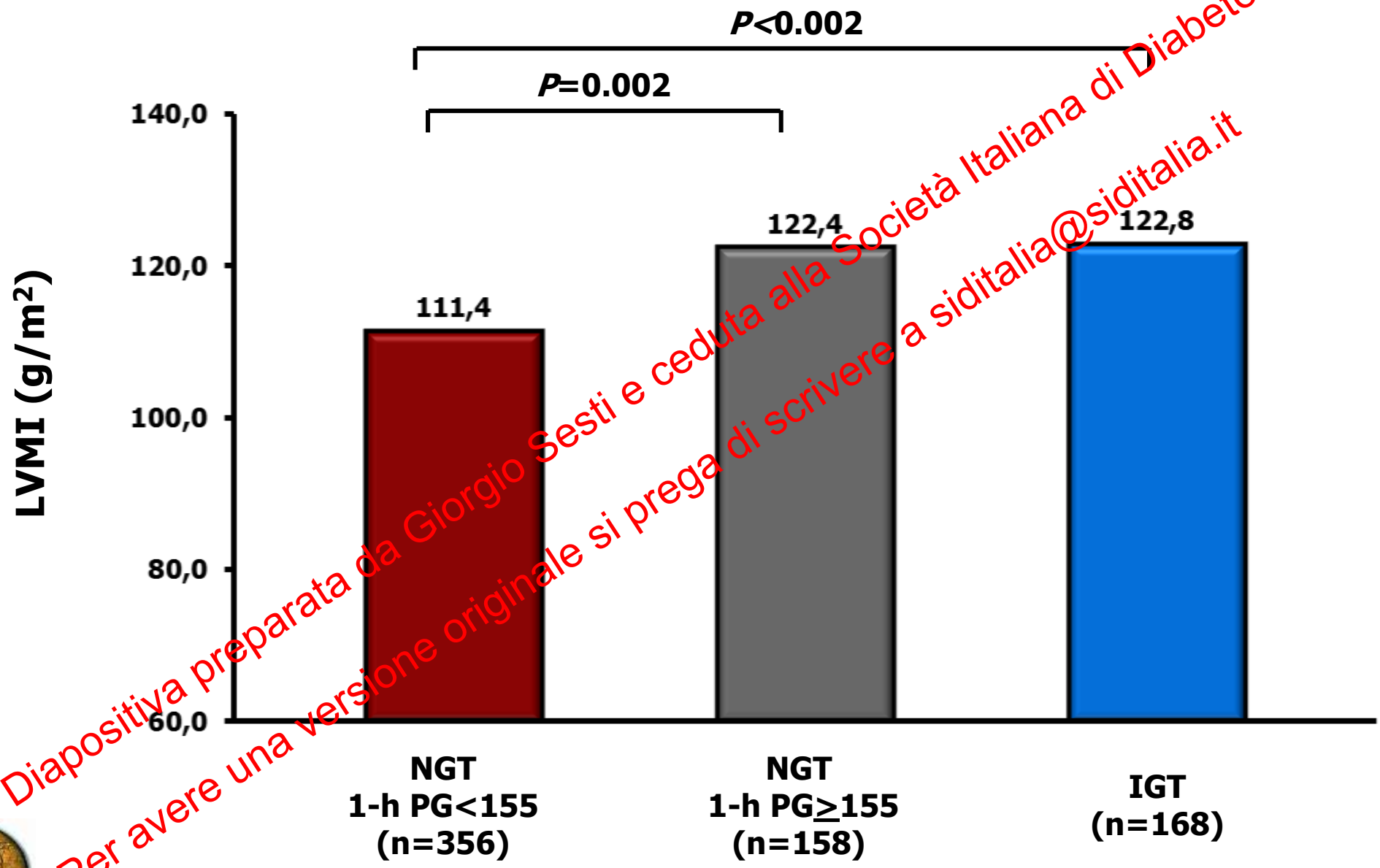
Fiorentino TV et al. J Clin Endocrinol Metab100:3744-3751, 2015

IMT is increased in NGT subjects with 1-h PG ≥155mg/dl as compared with individuals with 1-h PG<155 mg/dl



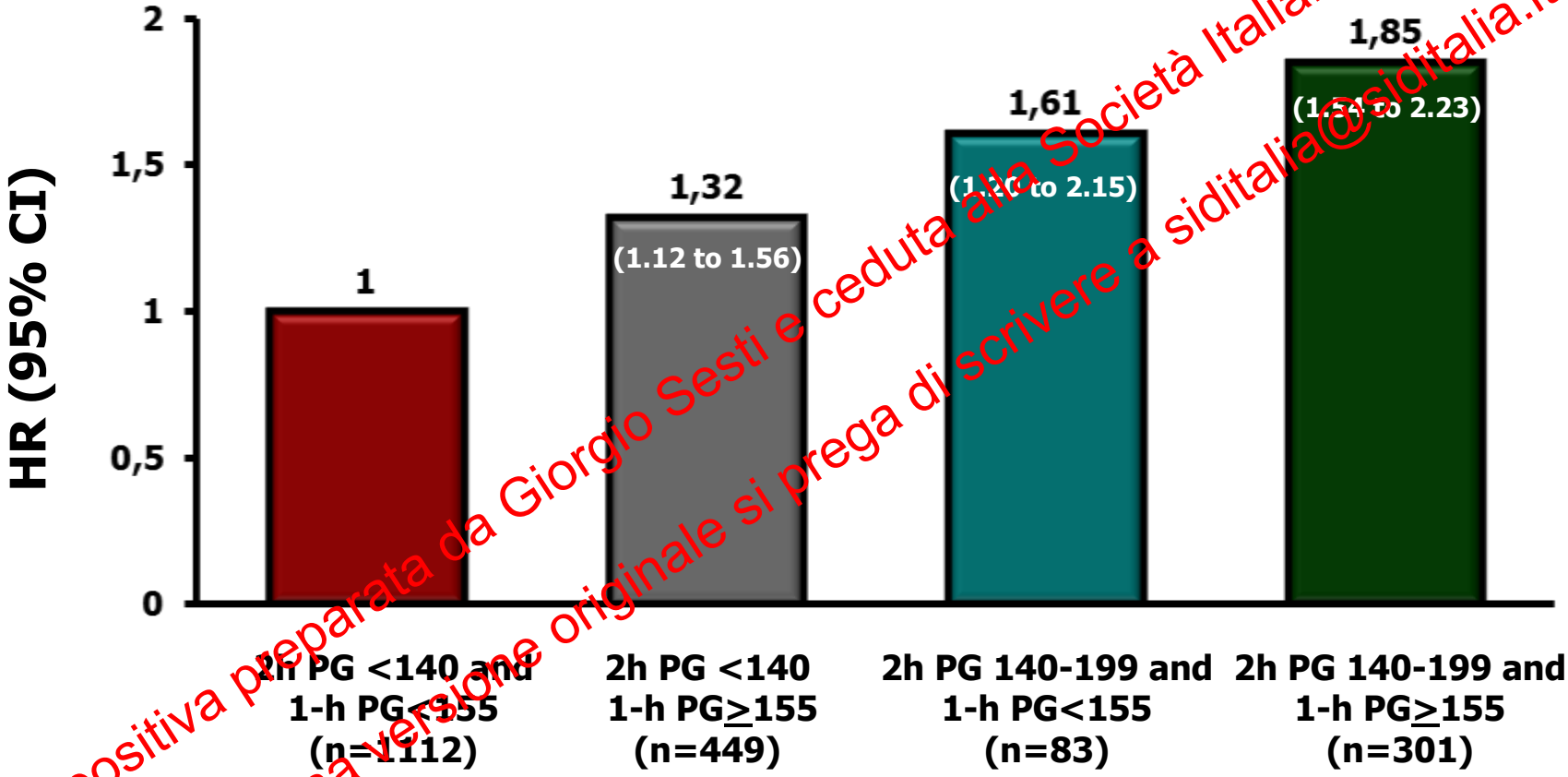
Succurro E. et al. Atherosclerosis 207 : 245–249, 2009

Left ventricular mass is increased in NGT subjects with 1-h PG ≥155mg/dl as compared with individuals with 1-h PG<155 mg/dl - the CATAMERI Study



Sciacqua A. et al. Diabetes Care 34:1406–1411, 2011

Total mortality is increased in subjects with 1-h PG ≥155 mg/dl as compared with individuals with 1-h PG<155 mg/dl - the Israel Study of Glucose Intolerance, Obesity and Hypertension (n= 1942)



P values refer to results after analyses with adjustment for sex, age, smoking, BMI, systolic and diastolic blood pressure and fasting blood glucose

Bergman M et al. Diabet. Med. 2016

The Bradford Hill criteria

1. Strength (effect size)
2. Consistency (reproducibility)
3. Specificity
4. Temporality
5. Biological gradient
6. **Plausibility: A plausible mechanism between cause and effect is helpful**
7. Coherence
8. Experiment
9. Analogy

Bradford Hill A Proceedings of the Royal Society of Medicine 58: 295–300, 1965

Hyperglycemia

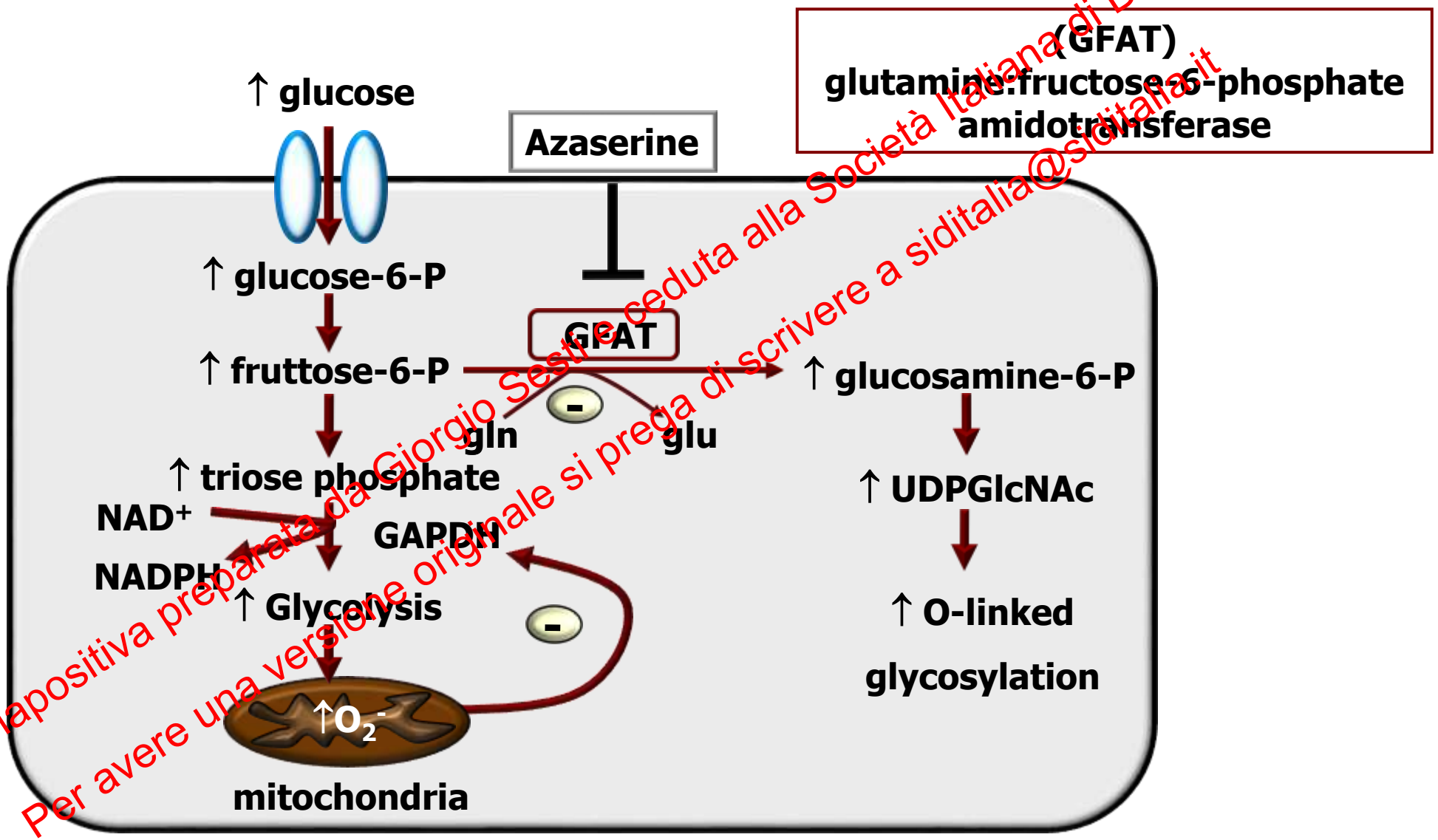
Vascular damage

The Bradford Hill criteria

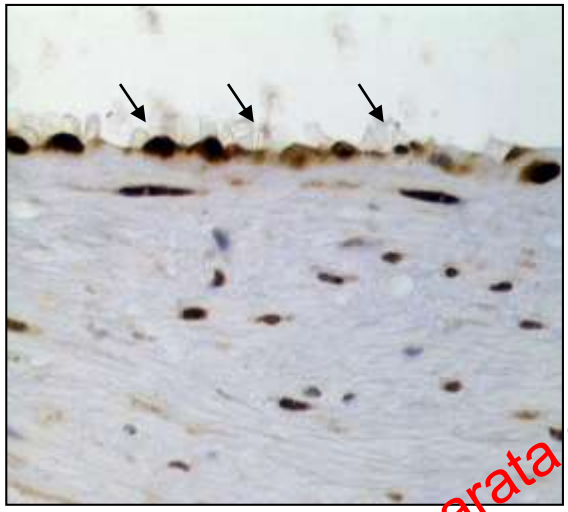
1. Strength (effect size)
2. Consistency (reproducibility)
3. Specificity
4. Temporality
5. Biological gradient
6. Plausibility
7. **Coherence: Coherence between epidemiological and laboratory findings increases the likelihood of an effect**
8. Experiment
9. Analogy

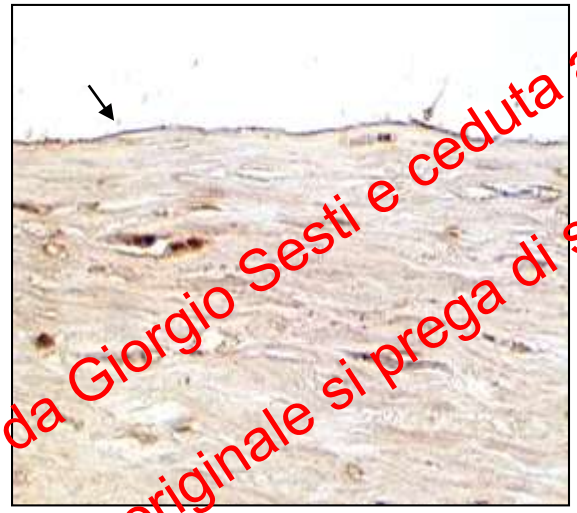
Bradford Hill A Proceedings of the Royal Society of Medicine 58: 295–300, 1965

Increased glucose metabolism through the hexosamine pathway enhances intracellular *O*-linked glycosylation

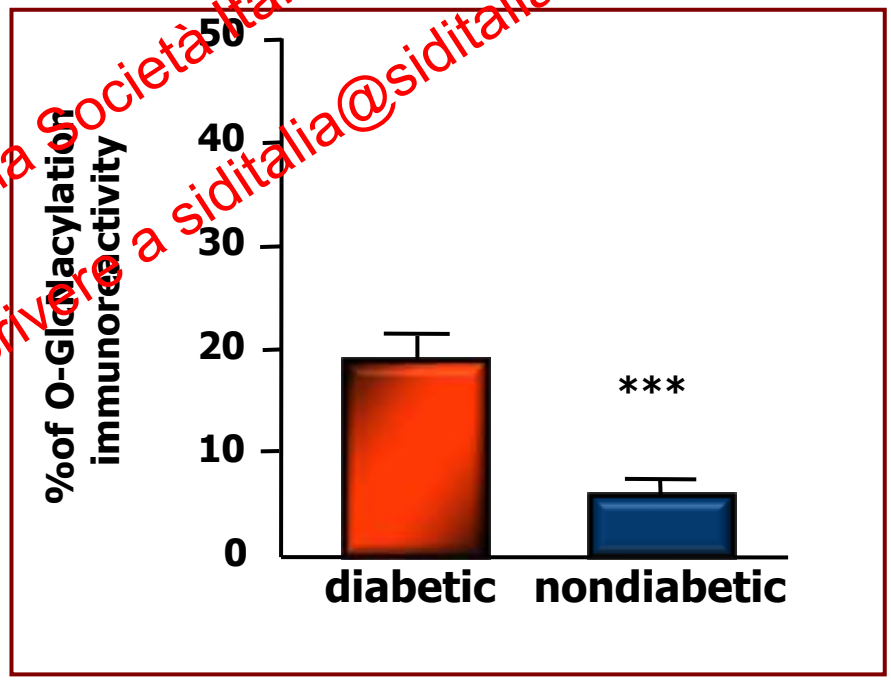


O-GlcNacylation is increased in carotid plaques from diabetic subjects



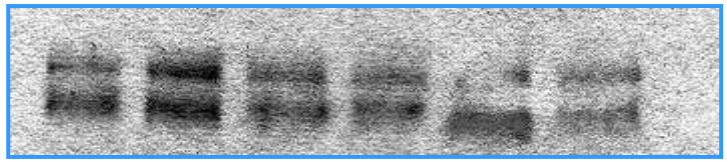


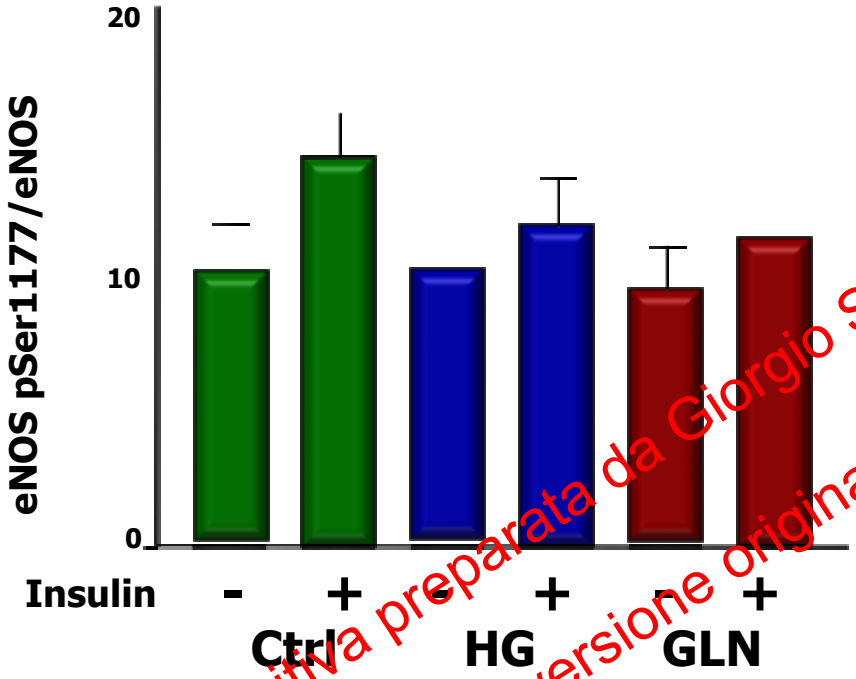
Diabetic **Nondiabetic**

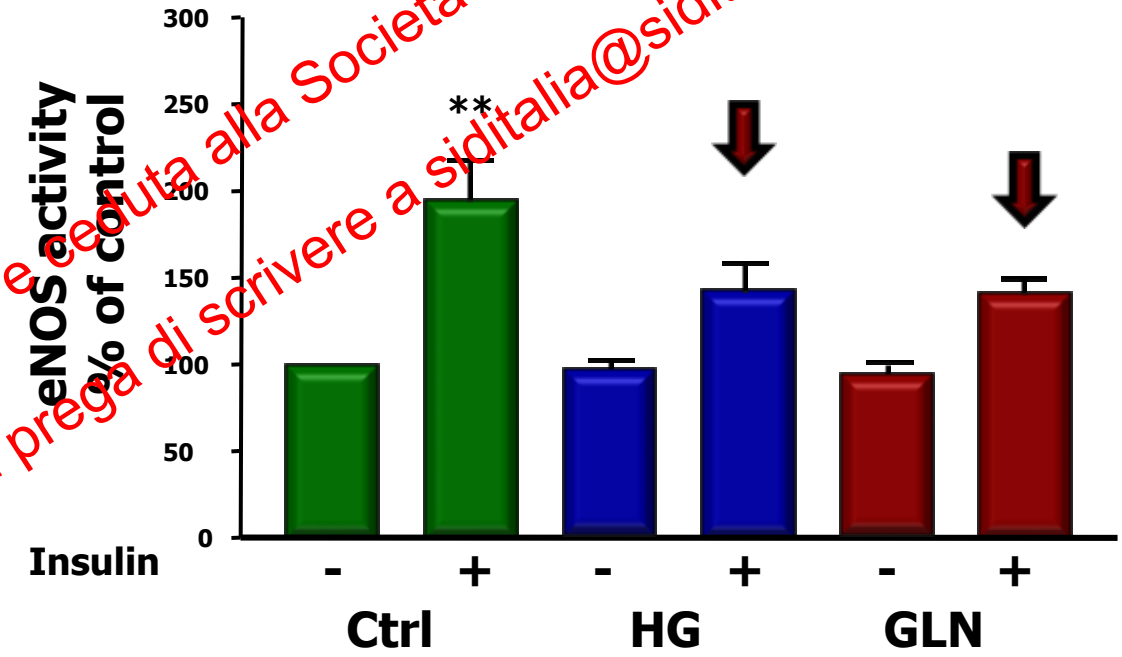


Federici M et al. Circulation 106:466-472, 2002

Effects of high glucose and glucosamine on eNOS phosphorylation and activity in HCAEC







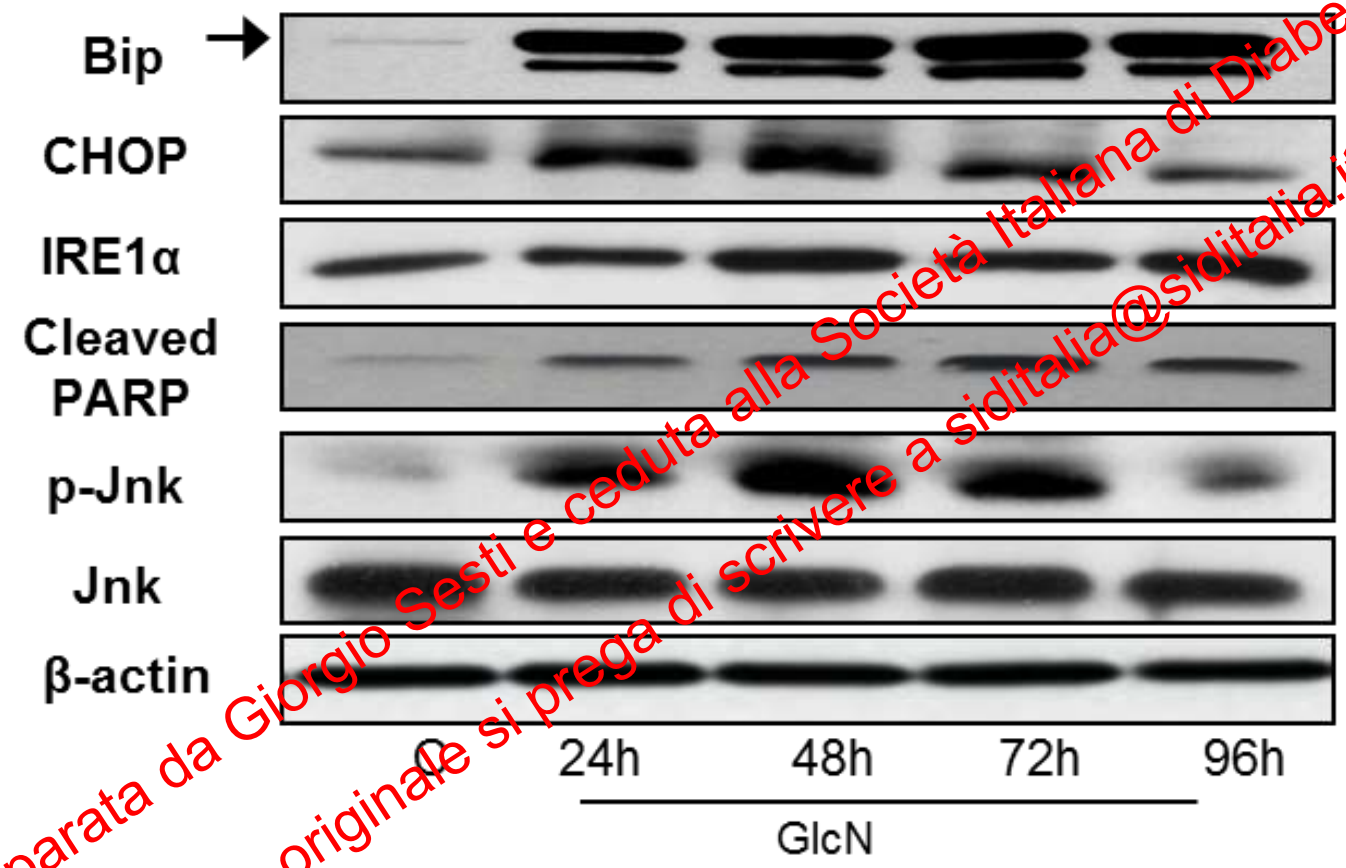
Federici M et al. Circulation 106:466-472, 2002

The Bradford Hill criteria

1. Strength (effect size)
2. Consistency (reproducibility)
3. Specificity
4. Temporality
5. Biological gradient
6. Plausibility
7. Coherence
8. **Experiment:** **Occasionally it is possible to appeal to experimental evidence.**
9. Analogy

Bradford Hill A Proceedings of the Royal Society of Medicine 58: 295–300, 1965

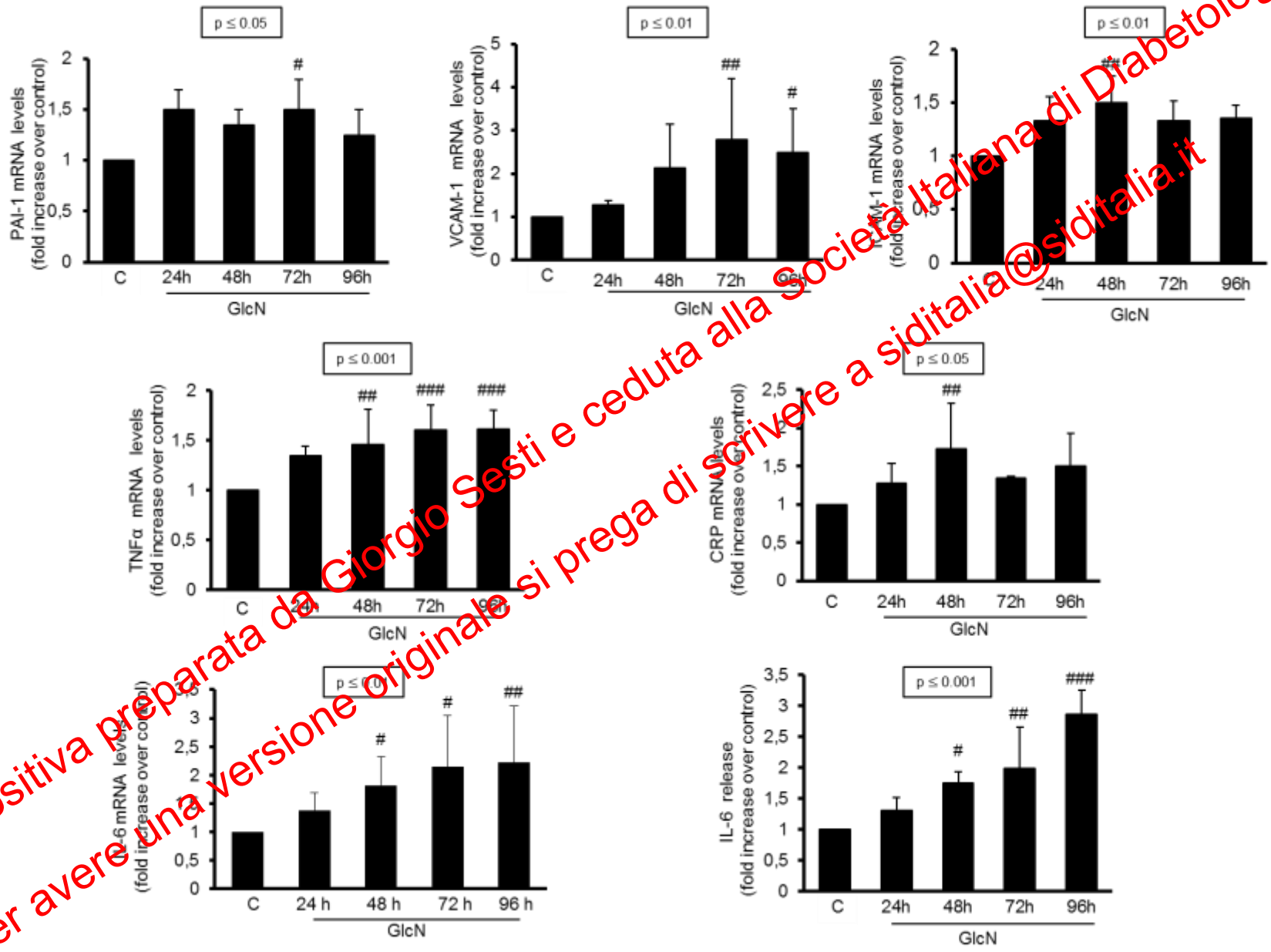
Glucosamine induces ER stress and promotes the activation of pro-inflammatory, pro-thrombotic, and pro-apoptotic pathways in HUVECs time-dependently



BIP= Binding immunoglobulin protein (chaperone)
CHOP=C/EBP homologous protein (promoter of ER stress-mediated apoptosis)
IRE1α=inositol-requiring enzyme (cleaves X-box binding protein 1 (XBP-1) mRNAactivate cell death and inflammatory pathways)
PARP=Poli-ADP-ribose polymerase (caspase substrate)
Jan= Jun N-terminal kinase (pro-inflammatory and pro-apoptotic kinase)

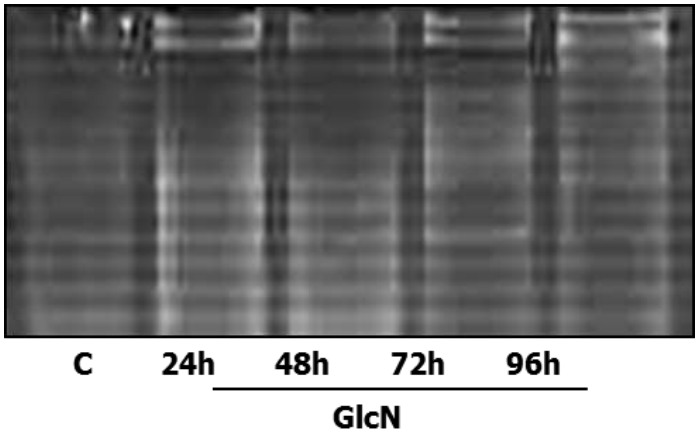
Fiorentino TV et al. Cardiovasc Res. 107:295-306, 2015

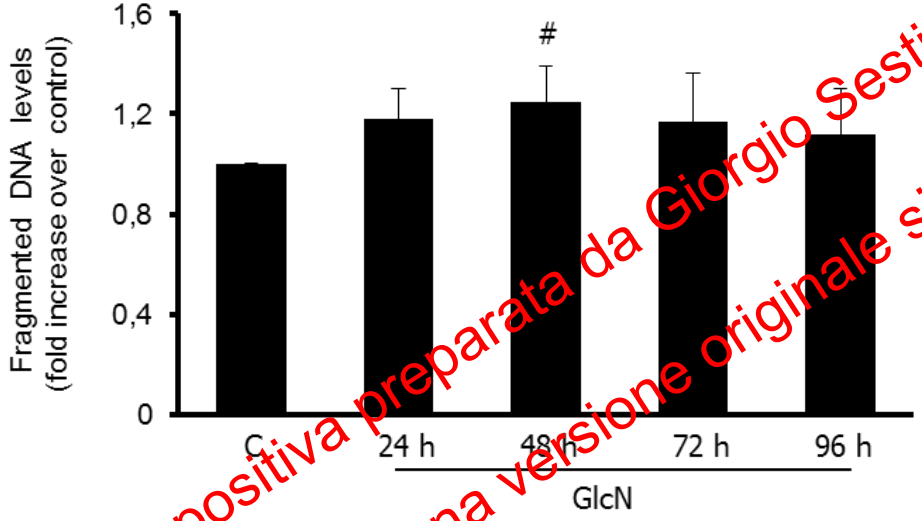
Glucosamine induces the expression of pro-coagulant factors and promotes the synthesis and release of pro-inflammatory cytokines in HUVECs



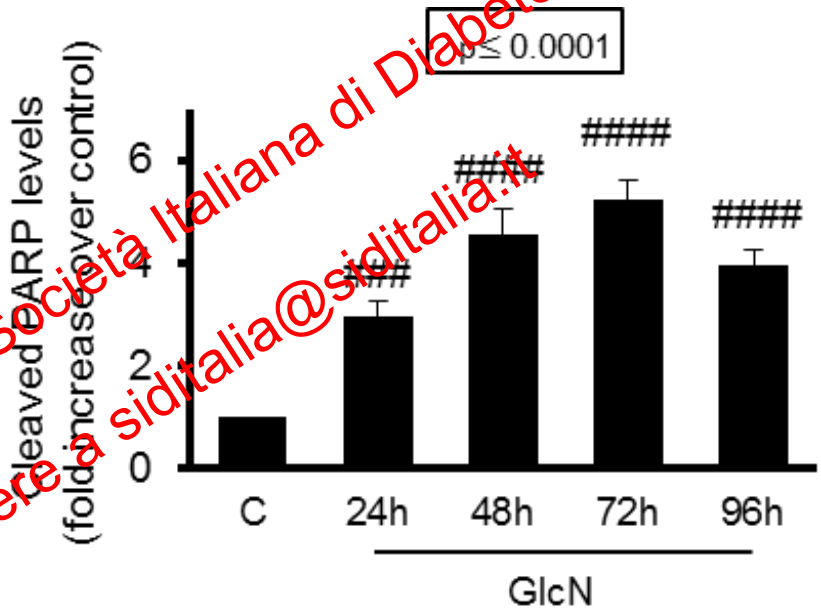
Fiorentino TV et al. Cardiovasc Res. 107:295-306, 2015

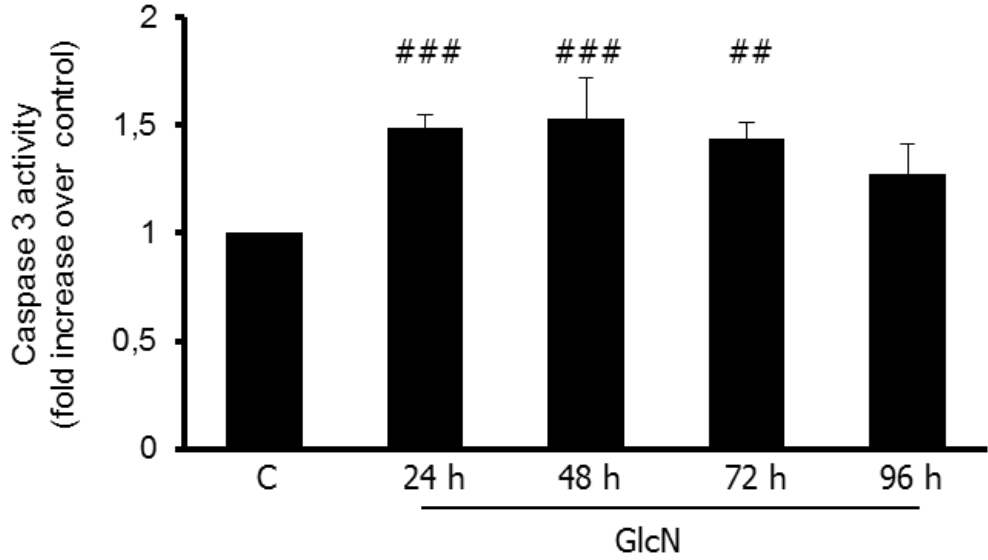
Glucosamine promotes pro-apoptotic pathways in HUVECs





PARP=Poli-ADP-ribose polymerase (caspase substrate)





Fiorentino TV et al. Cardiovasc Res. 107:295-306, 2015

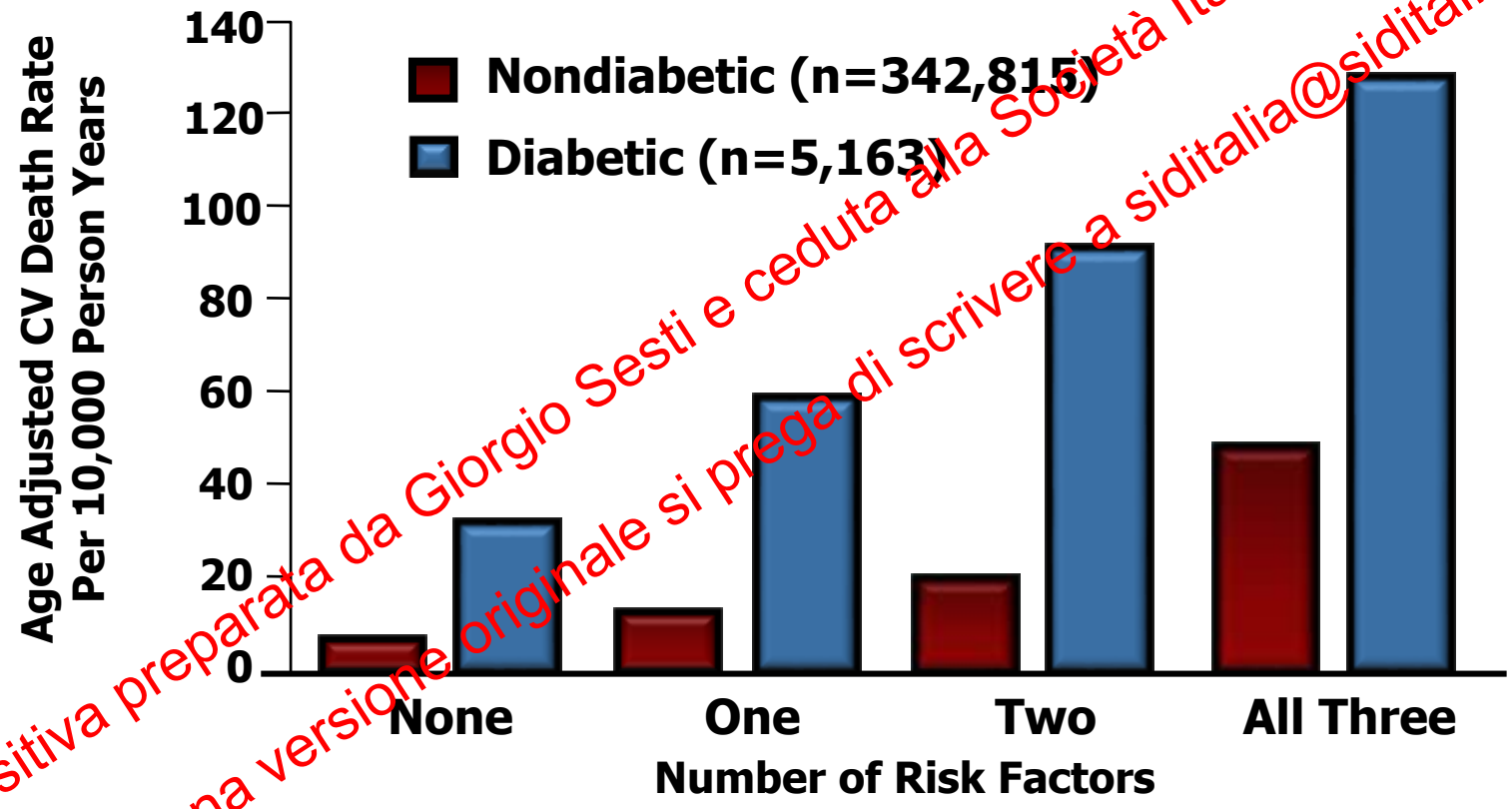
The Bradford Hill criteria

1. Strength (effect size)
2. Consistency (reproducibility)
3. Specificity
4. Temporality
5. Biological gradient
6. Plausibility
7. Coherence
8. Experiment
9. **Analogy:** **The effect of similar factors may be considered.**

Bradford Hill A Proceedings of the Royal Society of Medicine 58: 295–300, 1965

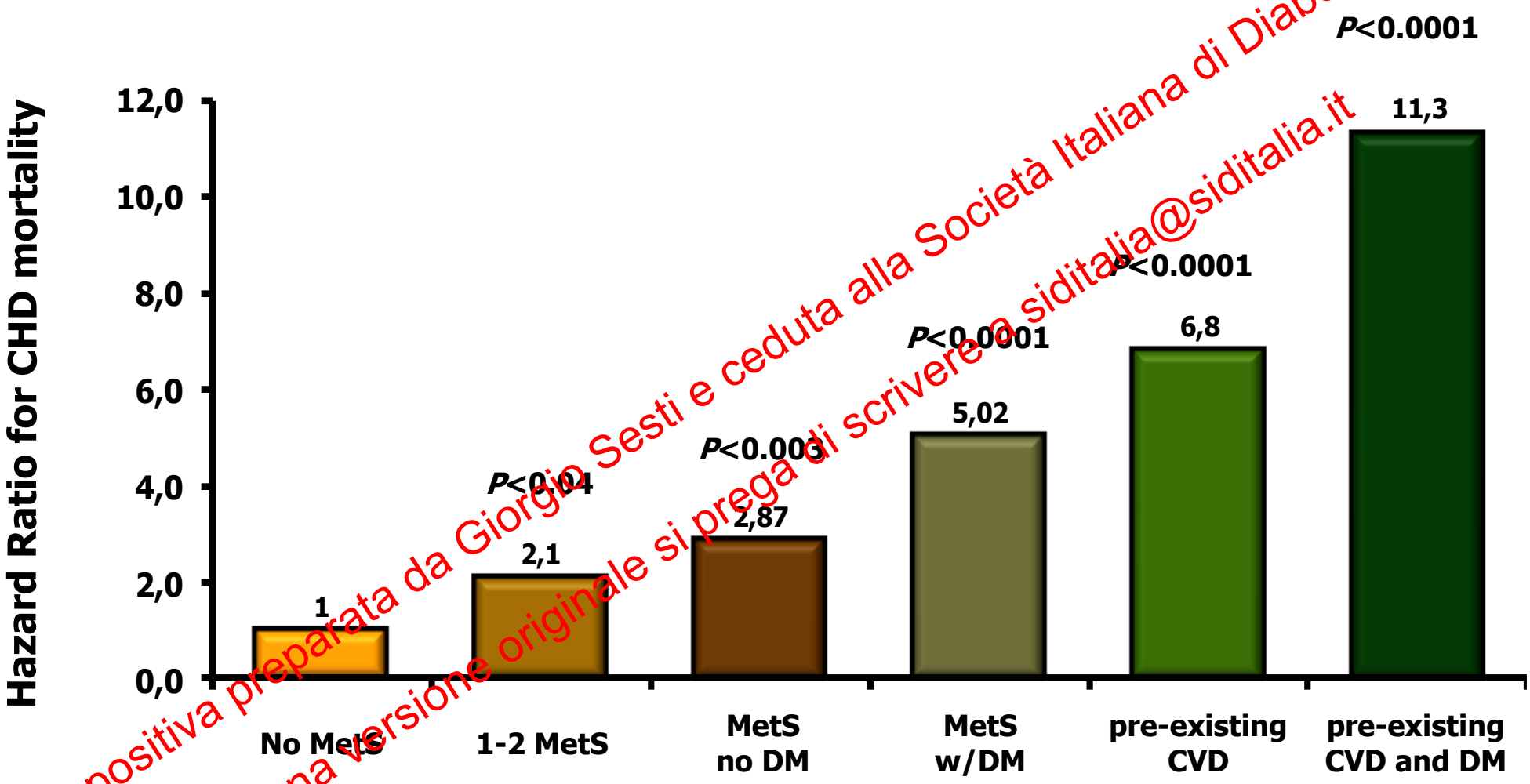
MULTIPLE RISK FACTOR INTERVENTION TRIAL (MRFIT)

Type 2 Diabetes is a CV Risk Factor Additive Effects of Hypertension, Hypercholesterolemia, and Smoking



Stamler J, et al. Diabetes Care 16:434-444, 1993

Hazard ratio for CHD Mortality in US Adults from the NHANES II (n=6255; 13.3 years follow-up)



Malik S. et al. Circulation 110:1245-1250, 2004