CONGRESSO INTERASSOCIATIVO SID-AMD-FTD TOSCANA

"DIABETE: IL NUOVO CHE AVANZA"

Il Vecchio da rottamare

L'OGTT ancora a 2 ore?

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Firenze, 3 Dicembre 2016

Dichiarazione Conflitto d'Interessi

La sottoscritta Dott.ssa Cristina Bianchi

DICHIARA

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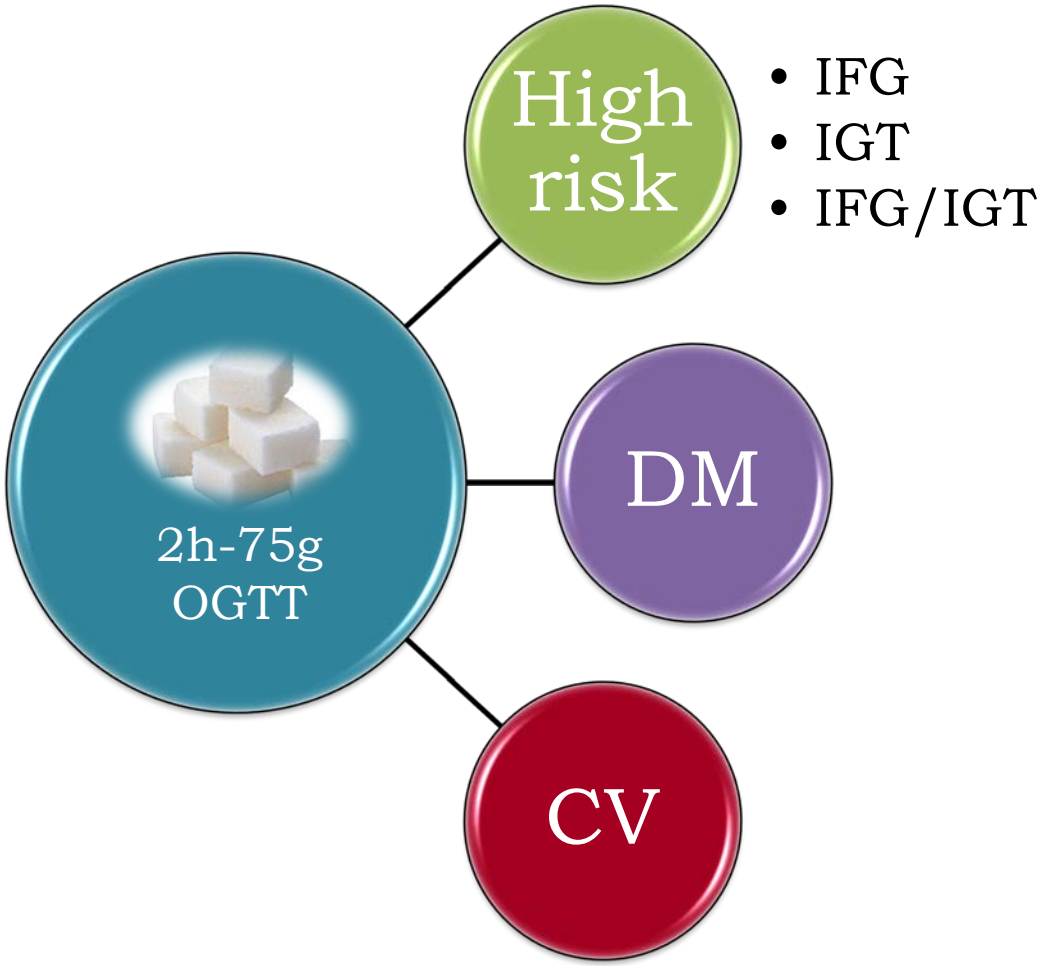
Boehringer Ingelheim Pharma
Lilly Diabetes
Novonordisk

Cristina Bianchi, *MD PhD*

CAMPAGNA ROTTAMAZIONE!

OGTT utility



Pre-history of OGTT-based diagnosis of type 2 diabetes

- Almost 2500 years ago it was noticed that ants were attracted to the urine of some individuals.
- 1674: Physician Thomas Willis of Oxford notes sweet flavor of urine in patients with diabetes.
- 18th-19° centuries: sweet test of urine was used for diagnosis of diabetes before chemical methods became available to detect sugars in the urine.
- 1913: Jacobsen ATB notes that carbohydrate ingestion results in blood glucose fluctuations.
- 1917: Oral glucose tolerance test was introduced
- Pre-1979: At least six different criteria used

OGTT-based diagnosis of type 2 diabetes and impaired glucose regulation

- 1979 National Diabetes Data Group (NDDG):
  - Diabetes: FPG ≥140 mg/dl or OGTT 2-hr glucose ≥200 mg/dl or Classic symptoms present

    They selected these criteria based on glucose concentrations that allegedly predicted the development of diabetic retinopathy (3 studies, 1,213 patients followed for 3 to 8 years after OGTT, 77 of whom developed retinopathy).
  - Impaired glucose tolerance: FPG ≤ 140 mg/dl and 2-hour OGTT glucose 140-200 mg/dl1.

- 1980-1985 WHO published diagnostic thresholds based on the 75-g oral glucose tolerance test (OGTT), which became the gold standard over subsequent years.

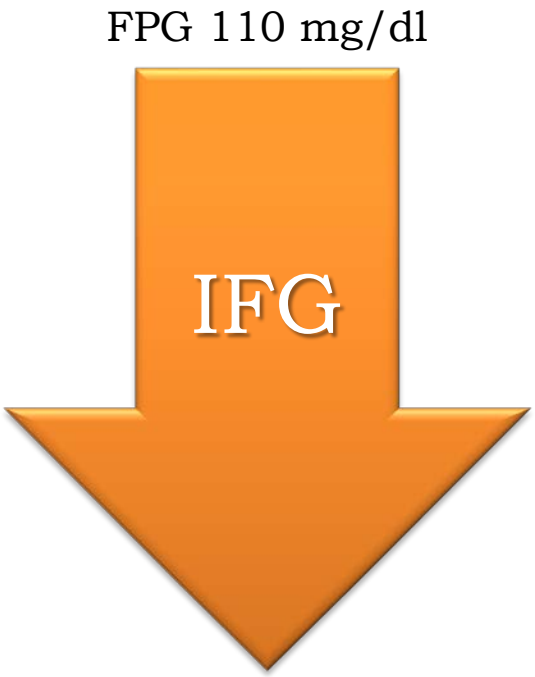
OGTT-based diagnosis of type 2 diabetes and impaired glucose regulation

- 1997 American Diabetes Association (ADA) convened an Expert Committee to reexamine the diagnosis of diabetes in light of any new information available:
  - To make FPG concentration and 2-hour OGTT glucose equivalent (and negate 2HPG as gold-standard test) → Only 25-50% of patients with 2-hour OGTT ≥200 mg/dl had FPG≥140 mg/dl so the FPG criteria was lowered to ≥126 mg/dl
  - To focus on making relationship between glucose levels and presence of long-term complications the basis for diagnosis.
  - Terms IDDM and NIDDM eliminated (now Type 1 and Type 2)
  - Impaired fasting glucose (FPG 110–125 mg/dl - 6.1–6.9 mmol/l) introduced as a new category of intermediate glucose metabolism.

- 1998 WHO
  - The threshold of 126 mg/dl (7.0 mmol/l) for the diagnosis of diabetes is maintained and so is the category of IFG;
  - The OGTT is recommended as a screening procedure whenever possible, and the condition of IFG is included together with IGT in the broader category of impaired glucose regulation.

Lower diagnostic threshold of IFG

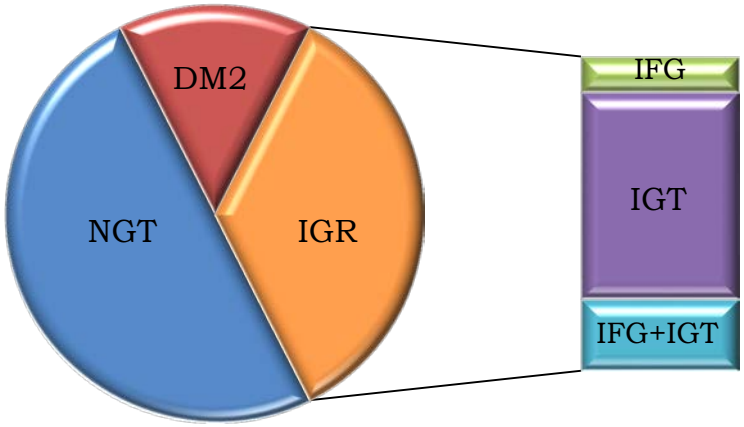
- 2003 ADA - Expert Committee on the Diagnosis and Classification of Diabetes Mellitus has recommended lowering the diagnostic threshold of impaired fasting glucose (IFG) from 6.1 to 5.6 mmol/l (100 mg/dl).



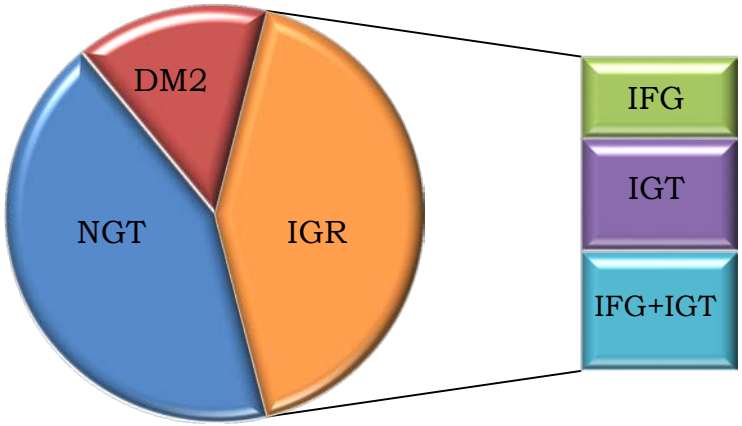
Categories of glucose regulation according with different definitions

- The GENFIEV Study -

ADA 1997



ADA 2003



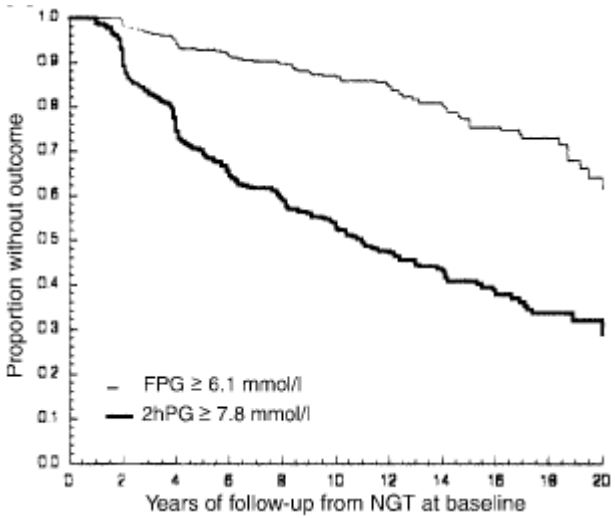
35% → 42%

Bianchi C. Nutrition, Metabolism & Cardiovascular Diseases 2011; 21, 699-705

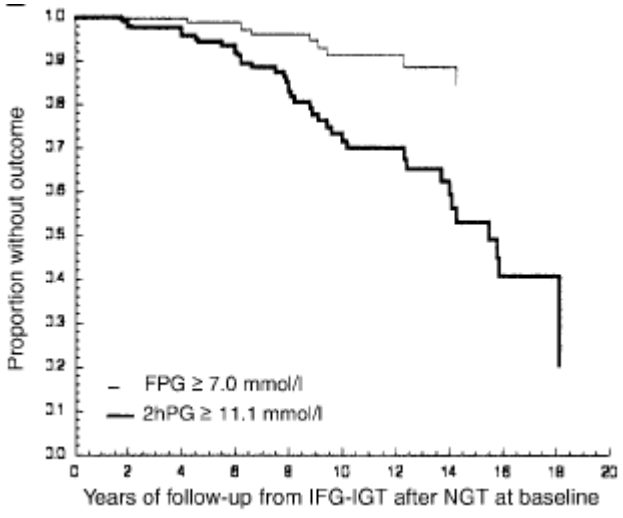
The Natural History of Progression from NGT to Type 2 Diabetes

- The Baltimore Longitudinal Study of Aging -

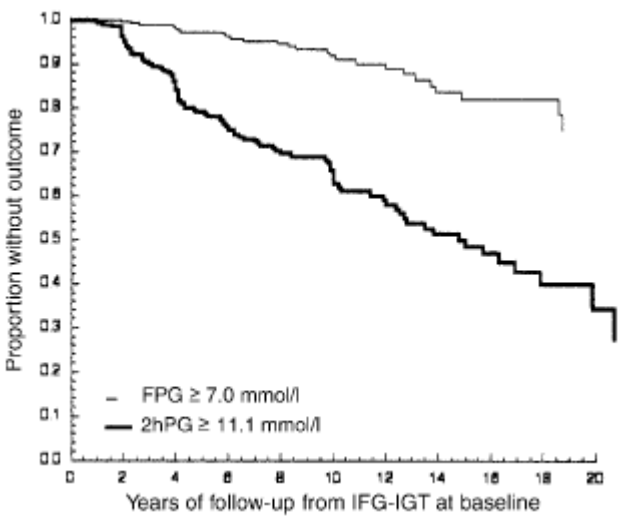
NGT → IFG/IGT



NGT → IFG/IGT → DM



IFG/IGT → DM



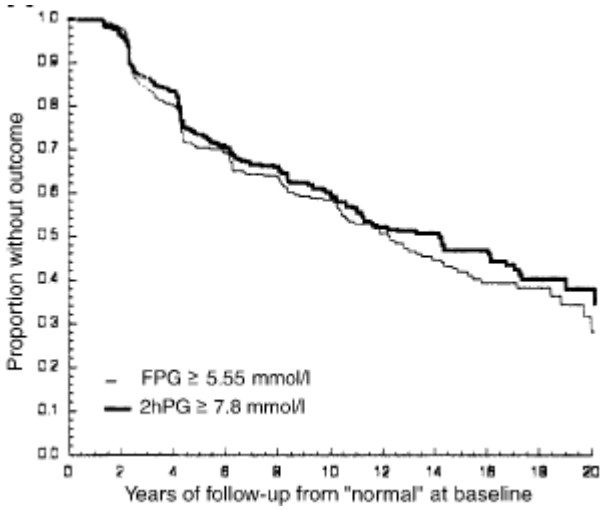
The more common pathway appeared to be the development of abnormal 2hPG levels with normal FPG levels. This pathway typically featured a prolonged decay in glucose tolerance, with slow progression from NGT to IGT to diabetic 2hPG. In only a few cases did subjects on this pathway manifest IFG or diabetic FPG. The less common, and even slower, pathway included development of IFG and, even more rarely, development of diabetic FPG levels.

Meigs JB. Diabetes 2003; 52: 1475–1484

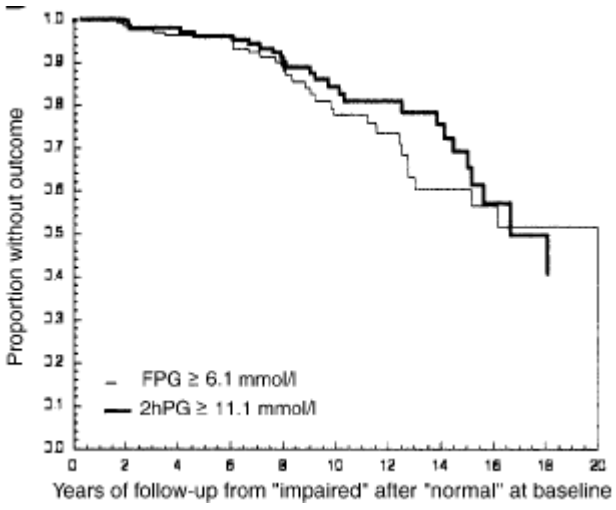
The Natural History of Progression from NGT to Type 2 Diabetes

- The Baltimore Longitudinal Study of Aging -

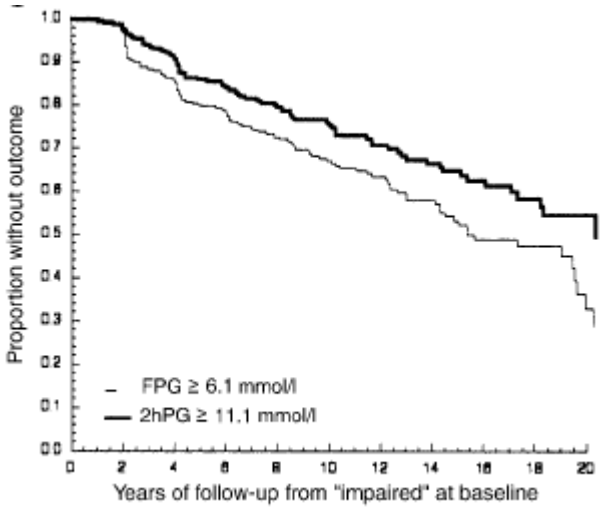
NGT → IFG/IGT



NGT → IFG/IGT → DM



IFG/IGT → DM

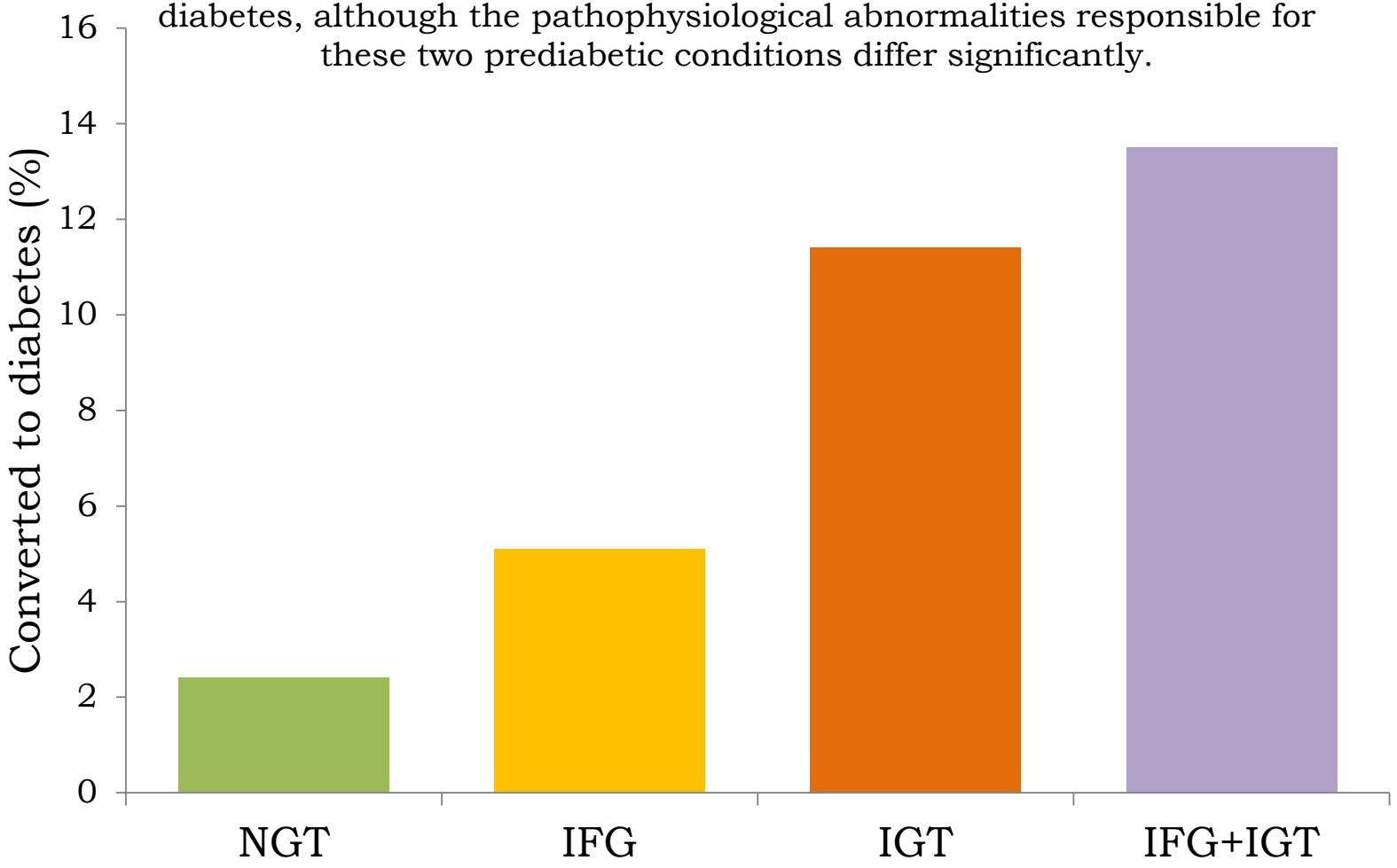


When the threshold for abnormal FPG was defined so that its prevalence approximated the prevalence of abnormal 2hPG, these differences in frequency and rate of progression of the two phenotypes virtually disappeared. Rates of progression to impaired or diabetic FPG were indistinguishable from rates of progression to IGT or postchallenge diabetes. However, in many cases the two pathways remained exclusive; about 42% of subjects developing abnormal FPG did not also develop abnormal 2hPG, and vice versa.

Meigs JB. Diabetes 2003; 52: 1475–1484

Progression to diabetes by categories of glucose regulation

IGT, IFG, and especially combined IFG+IGT are strong predictors of diabetes, although the pathophysiological abnormalities responsible for these two prediabetic conditions differ significantly.

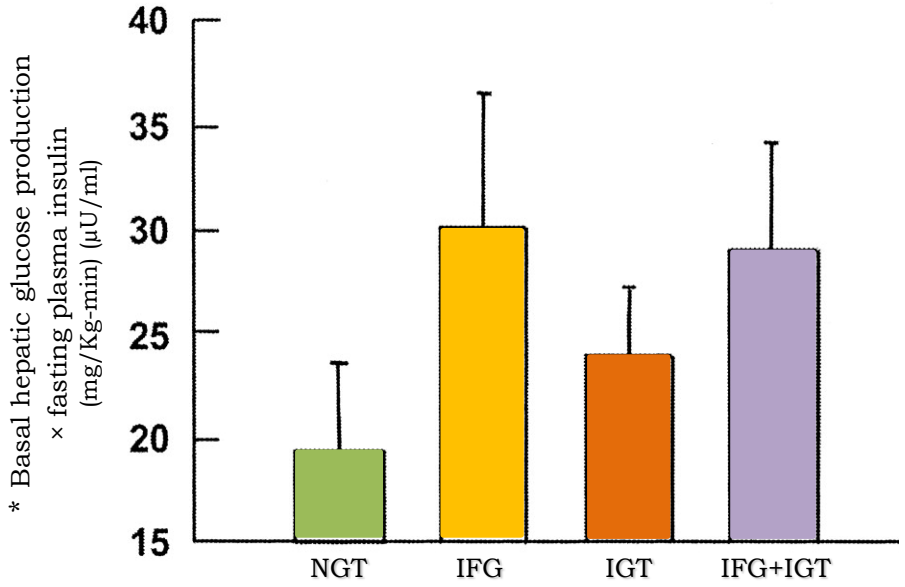


Defronzo R. J Clin Endocrinol Metab 2011; 96: 2354–2366

IFG and IGT: distinct physiological phenotypes

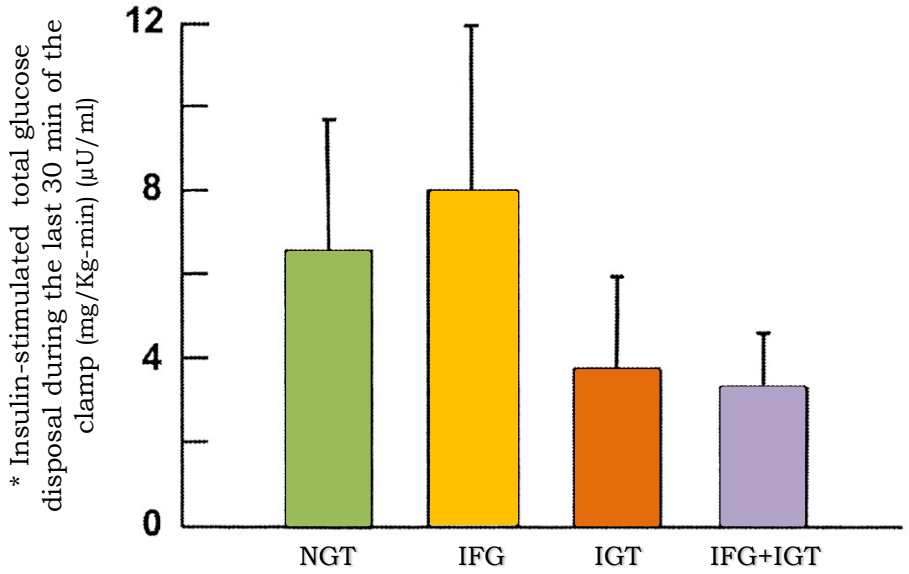
Isolated IFG and isolated IGT may define persons with different pathophysiological abnormalities and their combination marks a more advanced disturbance of glycemic homeostasis.

Hepatic insulin resistance



* Hepatic insulin sensitivity index measured with tritiated glucose

Muscle insulin sensitivity

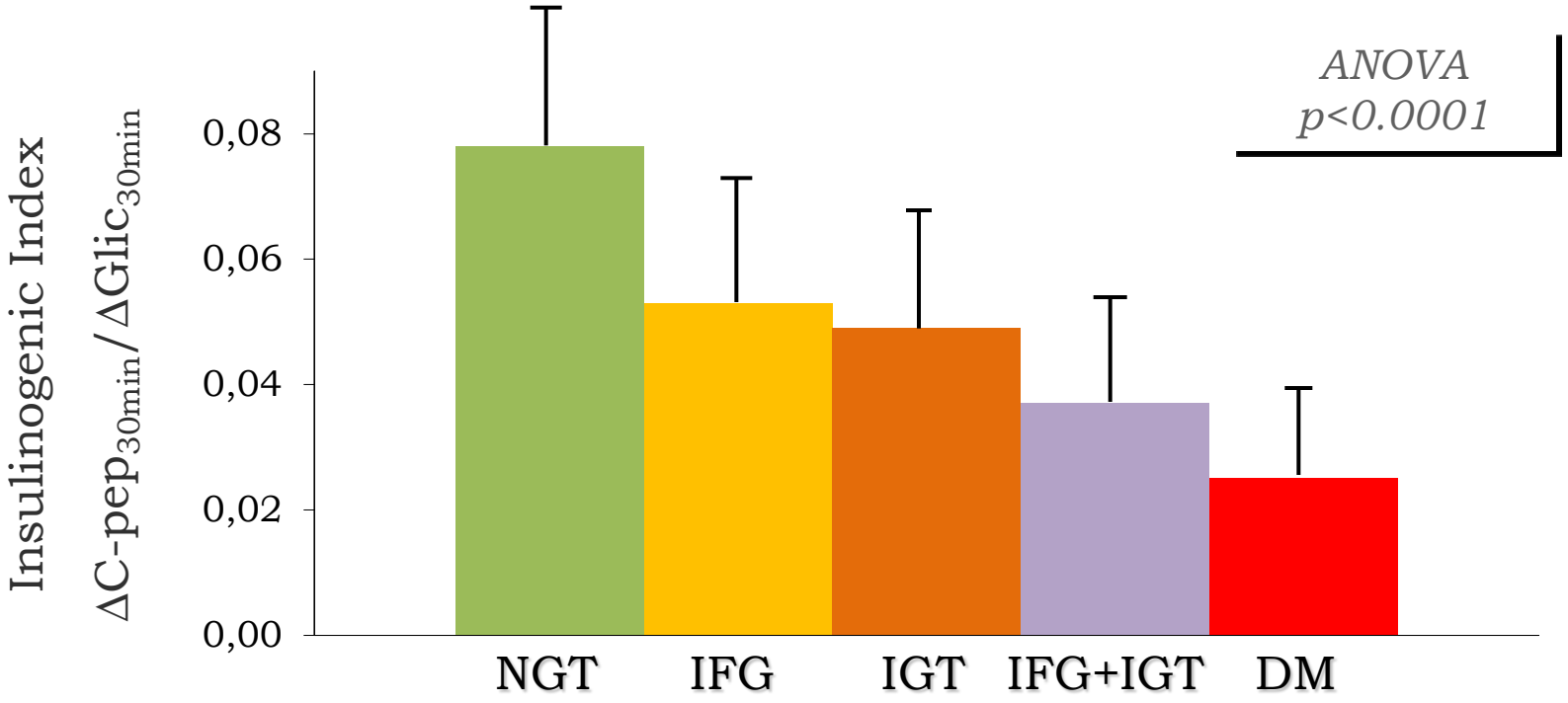


* Total-body insulin sensitivity, measured by insulin clamp, primarily reflects muscle insulin sensitivity

Abdul-Ghani MA. Diabetes 2006; 55(5): 1430-1435

β-cell function by glucose tolerance categories

- The GENFIEV Study -



Bianchi C. *Personal data*

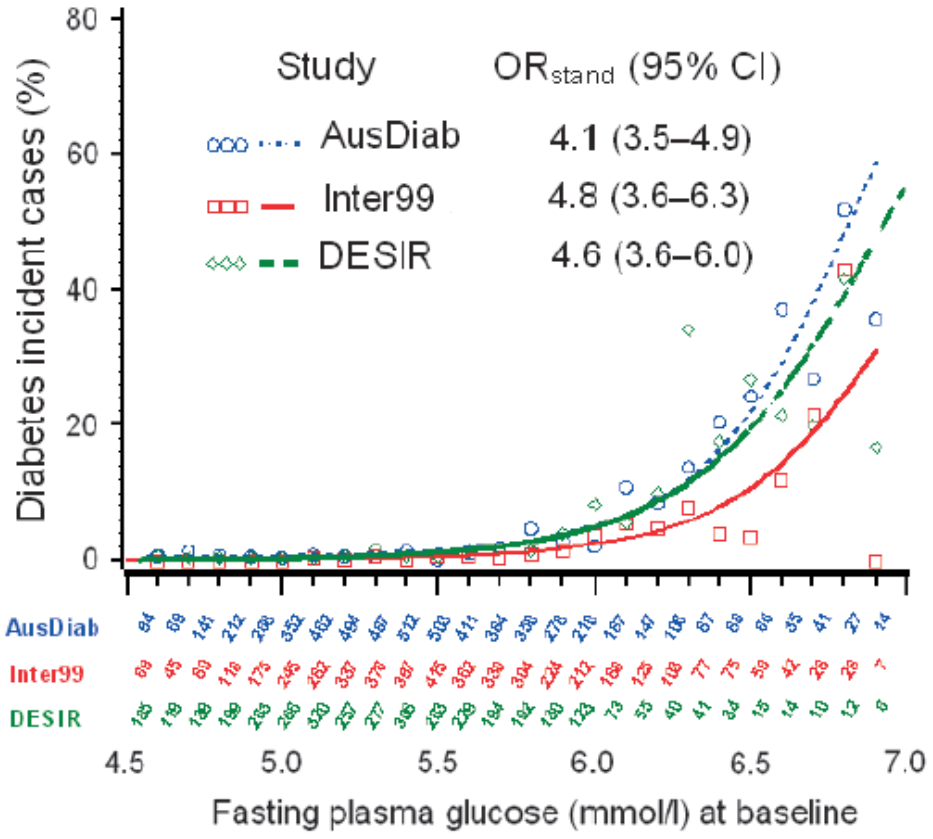
HbA1c for diagnosis of type 2 diabetes and risk of diabetes

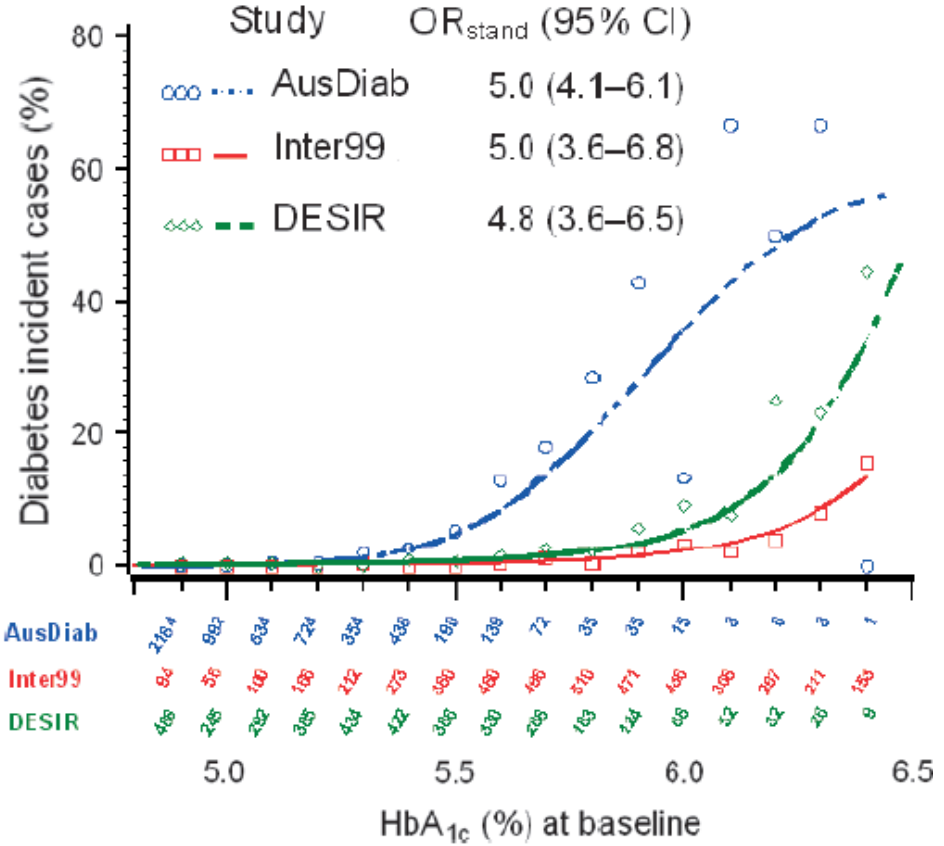
- 2010 ADA proposed new diagnostic criteria based on measurement of glycated haemoglobin (HbA1c):

	HbA1c
Normal	<5.7% (<39 mmol/mol)
High risk of progression to T2DM	5.7-6.49% (39-47 mmol/mol)
Diabetes	≥6.5 % (≥48 mmol/mol)

Incident diabetes as defined by fasting plasma glucose or by HbA1c

- The AusDiab, Inter99 and DESIR studies -





Soulimane S. Diabet Med 2011; 28: 1311–1318

HbA1c *vs.* Glucose testing for diagnosis of type 2 diabetes

FPG

Advantages

- Glucose assay easily automated
- Widely available
- Inexpensive
- Single sample

Disadvantages

- Patient must fast ≥8 h
- Large biological variability
- Diurnal variation
- Sample not stable
- Numerous factors alter glucose concentrations, e.g., stress, acute illness
- No harmonization of glucose testing
- Concentration varies with source of the sample (venous, capillary, or arterial blood)
- Concentration in whole blood is different from that in plasma
- Guidelines recommend plasma, but many laboratories measure serum glucose
- FPG less tightly linked to diabetes complications (than A1C)
- Reflects glucose homeostasis at a single point in time

OGTT

Advantages

- Sensitive indicator of risk of developing diabetes
- Early marker of impaired glucose homeostasis

Disadvantages

- Lacks reproducibility
- Extensive patient preparation
- Time-consuming and inconvenient for patients
- Unpalatable
- Expensive
- Influenced by numerous medications
- Subject to the same limitations as FPG, namely, sample not stable, needs to be performed in the morning, etc.

HbA1c

Advantages

- Subject need not be fasting
- Samples may be obtained any time of the day
- Very little biological variability
- Sample stable
- Not altered by acute factors, e.g., stress, exercise
- Reflects long-term blood glucose concentration
- Assay standardized across instruments
- Accuracy of the test is monitored
- Single sample, namely whole blood
- Concentration predicts the development of microvascular complications of diabetes
- Used to guide treatment

Disadvantages

- May be altered by factors other than glucose, e.g., change in erythrocyte life span, ethnicity
- Some conditions interfere with measurement, e.g., selected hemoglobinopathies
- May not be available in some laboratories/ areas of the world
- Cost

Sacks DB. Diabetes care 2011; 34: 518-523

Editorials
EDITORIAL (SEE SACKS, P. 518)

Diagnosing Diabetes With Glucose Criteria: Worshipping a False God

MAYER B. DAVIDSON, MD

DIABETES CARE, VOLUME 34, FEBRUARY 2011

The diagnosis of diabetes should be made by A1C levels ≥6.5%.

In addition to the measurement issues, the rationale for this conclusion is that:

1) The distribution of glucose concentrations in most populations is unimodal with no consistent cut point with which to diagnose diabetes;
2) bona-fide retinopathy, a specific complication of diabetes, is not seen in people whose A1C levels are <6.5%;
3) raised A1C levels cause the microvascular complications of diabetes, and lowering levels is beneficial;
4) increased glycation of proteins is one of the causes of diabetes complications, supplying a direct link between the diagnosis and the complications.

Davidson B. Diabetes Care 2011; 34: 524-526

Original Article
Clinical Care/Education
Diabetes Metab J 2016;40:118-128
http://dx.doi.org/10.4093/dmj.2016.40.2.118
pISSN 2233-6079 · eISSN 2233-6087

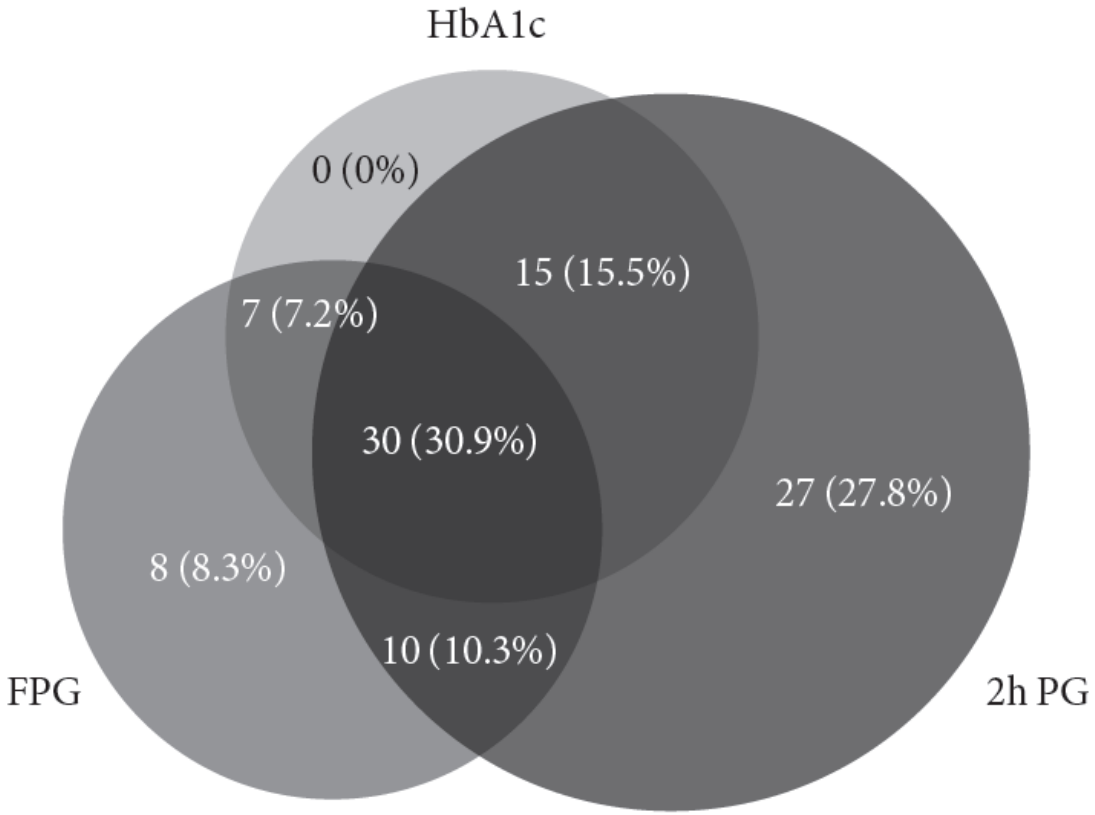
dmj
DIABETES & METABOLISM JOURNAL

Is an Oral Glucose Tolerance Test Still Valid for Diagnosing Diabetes Mellitus?

Dong-Lim Kim[1,*], Sun-Doo Kim[2,*], Suk Kyeong Kim[1], Soovoun Park[1], Kee-Ho Song[1]

Concordance rate between three different diagnostic criteria* of diabetes

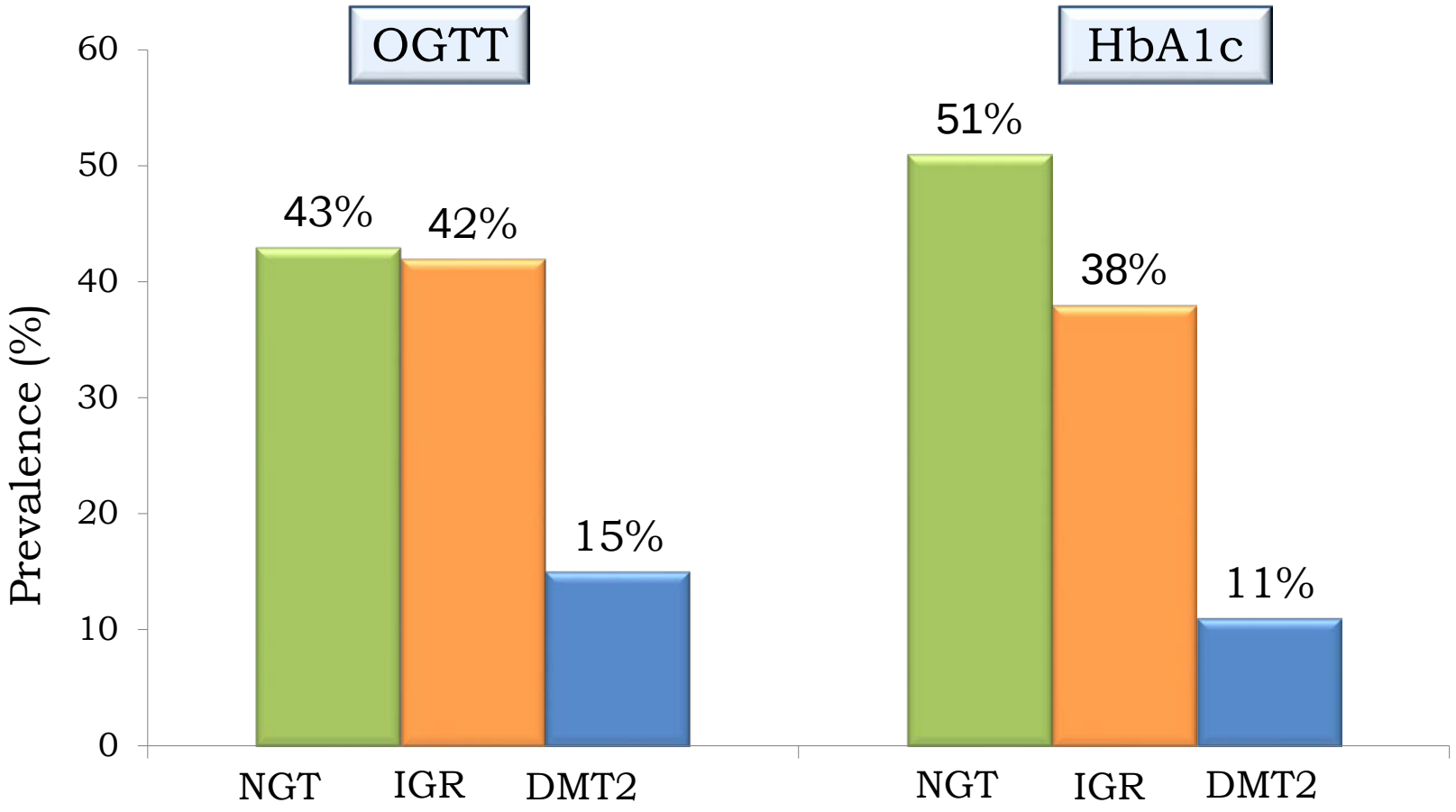
* FPG ≥126 mg/dL; 2h PG after 75 g OGTT ≥200 mg/dL; HbA1c ≥6.5%



Kim DL. Diabetes Metab J 2016;40:118-128

Pre-diabetes: OGTT *vs.* HbA1c

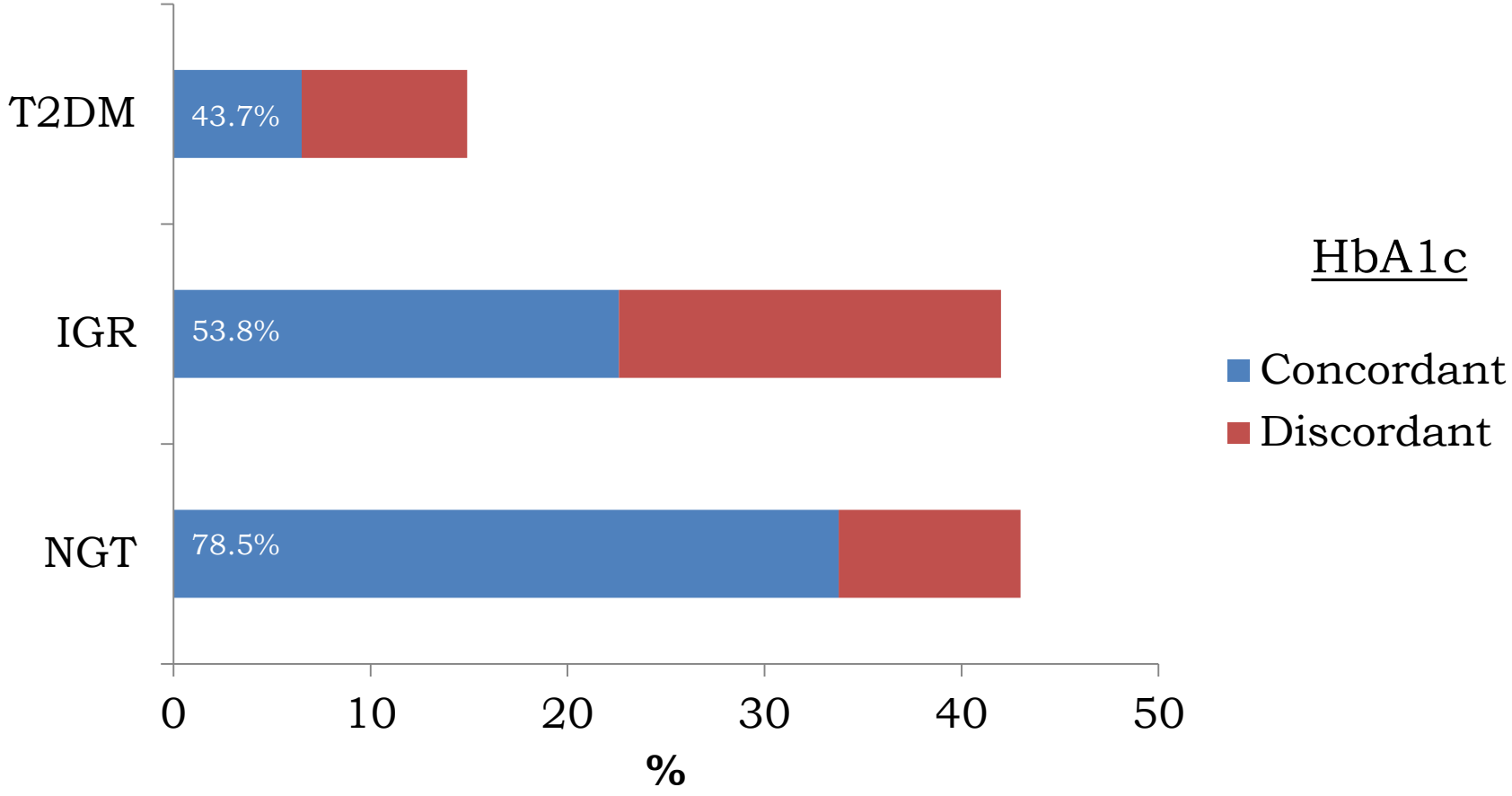
- The GENFIEV Study -



Bianchi C. Diabetes Care 2012;35(12):2607-2612

HbA1c sensibility in detecting T2DM and IGR

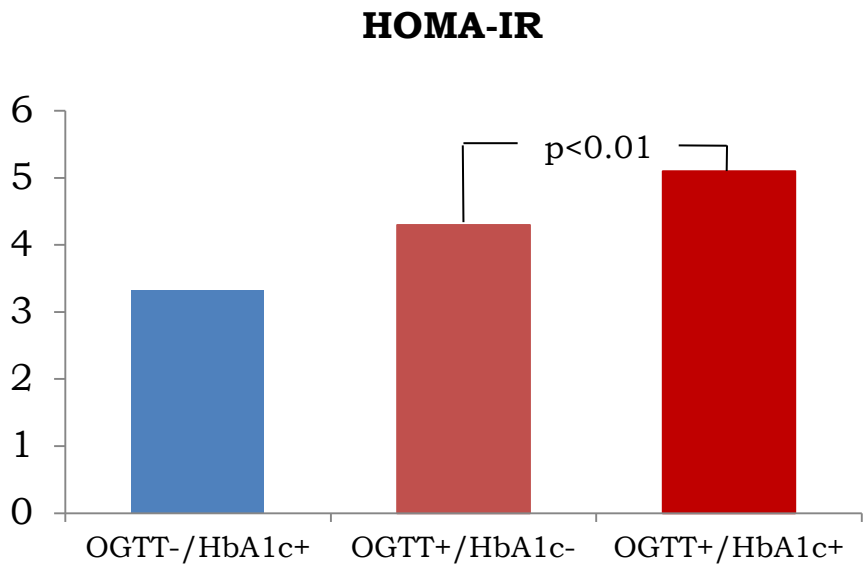
- The GENFIEV Study -

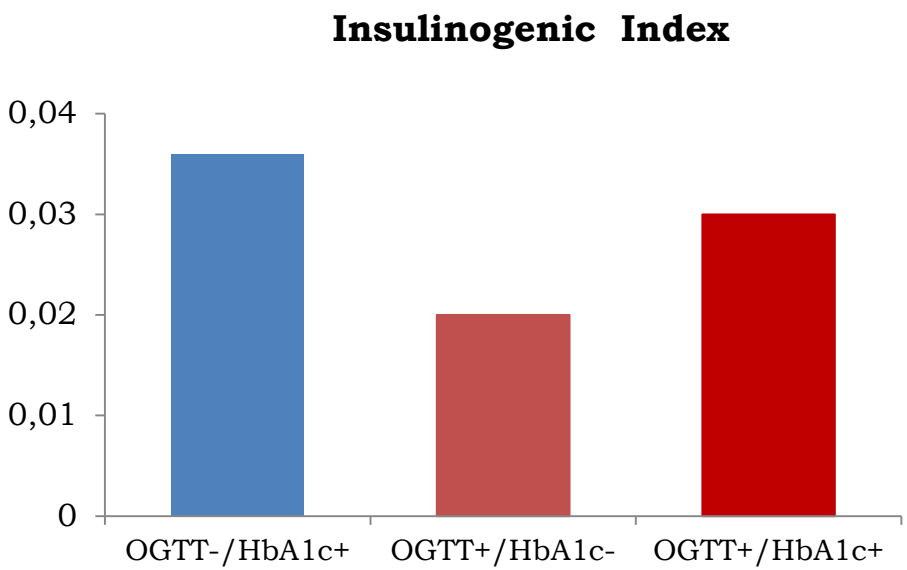


Bianchi C. Diabetes Care 2012;35(12):2607-2612

Insulin Secretion and action according with diabetes diagnosis criteria

- The GENFIEV Study -

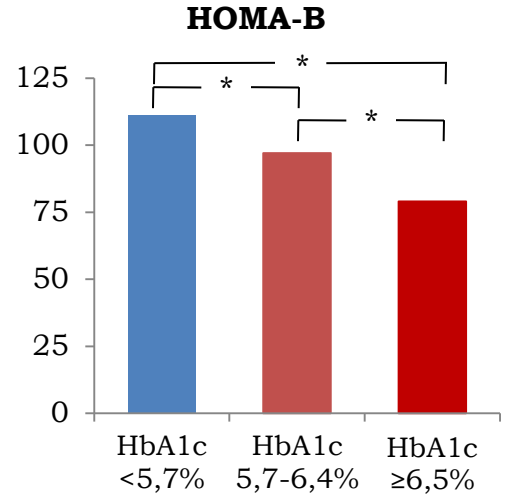


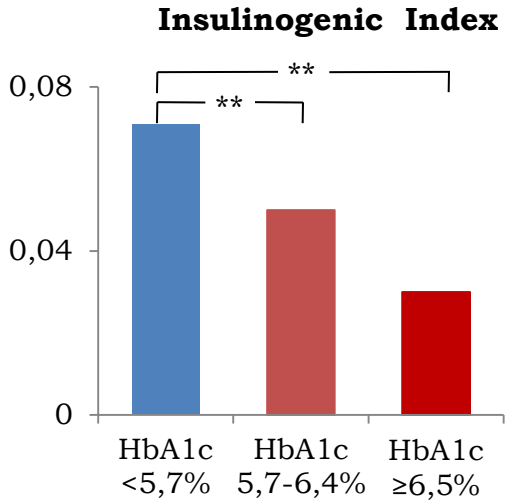


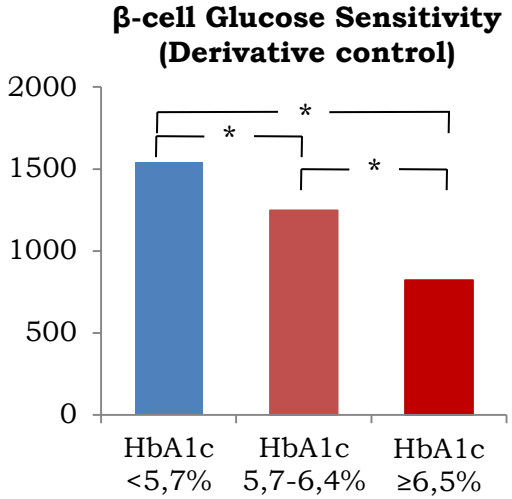
Bianchi C. Diabetes Care 2012;35(12):2607-2612

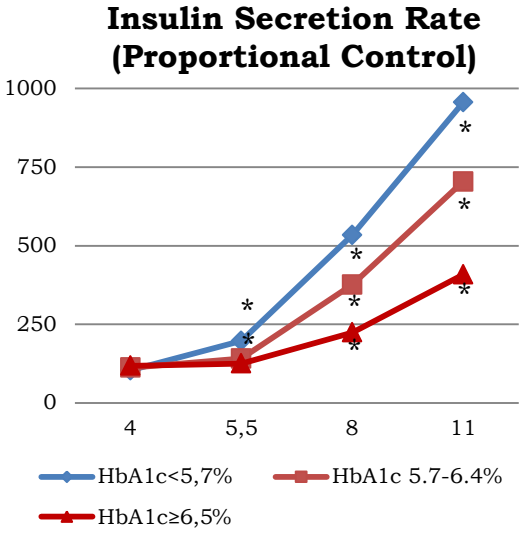
HbA1c and Insulin Secretion and Action

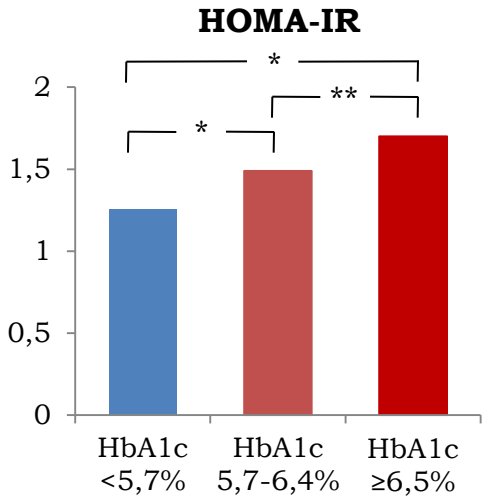
- The GENFIEV Study -

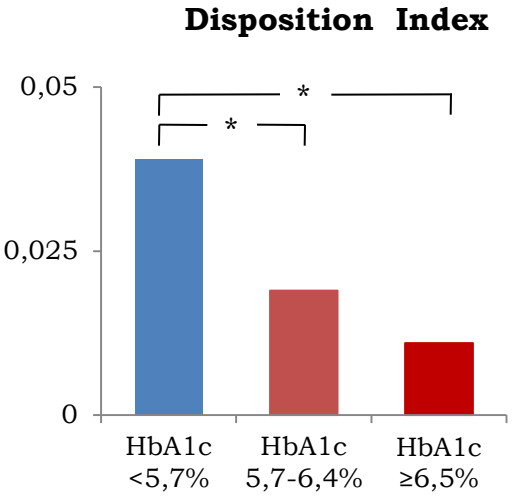










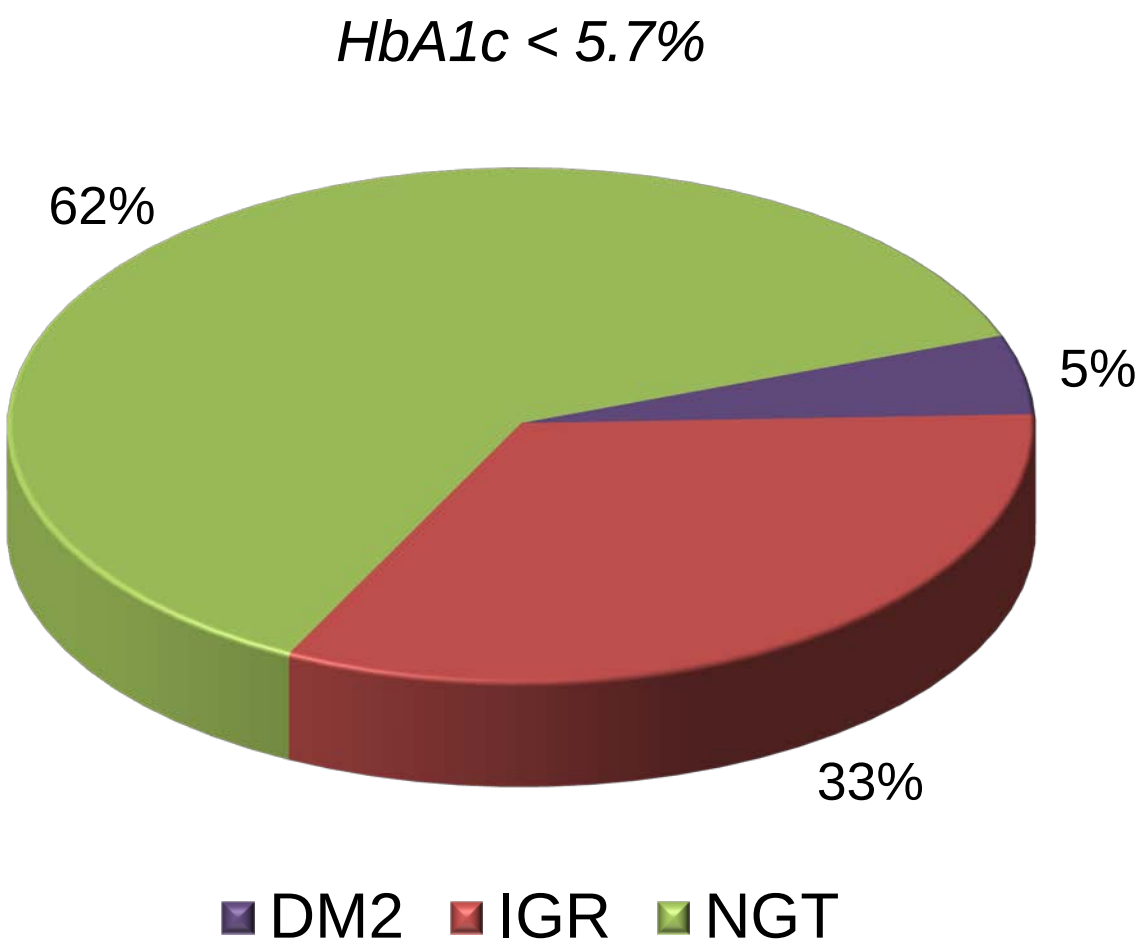


All measures are age-adjasted; * p <0.0001; ** p <0.05

Bianchi C. Diabetes Care 2012;35(12):2607-2612

Glucose tolerance in subjects with HbA1c <5.7%

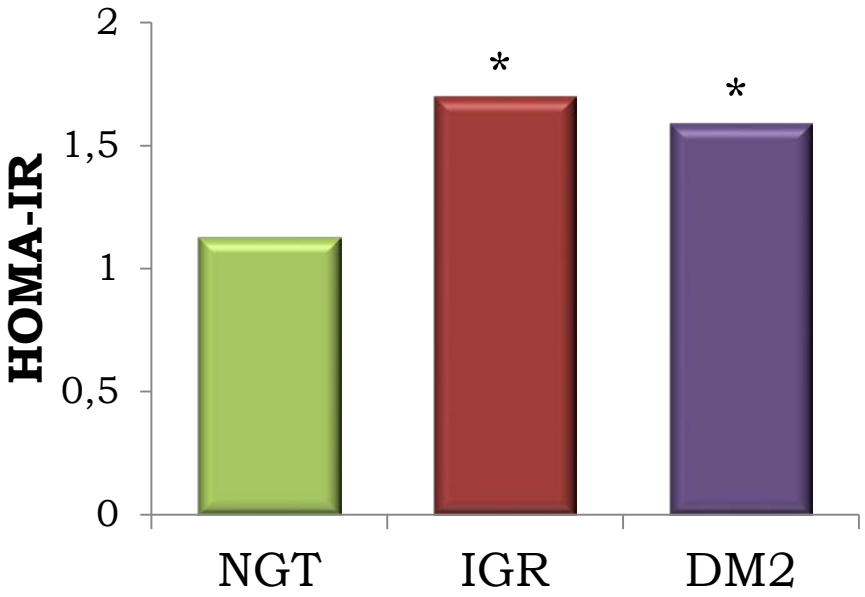
- The GENFIEV Study -



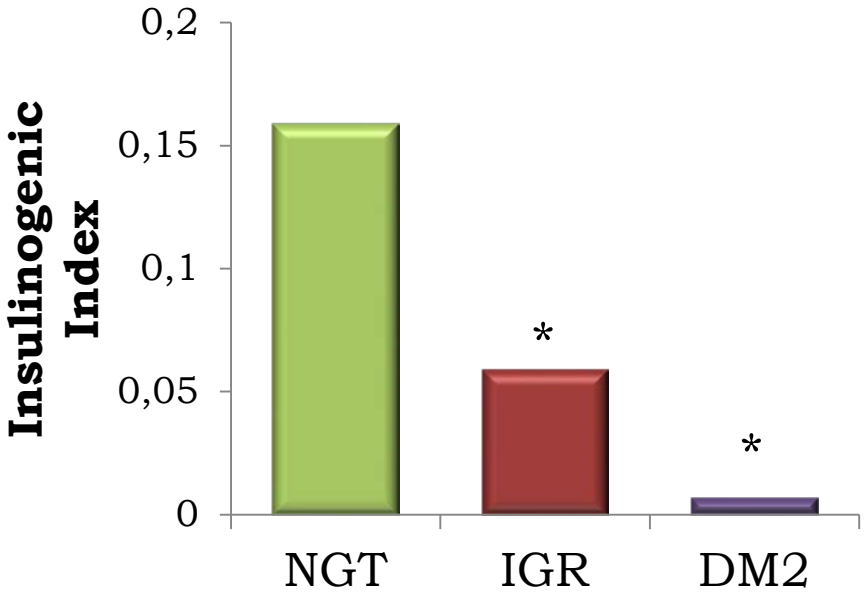
Bianchi C. Diabetes Care 2012;35(12):2607-2612

Insulin resistance and insulini secretion in subjects with HbA1c <5.7%

HOMA-IR



Insulinogenic Index



* p<0.05 *vs.* NGT

Bianchi C. Diabetes Care 2012;35(12):2607-2612

New cases of diabetes in persons with NGT

	Proportion from persons with NGT
Hoorn (50-75y)	38%
Mauritius (25-74y)	40%
Pima Indians (>15y)	44%
Nhanes III (40-74y)	40%

Longitudinal studies have reported that 30-40% of subjects that develop T2DM have normal glucose tolerance (NGT) at baseline. Therefore, to improve T2DM prevention, it would be important to identify also the NGT individuals with increased risk for developing T2DM.

Unwin N. Diabetic Medicine 2002; 19: 708–723

ORIGINAL ARTICLE

What Is the Best Predictor of Future Type 2 Diabetes?

The insulin secretion/insulin resistance index is useful as a predictor of future development of type 2 diabetes. 1-h plasma glucose concentration can equally predict future type 2 diabetes.

Area under the ROC curve for various predictive models for future development of type 2 diabetes

Parameter	ROC	*P* vs. G_{120}	ROC combined model*	Cutoff	Sensitivity	Specificity
Fasting plasma glucose	0.75	0.05				
Plasma glucose at 30 min	0.77	0.24				
Plasma glucose at 60 min	0.84	0.01	0.86†	155	0.75	0.79
Plasma glucose at 120 min	0.79			140	0.51	0.92
SADPM	0.80					
Glucose (AUC) 0–120 min	0.83	0.06	0.87†		0.83	0.71
$\Delta I_{0-120}/\Delta G_{0-120}$ × Matsuda index	0.86	<0.0001	0.86†	4.5	0.82	0.76
$\Delta I_{0-30}/\Delta G_{0-30}$ × Matsuda index	0.85	0.005	0.87†	3.1	0.83	0.77
$\Delta I_{0-30}/\Delta G_{0-30}$ × modified Matsuda index	0.83	0.1	0.86†	3.5	0.82	0.71

*The combined model is comprised of the combination of each parameter with SADPM. †$P < 0.0001$ vs. SADPM; P = NS vs. ROC. AUC, area under the curve.

Abdul-Ghani MA. Diabetes Care 2007; 30:1544–1548

1-h plasma glucose and metabolic syndrome identify subjects at high risk for type 2 diabetes

- The San Antonio Heart Study -

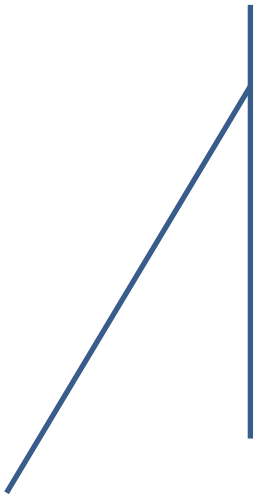
	Odds ratio (95% CI)
Model 1	
NGT, 1-h plasma glucose <155 mg/dl	1
NGT, 1-h plasma glucose >155 mg/dl without metabolic syndrome	3.4 (1.8–6.4)
NGT, 1-h plasma glucose >155 mg/dl with metabolic syndrome	15.2 (7.8–29.3)
IFG, 1-h plasma glucose <155 mg/dl	4.0 (1.3–11.9)
IFG, 1-h plasma glucose >155 mg/dl	19.5 (10.0–38.0)
IGT, 1-h plasma glucose <155 mg/dl	7.1 (3.0–16.5)
IGT, 1-h plasma glucose >155 mg/dl	18.1 (10.8–30.1)
Model 2(A)	
1-h plasma glucose <155 mg/dl without metabolic syndrome	1
1-h plasma glucose <155 mg/dl with metabolic syndrome	2.4 (1.2–4.8)
1-h plasma glucose >155 mg/dl without metabolic syndrome and FPG <95 mg/dl	3.6 (2.0–6.2)
1-h plasma glucose >155 mg/dl with metabolic syndrome or FPG >95 mg/dl	30.0 (19.4–46.3)
Model 2(B)	
1-h plasma glucose <155 mg/dl and triglyceride–to–HDL cholesterol ratio <3.5	1
1-h plasma glucose < 155 mg/dl and triglyceride–to–HDL cholesterol ratio >3.5	2.3 (1.3–4.2)
1-h plasma glucose >155 mg/dl and triglyceride–to–HDL cholesterol ratio <3.5 and FPG <95 mg/dl	4.3 (2.4–7.9)
1-h plasma glucose >155 mg/dl and triglyceride–to–HDL cholesterol ratio >3.9 or FPG >95 mg/dl	22.4 (14.2–35.3)

Abdul-Ghani MA. Diabetes Care 2008; 31:1650–1655

Fasting Versus Postload Plasma Glucose Concentration and the Risk for Future Type 2 Diabetes

- The Botnia study -

	aROC curve
FPG	0.672*
PG at 30 min	0.735*
PG at 60 min	0.795
PG at 120 min	0.688*
A1C	0.679*
ΔG_{0-120}	0.77†
Score Model I	0.646*
Score Model II	0.74*
SADPM	0.743*
MS	0.72*
MS + G60	0.813‡
Model I + G60	0.805‡
Model II + G60	0.822‡
SADPM + G60	0.832‡



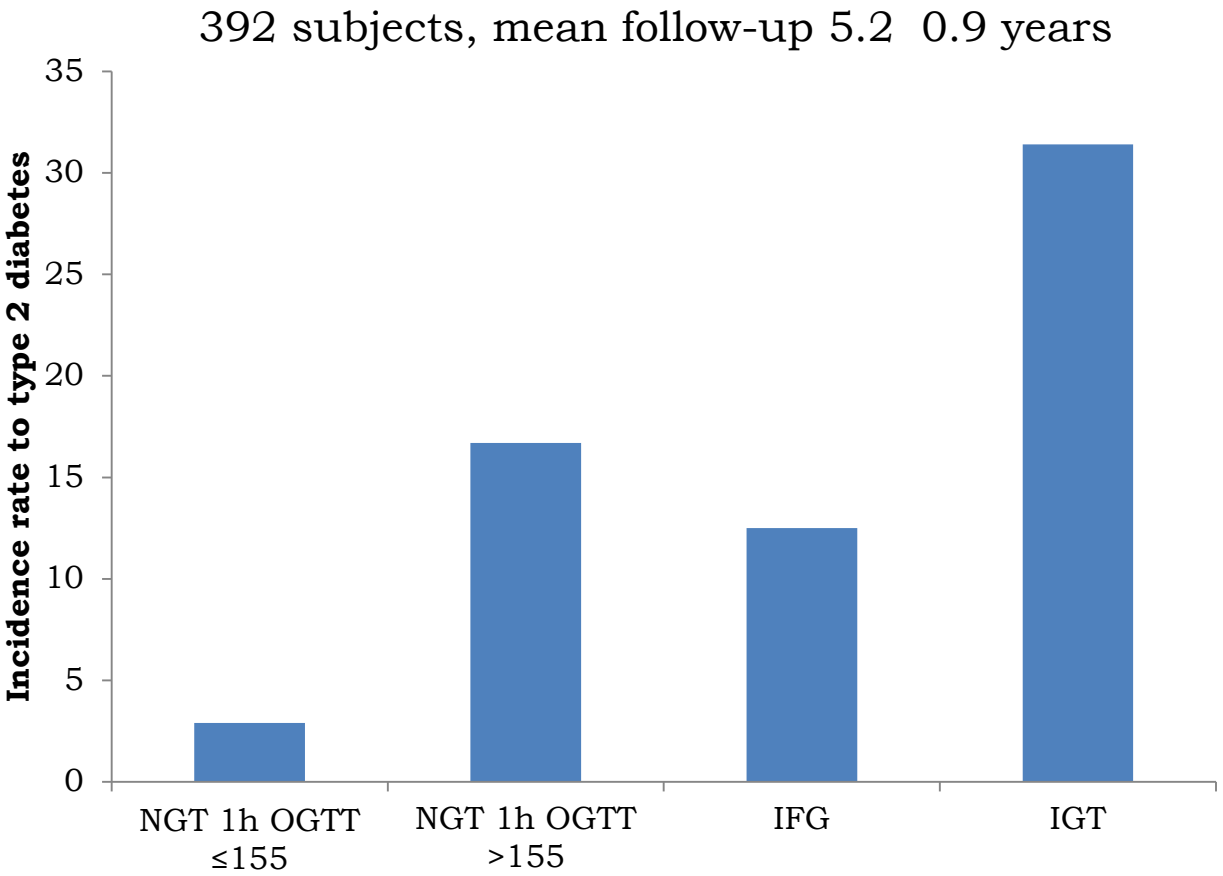
The plasma glucose concentration at 1 h during the OGTT is a strong predictor of future risk for type 2 diabetes and adds to the prediction power of models based on measurements made during the fasting state. A plasma glucose cut point of 155 mg/dl plus the Adult Treatment Panel III criteria for the metabolic syndrome can be used to stratify non-diabetic subjects into low-, intermediate-, and high-risk groups.

*P0.001 compared with the aROC curve for plasma glucose concentration at 60 min.
‡P 0.0001 compared with the aROC curve of the same model without G60.

Abdul-Ghani MA. Diabetes Care 2009; 32: 281-286

1h OGTT is a stronger predictor of Type 2 Diabetes than IFG

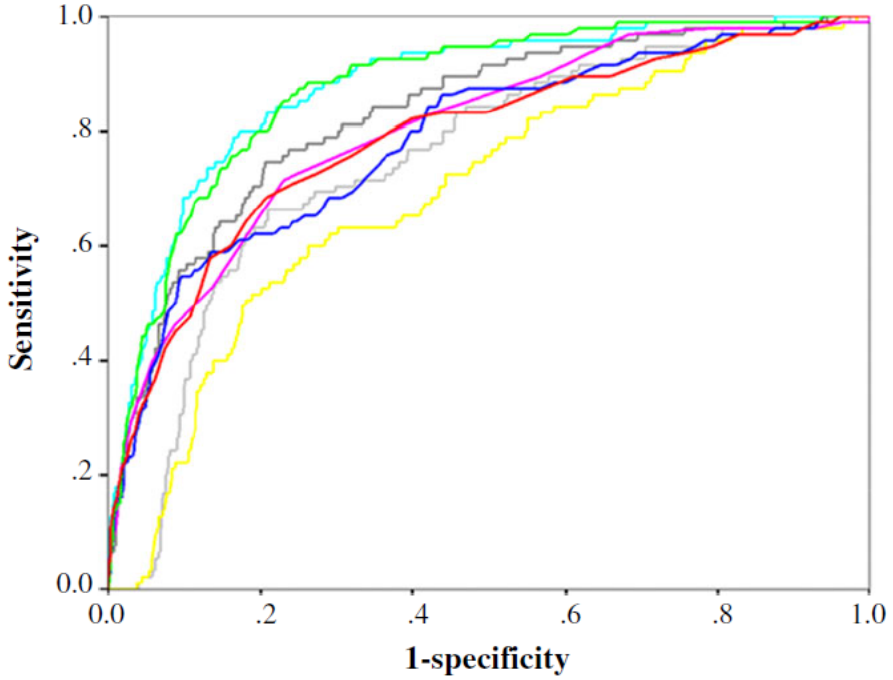
- The CATAMERI study -



Fiorentino TV. J Clin Endocrinol Metab 2015; 100: 374

1h OGTT as a predictor of Type 2 diabetes in Japanese adults

1445 Japanese (mean age 52±7 years); mean follow-up of 4.5 years



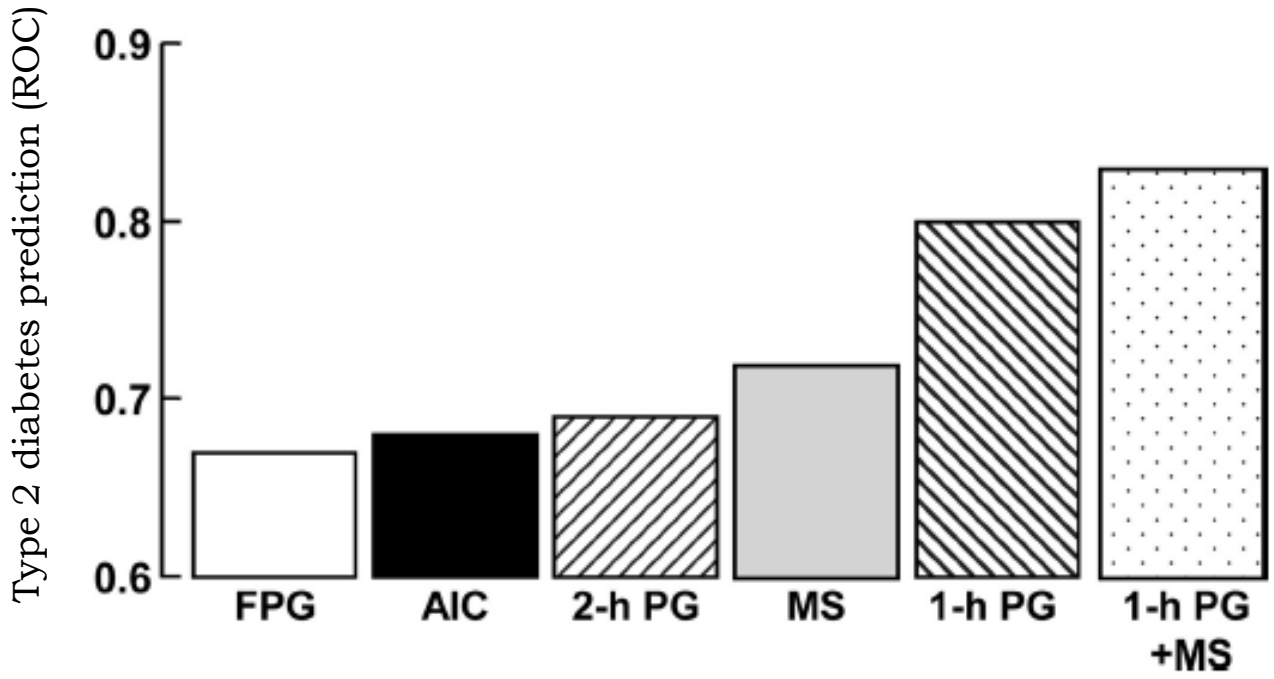
Parameter	Parameter	ROC	95% CI	p value compared to 1-hour PG
	Fasting plasma glucose	0.79	0.74-0.84	<0.01
	1-hour plasma glucose	0.88	0.84-0.91	
	2-hour plasma glucose	0.79	0.74-0.84	<0.01
	HbA1c (%)	0.80	0.76-0.85	0.01
	$GluAUC_{120}$	0.88	0.84-0.91	0.92
	Insulinogenic index	0.73	0.68-0.78	<0.01
	DI_{30}	0.79	0.74-0.84	<0.01
	DI_{120}	0.83	0.79-0.87	0.09

ROC, receiver-operating characteristic; DI, disposition index.

One-hour plasma glucose had a greater association with the future development of Type 2 diabetes than did 2-h plasma glucose, independently of oral glucose tolerance test-derived indices of insulin action in a Japanese population.

Oka R. Diabet Med 2016; 33: 1399–1405

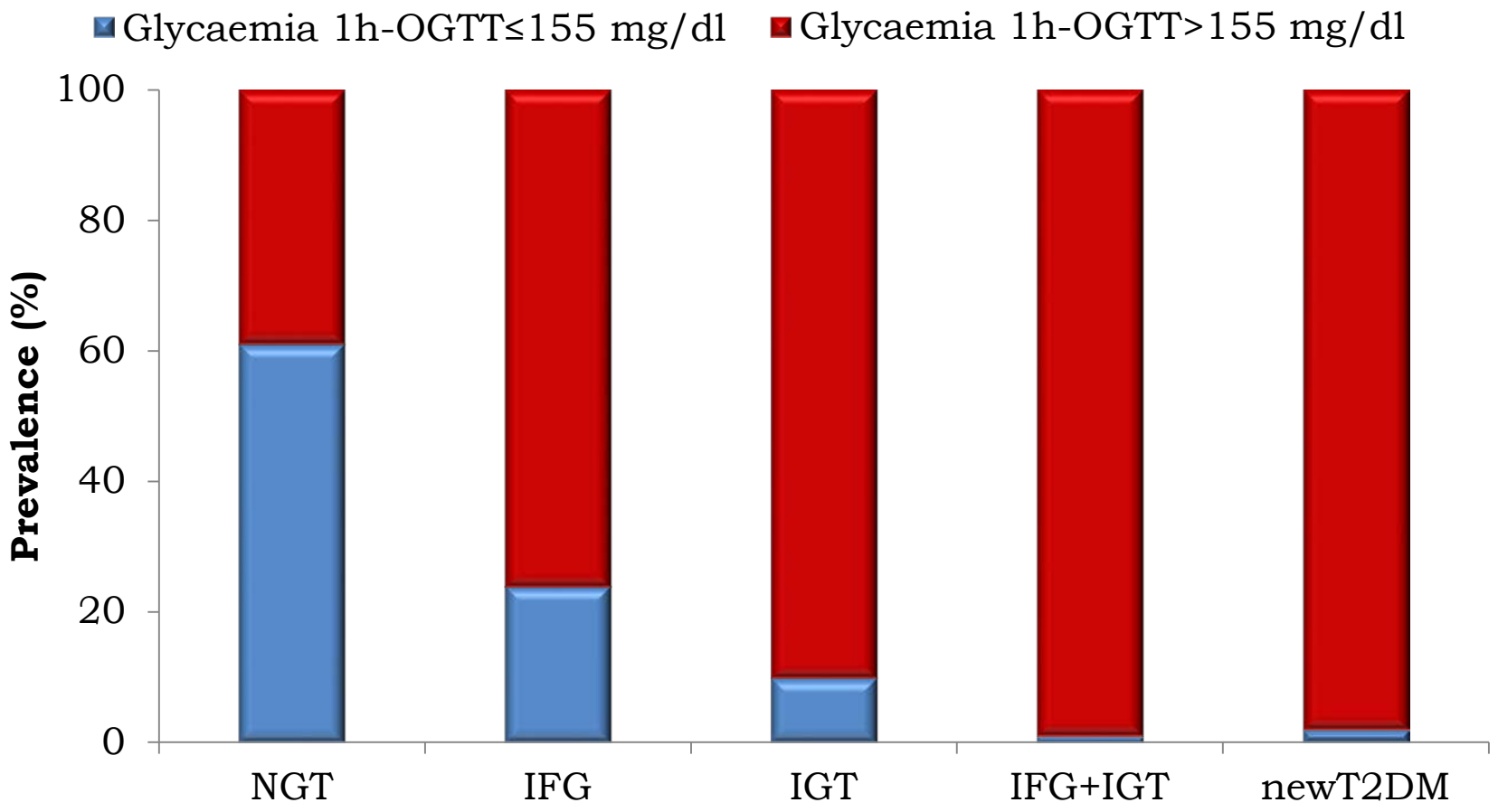
Risk of progression to diabetes



Defronzo R. J Clin Endocrinol Metab 2011; 96: 2354–2366

Prevalence of 1h-OGTT glucose >155 mg/dl by glucose tolerance categories

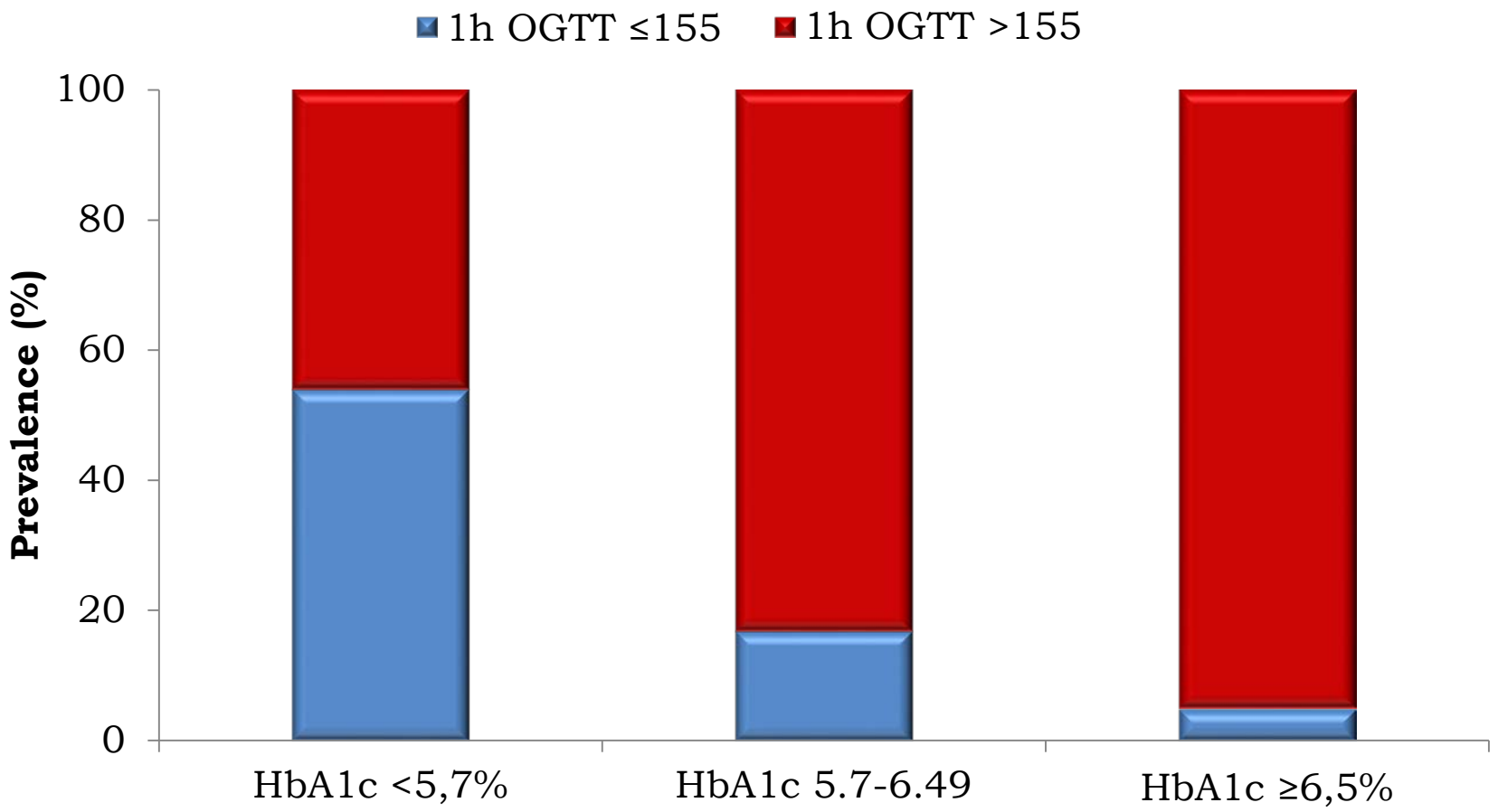
- The GENFIEV Study -



Bianchi C. JCEM 2013; 98(5): 2100-2105

Prevalence of 1h-OGTT glucose >155 mg/dl by glucose tolerance categories

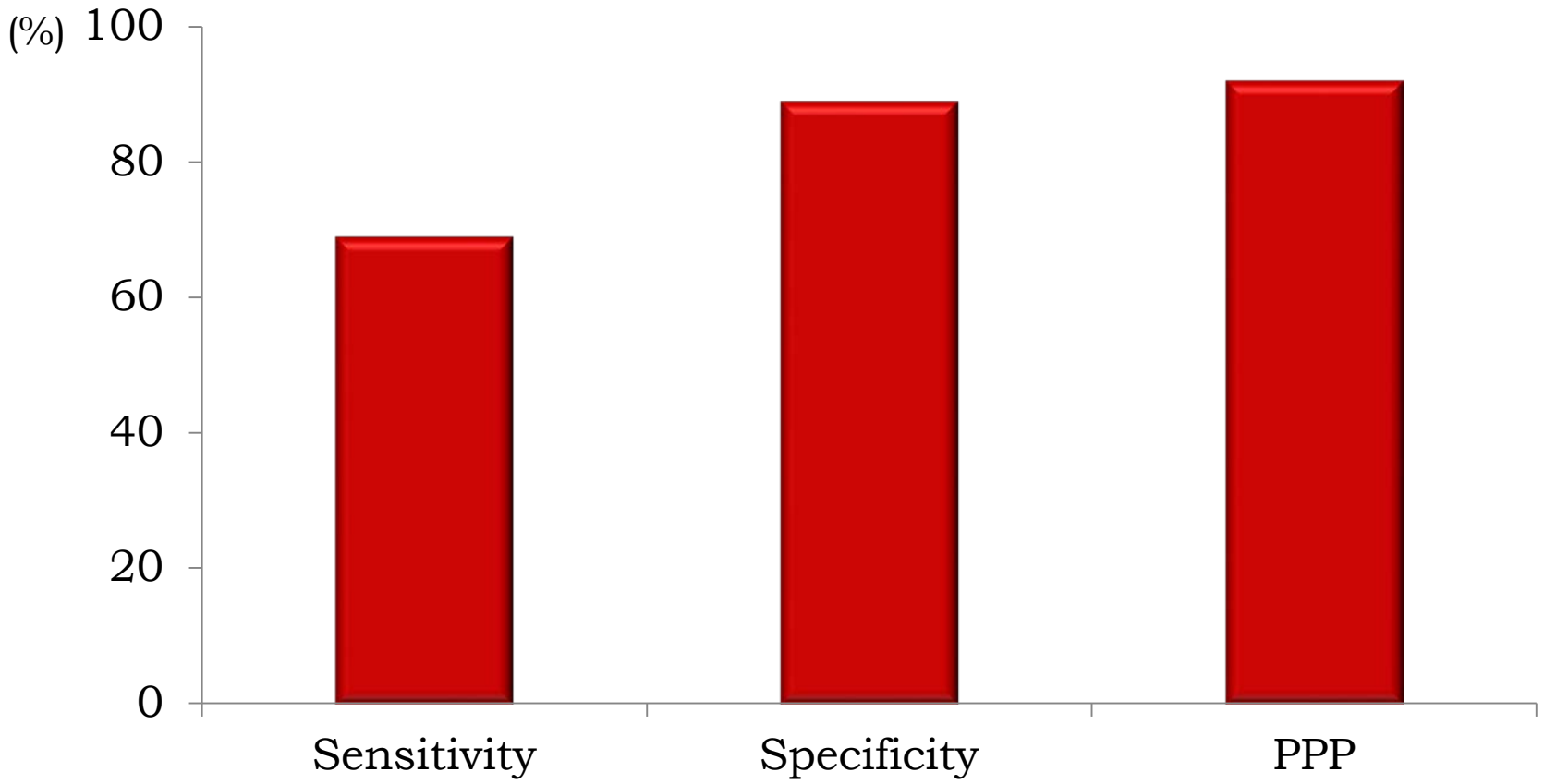
- The GENFIEV Study -



Bianchi C. *Personal data*

Preformance of 1h-OGTT glucose>155 mg/dl in identifing subjects with IGR or new-onset T2DM

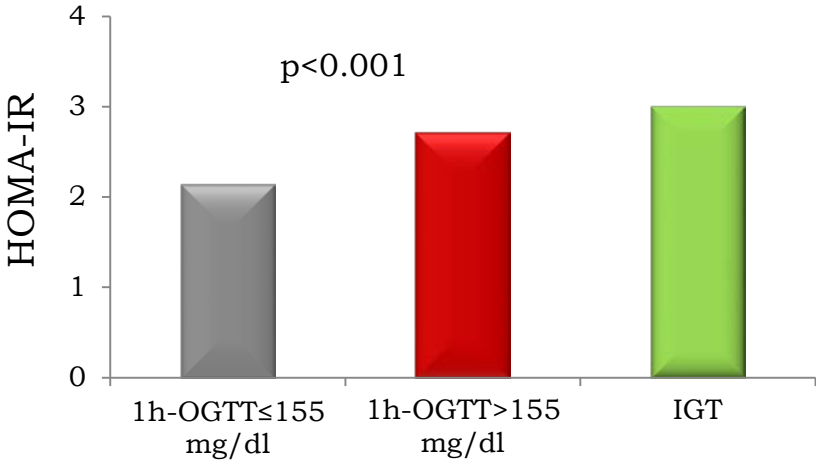
- The GENFIEV Study -

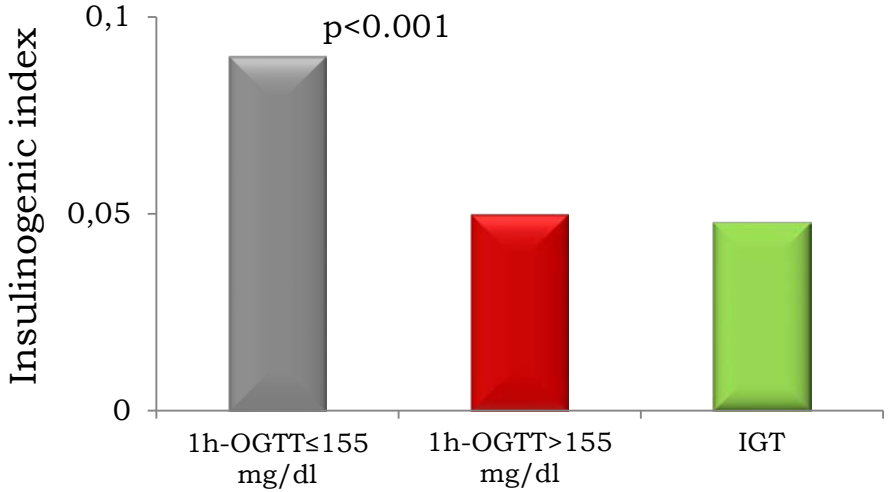


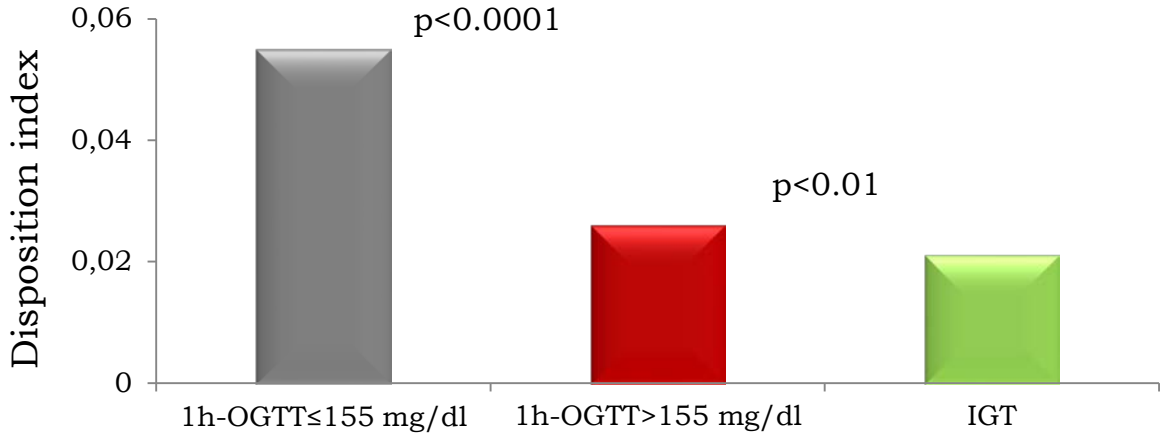
Bianchi C. J Clin Endocrinol Metab 2013; 98(5): 2100-2105

Insulin-resistance, insulin secretion and β-cell performance according with 1h-OGTT glucose

- The GENFIEV Study -



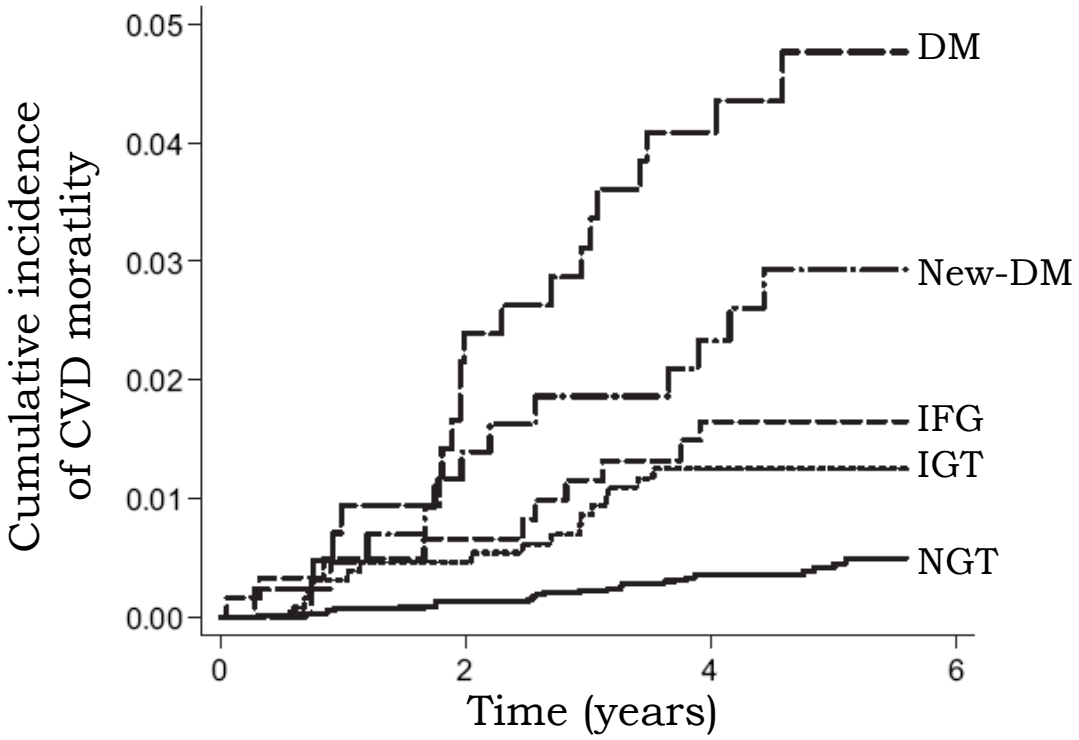




Bianchi C. J Clin Endocrinol Metab 2013; 98(5): 2100-2105

Intermediate Hyperglycaemia and cardiovascular mortality

- The AusDiab Study -



	Age and gender adjusted	Other confounders adjasted
NGT	1.00	1.00
IFG	2.9 (1.4-5.9)	2.5 (1.2-5.1)
IGT	1.3 (0.7-2.3)	1.2 (0.7-2.2)
New DM	2.2 (1.1-4.4)	1.8 (0.9-3.6)
DM	3.4 (1.9-6.0)	2.6 (1.4-4.7)

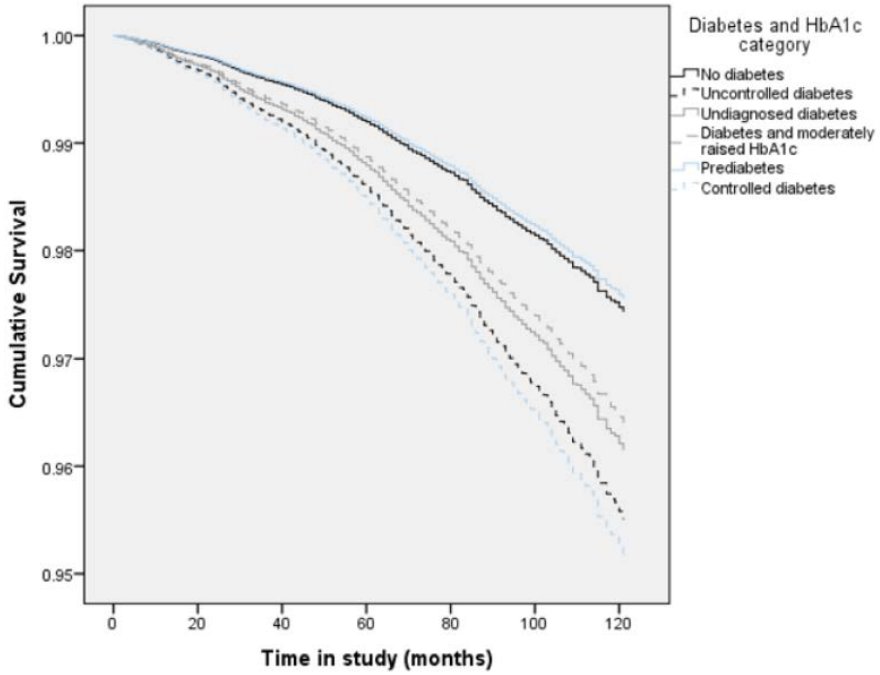
Barr EL. Circulation 2007; 116: 151-157

HbA1c determined pre-diabetes and mortality

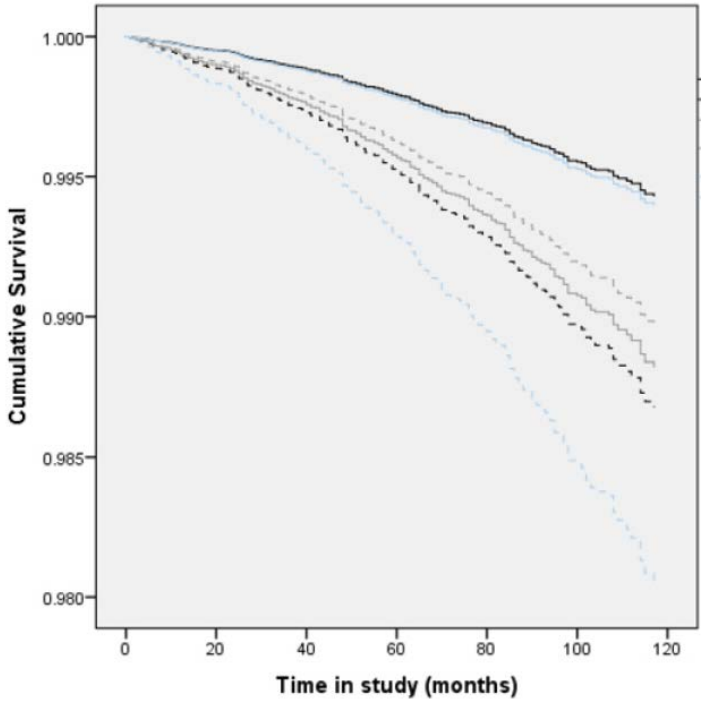
Cohort Study Using Health Survey for England Data

Cohort study of 22,106 subjects

All-cause mortality



CV mortality



Gordon-Dseagu VLZ. PLoS One 2015;10(3):e0119882

Cardiovascular risk profile in NGT* subjects with 1h-OGTT glucose ≤155 mg/dl or >155 mg/dl or IGT

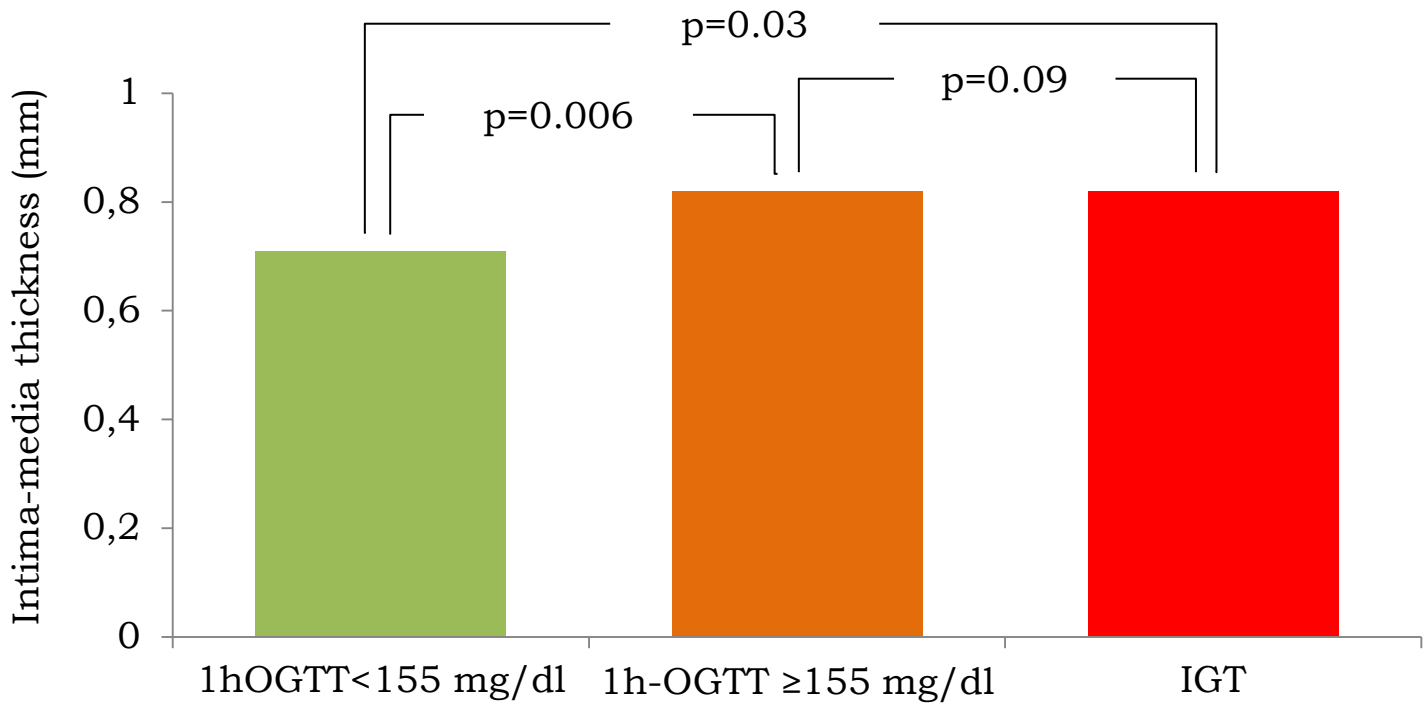
- The GENFIEV Study -

	NGT with 1h-OGTT glucose		IGT	NGT 1h-OGTT>155 mg/dl vs. NGT 1h-OGTT ≤155 mg/dl p	IGT vs. NGT 1h-OGTT>155 mg/dl p
	≤155 mg/dl	>155 mg/dl			
BMI (Kg/m2)	28.1±5.3	28.9±5.2	29.9±5.2	n.s.	n.s.
Waist (cm)	97±14	102±14	102±12	<0.0005	n.s.
Systolic blood pressure (mmHg)	122±14	128±13	133±17	<0.0001	<0.005
Diastolic blood pressure (mmHg)	77±11	81±10	84±12	<0.0001	<0.05
Total cholesterol (mg/dl)	206±41	210±41	213±40	n.s.	n.s.
LDL (mg/dl)	127±37	136±41	136±38	<0.05	n.s.
HDL (mg/dl)	56±16	52±14	51±14	<0.005	n.s.
Triglycerides (mg/dl)	117±96	136±96	155±93	<0.05	<0.05
HbA1c (%)	5.3±0.4	5.6±0.4	5.7±0.4	<0.0001	<0.005

* 474 NGT subjects (37% men and 63% women; age: 46±12 years, BMI: 28.4±5.3 Kg/m^2)

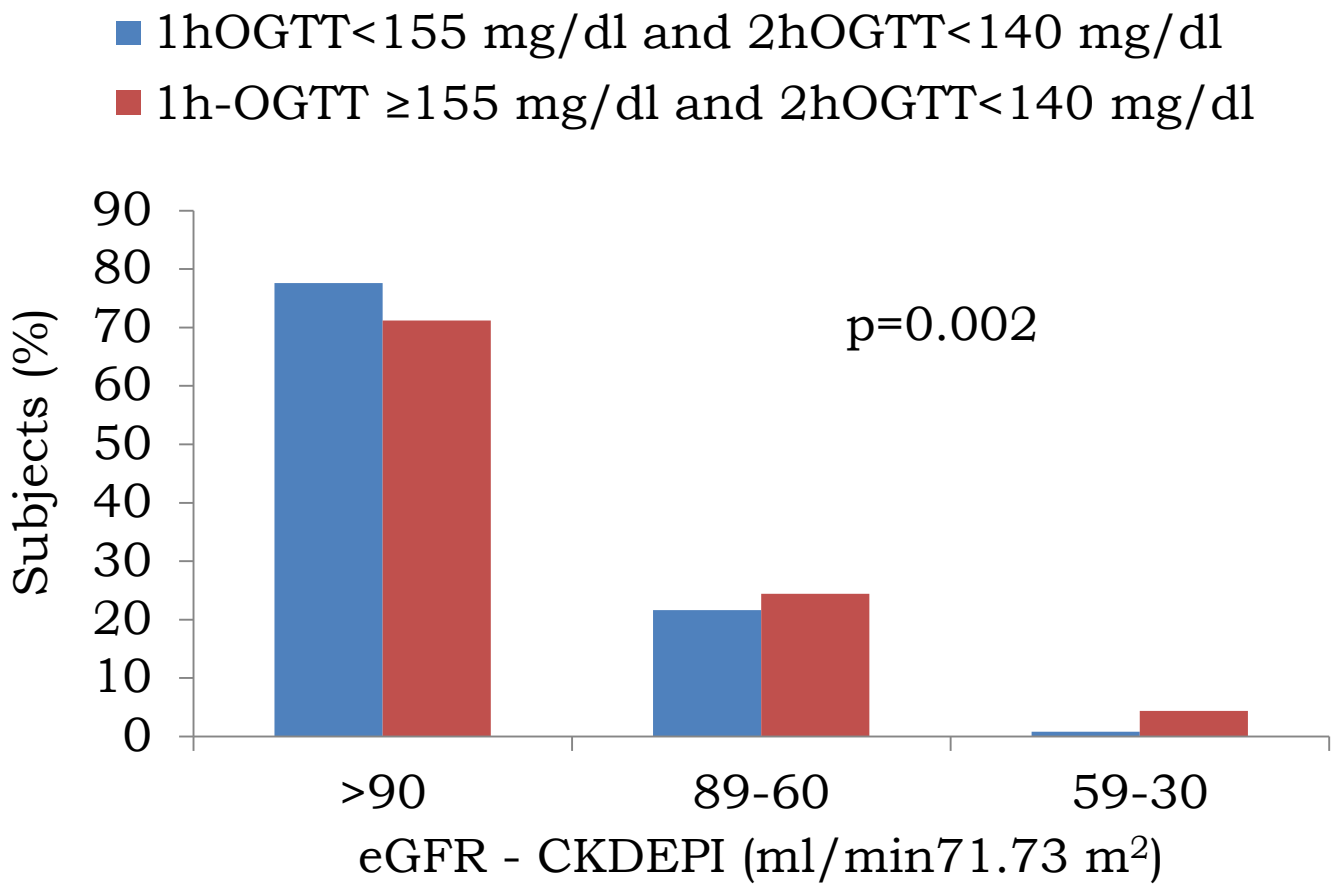
Bianchi C. J Clin Endocrinol Metab 2013; 98(5): 2100-2105

1-h Postload Plasma Glucose levels identifyed subjects with NGT but early carotid atherosclerosis



Succurro E. Atherosclerosis 2009;207(1):245-9

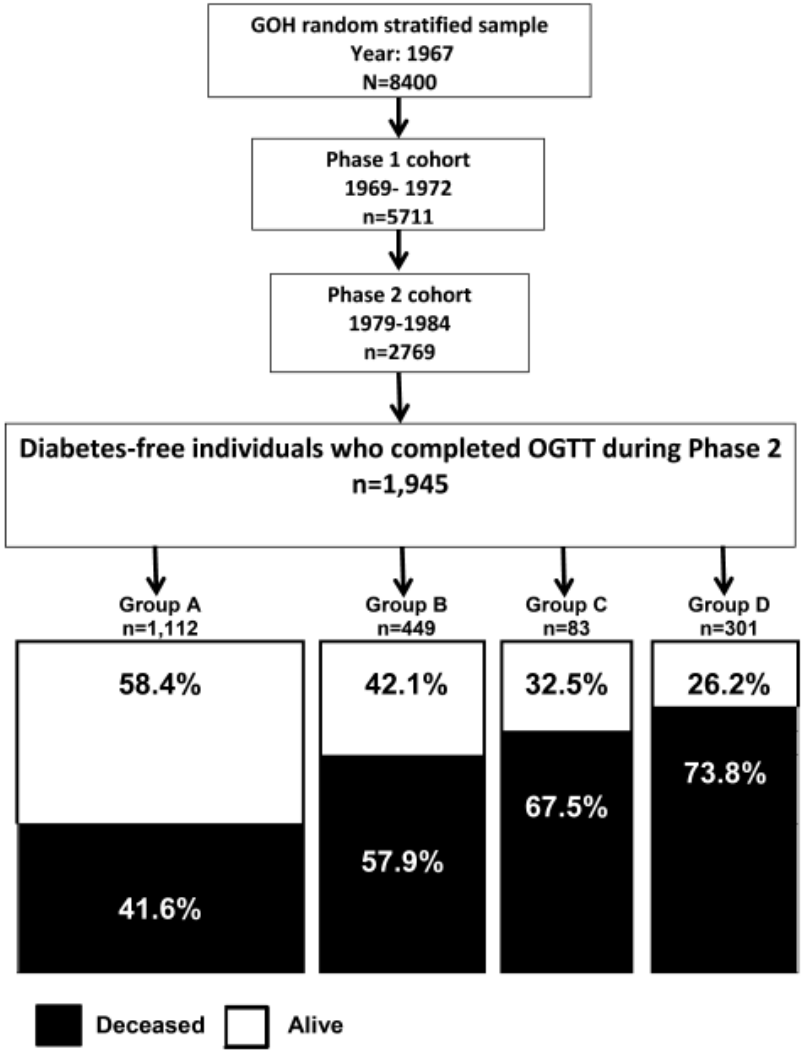
1-h Postload Plasma Glucose levels are associated with kidney dysfunction



Succurro E. Clin J Am Soc Nephrol 2010; 5(11): 1922–1927

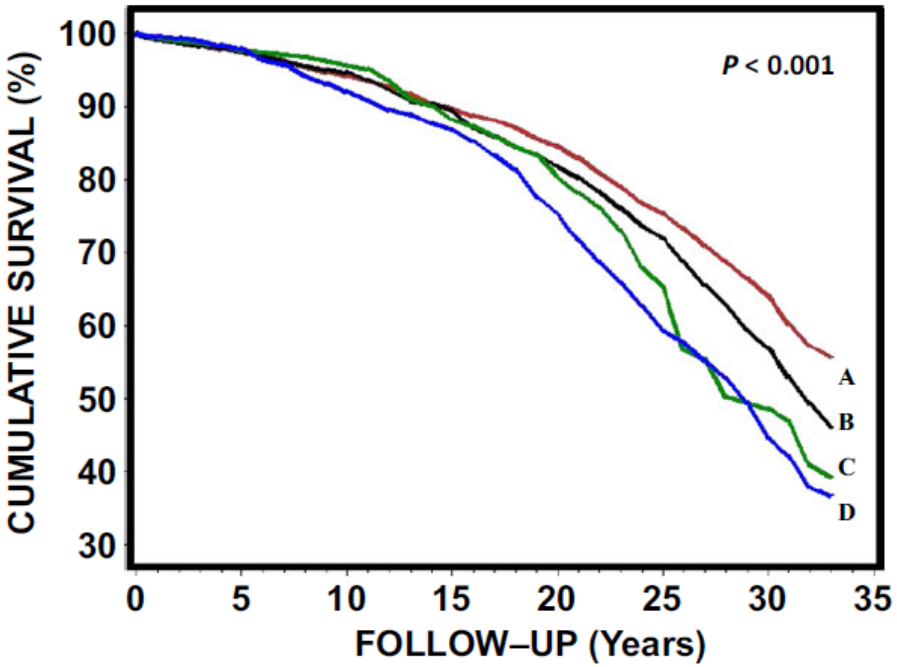
1h OGTT predicts mortality

- The Israel Study of Glucose Intolerance, Obesity and Hypertension -



Group:	1-hour glucose (mmol/l)	2-hour Glucose (mmol/l)	P value vs. Group-A
A	<8.6	<7.8	-
B	≥8.6	<7.8	0.003
C	<8.6	7.8–11.1	0.002
D	≥8.6	7.8–11.1	<0.001

Survival curves of 1945 individuals without diabetes according to baseline 1- and 2-h glucose. Adjusted for age, sex, BMI, blood pressure and smoking.



Bergman M. Diabet Med 2016; 33: 1060–1066

Conclusions

- ✓ The plasma glucose concentration at 1 h during the OGTT (cutoff point of 155 mg/dl) is a stro tor of future risk for type 2 diabetes, also in NGT s
- ✓ The prevalence o dl is high among IGR o ne ssociated with impairment
- ✓ Moreover, 1h associated with adverse cardiovascular
- ✓ These data sugg the possibility of shortening the OGTT duration or of introducing also the evaluation of 1h-postload plasma glucose.

unite for diabetes

Thank you for your attention!