VIII Convegno Nazionale Fondazione AMD

AMD ASSOCIAZIONE MEDICI DIABETOLOGI
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PALERMO, 17-19 NOVEMBRE 2016

TRIALS DI OUTCOME

Moderatori: **Maria Calabrese, Francesco Calcaterra**

Abbiamo necessità di altri trials?

Domenico Cucinotta

I trials di outcome cardiovascolare (CVOTs): una storia lunga 50 anni

Special Article

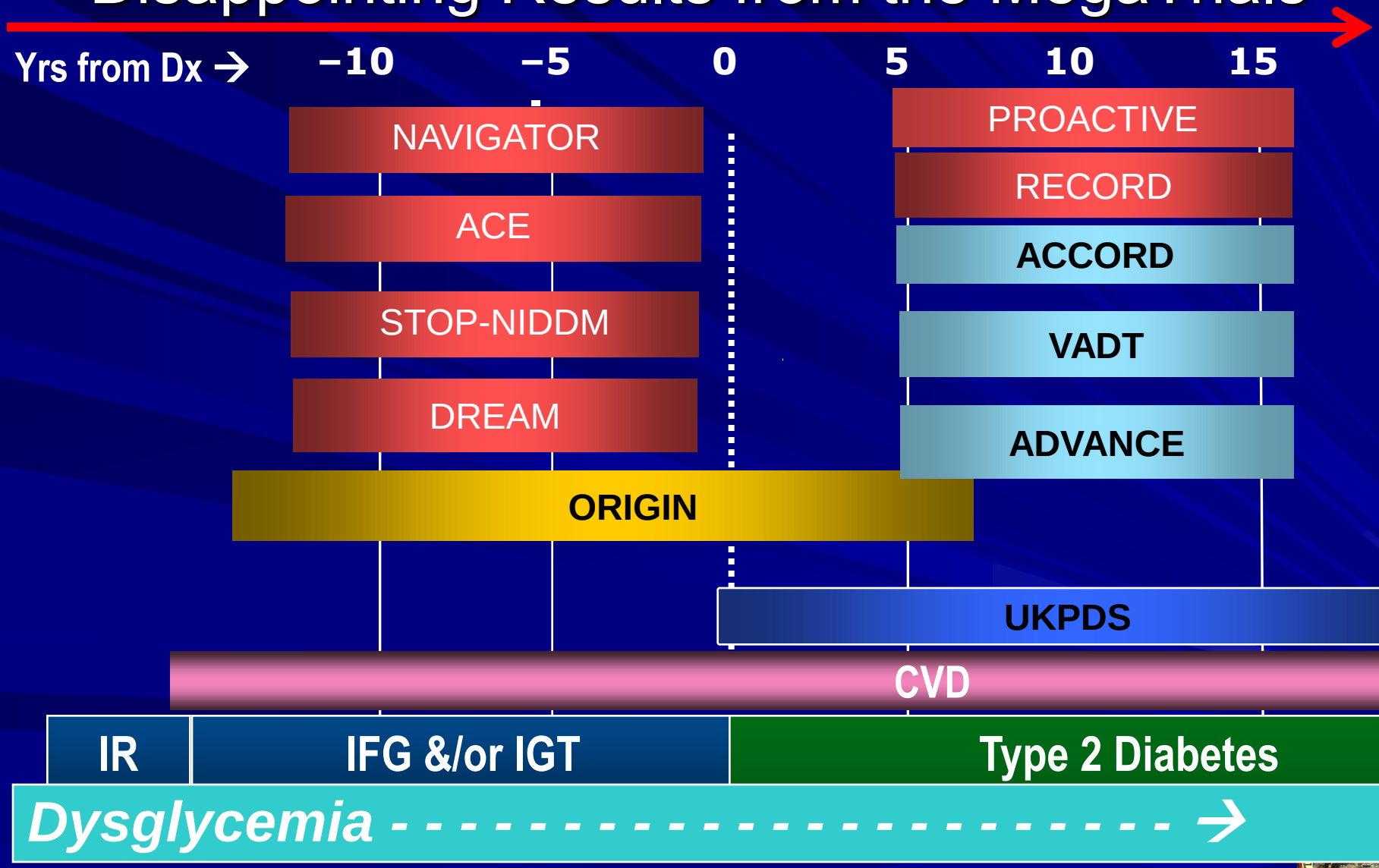
A Summary of Criticisms of the Findings and Conclusions of the University Group Diabetes Program (UGDP)

Holbrooke S. Seltzer, M.D., Dallas

DIABETES, VOL. 21, NO. 9
SEPTEMBER, 1972

Glucose Lowering to Prevent CVD:

Disappointing Results from the MegaTrials



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 14, 2007 VOL. 356 NO. 24

Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes

Steven E. Nissen, M.D., and Kathy Wolski, M.P.H.

Guidance for Industry

Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes

Additional copies are available from:

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

December 2008
Clinical/Medical

III. RECOMMENDATIONS

To establish the safety of a new antidiabetic therapy to treat type 2 diabetes, sponsors should demonstrate that the therapy will not result in an unacceptable increase in cardiovascular risk. To ensure that a new therapy does not increase cardiovascular risk to an unacceptable extent, the development program for a new type 2 antidiabetic therapy should include the following.

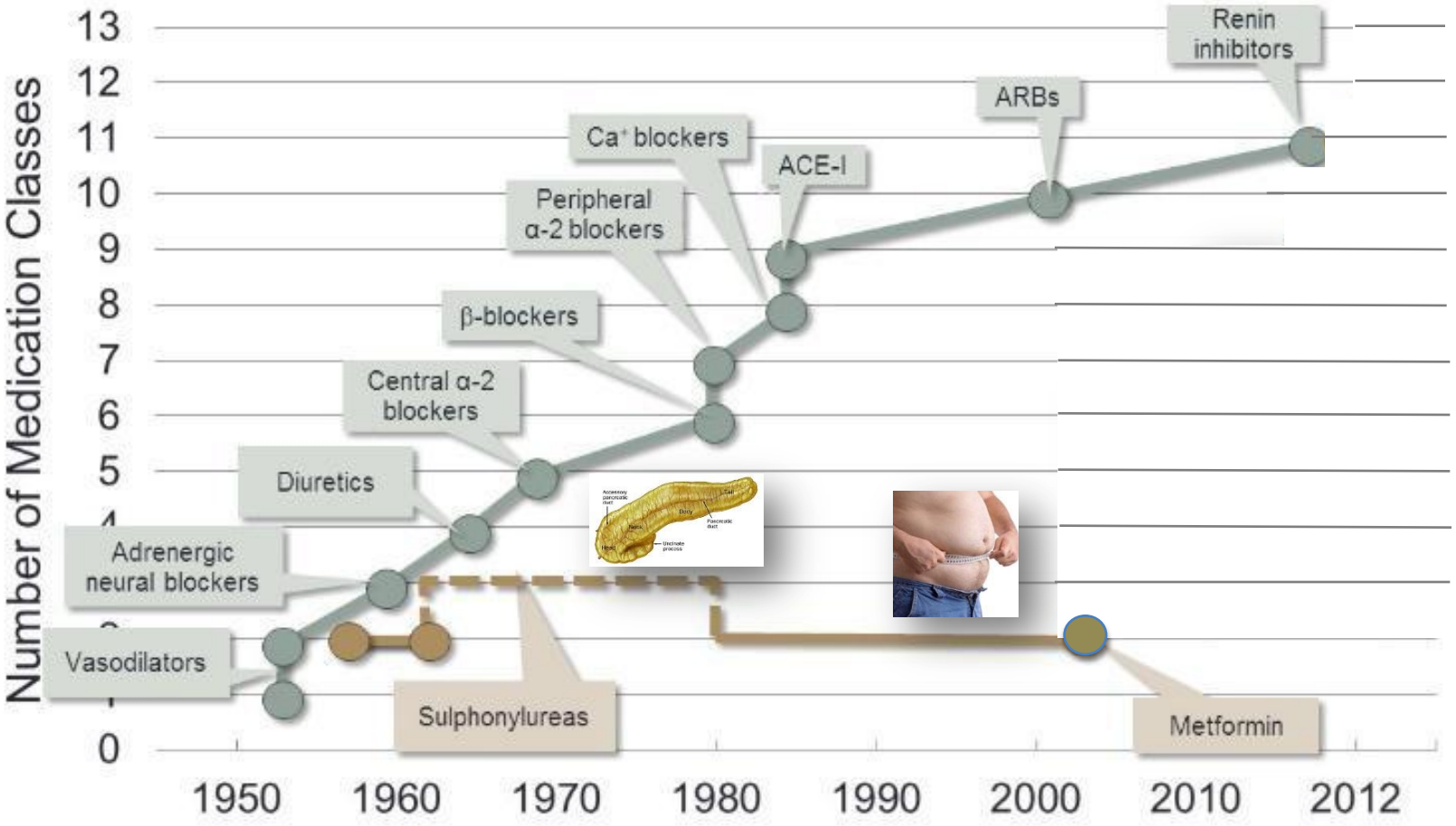
For new clinical studies in the planning stage:

- Sponsors should establish an independent cardiovascular endpoints committee to prospectively adjudicate, in a blinded fashion, cardiovascular events during all phase 2 and phase 3 trials. These events should include cardiovascular mortality, myocardial infarction, and stroke, and can include hospitalization for acute coronary syndrome, urgent revascularization procedures, and possibly other endpoints.

- Sponsors should ensure that phase 2 and phase 3 clinical trials are appropriately designed and conducted so that a meta-analysis can be performed at the time of completion of these studies that appropriately accounts for important study design features and patient or study level covariates. To obtain sufficient endpoints to allow a meaningful estimate of risk, the phase 2 and phase 3 programs should include patients at higher risk of cardiovascular events, such as patients with relatively advanced disease, elderly patients, and patients with some degree of renal impairment. Because these types of patients are likely to be treated with the antidiabetic agent, if approved, this population is more appropriate than a younger and healthier population for assessment of other aspects of the test drug's safety.

DIABETES REVOLUTION

Hypertension and diabetes:
Drug classes in U.S. over the past 50 years



Modificata da Stefano Del Prato, EASD 2014

Nuovi farmaci per la terapia del diabete mellito di tipo 2

- Incretino-mimetici
  - Analoghi GLP-1 (exenatide, liraglutide, lixisenatide, dulaglutide, ecc.)
  - Inibitori DPP-4 (sitagliptin, vildagliptin, saxagliptin, alogliptin, linagliptin, ecc)
- Inibitori di SGLT2
  - (dapagliflozin, canagliflozin, empagliflozin)

Cosa ci hanno insegnato i nuovi trial di intervento?

- **Empagliflozin e Liraglutide** riducono il rischio di eventi cardiovascolari fatali e non fatali e di sviluppo/progressione di nefropatia
- **Empagliflozin,** in particolare, riduce il rischio di morte per cause cardiovascolari e per tutte le cause, e di ricovero per scompenso cardiaco
- **Liraglutide,** in particolare, riduce il rischio di morte per cause cardiovascolari e per tutte le cause

I problemi ancora aperti

- Effetto farmaco o effetto classe?
- La sicurezza
- Gli studi meccanicistici
- Gli studi di farmaco-economia
- La necessità di osservazioni più prolungate
- Gli studi di traslazione e di *real world*

Ongoing Cardiovascular Outcomes Trials

- Linagliptin – CAROLINA and CARMELINA

- Exenatide – EXSCEL
- Lixisenatide – ELIXIR
- Dulaglutide – REWIND

- Canagliflozin – CANVAS

- Insulin Degludec – DEVOTE

AACE/ACE Position Statement

AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY POSITION STATEMENT ON THE ASSOCIATION OF SGLT-2 INHIBITORS AND DIABETIC KETOACIDOSIS

Yehuda Handelsman, MD, FACP, FNLA, FACE, Co-Chair[1]; Robert R. Henry, MD, FACE, Co-Chair[2]; Zachary T. Bloomgarden, MD, MACE[3]; Sam Dagogo-Jack, MD, DM, FRCP, FACE[4]; Ralph A. DeFronzo, MD, BMS, MS, BS[5]; Daniel Einhorn, MD, FACP, FACE[6]; Ele Ferrannini, MD[7]; Vivian A. Fonseca, MD, FACE[8]; Alan J. Garber, MD, PhD, FACE[9]; George Grunberger, MD, FACP, FACE[10]; Derek LeRoith, MD, PhD, FACE[11]; Guillermo E. Umpierrez, MD, FACP, FACE[12]; Matthew R. Weir, MD[13]

ENDOCRINE PRACTICE Vol 22 No. 6 June 2016 753

C.A., anni 46, familiarità per DM2. Da un mese poliuria e polidpsia. 7 giorni orsono glicemia >300 mg, non chetonuria. Inizia terapia con SGLT2+metformina. Da 2 gg algie addominali, nausea e vomito, obnubilamento del sensorio. Al momento del ricovero glicemia 220 mg, chetonemia >8mmol/l, pH 7.1

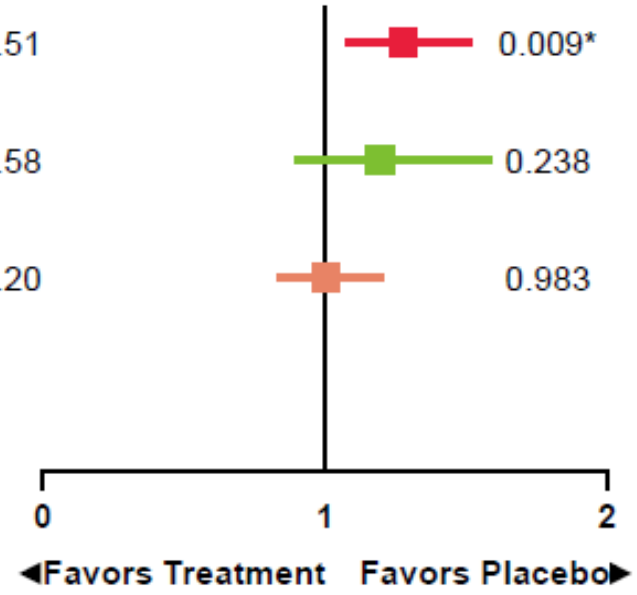
Table 2. Selected Adverse Events Reported during the Trial.*

Event	Liraglutide (N = 4668)	Placebo (N = 4672)	P Value
	no. of patients (%)		
Adverse event			
Any adverse event	2909 (62.3)	2839 (60.8)	0.12
Serious adverse event	2320 (49.7)	2354 (50.4)	0.51
Confirmed hypoglycemia†	2039 (43.7)	2130 (45.6)	0.06
Severe adverse event	1502 (32.2)	1533 (32.8)	0.51
Severe hypoglycemia†	114 (2.4)	153 (3.3)	0.02
Acute gallstone disease	145 (3.1)	90 (1.9)	<0.001
Cholelithiasis	68 (1.5)	50 (1.1)	0.09
Acute cholecystitis	36 (0.8)	21 (0.4)	0.046
Acute pancreatitis	18 (0.4)	23 (0.5)	0.44
Chronic pancreatitis	0	2 (<0.1)	0.16
Any benign neoplasm	168 (3.6)	145 (3.1)	0.18
Any malignant neoplasm	296 (6.3)	279 (6.0)	0.46
Pancreatic carcinoma	13 (0.3)	5 (0.1)	0.06
Medullary thyroid carcinoma	0	1 (<0.1)	0.32

Eventi avversi nello studio LEADER

Gliptine e scompenso cardiaco

	Study Drug n/N (%)	Placebo n/N (%)	Hazard Ratio	95% CI	p-Value
SAVOR-TIMI[1] (saxagliptin vs placebo)	289/8280 (3.5%)	228/8212 (2.8%)	1.27	1.07, 1.51	0.009*
EXAMINE[2] (alogliptin vs placebo)	106/2701 (3.9%)	89/2679 (3.3%)	1.19	0.89, 1.58	0.238
TECOS[3] (sitagliptin vs placebo)	228/7332 (3.1%)	229/7339 (3.1%)	1.00	0.83, 1.20	0.983



***Statistically significant increase in hospitalizations for heart failure associated with saxagliptin use in SAVOR-TIMI.**

Figure 3 SAVOR-TIMI 53, EXAMINE, and TECOS: hospitalization for heart failure.

Nutrition, Metabolism & Cardiovascular Diseases (2016) **26**, 767–772

Ulteriori limiti degli attuali CVOTs

- Non rappresentativi di tutta la popolazione con diabete di tipo 2 (soggetti a rischio cv basso, anziani, nefropatici, ecc.)
- Di durata non sufficiente per dimostrare appieno benefici e/o rischi
- Condotti verso placebo e non verso comparatore attivo
- Carenti di valutazioni sulla qualità di vita
- ……

CVOT follow-up may be too short to draw reliable conclusions

It took **10 years of follow-up in UKPDS** after the actual intervention period was complete to show a benefit of intensive glucose control on reducing myocardial infarction.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

10-Year Follow-up of Intensive Glucose Control in Type 2 Diabetes

Rury R. Holman, F.R.C.P., Sanjoy K. Paul, Ph.D., M. Angelyn Bethel, M.D., David R. Matthews, F.R.C.P., and H. Andrew W. Neil, F.R.C.P.

ABSTRACT

BACKGROUND

During the United Kingdom Prospective Diabetes Study (UKPDS), patients with type 2 diabetes mellitus who received intensive glucose therapy had a lower risk of microvascular complications than did those receiving conventional dietary therapy. We conducted post-trial monitoring to determine whether this improved glucose control persisted and whether such therapy had a long-term effect on macrovascular outcomes.

More Than 7 Years of Hindsight: Revisiting the FDA's 2008 Guidance on Cardiovascular Outcomes Trials for Type 2 Diabetes Medications

Emily E. Regier,[1,2] Manu V. Venkat,[1–3] and Kelly L. Close[1,2]

CLINICAL.DIABETESJOURNALS.ORG VOLUME 34, NUMBER 4, FALL 2016

Minimum Required Duration for CVOTs

Passive Follow-Up After Completion of Randomized Trials

Use of Observational Data to Complement or Replace Randomized Trials

Product-Specific CVOT Requirements

I nuovi trials: la validazione della Medicina di Precisione

DIABETES RESEARCH AND CLINICAL PRACTICE 117 (2016) 12–21

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International Diabetes Federation

Invited Review

Precision medicine: The future in diabetes care?

CrossMark

André J. Scheen *

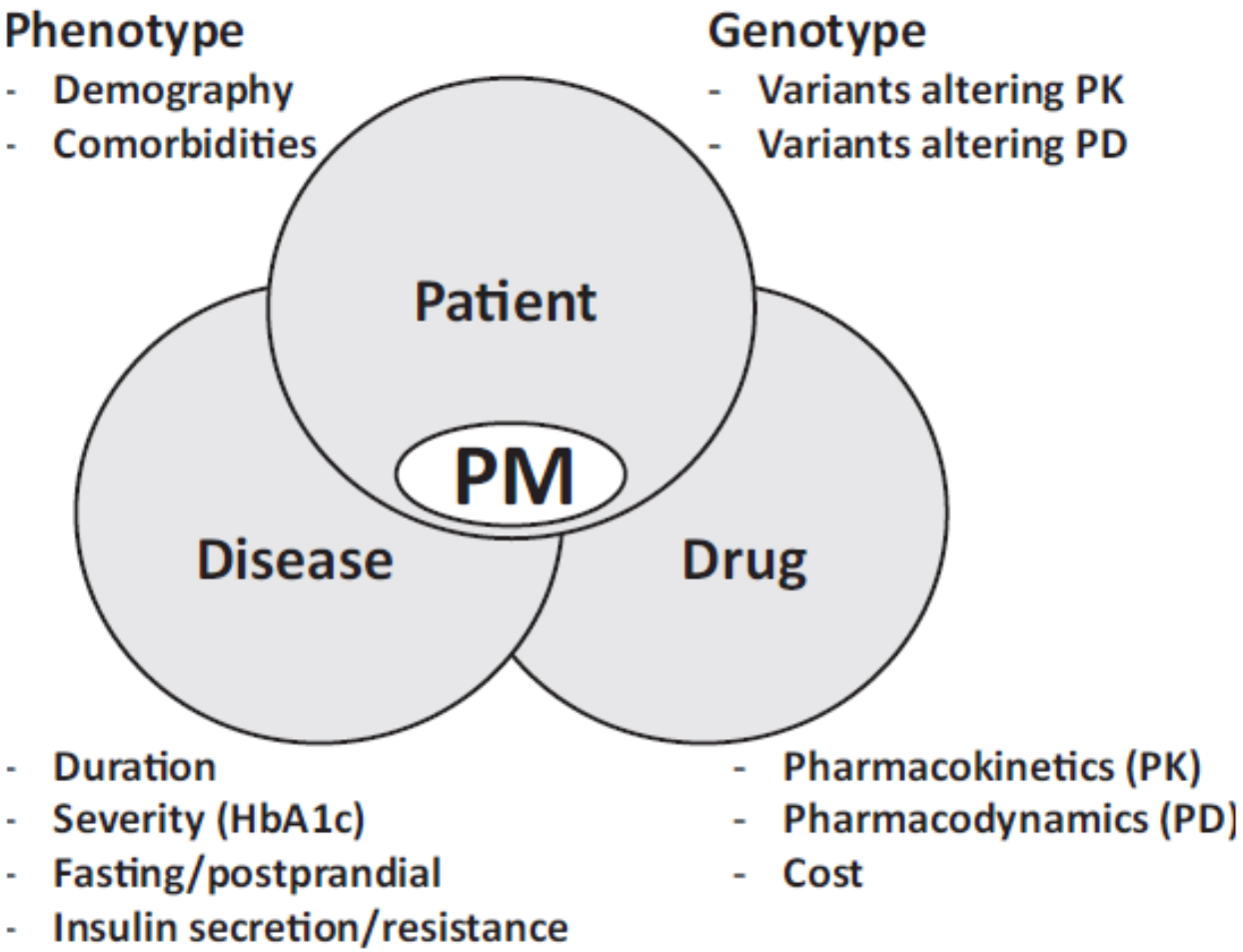

Fig. 1 – Personalized medicine or precision medicine (PM) for the management of type 2 diabetes: at the crossroad of patient, disease and drug characteristics.

Precision medicine is not just an academic discussion, as it already belongs to the political agenda of the most industrialized countries. President Barack Obama, in his State of the Union Address in January 2015, announced the launch of a "Precision Medicine Initiative to bring us closer to curing diseases like cancer and diabetes."

The NEW ENGLAND JOURNAL of MEDICINE

The End of Obamacare

Jonathan Oberlander, Ph.D.

La medicina di precisione ai tempi della Trumpcare…?

Grazie per l'attenzione….