

Equipose of Benefit versus Risk in Diabetes Drugs

Achieving Balance in the Risk – Benefit Discussion



Diabetes Complications

A Patient Centered Perspective

- **Fear of acute and chronic complications**
 - Hypoglycemia (100 cases per 100 patient-years in DCCT)
 - Vision threatening retinal disease affects 5-8% (NHANES cohort)
 - Leading cause of chronic kidney disease (USRDS, CDC)
 - Leading cause of non-traumatic amputation (CDC)
- **Cardiovascular risk**
 - Major contributor to public health and cost burden
 - Patient perception = focused on multiple risk factor interventions
- **Treatment options, acceptance and safety**
 - Tolerability, effectiveness and utility (including access and cost)
 - Safety: free from major risks that may supplant these benefits



A Broader View of Complications and Diabetes

Implications of the Major Glycemia Outcome Trials

Study	A1C	Microvascular
UKPDS	9 → 7.9 → 7	↓
DCCT/EDIC	9 → 7.1	↓
ACCORD	7.5 → 6.4	↓
ADVANCE	7.3 → 6.5	↓
VADT	8.4 → 6.9	↓

~29,500 subjects

Adapted from Bergenstal RM, Bailey C and Kendall DM. *Am J Med* 123:374e9-e18, 2010

UK Prospective Diabetes Study (UKPDS) Group. *Lancet*. 1998;352:854-865.

Holman RR. *N Engl J Med*. 2008 Oct 9;359(15):1577-89. DCCT Research Group. *N Engl J Med* 329:977-986, 1993

Nathan DM, et al. *N Engl J Med*. 2005;353:2643-2653. Gerstein HC, et al. *N Engl J Med*. 2008;358:2545-2559.

Patel A, et al. *N Engl J Med*. 2008;358:2560-2572. Duckworth W et al *N Engl J Med* 2009;360:129-39

EY Chew for ACCORD. *N Engl J Med* (10.1056/NEJMoa1001288) was published on June 29, 2010, at NEJM.org.



A Broader View of Complications and Diabetes

Implications of the Major Glycemia Outcome Trials

Study	A1C	Microvascular	CVD	Mortality
UKPDS	9 → 7.9 → 7	↓	↔*	↔*
DCCT/EDIC	9 → 7.1	↓	↔*	↔
ACCORD	7.5 → 6.4	↓	↔	↑
ADVANCE	7.3 → 6.5	↓	↔	↔
VADT	8.4 → 6.9	↓	↔	↔

* Reduced risk in long-term follow-up

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Drug Safety and Diabetes Treatment

Drug Class

Reported Adverse Events – Potential Concerns

Biguanides

- Lactic acidosis, ↑ mortality with phenformin

1st Gen SFU

- Increased death rate in UGDP, ↑ hypo and CV risk

Troglitazone

- Hepatotoxicity, hepatic failure

Pulmonary insulin

- Reduced DLCO, ? other

Rosiglitazone

- Variable reports of increased CVD risk

TZD/Pio

- Risk of heart failure, fracture risk?, bladder Ca?

Dual PPAR

- Increase CVD events, fluid retention, weight gain

GLP – 1 agonist

- Reports of pancreatitis, thyroid lesions (rodent)

DPP-4 inhibitor

- Reports of severe skin reactions, pancreatitis

SGLT2

- More frequent UTI, genital infection

Insulin, SFU

- Severe hypoglycemia, mortality and CV risk

Safe and Effective Therapy in Diabetes

Who Has a Role?

- **Patient perspective**
 - Little known of the patient perspective on benefit – risk
- **Clinical perspective**
 - Unmet patient need remains substantial – personalized care needs (PCOR)
 - Traditional therapies (SFU, insulin) with significant limitations
- **Volunteer health organization (ADA)**
 - Support need for broad array of effective, safe, well-tolerated therapies
 - Desire for data on long term outcomes, long-term effectiveness
- **Sponsor/industry requirements and demands**
 - Development plan – efficient, sensitive, acceptably broad and inclusive
- **Agency requirements and demands**
 - Balance of safety and efficacy derived from complex data sets
- **Risk of errors of omission vs errors of commission (e.g. metformin)**

Complexities in Diabetes Therapy and How to Live with Them

...After observation and analysis, when you find that anything agrees with reason and is conducive to the good and benefit of one and all, then accept it and live up to it

