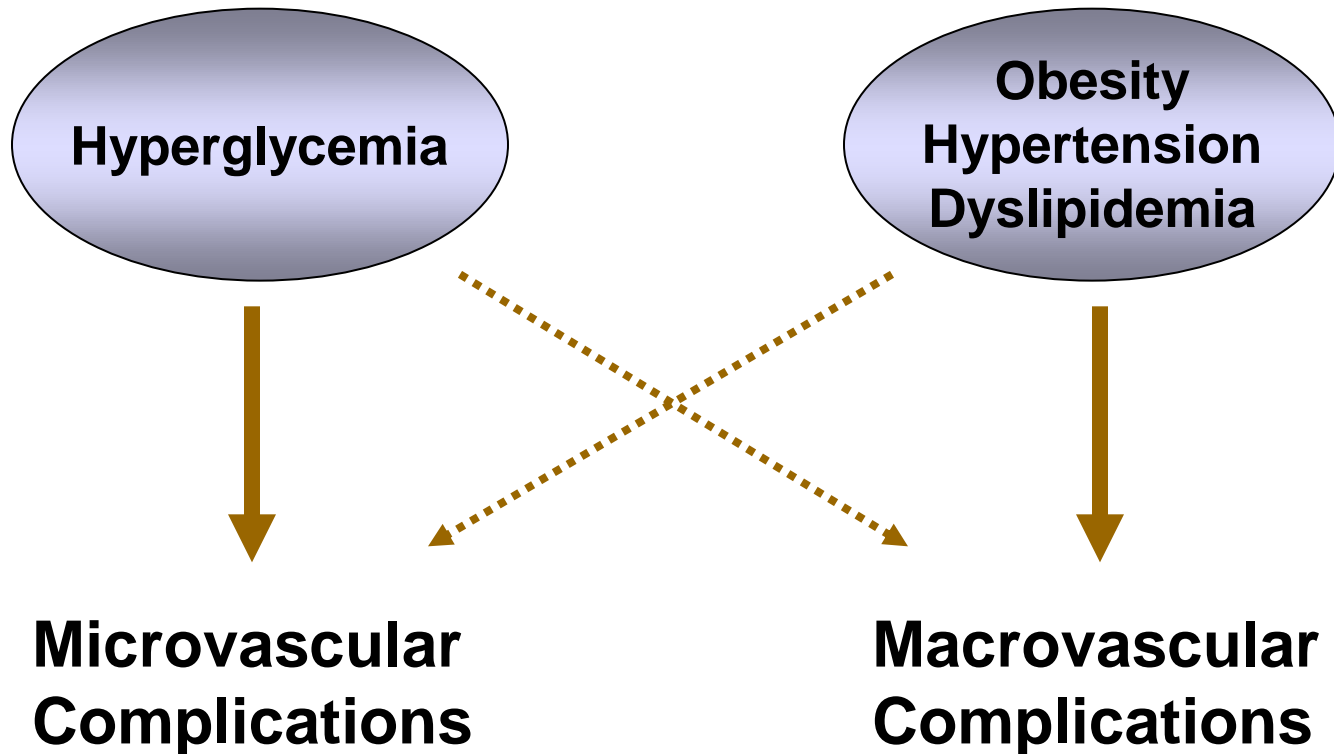

Equipose of Benefit vs. Risk in Drugs for Type 2 Diabetes

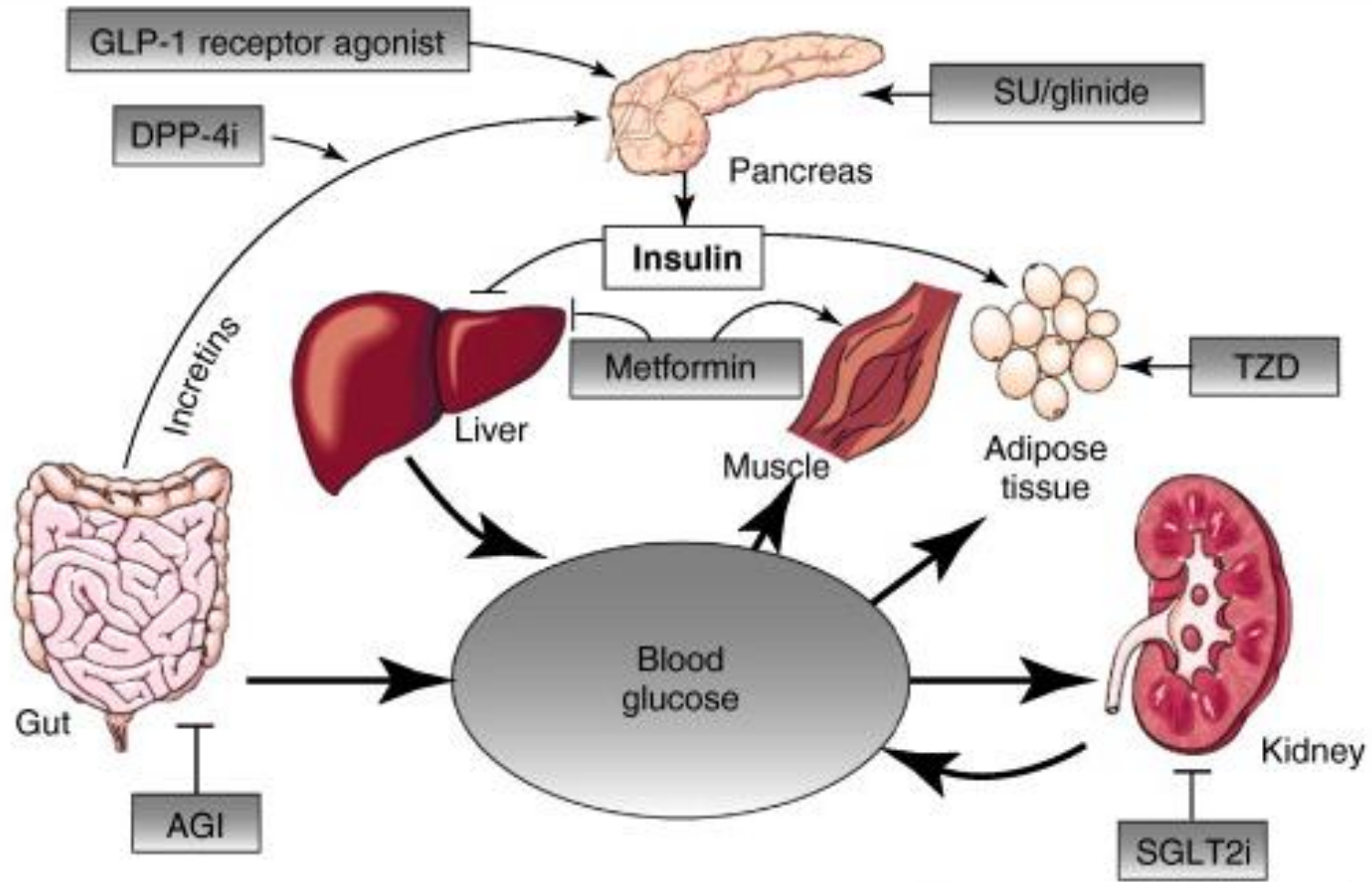
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T2DM Management is to Prevent Complications

- Hyperglycemia is a leading cause of renal failure, blindness, and lower limb amputation
- Diabetes increases the risk for CVD by 2-4 fold



Current Treatment Options for T2DM are Multiple, but Unmet Needs Remain



TRENDS in Pharmacological Sciences

Unmet Needs in Diabetes Treatment

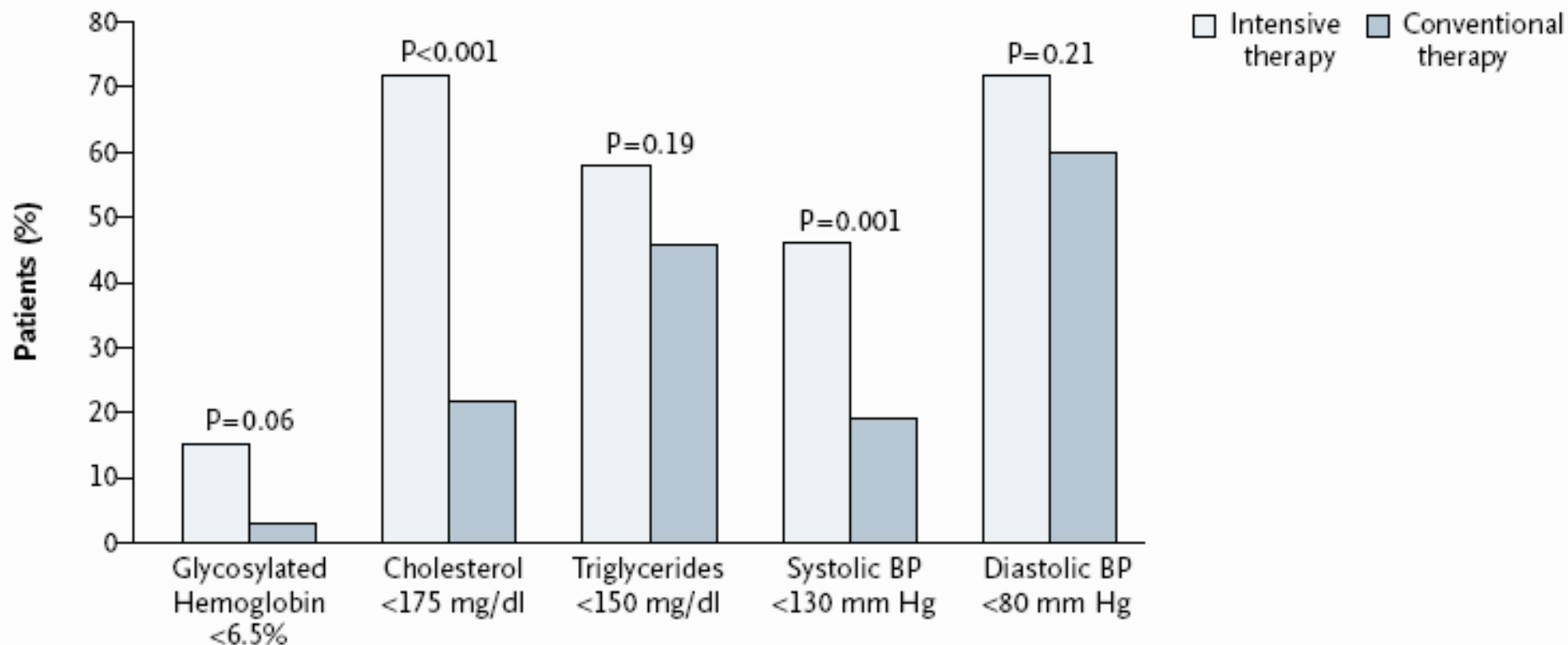
- Many patients around the world are not at goal for glucose and vascular risk factors
- Diabetes is a multifactorial disease – both in pathogenesis of the hyperglycemia as well as complications
- Treatment needs to address this – no magic bullets
- What is needed:
 - Improved glucose efficacy
 - Improved durability
 - Improved safety and tolerability (hypoglycemia, weight gain)
 - Improved compliance (how to achieve?)
 - Simultaneous control of glucose and comorbidities
 - Treatments for microvascular complications
 - Improved glucose variability?

Challenges in Diabetes Drug Development

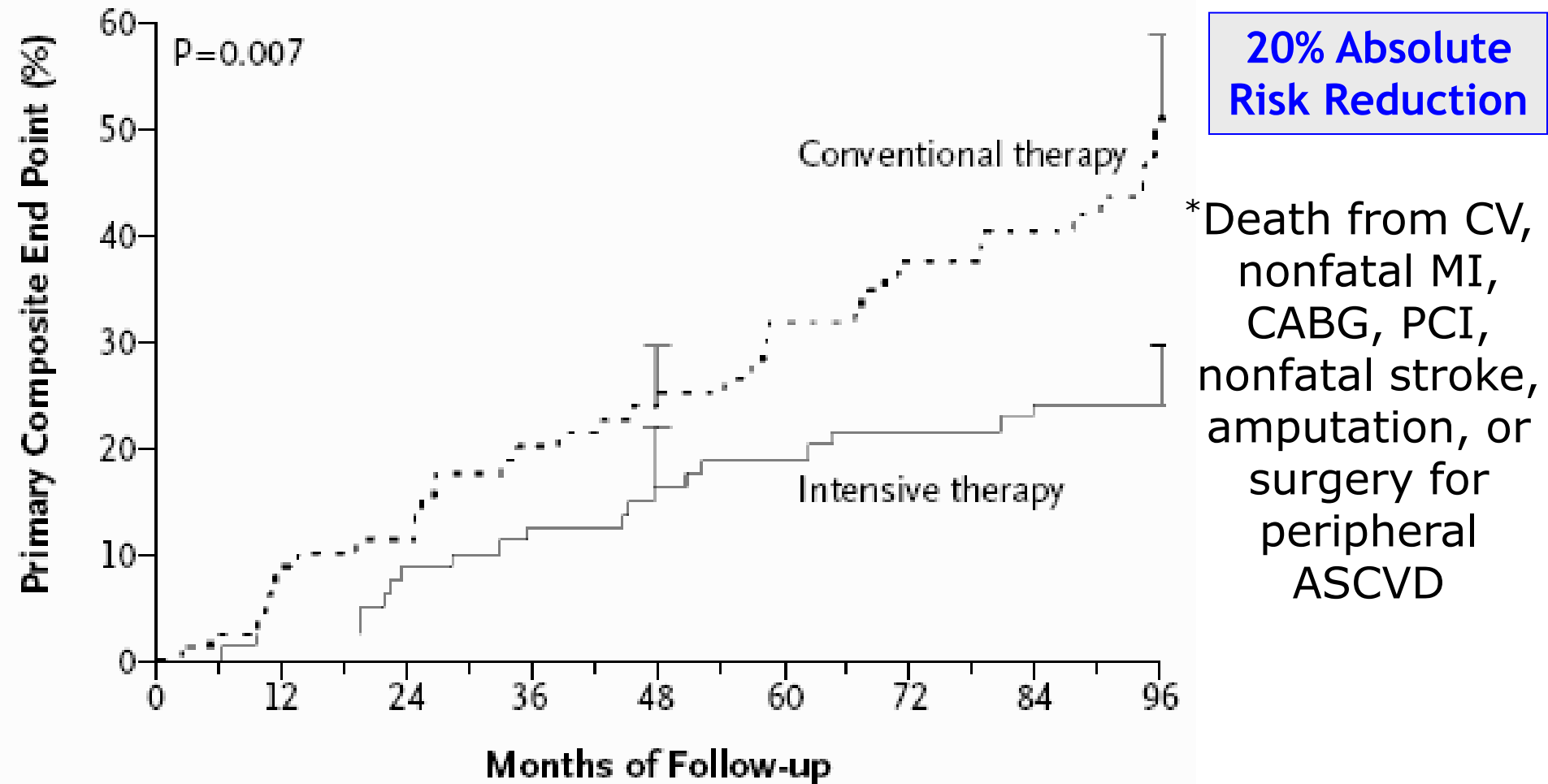
- How can relative value for patients be determined?
 - Benefit / risk / compliance \Rightarrow clinical outcomes
 - Is there a regulatory path?
 - Is there a development path?
 - What can be leveraged for earlier assessment in development (“de-risking” vs. added value)?
 - Are “added value” effects consistent with mechanism or considered “off-target”?
 - How can we establish reliable biomarkers for (microvascular) complications that take many years to develop?
-

Steno-2: Efficacy of Multiple Risk Factor Intervention in T2DM with Microalbuminuria

Patients Reaching Intensive-Treatment Goals at Mean 7.8 y, (%)



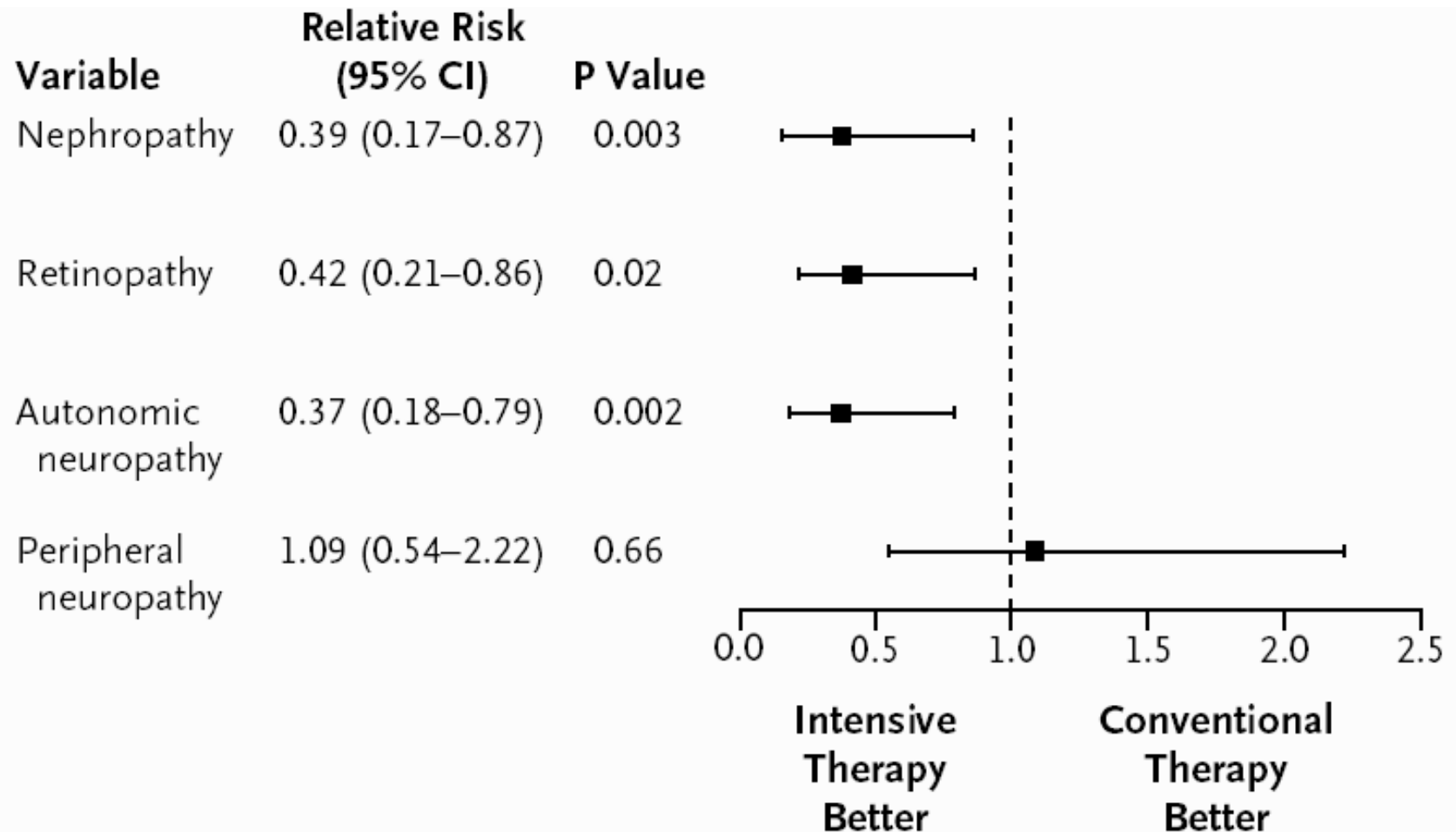
Steno-2: Efficacy of Multiple Risk Factor Intervention in T2DM with Microalbuminuria



N=160; follow-up = 7.8 years

Gæde P et al. *N Engl J Med* 2003;348:383

Steno-2: Efficacy of Multiple Risk Factor Intervention in High-Risk T2DM



Perspectives

- Type 2 diabetes is a multifactorial disease
- Goals of patient management in T2DM are multiple
- Diabetes drug development is highly targeted
 - Especially for glucose-lowering effects
- Additional benefits may be gained by mechanism-based effects
 - If not explainable by mechanism – considered off-target?
Poorly understood?
- What can be leveraged for additional benefit earlier in development?
 - Prior to long-term outcomes data which are difficult to obtain