

RCT analysis: Intercurrent Events/Drop-in

1. LEADER Cardiovascular outcomes trial: RCT comparing Liraglutide vs. SoC for treating diabetes patients at high cardiovascular risk
2. The study showed a significant Cox-PH RH with CI [0.78-0.97] on MACE time to event outcome
3. TMLE reproduced similar effect, with more precision; robust across many subgroups (Chen et al., 2023)
4. There was **significant additional drop-in insulin use in the control arm**.
5. An L-TMLE **stochastic intervention direct effect** analysis controlling for the differential post-treatment use of insulin was carried out

Results:

-*Significant **stochastically controlled** additive direct treatment effect*

-*Non-significant **statically controlled** additive direct treatment effect*

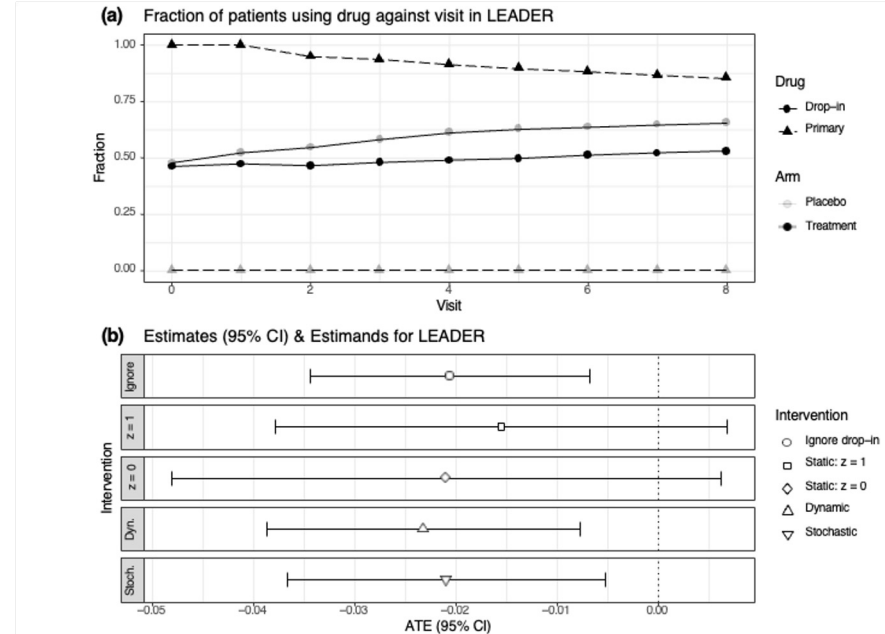


FIGURE 4 (a) Fraction of those at risk using main/drop-in treatment in each arm for LEADER and (b) LTMLE estimates with 95% confidence intervals.