Population adjusted indirect comparisons: an industry perspective

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Disclosure

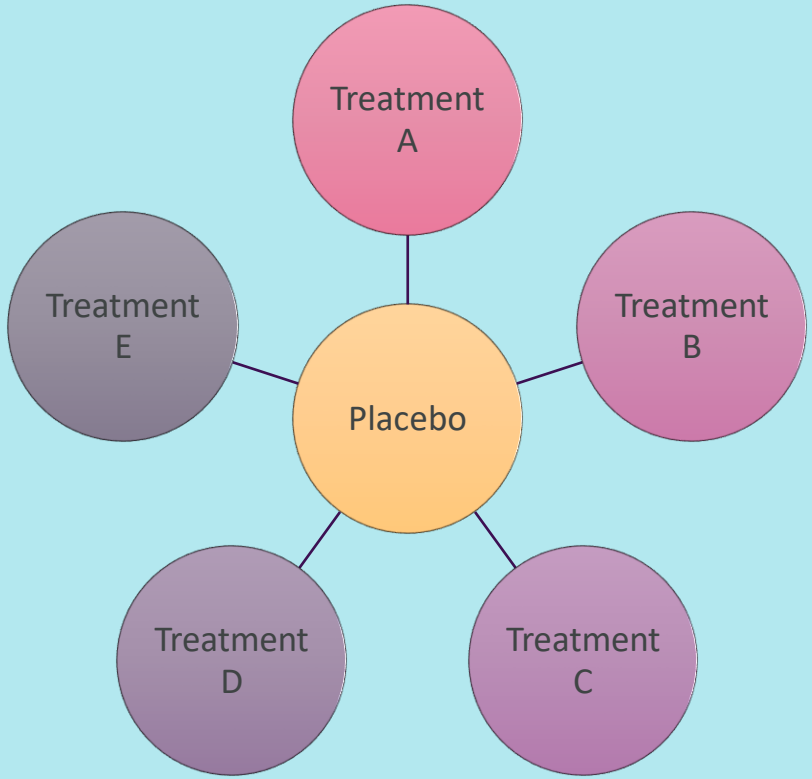
I am an AstraZeneca (AZ) employee. This presentation reflects my own views and not necessarily those of AZ.

Overview

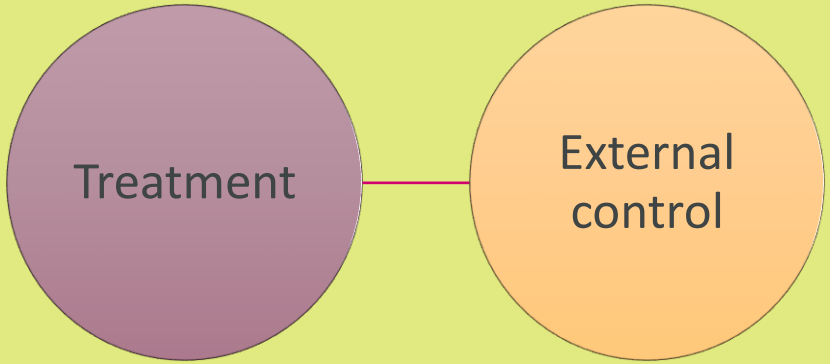
- Cross-study differences can bias comparisons (ITCs)
- MAIC is often used to adjust for population differences
- There are practical considerations for selecting an approach

ITCs inform decisions in the absence of head-to-head evidence

New treatment vs. approved treatments in HTA submissions



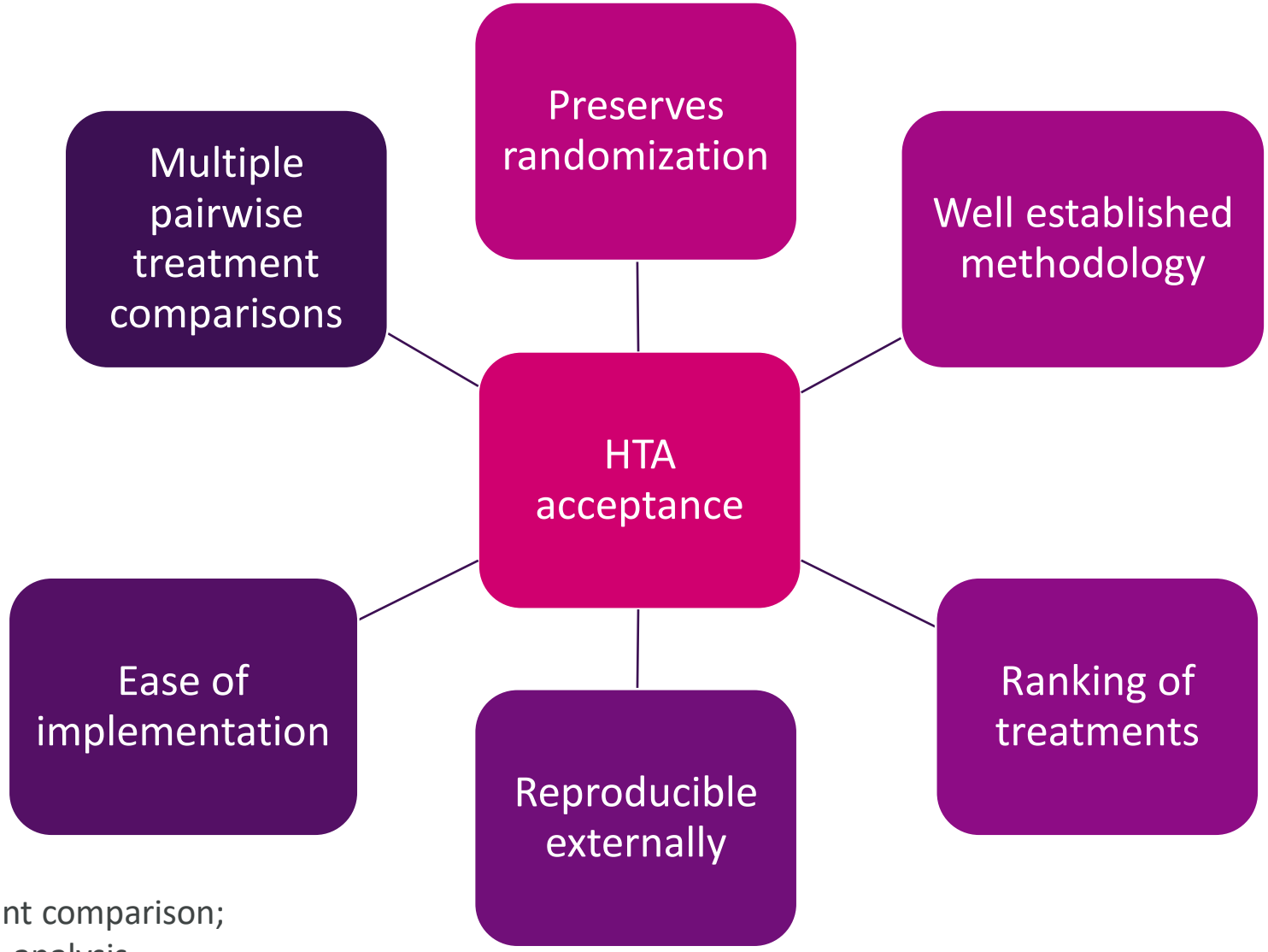
Contextualization of single arm trials



RCTs are not always possible

[4] ITC, indirect treatment comparison; RCT, randomised controlled trial; HTA, health technology assessment

NMA continues to be widely used for conducting ITCs



ITC, indirect treatment comparison;
NMA, network meta-analysis

Cross-study differences are of concern

- Patient characteristics
- Inclusion/exclusion criteria
- “Common” comparator - is placebo really placebo?
- Outcome measurements, e.g. definition, assessment frequency, imputation of missing data
- Setting, e.g. year of study, geographical location, disease definition
- Study design, e.g. blinding, allocation concealment, treatment crossover, follow-up duration
- Unobserved differences
- Data source, e.g. trials vs. claims data

- ❑ It is important to understand differences since they affect opinions on **validity** of results
- ❑ Statistical analyses can address some differences, but not all.

How can we improve trust in indirect treatment comparisons?

Population differences are why we turn to MAIC

Typical NMA situation:

- Insufficient data for meta-regression

- Subgroup analyses not reported in published studies

MAIC

- ✓ Evaluated similarly to PS weighting
- ✓ Practical guidance exists from HTA agencies
- ✓ Familiar to decision makers
- ✓ Leverages IPD on one study
- ✓ Applicable also to disconnected network
- ✓ Same adjustment model may be applied to multiple outcomes
- ✓ Targets a marginal treatment effect

STC is an alternative:

- ✓ MAIC may result in low ESS; imprecise estimates
- ✓ Allows extrapolation beyond study period
- ○ Requires one adjustment model per outcome
- ○ Question validity of STC if MAIC fails due to substantial differences between trials

ITCs are observational – use methods to minimise bias

Assess robustness of results

Perform diagnostic checks

MAIC, matching adjusted indirect comparison; PS, propensity score, IPD, individual participant data; HTA, health technology assessment; STC, simulated treatment comparison; ESS, effective sample size

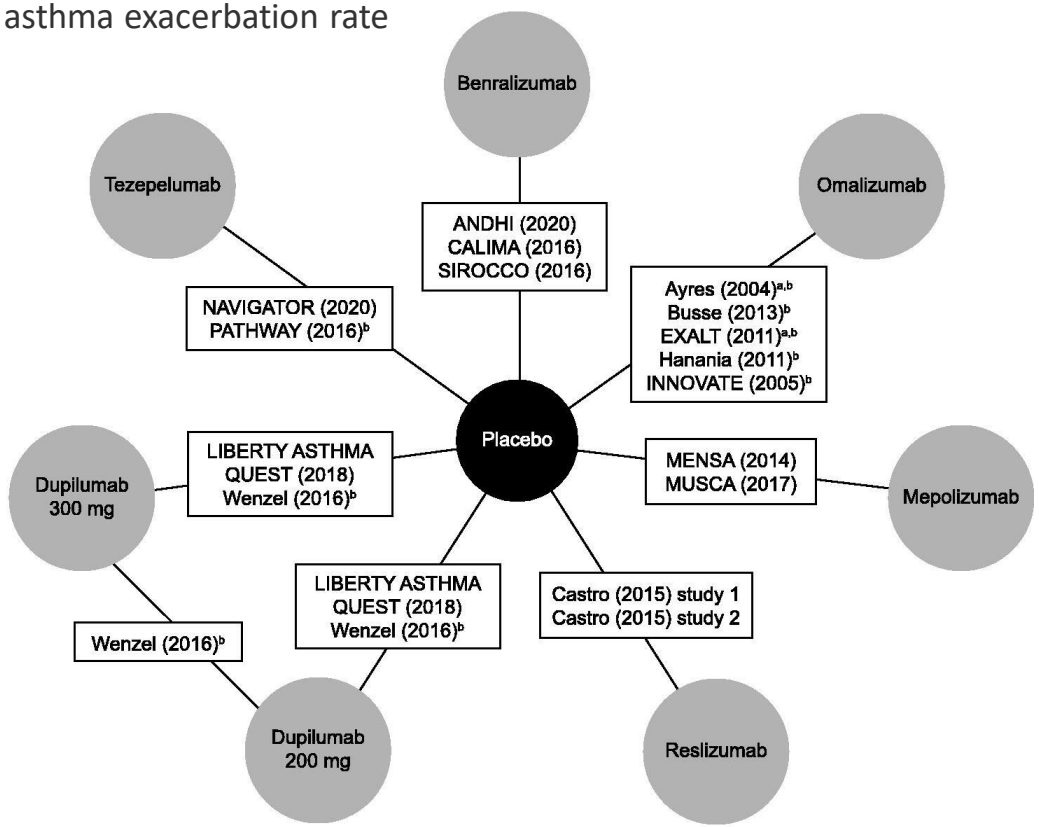
Example: Tezepelumab vs 5 other biologics

- Biologics are approved for patients with severe asthma and connected via a common comparator
- Clinical experts identified *potential* effect modifiers
- Distributions of potential effect modifiers differ across included trials
- Tezepelumab population with IPD is broader than the population without (ideal scenario)

Outcomes:

- Annualized asthma exacerbation rate (AAER)
- AAER for exacerbations leading to hospitalization or emergency room visit.

Outcome: Annualized asthma exacerbation rate



More than one method may be appropriate

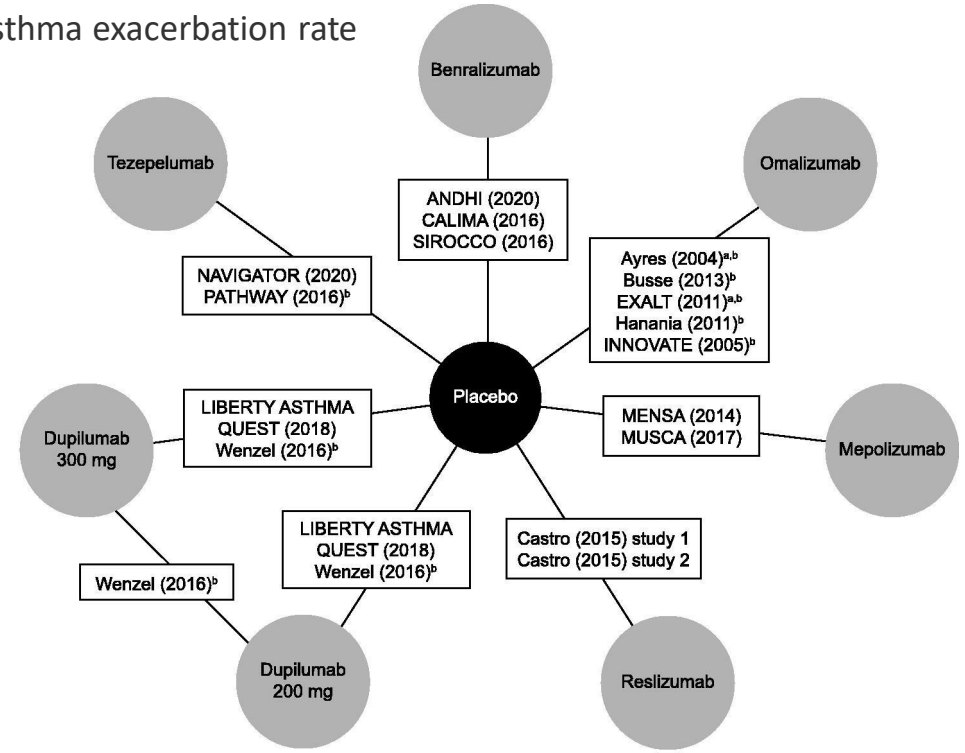
Applicable methods

- NMA
- NMA subgroup analyses
- STCs using IPD on Tezepelumab
  - STC subgroup analyses not possible; data not reported
- MAIC
- ML-NMR

Sensitivity NMAs were conducted

- Placebo-controlled trials
- Phase 3 or 4 studies

Outcome: Annualized asthma exacerbation rate



Limitations:

- Unmeasured confounding may play a role
- Cannot adjust for differences in exacerbation definition

What next for ITCs? - Statistical methods are evolving

ITCs inform decisions when RCTs are not possible, limited or unavailable.

MAIC and STC are often used for ITCs and are now very familiar to decision makers.

Recent population adjustment methods address key limitations:

- Ways to adjust to a common population
- Extensions to NMA models
- Leveraging of all published subgroup data on treatment effects

How to manage the growing number of methods?

Closing remarks

- MAIC adjusts for populations differences prior to analysis of study outcomes.
- Other adjustment methods may be appropriate and complimentary.
- Different methods may not lead to the same conclusions.
- Results should be carefully interpreted based on the approach taken and assumptions made.
- All methods require included studies to be sufficiently similar.

Back up

Choice of method depends on context and data availability

Focus on the established methodologies:

AgD only

- Anchored ITC (Bucher)
- NMA
- NMA with meta-regression

IPD for our trial and AgD for published study

- Anchored MAIC
- Anchored STC
- Unanchored MAIC
- Unanchored STC

IPD only

- Propensity score methods:
  - Matching
  - IPTW
  - Weighting by the odds
- Outcome regression

For non-collapsible effect measures, different methods target population average and conditional treatment effects.

AgD, aggregated data; IPD, individual patient data, ITC, indirect treatment comparison; NMA network meta-analysis; MAIC, matching adjusted indirect comparison; STC, simulated treatment comparison; IPTW, inverse probability of treatment weighting