Network meta-analysis using data from distributed health data networks

A general framework based on an application using acute myocardial infarction in association with use of anti-diabetic agents

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On behalf of Darren Toh and Bruce Fireman
Introduction

- Many medical conditions exist for which there are multiple treatment options that warrant consideration.
- Network meta-analysis is a method which allows comparison of multiple treatments simultaneously.
- The majority of network meta-analyses published to date have largely considered RCTs; however, inclusion of non-randomized studies may be desirable.
- Distributed health data networks are now available and could be a valuable data source for network meta-analyses of non-randomized data.
Distributed data networks

- A distributed health data network is a system that allows secure remote analysis of separate data sets, each comprising a different medical organization's or health plan's records.
- Allow data holders to control all uses of their data, which overcomes many practical obstacles related to confidentiality, regulation, and proprietary interests.
- Distributed health data networks such as CNODES in Canada and Sentinel (previously Mini-Sentinel) in the United States cover millions of people, permitting large studies of comparative clinical effectiveness.
Mini-Sentinel Distributed Database

Lead – HPHC Institute

Data partners

~178 million individuals
358 million person-years of observation time
36 million individuals have over 3 years of data
### Application – AMI with anti-diabetes drugs

<table>
<thead>
<tr>
<th>Population, Intervention (Index Node), Comparators, Outcomes and Study Design (PICOS)</th>
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</thead>
<tbody>
<tr>
<td><strong>Population</strong></td>
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<tr>
<td><strong>Intervention</strong></td>
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<tr>
<td><strong>Outcomes</strong></td>
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<tr>
<td><strong>Study design</strong></td>
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</table>
Evidence Network Options

A

- Saxagliptin
- Saxagliptin
- Saxagliptin
- Saxagliptin
- Sitagliptin
- Sitagliptin
- Sitagliptin
- Sitagliptin
- Pioglitazone
- Insulin
- SU

B

- Saxagliptin
- Sitagliptin
- Pioglitazone
- SU
- Sitagliptin
- Pioglitazone
- Insulin
Evidence Network* – AMI

*Propensity score matching using per protocol analyses which censor follow-up after run-out of study drug

* Size of node reflects person-years of follow-up and width of connections reflective of number of data partners
Network meta-analysis – AMI*

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*Random-effects Bayesian network meta-analysis using PP analyses censor follow-up after runout of study drug

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Higher risk of myocardial infarction

Lower risk of myocardial infarction

Sitagliptin versus Saxagliptin

Pioglitazone versus Saxagliptin

Sulfonylureas versus Saxagliptin

Pioglitazone versus Sitagliptin

Sulfonylureas versus Sitagliptin

Sulfonylureas versus Pioglitazone*
Consistent with RCTs?

Dipeptidyl peptidase-4 inhibitors and cardiovascular risk: a meta-analysis of randomized clinical trials

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**Aims:** Preliminary data from randomized trials with metabolic outcomes have shown that treatment with dipeptidyl peptidase-4 inhibitors (DPP4i) could be associated with a reduced incidence of major cardiovascular events (MACE). The present meta-analysis is aimed at verifying this protective effect, collecting all available data from randomized trials.

**Methods:** A comprehensive search for published and unpublished trials with a duration ≥ 24 weeks comparing DPP4i with placebo or other drugs was performed, retrieving all MACE reprinted as serious adverse events together with death from any cause. Mantel–Haenszel odds ratio (MHR-OR) was calculated with random effect models for MACE, myocardial infarction, stroke and mortality. When available, effects on glycated haemoglobin, lipid profile and blood pressure were also assessed and used for the estimation of the modification of risk for myocardial infarction using the UKPDS risk engine.

**Results:** A total of 70 trials, enrolling 41,959 patients with a mean follow-up of 44.1 weeks, was collected and included in the analysis. The MHR-OR (95% confidence interval) was 0.71 (0.59-0.86), 0.64 (0.44-0.94), 0.77 (0.48-1.24) and 0.60 (0.41-0.88) for MACE, myocardial infarction, stroke and mortality, respectively.

**Conclusions:** Treatment with DPP4i reduces the risk of cardiovascular events (particularly myocardial infarction) and all-cause mortality in patients with type 2 diabetes. The reduction in the incidence of myocardial infarction is greater than that predicted on the basis of conventional risk factors, suggesting a role for other mechanisms.

**Keywords:** cardiac complications, macrovascular disease, oral pharmacological agents

*Date submitted 15 May 2012; date of first decision 18 June 2012; date of final acceptance 23 July 2012*
Strengths of approach

- Compare multiple treatments simultaneously
- Maintain security and privacy of personally identifiable health information
- Higher quality non-randomized study designs
- Less heterogeneity – common data format allows checking, manipulation, and analysis via identical computer programs shared by all data partners
- Compare findings between data partners
- Large number of outcomes (e.g., MI’s) compared with RCTs
Limitations of approach

- Broad type 2 diabetes population considered; may mask differences in underlying populations
- Based on aggregate level data
- Potential differences in background therapy, doses, etc.
- Use of pair-wise PSM and DRS analyses may introduce heterogeneity
- Sulfonylureas lumped together
- Potential for confounding
- Potential for double counting – methods need to be developed
Conclusions

- Network meta-analysis can be used to integrate data from distributed health data networks
- Use of network meta-analysis provides a more holistic view of the evidence
- Researchers must ensure that treatments/populations included in evidence networks are similar enough to be compared, and even then there still may be issues with confounding
- There are significant opportunities for improving the application of methodology
Acknowledgements

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- CIHR Drug Safety and Effectiveness Network Meta-Analysis team grant (Funding reference number – 116573)
Thank you!
Key assumption - exchangeability

a) Network meta-analysis and assessment of exchangeability assumption

To assess exchangeability assumption, collect information about the patient and study characteristics, and carefully consider whether they are similar enough to be compared.

b) Summary of patient and study characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All studies</th>
<th>Drug A versus B</th>
<th>Drug A versus C</th>
</tr>
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<tbody>
<tr>
<td>Age</td>
<td>68</td>
<td>62</td>
<td>72</td>
</tr>
<tr>
<td>Duration of diabetes</td>
<td>15 years</td>
<td>10 years</td>
<td>20 years</td>
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<tr>
<td>Concomitant medication</td>
<td>15%</td>
<td>10%</td>
<td>20%</td>
</tr>
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</table>

c) Box Plot on risk of outcome in common arm

Risk of Outcome in Common Treatment A arm

- All Studies
- AB Studies
- AC Studies
Key assumption – exchangeability

- In a standard meta-analysis, the exchangeability assumption may be violated due to the presence of effect modifiers that are different from one trial to the next (between-study heterogeneity).
- When the amount of between-study heterogeneity is large, it may be inappropriate to pool estimates.
- Lack of exchangeability in network meta-analysis can produce disagreement between direct and indirect sources of evidence (inconsistency).
Potential Pitfalls – confounding

- **Randomized controlled trial**: True treatment effect small or negligible in the absence of confounding.

- **Higher quality non-randomized study**: Treatment effect somewhat inflated due to less unadjusted confounding.

- **Poor Quality non-randomized study**: Treatment effect largely inflated due to unadjusted confounding.
Potential Pitfalls – confounding

Indirect estimate from randomized controlled trial

<table>
<thead>
<tr>
<th></th>
<th>B</th>
<th>A</th>
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<tr>
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Effect estimate versus A

<table>
<thead>
<tr>
<th></th>
<th>C</th>
<th>A</th>
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<tr>
<td>B vs A</td>
<td>C vs A</td>
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Unbiased estimate of C vs B – No difference

Indirect estimate from non-randomized study

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Effect estimate versus A

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Biased estimate of C vs. B – Showing difference between them
Limitations – overlap & double counting

1. Potential for double counting saxagliptin and sitagliptin AMI’s

2. Potential for double counting some sitagliptin, insulin, pioglitazone, and SU data (purple)

Sitagliptin approved by FDA (October 17, 2006)

Saxagliptin approved by FDA (July 31, 2009)

Saxagliptin vs Sitagliptin, Saxagliptin vs Pioglitazone, Saxa vs SU

Sitagliptin vs Pioglitazone, Sitagliptin vs SU

Propensity score matching

- What is a propensity score? A propensity score is a patient’s predicted probability of receiving the treatment of interest given measured characteristics.
- The propensity score involves collapsing multiple covariates into a single summary variable.
- In the absence of RCT evidence, propensity score matching (PSM) can be used with IPD data to generate groups of patients, which are balanced on known variables.
Propensity score matching

**Total Population**

**Conventional propensity score matching**

**Study Cohort**
Propensity score matching vs Disease Risk score

- Both collapse multiple potentially confounding variables into a single summary measure
- Propensity score is the probability that each subject is exposed, as a function of his/her observed covariates
- The disease risk score estimates the probability or rate of disease occurrence as a function of the covariates.

Settings that favor propensity scores:

- tend to be those where there are more persons exposed to the treatment of interest than persons who have study outcomes.
- Another setting that favors propensity scores is when assessing a therapy’s effects on multiple outcomes.

Disease risk scores might be favored when:

- Assessing the effect of multiple exposures on a single outcome
- Disease risk scores may also be preferable summary measures when the exposure is infrequent or consists of multiple levels and the outcome is common.