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# Indirect treatment comparison

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**Abstract.** This article presents a command, `indirect`, for the estimation of effects of multiple treatments in the absence of randomized controlled trials for direct comparisons of interventions.

**Keywords:** st0325, indirect, Bucher, network meta-analysis

## 1 Introduction

Traditional meta-analyses that combine treatment effects across trials comparing the same interventions have been used in clinical medicine since the 1980s. In the absence of direct comparisons between two interventions, under certain conditions, a network of evidence can be constructed so that interventions may be compared indirectly (Glenny et al. 2005). The methods for indirect treatment comparison can be broadly categorized as frequentist or Bayesian. The frequentist methods are those described by Bucher et al. (1997), Lumley (2002), and White et al. (2012). The main difference between the two is that the former, also known as the adjusted indirect treatment comparison (AITC) method, is intended for situations where there is no direct evidence and comparisons are made pairwise. The Lumley method, like the Bayesian one, combines both direct and indirect comparisons within a total network of evidence. The Bayesian methods are statistically more flexible but computationally intensive and complex. They revolve around the choice of a prior estimate and depend on multiple-chain Monte Carlo simulations for the posterior estimates of treatment effects (Lu and Ades 2004; Caldwell, Ades, and Higgins 2005; Jansen et al. 2008). Interested readers are directed toward a special issue of *Research Synthesis Methods* for further information

 

(Salanti and Schmid 2012), especially about how network meta-analysis can accommodate more complicated networks in Stata (White et al. 2012; Chaimani et al. 2013). Motivated by AITC's desirability for simple networks, we implemented it as the Stata command `indirect`.

## 2 Adjusted indirect treatment comparison

The adjusted indirect method allows for the comparison of two treatments by using information from randomized controlled trials comparing each of the interventions with a common comparator. It assumes that the treatment effectiveness is the same across all trials used in the comparison. Formally and following notation by Wells et al. (2009), given $k$ number of treatments $T_1, T_2, \ldots, T_k$ such that all consecutive pairs have been compared ($T_1$ versus $T_2$, $T_2$ versus $T_3, \ldots, T_{k-1}$ versus $T_k$), the indirect $100(1-\alpha/2)\%$ confidence interval (CI) estimator of the measure of association $\widehat{A}$ for a pair of treatments $(T_i, T_{i+1})$ is given by

$$\sum_{i=1}^{k-1} \widehat{A}_{T_iT_{i+1}} \pm Z_{\frac{\alpha}{2}} \sqrt{\sum_{i=1}^{k-1} \mathrm{Var}\left(\widehat{A}_{T_iT_{i+1}}\right)}$$

where $\sum_{i=1}^{k-1} \widehat{A}_{T_iT_{i+1}}$ is the indirect estimator of treatments $T_1$ and $T_k$. The measure of association $\widehat{A}$ can be in the form of an odds ratio, a risk ratio, a hazard ratio (HR), a risk difference, or a mean difference. The test statistic for testing the indirect association between treatments $T_1$ and $T_k$ for $n$ number of studies used is

$$\chi^2_{df=n} = \frac{\sum_{i=1}^{k-2} \sum_{j=i+1}^{k-1} \left(\sum_{j=1}^{n} W_{T_iT_{i+1},j}\right) \left(\sum_{j=1}^{n} W_{T_jT_{j+1},j}\right) \left(\widehat{A}_{T_iT_{i+1}} - \widehat{A}_{T_jT_{j+1}}\right)^2}{\sum_{i=1}^{k-1} \sum_{j=1}^{n} W_{T_iT_{i+1},j}}$$

where the weight assigned for the $j$th study evaluating treatments $(T_i, T_{i+1})$ is defined as

$$W_{T_iT_{i+1},j} = \left\{\mathrm{Var}\left(\widehat{A}_{T_iT_{i+1},j}\right)\right\}^{-1}$$

AITC can calculate indirect treatment estimates for the networks given in figure 1 (star, ladder, and single loop) as long as the comparisons are made pairwise.

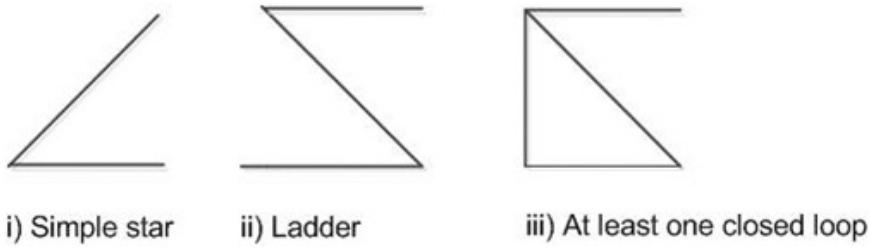


Figure 1. Examples of network patterns for the AITC

## 2.1 Syntax for indirect

Our command `indirect` assumes that Stata's `metan` command (Harris et al. 2008) has been installed. Because of the complexity of the syntax and to facilitate the ease of its implementation, we have included a dialog-box file, `indirect.dlg` (figure 2).

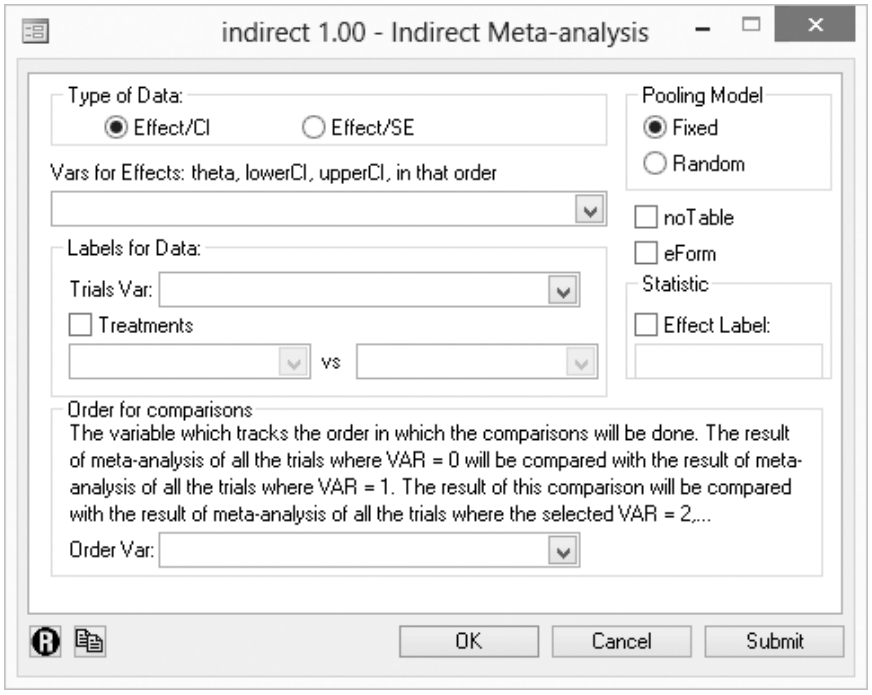


Figure 2. Dialog box used to process `indirect`

`indirect` *varlist* [ *if* ] [ *in* ], [ `random fixed eff(`*strvar*`) eform tabl`
`trta(`*strvar*`) trtb(`*strvar*`)` ]

*varlist* contains a summary statistic (relative risk, odds ratio, HR) on the log scale and its standard error (SE) or a summary statistic on the log scale and its 95% CI limits; a variable that specifies the studies; and a variable that tracks the order in which the comparisons are done (trials comparing the same interventions will have the same order number).

### 2.2 Options

`random` specifies that a random-effects model should be used (the default).

`fixed` specifies that a fixed-effects model should be used.

`eff(`*strvar*`)` specifies the effect size (hazard ratio, relative risk, ..., etc.).

`eform` specifies that `eformat` should be used.

`tabl` specifies that the table of studies used should be displayed.

`trta(`*strvar*`)` specifies the experimental treatment.

`trtb(`*strvar*`)` specifies the standard treatment.

## 3 Example: Zoledronate versus Pamidronate in multiple myeloma

We illustrate the `indirect` command by using data from a systematic review of 13 studies on the effects of bisphosphonates on overall survival in patients with multiple myeloma (Mhaskar et al. 2012). The network is given in figure 3, while the trials, logHRs, and their SEs are presented in table 1. The dashed lines represent indirect comparisons. Suppose we wish to indirectly compare Zoledronate with Pamidronate (30mg) and Pamidronate (90mg) under the random-effects model. For this comparison, we discard Clodronate, Etidronate, and Ibandronate. Because there may be many trials comparing the same interventions, a variable, `order`, is introduced to keep track of comparisons being made (table 2).

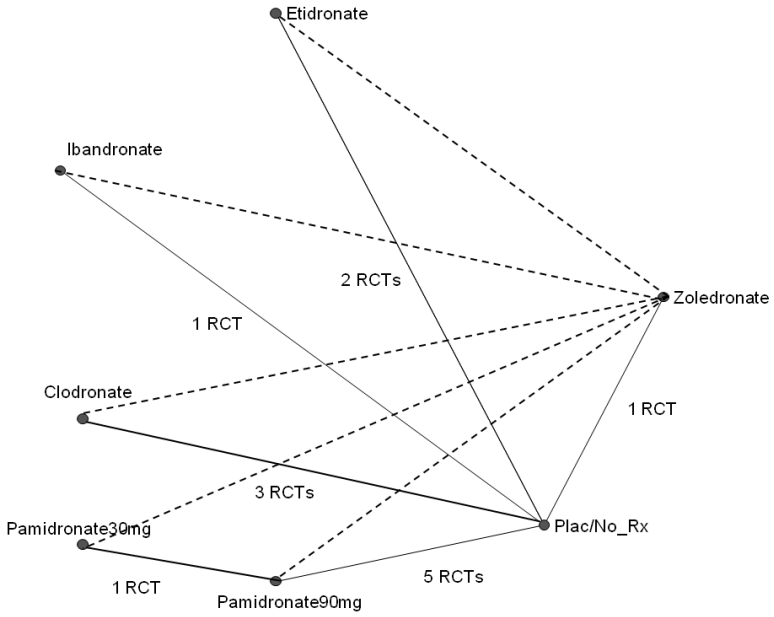


Figure 3. Evidence network of the reported 13 randomized controlled trials of bisphosphonates for overall survival in patients with multiple myeloma

Table 1. Effects of bisphosphonates on overall survival in multiple myeloma patients

| Study | Active | Control | ln(HR), SE{ln(HR)} |
|---|---|---|---|
| Avilés et al. (2007) | Zoledronate | Plac/NoRx | −0.859, 0.333 |
| Delmas et al. (1982) | Clodronate | Plac/NoRx | 1.288, 0.894 |
| Lahtinen et al. (1992) | Clodronate | Plac/NoRx | −0.287, 0.181 |
| McCloskey et al. (2001) | Clodronate | Plac/NoRx | −0.016, 0.095 |
| Belch et al. (1991) | Etidronate | Plac/NoRx | 0.461, 0.198 |
| Daragon et al. (1993) | Etidronate | Plac/NoRx | 0.071, 0.034 |
| Menssen et al. (2002) | Ibandronate | Plac/NoRx | 0.063, 0.221 |
| Brincker et al. (1998) | Pamidronate90mg | Plac/NoRx | −0.107, 0.945 |
| Kraj et al. (2000) | Pamidronate90mg | Plac/NoRx | 0.1168, 0.4 |
| Terpos et al. (2000) | Pamidronate90mg | Plac/NoRx | −2.08, 1.41 |
| Berenson et al. (1998) | Pamidronate90mg | Plac/NoRx | −0.29, 0.167 |
| Musto et al. (2003) | Pamidronate90mg | Plac/NoRx | −0.02, 0.203 |
| Gimsing et al. (2010) | Pamidronate30mg | Pamidronate90mg | −0.050, 0.120 |

Table 2. Network branches used to compare Zoledronate with Pamidronate

| Study | Active | Control | ln(HR), SE{ln(HR)} | Order |
|---|---|---|---|---|
| Avilés et al. (2007) | Zoledronate | Plac/NoRx | −0.859, 0.333 | 0 |
| Brincker et al. (1998) | Pamidronate90mg | Plac/NoRx | −0.107, 0.945 | 1 |
| Kraj et al. (2000) | Pamidronate90mg | Plac/NoRx | 0.1168, 0.4 | 1 |
| Terpos et al. (2000) | Pamidronate90mg | Plac/NoRx | −2.08, 1.41 | 1 |
| Berenson et al. (1998) | Pamidronate90mg | Plac/NoRx | −0.29, 0.167 | 1 |
| Musto et al. (2003) | Pamidronate90mg | Plac/NoRx | −0.02, 0.203 | 1 |
| Gimsing et al. (2010) | Pamidronate30mg | Pamidronate90mg | −0.050, 0.120 | 2 |

```
. use example
. indirect ln_hr se_ln_hr study order,  random eff(HR) eform trta(inn_rx)
> trtb(std_rx)
Meta-Analysis: comparing treatments  Zoledronate  and  Plac/No_Rx
Exponential Statistic HR = .424
Log statistic ln(HR) = -.859 and standard error = .333(var = .111)
----------------------------------------
Meta-Analysis: comparing treatments Pamidronate90  and  Plac/No_Rx
Exponential Statistic HR= .846
Log statistic ln(HR) = -.167 and standard error = .121 (var = .015)
----------------------------------------
----------------------------------------
Indirect comparison: Zoledronate vs Pamidronate90
Exponential Statistic HR =.5 with CI [ .25, 1.003]
Log statistic ln(HR) = -.692 and standard error =  .355 (var = .126)
Confidence Interval: [-1.387, .003]
Heterogeneity statistic ChiSquared: =3.81, p-value: = .051
----------------------------------------
Meta-Analysis: comparing treatments Pamidronate30  and  Pamidronate90
Exponential Statistic HR= .951
Log statistic ln(HR) = -.05 and standard error = .12 (var = .014)
----------------------------------------
----------------------------------------
Indirect comparison: Zoledronate vs Pamidronate30
Exponential Statistic HR =.526 with CI [ .253, 1.096]
Log statistic ln(HR) = -.642 and standard error =  .374 (var = .14)
Confidence Interval: [-1.376, .092]
Heterogeneity statistic ChiSquared: =2.942, p-value: = .086
```

In the network in figure 3, the indirect estimates favor Zoledronate over Pamidronate 30mg (HR = 0.526, 95% CI: [0.253, 1.096]) and Pamidronate 90mg (HR = 0.5, 95% CI: [0.25, 1.003]); however, they are both statistically nonsignificant. Both heterogeneity statistics are nonsignificant at $P = 0.05$. The remaining AITC estimates are given in table 3, and all significantly favor Zoledronate over Clodronate, Etidronate, and Ibandronate.

Table 3. Indirect comparison of Zoledronate versus other bisphosphonates under random effects

| Comparison | Branches used: HR [95% CI] | HR [95% CI] |
|---|---|---|
| Zol versus Clo | Zol versus Plac: 0.42 [0.22, 0.81] | |
| | Clo versus Plac: 0.93 [0.77, 1.51] | 0.46 [0.22, 0.95] |
| Zol versus Etid | Zol versus Plac: 0.42 [0.22, 0.81] | |
| | Etid versus Plac: 1.24 [0.66, 1.29] | 0.34 [0.16, 0.72] |
| Zol versus Iban | Zol versus Plac: 0.42 [0.22, 0.81] | |
| | Iban versus Plac: 1.07 [0.69, 1.64] | 0.39 [0.18, 0.87] |
| Zol versus Pam30 | Zol versus Plac: 0.42 [0.22, 0.81] | |
| | Pam90 versus Plac: 0.85 [0.67, 1.07] | |
| | Pam30 versus Pam90: 0.95 [0.75, 1.2] | 0.526 [0.253, 1.096] |
| Zol versus Pam90 | Zol versus Plac: 0.42 [0.22, 0.81] | |
| | Pam versus Plac: 0.85 [0.67, 1.07] | 0.5 [0.25, 1.003] |

# 4 Conclusion

The application of indirect methods has grown in journal publications, and the issues related to the bias and power of indirect meta-analysis are well documented (Song et al. 2009; Mills et al. 2011). In the absence of direct treatment comparisons and in less complex networks, the AITC method we implemented has been found more favorable to Bayesian mixed-treatment comparisons because of its simplicity (O'Regan et al. 2009). Also, in the absence of systematic bias in primary studies, both methods are on average unbiased (Song et al. 2012). The major limitation of AITC is its inability to satisfactorily handle correlations that may exist between treatment effects in multiarm trials, which is a major advantage of the Bayesian approach. Bayesian methods can also be used to analyze more complex networks of evidence and can include study-level covariates. As we have pointed out, however, these advantages have to be weighed against their complexities. Because of the complexity and diversity of methods involved, the tools for the critical appraisal of methods do not yet exist, though there has been work in recent years to establish guidelines for conducting and interpreting indirect treatment comparisons (Jansen et al. 2011; Hoaglin et al. 2011). Direct meta-analyses estimate average treatment effects across trials and are fairly straightforward to interpret. The results obtained from indirect treatment comparisons rarely are, and readers are cautioned to interpret them with skepticism.

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