Sidesplitting using network meta-regression

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Abstract

Consistency is an important assumption to justify evidence synthesis in network meta-analysis. Sidesplitting is a representative method used to evaluate inconsistency; it decomposes the overall estimate of network meta-analysis on a specific treatment pair to those of direct and indirect comparisons and assesses their concordance. A relevant issue in sidesplitting is that adequate adjustments are needed in multi-arm trials (≥3 arms) to prevent biases. In existing methods, sidesplitting requires several restrictions on model parameters or additional parameter modeling and the computations are complicated. In this article, we show that sidesplitting involving the adjustments of multi-arm trials can be uniformly treated within a network meta-regression framework, especially via the modeling method of Noma et al. (2017; *Stat Med* 36:917-927), which introduces additional free parameters to adjust the biases caused by multi-arm trials. The proposed approach can be interpreted as a specific version of the design-by-treatment interaction model, and any inference methods for the network meta-regression can be applied involving higher-order asymptotic approximations. The proposed method is applied to two network meta-analyses of hypertensive drugs.

Key words: network meta-analysis; contrast-based approach; sidesplitting; inconsistency; design-by-treatment interaction.

1. Introduction

Consistency is a relevant assumption to justify evidence synthesis in network meta-analysis (Nikolakopoulou, White and Salanti, 2021; Salanti, 2012). Conventionally, consistency refers to the agreement between evidence of direct and indirect comparisons (Salanti, 2012; Strom, Kimmel and Hennessy, 2013); however, Higgins et al. (2012) and Jackson et al. (2016) showed that this concept is rigorously explained as design-by-treatment interactions on the network. "Design" refers to the combination of treatments compared in the corresponding studies (although this word is generally used with broader meaning). Inconsistency means a disagreement of treatment effects across different combinations of treatment comparisons on the network.

Sidesplitting (Dias et al., 2010; Noma et al., 2017) is a representative method to evaluate inconsistency and is used as a standard analysis tool in many standard statistical packages of network meta-analysis, e.g., `network` (White, 2015) of Stata and `gemtc` (van Valkenhoef et al., 2016; van Valkenhoef et al., 2012) and `netmeta` (Balduzzi et al., 2023) of R. This method decomposes the overall estimate of network meta-analysis on a specific treatment pair to those of direct and indirect comparisons and assesses their concordance (i.e., the inconsistency). From a modern viewpoint, it can be interpreted as a design-by-treatment interaction assessment for specific studies involving the corresponding treatment pair. Originally, Dias et al. (2010) proposed a back-calculation and node-splitting approach under a Bayesian framework. Noma et al. (2017) suggested an alternative frequentist approach for the contrast-based model (White et al., 2012) using Lindsay's composite likelihood method (Lindsay, 1988). One of the drawbacks of the approach of Dias et al. (2010) is that their methods do not address possible biases caused by the consistency restrictions of the other treatment pairs in multi-arm (≥3 arms) trials (Noma et al., 2017; White, 2015). Noma et al. (2017) proposed adding the design-by-

treatment interaction parameters to the corresponding treatment pairs, and White (2015) provided a "symmetric" assumption of the remaining treatment pairs to adjust the potential bias. The simulation studies of Noma et al. (2017) showed that these adjustments are necessary to provide valid inference results.

Although these methods provide effective solutions, they cannot be easily handled by current standard computational tools. In this article, we show that the sidesplitting can be uniformly treated within the framework of a network meta-regression model via a contrast-based approach (White et al., 2012). We also show that the bias adjustments for multi-arm trials can also be handled within this framework, especially when Noma et al. (2017)'s adjustment method is used. These methods enable effective computations for the sidesplitting, and various inference methods can be applied using the network meta-regression framework (Jackson and Riley, 2014; Jackson, White and Riley, 2013; Noma et al., 2023; Noma et al., 2018).

2. Network meta-regression model for contrast-based approach

We here consider the contrast-based network meta-regression model (Noma et al., 2023; White et al., 2012). We consider synthesizing N trials and a comparison of $p+1$ treatments. Y_{ij} denotes an estimator of a treatment effect in contrast to a reference treatment (e.g., placebo) for the jth treatment in the ith trial ($i = 1, 2, \dots, N; j = 1, 2, \dots, p$). Commonly used effect measures are the mean difference, standardized mean difference, risk difference, risk ratio, odds ratio, and the hazard ratio; the ratio measures are usually transformed on a logarithmic scale (Higgins and Thomas, 2019). For the multivariate meta-regression, we consider the following multivariate random-effects model for the outcome variable $\boldsymbol{Y}_i = \left(Y_{i1}, Y_{i2}, \dots, Y_{ip}\right)^T$:

$$\boldsymbol{Y}_i = \boldsymbol{\theta}_i + \boldsymbol{e}_i \quad (1)$$

$$\boldsymbol{\theta}_i = \boldsymbol{X}_i^T \boldsymbol{\beta} + \boldsymbol{\varepsilon}_i$$

where $\boldsymbol{\theta}_i = \left(\theta_{i1}, \theta_{i2}, \ldots, \theta_{ip}\right)^T$ and $\boldsymbol{\beta} = \left(\boldsymbol{\beta}_1^T, \ldots, \boldsymbol{\beta}_p^T\right)^T$. The regression function model $\boldsymbol{X}_i^T \boldsymbol{\beta}$ involves a design matrix,

$$\boldsymbol{X}_i = \begin{pmatrix} \boldsymbol{x}_{i1} & \mathbf{0} & \cdots & \mathbf{0} \\ \mathbf{0} & \boldsymbol{x}_{i2} & \ldots & \mathbf{0} \\ \vdots & \vdots & \ddots & \vdots \\ \mathbf{0} & \mathbf{0} & \cdots & \boldsymbol{x}_{ip} \end{pmatrix}$$

where $\boldsymbol{x}_{ij}$ is a $q_j \times 1$ covaraiate vector for Y_{ij} (q_j is the number of the covariates) and $\boldsymbol{\beta}_j$ is its $q_j \times 1$ regression coefficient vector. Also, $\boldsymbol{e}_i$ and $\boldsymbol{\varepsilon}_i$ are independent random variation terms within and across studies ($p \times 1$ random vectors), assumed to be distributed as $\boldsymbol{e}_i \sim \text{MVN}(\mathbf{0}, \boldsymbol{S}_i)$ and $\boldsymbol{\varepsilon}_i \sim \text{MVN}(\mathbf{0}, \boldsymbol{\Sigma})$. $\boldsymbol{S}_i$ (a $p \times p$ matrix) is the within-study covariance matrix:

$$\boldsymbol{S}_i = \begin{pmatrix} s_{i1}^2 & \rho_{i12} s_{i1} s_{i2} & \cdots & \rho_{i1p} s_{i1} s_{ip} \\ \rho_{i21} s_{i2} s_{i1} & s_{i2}^2 & \ldots & \rho_{i2p} s_{i2} s_{ip} \\ \vdots & \vdots & \ddots & \vdots \\ \rho_{ip1} s_{ip} s_{i1} & \rho_{ip2} s_{ip} s_{i2} & \cdots & s_{ip}^2 \end{pmatrix}$$

which is usually assumed to be known and fixed to its valid estimate. In addition, $\boldsymbol{\Sigma}$ is the between-studies covariance matrix:

$$\boldsymbol{\Sigma} = \tau^2 \boldsymbol{P} = \tau^2 \begin{pmatrix} 1 & 1/2 & \cdots & 1/2 \\ 1/2 & 1 & \ldots & 1/2 \\ \vdots & \vdots & \ddots & \vdots \\ 1/2 & 1/2 & \cdots & 1 \end{pmatrix}$$

for $\tau^2 > 0$. Notably, the correlation structure of $\boldsymbol{\Sigma}$ can be assumed to be unstructured; however, there are rarely a sufficient number of studies for all of the variance–covariance parameters to be identified. Thus, most network meta-analyses adopt the equal-variance assumption for the p components of $\boldsymbol{\varepsilon}_i$; all the pairwise correlation coefficients should then be equal to 0.50 because of the consistency restriction (Higgins and Whitehead, 1996; Lu and Ades, 2009). In the present work, similar to the approach of Jackson et al.

(2014), we adopt the equal-variance assumption as a standard assumption of this model. For trials that do not include a reference treatment, the data augmentation approach of White et al. (2012) was adopted, where a quasi-small dataset was added into the reference arm (e.g., 0.0001 events for 0.001 patients for a binary outcome). Also, we denote the inverse of the marginal covariance matrix of $\boldsymbol{Y}_i$ as $\boldsymbol{W}_i = (\boldsymbol{\Sigma} + \boldsymbol{S}_i)^{-1}$.

The restricted maximum likelihood (REML) estimation is the standard method used to estimate the model parameters in practice. The REML log-likelihood function is

$$\ell(\boldsymbol{\beta}, \tau^2) = \text{const.} - \frac{1}{2}\sum_{i=1}^{N}\{\log\{\det(\boldsymbol{W}_i^{-1})\} + (\boldsymbol{y}_i - \boldsymbol{X}_i^T\boldsymbol{\beta})^T\boldsymbol{W}_i(\boldsymbol{y}_i - \boldsymbol{X}_i^T\boldsymbol{\beta})\}$$

$$-\frac{1}{2}\log\left\{\det\left(\sum_{i=1}^{N}\boldsymbol{X}_i\boldsymbol{W}_i\boldsymbol{X}_i^T\right)\right\}$$

Note that most individual clinical trials typically involve only two to three or four arms; thus, we formally replace $\boldsymbol{Y}_i$, $\boldsymbol{X}_i$, and $\boldsymbol{S}_i$ with their subvectors and submatrices. We denote the REML estimators of $\{\boldsymbol{\beta}, \tau^2\}$ as $\{\widehat{\boldsymbol{\beta}}, \hat{\tau}^2\}$; $\widehat{\boldsymbol{\beta}}$ is given as the generalized least-squares estimator (Noma et al., 2023; White et al., 2012),

$$\widehat{\boldsymbol{\beta}} = \left(\sum_{i=1}^{N}\boldsymbol{Y}_i^T\widehat{\boldsymbol{W}}_i\boldsymbol{X}_i^T\right)\left(\sum_{i=1}^{N}\boldsymbol{X}_i\widehat{\boldsymbol{W}}_i\boldsymbol{X}_i^T\right)^{-1}$$

where $\widehat{\boldsymbol{W}}_i = \left(\widehat{\boldsymbol{\Sigma}} + \boldsymbol{S}_i\right)^{-1}$ and $\widehat{\boldsymbol{\Sigma}} = \hat{\tau}^2\boldsymbol{P}$. The covariance matrix of $\widehat{\boldsymbol{\beta}}$ is estimated by $\mathrm{V}[\widehat{\boldsymbol{\beta}}] = \left(\sum_{i=1}^{N}\boldsymbol{X}_i\widehat{\boldsymbol{W}}_i\boldsymbol{X}_i^T\right)^{-1}$. The resultant REML-based Wald-type tests and confidence intervals are assured to be valid and efficient under large sample settings. Notably, the other estimators are applicable for the proposed methods discussed in the following sections, such as Jackson's method-of-moment estimator (Jackson et al., 2013).

3. Sidesplitting using network meta-regression

Sidesplitting factorizes the overall estimator of network meta-analysis on a specific treatment pair to those of direct and indirect comparisons (Dias et al., 2010; Noma et al., 2017). In this section, we formally denote the treatments on the network as A, B, C,…, where A is set to the reference. Without loss of generality, we focus on the comparison between A and B and consider decomposing the treatment effect estimator into direct and indirect comparison estimators and assessing their inconsistency. In this section, we will show that the sidesplitting is implementable using the aforementioned network meta-regression framework.

3.1 Case 1: Only two-arm trials

The simplest case is the network that does not involve multi-arm trials that include both A and B (i.e., only two-arm trials exist for this pair). In this case, we can model the possible inconsistency of the network meta-regression model by modeling the covariate vector $\boldsymbol{x}_{i1}$ as a two-component vector,

$$\boldsymbol{x}_{i1} = \left(x_{i1,\mathrm{dir}}, x_{i1,\mathrm{ind}}\right)^T$$

where $x_{i1,\mathrm{dir}} = 1$ and $x_{i1,\mathrm{ind}} = 0$ if the corresponding trial design is A vs. B; otherwise, $x_{i1,\mathrm{dir}} = 0$ and $x_{i1,\mathrm{ind}} = 1$. This scenario is regarded as a special case of the design-by-treatment interactions. The corresponding regression coefficients that constitute $\boldsymbol{\beta_1}$,

$$\boldsymbol{\beta_1} = \left(\beta_{1,\mathrm{dir}}, \beta_{1,\mathrm{ind}}\right)^T$$

are then interpreted as the summaries of treatment effects of direct and indirect comparisons. In addition, for the other treatment contrasts, we set the covariate vector as $x_{ij} = 1$ (for all $i = 1, 2, \dots, N;\ j = 2, 3, \dots, p$). When the consistency assumption is fulfilled for the other components on the network, the REML estimators $\hat{\beta}_{1,\mathrm{dir}}$ and $\hat{\beta}_{1,\mathrm{ind}}$ are directly used as the summary estimators of direct and indirect comparison

evidence. Also, the REML estimators $\hat{\beta}_{1,\mathrm{dir}}$ and $\hat{\beta}_{1,\mathrm{ind}}$ accord to those of pairwise meta-analysis for the studies of direct comparison and a subgroup analysis that excludes the studies with direct comparisons.

Notably, the REML estimators $\hat{\beta}_{1,\mathrm{dir}}$ and $\hat{\beta}_{1,\mathrm{ind}}$ are orthogonal in the sense of Cox and Reid (1986). Thus, the inconsistency test for the null hypothesis H_0: $\beta_{1,\mathrm{dir}} = \beta_{1,\mathrm{ind}}$ is performed using the Wald statistic:

$$W = \frac{\hat{\beta}_{1,\mathrm{dir}} - \hat{\beta}_{1,\mathrm{ind}}}{\sqrt{V[\hat{\beta}_{1,\mathrm{dir}}] + V[\hat{\beta}_{1,\mathrm{ind}}]}}$$

where W follows the standard normal distribution under H_0.

3.2 Case 2: Involving multi-arm (≥3 arms) trials

In the case of multi-arm (≥3 arms) trials that include both A and B, additional adjustments are required. As a simple example, we consider three-arm trials that involve A, B, and C. In these cases, if the network meta-regression model in Section 3.1 is simply applied, the REML estimators $\hat{\beta}_{1,\mathrm{dir}}$ and $\hat{\beta}_{1,\mathrm{ind}}$ can be biased when $\beta_{1,\mathrm{dir}} \neq \beta_{1,\mathrm{ind}}$ because the other treatment contrasts of this design (A vs. B vs. C) assume the consistency restriction with the other components of the evidence network. Within the three-arm trials, the differences in treatment effects of B vs. C and A vs. C are expressed as $\beta_2 - \beta_{1,\mathrm{dir}}$ and β_2, respectively. However, for the other components of the network, the differences in treatment effects of B vs. C and A vs. C should be expressed as $\beta_2 - \beta_{1,\mathrm{ind}}$ and β_2, respectively. When $\beta_{1,\mathrm{dir}} \neq \beta_{1,\mathrm{ind}}$, they disagree and the regression function model is regarded as "misspecified." Under this condition, the regression parameter estimators are theoretically well known to be biased; Noma et al. (2017)'s simulation studies have also shown that the naïve approach explained in Section 3.1 (corresponding to the methods of Dias et al., 2010) produces biased estimators.

To address this issue, Noma et al. (2017) proposed a composite likelihood method that involves free parameters in the other contrasts in the multi-arm trials. This approach means introducing design-by-treatment interaction parameters into the other contrasts in the corresponding studies. White (2015) proposed a similar adjustment using a symmetric assumption of the other treatment contrasts. Although he discussed only three-arm trial cases, his method can be straightforwardly generalized to cases with more than three arms; however, if the symmetry assumption is not fulfilled, the regression function model is also misspecified and the REML estimators can be biased.

To circumvent the model misspecification problems, we propose adding free parameters to all of the other contrasts in the corresponding studies, similar to the approach of Noma et al. (2017), within the network meta-regression model. As the simplest example, for the three-arm case that involves three-arm trials A vs. B vs. C, the remaining treatment involved in the design is C. We should then add a covariate $x_{i2,\mathrm{adj}}$ to $\boldsymbol{x}_{i2}$ to adjust the consistency restriction on this study; we denote the corresponding regression parameter as $\beta_{2,\mathrm{adj}}$. Parameter $\beta_{2,\mathrm{adj}}$ is fundamentally a nuisance parameter, and its estimate is not reported in general; however, by adopting this regression modeling, we can effectively circumvent the model misspecification problems and obtain consistent estimators of $\beta_{1,\mathrm{dir}}$ and $\beta_{1,\mathrm{ind}}$.

For trials designed with more than three arms, the same covariates that adjust the design-by-treatment interactions should be modeled for all remaining treatments similarly. Notably, however, if the corresponding treatment does not appear in the other designs on the network, these covariates should not be added because the overall model would become unidentifiable. In these cases, the corresponding regression parameters (for the remaining treatments) might not be interpreted as treatment effect measures; however, they are nuisance parameters for the sidesplitting analyses and are not reported generally.

In these cases, the inconsistency test for the null hypothesis H_0: $\beta_{1,\mathrm{dir}} = \beta_{1,\mathrm{ind}}$ is constructed using the same Wald statistic described in Section 3.1. The REML estimators $\hat{\beta}_{1,\mathrm{dir}}$ and $\hat{\beta}_{1,\mathrm{ind}}$ are also orthogonal in the sense of Cox and Reid (1986) in these cases.

4. Applications

4.1 Heart failure data

Sciarretta et al. (2011) performed a network meta-analysis of antihypertensive drugs based on 26 randomized controlled trials (n = 223,313), which involved seven antihypertensive drug classes [α-blocker (AB), angiotensin-converting enzyme inhibitor (ACE), angiotensin II receptor blocker (ARB), β-blocker (BB), calcium channel blocker (CCB), conventional treatment (CT), and diuretic (DD)] and placebo. The incidence of heart failure was adopted as the outcome. The network plot for this network meta-analysis is presented in Figure 1(a).

We adopted the odds-ratio (OR) as the effect measure, in accordance with the original analysis of Sciarretta et al. (2011). We adapted two sidesplitting methods: (1) one that did not adjust the multi-arm trial issue (unadjusted method; calculated using the `network` routine in Stata (White, 2015)) and (2) the proposed network meta-regression approach. The results are presented in Table 1. Because most of the trials were two-arm trials and only two were three-arm trials (STOP-2 and ALLHAT), most of the results were similar. However, for several treatment pairs involved in multi-arm trials, the two methods provided substantially different results. Note that small discordances can occur because of differences in software platforms and computational modules. As explained in Section 3, the unadjusted method might provide biased results and the proposed method could adjust the biases via the proposed simple network meta-regression modeling.

Notably, the inconsistency test of treatment pair ARB vs. CT was significant, mainly

because this network involved the Jikei Heart Study, the main paper of which was retracted from *Lancet* because of misconduct (Mochizuki et al., 2007); some falsifications appeared in the published data, and the treatment effect of ARB might have been overestimated. Both of the sidesplitting results showed that, compared with the indirect comparison evidence, the direct comparison evidence indicated a significantly large treatment effect of ARB. The Jikei Heart Study was also detected as an outlying trial in the study of Noma et al. (2020).

4.2 Diabetes data

Elliott and Meyer (2007) reported a network meta-analysis that assessed the effects of antihypertensive drugs on incident diabetes. 22 clinical trials (total participants: 143,153) comparing five antihypertensive drug classes [ACE, ARB, BB, CCB, and DD] and placebo were involved. The network plot is presented in Figure 1(b). The outcome was incidence of diabetes and we adopted the OR as the effect measure, in accordance with the original analyses of Elliott and Meyer (2007).

Table 2 shows the results of sidesplitting; the same two methods with Section 4.1 were applied to this network meta-analysis. This network involves 4 three-arm trials (AASK, ALLHAT, MRC-E, and STOP-2) and most of the six treatments (except for ARB) were included in any of these trials. Thus, the two methods provided substantially different estimates for the direct and indirect evidence and their differences for most of the treatment pairs. Especially, the differences of DD vs. BB and ACE vs. CCB were relatively large. Although the results of inconsistency tests were not altered, the possible biases should be carefully considered. For the inconsistency tests, those of ACE vs. BB and BB vs. placebo were significant ($P < 0.05$) for both of the two approaches. The reasons were not clear, but these results should be useful information to interpret the overall results.

5. Concluding remarks

Network meta-analyses and their evidence have been widely utilized in public health, clinical practice, health technology assessment, and policy making. If misleading evidence has been reported and the checking methods have been inaccurate or insufficient, the impact might be enormous. Inconsistency evaluations are critical processes in good practices of these studies (Hutton et al., 2015). Sidesplitting has been one of the primary analysis tools, and the potential biases resulting from the adoption of inadequate modeling, as discussed in Section 3, should be carefully addressed. In this article, we provided an effective adjustment method based on the network meta-regression framework. It can be implemented using well-established multivariate meta-regression methods if the contrast-based approach is adopted, and it can be similarly adapted to the arm-based approach by the same regression modeling (White et al., 2012). In network meta-analysis practice, the proposed method would be an effective tool for preventing misleading results and providing precise evidence.

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Table 1. Results of the sidesplitting analysis for the network meta-analysis of heart failure data [†].

	Unadjusted method				Network meta-regression approach			
	Direct	Indirect	Difference	*P*-value	Direct	Indirect	Difference	*P*-value
Placebo vs. ACE	−0.276 (0.143)	−0.407 (0.131)	0.131 (0.194)	0.499	−0.276 (0.143)	−0.407 (0.126)	0.131 (0.191)	0.491
Placebo vs. ARB	−0.155 (0.131)	−0.440 (0.161)	0.284 (0.204)	0.163	−0.155 (0.131)	−0.440 (0.137)	0.284 (0.189)	0.133
Placebo vs. CCB	−0.392 (0.180)	−0.100 (0.093)	−0.292 (0.202)	0.148	−0.394 (0.185)	−0.103 (0.103)	−0.291 (0.211)	0.168
Placebo vs. DD	−0.982 (0.261)	−0.428 (0.094)	−0.554 (0.277)	0.046	−0.982 (0.272)	−0.426 (0.116)	−0.556 (0.296)	0.060
AB vs. DD	−0.705 (0.120)	−0.740 (2085.5)	0.035 (2085.5)	1.000	−0.705 (0.120)	−1.848 (66.67)	1.143 (66.67)	0.986
ACE vs. ARB	0.051 (0.145)	0.061 (0.113)	−0.010 (0.184)	0.956	0.051 (0.145)	0.061 (0.112)	−0.010 (0.184)	0.956
ACE vs. BB	−0.182 (0.458)	0.235 (0.125)	−0.417 (0.475)	0.380	−0.182 (0.458)	0.235 (0.125)	−0.417 (0.475)	0.380
ACE vs. CCB	0.172 (0.099)	0.158 (0.105)	0.014 (0.132)	0.916	0.193 (0.127)	0.127 (0.133)	0.066 (0.184)	0.720
ACE vs. CT	0.056 (0.123)	0.121 (0.141)	−0.065 (0.180)	0.719	0.054 (0.144)	0.130 (0.155)	−0.075 (0.212)	0.721
ACE vs. DD	−0.123 (0.094)	−0.446 (0.188)	0.323 (0.202)	0.109	−0.089 (0.114)	−0.465 (0.203)	0.376 (0.233)	0.106
ARB vs. BB	0.057 (0.150)	0.252 (0.166)	−0.195 (0.224)	0.384	0.057 (0.179)	0.238 (0.192)	−0.182 (0.262)	0.488
ARB vs. CCB	0.136 (0.147)	0.093 (0.106)	0.043 (0.182)	0.813	0.136 (0.147)	0.093 (0.105)	0.043 (0.181)	0.813
ARB vs. CT	0.400 (0.192)	−0.093 (0.112)	0.493 (0.224)	0.027	0.400 (0.181)	−0.064 (0.081)	0.460 (0.199)	0.021
BB vs. CCB	−0.176 (0.149)	0.109 (0.160)	−0.284 (0.219)	0.193	−0.176 (0.242)	0.149 (0.245)	−0.325 (0.345)	0.345
CCB vs. CT	−0.123 (0.102)	0.029 (0.166)	−0.151 (0.191)	0.428	−0.156 (0.110)	0.071 (0.170)	−0.227 (0.202)	0.263
CCB vs.DD	−0.355 (0.106)	−0.300 (0.181)	−0.054 (0.199)	0.785	−0.361 (0.132)	−0.304 (0.202)	−0.057 (0.241)	0.814

[†] Estimates and standard errors are presented. Abbrebiations: α-blocker (AB), angiotensin-converting enzyme inhibitor (ACE), angiotensin II receptor blocker (ARB), β-blocker (BB), calcium channel blocker (CCB), conventional treatment (CT), and diuretic (DD).

Table 2. Results of the sidesplitting analysis for the network meta-analysis of diabetes data [†].

	Unadjusted method				Network meta-regression approach			
	Direct	Indirect	Difference	*P*-value	Direct	Indirect	Difference	*P*-value
DD vs. ACE	−0.439 (0.112)	−0.376 (0.107)	−0.063 (0.146)	0.663	−0.416 (0.118)	−0.412 (0.113)	−0.004 (0.163)	0.981
DD vs. ARB	−2.116 (1.072)	−0.457 (0.103)	−1.659 (1.077)	0.123	−2.116 (1.072)	−0.457 (0.102)	−1.659 (1.077)	0.123
DD vs. BB	0.132 (0.150)	−0.143 (0.096)	0.274 (0.173)	0.112	0.020 (0.150)	−0.090 (0.089)	0.110 (0.175)	0.531
DD vs. CCB	−0.191 (0.110)	−0.283 (0.104)	0.091 (0.143)	0.523	−0.204 (0.117)	−0.267 (0.114)	0.064 (0.163)	0.697
DD vs. Placebo	−0.427 (0.132)	−0.190 (0.105)	−0.237 (0.164)	0.148	−0.412 (0.134)	−0.203 (0.108)	−0.209 (0.173)	0.226
ACE vs. BB	0.186 (0.084)	0.461 (0.082)	−0.274 (0.108)	0.011	0.163 (0.087)	0.496 (0.090)	−0.333 (0.125)	0.008
ACE vs. CCB	0.239 (0.103)	0.116 (0.086)	0.123 (0.118)	0.299	0.227 (0.120)	0.138 (0.103)	0.089 (0.158)	0.574
ACE vs. Placebo	0.204 (0.085)	−0.014 (0.110)	0.219 (0.140)	0.117	0.204 (0.084)	−0.014 (0.110)	0.219 (0.139)	0.115
ARB vs. BB	0.311 (0.151)	0.456 (0.113)	−0.144 (0.189)	0.444	0.311 (0.151)	0.456 (0.112)	−0.144 (0.188)	0.443
ARB vs. CCB	0.242 (0.138)	0.229 (0.119)	0.012 (0.182)	0.946	0.242 (0.138)	0.229 (0.117)	0.012 (0.181)	0.945
ARB vs. Placebo	0.224 (0.125)	0.152 (0.132)	0.071 (0.182)	0.694	0.224 (0.125)	0.152 (0.132)	0.071 (0.181)	0.694
BB vs. CCB	−0.215 (0.064)	−0.066 (0.100)	−0.149 (0.117)	0.203	−0.213 (0.067)	−0.070 (0.109)	−0.142 (0.128)	0.265
BB vs. Placebo	−0.862 (0.227)	−0.150 (0.076)	−0.712 (0.234)	0.002	−0.800 (0.260)	−0.155 (0.077)	−0.645 (0.271)	0.017
CCB vs. Placebo	−0.150 (0.161)	−0.008 (0.090)	−0.142 (0.185)	0.441	−0.150 (0.161)	−0.008 (0.087)	−0.142 (0.183)	0.437

[†] Estimates and standard errors are presented. Abbrebiations: α-blocker (AB), angiotensin-converting enzyme inhibitor (ACE), angiotensin II receptor blocker (ARB), β-blocker (BB), calcium channel blocker (CCB), conventional treatment (CT), and diuretic (DD).

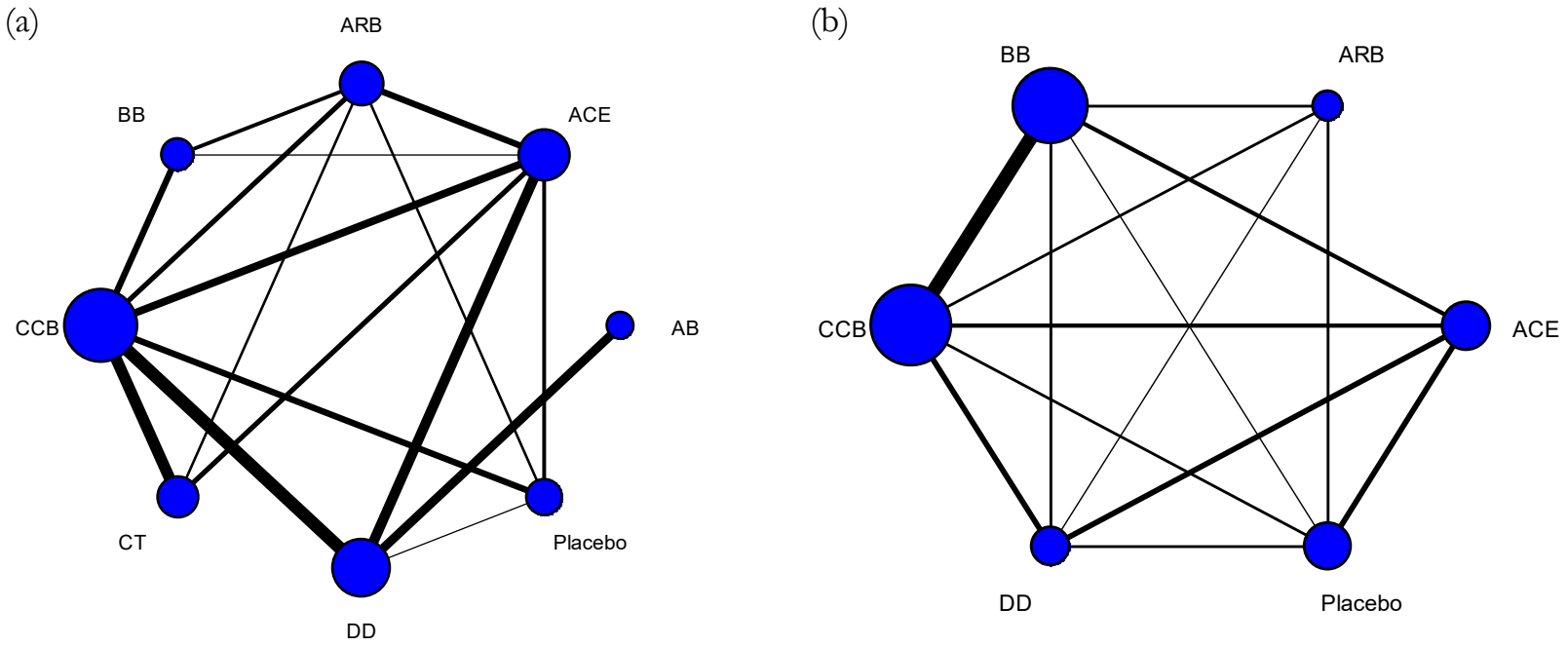

Figure 1. Network plot for the network meta-analysis of (a) heart failure data, and (b) diabetes data.