

ตัวอย่างการวิเคราะห์อภิมานเครือข่ายด้วยซอฟต์แวร์ R สำหรับบริบทการวิจัยทางการแพทย์และวิทยาศาสตร์สุขภาพ

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บทคัดย่อ

งานวิจัยที่ใช้การวิเคราะห์อภิมานเครือข่าย หรือ network meta-analysis (NMA) ได้รับการตีพิมพ์อย่างกว้างขวางในระดับสากล ในบริบทไทยนักวิจัยไทยบางท่านได้ตีพิมพ์ผลงานการวิเคราะห์อภิมานแบบดั้งเดิม ซึ่งเป็นการวิเคราะห์อภิมานตัวแปรเดียว อาจมีนักวิจัยไทยเพียงไม่กี่คนที่ตีพิมพ์ผลงานโดยใช้ NMA โดยเฉพาะอย่างยิ่งในสาขาการแพทย์และวิทยาศาสตร์สุขภาพ นอกจากนี้ ยังมีนักวิจัยไทยเพียงไม่กี่คน (ถ้ามี) ที่ใช้ซอฟต์แวร์ R เพื่อทำการวิจัยและตีพิมพ์ สิ่งนี้สามารถมองได้ว่าเป็นช่องว่างเชิงการปฏิบัติ ดังนั้น วัตถุประสงค์ของการศึกษานี้ เพื่อแสดงให้เห็นถึงวิธีการดำเนินการ NMA โดยใช้ซอฟต์แวร์ R เป็นโปรแกรมฟรีและเป็นที่ยอมรับทั่วโลก และสามารถวิเคราะห์ NMA ได้อย่างสมบูรณ์ ในแง่ของวิธีการศึกษานี้ได้ใช้ข้อมูลทุติยภูมิเพื่อแสดงการวิเคราะห์ชุดข้อมูลเรียกว่า Dogliotti2014 ซึ่งมีให้ใช้งานฟรีในซอฟต์แวร์ R วิธีการวิเคราะห์ NMA ใช้เป็นวิธีทางสถิติในการวิเคราะห์ข้อมูลดังกล่าว ในแง่ของการวิเคราะห์ มีแสดงขั้นตอนและรหัส R เพื่อแสดงการวิเคราะห์ NMA ในแง่ของผลลัพธ์ของการศึกษากล่าวได้ว่าการรักษาที่แตกต่างกัน ให้ผลลัพธ์ของการรักษาที่แตกต่างกัน ซึ่งได้ข้อสรุปว่าควรใช้ยาในกลุ่มต้านลิ่มเลือด หรือ Anti-thrombotic drug ที่ดีที่สุด เพื่อป้องกันโรคหลอดเลือดสมองสำหรับผู้ป่วยที่เสี่ยงต่อการเกิดลิ่มเลือดอุดตัน โดยสรุป ซอฟต์แวร์ R มีความสามารถในการดำเนินการ NMA อย่างสมบูรณ์ จึงขอแนะนำนักวิจัยด้านการแพทย์และวิทยาศาสตร์สุขภาพไทยใช้ซอฟต์แวร์ R เพื่อวิเคราะห์ NMA สำหรับการวิจัยและตีพิมพ์ทั้งในประเทศและต่างประเทศต่อไป

คำสำคัญ: ซอฟต์แวร์ R; การวิเคราะห์อภิมาน; การวิเคราะห์อภิมานเครือข่าย; การวิจัยทางการแพทย์และวิทยาศาสตร์สุขภาพ

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An example analysis of network meta-analysis using R software for medical and health science research contexts

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Abstract

Research utilizing network meta-analysis (NMA) is widely published internationally. In the Thai context, some Thai researchers have published traditional meta-analysis works, referring to univariate meta-analysis. However, few researchers have published their works using NMA, particularly in the field of medical and health science. Additionally, few Thai researchers (if any) utilize the R software to conduct NMA for their research and publications. This indicates a notable practice gap. Therefore, the objective of this study is to demonstrate how to conduct NMA using the R software. R is freely available, globally accepted, and fully capable of analyzing NMA. Methodologically, secondary data is employed to illustrate our analysis. The dataset utilized is Dogliotti2014, which is freely available in R. NMA serves as the statistical method to analyze the data. In terms of analysis, the R procedures and codes are provided to demonstrate how to conduct NMA. Regarding results, different treatments (medications) yield varying outcomes. This leads to the conclusion that Antithrombotic drugs are the most effective in preventing strokes and should be considered for patients at risk of thromboembolism. In conclusion, the R software is fully capable of conducting comprehensive NMA. It is recommended that Thai medical and health science researchers utilize the R software for conducting NMA in their research and publications at both national and international levels.

Keywords: R software; meta-analysis; network meta-analysis; medical and health science

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Introduction

In the Thai academic research context, some Thai researchers conducted (traditional) meta-analyses, but not network meta-analyses (NMA). Here, a traditional meta-analysis is referred to as a univariate meta-analysis (UMA). An example of a traditional meta-analysis conducted by Thai researchers is a paper titled “An application of R on analyzing meta-analysis for research: health science context”.¹ However, few Thai researchers have conducted network meta-analyses. There is some evidence that Thai researchers discussed network meta-analysis but only in principle, not actually carrying out the actual network meta-analysis. A case in point is a study in the medical field titled “Network meta-analysis: the concept and its applications for healthcare professionals”.² In addition, there is one work that goes beyond discussing network meta-analysis in principle, which is titled “Network meta-analysis of teaching method influencing mathematics achievement of students”.³ This work conducted a network meta-analysis in the field of education, but did not specify which software they used to carry out the NMA. Based on our literature review, it can be concluded initially that Thai researchers have not used R to conduct network meta-analysis in the medical and health science contexts in Thailand. This could be viewed as a practice gap. This article, thus, attempts to fill such a gap by illustrating how to use R to conduct NMA. This is our contribution to the body of literature. The example used in this article applies to the medical and health science

research contexts. We are using an R package called netmeta package⁴ as the main package to conduct our example analysis of network meta-analysis. Other R packages used in this article will be introduced later, where appropriate.

Objective

The objective of this paper is to illustrate how to conduct network meta-analysis using R.

Literature review

This literature review section comprises four major topics: traditional meta-analysis, network meta-analysis, comparing direct and indirect effects in NMA, and comparison between UMA (traditional meta-analysis) vs. NMA.

The traditional meta-analysis

When performing meta-analyses of clinical trials or other types of intervention studies, we usually estimate the true effect size of one specific treatment (see Figure 1 and Table 1). We include studies in which the same type of treatment/intervention is compared between experimental groups and control (placebo) groups. All else being equal, this allows us to assess the effectiveness of treatment (A), in favor of the experimental group or control group. Table 1 summarizes the structure of the traditional meta-analysis. This is also called a univariate meta-analysis (assessing one treatment/intervention).



Treatment A = Apixaban

Figure 1 A single treatment, treatment A = Apixaban

Table 1 A structure of the traditional (univariate) meta-analysis

Study	Sample size	Treatment/ Intervention	Effect size (proportion)	
			Experimental group	Control group
Study 1	n_1	A	event/total _{e1}	event/total _{c1}
Study 2	n_2	A	event/total _{e2}	event/total _{c2}
Study 3	n_3	A	event/total _{e3}	event/total _{c3}
Study 4	n_4	A	event/total _{e4}	event/total _{c4}
Study 5	n_5	A	event/total _{e5}	event/total _{c5}
Study 6	n_6	A	event/total _{e6}	event/total _{c6}

Network meta-analysis

Traditional meta-analysis only measures one treatment effect, however, in reality, the treatment effects can be multiple in nature. In our example, a stroke can be treated with different types of treatments (see Figure 2 and Table 2). This often means that traditional meta-analyses cannot be used to establish solid evidence on the relative effectiveness of several treatments. This led

to the development of NMA. Let's examine Table 2. We are interested in more than one treatment effect. In addition, we are also interested in which treatment is the most effective in dealing with a stroke. In short, NMA is interested in the effects of more than one treatment/intervention on experimental groups, while using control groups as benchmarks.

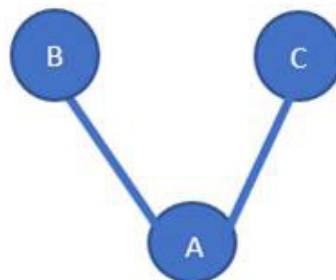


Figure 2 Treatments A = Apixaban, B = Aspirin, and C = Aspirin + Clopidogrel

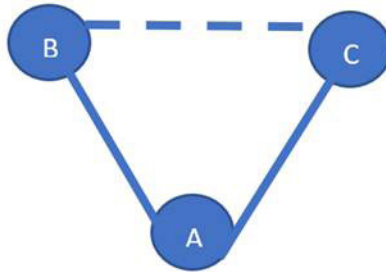
Table 2 Network meta-analysis

Study	Sample size	Treatment/ Intervention	Effect size (proportion)	
			Experimental group	Control group
Study 1	n_1	A	event/total _{e1}	event/total _{c1}
Study 2	n_2	A	event/total _{e2}	event/total _{c2}
Study 3	n_3	B	event/total _{e3}	event/total _{c3}
Study 4	n_4	B	event/total _{e4}	event/total _{c4}
Study 5	n_5	C	event/total _{e5}	event/total _{c5}
Study 6	n_6	C	event/total _{e6}	event/total _{c6}

While direct comparisons between two or more treatments may not exist, indirect evidence is typically available. Different treatments may have been evaluated in separate trials, but all of these trials may have used the same control group. For example, it is possible that two treatments were never compared directly, but that the effects of both treatments compared to the control (placebo) groups have been studied extensively. The comparisons between direct and indirect effects are clearly explained in the next section. Finally, for a historical development of NMA, please consult the work called “The development of network meta-analysis”.⁵

Comparing direct and indirect effects in NMA

In the traditional meta-analysis, we are only interested in one experimental group, for example, the effect of A = apixaban (on stroke). In other words, we only directly compare the effects of the experiment groups versus those of the control groups. In NMA, both direct and indirect effects are permitted. Let’s illustrate this point. The first direct comparison is the comparison of the effects of A’s against B’s. The second direct comparison is the comparison of the effects of A’s against C’s. However, there is also an indirect comparison. The indirect comparison is between B against C. Thus, the effect of B-C could be indirectly compared through B-A versus C-A. For more information on the direct and indirect effects of using NMA, please consult the work of Harrer.⁶



Treatments A = Apixaban, B = Aspirin, and C = Aspirin + Clopidogrel

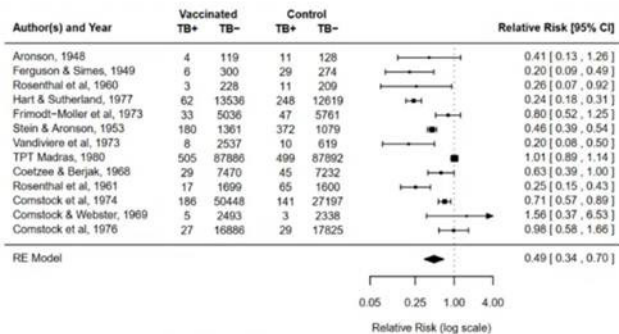
Figure 3 Direct and indirect effects comparisons

Comparing between UMA (traditional meta-analysis) vs. NMA

Let's start with UMA on the left side of Figure 4. UMA only uses one treatment. Based on Figure 4, the treatment for tuberculosis is isoniazid INH. This study comprises fifteen primary studies⁷. The individual effect sizes are relative risks. The pooled effect size is also a relative risk. On the other hand, NMA has multiple treatments. This is on the right side of Figure 4⁸. For

example, schizophrenia can be treated using different treatments (medications), for example, Haloperidol, Divalproex, and Carbamazepine. In short, NMA allows multiple treatments in a single meta-study. In summary, the difference between UMA vs. NMA lies in the number of treatments. UMA only uses one treatment in a single meta-analysis study. On the other hand, NMA uses multiple treatments in a single meta-analysis study.

Univariate meta-analysis (UMA)



Network meta-analysis (NMA)

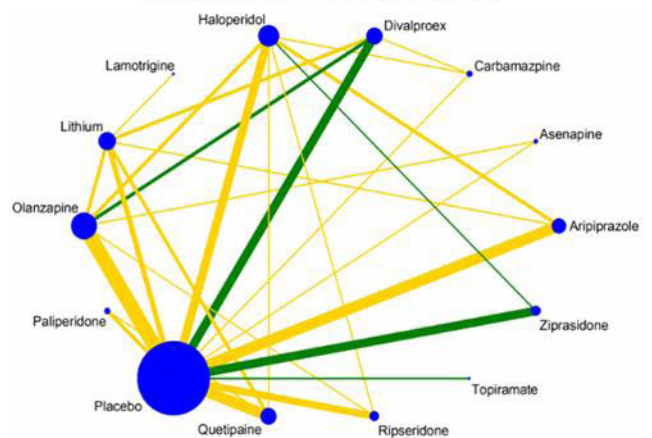


Figure 4 Comparing between traditional meta-analysis, UMA vs. NMA

Material and Methods

An example analysis of NMA using R

An example analysis uses the data from the article called “Current and new oral antithrombotics in non-valvular atrial fibrillation: a network meta-analysis of 79,808 patients”.⁹ They examined the effectiveness of antithrombotic treatments to prevent strokes in patients with non-valvular atrial fibrillation. These patients belong to the experimental group. They presumed that antithrombotic therapy reduces strokes, embolisms, and mortality in patients with atrial fibrillation (AF). Thus, they performed a meta-analysis comparing treatments (experimental groups) against the control (placebo) groups using a pairwise comparison statistical method. They are interested in whether these treatments reduce the risk of stroke. The emphasis here is comparing the effects of multiple treatments, not just one treatment.

Dataset

The example dataset (Dogliotti2014) is publicly available in the netmeta package. Based on Figure 5, the data is obtained from 19 trials (under the id column) which use eight treatments (including placebo, under the treatment column) with a total of 79,808 samples. A detailed description of the dataset is available at R: “Studies on Antithrombotic Treatments to Prevent Strokes”.¹⁰ Based on Figure 5, there are five columns. The first column is study (study label). The second column is id (study ID). The third column is treatment. The fourth column is stroke (number of strokes). Finally, the last column is the total (number of individuals/subjects). Stroke (event)/total (n, sample size) leads to proportions (effect sizes). There are 44 entries (rows). But, Figure 5 only shows the first 11 rows. In summary, we used Dogliotti2014 as an example dataset to run the NMA in this paper.

	study	id	treatment	stroke	total
1	AFASAK-I 1989	1	VKAs	9	335
2	AFASAK-I 1989	1	Aspirin	16	336
3	AFASAK-I 1989	1	Placebo/Control	19	336
4	BAATAF 1990	2	VKAs	3	212
5	BAATAF 1990	2	Placebo/Control	13	208
6	CAFA 1991	3	VKAs	6	187
7	CAFA 1991	3	Placebo/Control	9	191
8	SPAF-I 1991	4	VKAs	8	210
9	SPAF-I 1991	4	Aspirin	24	552
10	SPAF-I 1991	4	Placebo/Control	42	568
11	SPINAF 1992	5	VKAs	7	260

Showing 1 to 12 of 44 entries, 5 total columns

Figure 5 The dataset

Results

R software and packages used for NMA

R is a language and environment for statistical computing and graphics.¹¹ To use R, you need to install R base on your computer first. Then, you could also install RStudio.¹² This is optional, but strongly recommended. RStudio is a user interface that runs on top of R (computing engine). Finally, you need to install the R packages you wish to use. For NMA, there is more than one R package that could run such an analysis. This paper mainly used the netmeta package, with the addition of a dplyr package also.¹³

R codes for NMA analysis

Based on Figure 6, there are 13 lines. Lines 1-2 call the packages used for NMA at hand. Here, we use two packages: the netmeta

and dplyr packages. Line 3 specifies which built-in data is used. The dataset (Dogliotti2014) is used, which comes with the netmeta package. Line 4 is intentionally left blank. Lines 5-6 arrange the treatments to be compared using the pairwise comparison method. The summary measure (sm) is OR (odds ratio) because the raw data is, as already mentioned, proportional. Line 7 initiates the analysis of the data set using NMA. Line 8 generates NMA text outputs. Line 9 is a command to generate an NMA graph. Line 10 displays the NMA graph (forest plot, default version). Lines 11-12 pull effect sizes of individual studies using inverse variance and Mantel-Haenszel methods. Finally, line 13 displays the NMA forest plot (extended version).


```
1 library(netmeta)
2 library(dplyr)
3 data("Dogliotti2014")
4
5 pw1 <- pairwise(treat = treatment, n = total,
6 event = stroke,
7 studlab = study, data = Dogliotti2014, sm =
8 "OR")
9 net1 <- netmeta(pw1, ref = "plac")
10 net1
11 netgraph(net1, seq = "optimal", number = TRUE)
12 forest(net1)
13 net1.mh <- netmetabin(pw1, ref = "plac")
14 nb2 <- netbind(net1, net1.mh, random = FALSE,
15 name = c("Inverse variance", "Mantel-Haenszel"))
16 forest(nb2)
```

Figure 6 Code for instructing R to run NMA

Text outputs, NMA, R

This section summarizes the text outputs of NMA. The outputs can be divided into four major sections (see Figure 7). The first section includes general information, including the number of studies ($k=19$), number of pairwise comparisons ($m=27$), number of observations ($o=79733$), and number of designs (10) included in the NMA at hand. The second section includes the results of the common (fixed) effects model (measuring treatment weights). The odds ratio (OR) is used as the effect size for individual treatment effect sizes. For example, in the common (fixed) effect model treatment A has an OR value of 0.3303, representing its treatment effect size. The third part includes the results of the random effects model (treatment weights). Finally, the fourth part includes results on heterogeneities of the NMA study at hand, which includes two subsections. The first subsection is quantifying heterogeneity/inconsistency. Note that the I^2 is low (14.7%), which is agreeable as an I^2 value closer to 0% signifies lower heterogeneity, which is more

desirable. The second subsection is tests of heterogeneity. For this section, we do not want inconsistency between designs to be significant.

In summary, based on Figure 7, all treatment effect sizes are significant in both common (fixed) and random models. If the pooled effect sizes are assumed to be close, the researcher may wish to use the fixed model to combine (pool) the individual studies' effect sizes. On the other hand, if the pooled effect sizes are assumed to be far apart, the researcher may wish to use the random model to combine (pool) the individual studies' effect sizes. These can be confirmed by the CI and p-values provided in Figure 7. With an I^2 value of 14.7%, the quantified heterogeneity is low. Test results of heterogeneity within designs and inconsistency between designs are non-significant. These are also desirable because we do not typically want the heterogeneities to be significant. If the heterogeneities are not significant, it implies that the 19 studies used to conduct the NMA analysis at hand are similar.

```

Number of studies: k = 19
Number of pairwise comparisons: m = 27
Number of observations: o = 79733
Number of treatments: n = 8
Number of designs: d = 10

Common effects model

Treatment estimate (sm = 'OR', comparison: other treatments vs 'Placebo/Control'):
      OR      95%-CI      z      p-value
Apixaban      0.3303 (0.2500-0.4365) -7.79 < 0.0001
Aspirin       0.7768 (0.6254-0.9649) -2.28  0.0224
Aspirin+Clopidogrel 0.5753 (0.4462-0.7418) -4.26 < 0.0001
Dabigatran 110mg 0.3801 (0.2759-0.5236) -5.92 < 0.0001
Dabigatran 150mg 0.2662 (0.1906-0.3717) -7.77 < 0.0001
Placebo/Control .          .          .          .
Rivaroxaban   0.3205 (0.2353-0.4366) -7.21 < 0.0001
VKAs          0.4117 (0.3236-0.5238) -7.22 < 0.0001

Random effects model

Treatment estimate (sm = 'OR', comparison: other treatments vs 'Placebo/Control'):
      OR      95%-CI      z      p-value
Apixaban      0.3320 (0.2362-0.4667) -6.35 < 0.0001
Aspirin       0.7648 (0.5994-0.9757) -2.16  0.0310
Aspirin+Clopidogrel 0.5909 (0.4268-0.8181) -3.17  0.0015
Dabigatran 110mg 0.3808 (0.2530-0.5730) -4.63 < 0.0001
Dabigatran 150mg 0.2666 (0.1753-0.4057) -6.17 < 0.0001
Placebo/Control .          .          .          .
Rivaroxaban   0.3211 (0.2152-0.4790) -5.56 < 0.0001
VKAs          0.4124 (0.3159-0.5384) -6.51 < 0.0001

Quantifying heterogeneity / inconsistency:
tau^2 = 0.0134; tau = 0.1158; I^2 = 14.7% (0.0%-51.2%)

Tests of heterogeneity (within designs) and inconsistency (between designs):
      Q      d.f.      p-value
Total      18.76      16      0.2815
within designs 13.17      11      0.2827
Between designs 5.59       5      0.3480

```

Figure 7 Text outputs, NMA, R

NMA plot, NMA, R

Figure 8 is the NMA plot output generated by the netmeta package. There are two graphical components to the graph. The first component is the node which is a red circle. The second component is the edge which is a line connecting the nodes. At each node, there are two descriptions. The first description is the name of the treatment. The second description is the sample size of that particular study. Lastly, the sizes of red circles represent the sizes of those treatment effects. In the 19 studies included in the network-meta analysis, there were eight types of treatments (including the placebo/control). There were 27 pairwise comparisons. Let's start with VKAs

(n=28672) and dabigatran 110 mg (n=6015) were compared once (labeled on the edge of the two treatments). To elaborate, out of 28672 VKA samples, 6015 VKA samples were compared against 6015 dabigatran 110 mg samples. The same logic applies to the remaining comparisons. Following clockwise, VKAs (n=28672) and dabigatran 150 mg (n=6075) were compared once. VKAs (n=28672) and placebo/control (n=2482) were compared six times. VKAs (n=28672) and aspirin (n=10372) were compared eight times. VKAs (n=28672) and apixaban (n=11928) were compared once. VKAs (n=28672) and aspirin + clopidogrel (n=7107) were compared once. VKAs (n=28672) and rivaroxaban (n=7081) were compared

once. Dabigatran 100 mg (n=6015) and dabigatran 150 mg (n=6076) were compared once. Placebo/control (n=2482) and aspirin (n=10372) were compared five times. Finally, aspirin (n=10372) and apixaban (n=11928)

were compared once. The reason sample sizes (n) are different is because all 19 studies are included together, and each treatment is compared with one or more treatments. All these are captured in Figure 8.

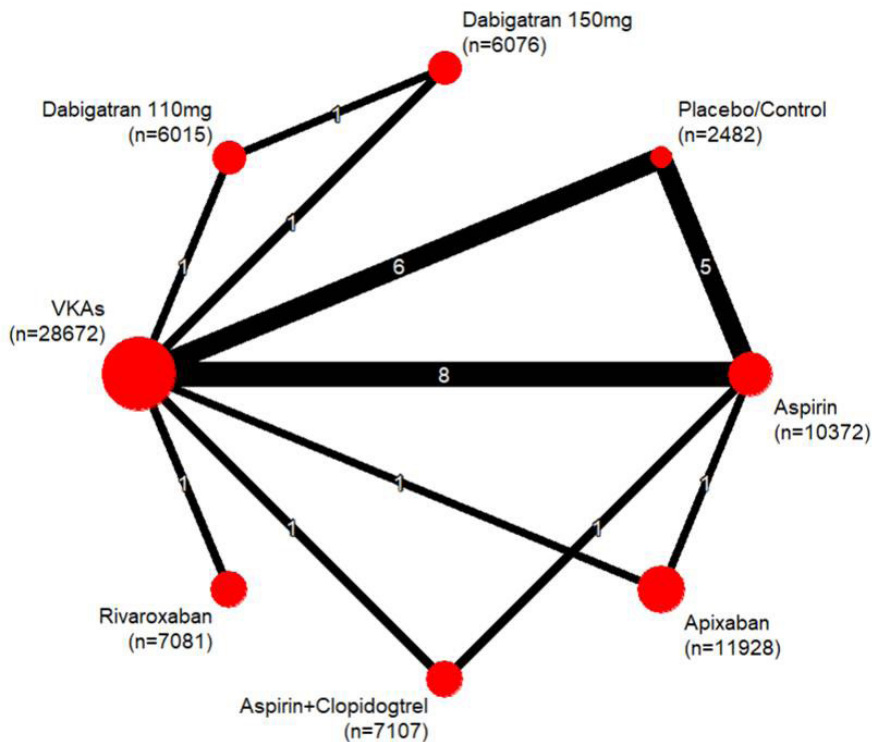


Figure 8 Graphical NMA plot, R

Forest plots, NMA, R

There are two types of forest plots presented here. The first one is the regular version (see Figure 9) and the second is the extended version (see Figure 10). Let's start with the short version. Figure 9 labels treatment against placebo/control at the top. All treatments are under the treatment column. The random effects model is used to pool the effect sizes of individual studies.

The results indicate that treatments are more effective compared to the placebos, as indicated by the OR values representing individual effect sizes. A 95% confidence interval accompanies each effect size. An effect size is the weight difference between treatment vs. control. Please note that the limitation of R is that it does not have a convenient way to produce a League Table (ranking). But, based on Figure 8, the ranking

can be done by using ORs, for example, the lowest (0.27) OR is Dabigatran 150 mg., the lower the OR the better. Thus, it can be concluded that Dabigatran 150 mg. is the most effective treatment. In addition, the metafor

package also offers a way to rank the treatment outputs. The audience is encouraged to explore the package for this ranking of treatment outputs.

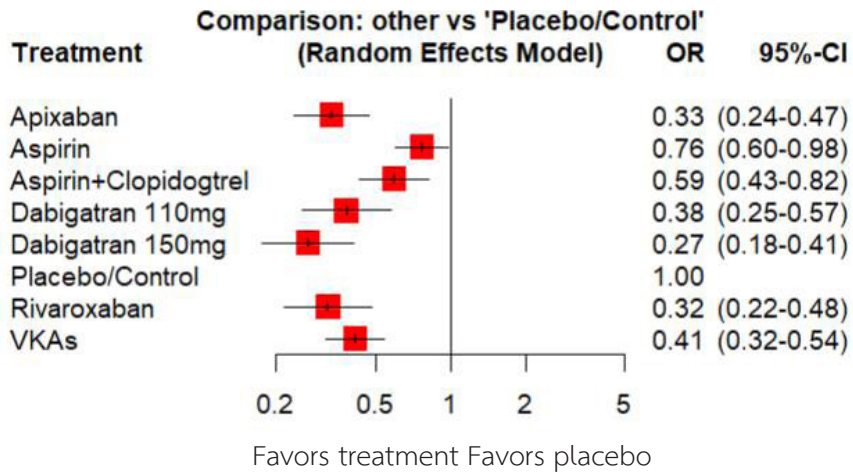


Figure 9 Forest plot, NMA, R

On the long version of the forest plot (see Figure 10), at the top, the Figure labels “Comparison: other vs ‘Placebo/Control’”. Here, other refers to different types of

treatments. All treatments are on the left column. Under each treatment, there are methods used to pull the effect sizes of individual studies.

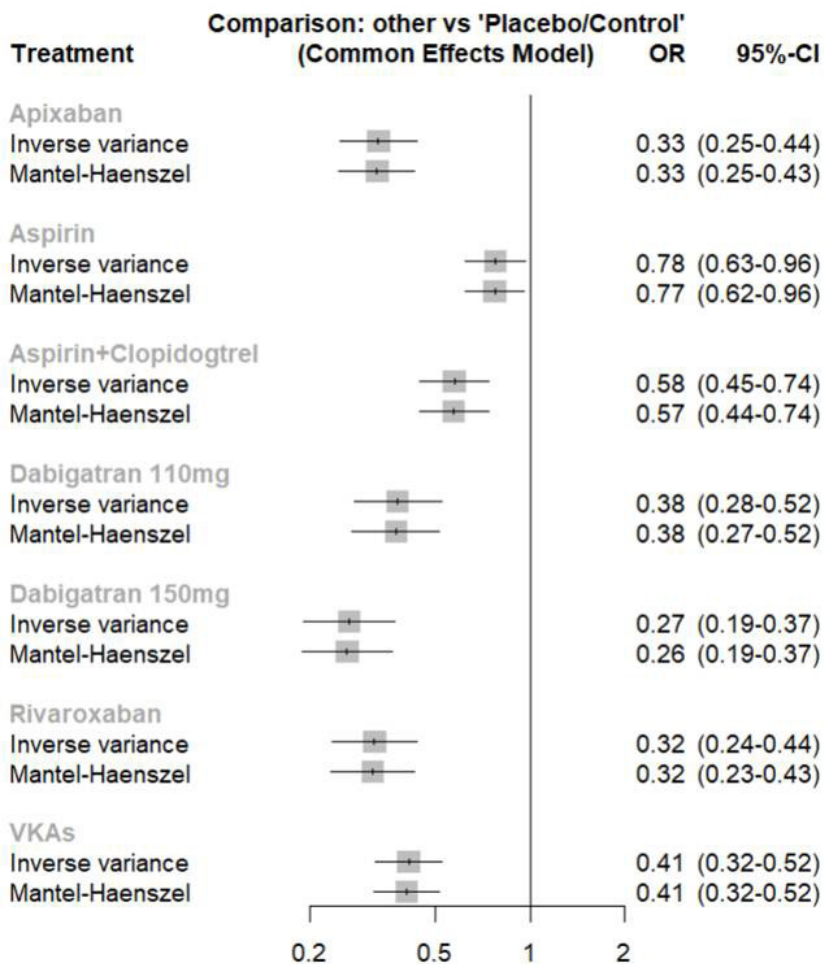


Figure 10 Forest plot, illustrating treatment effects using Inverse variance and Mantel-Haenszel methods, NMA, R

The first one is the inverse variance method. The second one is the Mantel-Haenszel method. The zero-effect line (or the line of no effect, value = 1) lies in the middle of Figure 10. All effect sizes of individual studies are under OR and all confidence intervals are under the 95%-CI column.

Discussion

The objective of this paper is to demonstrate how to conduct NMA using R.

First, the dataset was from the article called “Current and new oral antithrombotics in non-valvular atrial fibrillation: a network meta-analysis of 79,808 patients”. R can read an Excel file. However, the dataset can be brought into R in multiple ways. Audiences are encouraged to explore further how to bring in a dataset into R. The main R package used is the netmeta package. The codes were provided for audiences to practice conducting NMA identical to this paper. The text outputs

were generated. In addition, the required graphical outputs (e.g. Forest plot) also were generated. The results of analyses are consistent with the work of Dogliotti A, Paolasso E, & Giugliano R. P.⁷

Conclusion

This article has illustrated how to conduct NMA analysis using R. As illustrated, R is fully capable of conducting NMA. R is free and accepted worldwide. However, R is not the only software that can run NMA. There are other popular (proprietary) software packages, for example, STATA¹⁴ and CMA¹⁵. International researchers use R to conduct their NMA analyses and publications. Likewise, Thai medical and health science researchers can also use R to conduct their NMA on their chosen sample data and publish their research in the medical and health science contexts and beyond. Thus, we strongly encourage Thai researchers in the medical and health science fields in Thailand to adopt R as an additional (or main) platform to perform NMA analysis for their research and publications.

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