International Journal of Clinical Trials
Indani A et al. Int J Clin Trials. 2016 Nov;3(4):254-266
http://www.ijclinicaltrials.com
pISSN 2349-3240 | eISSN 2349-3259
DOI: http://dx.doi.org/10.18203/2349-3259.ijct20163965

Original Research Article

RADHIKa: Ratio-based analysis deriving basis for comparison of historical, parallel or interdependent reported ken of studies - a novel method for comparing interconnected and disconnected data sets

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Received: 28 July 2016
Revised: 02 August 2016
Accepted: 27 September 2016

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ABSTRACT

Background: Control arm selection is difficult for devices clinical trial due to the complexity and uniqueness of every device. Therefore, we propose RADHIKa - ratio-based analysis deriving basis for comparison of historical or parallel interdependent reported ken of studies that can be used to compare the relative performance or safety of independent studies.
Methods: A ken (set of studies) has four basic prerequisites to qualify for RADHIKa. Comparison and calculations are based upon assessment of two major factors, effect and influence. RADHIKa is a three step methodology that includes construction of ken, ratio calculations, and plotting box plots.
Results: Inferences of RADHIKa has ratio and box plot interpretation. When the RADHIKa ratio is 1 or close to 1, both the control arm and the evaluation arm are equal. The box plot indicates the tendency of the parameter along with the difference in two arms. When the dark box is above line of unity, it indicates that the evaluation arm has performed better or if it's vice versa the predicate has performed better. The tails of the box indicate significance of the outcome in each direction.
Conclusions: RADHIKa method is a useful tool to compare the relative performance or safety of independent studies, especially single arm device studies.

Keywords: Meta-analysis, Medical device clinical trials, Medical devices comparison, Statistics, Research methodology, Clinical evaluation medical devices, Substantial equivalence

INTRODUCTION

Control arm selection is an important aspect of a clinical trial. However, in medical device trials control selection becomes difficult due to the complexity and uniqueness of every device. For first-in-class devices, surgery or drugs are often used as the control arm, due to unavailability of predicate devices. For example, studies comparing hormone eluting intrauterine device for dysmenorrhea with surgery, ASD closure surgery with trans-catheter device, or many studies having stents compared with coronary artery bypass graft surgery.[1-4] In such cases, correct and clear comparison is not possible because criteria of failure are different for devices, drugs and medical procedures. In some device studies, such as STEALTH, RAVEL and a study comparing harmonic scalpel with Ligasure device, previous versions of the devices are used in the control arm to compare the latest advances in technology.[5-7] Even newer study designing strategies such as SYNTAX, the study with score based allocation and default arm extension did not provide a universal solution.[8] In addition, due to differences in the

physical characteristics of the device, its identity is revealed as soon as the package is opened. These blinding limitations in turn limit the use of placebo and peer technology as controls. Due to these limitations in assigning a control arm in device trials, data is mostly generated from single arm studies and registries, and eventually submitted to regulatory agencies for market approval. However, data generated from single arm studies is often debatable and generally has low scientific acceptance.

Retrospective studies and historical control studies tend to have a selection bias even after careful design.[9] Therefore, establishing a method for standardization of study outcomes to enhance their scientific acceptance is a priority. Comparing studies either through meta-analyses or numerically are commonly accepted methods.[10,11] However, they have limited value due to differences in designing credentials.[12] Each study has different eligibility criteria, study conduct, as well as different outcome parameters. Yet another challenge is that the variety of data types viz. mean, median, proportion, rates etc. are different in their statistical nature and hence cannot be calculated using any single statistical method. In an attempt to establish a method to compare clinical trials and get relative performance or safety evaluation, we tried flat data comparison, scoring data points for comparison and meta-analysis. However, in our opinion these methods are complex and have limited utility.

Therefore, we propose a ratio based statistical expression, RADHIKa - ratio-based analysis deriving basis for comparison of historical or parallel interdependent reported ken of studies that can be used to compare the relative performance or safety evaluation of independent studies.

METHODS

Prerequisites for RADHIKa calculations

The RADHIKa method can be applied when data of both, the effects (endpoints or outcome measures) and the Influencers (demographics or risk factors) is available. The philosophy of this method is from effects to Influencers, meaning that the entire process is oriented for comparison of the effects. To compare the effects effectively and comprehensively, factors influencing the effects (the precursor Influencers) are compared. Consequently, in order to apply the RADHIKa method, there are four major prerequisites.

Common effects factor

To compare two or more studies, the outcome measure parameter (effect) that is used to establish either safety or efficacy of the treatment must be common. In addition, the mode of expression, unit and technique of measurement should also be the same. If the unit of measurement or expression is different, it should be converted appropriately.

Further, it is not mandatory that the outcome measure parameter be a primary endpoint. It can remain a secondary endpoint in one or all of the studies.

For example, in a hypertension study, several different outcome measure parameters are possible. These include 'mean systolic pressure' and/or 'mean change in systolic pressure'. Both these parameters have their own significance in evaluation of efficacy of the treatment. However, 'mean systolic pressure' cannot be compared with 'mean change in systolic pressure'.

Precursor relationship

RADHIKa calculations are based upon assessment of two major factors:

- Factors that are considered as "effect" and are actually compared to evaluate the efficacy or safety or any such parameter and
- Factors that "influence" the effect, and which are compared to bring-in logical equivalence for the comparison.

In a study there can be various endpoints and risk factors. All the risk factors may not be direct influencers for every endpoint. This relationship between a risk factor and its ability to influence the outcome or endpoint (the effect) is called a 'precursor relationship'. To establish the correct logic for comparison, careful identification and selection of the risk factors that influence the selected effect is required.

For instance, in the example given above the commonly evaluated effect is 'mean change in systolic blood pressure at 8 weeks'. The commonly recorded demographic and clinical risk factors for the hypertension study are age, sex, race, exercise, BMI, salt intake, baseline heart rate, baseline systolic blood pressure and some medical history like COPD, ischaemic heart disease, diabetes and renal disease. The mean change in blood pressure is influenced by all factors except baseline heart rate. Hence, when considering precursor relationship, this parameter should be eliminated.

Parameter value and null expressions

All entities - effects and influencers - must be expressed as a real number (including percentages and ratios). The final evaluable expression of RADHIKa is a ratio, which is possible only with real numbers. In addition, amongst influencers, a maximum of two null or missing values can be accepted. When using RADHIKa, null values are adjusted with one property of equal ratios. Hence, if null values are more than two, the adjustments lead to high deviation and subsequently vague results.

Defined objective and qualifications

Like any scientific experiment, objectives must be predefined before implementing RADHIKa analysis. The

objective of analysis may have various dimensions. These dimensions include interval based analysis of measurements or events, time to event analysis, effect time and sometimes even precursor analysis.

Selection of correct effect, its precursors, expression, sensitivity and establishment of literature search criteria for finding out correct predicate studies depends majorly upon the objective of the analysis. For example, if the objective is to demonstrate equivalence of safety in general population, the literature search criteria will be adjusted to find epidemiological studies or disease surveillance reports along with precursor studies. The objective of analysis is also determines which Ken of studies is defined as "part under evaluation" (PUE), so that other studies can be defined as predicates.

Under this prerequisite, we also define the modality of the outcome. For certain effects, better outcomes tend to produce lower value (lower the better). The same situation, lower the better, is considered when a positive change is an indicator of better outcomes. On the other hand, for some effects, better outcomes tend to produce higher value (higher the better). The same situation, higher the better, is considered when a negative change is an indicator of better outcomes. For example, in a study with number of failure events as the effect, a lower numerical value is better (lower the better) whereas in case of a study with event free survival as the effect, a higher numerical value is better (higher the better).

Steps in RADHIKa calculation

RADHIKa methodology has three components:

- Construction of ken
- Calculations and box plot
- Final analysis and inferences

Construction of Ken

Ken is a collection of data of predicate studies, in which values of effect and influencers are tabulated in a uniform fashion. Based upon the prerequisites for calculations, the predicates and variables to be analysed are determined and used to construct the table. Required study data is obtained, by literature search and is then tabulated.

Once all available data is tabulated and rechecked for validity, a series of calculations follows. As these calculations are based upon real numbers, outcomes in the form of ratios are also real numbers. In case there is a null value in PUE arm and division is not possible, the property of equal ratios componendo and dividendo is applied. The rationale being that in two exactly comparable studies, both arms must have equal values. This hypothesis has been validated by actual calculations.

Calculations and Box Plot

The steps in calculations are as follows:

A. Calculate the primary influencers ratio R(In) and mean influencers ratio (ψ)

The primary Influencers ratio is defined as a number obtained by division of value of an individual influencer (demographics and risk factors) in the predicate array by value in the PUE array. For clarity, value in any format (mean, frequency, median, score etc.) is considered as a number only without its unit. The mean of all R(In) is mean influencers ratio (ψ).

$$R(In) = \frac{Value\ of\ Influencer\ parameter\ \boldsymbol{n}\ in\ Predicate\ array}{Value\ of\ corresponding\ Influencer\ parameter\ \boldsymbol{n}\ in\ PUE\ array}$$

$\psi = \frac{\sum R(I1 \ldots n)}{n}$ or in other expression, $\psi = average\ of\ R(I)1 \ldots . R(I)n$

In case of null value, calculation after componendo and dividendo applied will be:

$$R(In) = \frac{\left(\frac{Value\ of\ Influencer\ parameter\ \boldsymbol{n}\ in\ Predicate\ array+SE}{Value\ of\ Influencer\ parameter\ \boldsymbol{n}\ in\ Predicate\ array-SE}\right)}{\left(\frac{Value\ of\ corresponding\ Influencer\ parameter\ \boldsymbol{n}\ in\ PUE\ array+SE}{Value\ of\ corresponding\ Influencer\ parameter\ \boldsymbol{n}\ in\ PUE\ array-SE}\right)}$$

In this equation SE stands for standard error and is calculated by routine statistical methods.

B. Ratio of effects R(E)

The ratio R(E) is taken for endpoints that we have defined as effects. The R(E) is calculated by dividing the value in predicate by the value in PUE.

$$R(E)i = \frac{Value\ of\ Effect\ parameter\ \boldsymbol{i}\ in\ Predicate\ array}{Value\ of\ corresponding\ effect\ parameter\ \boldsymbol{i}\ in\ PUE\ array}$$

Calculations in case of a null value are done in the same way as the Influencers. However, as there is no standard error value available, the value for type I error used to calculate confidence interval (usually 0.03 or 0.05) is used instead.

C. Determining the range of equivalence

Range of equivalence is the predefined range used to determine if the effect is equivalent in both the arms. For calculation of range of equivalence, 97% to 95% inclusive confidence interval of the table array of R(I)s is calculated with mean taken as 1. The confidence interval

boundaries are calculated as Ψ ± CI. The boundaries of confidence interval form the range of equivalence for R(I) and R(E). It should be noted that the range of equivalence may be vague if the effect parameter is less sensitive.

D. Absolute risk ratio or RADHIKa ratio (RR')

RADHIKa ratio is the final step of comparison. This is the ratio of R(E) with Mean R(I) or Ψ. Before actual calculation, an adjustment of effect parameters is required to maintain the uniformity of inference. In case of "lower the better" scenario described above for outcomes, the RR' is a simple ratio.

$$RR'(lower\ the\ better) = \frac{R(E)}{\psi}$$

In the second scenario - "*higher the better*", the ratio inverse is taken.

$$RR'(Higher\ the\ better) = \left(\frac{R(E)}{\psi}\right)^{-1}$$

E. Plotting the box plots

For generating a box plot, four values are needed namely RR', the two CI boundary values for RR' and z value of RR with alpha taken as 0.03 (for 97% CI) or 0.05 (for 95% CI), mean as 0 and standard deviation as 1. A Logarithmic scale with base 2 is used to plot the values. One limitation of the box plot is that the graph will not be produced unless there are at least 4 data points to evaluate. It is also extremely important to analyse the data along with the box plot, to avoid misleading interpretations of numbers alone.

3. Final analysis and inferences

Ratios

When the ratio is 1, both the control arm and the evaluation arm are equal. However, this situation is extremely rare. Hence for all practical purposes equivalence is considered when all ratios are within the equivalence range of Ψ ± CI.

Graphics

The box plot indicates the tendency of the parameter along with the difference in two arms. Thus, when the box in the plot is dark, the inference is that the PUE and predicate arms have performed as expected for the given parameter. On the other hand, when the box is white, the interpretation should be reversed. The position of the box plot with reference to the line of unity is indicative of the performance of PUE. When the dark box tends to be in area above line of unity or white box tends to be in the area below the line of unity, it indicates that the PUE has performed better. When the dark box tends to be in an area above the line of unity or the white box tends to be in an area below the line of unity, it indicates that the PUE has performed better. The tails of the box indicate significance of the outcome in each direction. If the tails are long, they are indicative of a lower significance.

RESULTS

We validated the RADHIKa method by performing calculations for randomized studies. Here are some examples where RADHIKa is applied to compare the outcomes of various clinical studies:

Example 1: SPIRIT – III study

This is a benchmark study in cardiology. The Xience V stent was compared with Taxus Libertè in a 2:1 randomized clinical trial. The endpoints were defined as Major Adverse Cardiac events at 284 days, ischaemia driven target vessel (i-TLR) revascularization at 284 days and target vessel revascularization (TVR) at 284 days. It had comparable demographics and the outcomes were clearly in favour of Xience V, the PUE arm was as shown in Table 1. When RADHIKa method was used to evaluate this study, we observed that the ratio of each influencer and the ψ value were close to 1. This corresponds with the fact that being a randomized study, the arms (Xience in test and Taxus in control) had similar demographics. We could establish the precursor relationship of 9 influencers with each of the 3 effects. Results of RADHIKa analysis corresponded with the study inferences. Further, in this case we had effect scenario of lower the better hence, RR' was calculated by division of R(E) for each effect with ψ. In each case, the ratio was more than the upper limit of confidence interval, indicating that the study arm performed better. The RR' of each effect also confirmed the same. With this and several other analyses we could successfully validate the RADHIKa method in randomized studies.

In the box plot analysis as given in Figure 1 of the above comparison, the dark boxes indicate that the devices performed as expected and a large proportion of the boxes is above 1 indicating that outcomes favor the study arm in comparable demographics.

Example 2: SYMPLICITY HTN-3 Study

The SYMPLICITY HTN-3 study had randomization between sham procedure (placebo) and renal denervation for resistant hypertension.[13] This trial randomized 535 patients with resistant hypertension with certain demographic variations in both study arms as in Table 2. The mean change in systolic blood pressure at 6 months was −14.13 in the study arm which was slightly better than −11.74 ± 25.94 in the control arm. The change in 24-hour ambulatory systolic blood pressure was −6.75 in the study arm vs. −4.79 in the control arm, showing superiority of the study arm as given in Table 3. RADHIKa analysis performed for influencers and effects confirmed that the two arms were comparable. However,

the ψ value of 1.102 indicated that the control group was more challenging. This was mainly due to significantly higher number of renal artery stenosis cases in the control arm. The effects analysis revealed that most of the performance parameters favored the study arm and most of the safety parameters were equivalent. The same I1 to I15 influencers have precursor relationship with each effect parameter E1 to E14 as presented in Table 3.

Table 1: RADHIKa method applied to SPIRIT III study.

	Factor code	Arm 1	Arm 2	R(I)	
Arm		Control (Predicate)	Evaluation (PUE)		
Device name		Taxus Libertè	Xience V		
Age (in years)	I1	62.8	63.2	0.99	
Male (%)	I2	65.7	70.1	0.94	
Hypertension (%)	I3	74	76.2	0.97	
Hypercholesterolemia (%)	I4	71.5	74.2	0.96	
Diabetes mellitus (%)	I5	27.9	29.6	0.94	
Current smoker (%)	I6	22.5	23.4	0.96	
Prior MI (%)	I7	18	19.9	0.90	
Unstable angina (%)	I8	25.1	18.7	1.34	
Lesion per patient	I9	1.3	1.3	1	
Mean ratio (ψ)				1.002	
CI 97% range			1.029	0.975	
				R(E)	(R(E)/ ψ)
Ischaemia driven TLR @284 days	E1	5	2.6	1.92	1.92
MACE @284 days	E2	8.1	4.6	1.76	1.76
TVR @284 days	E3	6.5	5.3	1.23	1.22

Table 2: RADHIKa applied to SYMPLICITY HTN-3 study – demographics.

		Arm 1	Arm 2	R(I)
		Control / predicate - sham procedure	Evaluation / PUE - renal denervation	
Age (years)	I1	56.2	57.9	0.971
Male sex (%)	I2	64.3	59.1	1.088
In-Office systolic blood pressure (mm Hg)	I3	180	180	1.000
24 hour mean systolic ABPM (mm Hg)	I4	160	159	1.006
BMI (kg/m^2)	I5	33.9	34.2	0.991
African American Race	I6	29.2	24.8	1.177
White Race	I7	69.6	73	0.953
Renal insufficiency (eGFR<60 ml/min/1.73m^2)	I8	9.9	9.3	1.065
Renal artery stenosis	I9	2.3	1.4	1.643
Obstructive sleep apnea	I10	31.6	25.8	1.225
Stroke	I11	11.1	8	1.388
Type 2 diabetes	I12	40.9	47	0.870
Hospitalization for hypertensive crisis	I13	22.2	22.8	0.974
Hyperlipidemia	I14	64.9	69.2	0.938
Current smoking	I15	12.3	9.9	1.242
RADHIKa score (ψ)				1.102
CI 97% range			1.225 to 0.979	

Table 3: RADHIKa applied to SYMPLICITY HTN-3 study – outcomes.

		P1	P2	R(E)	RR'=R(E)/ψ
Change in In-office mean systolic BP	E1	-11.70	-14.10	0.83	1.33 (inv)
Change in 24 hour mean systolic ABPM (mm Hg)	E2	-4.80	-6.80	0.71	1.56 (Inv)
6-Month composite safety	E3	5.80	4.00	1.45	1.32
Death	E4	0.60	0.60	1.00	0.91
Myocardial infarction	E5	1.80	1.70	1.06	0.96
Serum creatinine >50%	E6	0.60	1.40	0.43	0.39
Embolic event resulting in end-organ damage	E7	1.00	1.40	0.71	0.65
Renal artery intervention	E8	1.00	1.00	1.00	0.91
Vascular complication requiring treatment	E9	1.00	1.40	0.71	0.65
Hypertensive crisis/emergency	E10	5.30	2.60	2.04	1.85
Stroke	E11	1.20	1.10	1.09	0.99
Hospitalization for new onset heart failure	E12	1.80	2.60	0.69	0.63
Hospitalization for atrial fibrillation	E13	0.60	1.40	0.43	0.39
New renal artery stenosis >70%	E14	1.00	1.40	0.71	0.65

Figure 1: Box plot for SPIRIT III.

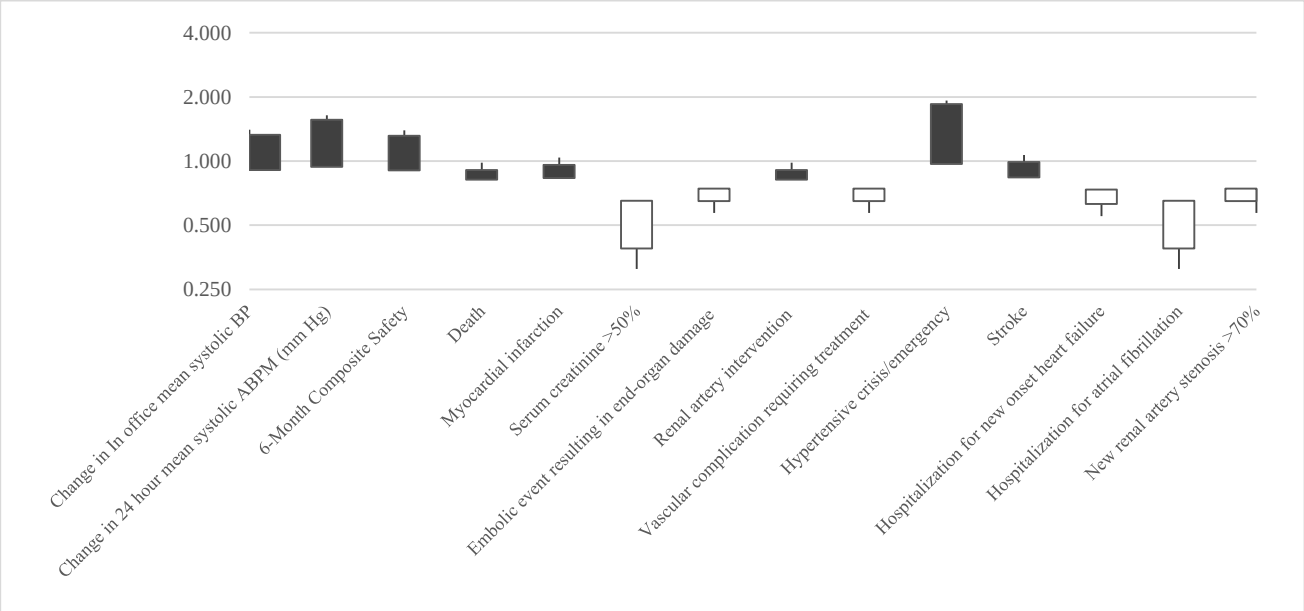

Figure 2: Box plot for RADHIKa with SYMPLICITY HTN-3 study.

Also note that in the first 2 endpoints, we considered the ratio inverse because here higher mean change in SBP indicates better response to the treatment.

Inferences from the box plot also favour the treatment arm and supports its claims of superiority as in Figure 2. A few indicators with white boxes require reverse interpretation with respect to their scatter below the line of unity. This indicates that the treatment arm performed better over the control. In some dark boxes the skewed distribution towards <1, indicate that the effects are slightly in favour of placebo. These trends are despite having deemed equivalence influencers on both arms, as RR' has RADHIKa score (ψ) in the denominator.

To evaluate robustness of the RADHIKa method, we compared various drug eluting stents from different studies. To start with, we compared the performance of same device from different studies followed by different devices from different studies using RADHIKa method.

Example 1: Xience V stent compared for its performance in SPIRIT –III and SPIRIT IV studies.

Both these were independent studies for comparing the same device (Xience V), randomized against another drug eluting stent. Since the device is the same, its expected outcomes in similar demographics also are expected to remain the same as given in Table 4. The demographics (influencers) had a ratio of 0.95 for SPIRIT III:SPIRIT IV indicating that SPIRIT III group presented more challenges.

In the analysis effects considered were total major adverse cardiac events, death events, myocardial infarction events, target lesion revascularization events and stent thrombosis events as given in Table 5. All these are in lower-the-better scenarios.

Table 4: RADHIKa comparison for Xience V in SPIRIT III and SPIRIT IV studies – demographics.

Stent	Xience V	Xience V	Xience V
Study	SPIRIT III	SPIRIT IV	SPIRIT III vs. SPIRIT IV
Average age	63.2	63.25	1.00
Male (percent)	70.1	63.73	1.10*
Diabetes mellitus (percent)	29.6	32	0.93
Hypertension (percent)	76.2	77.4	0.98
Dyslipidemia (percent)	74.2	76.1	0.98
Smoking (percent)	23.4	21.9	1.07
H/o MI (percent)	19.9	21.1	0.94
H/o revascularization (percent)	0	0	1.00
Unstable angina status (percent)	18.7	27.2	0.69*
LAD (percent)	41.3	40.5	1.02
LCX (percent)	27.6	24.2	1.14*
RCA (percent)	31	35.4	0.88
Lesion per patient	2	3	0.67*
RADHIKa Score (ψ)			0.95
97% CI range			1.07 to 0.84

* The values outside CI range.

Table 5: RADHIKa comparison for Xience V in SPIRIT III and SPIRIT IV studies – MACE (outcomes).

	SPIRITIII	SPIRIT IV	R(E)	RR' = R(E)/ ψ
Total MACE	4.79	4.2	1.14	1.20
Death	0.4	0.4	1.00	1.05
MI	1.8	1.9	0.95	0.99
TLR	2.3	2.5	0.92	0.97
Late thrombosis	0.29	0.16	1.81	1.90

The box plot of the Xience V comparison in different studies indicate that Xience V performance was similar in both as in Figure 3. There is a significant difference between the results of stent thrombosis where SPIRIT – IV study looks to have performed better. This shift may be explained by looking deeper into the influencers or performing a secondary analysis.

However, from RADHIKa analysis, we can conclude that the device performance was equivalent in both studies with equivalent demographics. Another indicator of robustness of analysis is its ability to detect executable differences in a manner similar to the ODD's analysis. In all above examples, when we look at the box plots together with numerical representation, we are able to

better appreciate the executable differences. Thus, in case of SPIRIT III vs. SPIRIT IV, the demographic differences correspond closely to the outcomes, proving the robust nature of RADHIKa. We also performed some additional analyses of various devices, procedures and treatments of other systems using RADHIKa. For practical application of the method, we present three scenarios. The first-three drug eluting stents from three different generations. The second-two drug eluting stents of different compositions and third-three knee prostheses.

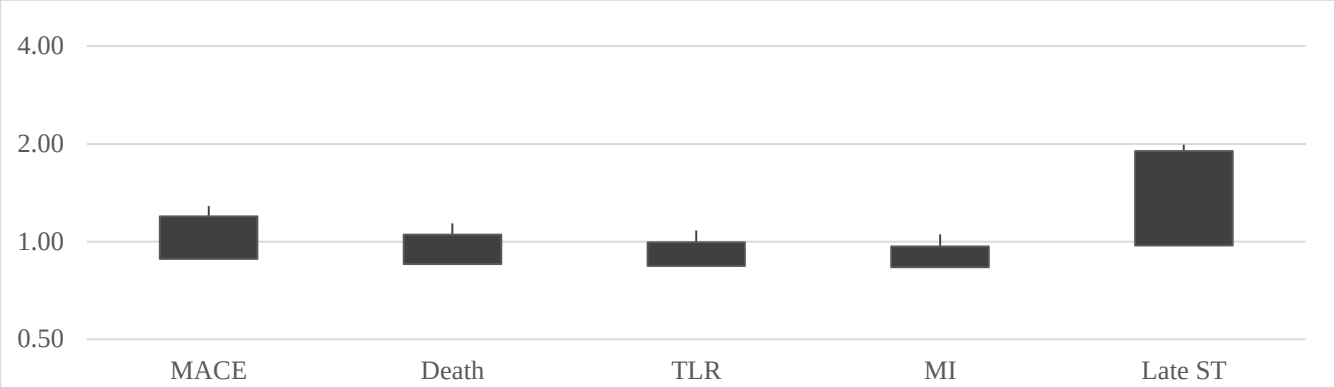

Figure 3: Box plot for SPIRIT III Vs. SPIRIT IV comparison for Xience V performance.

Table 6: Data of different drug eluting stents in different studies.

Stent	Xience V	Xience P	Xience V	Taxus L	Taxus L	Orsiro	Orsiro
Study	SPIRIT III	BIOFLOW II	SPIRIT IV	SPIRIT III	SPIRIT IV	BIOFLOW I	BIOFLOW II
Average age	63.2	64.82	63.25	62.8	63.34	58.1	62.72
Male (percent)	70.1	74.68	63.73	65.7	67.77	60	78.2
Diabetes mellitus (percent)	29.6	28.2	32	27.9	32.5	23.3	28.19
Hypertension (percent)	76.2	77.57	77.4	74	76.1	66.6	77.78
Dyslipidemia (percent)	74.2	67.8	76.1	71.5	75.5	93.3	68.01
Smoking (percent)	23.4	66.4	21.9	22.5	22.4	53.3	29.19
H/o MI (percent)	19.9	20.13	21.1	18	19.9	73.3	30.2
H/o revascularisation (percent)	0	0	0	0	0	0	0
Unstable angina status (percent)	18.7	0	27.2	25.1	28.9	37	0
LAD (percent)	41.3	39.9	40.5	42.9	39.8	53	44.6
LCX (percent)	27.6	31.8	24.2	28.3	25.4	17	22
RCA (percent)	31	28.3	35.4	28.5	34.8	30	32.83
Total MACE	4.79	8	9	8.9	6.9	10	6.5
Death	0.4	0.7	2.2	0.4	1.15	3.3	0.7
MI	1.8	2.6	1.9	2.9	3.25	0	2.7
TLR	2.3	4.7	5.6	4.5	0	6.7	3.5
Late thrombosis	0.29	0	0.16	1.1	0.39	0	0

Table 7: Comparison of different drug eluting stents in different studies with RADHIKa – demographics.

Analysis	Xience V SPIRIT III / Orsiro Bioflow I	Xience V SPIRIT III / Orsiro Bioflow II	Taxus L SPIRIT III / Orsiro Bioflow I	Taxus L SPIRIT III / Orsiro Bioflow II	Xience V SPIRIT IV / Orsiro Bioflow I	Xience V SPIRIT IV / Orsiro Bioflow II	Taxus L SPIRIT IV / Orsiro Bioflow I	Taxus L SPIRIT IV / Orsiro Bioflow II
Average age	1.088	1.008	1.081	1.001	1.089	1.008	1.090	1.010
Male (percent)	1.168	0.896	1.095	0.840	1.062	0.815	1.130	0.867
Diabetes mellitus (percent)	1.270	1.050	1.197	0.990	1.373	1.135	1.395	1.153
Hypertension (percent)	1.144	0.980	1.111	0.951	1.162	0.995	1.143	0.978
Dyslipidemia (percent)	0.795	1.091	0.766	1.051	0.816	1.119	0.809	1.110
Smoking (percent)	0.439	0.802	0.422	0.771	0.411	0.750	0.420	0.767
H/o MI (percent)	0.271	0.659	0.246	0.596	0.288	0.699	0.271	0.659
H/o revascularization (percent)	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
Unstable angina status (percent)	1.003	-1.005	1.001	-1.004	1.001	-1.004	1.001	-1.003
LAD (percent)	0.779	0.926	0.809	0.962	0.764	0.908	0.751	0.892
LCX (percent)	1.624	1.255	1.665	1.286	1.424	1.100	1.494	1.155
RCA (percent)	1.033	0.944	0.950	0.868	1.180	1.078	1.160	1.060
RADHIKa score (ψ)	0.968	0.800	0.945	0.776	0.964	0.800	0.972	0.804
Standard deviation	0.347	0.562	0.350	0.560	0.331	0.561	0.345	0.564
97% CI - Upper	0.217	0.352	0.219	0.351	0.208	0.352	0.216	0.353

Table 8: Comparison of different drug eluting stents in different studies with RADHIKa - outcomes.

Analysis	Xience V SPIRIT III / Orsiro Bioflow I	Xience V SPIRIT III / Orsiro Bioflow II	Taxus L SPIRIT III / Orsiro Bioflow I	Taxus L SPIRIT III / Orsiro Bioflow II	Xience V SPIRIT IV / Orsiro Bioflow I	Xience V SPIRIT IV / Orsiro Bioflow II	Taxus L SPIRIT IV / Orsiro Bioflow I	Taxus L SPIRIT IV / Orsiro Bioflow II
Total MACE	0.479	0.737	0.890	1.369	0.900	1.385	0.690	1.062
Death	0.121	0.571	0.121	0.571	0.667	3.143	0.348	1.643
MI	-1.057	1.019	-1.035	0.997	-1.054	1.016	-1.031	0.994
TLR	0.343	0.657	0.672	1.286	0.836	1.600	-0.149	-0.286
Late thrombosis	-1.417	-1.417	-1.095	-1.095	-1.909	-1.909	-1.294	-1.294
Total MACE RR'	0.495	0.921	0.941	1.764	0.933	1.730	0.710	1.320
Death RR'	0.125	0.714	0.128	0.736	0.691	3.927	0.359	2.043
MI RR'	-1.092	1.273	-1.095	1.285	-1.093	1.269	-1.061	1.236
TLR RR'	0.355	0.821	0.710	1.657	0.867	1.999	-0.154	-0.355
Late thrombosis RR'	-1.464	-1.770	-1.159	-1.411	-1.980	-2.385	-1.331	-1.610

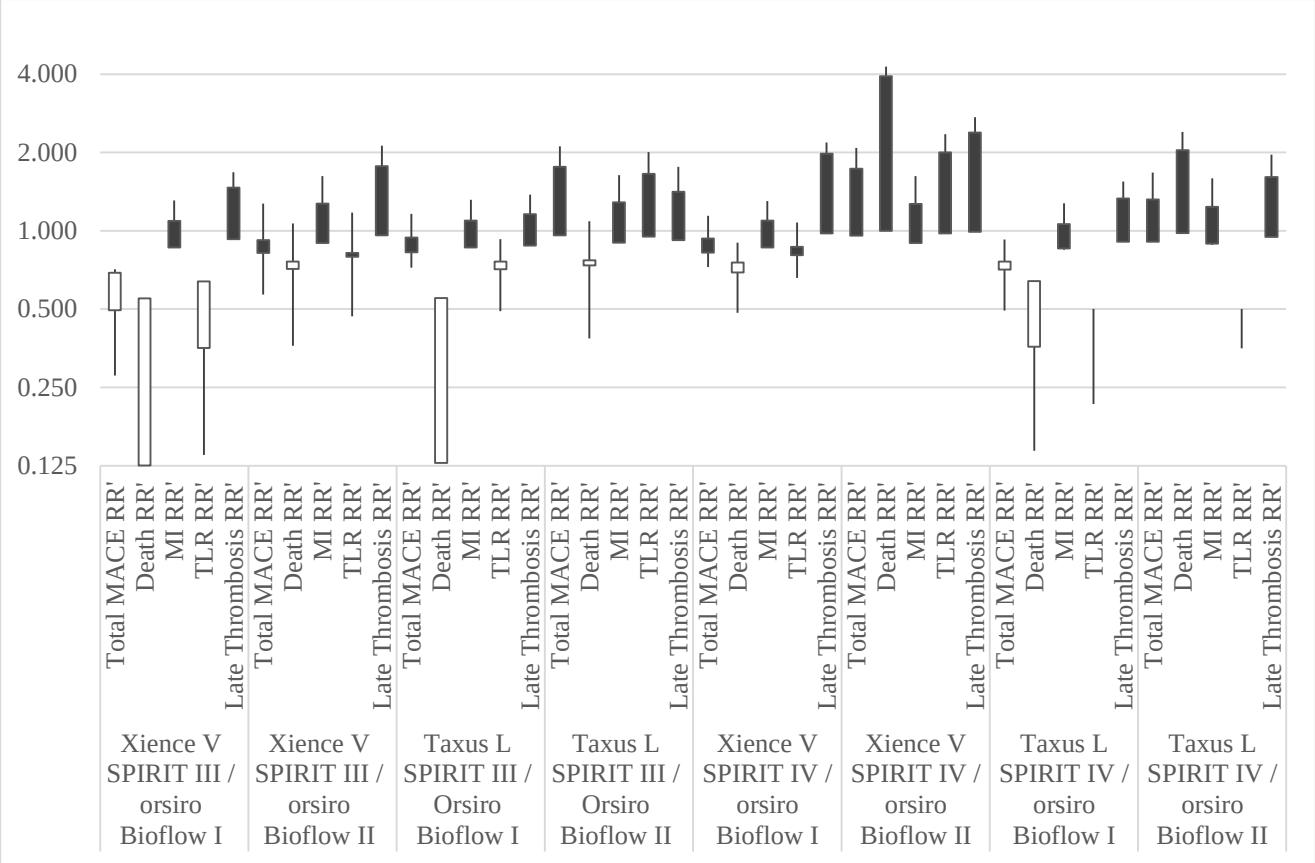

Figure 4: RADHIKa applied to knee replacement devices study.

Example I

Taxus Libertè (First generation Paclitaxel eluting stent), Xience V (Second generation Everolimus eluting stent) and Orsiro (Third generation Sirolimus eluting stent) are compared by RADHIKa Method. Data of influencers and effects is presented in the table below as given in Table 6 and Table 7. Effects and RADHIKa analysis is presented in the Table 8.

Numerical and box plot representation of the analysis of Orsiro studies vs. Xience V studies and Orsiro studies vs. Taxus studies are in sync with conventional clinical performance of these devices. Orsiro appears to be clearly superior in many parameters compared to Taxus Libertè and marginally superior to Xience V, as indicated by many white boxes below the line of unity, in the comparison as shown in Figure 4. This is supportive of improvisation of the technology from first generation Taxus to second generation Xience V to third generation Orsiro.

Example II

Compared data of three knee prostheses namely Indus, Logic and Optetrack to compare post implantation range of motion assessment.[14,15] In this analysis, the data for Logic and Optetrack devices were taken from the pair match study.[7] This study shows marginally better results for Optetrack system, despite similar demographics as produced in Table 9. Data for logic was taken from an independent study.[9]

Our analysis indicates that Optetrack device performs similar to the Logic device ($R(E)/\psi = 1.03$), when precursors are similar ($\psi = 1.01$). This observation is in agreement with earlier reported analysis of the pair-matched study.[7] The analysis of an independent study performed to compare Indus, India specific design of knee, reveals that in similar demographic precursor conditions ($\psi = 1.03$), the Indus device performs similar to Logic and Optetrack devices, with $R(E)/\psi = 1.03$ and 1, respectively. The box plot also indicates that all the devices have equivalent performance in similar demographics as in Figure 5.

Example III

In the third example we compare data of BioMatrix flex from e-BioMatrix registry with that of Nobori in Nobori - 2 study. BioMatrix and Nobori have very similar technology. Hence, when the demographics are similar these two devices are expected to perform in a similar way. However, wide demographic differences in the two studies limit meta-analysis comparison of the study data as in Table 10. As we can observe, the ψ value was 0.86, indicating that there was a major difference in the two groups. The group with Nobori stent implanted

apparently had more adverse influencers. Looking at MACE and its components, the effects were favouring the Nobori group as given in Table 11. Box plot is presented in Figure 6.

Table 9: RADHIKa applied to knee replacement devices study.

	Logic	Optetrack	Indus	Logic : Indus	Optetrack : Indus	Logic : Optetrack
Average age	68	68	69.95	0.97	0.97	1.00
BMI	29.76	29.56				1.01
Female %	74	74	100	0.74	0.74	1.00
Pre-op ROM	104.8	108.2	110.4	0.95	0.98	0.97
Pre-op WOMAC	52.5	49.6	44.35	1.18	1.12	1.06
OA	100	100	75.6	1.32	1.32	1.00
Mean				1.03	1.03	1.01
STDEV				0.23	0.21	0.03
97% CI upper limit				1.37	1.34	1.05
97% CI lower limit				0.70	0.71	0.96
Post operative ROM	120.9	125	128.17	0.94	0.98	0.97
Inverse RADHIKa Ratio RR”				1.03	1.0	1.03

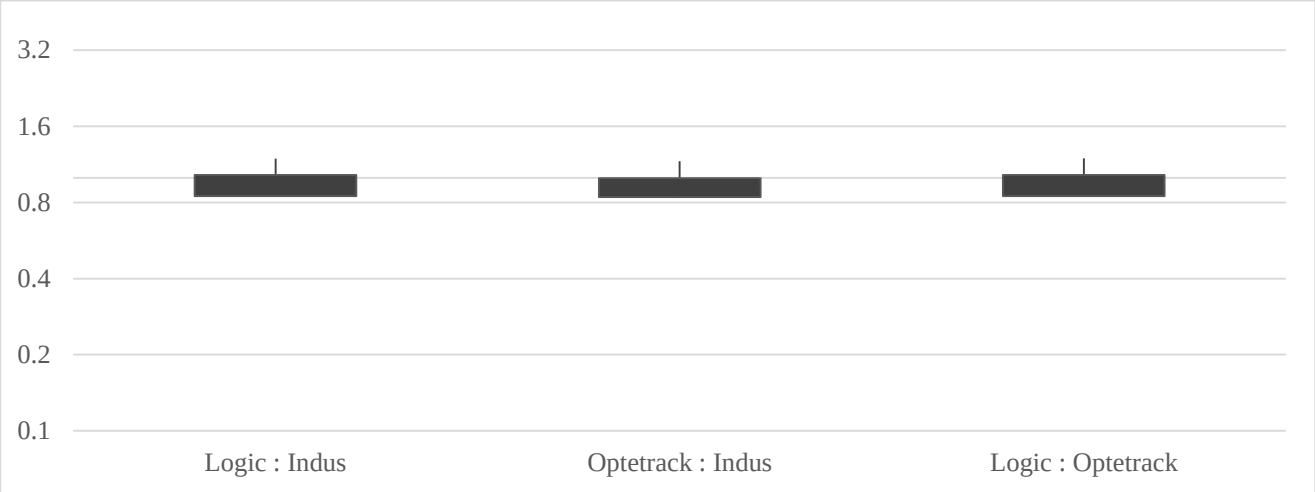

Figure 5: RADHIKa box plot for knee prosthesis comparison.

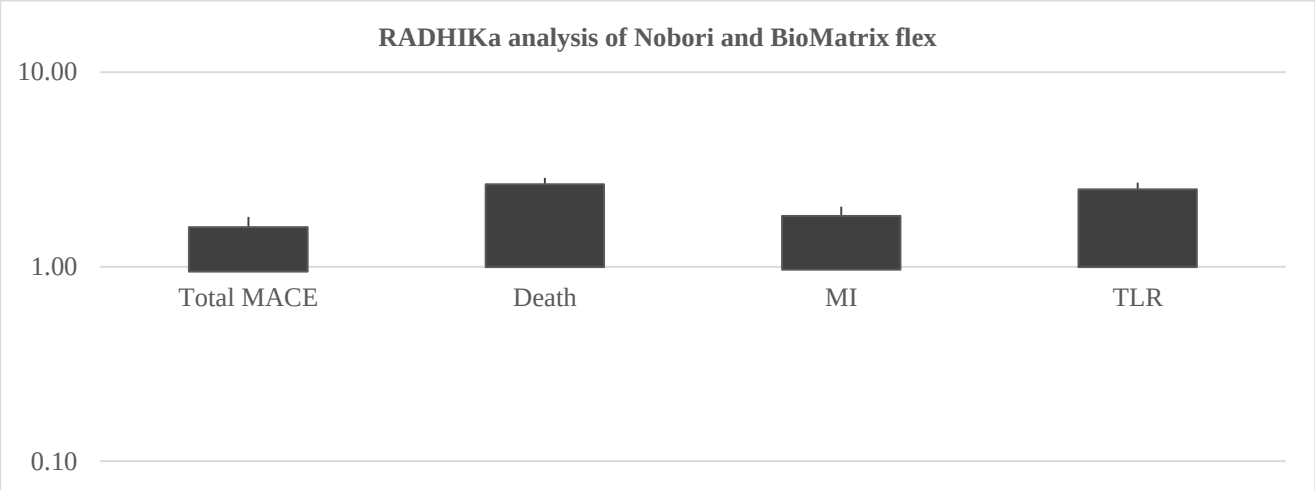

Figure 6: Box plot for RADHIKa comparison of very similar devices used in different populations.

Table 10: RADHIKa analysis for comparison of very similar devices – demographics.

	BioMatrix	Nobori	R(E)
Average Age	64.1	64.4	1.00
Male (percent)	77.4	78	0.99
Diabetes mellitus (percent)	24	29.5	0.81
Hypertension (percent)	66.5	69.1	0.96
Dyslipidemia (percent)	67.5	71.1	0.95
Smoking (percent)	28.1	25.6	1.10
H/o MI (percent)	21.4	41	0.52
H/o revascularisation (percent)	33.8	32.1	1.05
ACS	68.3	53.5	1.28
Slient ischaemia	9.5	15.1	0.63
Multivessel disease	16.1	26.23	0.61
Comorbidity score	1.2	3.2	0.38
RADHIKa ratio (ψ)			0.86
STDEV			0.26
97% CI - Upper bound			1.07

Table 11: RADHIKa analysis for very similar devices in different populations.

	BioMatrix	Nobori	Ratio R(E)	(R(E)/ψ)
Total MACE	6.70	4.90	1.37	1.60
Death	2.50	1.10	2.27	2.65
MI	2.50	1.60	1.56	1.82
TLR	4.70	2.20	2.14	2.49

DISCUSSION

RADHIKa method is useful tool to compare studies and treatment or exposure principles, especially medical devices. The RADHIKa outcomes are in sync with the results of the randomized trials that prove its validity. In many different clinical trials and comparisons, the outcomes are unambiguous and clear that proves the robust nature of the method. This can be progressively used in the current scenario where most medical devices need to generate data from a single arm study. It not only has clinical relevance, but also can help the scientific community to judge influence of a single factor change in a device, which presently remains as a major limitation of meta-analysis. In addition, this method can be used in virtual randomization of the single arm studies and pair matching method design of medical device studies.

There are certain limitations for using the RADHIKa method. RADHIKa is a sensitive method and thus is greatly influenced by missing data. If the data of critical parameter or precursor of the parameter is missing, the outcomes of RADHIKa may show higher variance. However, the outcomes can still provide some understanding of comparability of the devices. Another important limitation of RADHIKa is that if wrong precursors are used to interpret the data, results may often be misleading or non-critical. It therefore requires a clear understanding of the precursors of an endpoint. The precursor relationship should be determined on basis of the actual pathophysiological correlation of the influencer parameter with the effect parameter. In many cases, sub-set analyses and odds analyses may also be referred for such precursor relationships.

CONCLUSION

RADHIKa method is a useful tool to compare the relative performance or safety of independent studies, especially single arm device studies.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Indani A, Boreddy SR, Deshpande T. RADHIKa: Ratio-based analysis deriving basis for comparison of historical, parallel or interdependent reported ken of studies - a novel method for comparing interconnected and disconnected data sets. Int J Clin Trials 2016;3(4):254-66.