

# Prevalence of randomised controlled trials in Japanese cardiovascular journals: a descriptive study

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Received 19 May 2017

Revised 7 July 2017

Accepted 20 July 2017

## ABSTRACT

**Background** Little is known about the recent proportion and trends of randomised controlled trials (RCTs) published in Japanese cardiovascular journals.

**Methods and results** This study retrospectively reviewed all original research articles published between 2006 and 2015 in six English-language journals issued by societies related to cardiovascular medicine in Japan. All these journals had been indexed in PubMed for more than 5 years until 2015. We examined the 2-year trends in the prevalence of RCTs, as well as the types of study subjects and interventions investigated. In addition, we applied a multivariable logistic regression analysis to assess the factors related to the publication of RCTs. A total of 7117 articles were eligible for our analyses. The proportion of RCTs among Japanese journals was 3.5% (252/7117). No significant change in the prevalence of RCTs among all included journals was noted (3.8% vs 3.1%,  $p=0.751$ ). RCTs related to ischaemic heart disease were the most frequently published (85/252, 33.7%). In the multivariable analysis, a male first author (adjusted OR (AOR) 1.97; 95% CI 1.30 to 2.99) and reports from Asia (AOR 1.62; 95% CI 1.19 to 2.21) were significantly associated with the publication of RCTs.

**Conclusions** In Japanese cardiovascular journals, RCTs accounted for 3.5% of all original research articles published, and there was no change in the prevalence of RCTs during the study period.

number of clinical trials in the field of cardiology, including RCTs, has been increasing.<sup>8</sup> Hayashino and colleagues reported that the proportion of RCTs was 2.3% of all Japanese research articles published in the top 10 foreign cardiovascular journals in the 1990s<sup>9</sup>; however, little is known about the recent proportion and trend of RCTs published in Japanese cardiovascular journals.

The aim of this study was to assess the prevalence of the RCTs published in Japanese cardiovascular journals that have been published in English for a period of years. In addition, we sought to determine the types of study patients and the interventions investigated in those studies.

## METHODS

This was a retrospective descriptive study assessing the prevalence of RCTs among original research articles published in Japanese cardiovascular journals from 2006 to 2015. We examined their changes over time among journals, as well as the type of study subjects and interventions. As this study consisted only of a journal review and did not involve individual patients, ethical approval was not required.

## Data collection

### Inclusion and exclusion criteria

We selected all the six journals that were published in English by societies in Japan related to cardiovascular disease and that had been indexed in PubMed for more than 5 years until the year of 2015. We excluded journals published by societies that had both Japanese and overseas parts. The six journals were as follows: *Circulation Journal*, *Journal of Cardiology (JC)*, *Journal of Atherosclerosis and Thrombosis*, *Hypertension Research (HR)*, *Heart and Vessels* and *International Heart Journal (IHJ)*. The total number of authors, their first and last names, the country where the study was conducted and the article type, study subjects and study design were extracted from the full text of the articles. Data for original research articles, including meta-analyses, published in the six journals from January 2006 to December 2015 were analysed, but short papers, case reports, review articles, editorials and letters were excluded.

## Variables of interest

For each original research article, the following data items were collected: year of publication, journal, gender of first author (male, female, group and unknown), country of first author's affiliation (Japan, overseas Asian and non-Asian), type of first

## INTRODUCTION

More than 17 million people worldwide die from cardiovascular diseases every year, accounting for an estimated 31% of all deaths.<sup>1</sup> In Japan, heart diseases were the second leading cause of death in 2012,<sup>2</sup> while the cost of treating cardiovascular diseases accounted for approximately 20% of all national medical expenses, the highest percentage among all illnesses.<sup>3</sup> The financial burden is expected to increase with population ageing in Japan, as in other industrialised countries.<sup>3,4</sup> Thus, the effective prevention of cardiovascular diseases and interventions to treat them represent one of the most important issues in industrialised countries.<sup>1</sup>

Randomised controlled trials (RCTs) are considered to be one of the most valuable study designs for investigating the causal relationships between interventions and their possible effects.<sup>5</sup> Evidence-based interventions may be able to reduce the burden of disability and death from heart diseases. Therefore, the results of RCTs make an essential contribution to the guidelines for any intervention.<sup>6</sup> The number of RCTs published worldwide is showing a tendency to rise significantly,<sup>7</sup> and the



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**To cite:** Matsuyama T, Fujii T, Takeuchi J, et al. *Heart Asia* 2017;9:1–5. doi:10.1136/heartasia-2017-010929

author's affiliation (university and non-university), total number of authors, corresponding author (first author and others) and study design (RCT, non-RCT human studies, animal studies and others). RCTs were defined as clinical studies whose study subjects were human and were randomly assigned among several groups and which investigated the efficacy of an intervention such as treatment. Only articles that reported the main results of RCTs were included in our analysis, whereas articles that only reported subgroup analysis and protocol articles were considered ineligible. The target disease of each RCT was classified into the following categories: ischaemic heart disease (IHD), hypertension, heart failure, dyslipidaemia, atrial fibrillation, cardiac surgery, chronic kidney disease, healthy volunteer, diabetes mellitus and others. In addition, the type of main intervention in each RCT was determined as drug, procedure, device or others. This study included the following Asian countries: China, Republic of Korea, Taiwan, India, Iran and Turkey.

The gender of the first author was noted, based on inspection of the first name. If the gender was not clearly indicated by the name, institutional websites, social media accounts that listed their publications (such as ResearchGate, Researchmap, LinkedIn and Facebook) and internet search engines (such as Google) were used to find photographs. Any first authors whose genders were not clearly identifiable were classified as 'unknown'. The total number of authors was defined as the count of the named authors, excluding any group listed at the end.

### Data quality

Four reviewers (TM, TF, JT and TK) used a standardised data collection sheet to collect data. Reviewers retrieved data independently, and the data were double-checked. Discrepancies were resolved through discussion among the reviewers.

### Statistical analysis

We investigated the 2-year trend of study characteristics of all included articles using the Cochran-Armitage trend test for categorical variables and the Jonckheere-Terpstra test for continuous variables. The 2-year trends in the prevalence of RCTs by journal and by year of publication were also evaluated using the Cochran-Armitage trend test. We applied univariable and multivariable logistic regression analyses and calculated crude or adjusted ORs (AORs) and their 95% CIs to assess the factors related to the publication of RCTs. The factors included the following independent variables: author gender, location of first author's affiliation, type of first author's affiliation, total number of authors, corresponding author and publication year. All statistical analyses were performed using SPSS statistical package V.22.0J. All tests were two tailed;  $p$  values of  $<0.05$  were considered statistically significant.

## RESULTS

Among the six journals, *JC* had been published for the last 8 years, whereas the other five journals had a history of publication that spanned the entire 10 years of the study period. During the study period, we retrieved 7124 original articles; after seven retracted articles had been excluded, 7117 articles were eligible for our final analyses.

The study characteristics of the included original articles by the year of publication are shown in [table 1](#). There was no significant change in the prevalence of a female first author or in the first author's affiliation ( $p$  for trend 0.066 and  $p$  for trend 0.298, respectively). The number of original articles from both Asian and non-Asian countries increased greatly (from 19.1% to

23.4%,  $p$  for trend 0.001 and from 8.0% to 15.2%,  $p<0.001$ , respectively). The proportion of RCTs among Japanese journals was 3.5% (252/7117). No significant change in the prevalence of RCTs among all included journals was noted (3.8% vs 3.1%,  $p$  for trend 0.751).

[Table 2](#) shows the prevalence of RCTs by journal and by year of publication. *HR* showed a slight increase from 1.1% (4/376) to 3.4% (8/234) ( $p=0.017$ ), whereas there was a trivial decrease for *IHJ* (4.1% (5/121) to 2.5% (4/157),  $p=0.045$ ). There was no significant change in the prevalence of RCTs in the other four journals. The types of patients and interventions in the 252 eligible RCTs are shown in [table 3](#). The largest proportion of patients was 33.7% (85/252) with IHD, followed by 13.5% (34/252) with hypertension and 12.7% (32/252) with heart failure. As for the type of intervention, research into drug effects was the most frequent (78.2%, 197/252).

We assessed the factors associated with the publication of RCTs. Male first author (AOR 1.97; 95% CI 1.30 to 2.99) and first author being corresponding author (AOR 1.60; 95% CI 1.22 to 2.10) were positively associated with RCTs. The RCTs from Asian countries were more likely to be published compared with ones from Japan (AOR 1.62; 95% CI 1.19 to 2.21), whereas those from non-Asian countries showed no significant difference (AOR 0.72; 95% CI 0.47 to 1.11) ([table 4](#)).

## DISCUSSION

Our findings demonstrated that the overall proportion of RCTs among all original research articles was 3.5% and that this showed no change during the study period. In addition, RCTs related to IHD were the most frequently published according to our data. In the multivariable analysis, a male first author and reports from Asia were significantly associated with the publication of RCTs. Our findings will provide fundamental information helpful for future directions in the cardiovascular field in Japan.

In this study, RCTs comprised 3.5% of all original research articles. In earlier reports, Hayashino and colleagues demonstrated that RCTs accounted for 2.1% of all research articles from Japan published in the top 10 cardiovascular journals overseas.<sup>9</sup> Kuroki and colleagues reported that the proportion of RCTs among published articles in the gynaecology field was 35% in high impact factor journals, such as the *New England Journal of Medicine*, the *Lancet*, and the *Journal of the American Medical Association*, and 12% in journals with a moderate impact factor, similar to that of Japanese cardiovascular journals.<sup>10</sup> This study only assessed the recent 10-year trends in the proportion of RCTs published in Japanese cardiovascular journals, and further continuous observation is needed to evaluate whether the proportion of RCTs in the cardiovascular field will increase or not.

We observed that RCTs related to IHD were the most frequently reported in Japanese cardiovascular journals during the study period. Kapoor and colleagues also demonstrated that clinical trials involving IHD made up the biggest group among all clinical trials on cardiovascular disease published from 1993 to 2013.<sup>8</sup> The global burden of IHD is exceedingly large; IHD is the leading cause of death in the world, but even non-fatal disease affects patients' lives negatively with the disabling symptoms of angina pectoris or ischaemic heart failure.<sup>11</sup> However, age-standardised IHD incidence and mortality rates have actually decreased in most world regions, especially those with high incomes, over the last several decades.<sup>12 13</sup> In Japan, age-standardised IHD incidence and mortality per 100 000 persons decreased from 111.0 and 79.5 in 1996 to 59.0 and 45.5 in

**Table 1** Study characteristics by year of publication

	Total		2006–2007		2008–2009		2010–2011		2012–2013		2014–2015		p for trend*
	(n=7117)		(n=1121)		(n=1415)		(n=1544)		(n=1507)		(n=1530)		
Gender of first author													
Female	1330	(18.7)	161	(14.4)	290	(20.5)	290	(18.8)	310	(20.6)	279	(18.2)	0.066 <sup>†</sup>
Male	5675	(79.7)	946	(84.4)	1110	(78.4)	1226	(79.4)	1163	(77.2)	1230	(80.4)	
Group	11	(0.2)	4	(0.4)	3	(0.2)	3	(0.2)	1	(0.1)	0	(0.0)	
Unknown	101	(1.4)	10	(0.9)	12	(0.8)	25	(1.6)	33	(2.2)	21	(1.4)	
Location of affiliation													
Japan	4656	(65.4)	817	(72.9)	973	(68.8)	987	(63.9)	939	(62.3)	939	(61.4)	<0.001
Asia	1443	(20.3)	214	(19.1)	256	(18.1)	306	(19.8)	309	(20.5)	358	(23.4)	0.001
Non-Asia	1018	(14.3)	90	(8.0)	185	(13.1)	251	(16.3)	259	(17.2)	233	(15.2)	<0.001
Affiliation													
University	5752	(80.8)	915	(81.6)	1137	(80.4)	1259	(81.5)	1227	(81.4)	1214	(79.3)	0.298
Others	1365	(19.2)	206	(18.4)	278	(19.6)	285	(18.5)	280	(18.6)	316	(20.7)	
Total no. of listed authors, median (IQR)	8	(6–10)	8	(6–10)	8	(6–10)	8	(6–10)	9	(6–11)	9	(6–11)	<0.001
Correspondence													
First author	3163	(44.4)	577	(51.5)	676	(47.8)	663	(42.9)	613	(40.7)	634	(41.4)	<0.001
Other	3954	(55.6)	544	(48.5)	739	(52.2)	881	(57.1)	894	(59.3)	896	(58.6)	
Study design													
RCT	252	(3.5)	43	(3.8)	34	(2.4)	63	(4.1)	65	(4.3)	47	(3.1)	0.751 <sup>†</sup>
Other non-RCT human study	5944	(83.6)	906	(80.9)	1182	(83.5)	1287	(83.3)	1251	(83.0)	1318	(86.1)	
Animal study	905	(12.7)	169	(15.1)	196	(13.9)	190	(12.3)	189	(12.5)	161	(10.5)	
Others (simulation and hospital questionnaire)	16	(0.2)	3	(0.3)	3	(0.2)	4	(0.3)	2	(0.1)	4	(0.3)	

IQR, first to third quartile.

Values are expressed as numbers (percentages) unless indicated otherwise.

\*Comparisons between the five groups were evaluated with the Cochran-Armitage trend test for categorical variables and the Jonckheere-Terpstra test for continuous variables.

†Compared between female first author and others

‡Compared between RCT and all other studies.

RCT, randomised controlled trial.

2014, respectively.<sup>2 14</sup> This is probably because active research into IHD may successfully improve lifestyle interventions (eg, weight management, smoking cessation or encouragement of physical activity), drug therapies for hypertension, dyslipidaemia or diabetes mellitus, and invasive procedures such as coronary interventions.<sup>15 16</sup> However, despite the decline in age-standardised IHD incidence and mortality, population ageing continues to lead to a higher burden of IHD globally.<sup>12</sup> Therefore, clinical trials involving other diseases whose incidence

increases with population ageing, such as atrial fibrillation or heart failure, will also become more important.

In this study, the prevalence of clinical studies from overseas increased; in particular, researchers in Asia made the greatest contribution to publishing RCTs. According to one previous report, the number of research articles published from Asia showed a marked increase recently in the world as well as in the Japanese cardiovascular journals.<sup>17</sup> Our findings would also indicate that Japanese cardiovascular journals have become more

**Table 2** Prevalence of randomised controlled trials by journal and year of publication

	2006–2007		2008–2009		2010–2011		2012–2013		2014–2015		p for trend*
<b>Total</b>	<b>3.8</b>	<b>(43/1121)</b>	<b>2.4</b>	<b>(34/1415)</b>	<b>4.1</b>	<b>(63/1544)</b>	<b>4.3</b>	<b>(65/1507)</b>	<b>3.1</b>	<b>(47/1530)</b>	<b>0.751</b>
<i>Circulation Journal</i>	3.9	(22/566)	3.3	(18/546)	3.7	(20/547)	6.1	(33/539)	2.9	(14/481)	0.669
<i>Heart and Vessels</i>	7.9	(8/101)	3.5	(4/115)	6.4	(10/156)	3.6	(6/165)	3.8	(7/185)	0.182
<i>Hypertension Research</i>	0.4	(1/252)	1.1	(4/376)	2.5	(8/321)	1.1	(3/263)	3.4	(8/234)	0.017
<i>International Heart Journal</i>	7.5	(10/133)	4.1	(5/121)	4.5	(6/132)	3.2	(4/126)	2.5	(4/157)	0.045
<i>Journal of Atherosclerosis and Thrombosis</i>	2.9	(2/69)	0.8	(1/126)	4.3	(10/235)	3.3	(6/183)	4.4	(9/203)	0.226
<i>Journal of Cardiology</i>			1.5	(2/131)	5.9	(9/153)	5.6	(13/231)	1.9	(5/270)	0.644

Values are expressed as percentages (numbers) unless indicated otherwise.

\*Comparisons between the five groups were evaluated with the Cochran-Armitage trend test.

**Table 3** Type of patients and interventions in randomised controlled trials

	Total (n=252)		Drug (n=197)		Procedure (n=40)		Device (n=10)		Others (n=5)	
Ischaemic heart disease	85	(33.7)	70	(35.5)	8	(20.0)	7	(70.0)	0	(0.0)
Hypertension	34	(13.5)	30	(15.2)	3	(7.5)	0	(0.0)	1	(20.0)
Heart failure	32	(12.7)	23	(11.7)	8	(20.0)	0	(0.0)	1	(20.0)
Dyslipidaemia	25	(9.9)	24	(12.2)	0	(0.0)	0	(0.0)	1	(20.0)
Atrial fibrillation	16	(6.3)	11	(5.6)	5	(12.5)	0	(0.0)	0	(0.0)
Cardiac surgery	10	(4.0)	4	(2.0)	6	(15.0)	0	(0.0)	0	(0.0)
Chronic kidney disease	9	(3.6)	7	(3.6)	1	(2.5)	0	(0.0)	1	(20.0)
Healthy volunteer	8	(3.2)	6	(3.0)	1	(2.5)	1	(10.0)	0	(0.0)
Diabetes mellitus	2	(0.8)	2	(1.0)	0	(0.0)	0	(0.0)	0	(0.0)
Others	31	(12.3)	20	(10.2)	8	(20.0)	2	(20.0)	1	(20.0)

Values are expressed as numbers (percentages).

internationally recognised since the 2000s. Importantly, globalisation can help foster cross-cultural understanding, widespread collaboration and the valuable exchange of ideas and products.<sup>18</sup> The Japanese Circulation Society promotes the development of cardiovascular medicine in Japan and throughout all Asia and has created the Circulation Journal Asian Award for Asian cardiovascular researchers.<sup>19</sup> The promotion might successfully attract a great number of Asian cardiovascular researchers.

The present study underscored that females accounted for 18.7% of first authors of original research articles, whereas males were about twice as likely to be the first author of an RCT. Filardo and colleagues observed that the proportion of female first authors in original research articles was 34.0% among worldwide high-impact general medical journals.<sup>20</sup> Gender inequality has been noted in Japan. For example, according to the Global Gender Gap Report 2016, Japan was ranked 111th out of 144 countries in terms of gender equality based on economic, political and health criteria.<sup>21</sup> In Japan, the proportion of female physicians gradually increased from 16.5% in 2004 to 20.4% in 2014.<sup>22</sup> As for the Japanese Circulation Society, female members accounted for 12.5% of all members in 2015, and there was only 1.4% increase compared with 11.1% in 2005. However, Yamauchi-Takahara demonstrated that the proportion of the female presenter at its annual

scientific meeting increased from 11.0% in 2006 to 15.4% in 2015.<sup>23</sup> Although there is no proven association between presenter at a scientific meeting and an increase in the number of any kinds of research articles, gender disparities have gradually improved,<sup>21 22</sup> and further observation and efforts will be required to achieve gender equality.

#### STUDY LIMITATIONS

This study has several inherent limitations. First, some misclassification might have occurred because each reviewer retrieved data manually by reading the manuscript. However, to minimise errors, the data were double-checked. Second, our findings cannot be generalised to the whole of Japanese cardiovascular research, because we investigated only the six Japanese cardiovascular journals that have years of history of publication in English. RCTs might be submitted to other journals with a higher impact factor worldwide, and we were not able to determine how many times papers including RCTs published in Japanese cardiovascular journals were submitted to other journals. Third, we assessed the factors associated with RCTs, but we could not exclude possible residual confounding factors.

**Table 4** Factors associated with randomised controlled trials

	Total	RCT	(%)	Crude OR	(95% CI)	p Value	Adjusted OR	(95% CI)	p Value
Gender of first author									
Male	5675	226	(4.0)	2.07	(1.36 to 3.04)	<0.001	1.97	(1.30 to 2.99)	0.001
Female	1330	26	(2.0)	Reference			Reference		
Location of affiliation									
Japan	4632	163	(3.5)	Reference			Reference		
Asia	1371	64	(4.7)	1.34	(1.00 to 1.80)	0.051	1.62	(1.19 to 2.21)	0.002
Non-Asia	1002	25	(2.5)	0.70	(0.46 to 1.08)	0.103	0.72	(0.47 to 1.11)	0.133
Affiliation									
University	5662	207	(3.7)	1.09	(0.80 to 1.50)	0.589	1.21	(0.87 to 1.69)	0.255
Others	1343	45	(3.4)	Reference			Reference		
Correspondence									
First author	3142	136	(4.3)	1.44	(1.13 to 1.84)	0.003	1.60	(1.22 to 2.10)	0.001
Other	3863	116	(3.0)	Reference			Reference		
Total no. of listed authors (for increment of authors by one)				1.00	(0.97 to 1.04)	0.859	1.01	(0.87 to 1.69)	0.630
Publication year (for increment of year by one)				1.01	(0.96 to 1.05)	0.766	1.02	(0.97 to 1.06)	0.534

Analysed by eliminating 11 papers by a group author and 101 where the first author's gender was unknown.  
RCT, randomised controlled trial.



## CONCLUSION

Since the 2000s, RCTs accounted for 3.5% of all original research articles published in Japanese cardiovascular journals, and there was no change in the prevalence of RCTs over the last decade. Future continuous observation will be required to evaluate trends in the proportion of RCTs in Japanese cardiovascular journals.

## Key messages

## What is already known about this subject?

- The number of randomised controlled trials (RCTs) published worldwide is showing a tendency to rise significantly, and the number of clinical trials in the field of cardiology, including RCTs, has been increasing.

## What might this study add?

- In Japanese cardiovascular journals, RCTs accounted for 3.5% of all original research articles published, and there was no change in the prevalence of RCTs during the study period from 2006 through 2015.

## How might this impact on clinical practice?

- Our findings will provide fundamental information helpful for future directions in the cardiovascular field in Japan.

**Acknowledgements** We would like to thank Ms Ling Zha, Ms Rong Liu and Ms Son Hyesoon for determining the genders of authors in China, Taiwan and South Korea.

**Contributors** Conceived and designed the study: TM, TF, JT and TK. Analysed the data: TM, JT, MH and TK. Wrote the paper: TM, TF, MH and TK.

**Competing interests** None declared.

**Patient consent** As this study consisted only of a journal review and did not involve individual patients, ethical approval or any consents are not required.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data sharing statement** TM and TK had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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