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EDITORIAL

Subgroup analyses of randomized clinical trials in heart failure: facts and numbers

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Abstract

Subgroup analyses of major randomized clinical trials in heart failure are published frequently, but their impact on medical knowledge and practice guidelines has not been previously reported. In a novel analysis, we determined number of citations, impact factors, number of authors, and citations in guidelines of both parent trials and sub-studies; we also qualitatively assessed whether the analyses were described as post-hoc and non-pre-specified. A total of 229 sub-studies evaluating outcomes in patient subgroups were published (median 6, range 0–36 per trial). The number of subjects in the parent trials positively correlated with number of sub-studies (rho = 0.51, $P = 0.009$). The subgroups are frequently not pre-specified. The impact factors of sub-studies were lower in comparison to the parent trials as were the number of citations two years after the publication date; in addition, parent trials were cited more frequently in European and American professional guidelines compared with the sub-studies. We maintain that the sub-studies derived from major heart failure trials are frequently published, but their contribution to clinical guidelines and medical knowledge are highly debatable.

Keywords Heart failure; Sub-studies; Randomized clinical trials

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Major advances in the management of heart failure have been established in large, double-blind, randomized placebo-controlled clinical trials (RCTs) of both device and drug interventions. Data derived from these trials have influenced clinical practice guidelines, quality metrics, and patient care. Following the dissemination of the results of RCTs, additional analyses evaluating the efficacy and/or safety of the particular intervention in specific patient subgroups are published frequently. However, it is not clear whether these sub-studies add meaningfully to general medical knowledge, in large part because the analyses are often not pre-specified and the specific patient subgroups were not included in the randomization schema.[1,2]

Wittes has stated that 'if reporting on subgroups is tempting but treacherous, failing to report on them seems unscientific and incurious'.[3] This tension was also highlighted by Feinstein who termed subgroup analysis a 'clinic-statistical tragedy'; that is, statisticians and clinicians approach subgroups from different perspectives. Broadly stated, he summarized the challenge of placing subgroup analysis in context by area of expertise: 'The statisticians are right in denouncing subgroups that are formed post hoc from exercises in pure data dredging. The clinicians are also right, in insisting that a subgroup is respectable and worthwhile when established a priori from pathophysiological principles'.[4]

In light of this ongoing controversy and the plethora of subgroup analyses that populate the medical literature following reporting of the results of the parent trial, we sought to characterize the types of sub-studies that appear after the initial RCT report and to critically analyse their impact. The major goal was to evaluate the number and scope of these sub-studies and their contribution to clinical practice guidelines, specifically the 2013 American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) Guideline for the Management of Heart Failure and the 2012 European Society of Cardiology Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure.[5,6] We were also interested in the proportion of sub-studies that directly referenced an interaction effect as represented in the forest plot of the parent trial publication.[2]

A method to assess the impact of subgroup analyses

We employed a widely used CHF Trials application[7] to identify major RCTs published in the last two decades that evaluated classes of medications and devices, many of which are accepted as guideline-directed therapies for the treatment of congestive heart failure (CHF). Only trials with more than 500 participants were included in five major therapy groups: angiotensin receptor blockers/angiotensin converting enzyme inhibitors (ARB/ACEI), beta-blockers, aldosterone antagonists, implantable cardioverter defibrillators (ICDs), and cardiac resynchronization therapy (CRT). The three studies from the Candesartan in Heart failure—Assessment of Mortality and Morbidity (CHARM) programme (CHARM-Added, CHARM-Alternative and CHARM-Preserved) were considered to be a single trial.

To focus the analysis on sub-studies that involved comparison of treatment effect centred on baseline patient characteristics, we refined our sample by excluding meta-analyses and sub-studies that focused on biomarkers or imaging, mode of death, risk models, cost-analyses, registries, and evaluation of quality-adjusted life years (QALYs) (*Table 1*). These latter analyses can provide insight into mechanism of action and pathophysiology and may use outcome measures that are not part of the primary or secondary endpoints (e.g. impact of an intervention on a biomarker).

The Web of Science Database was used to identify a comprehensive list of all English language sub-studies pertaining to the parent RCTs.[8] Using the 'Times Cited' option on Web of Science, we identified all sub-studies that cited the original article. Similarly, we analysed the number of citations of sub-studies over a two-year window following the publication date of the sub-study. Therefore, sub-studies published after November 2012 were excluded. The impact factors for the journals in which the parent trials and sub-studies were published were obtained from Journal Citation Reports (JCR) for the specific year of publication.[9] Sub-studies published in 2014 were excluded from this part of the analysis as the impact factors were not known.

Table 1 Inclusion and Exclusion Criteria

Inclusion criteria	Exclusion criteria

• >500 study subjects
• Trial listed in the application found at www.imedicalapps.com for the key therapeutic classes:
  ° ACEi/ARB
  ° Beta-blocker
  ° Mineralocorticoid receptor antagonist
  ° ICD/CRT device
• Trial dates between 1996 and 2013
	• Meta analyses
	• Biomarker substudies
	• Imaging substudies
	• Mode of death analyses
	• Risk model development
	• Cost and QALY analyses

The endpoints used in the sub-studies were examined for whether or not they were the primary endpoint(s) or secondary endpoint(s) in the parent RCT. We also examined (1) whether parent trial characteristics (size, impact factor, number of authors) predicted the publication of subgroup analyses and (2) whether the parent trial and sub-studies were referenced in the 2013 ACCF/AHA Guidelines by searching on author name, title of study and name of drug or device. Studies published in 2013, 2014 or 2015 were excluded from this part of the analysis as they were published too late to be referenced. Similarly we evaluated the 2012 European Society of Cardiology Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure, excluding studies published in 2012 to 2015 inclusive.

Descriptive statistics were calculated for all variables. Means and standard deviations were used where applicable; in the case of extreme skewness, median and range were used. Spearman rho correlation coefficients were calculated between some sub-study and parent study variables.

The data on subgroup analyses: large numbers, uncertain impact

Our findings raise issues about the value of subgroup analyses. Of 25 major clinical trials relevant to guideline-directed optimal medical therapy in heart failure published between 1996 and 2013 with greater than 500 participants, a total of 477 publications were identified that included analyses of data derived from the parent RCT. As shown in *Figure 1*, we subsequently removed 248 papers that met our exclusion criteria.

The median number of study patients was 3043 (range 571–14 703). The mean numbers of primary and secondary endpoints in the RCTs were 1.4 ± 0.6 and 3.0 ± 2.3, respectively. One or more pre-specified primary endpoints were met in 88% (22/25) of RCTs. The number of subgroups mentioned in the parent study (in text or forest plots) ranged from 1 to 19 (mean 8.9 ± 5.0). All but one of the RCTs was financially supported by industry (pharmaceutical or device).

The median number of sub-studies per RCT was 6.0 (range 0–36). The number of subjects in the main study was positively correlated with the number of sub-studies (rho = 0.51, $P = 0.009$). The median number of new endpoints introduced in the sub-studies was 3.5 (range 0–45). The median number of months between publication of the parent RCT and publication of the sub-studies was 48 (range 4–178); thus, 50% of sub-studies were published more than 4 years after publication of the parent study (*Figure 2*). Excluding three RCTs where the author byline indicated a consortium rather than individual authors, the numbers of authors on the parent RCTs and the sub-studies were comparable, with means of 10.9 ± 3.6 and 9.2 ± 2.8, respectively.

Sub-study analyses of subgroups that were not pre-specified or part of the randomization scheme in the parent

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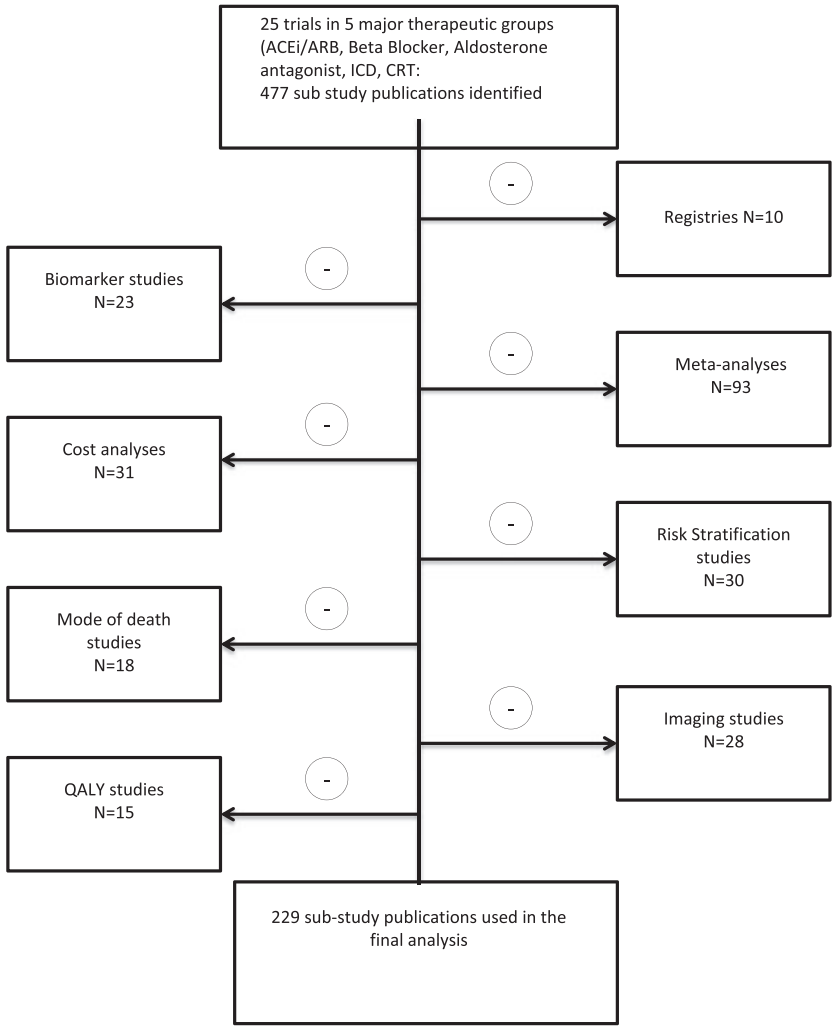
Figure 1 CONSORT diagram outlining derivation of the sample.



RCT were common (186/229 or 81.2% and 183/229 or 79.9%, respectively). The number of subjects in the parent RCTs was positively correlated with the number of sub-studies with subgroups that were not pre-specified (rho = 0.44, $P = 0.03$).

The impact factor of the parent RCT publication (mean 31.6 ± 14.0) was much higher than the sub-study impact factors (mean 6.5 ± 4.3), as were the number of citations (main study mean 233.7 ± 102.2 vs. sub-study mean 10.8 ± 10.0) (*Table 2*). The parent study impact factor was negatively correlated with median months to publication of sub-studies (rho = −0.41, $P = 0.04$): higher parent RCT impact factor was associated with faster publication of sub-studies. In addition, higher impact factor parent RCTs generated higher average impact factor sub-studies (rho = 0.44, $P = 0.03$).

The parent RCT was much more likely to be referenced in the ACCF/AHA and ESC Guidelines (87.5% and 83.3%, respectively) compared with the sub-studies (5.2% and 1.8%, respectively) (*Table 3*). Although a slight majority (141/229, 61.6%) of sub-studies tested an interaction effect (e.g. moderation of parent trial efficacy as a function of a subject characteristic variable), only one-third examined an interaction effect represented in the parent trial forest plot.

Prior evaluations of the value of subgroup analyses derived from HF Trials

An extensive literature exists about the limitations of subgroup analyses derived from RCTs.[1–4,10,11] While these analyses, in theory, permit evaluation of treatment effects in select patient subgroups defined by baseline characteristics, there are multiple statistical pitfalls that can lead to inappropriate conclusions and, by extension, misguided clinical decision-making. Assman and colleagues reviewed original RCT reports published in four prominent journals in 1997 and found a numerical range of subgroups from 1 to 24, often accompanied

Figure 2 Temporal relationship between publication date of parent trial and substudy. ● = parent trial publication ○ = substudy publication.

		'96	'97	'98	'99	'00	'01	'02	'03	'04	'05	'06	'07	'08	'09	'10	'11	'12	'13	'14
ARB	Val-HeFT						●○○	○	○○	○○ ○	○	○ ○	○	○	○					○
	CHARM								●	○ ○	○○○○ ○○	○○○○ ○○	○ ○	○○○○ ○	○○				○	
	VALIANT								●	○	○○○○ ○○○		○○○○	○○○○	○ ○					
	I-PRESERVE													●			○	○	○	
	HEAAL														●		○		○	
BB	US-Carvedilol	●					○													
	CIBIS-II				●	○	○○		○○			○				○				
	MERIT-HF				●		○○○○ ○	○ ○	○	○○	○	○		○○					○	
	CAPRICORN						●			○			○							
	COPERNICUS						●	○	○		○									
	COMET								●	○○	○	○○○○	○							
	SENIORS										●		○		○○	○	○○	○		
ALDO ANTAGONIST	RALES				●													○ ○	○	
	EPHESUS								●		○ ○	○		○ ○	○ ○○	○ ○	○ ○○	○ ○	○○	
	EMPHASIS																●	○○ ○	○ ○	○
ICD	AVID		●	○ ○		○ ○ ○	○ ○	○	○ ○		○									
	MADIT-II							●		○	○○○○ ○	○○○○ ○○	○○○○	○	○○○○		○	○○	○○	
	SCD-HeFT										●		○○○	○○○○ ○			○		○ ○	○
CRT	MIRACLE							●		○○				○						
	MIRACLE-ICD								●	○										
	COMPANION									●		○○					○			
	CARE-HF										●	○	○	○	○					
	MADIT-CRT														●	○○○○ ○○○○ ○○	○ ○ ○	○○○○ ○○○○ ○○○○	○○○○ ○○○○ ○○○	
	RAFT															●	○ ○			
	BLOCK-HF																		●	

Table 2 Comparisons of parent RCT and sub-study impact factors and citation indices

Drug/device class	Impact factor of parent RCT	Citation index of parent RCT	Impact factor of sub-studies	Citation index of sub-studies
Aldosterone Antagonist	39.0 (12.7), 3	293.7 (57.1), 3	8.0 (4.7), 22	12.4 (11.4), 18
ARB/ACEI	32.6 (11.5), 5	165.2 (79.9), 5	7.2 (4.4), 59	11.8 (10.3), 57
Beta-Blocker	16.5 (8.1), 7	226.4 (114.8), 7	5.4 (3.1),42	11.1 (9.4), 40
CRT	41.5 (11.9), 7	244.8 (109.2), 6	7.9 (4.9), 44	13.0 (12.7), 27
ICD	34.5 (8.5), 3	283.0 (115.6), 3	4.8 (3.1), 48	7.2 (6.7), 44
Total	31.6 (14.0), 25	233.7 (102.2), 24	6.5 (4.3), 215	10.8 (10.0), 186

ARB/ACEI, angiotensin receptor blocker/angiotensin converting enzyme inhibitor; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter defibrillator.
RCTs on aldosterone inhibitors are the following: EMPHASIS-HF, EPHESUS, RALES. The RCTS of ARB/ACEI include the following: VALIANT, CHARM, HEAAL, i-PRESERVED, Val-HeFT. The RCTs under beta-blocker include the following: CAPRICORN, CIBIS-II, COMET, COPERNICUS, MERIT-HF, SENIORS, US-Carvedilol Studies. The RCTs on CRT are as follows: BLOCK-HF, CARE-HF, COMPANION, MADIT-CRT, MIRACLE, MIRACLE-ICD, RAFT. The RCTs on ICD are as follows: AVID, MADIT-II, SCD-HeFT.
Data are mean (SD), N.

by improper statistical testing.[3] In a subsequent analysis by Sun et al., 207 of 469 published RCTs were found to include subgroup analyses; the number of subgroup analyses was correlated with higher impact factors and a larger number of patients in the clinical trial. Subgroup analyses without statistical significance were more likely to be published from parent studies that were industry funded.[12] Hernandez et al. noted subgroup analyses in 39 of 63 RCTs from the cardiovascular discipline, but with only 11 reporting tests of interaction between average and subgroup treatment effects; larger studies were more likely to include subgroup analyses.[13] None of these studies critically evaluated the publication of separate papers that involved subgroup analyses and followed the publication of the parent RCT.

We noted that the impact factor of the journals and citation index regarding sub-studies are much lower compared with parent RCTs. From our perspective, we believe that there is a general lack of clarity in defining the endpoints as post hoc and/or not pre-specified, consistent with a prior report.[3] Importantly, very few sub-studies are referenced in the major professional guidelines, suggesting that they may be seen at best as hypothesis generating. As such, they have relatively limited relevance and/or do not meet a more rigorous threshold upon which formal recommendations for clinical care can be made. Lastly, sub-study investigations of interaction effects originated from parent trial interaction forest plots in only about one-third of the cases, indicating that two-thirds of interaction sub-studies were post hoc in nature.

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Table 3 Representation of parent RCTs and sub-studies in guideline statements

	ACCF/AHA guidelines[a]		ESC guidelines[b]	
Drug/device class	Parent RCT	Sub-studies	Parent RCT	Sub-studies
Aldosterone Antagonist	100% (3/3)	0% (0/20)	100% (3/3)	0% (0/12)
ARB/ACEI	80% (4/5)	5% (3/58)	80% (4/5)	5% (3/55)
Beta-blocker	86% (6/7)	9% (4/42)	100% (7/7)	0% (0/38)
CRT	100% (6/6)	7% (2/27)	67% (4/6)	0% (0/21)
ICD	67% (2/3)	2% (1/46)	67% (2/3)	0% (0/43)
Total	87% (21/24)	5% (10/193)	83% (20/24)	2% (3/169)

ACCF/AHA, American College of Cardiology Foundation/American Heart Association; ARB/ACEI, angiotensin receptor blocker/angiotensin converting enzyme inhibitor; CRT, cardiac resynchronization therapy; ESC, European Society of Cardiology; ICD, implantable cardioverter defibrillator; RCT, randomized controlled clinical trial.
Data are % (n/N).
[a]Reference 5.
[b]Reference 6.

Despite this, papers that include subgroup analyses continue to be published for years following the publication of the parent RCT (median 4 years). In our analysis, the size of the study was positively correlated with the number of sub-studies, and the higher the impact factor of the parent RCT, the faster the sub-studies were published. Nevertheless, because it is generally not feasible to critically assess the impact of subgroup analyses on clinical care, we can ask: do the results of these analyses impact clinician decision-making? If so, how and to what degree? Well-designed focus groups with clinicians could provide some insight into the extent to which results from these studies are incorporated into daily practice. Whether they should in fact influence decisions about patient selection for specific therapy is less clear.

Concluding thoughts

Although a guideline exists that supports the publication of subgroup analysis,[14] this is far from universally accepted. In a frequently cited example, the authors of the definitive paper from the ISIS-2 study were asked by the journal editors to include patient astrologic sign in one of the tables in order to highlight the 'trap' associated with subgroup analysis.[15] Peter Sleight has also commented that there are '…examples of erroneous interpretation of subgroup analyses that have caused harm to patients'.[16]

Subgroups have the potential to generate hypotheses for further prospective investigation; there is one such example in the heart failure discipline in which the combination of hydralazine and nitrates was determined to be effective in African Americans in the Vasodilator-Heart Failure Trial (V-HeFT),[17] and subsequently this group was examined in the African–American Heart Failure Trial (A-HeFT).[18] However there are also a significant number of examples in which subgroups led to additional negative studies, such as amlodipine in the elderly[19] and amlodipine in patients with non-ischemic cardiomyopathy[20] or more commonly to no studies at all.

In summary, subgroup analyses are frequently published, vary in their transparency about the nature of the statistics (in particular whether the subgroups were pre-specified), and infrequently contribute to recommendations in published clinical guidelines. We believe that a uniform approach[4,21] and greater degree of rigour may be required in assessing the value of these studies prior to publication, incorporation into clinical practice guidelines, and by extension, clinical practice itself.

Conflicts of interest

None declared.

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