Letters

RESEARCH LETTER

Subgroup Analyses in Trial Reports Comparing Percutaneous Coronary Intervention With Coronary Artery Bypass Surgery

Subgroup analyses within randomized clinical trials (RCTs) may not be valid,[1,2] although they may identify important treatment heterogeneity. Reviews of subgroup analyses in primary reports of RCTs have found low credibility due to methodological or reporting issues.[2] Subgroup analyses may also be presented in separate reports of extended follow-up beyond the primary end point or specific subgroups of patients.

No data are available on the quality of subgroup analyses in these subsequent reports. We evaluated subgroup analyses in reports from RCTs comparing percutaneous coronary intervention (PCI) with coronary artery bypass grafting (CABG).

Methods | PubMed was searched up to January 1, 2011, to identify primary end point reports of RCTs comparing PCI with CABG for complex coronary artery disease using the following search: "(PCI OR PTCA OR percutaneous coronary intervention) AND (CABG OR coronary bypass) AND (random*)." A second search through January 1, 2012, identified subsequent reports of extended follow-up beyond the primary end point or subgroups of patients (eg, patients with diabetes).

Two researchers collected data on characteristics of subgroup analyses from the reports: (1) subgroups prespecified in the trial protocol; (2) reported groups complementary to the investigated subgroup (eg, patients with diabetes but also those without diabetes); (3) number of subgroup analyses; (4) primary or secondary end points analyzed; (5) interaction tests used; (6) subgroup differences claimed; (7) subgroup results emphasized in the text or abstract; and (8) caution advised about interpretation of subgroup results. These characteristics were chosen based on expert consensus and quality measures of subgroup analyses used in other reports.[1-3]

Results | Seventeen trials reporting primary end points were published, along with 19 follow-up and 28 subgroup reports. Subgroup analyses appeared in 5 primary reports (29%), 13 follow-up reports (68%), and 28 subgroup reports (100%). Thirteen trials reported subgroup analyses: 5 in the primary reports (29%), 8 in follow-up reports (47%), and 9 in subgroup reports (53%).

Prespecification of subgroups was mentioned in 4 trials and 12 reported exploratory post hoc subgroup analyses on groups not prespecified. All primary and follow-up reports included the complementary subgroups, whereas 10 subgroup reports (36%) only reported results of the subgroup of interest.

There were differences between primary, follow-up, and subgroup reports in the total number of subgroup analyses performed (70 vs 372 vs 952, respectively) and the median number of analyses per report (0 vs 12 vs 26, respectively) (**Table 1**). Subgroup analyses were performed on secondary end points in 25% vs 52% vs 84%, respectively.

An interaction test was not reported in 40% of primary reports, 54% of follow-up reports, and 71% of subgroup reports (**Table 2**). Nevertheless, subgroup differences were claimed in 70% of reports, with an emphasis on these results in 87%. Caution in interpretation was mentioned in only 22%.

Discussion | We identified many shortcomings in subgroup analyses in reports of RCTs of PCI vs CABG. We found an increase in the number of subgroup analyses from primary to follow-up to subgroup reports, which were also more often performed on secondary end points. Moreover, subgroup analyses appeared to be of poorer methodological quality from primary to follow-up to subgroup reports.

Subgroup analyses, particularly those that are published separately from the main trial result, must be interpreted cautiously. Some prespecified analyses are of clinical importance, but conclusions from exploratory analyses may not be sufficiently robust to justify changes in treatment for specific subgroups. Still, these analyses are considered for drug and device approval and are used to establish guidelines.[4,5]

The Consolidated Standards of Reporting Trials (CONSORT) statement provides little guidance on how subgroup analyses should be reported and lacks any specific guidance on drafting follow-up or subgroup reports.[6] To prevent spurious observations

Table 1. Number of Subgroup Analyses in Trial Reports

	No. (%) of Reports			
	All (n = 64)	Primary (n = 17)	Follow-up (n = 19)	Subgroup (n = 28)
No. of subgroup analyses				
0	18 (28)	12 (71)	6 (32)	0
1-10	10 (16)	2 (12)	1 (5)	7 (25)
11-20	12 (19)	1 (6)	6 (32)	5 (18)
21-30	6 (9)	2 (12)	0	4 (14)
>30	18 (28)	0	6 (32)	12 (43)
Total No. of subgroup analyses (median) [IQR]	1394 (NA)	70 (0) [0-3]	372 (12) [0-34][a]	952 (26) [10-44]

Abbreviations: IQR, interquartile range; NA, not applicable.

[a] In 3 reports, it could not be determined what the total amount of subgroup analyses were.

Table 2. Reporting of Subgroup Analyses in Trial Reports

	No. (%) of Reports With Subgroup Analyses			
	All (n = 46)	Primary (n = 5)	Follow-up (n = 13)	Subgroup (n = 28)
Subgroup variables, median (IQR)[a]	NA	2 (1-5)	3 (1-7)	1 (1-1)
Complexity of coronary disease	NA	3 (60)	8 (62)	5 (18)
Diabetes	NA	2 (40)	13 (100)	11 (39)
Sex	NA	2 (40)	5 (38)	3 (11)
Angina grade	NA	2 (40)	5 (38)	0
Age	NA	1 (20)	5 (38)	3 (11)
Left ventricular function	NA	1 (20)	4 (31)	2 (7)
Proximal LAD artery lesion	NA	1 (20)	5 (38)	2 (7)
Interaction test reported				
Yes	9 (20)	2 (40)	2 (15)	5 (18)
Yes, but for only part of the analyses	8 (17)	1 (20)	4 (31)	3 (11)
No	29 (63)	2 (40)	7 (54)	20 (71)
Subgroup difference claimed				
Yes	32 (70)	5 (100)	8 (62)	19 (68)
No	14 (30)	0	5 (38)	9 (32)
Emphasis on subgroup results				
Yes	40 (87)	3 (60)	9 (69)	28 (100)
No	6 (13)	2 (40)	4 (31)	0
Advised caution with interpretation or reported as hypothesis-generating				
Yes	10 (22)	1 (20)	2 (15)	7 (25)
No	36 (78)	4 (80)	11 (85)	21 (75)

Abbreviations: IQR, interquartile range; LAD, left anterior descending; NA, not applicable.

[a] Does not add up to the number of reports in each category because analysis of multiple subgroups within a single report is possible. Other variables on which subgroup analyses were based that were not included in the table because performed infrequently, were analyses according to acute coronary syndrome, reoperation, body mass index, peripheral vascular disease, hypertension, hypercholesterolemia, stent use, type of lesion, smoking, electrocardiogram abnormalities, congestive heart failure, metabolic syndrome, renal disease, occluded vessel, and completeness of revascularization.

and minimize treatment errors, improving analysis and interpretation of subgroup data should receive more attention.

The limitations of this study include the sample size and potential lack of generalizability because of its focus on PCI vs CABG trials.

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Author Contributions: Drs Head and Kappetein 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.
Study concept and design: Kaul, Tijssen, Kappetein.
Acquisition of data: Head.
Analysis and interpretation of data: Head, Kaul, Tijssen, Serruys, Kappetein.
Drafting of the manuscript: Head, Kaul, Kappetein.
Critical revision of the manuscript for important intellectual content: Kaul, Tijssen, Serruys, Kappetein.
Statistical analysis: Head, Kaul, Tijssen, Kappetein.
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COMMENT & RESPONSE

Surgery vs Watchful Waiting for Mitral Regurgitation

To the Editor Dr Suri and colleagues[1] reported data on 1021 patients with flail mitral valve regurgitation and no or mild symptoms and compared outcomes of surgery within 3 months vs