Heterogeneity of patients in clinical trials

Subgroup analysis and covariate adjustment in cardiovascular and neurosurgical trials

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Heterogeniteit van patiënten in gerandomiseerde klinische studies
Subgroep en covariaat analyse in cardiovasculaire en neurochirurgische studies

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A la memoria de mi madre Luz y de mi padre Edgardo

A Daniela

A mis hermanos y familiares

A mis amigos de ayer, hoy y siempre
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**Chapter 2.2**
Hernández AV, Eijkemans MJC, Steyerberg EW. Randomized controlled trials with time-to-event outcomes: how much does pre-specified covariate adjustment increase power?. Ann Epidemiol 2006; 16: 41-8

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**Chapter 4.1**

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General Introduction
1.1 Heterogeneity of patients in clinical trials

Randomized clinical trials (RCTs) are essential to evaluate the usefulness of treatments and interventions. Trials inform and influence clinical practice. Clinicians rely increasingly on RCTs to distinguish between worthwhile, useless and harmful interventions.

RCTs are often performed in patients who are heterogeneous with respect to prognosis. Heterogeneity occurs in many clinical fields, such as traumatic brain injury (TBI), acute coronary syndromes (ACS), stroke, and cancer. Even with strict inclusion criteria, patient prognosis can vary according to baseline characteristics (e.g. age, gender, disease severity). For instance, the 6-month mortality for TBI patients older than 65 years is around 72%, in contrast to 21% for patients younger than 35 years. Likewise, patients with unstable angina/non-ST-segment elevation acute coronary syndromes and 7 strong prognostic variables have a much higher risk to develop an adverse outcome than those without prognostic variables (41% vs. 5%).

1.2 Problems related to heterogeneity of patients

Heterogeneity may lead to imbalance of randomized groups with respect to prognosis. This imbalance is due to pure chance when a proper randomization procedure was followed. Stratified randomization reduces the chances of imbalance between treatment groups for known factors. This is a two-stage procedure in which patients who enter a clinical trial are first grouped into strata according to predictors. Within each stratum, patients are then assigned to a treatment according to separate randomization schedules. For example, patients over 65 years may be randomized separately from patients under 65.

Heterogeneity may dilute the beneficial effect of treatments in some subgroups of patients satisfying the inclusion criteria. For instance, TBI patients with good prognosis (<20% of 6-month unfavorable outcome) or bad prognosis (>80% of 6-month unfavorable outcome) may not receive benefit from a treatment, because they are too healthy or too sick. It can be hypothesized that patients with an intermediate prognosis (e.g. between 20% and 80%) may benefit most from a treatment. Such a prognostic category can be defined by a combination of baseline characteristics. Clinical staging in cancer is a way to combine patients characteristics, and it is frequently used in oncology clinical trials. Moreover, a treatment may be more effective in subgroups of patients with some characteristics, especially those related to a mechanism of action of the treatment. For example, it could be that TBI patients with mass
lesions may benefit more from certain treatments than others. 

1.3 Possibilities of analysis in trials with heterogeneous patients

The heterogeneity of patients offers some possibilities to deal with the cited problems. Two methods are often used in the analysis phase of a trial: covariate adjustment and subgroup analysis. Covariate adjustment leads to adjusted estimates of the treatment effects, in contrast to unadjusted estimates. An unadjusted estimate of the treatment effect may be interpreted as relating to an “average” patient with a certain disease. Adjusting for one predictor (e.g. age) results in an estimate for “a patient with a certain age”. Adjusting for all known predictive baseline characteristics results in a treatment effect in patients with “a certain risk profile”.

Covariate adjustment also corrects for imbalance, and increases the statistical power to detect a significant treatment effect. Thus, it potentially reduces the sample size requirements. For instance, adjustment of the treatment effect for 17 predictors of 30-day mortality of patients with acute myocardial infarction (MI) enrolled in the GUSTO-I trial reduced the required sample size by 15%. In a simulation study using a TBI registry, adjustment for age and Glasgow Coma Scale (GCS) motor score reduced the sample size requirements by 30%. However, the quantification of the increase in power and the potential reductions in sample size requirements in empirical RCTs has been insufficiently studied.

Subgroup analysis assesses differences in treatment effect between different subpopulations of patients. A subgroup is a group of patients with a common set of baseline characteristics. Journals have devoted a large number of pages describing treatment effects in particular groups of patients. However, subgroup analyses have been generally misused and overinterpreted in the last two decades, and it is not known if their use has improved in recent years. Trials of a size adequate to detect an overall effect cannot be expected to provide reliable effect estimates within smaller groups. This problem can be tackled by a meta-analysis of RCTs, which may substantially increase the power to detect differential treatment effects across subgroups of patients.

1.4 Heterogeneity in traumatic brain injury and acute coronary syndrome trials

Heterogeneity is a major problem in the field of TBI, where the risks of a poor 6-month outcome vary widely between patients (e.g. risks varying from <10% to >90%). All recent RCTs in TBI have shown negative results, i.e. that the
new treatment was not significantly better than placebo. Heterogeneity was insufficiently considered in the design and analysis of the treatment effect in these studies. Adjustment for important predictors of the outcome may decrease the sample size requirements in TBI trials. The reduction is sample size will be larger where the inclusion criteria are less strict, and hence the population is more heterogeneous.

Patients with non-ST-segment elevation acute coronary syndromes essentially differ in their short and long term outcome, and prognostic categories are commonly used to allocate a less or more aggressive treatment. Platelet glycoprotein IIb/IIIa (GP IIb/IIIa) receptor blockers decrease the risk of death or MI at 30 days in patients with non-ST-segment elevation acute coronary syndromes not routinely scheduled for early revascularization. Elderly patients (>80 years) may be undertreated with these drugs because they were underrepresented in previous RCTs, and because the drugs can produce more harmful effects than in younger patients. There has been no demonstration that these drugs are equally efficacious in old and young patients. A meta-analysis of large international RCTs may help to define the benefits and risks of GP IIb/IIIa receptor blockers in elderly patients.

Stroke is an uncommon and serious event in patients with non-ST-segment elevation acute coronary syndromes. However, few papers have been performed to establish which patients are at higher risk to develop this serious complication. This group of patients can potentially benefit from preventive interventions after the ACS, such as statins. An evaluation of predictors in a population with a larger number of stroke events is required to define predictors accurately.

**1.5 Scope of the Thesis**

This thesis describes both methodological aspects and clinical applications of covariate adjustment and subgroup analysis in RCTs. The following research questions are addressed in this thesis:

1. Which are the pros and the cons of adjustment of the treatment effect in RCTs for baseline covariates?

2. How well are covariate adjustment and subgroup analysis used, reported and interpreted in current internal medicine, oncology, cardiology, and neurosurgery trials?
3. How much reduction in sample size can be obtained from adjustment for important predictors of unfavorable outcome in TBI trials?

4. Are the effects of GP IIb/IIIa receptor blockers similar in the young and the elderly in a meta-analysis of non-ST-segment elevation acute coronary syndrome trials?

5. Which subgroups of patients are at higher risk to develop a stroke after a non-ST-segment elevation acute coronary syndrome?

These issues have been insufficiently studied and quantified in theoretical and empirical data. The first part of this thesis considers simulation studies to quantify the gain in power and the reduction in sample size requirements in trials with dichotomous outcomes, with the use of the logistic regression model (Chapter 2) and the Cox proportional hazards models (Chapter 3). The reduction in sample size indicates that adjusted analyses might give the same power as an unadjusted analysis but with smaller sample size.

The second part describes the current practices of reporting and interpretation of covariate adjustment and subgroup analysis in 84 trials from high Impact Factor journals in General Internal Medicine, Cardiology and Oncology (Chapter 4), in 63 therapeutic cardiovascular clinical trials (Chapter 5), and in 18 trials of moderate and severe traumatic brain injury with more than 100 patients (Chapter 6).

The third part describes clinical applications of relevant methods in heterogeneous trial populations: an analysis of the reduction in sample size requirements with covariate adjustment for strong predictors in 8 trials of moderate-severe traumatic brain injury (n=6298) (Chapter 7), a subgroup analysis of the effects of the platelet glycoprotein IIb/IIIa receptors blockers by age in a meta-analysis of 6 trials of patients with non-ST-segment elevation acute coronary syndromes (n=31402) (Chapter 8), and an analysis to find predictors of all-cause stroke in heterogeneous patients with non-ST-segment elevation acute coronary syndromes (Chapter 9).

This thesis ends with a discussion of the theoretical and practical results, and gives recommendations for appropriate analysis of RCTs with heterogeneous populations.
References

Simulation Studies
Covariate adjustment in randomized controlled trials with dichotomous outcomes increases statistical power and reduces sample size requirements.
ABSTRACT

Background and Objective: Randomized controlled trials (RCTs) with dichotomous outcomes may be analyzed with or without adjustment for baseline characteristics (covariates). We studied type I error, power and potential reduction in sample size with several covariate adjustment strategies.

Methods: Logistic regression analysis was applied to simulated data sets (n=360) with different treatment effects, covariate effects, outcome incidences and covariate prevalences. Treatment effects were estimated with or without adjustment for a single dichotomous covariate. Strategies included always adjusting for the covariate (‘pre-specified’), or only when the covariate was predictive or imbalanced.

Results: We found that the type I error was generally at the nominal level. The power was highest with pre-specified adjustment. The potential reduction in sample size was higher with stronger covariate effects (from 3% to 46%, at 50% outcome incidence and covariate prevalence) and independent of the treatment effect. At lower outcome incidences and/or covariate prevalences, the reduction was lower.

Conclusion: We conclude that adjustment for a predictive baseline characteristic may lead to a potentially important increase in power of analyses of treatment effect. Adjusted analysis should hence be considered more often for RCTs with dichotomous outcomes.
Covariate adjustment in trials with dichotomous outcomes using logistic regression

Introduction

Randomized controlled trials (RCTs) have emerged as the principal research tool to inform and influence clinical practice \(^1\), \(^2\). Clinicians rely increasingly on efficient, well designed RCTs to distinguish between worthwhile, useless or harmful interventions \(^2\). Efforts have been made to improve quality in reporting RCTs \(^3\), but the way to analyze RCTs properly is still under discussion \(^4\)-\(^7\).

In particular, the treatment effect in a RCT can be analyzed and shown either as an average effect, as an adjusted effect, or both \(^8\). Adjusted effect estimates attempt to take the heterogeneity of patients in RCTs into account. The heterogeneity of patients is related to their prognostic baseline characteristics \(^4\), which may be used to obtain adjusted treatment effects. Common methods of adjustment are baseline imbalance adjustment \(^5\), \(^9\), subgroup analysis \(^5\), \(^10\)-\(^12\), stratified randomization plus adjustment \(^13\), and covariate adjustment (post-stratification) \(^14\)-\(^18\).

Covariate adjustment provides more individualized effect estimates, especially in non-linear models such as logistic regression and Cox proportional hazards regression \(^8\), \(^13\)-\(^20\). Further, adjusted effect estimates take into account chance differences in baseline characteristics between treatment arms \(^14\), \(^15\) and improve the power, i.e. the ability to identify treatment effects when they really exist \(^15\)-\(^22\).

The use of covariate adjustment in the current literature is not consistent \(^5\), \(^11\), probably because the strategies have not been fully developed and tested \(^23\), \(^24\). A key aspect of the adjustment strategies is the way of selection of the covariate to be adjusted for \(^25\). Moreover, the effects on power and type I error after adjustment have not been studied thoroughly.

We used various strategies for covariate adjustment in simulated logistic regression models with one dichotomous covariate. Our aim was to identify the pros and the cons of each covariate adjustment strategy, with a focus on changes in statistical power. We expressed any increase in statistical power as the decrease in sample size that gives the same power as an unadjusted analysis.

Methods

Treatment effects and adjustment strategies

Logistic regression models were used to analyze the effects of treatment on a
dichotomous outcome (e.g. 30-day mortality). A dichotomous baseline characteristic was entered as covariate to achieve adjustment of the treatment effect. The formula is: log odds (outcome) = β0 + β1*Treatment + β2*Covariate. The logistic regression coefficients and their standard errors (SE) were estimated with standard maximum likelihood procedures. Statistical significance was based on the Wald statistic (coefficient/SE), with two-sided p-values < 5% considered significant.

We used three approaches for covariate adjustment. In practice, they should be clearly described in the protocol. ‘Adjustment’ refers to a pre-specified adjusted analysis. Pre-specified analysis uses a known predictive covariate, e.g. derived from previous research. This leads to a stratified estimate of the treatment effect, which is also corrected for imbalance 14. Further, the predictive effect of a baseline characteristic can be used for adjustment if statistically significant using chi-square test (p< 5%) and this is referred to as ‘Predictor p<5%’. This chi-square is not adjusted for treatment. The imbalance according to a baseline characteristic may also be used for adjustment if statistically significant according to a chi-square test (p<5%) and it is referred to as ‘Imbalance p<5%’. Moreover, ‘No adjustment’ refers to an unadjusted analysis of the treatment effect. We report the results with the default significance level of 5%. We also explored the effects of applying a more liberal criterion for covariate selection (p<20%).

**Data sets and simulations**

The various approaches to estimation of the treatment effect were applied in different data sets. First, we simulated RCTs of 360 patients, 180 randomized to treatment A and 180 to treatment B, based on a previously discussed hypothetical example (Table 1), using mortality as outcome (number of events equal to 180 on average) 14. The distributions of gender and outcome were generated by sampling with replacement from the data set underlying the same table. Here, the prognostic effect of gender was very strong, with a 16% mortality rate in men compared to 84% in women (Odds Ratio [OR] = 30). The treatment effect for treatment B showed a mortality OR of 1.43 in comparison with treatment A in the unadjusted analysis, which used the total table and ignored heterogeneity (p=0.09). In contrast, the mortality OR was 2.0 in the strata formed by gender, meaning that treatment A reduced the odds of death in men and women by half (p=0.02). This example illustrates that the unadjusted OR may substantially differ from the adjusted OR.

We analyzed more hypothetical data sets using combinations of different unadjusted covariate effects (No covariate effect [OR=1], moderate covariate
Covariate adjustment in trials with dichotomous outcomes using logistic regression

Unadjusted treatment effects were varied from no treatment effect \([\text{OR}=1]\), weak treatment effect \([\text{OR}=1.4]\) to mild treatment effect \([\text{OR}=1.7]\). These effects are within the range of 1.1 to 1.9 that we observed in a survey of 13 large cardiovascular RCTs reported in The Lancet, The New England Journal of Medicine and JAMA during 2001 and 2002.

We simulated RCTs of 360 patients (180 to treatment A and 180 to treatment B, on average) and their distributions were generated by sampling with replacement from each hypothetical data set. The number of outcomes considered in the main analysis was 180 on average (50% of total number of patients). Because the outcome incidence and the covariate prevalence may be lower in RCTs, we also considered situations with a lower outcome incidence and a lower covariate prevalence (25%, 12.5% and 6.25% of the total number of patients in both cases). Simulations were performed with 20,000 repetitions when a treatment effect was truly present and 100,000 when no treatment effect was present (i.e. under the null hypothesis).

Table 2 shows the 12 logistic regression models considered. For example, the model with weak treatment effect and very strong covariate effect was made from a data set such as shown in Table 1. Unadjusted covariate and treatment ORs are the univariate ORs (either covariate or treatment introduced in the logistic model). Adjusted covariate and treatment ORs are the multivariate ORs (both covariate and treatment introduced in the logistic model). The covariate and treatment ORs are higher in adjusted analyses, specially when the covariate effects are stronger. We repeated the analyses using double sample size (i.e. 720 patients, with 360 in each treatment arm). When the outcome incidences and

<table>
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<th>Dead</th>
<th>Survive</th>
<th>Total</th>
<th>Dead</th>
<th>Survive</th>
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<td>98</td>
<td>180</td>
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<td>80</td>
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<td>B</td>
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<td>180</td>
<td>18</td>
<td>72</td>
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<td>10</td>
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<tr>
<td>% of death</td>
<td>(50%)</td>
<td>(16%)</td>
<td>(84%)</td>
<td></td>
<td></td>
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</tr>
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</table>

Table 1. Hypothetical example of stratification in a randomized clinical trial, where treatment A is compared to treatment B, while gender is balanced.
Table 2. Characteristics of the models used for adjusted and unadjusted analyses of the treatment effect.

covariate prevalences were small (12.5% and 6.25%), we used bigger sample sizes (n=1200) to facilitate the construction of adequate data sets.

**Evaluation**

We studied the actual type I error (α) when there was no treatment effect (OR=1),
and power (1-β, where β indicates type II error) when there truly was a treatment effect (OR>1), in each of the strategies of covariate adjustment. The 95% CI for the type I error of 5% ranged from 4.87% and 5.14% with 100 000 simulations. The formula used to calculate the type I error and the power for each strategy was: 100* (number of simulations with statistically significant treatment effect / total number of simulations), where the statistical significance was established according to the Wald statistic. We calculated the reduction of sample size to express the gain in power with each of the adjustment strategies. The formula used was: 100 - 100*[(mean of Z score of unadjusted strategy)/(mean of Z score of the adjusted strategy)]² (see appendix), where Z score is equal to the Wald statistic of the treatment effect coefficient ⁶. We used S-plus software (version 2000, Insightful Inc, Seattle, WA) for all calculations.

Results

Table 3 shows the main results of our simulations. When there was no treatment effect (OR=1), SEs from adjusted analysis were larger in direct relation to the strength of the covariate effect. The type I error was rather similar for most adjustment strategies and for all covariate effects. The results were mainly slightly below 5%, especially when the covariate effect was strong and the significant imbalance strategy was used (type I error 3.8%). When there were no covariate effects, covariate adjustment strategies did not markedly change the treatment effect coefficients and SEs. The power was slightly reduced and the required sample size was slightly increased (<0.1%). This indicates that very limited damage was done when a noise covariate was included in the adjusted analysis.

When there were treatment effects and covariate effects (OR>1), the pre-specified covariate adjustment strategy yielded on average a more extreme treatment effect coefficient compared to no adjustment. Consequently, power increased, as expected. Adjustment for one statistically significant predictor generated similar results to pre-specified adjustment, since the latter was nearly always statistically significant. Statistically significant imbalance adjustment generated on average only a slightly higher coefficient than the unadjusted coefficients, leading to a small increase in power.

A potential reduction in sample size was evident when covariate adjustment was pre-specified or based on the predictive significance of the covariate. The reduction in sample size was largest when the covariate effect was strongest. The range of reductions in sample size was from 3% to 46%, corresponding to unadjusted covariate OR from 2 to 30. When the significant imbalance strategy was used, the reduction in sample size was less than 3%. Remarkably, we observed
### Table 3. Results of simulations of various covariate adjustment procedures.

<table>
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<tr>
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<th>No treatment effect</th>
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<th>Unadjusted Treatment effect OR = 1.7</th>
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<td>Coef ± SE</td>
<td>Type I error (%)</td>
<td>Coef ± SE 1-type II error (%) Reduction in sample size(%)</td>
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<td>Imbalance p&lt;5%</td>
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<td>5.1</td>
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<td>Very strong unadjusted covariate effect (OR = 30)</td>
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<tr>
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<td>3.8</td>
<td>0.38 ± 0.22 40.4</td>
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the same reduction in sample size when different treatment effects were used, given a certain covariate effect. For example, when pre-specified adjustment was used, the reduction in sample size was 13.8% if the treatment effect was weak (OR=1.4) and 13.6% if it was mild (OR=1.7).

When either the outcome incidence or the covariate prevalence or both were lower, the reduction in sample size was also lower (Table 4). For example, with a covariate OR of 5, an outcome incidence of 25% and a covariate prevalence of 50%, the average reduction in sample size was 10.4% instead of 13.7%. The reduction in sample size was the same when the outcome incidence was 50% with a covariate prevalence of 25% and when the outcome incidence was 25% with covariate prevalence of 25%. Smaller outcome incidences and/or covariate prevalences yielded even lower reductions in sample (e.g. 3.0% when outcome incidence 6.25% and covariate prevalence 6.25%). The reductions in sample size were similar when the sample size was increased, and when we considered p<20% instead of p<5% as covariate selection limit.

Discussion

Covariate adjustment increased the power of statistical analyses of a treatment effect in the context of a randomized trial, without inflation of type I error. The increase in power was translated into moderate potential reductions in sample size, indicating that adjusted analyses might give the same power as an unadjusted analysis but with a smaller sample size. We found that pre-specified covariate and significant predictor covariate adjustment strategies were the most statistically efficient, with reductions in sample size between 3% and 46%, depending on the covariate strength. The potential reduction in sample size was independent of the magnitude of the treatment effect or sample size, which makes it an attractive summary measure to express the benefit of adjustment strategies. There was very limited damage when adjustment was performed if there was no true covariate effect.

Adjusted and unadjusted estimates in RCTs with homogeneous groups show on average similar results, as confirmed by our simulations with no covariate effects. However, several problems arise when dealing with heterogeneous populations. For example, adequate randomization sometimes produces unbalanced groups (statistically or non-statistically different at the 5% level) with respect to the baseline characteristics. Moreover, the effect of non-statistically significant imbalance between groups is not negligible, especially if the prognostic effect is strong. Further, the overall clinical trial result is not directly applicable to individuals.
Covariate adjustment may overcome some of the problems of heterogeneous populations \(^4, 5, 8, 13-17, 24\). The reported potential benefits of adjustment for covariates include the removal of confounding due to imbalance \(^4, 8, 14, 19\), the acquisition of a more subject-specific estimate instead of a population-averaged estimate \(^8, 14\), and the gain in statistical power \(^8, 14, 15, 17, 19, 24\). The gain in statistical power in logistic regression is explained by a larger increase in expected size of the adjusted treatment effect than the increase in the SE \(^16, 19, 24\).

We found that adjustment for a strong covariate (either pre-specified or tested) led to a more extreme estimate of the treatment effect, as expected \(^5\). The relative difference between unadjusted and adjusted estimates on the logistic scale was approximately constant for a given covariate effect and independent of the treatment effect. We also confirmed that the variability (SE) of the adjusted estimates was larger in direct relation to the strength of the covariate \(^14-18\); the opposite of what happens in linear regression \(^19, 25\). We obtained a conservative type I error when the covariate effect was strong and the imbalance strategy was used. This conservatism is explained by the fact that imbalance constrains the outcome variability between treatment groups \(^17\).

The power to detect a true treatment effect increased with the pre-specified and the statistically significant predictor strategies, which was translated into reductions in sample size up to 46%. In practical situations, the covariate effect may be either moderate or strong (OR from 2 to 5, corresponding to Spearman’s correlations (\(\rho\)) between 0.17 and 0.38 \(^9, 17\)), and the treatment effect may be weak (OR of 1.4). Therefore, the potential reductions in sample size would be moderate, maximally between 3% and 14% with a 50% outcome incidence and 50% covariate prevalence.

Our results agree with Pocock et al. \(^17\) who found a reduction in sample size of 10% with adjustment for a covariate with \(\rho = 0.3\), in the context of RCTs with continuous outcomes. When the covariate was very strong (OR: 30; \(\rho = 0.69\)) the reduction of sample size was highest (46%), in agreement with a previously found 50% reduction at \(\rho = 0.7\). These similarities in the reduction in sample size are attributed to the similarity of effects of the covariates in the linear and logistic regression models with 50% outcome incidence.

When we chose a covariate with the significant imbalance strategy the gain in power was not observed. Therefore, this procedure is not advised, in concordance with others \(^4, 5, 8\). The results of the combination of strategies (‘predictor and imbalance’ and ‘predictor or imbalance’) were similar to the significant imbalance
In contrast to the scenario with 50% outcome incidence and 50% covariate prevalence, we found that the potential reduction in sample size was lower when the event incidence or the covariate prevalence were lower than 50%. For example, this situation is commonly seen in published cardiovascular RCTs, where the outcome incidences range typically from 5% to 25% \(^{26-28}\). Remarkably, the reduction in sample size was similar given a value of either the event incidence or the covariate prevalence or both. Moreover, when the event incidence was lower and the covariate prevalence was higher than 50%, the reduction in sample size was the lowest (1.6 % in the example given in table 4).

The unadjusted strategy yields an average treatment effect, without any consideration of heterogeneity in prognosis among patients. Covariate adjustment and subgroup analyses both consider heterogeneity and attempt to provide more individualized estimates of the treatment effect. They are however substantially
different. Covariate adjustment obtains a single more individualized treatment effect estimate, which is assumed to be applicable to all patients. Subgroup analyses provide multiple treatment effect estimates, assuming that treatment effects differ between particular groups of patients. Covariate adjustment commonly is achieved with regression models while adequately performed subgroup analyses apply tests of interaction. Covariate adjustment is sometimes used in the primary analysis of RCTs. Remarkably, unadjusted analyses receive generally more emphasis. This may be caused by a suspicion of data-driven adjustment, or because adjustment is more difficult for readers to understand. Subgroup analyses are often performed, but they rarely have enough power to detect differential treatment effects. Tests of interaction are underused and subgroup analyses results are commonly over-interpreted.

We advise to perform adjusted analyses because of several advantages, including a more individual-oriented treatment effect corrected for imbalance, a gain in power and, as a consequence, a potential reduction in sample size. Even when the event incidence and covariate prevalence are low, there is a potential reduction in sample size. If a strong predictive covariate is known before the analysis of the RCT, for example, after a literature review, the best strategy of covariate adjustment is to pre-specify adjustment. If a number of covariates are potentially predictive, a second best option is to use the ‘significant predictor’ strategy. Here, bias may be introduced by the selection procedure, particularly in the context of small sample sizes. This theoretical objection was not found important in our simulations. Moreover, Edwards pointed out that if the model is chosen with blinding of the treatment indicator variable, the type I error may be controlled.

We did not present calculations for covariate adjusted sample size in RCT design. To quantify any anticipated sample size gains with covariate adjustment, we would need to specify covariate effects and covariate distributions. In practice, the study would then have to meet these assumptions to achieve the calculated power. Therefore, we advise to perform an unadjusted sample size calculation, which needs less assumptions.

Our work has several limitations. We presented results from analyses of simulated models, using hypothetical treatment effects and covariate effects, without real patient data. We did not study the effect of covariate adjustment using continuous covariates. We used the Wald test for statistical significance, although the Likelihood Ratio test may yield better results. We chose only one covariate to simplify the simulation process and to clarify the presentation. When more prognostic covariates are pre-specified for adjusted analysis, the same conclusions are expected on treatment effect estimation, power and potential reduction.
in sample size \(^8, 17, 18\). However, when many potential predictors are available, a complication may be which variables to choose. A selection procedure, e.g. stepwise backward elimination, might be considered to choose a limited number of covariates, but the effects of such a procedure on effect estimation and power require further study.

In conclusion, adjustment for a predictive baseline characteristic increased the power of statistical analyses of a treatment effect, without inflation of Type I error and with potentially important reductions in sample size. The covariate ideally has to be pre-specified in the RCT protocol. Alternatively, testing for a statistically significant predictive effect is suggested. Adjustment for important predictors should be considered more often in the analysis of RCTs with dichotomous outcomes.

### Appendix

**Deduction of the Reduction of Sample Size formula**

In the context of a RCT, we defined \(n_u\) and \(n_a\) as the unadjusted and adjusted sample sizes respectively, \(Z_{\alpha}\) is \(Z\) value at \(\alpha = 0.05\), \(Z_{\beta_u}\) is the \(Z\) value of the unadjusted power \(1-\beta_u\), \(Z_{\beta_a}\) is the \(Z\) value of the adjusted power \(1-\beta_a\), \(Z_u\) is the mean standardized \(Z\) score of the estimated unadjusted coefficient defined as coefficient /SE for each simulation, and, \(Z_a\) is the mean standardized \(Z\) score of the estimated adjusted coefficient defined as coefficient /SE for each simulation.

We expressed any increase in statistical power of the adjusted analysis as the decrease in the sample size that gives the same power of an unadjusted analysis (i.e. \(Z_{\beta_u} = Z_{\beta_a}\)). This assumption gives approximately:

\[
\frac{n_a}{n_u} = \left( \frac{Z_u}{Z_a} \right)^2
\]

(1)

The potential reduction in sample size (RSS) between unadjusted and adjusted strategies is expressed in percentage as:

\[
\left[ \frac{(n_u - n_a)}{n_u} \right] * 100, \text{ or } 100 - \left[ 100 * \left( \frac{n_a}{n_u} \right) \right]
\]

(2)

Replacing (1) in (2):

\[
\text{RSS} = 100 - 100 * \left( \frac{Z_u}{Z_a} \right)^2
\]

(3)
Chapter 2.1

References

18. Ford I, Norrie J. The role of covariates in estimating treatment and risk in long
Randomized controlled trials with time-to-event outcomes: how much does pre-specified covariate adjustment increase power?

2.2
ABSTRACT

**Purpose:** We evaluated the effects of various strategies of covariate adjustment on type I error, power and potential reduction in sample size, in randomized controlled trials (RCTs) with time-to-event outcomes.

**Methods:** We used Cox models in simulated datasets with different treatment effects (Hazard Ratio [HR] = 1, 1.4, 1.7), covariate effects (HR = 1, 2, 5), covariate prevalences (10%, 50%) and censoring levels (No, low, high). The treatment and a single covariate were dichotomous. We examined the sample size that gives the same power as an unadjusted analysis, for three strategies: pre-specified, significant predictive and significant imbalance.

**Results:** Type I error was generally at the nominal level. The power to detect a true treatment effect was higher with adjusted than with unadjusted analyses, especially with pre-specified and significant predictive strategies. Potential reductions in sample size with covariate HR between 2 and 5 were between 15% and 44% (covariate prevalence 50%) and between 4% and 12% (covariate prevalence 10%). The significant imbalance strategy yielded small reductions. The reduction was higher with stronger covariate effects, but was independent of the treatment effect, sample size and censoring level.

**Conclusions:** Adjustment for one predictive baseline characteristic yields higher power to detect a true treatment effect than unadjusted analysis, without inflation of type I error and with potentially moderate reductions in sample size. The analysis of RCTs with time-to-event outcomes should adjust for predictive covariates.
Introduction

Randomized controlled trials (RCTs) are important research tools to evaluate the usefulness of treatments and interventions. Heterogeneity is common among patients participating in RCTs with time-to-event outcomes. Prognosis commonly varies according to patient baseline characteristics, which are routinely recorded in RCTs. After proper randomization, imbalance in patient characteristics may arise by chance.

Covariate adjustment for prognostic baseline characteristics is usually performed with Cox proportional hazards model in RCTs with time-to-event outcomes. The inclusion of a strongly predictive covariate in addition to the treatment variable in a Cox model provides three important benefits: correction for imbalance, acquisition of more individualized treatment effects and increase in statistical power, i.e., the ability to detect a treatment effect when it really exists. Moreover, omission or misspecification of prognostic covariates in the analysis produces deviations from the proportional hazards assumptions.

The power of covariate adjustment strategies in RCTs with time-to-event outcomes depends on various characteristics: strength of treatment effect, strength of covariate effect, covariate prevalence and censoring level. The effects of the covariate adjustment strategies on statistical power and type I error, using plausible clinical scenarios, have been insufficiently studied. Some examples of covariate adjustment in RCTs with survival outcomes are available in the medical literature, specially in oncology and cardiology.

We used various strategies for choice of covariates (pre-specified, predictive and imbalance strategies) in simulated Cox proportional hazards models with one dichotomous covariate, using different treatment effects, covariate effects, covariate prevalences and censoring levels. We aimed to identify the pros and the cons of each covariate adjustment strategy, with a focus on the quantification of changes in statistical power. We expressed the gain in statistical power in the decrease in the sample size that gives the same power as an unadjusted analysis.

Methods

Models and adjustment strategies

Cox proportional hazards models were used to analyze the effects of treatment on a time-to-event outcome (e.g. time to death). For simplicity, a single dichotomous baseline characteristic was considered as covariate to adjust the treatment effect.
We expected that our results were generalizable to more complex cases (i.e. more covariates included), as demonstrated by others 2, 5-7, 9, 11, 13, 22. The Cox model coefficients and standard errors (SE) were estimated with standard maximum likelihood procedures.

We used three strategies for choice of covariates. The ‘adjustment’ strategy refers to a pre-specified adjusted analysis, which uses a known predictive covariate. This strategy should be written in advance in the protocol. This leads to a stratified estimate of the treatment effect, which is also corrected for imbalance. ‘Predictor p<5 percent’ refers to a strategy in which the predictive effect of a baseline characteristic can be used for adjustment if statistically significant using Pearson’s chi-square test (p<5 percent). The treatment effect was not included in this predictive model. The imbalance according to a baseline characteristic may also be used for adjustment if statistically significant (‘Imbalance p<5 percent’) 16, 22. Statistically significant imbalance was based on Pearson’s chi-square test with 1 degree of freedom.

Data and simulations

The various approaches to estimate the treatment effect were applied in different hypothetical data sets. We simulated RCTs of 200 patients, 100 randomized to treatment A and 100 to treatment B on average. Simulations were performed with 20,000 repetitions when a treatment effect was truly present and 100,000 when no treatment effect was present (i.e. under the null hypothesis).

In each simulation, survival times were generated from an exponential distribution with hazard rate \( \exp(\gamma U + \beta V) \), where \( \gamma \) was the coefficient of the treatment effect, \( \beta \) the coefficient of the covariate effect, \( U \) the random dichotomous value of treatment with 50 percent prevalence for treatment A on average and \( V \) the random dichotomous value of covariate at a given prevalence 7, 8. The coefficients (\( \gamma \) and \( \beta \)) are equal to the natural logarithm of the Hazard Ratio (HR) of the treatment effect and covariate effect, respectively. Censoring times were independently generated from an exponential distribution given a pre-defined censoring hazard rate and a randomly selected censoring prevalence (i.e. censoring time = -log [1-(censoring prevalence)] /censoring hazard rate) during each simulation. The survival and censoring prevalences followed a uniform distribution.

Multivariable models were constructed using different covariate effects: No covariate effect (HR = 1), moderate covariate effect (HR = 2) and strong covariate effect (HR = 5). Treatment effects varied from no treatment effect (HR = 1), weak treatment effect (HR = 1.4) to mild treatment effect (HR = 1.7).
covariate prevalence (proportion of patients with a positive covariate value) was set at 50 percent and 10 percent. Three censoring levels were defined according to censoring hazard rates: No censoring (hazard rate 0), low level censoring (censoring between 8 percent and 18 percent, corresponding to a censoring hazard rate of 0.22) \(^7\) and high level censoring (censoring between 25 percent and 50 percent, corresponding to a censoring hazard rate of 1). We repeated the analyses using sample sizes of 500 and 1000 patients.

An example of one of the simulations with treatment HR of 1.7, 50 percent covariate prevalence, and no censoring is displayed in Figures 1a and 1b. We observe that the average treatment and placebo survival curves (Figure 1a) are in between the survival curves fitted with the covariate with strong effect (HR=5), (Figure 1b).

![Figure 1a](image)

**Figure 1a:** Average survival curves for the treatment (Tx) and placebo (Pl) arms in a hypothetical RCT (Treatment HR= 1.7, covariate HR=5, covariate prevalence 50% , No censoring, n=1000).

**Evaluation**

We studied the actual type I error (\(\alpha\)) when there was no treatment effect, and power (1-\(\beta\), where \(\beta\) indicates type II error) when there was a true treatment effect, in each of the strategies of covariate adjustment. Statistical significance
was based on the Wald statistic (coefficient/SE) (16), with p-values < 5 percent considered significant. We expressed the gain in statistical power with adjusted strategies as the potential decrease in the required sample size that gives the same power of an unadjusted analysis. The formula of the potential reduction in sample size is shown in the Annex I

We report the results with the default significance level of 5 percent. We also explored the effects of applying a more liberal criterion for selection (p<20 percent). We used S-PLUS software (version 2000, Insightful Inc, Seattle, WA, USA) for all calculations.

**FIGURE 1b:** Survival curves for the treatment and placebo arms in the same hypothetical RCT as Fig. 1a. The covariate (Cov) was included in the Cox model. The upper 2 curves correspond to each arm in the absence of the covariate. The lower 2 curves correspond to each arm in the presence of the covariate. The difference between the upper and lower curves corresponds to a HR=5.

**Results**

*Covariate prevalence 50 percent and no censoring*

When there was no treatment effect, the type I error was rather similar in all adjustment strategies and with all covariate effects (Table 1). The type I error was mainly slightly below 5 percent, especially when the covariate effect was very
How much does covariate adjustment increase power in trials with time-to-event outcomes?

Table 1. Simulations with covariate prevalence 50% and No censoring (n=200).

<table>
<thead>
<tr>
<th>Covariate effect and adjustment strategy</th>
<th>Treatment Effect (HR=1.0)†</th>
<th>Treatment Effect (HR=1.4)</th>
<th>Treatment effect (HR=1.7)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Coeff (SE)‡</td>
<td>Type I error (%)</td>
<td>Coeff (SE)</td>
</tr>
<tr>
<td>Moderate covariate effect (HR =2):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No adjustment</td>
<td>0.00 (0.09)</td>
<td>5.1</td>
<td>0.33 (0.15)</td>
</tr>
<tr>
<td>Adjust/Predict p&lt;5% §</td>
<td>0.00 (0.09)</td>
<td>5.0</td>
<td>0.36 (0.15)</td>
</tr>
<tr>
<td>Imbalance p&lt;5%</td>
<td>0.00 (0.09)</td>
<td>4.8</td>
<td>0.33 (0.15)</td>
</tr>
<tr>
<td>Strong covariate effect (HR =5):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No adjustment</td>
<td>0.00 (0.09)</td>
<td>5.2</td>
<td>0.27 (0.15)</td>
</tr>
<tr>
<td>Adjust/Predict p&lt;5% §</td>
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<td>4.9</td>
<td>0.36 (0.15)</td>
</tr>
<tr>
<td>Imbalance p&lt;5%</td>
<td>0.00 (0.09)</td>
<td>4.2</td>
<td>0.27 (0.15)</td>
</tr>
</tbody>
</table>

† HR=Hazard ratio, defined as exp(regression coefficient); ‡ Coeff= Coefficient; § Adjustment or predictor <5% strategy.
strong (3.8 percent for imbalance adjusted strategy at covariate HR=10). This conservative estimate implies that fewer false-positive effects were identified. When there was no covariate effect, covariate adjustment strategies on average did not change the treatment effect coefficients and slightly reduced the power and increased the required sample size (around 0.1 percent).

When there were treatment and covariate effects (Table 1), the pre-specified covariate adjustment (‘adjustment’) strategy yielded on average a more extreme treatment effect compared to no adjustment, as theoretically expected. Adjustment for one statistically significant predictor (‘predictor p<5 percent’) generated similar results to pre-specified adjustment since nearly always the pre-specified covariate was a statistically significant predictor. Significant imbalance adjustment (‘imbalance p<5 percent’) on average generated coefficients smaller than both pre-specified and significant predictive coefficients and nearly similar to the unadjusted coefficients.

With both the pre-specified and the significant predictor strategies, power was higher than with unadjusted analyses. In contrast, power with the significant imbalance strategy was only slightly increased. The increase in power was directly related to the strength of the covariate effect. A potential reduction in sample size was evident when pre-specified and significant predictor strategies were performed (between 15 percent and 44 percent, corresponding to covariate HR between 2 and 5) as shown in Table 1. The imbalance adjustment yielded smaller reductions (between 1 percent and 3 percent, covariate HR 2 to 5).

Remarkably, we observed a similar reduction in sample size when different treatment effects were used given a certain covariate effect (e.g. 44 percent if treatment effect was weak and 43 percent if treatment effect was mild, with covariate HR=5). The potential reduction in sample size was similar in simulations with larger sample sizes (n=500, n=1000) and when we considered p<20 percent instead of p<5 percent as covariate selection limit. The same similarities were also found in all the following scenarios.

_Covariate prevalence 50 percent and censoring_

Compared to covariate prevalence 50 percent and no censoring, the treatment effect coefficients and type I error were similar. In the same comparison, power was slightly reduced with all unadjusted and adjusted strategies with low level censoring, but moderately reduced with high level censoring (e.g. from 96 percent to 84 percent, with covariate HR=2, treatment HR=1.7, n=200). The potential reduction in sample size was similar with the pre-specified and significant predictor strategies (between 12 percent and 44 percent, covariate HR 2 to 5). There
How much does covariate adjustment increase power in trials with time-to-event outcomes?

Table 2. Simulations with covariate prevalence 10% and No censoring (n=200).

<table>
<thead>
<tr>
<th>Covariate effect and adjustment strategy</th>
<th>Treatment effect (HR=1)†</th>
<th>Treatment Effect (HR=1.4)</th>
<th>Treatment effect (HR=1.7)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Coeff (SE)</td>
<td>Type I error (%)</td>
<td>Coeff (SE)</td>
</tr>
<tr>
<td>Moderate covariate effect (HR =2):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No adjustment</td>
<td>0.00 (0.09)</td>
<td>5.1</td>
<td>0.35 (0.15)</td>
</tr>
<tr>
<td>Adjust/Predict p&lt;5% §</td>
<td>0.00 (0.09)</td>
<td>5.0</td>
<td>0.36 (0.15)</td>
</tr>
<tr>
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<td>0.35 (0.15)</td>
</tr>
<tr>
<td>Strong covariate effect (HR =5):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No adjustment</td>
<td>0.00 (0.09)</td>
<td>5.2</td>
<td>0.33 (0.15)</td>
</tr>
<tr>
<td>Adjust/Predict p&lt;5% ¥</td>
<td>0.00 (0.09)</td>
<td>5.1</td>
<td>0.36 (0.15)</td>
</tr>
<tr>
<td>Imbalance p&lt;5%</td>
<td>0.00 (0.09)</td>
<td>5.0</td>
<td>0.34 (0.15)</td>
</tr>
</tbody>
</table>

† HR=Hazard ratio, defined as exp(regression coefficient); ‡ Coeff= Coefficient; § Adjustment or predictor <5% strategy.
Table 3. Summary of the percentage of reduction in sample size according to censoring, covariate prevalence and covariate effect.

was only a small reduction in sample size with the imbalance strategy (between 1 percent and 3 percent, covariate HR 2 to 5).

Covariate prevalence 10 percent and no censoring

Adjusted treatment effect coefficients had slightly higher values than the unadjusted ones, in contrast to the situation with covariate distribution 50 percent and no censoring, where the difference was larger. Type I error was close to the nominal level, without important conservative estimates (Table 2). Power estimates of adjusted strategies were closer to the unadjusted power estimate, because of the similarity of unadjusted and adjusted treatment effects. Consequently, the potential reduction in sample size was lower with adjustment for pre-specified or significant predictor covariates (between 4 percent and 12 percent, covariate HR between 2 and 5) as shown in Table 2. The imbalance strategy reduced the sample size only slightly (between 0.4 percent and 0.6 percent).

Covariate prevalence 10 percent and censoring

Compared to covariate distribution 10 percent and no censoring, the treatment effect coefficients were similar. Type I error was mainly slightly below 5 percent, without a clear relation among adjustment strategies. The power was slightly lower for all unadjusted and adjusted strategies with low level censoring, but mildly reduced with high level censoring. The potential reduction in sample size with pre-specified and significant predictive strategies was between 4 percent and
14 percent (covariate HR 2 to 5). The imbalance strategy only slightly reduced the sample size (0.1 percent to 0.8 percent). Table 3 shows a summary of the potential reductions in sample size within plausible scenarios.

**Discussion**

Covariate adjustment yields a higher statistical power than an unadjusted analysis of a randomized controlled trial with time-to-event outcomes. In our study, the gain in power was translated into potential reductions in sample size, without inflation of the type I error. We used several approaches of covariate adjustment in simple simulated Cox models with different treatment effects, covariate effects, covariate prevalences and censoring levels. We found that pre-specified and significant predictor adjustment strategies, with covariate HR between 2 and 5, yielded a potential reduction of sample size between 15 percent and 44 percent (covariate prevalence 50 percent) and between 4 percent and 12 percent (covariate prevalence 10 percent). This reduction was greater if the covariate effect was higher. The reduction in sample size was independent of the treatment effect, sample size and censoring level. The significant imbalance adjustment strategy showed smaller potential reductions in sample size. There was very limited damage when adjustment was used in the absence of a true covariate effect.

The use of covariate adjustment strategies has been previously studied in RCT with different outcomes: continuous 22, dichotomous 23, 24, and time-to-event 7-9, 16. However, it is not known what truly constitutes the best strategy for covariate-adjusted analyses 22. The significant predictor, significant imbalance and predictor plus imbalance adjustment strategies were previously described by Beach and Meier in RCTs with time-to-event outcomes analyzed with Cox proportional hazards models 16. The imbalance strategy for one covariate yielded similar values of treatment effect than the predictive strategy, probably related to the low number of events or low predictive significance of the variable included in their example. However, they did not give a clear recommendation about the most efficient strategy to perform covariate adjustment. Pocock et al. 22 described the pre-specified, significant predictor and significant imbalance adjustment strategies in RCTs analyzed with linear and non-linear regression models, and they advised to use pre-specified predictors in the analysis. Our results agree with this recommendation. We did not report the results of the combination of strategies (‘predictor and imbalance’ and ‘predictor or imbalance’) because they were similar to the significant imbalance and significant predictor strategies, respectively.

A potential problem of covariate adjustment when analyzing RCTs with Cox
models is that we may misspecify a prognostic variable (e.g. by categorizing a continuous variable or by linear modeling of a non-linear relationship). This situation produces deviations of the proportional hazards assumption and underestimation of the treatment effect \(^{5,10-15}\). This leads to a loss of power of the test of no treatment effect. In contrast, the misspecification of predictive covariates in linear models does not produce biased estimates of the treatment effect. It however leads to a loss of precision of the estimate \(^3,5\). Consequently, the recommendation to adjust for a predictive covariate in Cox models is based on really different arguments than in the classical linear models \(^6,10\).

We found that type I error was maintained closely below to the nominal level with the pre-specified and predictive adjustment strategies, using the Wald test. Li \(^7\) found type I error values very close to the nominal level of 5 percent in the context of the covariate-adjusted Cox score test. The imbalance adjustment strategy was conservative, since this strategy constrains the outcome variability between treatment groups \(^22\). We also confirmed that there was only a small loss in power when adjustment was used in the absence of covariate effect, as suggested by others \(^7,9,22,25\). Further, we quantified a substantial gain in power when a strong predictive covariate was included in the Cox model, especially with 50 percent covariate prevalence and independently of censoring.

We expressed the gain in statistical power as a potential reduction in the required sample size. The potential reductions in sample size with pre-specified and significant predictor strategies were moderate (between 12 and 44 percent) in plausible scenarios (treatment HRs between 1.4 and 1.7, covariate HRs between 2 and 5 [Spearman’s correlation between 0.29 and 0.57], covariate prevalence of 50 percent). The imbalance strategy yielded lower reductions (below 3 percent). With 10 percent covariate prevalence, the reductions in sample size were below 13 percent in the pre-specified/predictor strategies, and below 1 percent in the significant imbalance strategy. Furthermore, censoring levels in RCT populations in some medical fields are high (e.g. Oncology). Remarkably, the proposed potential reduction in sample size in the high level censoring situation was similar to the no or low censoring scenarios. Hence, censoring was not relevant to the choice of adjustment strategy.

Moreover, the potential reduction in the sample size was independent of the treatment effect. We used treatment effects (HRs 1.4 and 1.7) in the range suggested in simulations by others (range of treatment effects HRs from 1 to 2.7) \(^2,5-7,16\) and similar to the treatment HR of some recently published RCTs in Oncology and Cardiology, which range from 1.1 to 1.5 \(^18-21\). Different sample sizes of the simulated RCTs did not change the benefit in the potential reduction in sample size, as suggested previously \(^22\). Nevertheless, low covariate prevalence
(10 percent) yielded lower reductions in sample size. The stability of the potential reduction of sample size calculations in common clinical scenarios makes it an attractive summary measure to express the benefit of adjustment strategies, as was suggested in RCTs analyzed with logistic models.

Reductions in sample size given a covariate effect are not directly comparable between a RCT with dichotomous outcomes and a RCT with survival outcomes, using covariate prevalence of 50 percent and no censoring. Values of Odds Ratios (OR) and HR are related to each other through the formula: \( OR = HR \times \frac{p2}{p1} \), where \( p2 \) is the survival in the covariate group with the best prognosis and \( p1 \) is the survival in the covariate group with the worst prognosis (see Annex II). So, a given value of HR corresponds to a higher OR. For example, a reduction of sample size of 16 percent can be achieved after adjustment for a covariate effect with \( HR = 2 \). A comparable reduction of sample size (14 percent) can be obtained after adjustment for a covariate effect with \( OR = 5 \) ref. Conversely, for the same numerical values of OR and HR (e.g. 2), we obtained reductions in sample size after adjustment of 3 percent and 16 percent, respectively.

We did not present calculations for covariate adjusted sample size in RCT design. To quantify any anticipated sample size gains with covariate adjustment, we would need to specify covariate effects and covariate distributions. In practice, the study would then have to meet these assumptions to achieve the calculated power. Therefore, we advise to perform an unadjusted sample size calculation, which needs fewer assumptions. The actual analysis will have more power if the pre-specified or significant predictor strategy is followed.

The role of covariate adjustment in nonlinear analyses of randomized controlled trial is a matter of debate. Hauck et al. recommended that the primary analysis should be adjusted for important prognostic covariates in order to come as close as possible to the clinically most relevant subject-specific measure of treatment effect. However, this practice is not common. Further, Chastang et al. also noted that if important differences are found between unadjusted and adjusted analyses, it is probably preferable to base inference on the latter. However, a recent survey indicated that the number of trials with a difference between adjusted and unadjusted analyses sufficient to affect the conclusions is very low. The importance to pre-specify the covariates to adjust for has been also highlighted. Nevertheless, this recommendation may be unrealistic because prognostic covariates might not be available in the study design stage. Despite of the criticisms about their data-driven nature and potential for manipulation, variable selection procedures may have a useful role on formulating covariate adjustment, especially in large trials. Further, the variable selection procedures may be applied to select covariates in a way that
does not affect the type I error for the test for no treatment effect 26.

Finally, if a covariate is not predictive of an outcome, a statistically significant imbalance of this covariate is irrelevant 22. What it is useful is to adjust for predictive covariates, independently of their imbalance status. Thus, some researchers have suggested the use of a limited number of pre-specified, prognostic covariates, and the avoidance of the assessment of and the adjustment for imbalance 22-25.

Our work has several limitations. We only included results of simulations with plausible covariate and treatment effects and not real data. We only considered covariate prevalences of 10 percent and 50 percent. Nevertheless, results with covariate distribution of 90 percent are rather similar to results of covariate distribution of 10 percent 5, 12. We did not study the effect of covariate adjustment using a continuous covariate. We used the Wald test for statistical significance, although the Likelihood Ratio test may yield statistically more appropriate results. Also, we did not address the consequences of covariate adjustment when more than one covariate is available. If we had ten covariates, five of them were predictive and five were not but allowed the choice to vary randomly from simulation to simulation, then a strategy of pre-specification would work less well. A selection procedure, e.g. stepwise backward elimination, might be considered to choose a limited number of the covariates, but the effects of this procedure would require further study. Edwards 26 has suggested a method of blinded selection of covariates, in which a family of possible models and a model selection criterion are pre-specified.

We recommend use of the adjusted analysis in time-to-event RCTs because we obtained more appropriate treatment effects (corrected for imbalance, individually oriented), a higher power than the unadjusted effects and consequently a reduction in sample size. The best strategy of covariate adjustment should be pre-specified adjustment if a strong predictive covariate is known before the RCT analysis 7, 9, 22. An alternative is to use the significant predictor strategy, when a strong predictive covariate is not known. The analysis of RCTs with time-to-event outcomes should adjust for predictive covariates.
Annexes

I. Deduction of the Reduction in Sample Size (RSS) formula

In the context of a RCT, we defined $n_u$ and $n_a$ as the unadjusted and adjusted sample sizes respectively. $Z_\alpha$ is $Z$ value at $\alpha = 0.05$, $Z_{\beta u}$ is the $Z$ value of the unadjusted power $1-\beta_u$, $Z_{\beta a}$ is the $Z$ value of the adjusted power $1-\beta_a$, $Z_u$ is the mean standardized $Z$ score of the estimated unadjusted coefficient defined as coefficient /SE for each simulation, and, $Z_a$ is the mean standardized $Z$ score of the estimated adjusted coefficient defined as coefficient /SE for each simulation.

We expressed any increase in statistical power of the adjusted analysis as the decrease in the sample size that gives the same power of an unadjusted analysis (i.e. $Z_{\beta u} = Z_{\beta a}$). This assumption gives approximately:

$$\frac{n_a}{n_u} = \left( \frac{Z_u}{Z_a} \right)^2$$

(1)

The potential reduction in sample size (RSS) between unadjusted and adjusted strategies is expressed in percentage as:

$$\frac{(n_u - n_a)}{n_u} \times 100 \text{, or } 100 - \left[ 100 \times \frac{n_a}{n_u} \right]$$

(2)

Replacing (1) in (2):

$$\text{RSS} = 100 - 100 \times \left( \frac{Z_u}{Z_a} \right)^2$$

(3)

II. Relation between Hazard Ratio (HR) and Odds Ratio (OR)

Let us consider a randomized controlled trial with survival outcomes, one dichotomous covariate, covariate prevalence of 50 percent and no censoring. Each covariate group has different prognosis, according to its baseline characteristics. Survival curves of each covariate group (group 1 and group 2) go from time $t_0$ until time $t_1$ ($t_1 > t_0$). The survival proportions at $t_1$ are $p_1$ (group 1) and $p_2$ (group 2). The number of patients is the same for each covariate group ($n = n_1 = n_2$).

Let us assume that group 1 has worse prognosis and that the hazard rates ($h$) are constant from $t_0$ until $t_1$. So, the $h$ for each covariate group ($g_1$ and $g_2$) are defined as:

$$h_1 = \frac{\text{number events } g_1}{\text{total follow-up} 1} = \frac{[(1-p_1)^*n_1]}{t_1*n_1} = \frac{(1-p_1)}{t_1}$$

$$h_2 = \frac{\text{number events } g_2}{\text{total follow-up} 2} = \frac{[(1-p_2)^*n_2]}{t_1*n_2} = \frac{(1-p_2)}{t_1}$$
The hazard ratio (HR) of the covariate \((g_1 \text{ vs. } g_2)\) is defined as:
\[
HR = \frac{h_1}{h_2} = \frac{[(1-p_1)/t_1]}{[(1-p_2)/t_1]} = \frac{(1-p_1)}{(1-p_2)}
\]  
(4)

At time \(t_1\), the Odds Ratio (OR) of death of \(g_1\) vs. \(g_2\) is defined as:
\[
OR = \frac{[(\text{death } g_1)\times(\text{alive } g_2)]}{[(\text{death } g_2)\times(\text{alive } g_1)]} = \frac{[(1-p_1)\times p_2]}{[(1-p_2)\times p_1]}
\]  
(5)

Then, replacing (4) in (5), we have:
\[
OR = HR\times \frac{p_2}{p_1}
\]  
(6)

which implies that OR is always larger than HR in this particular situation.

References

How much does covariate adjustment increase power in trials with time-to-event outcomes?

Current practice of reporting clinical trials
Inappropriate use of baseline characteristics in clinical trials: Assessment of high impact medical journals
ABSTRACT

We aimed to describe current reporting of uses of patient baseline characteristics (baseline comparability, covariate adjustment, and subgroup analysis) in randomized controlled trials (RCTs), and to determine whether reporting violations decreased since the introduction of the revised CONSORT (Consolidated Standards of Reporting Trials) statement. Main reports of phase III RCTs with more than 100 patients, published in high impact factor clinical journals between September 1 and November 30, 2002 were used. Our main outcome measure was the appropriateness of reporting of baseline comparability, covariate adjustment and subgroup analysis. We identified 84 RCTs (general medicine=46, cardiology=21 and oncology=17). Remarkably, 34 RCTs (40%) tested baseline imbalances, which is methodologically unjustified. Forty-four RCTs (52%) performed covariate adjustment as the primary analysis, and they used mainly predictive covariates. Of these, 30 RCTs gave more emphasis to the adjusted analysis. Forty-seven RCTs (56%) reported subgroup analyses. Appropriate statistical interaction tests were used in only 20 of these trials, while subgroup differences were emphasized in 22. Adherence to methodological standards was not better in CONSORT adopting journals. Inappropriate analyses of baseline characteristics, especially subgroup analyses, are still frequent. Recommendations on appropriate reporting need to be further implemented in current practice, since conclusions of RCTs may be misleading otherwise.
Introduction

In the current era of evidence-based medicine, randomized controlled trials (RCTs) are the key to guide clinical decision making. Adequate reporting of RCTs provide clinicians with valuable information that helps them to accept or reject treatments or interventions, and, therefore, to improve their practice. Several patient characteristics are usually recorded at inclusion. These baseline characteristics may serve several purposes, including demonstration of balance between treatment groups (baseline comparability), and implementation of more elaborate analyses (such as covariate adjustment and subgroup analyses).

The revised recommendations of the Consolidated Standards of Reporting Trials (CONSORT) statement has condensed some appropriate and inappropriate uses of baseline characteristics in RCTs. Baseline characteristics among trial arms should be displayed without testing for imbalances, since these are the product of chance if a proper randomization method was followed. Important covariates might be used for covariate adjustment. Such adjustment should be pre-specified, and be focused on a limited number of covariates. The reasons for choosing covariates should be clearly described. Likewise, subgroup analyses should be pre-specified and be restricted to a small number of subgroups. Interaction tests should be applied when differences in treatment effect are claimed. Subgroup analyses should generally be considered as secondary analyses.

The reporting of the use of baseline characteristics in RCTs has been found inappropriate: overuse of baseline comparisons, misuse of significance tests for baseline comparisons, inconsistencies in the use of covariate adjustment, underuse of tests of interactions, and overinterpretation of subgroup analyses. These problems were demonstrated in RCTs from general medical journals during the past two decades. The use of the revised CONSORT statement led to improvements in the quality of reporting, but whether the reporting of the use of baseline characteristics has also improved has not yet been evaluated. Moreover, the quality of reporting on RCTs may be better in general medical journals than in specialist journals.

We studied adherence of the reporting of baseline data in RCTs to methodological standards. Secondarily, we studied differences between CONSORT-adopting and non-adopting journals, and explored differences according to type of journal and overall result.
Chapter 3.1

Methods

Selection of clinical trial reports

We handsearched RCTs from 16 journals with the highest Impact Factor in their categories (general medicine, cardiology, and oncology), published between September 1 and November 30, 2002. This period was arbitrarily chosen, and the 3-month period resembled the one used in a previous study \(^4\). The journals were at the top of the list in their respective subject category (ISI Journal Citation Reports 2002) and published RCTs regularly.

General medicine journals were N Engl J Med, JAMA, Lancet, Ann Intern Med, BMJ, and Arch Intern Med. Cardiology journals included Circulation, J Am Coll Cardiol, Eur Heart J, Am Heart J, and Am J Cardiol. Oncology jour-
Use of baseline characteristics in clinical trials from high impact medical journals

Journals included J Nat Cancer Inst, J Clin Oncol, Cancer, Brit J Cancer, and Eur J Cancer. We included main reports of phase III parallel RCTs, with individual randomization 13, and excluded cross-over trials, cluster-randomized trials, equivalence/non-inferiority trials, trials with less than 50 patients per arm, and factorial trials 7, 14. We excluded secondary trial reports designed to address additional hypotheses and subgroup comparisons specifically.

Assessment of trial reports and definitions

We examined RCTs and collected information in standard formats. Information about reporting of background information, baseline comparability, covariate adjustment and subgroup analyses was similar to a previous study 4 (Table 2). We measured the correspondence between the reporting of uses of baseline characteristics and methodological standards (Table 1). Our main outcome measure was the appropriateness of reporting of baseline comparability, covariate adjustment and subgroup analysis.

For consistency of evaluation across RCT reports, one of us (A.V.H.) selected the RCTs, checked inclusion and exclusion criteria and collected the information. To examine the reproducibility of the information, another reviewer (E.W.S.) also assessed the RCTs while blinded to the initial assessments. We found small differences in the extracted data, which were resolved by consensus.

An interaction test directly assesses differences in treatment effect between complementary subgroups and involves one statistical test irrespective of the number of subgroups. A significant interaction test means that the treatment effect in one subgroup is different from the treatment effect in the other subgroup. In contrast, the separate subgroup p value method assesses treatment effects in each group independently, which is inappropriate from a methodological point of view 5.

Secondary analyses

We compared baseline use between RCTs from journals which adopted the CONSORT statement (JAMA, Lancet, Ann Intern Med, BMJ, Arch Intern Med, J Nat Cancer Inst, Eur J Cancer) and journals which did not (N Engl J Med, Circulation, J Am Coll Cardiol, Am Heart J, Am J Cardiol, J Clin Oncol, Brit J Cancer) 15. Our focus was on baseline data (revised CONSORT item 15), covariate adjustment and subgroup analyses (revised CONSORT items 12 and 18). We hypothesized that CONSORT-adopting journals would report these issues better than non-adopting journals 10, 11.
Chapter 3.1

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</tr>
<tr>
<td>Emphasis of subgroups effects with respect to overall effect</td>
</tr>
<tr>
<td>General judgement</td>
</tr>
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</table>

RCT denotes randomized controlled trial.

Table 2. Data collected from RCT reports

The baseline use between RCTs published in general medicine journals and those in specialty journals (cardiology and oncology) was also compared. The reporting of baseline characteristics would be better in general medicine journals than specialty journals, based on a recent paper comparing the quality of
reporting (12). Finally, we searched whether covariate adjustment and subgroup analyses were related to the overall trial results (positive or negative). A positive trial reports a statistically significant treatment effect. Negative RCTs might report covariate adjustment and/or subgroup analyses more frequently.

Statistical analyses

Differences between continuous variables were compared with t-tests or Mann-Whitney U tests. Categorical variables were tested with Chi-square tests. We used tests for trend (one degree of freedom) for testing differences in time and differences in ordered variables. Statistical significance was defined as p<0.05. The software used was EXCEL and SPSS 10.0 (SPSS Inc., Chicago, USA, 1999).

Results

General characteristics of trial reports

Eighty-four RCTs were chosen from 14 journals (46 in general medicine, 21 in cardiology and 17 in oncology journals). They included 44 treatment, 27 management, 11 prevention, and 2 screening RCTs. One N Engl J Med paper reported two trials. Reasons for exclusion were: phase II trials (n=5), substudies (n=23), cross-over trials (n=1), equivalence/non-inferiority trials (n=6), small trials (n=25) and factorial trials (n=8). The RCTs mainly had 2 arms (n=68). The number of patients per RCT ranged from 103 to 266,064 (median 505). 76 RCTs were multicentric (range 2 to 519, median 15 centers). The follow-up time ranged from 3 days to 11 years (median 1 year).

Baseline comparability

Fifty-five RCTs (65 percent) presented comparability of 10 or more variables (range 0 to 31) (Table 3). Thirty-four tested for baseline differences, and 9 noted baseline imbalances. There were 11 significant imbalances at p<0.05, with a total of 145 reported tests (7 percent of tests).

Covariate adjustment

Covariate adjustment was reported in 44 (52 percent) RCTs, using mainly logistic or Cox regression analyses. The RCTs included between 1 and 12 baseline characteristics (Table 4). When both adjusted and unadjusted results were given (n=24), covariate adjustment did not alter the conclusions of the unadjusted
analyses, and unadjusted analyses received more emphasis (n=14). Twenty RCTs only gave adjusted results. Eight RCTs with covariate adjustment did not state any reason to choose a covariate. Half of the adjusted analyses (22 out of 44) were motivated by prognostic characteristics, which we consider appropriate.

Subgroup analysis

Forty–seven (55 percent) RCTs reported subgroup analysis, which were fully pre-specified in 22 (Table 5). The median number of subgroup factors was three (range 1 to 23). Twenty-three RCTs used more than two outcomes. Sixteen and six RCTs performed ≥12 and ≥25 subgroup analyses, respectively. Only 20 RCTs used the appropriate tests of interaction. Overall, 40 significant subgroups were found among 482 tests performed (9 percent), and 16 significant results among 235 reported interaction tests (7 percent). Twenty-two RCTs overemphasized the subgroup findings.

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</tr>
<tr>
<td>1 to 4</td>
<td>3</td>
<td>4</td>
</tr>
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<tr>
<td>Significant imbalance per test</td>
<td>11</td>
<td>7</td>
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Secondary analyses

The use of baseline characteristics was slightly better in CONSORT-adopting in comparison with non-adopting journals: testing for imbalances (13/36 vs. 18/48), reporting of covariate adjustment (16/36 vs. 28/48), number of subgroup analyses (median 5 vs. 9), and use of interaction tests (11/25 vs. 9/22). Although reporting of subgroup analysis was more frequent in CONSORT-adopting journals (25/36 vs. 10/48).

<table>
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<th>Which analysis received more emphasis?</th>
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* more than one reason in some trials.

Table 4. Reporting of covariate adjustment in 44 clinical trials.
### Table 5. Reporting of subgroup analysis in 47 clinical trials.

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<tr>
<td>3 to 5</td>
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<td>36</td>
</tr>
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<td>6 or more</td>
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<td>13</td>
</tr>
<tr>
<td><strong>Total number of subgroup analysis</strong></td>
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<td>43</td>
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<tr>
<td>No</td>
<td>27</td>
<td>57</td>
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vs. 22/48; p=0.03), it was mainly pre-specified (14/25 vs. 8/22).

RCTs from general medicine and cardiology journals compared more baseline characteristics than oncology journals (≥ 10 characteristics: 67 percent
vs. 90 percent vs. 29 percent; p=0.03). Reporting of other aspects of baseline comparability, covariate adjustment, and subgroup analysis was similar among specialties.

Negative and positive trials reported covariate adjustment in similar frequency (22/39 vs. 22/45), as well as subgroup analyses (22/39 vs. 25/45). Negative trials reported post-hoc subgroups more frequently (15/22 vs. 10/25), but tended to use a lower number of subgroups than positive trials (median 7 vs. 9). Subgroup differences were claimed in similar frequency in both groups (10/22 vs. 12/25). These differences were not significant.

**Discussion**

Despite the introduction of the revised CONSORT statement and publication of a number of methodological papers, the reporting of baseline comparability, covariate adjustment and subgroup analysis was not appropriate in RCTs from top journals. A third of the 84 RCTs tested for baseline imbalance, which has no methodological justification. From the 47 RCTs that performed subgroup analyses, half were pre-specified, and only 43 percent used the appropriate interaction tests.

The first CONSORT statement suggested that appropriate reporting of design, conduct, and analysis of parallel RCTs should enable the reader to make informed judgements regarding the internal and external validity of the trial. The revised CONSORT statement sharpened these recommendations further. The adoption of the first CONSORT guidelines led to improvements in quality of reporting. We provide empirical evidence that, after the introduction of the revised CONSORT statement, reporting of baseline comparisons, covariate adjustment and subgroup analysis is still a problem.

Baseline comparisons increased over time. A previous review of 80 RCTs published in 1987 in Ann Intern Med, BMJ, Lancet, and N Engl J Med showed that 39 percent of the RCTs compared ≥10 baseline characteristics. In 1997 these comparisons were found in 62 percent (31 out of 50) of the RCTs, and we found 65 percent (55 out of 84) in 2002. A review of 206 RCTs from 10 surgical journals, published between 1997 and 1999, found that only one-third tested baseline differences.

The proportion of significant tests for baseline differences was around the 5 percent expected by chance. Testing for baseline differences is inappropriate, and without practical value, especially if multiple variables are compared.
Covariate adjustment is especially advantageous when strong predictors are used\textsuperscript{106, 108, 109}. Prognostic covariates were preferentially used in the reviewed RCTs. For example, the SoS investigators properly adjusted for five pre-specified prognostic characteristics (age, angina grade, diabetes mellitus, ejection fraction, and angiographic severity)\textsuperscript{84}. However, a fifth of RCTs did not specify the number of covariates, or whether adjustment changed the conclusion of the unadjusted analysis. Recommendations to perform covariate adjustment include the use of a limited number of pre-specified, prognostic covariates, and the avoidance to use non-prognostic, imbalanced covariates\textsuperscript{4, 6, 106, 109}. Pre-specification aims to preclude that investigators perform multiple analyses before arriving at the “final” set of adjustment variables that best support their conclusions\textsuperscript{110}. However, the choice of prognostic covariates and the emphasis on adjusted analyses has not been fully agreed upon. Reviewers may sometimes have suggested to adjust for baseline variables that may be important, but were over-looked by the authors.

Subgroup analysis was overused and overinterpreted. Examples are easy to find in cardiology journals, where authors searched subgroups effects in separate publications intensively (e.g. pravastatin, metoprolol and estrogen/progestin trials)\textsuperscript{111-114}. This may be related to the fact that investigators re-analyze data in response to findings from other studies, and suggestions from reviewers to examine additional subgroups. Likewise, the total number of subgroups evaluated was high. For instance, among the reviewed reports, 4 RCTs reported between 28 and 33 subgroups\textsuperscript{44, 47, 71, 82}. As expected, some did not succeed\textsuperscript{44, 47}, and some found subgroup effects and claimed differences\textsuperscript{71, 82}. Subgroups effects were usually consistent with the overall trial results\textsuperscript{9, 115}. Importantly, only 22 out of 47 reported pre-specified subgroups, and probably the majority were post-hoc subgroups\textsuperscript{116, 117}.

Interaction testing is the appropriate method to analyze subgroups\textsuperscript{7, 118, 119}, but it was amazingly underutilized in trial reports (only 20 out of 47). However, the power of the interaction test is low\textsuperscript{118-120}. In a trial with 80 percent power for the overall effect, the interaction test only has at most 29 percent power to detect an interaction effect of the same magnitude of the overall effect\textsuperscript{119}. For smaller interactions effects or unequal distribution of covariates, its power is even more limited. In our review, only 7 percent of the interactions tests yielded significant results. This finding suggests that substantial true interactions are rare. Moreover, RCTs of a size adequate to detect an overall effect cannot be expected to provide reliable effect estimates within smaller groups\textsuperscript{118}. For example, for interactions of the same size and the same power of the overall effect, sample sizes should at least be inflated fourfold\textsuperscript{119}.
The evaluation of treatment effects in separate groups is misleading since false positive subgroup effects can often be found. Subgroup-specific tests are unreliable: A significant effect in one subgroup can be observed in 7 to 64 percent, depending on trial characteristics. This problem worsens when post-hoc subgroups and multiple comparisons are performed. For example, one RCT evaluated the effect of antiplatelet therapy following percutaneous coronary intervention in the composite end-point of death, myocardial infarction or stroke. The authors used 3 baseline factors (gender, diabetes, acute coronary syndrome) and 10 outcomes, used separate subgroups, and found 5 significant subgroups among 60 tests. Likely, some of these subgroup effects are the product of chance.

Subgroups therefore should not be overinterpreted, and should be reported with caution. A recent RCT and its editorial stressed the finding that vasopressin was more effective than epinephrine for cardiopulmonary resuscitation only in asystolic patients, and claimed a change in treatment guidelines in these patients. This seems an overinterpretation. Subgroup findings must be replicated in other populations before they are accepted, even if an interaction test is significant in a limited number of subgroups. For example, the PRAISE II trial could not replicate the subgroup effect found in the PRAISE trial, which showed a beneficial treatment effect of amlodipine in a subgroup of patients with nonischemic heart failure. Subgroups should also be interpreted in the context of known biological mechanisms and patient prognosis. Thus, some researchers consider it reasonable to rely only on main effects. This reasoning is supported by the finding of only 9 percent of significant subgroups among the 482 assessed, and 7 percent significant results of 235 interaction tests.

A previous paper found that RCTs from CONSORT-adopting journals (JAMA, Lancet, BMJ) were reported significantly better than those from a non-adopting journal (N Engl J Med). Another paper showed that reports from 10 CONSORT-adopting journals improved the presentation of 11 methodological factors (including description of prognostic baseline characteristics) in comparison with 16 non-adopting journals. However, these two papers evaluated the adoption of the first CONSORT guidelines. We found no differences according to the CONSORT adoption. This finding may be related to the fact that we included RCTs from late 2002 only, a year and a half after the publication of the revised CONSORT guidelines. Moreover, editors and reviewers of RCTs may be aware of the CONSORT guidelines, and may apply them informally in their practice. Thus, less differences in reporting can be expected.

We noted few differences in trial reporting between general medicine and specialty journals. A previous paper found subgroup analysis in 58 of 67 (87
percent) cardiology RCTs (n>1000) published between 1980 and 1997, addressing
unstable angina, myocardial infarction, left ventricular dysfunction and congestive heart failure. Only 24 RCTs had fully pre-specified subgroups, and 27 reported interaction tests. These reporting deficiencies have the same direction as our findings.

Our study has some limitations. First, we reviewed a limited number of RCTs (n=84), although this number is larger than in two previous studies (38 and 50, respectively). This aspect may not affect the general conclusions on reporting, but it makes comparisons between CONSORT adoption, among types of journal, and between overall results of limited power. Second, the information provided in an RCT may not necessarily be the same as what was planned in the study protocol. Finally, it is possible that the influence of the CONSORT guidelines on reporting requires more time to be adopted.

In conclusion, the reporting of baseline characteristics in RCTs from highly influential journals can be improved considerably. Despite the introduction of the revised CONSORT recommendations, a number of important problems remain, particularly with regard to testing for imbalance, the use of large numbers of subgroup analyses, the underuse of interaction tests, and the overinterpretation of subgroup effects. The CONSORT guidelines may need to further emphasise appropriate reporting recommendations of subgroup analysis, since conclusions of RCTs may be misleading otherwise.

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Subgroup analyses in therapeutic cardiovascular clinical trials: Are most of them misleading?

3.2
ABSTRACT

**Background:** Treatment decisions in clinical cardiology are directed by results from randomized clinical trials (RCTs). We studied the appropriateness of the use and interpretation of subgroup analysis in current therapeutic cardiovascular RCTs.

**Methods:** We reviewed main reports of phase III cardiovascular RCTs, with at least 100 patients, published in 2002 and 2004, and from major journals (Circulation, JACC, Am Heart J, Am J Cardiol, N Engl J Med, Lancet, JAMA, BMJ, Ann Intern Med). Information on subgroups included: pre-specification, number, interaction test use, significant subgroups found, and emphasis on findings. We examined appropriateness of reporting, and differences according to sample size, overall trial result, and CONSORT (Consolidated Standards for Reporting of Trials) adoption.

**Results:** We selected 63 RCTs, with a median of 496 patients (range: 100–15245). Thirty-nine RCTs were reported with subgroup analyses, and 26 with >5 subgroups. No trial was specifically powered to detect subgroups effects, and only 14 RCTs were reported with fully pre-specified subgroups. Only 11 RCTs were reported with interaction tests. Furthermore, 21 RCTs were reported with claims of significant subgroups, and 15 with equal or more emphasis to subgroups than to the overall results. Subgroup analyses in large RCTs (>500 patients) were reported more often than in small ones (24/30 vs. 15/33; P=0.005). No differences were found according to overall result (positive/negative) or CONSORT adoption.

**Conclusions:** Subgroup analyses in recent cardiovascular RCTs were reported with several shortcomings, including a lack of pre-specification, and testing of a large number of subgroups, without the use of the statistically appropriate test for interaction. Reporting of subgroup analysis needs to be substantially improved, since emphasis on these secondary results may mislead treatment decisions.
Subgroup analysis in cardiovascular clinical trials

Introduction

Treatment decisions in clinical cardiology are driven by results from randomized clinical trials (RCTs). As the number of drugs, devices, and treatment strategies has proliferated during the last two decades, so have the trials evaluating them. Indeed, some of these RCTs have provoked major changes in clinical practice (e.g. GISSI-1, SOLVD, 4S, NINDS, MERIT-HF, SIRIUS).

A result of a RCT represents the effect of a particular intervention in an ‘average’ patient. However, clinicians treat individual patients with complex combinations of characteristics. Thus, RCT results may not directly be applicable to one patient. Therefore, many investigators are interested to know treatment effects in specific subpopulations of patients (‘subgroup analysis’). Subgroups are based on patient characteristics measured before randomization. Treatment effects in subgroups might offer clinicians more insight into treating individual patients.

Main RCT reports or separate publications have investigated effects of treatments in subgroups. For instance, a substantial number of separate publications have given special attention to gender subgroups in acute coronary syndromes or heart failure. Usually the overall treatment effect was consistent with that in subgroups. However, differential subgroup effects may be identified by chance, because multiple tests are performed in many subgroups, and by the use of inadequate methods.

Even though subgroup analyses are popular and occupy a large number of pages in the cardiovascular literature, little attention has been directed to their adequate reporting and interpretation. We aimed to review the appropriateness of reporting of subgroup analysis in RCTs recently published in major cardiology and internal medicine journals.

Methods

Selection of RCT reports

We handsearched therapeutic cardiovascular RCTs from journals with high impact factor in the ISI Journal Citation Report 2002 (categories cardiology and general internal medicine). Cardiology journals included Circulation, J Am Coll Cardiol, Am Heart J, and Am J Cardiol. General internal medicine journals included N Engl J Med, Lancet, JAMA, Br Med J, and Ann Intern Med. Two periods of 3 months were arbitrarily chosen: September 1 to November 30 2002, and May 1 to July 31 2004.
Therapeutic RCTs included interventions such as drugs, devices or therapeutic strategies. The diseases included acute coronary syndromes, left ventricular dysfunction, heart failure, arrhythmia, cardiac valve disease, hypertension, stroke, atherosclerosis of peripheral arteries (carotid, renal, lower limb), pulmonary embolism and venous thromboembolism, venous insufficiency, diabetes mellitus, and hypercholesterolemia. We included main reports of phase III parallel RCTs, with individual randomization, and we excluded cross-over trials, cluster-randomized trials, equivalence/non-inferiority trials, factorial trials, and trials with less than 100 patients. Because it was not the focus of our review, we excluded secondary trial reports designed to specifically address post-hoc hypotheses and subgroup comparisons.

Subgroup analysis reporting

Information about subgroup analysis was extracted, which was considered essential to evaluate the appropriateness of the method, and the validity of the results. This information included: Pre-specification of subgroup analysis (as reported in methods), number of subgroup factors (patient baseline characteristics measured before randomization), number of subgroup outcomes (primary or secondary endpoints), total number of subgroups (the product of the number of subgroup factors and the number of subgroup outcomes), statistical method (interaction test or separate analysis), number of significant subgroups found, and emphasis in subgroup findings (subgroup results mentioned in abstract and/or conclusion).

An interaction test directly assesses differences in treatment effect between complementary subgroups, and involves one statistical test irrespective of the number of subgroups. A significant interaction test means that the treatment effect in one subgroup is significantly different from the treatment effect in the other subgroup. In contrast, the separate subgroup method assesses treatment effects in each group independently, and it involves two or more tests. This is inappropriate from a statistical point of view.

For consistency in the gathering of information, one of us (A.V.H.) selected the RCT reports, checked the inclusion and exclusion criteria, and collected the information. Another of us (E.W.S.) independently assessed the same RCT reports, and was blinded to the assessments of the first reviewer. There were few differences, which were resolved by consensus.

Secondary analyses

We examined differences in reporting between relatively small (<500 patients)
and large trials (≥500 patients). We expected that researchers in large trials would feel more confident to search for differential treatment effects in subgroups. We also examined subgroup reporting between negative (non-significant overall result) and positive trials. Researchers might try to explore subgroup effects if the overall effect was non-significant. Finally, we examined differences according to adoption of the CONSORT (Consolidating Standards for Reporting Trials) Statement 20, which might improve reporting of subgroup analysis.

**Statistical analysis**

Descriptive statistics included percentages and medians. Categorical variables were tested with Chi-square tests. The software used was EXCEL and SPSS 10.0 (SPSS Inc., Chicago, USA, 1999).

**Results**

**RCT reports**

In total, 63 RCTs 21-83 satisfied the inclusion criteria (Table 1). Fifty-three (84%) ...
RCTs had two arms. Two thirds (n= 42) of the RCTs evaluated drugs, and one third (n=21) devices or strategies. Half of the RCTs had more than 500 patients, and the follow-up ranged between 3 days and 4.5 years. Most of the RCTs were multicenter. Approximately half of the RCTs yielded negative overall results. One third of the RCTs were published in journals which adopted the CONSORT statement.

Subgroup reporting

Two-thirds (39 out of 63) of the RCTs were reported with subgroup analyses (Table 2), while 24 RCTs only performed crude analyses. According to what was described, full pre-specification of all subgroups was only done in 14 reports, and 4 others included both pre-specified and non-pre-specified subgroups. Subgroups in the other 21 RCTs were reported without a rationale, and these may represent after-analysis subgroups.

The median number of patient baseline characteristics used as subgroup factors was three. However, some RCTs included higher numbers, with a maximum of 23. Two thirds (26 out of 39) of the RCTs were reported with >5 subgroups. The main factors were: gender (n=20), age (n=16), comorbidities other than diabetes (n=15), severity of disease (n=13), and diabetes (n=11). Likewise, the median number of subgroup outcomes was two, and some reported as many as seventeen. Therefore, the number of total subgroups (product of factors by outcomes) was high, ranging from 7 to 60. We found 63 significant subgroups among the 508 subgroups assessed (12%): 25 significant subgroups were pre-specified, and 38 were post-specified.

The interaction test was used in 11 out of 39 RCTs, and separate tests in 28. When interaction tests were used, the authors identified 10 (6%) significant subgroup effects among 175 tests performed. With separate subgroups, the authors identified 53 (16%) significant subgroup effects among 333 tests performed. Nearly half (21 out of 39) of the RCTs claimed differences between subgroup treatment effects and the average treatment effects, and showed them in their result sections. Moreover, fifteen reports emphasized their subgroup findings by highlighting them either in the main conclusions or in the abstract. Only 6 RCTs reports included the appropriate interaction test and did not put emphasis on subgroup results.

Secondary analysis

Large trials (n>500) more often reported subgroup analyses than small trials (24/30
vs. 15/33, p=0.005). However, we did not observe differences in pre-specification, number of subgroups, statistical methods or emphasis in results. Moreover, these features of subgroup reporting did not differ between CONSORT-adopting and non-adopting trials, and between negative and positive trials.

**Table 2. Description of reporting of subgroup analysis.**

RCTs denotes randomized clinical trial.

We found several shortcomings in the use and reporting of subgroup analysis in recent cardiovascular RCTs from major general medicine and cardiology jour-
nals. Many subgroups, frequently not pre-specified, were reported. The test of interaction was underused, and subgroup findings were commonly emphasized. These shortcomings may mislead treatment decisions when particular subgroups of patients are being evaluated.

During the last two decades the number of RCTs in cardiology has dramatically increased: from 5,410 in the period 1980-1989 to 14,845 in the period 1990-2000. Simultaneously, the interest to explore treatment effects in subgroups of patients has increased. In the last two decades, many pages have been devoted to look at differential treatment effects in particular subgroups such as elderly people, female patients, diabetic patients, and severely-ill patients in diseases such as acute coronary syndromes, heart failure, hypertension, stroke, and hypercholesterolemia.

Although subgroups should be clearly defined in the RCT protocol ('pre-specified subgroups') 18, researchers may decide to perform subgroup analysis when the RCT is running ('pre-analysis subgroups') or when the RCT analysis has been completed ('after-analysis subgroups'). Frequently, the RCT reports do not clearly make this differentiation.

One review evaluated 67 large RCTs in unstable angina, myocardial infarction, left ventricular dysfunction or heart failure. Some shortcomings in subgroup reporting were noticed: little supporting rationale, lack of pre-specification, overuse of separate analyses, and underuse of the formal statistical test of interaction. However, the authors limited the review to large (>1000 patients) drug RCTs, from 1980 to 1997. We included more recent RCTs (2002 and 2004), with medium size (two-thirds <1000 patients) and a broader perspective (evaluation of drugs, devices and strategies). Our review may reflect the scope of RCTs reviewed by cardiologists nowadays.

Two thirds of the RCTs in our study reported pre-analysis, after-analysis, or partially pre-specified subgroups. These findings may be related to the fact that investigators re-analyze data in response to preliminary results, results from other studies, and suggestions from reviewers. It is possible that investigators evaluated an unplanned, large number of subgroups: two thirds of the RCTs reported more than 5 subgroups. Remarkably, seven RCTs reported more than 25 subgroups. Three of these RCTs found a high number of statistically significant subgroups, ranging from 5 to 18. Moreover, the proportion of significant subgroups was higher than the 5% expected (Z test= 4.19, p<0.01), especially for separate tests. Most of these subgroups were based on non-prognostic baseline characteristics, and may hence be considered
with suspicion. Pre-specification of a limited number of subgroups based on predictive baseline characteristics may decrease the probability of spurious subgroup effects (false positives).

Interaction testing is the appropriate method to analyze subgroups. Remarkably, interaction tests were only used in around 30% of cardiovascular RCTs which reported subgroups. This method decreases the risk to find false positive subgroups, but its power to detect true subgroups is low. For instance, in a trial with 80% power for the overall treatment effect, the interaction test has at most 29% power to detect an interaction effect of the same magnitude of the overall effect. The sample size should be increased at least four-fold to achieve the same power. Likewise, the evaluation of treatment effects in separate groups is misleading since false positive subgroup effects can be found: A significant effect in one subgroup can be expected in 7%, when the observed overall effect was nonsignificant.

The interpretation of subgroups is important for treatment decisions in cardiology. Thus, some treatments may be withheld for some patients who require them, and some other patients may be treated with drugs that are not needed. For instance, aspirin was studied in few women in primary and secondary prevention RCTs of coronary heart disease, and a non-significant effect of aspirin was found in subgroup analysis in women. An overinterpretation of this subgroup may have led to the undertreatment of women for years, although we now know that aspirin is effective in women. Other classic examples include the use of thrombolytic therapy and beta blockade only in patients with anterior myocardial infarctions.

Half of the cardiovascular RCTs claimed significant subgroup effects, and 40% gave equal emphasis to subgroup and overall results. This is worrying, because subgroup analysis is a secondary, hypothesis-generating exercise to stimulate further research. Thus, less emphasis should be placed on subgroup results. The best estimate of treatment effect to be expected for a patient treated outside the trial may be still the overall effect. Rather, subgroup analyses should measure the consistency of beneficial and harmful treatment effects across different risk and demographic groups. This was shown in recent RCTs on beneficial treatment effects for heart failure, coronary intervention, coronary reperfusion and secondary prevention with statins, and on harmful effects of inotropic drugs for heart failure and oral glycoprotein IIb/IIIa inhibitors for unstable angina.

An example of satisfactory reporting and interpretation of subgroup analysis is the MATCH trial. This RCT compared the use of aspirin and clopidogrel...
versus clopidogrel alone after ischemic stroke or transient ischemic attack in high-risk patients (n=7599). The overall treatment effect was not significant. The authors used 13 pre-specified patient baseline characteristics to define subgroups. They used interaction tests to explore differential treatment effects by baseline characteristics on one composite outcome, and found that the treatment effect differed by patient age (p=0.012). They considered this finding with scepticism, and showed the overall effect as the main result.

On the other hand, the ACST trial reported its subgroup analyses less satisfactorily. The authors evaluated the prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms (n=3120). They extensively reported 27 partially pre-specified subgroup analyses, based on 9 baseline characteristics and 3 outcomes. However, it is not clear how many analyses really were performed. Moreover, they analyzed these subgroups independently, resulting in 72 p-values. Although the overall effect was positive, three subgroup findings were emphasized: effects in women, in patients with hypercholesterolemia, and in patients older than 75 years. These subgroups were of limited sample size and had few events. In particular, the investigators concluded that both men and women had a significant benefit with carotid endarterectomy on the risk of stroke, although the effect in women was ‘not as definite as in men’.

We summarize some recommendations to appropriately perform and interpret subgroup analysis in cardiovascular RCTs, based on current recommendations and methodologic papers (Table 3). Apart from looking at subgroup results of prior RCTs and independent subgroup confirmation, meta-analyses can be used to study subgroups. Meta-analyses have higher power to detect significant subgroup effects in comparison to individual RCTs, and hence give readers more confidence to believe in a potential subgroup. Nice examples are readily available from the literature. For instance, a small meta-analysis of the results of the ACST and the ACAS trials has highlighted a significant effect of endarterectomy in men and a nonsignificant effect in women on the combined risk of any stroke and operative death. If a subgroup is still not completely reliable and there is a special interest on it, probably the best, but less feasible alternative is to design a RCT specifically targeted to study the subgroup. One example is to design a confirmatory subgroup analysis within a RCT, which aims to find explicit effects of interventions in a prospectively defined subgroup stratum of interest. This method usually defines a subgroup sample size between 40 to 60% of the total sample size.

Our paper has some limitations. We reviewed a limited number of RCTs. However, we used a broad sample of major journals, which publish the most
influential RCTs in cardiology. Moreover, our main aim was to highlight the appropriateness of use and interpretation of subgroup analysis, and this sample may well be considered representative of current practice. Finally, we only used information that was published in the RCT reports. The information provided in the reports may not necessarily be the same as in the RCT protocol, nor comprise all analyses that were performed.

In conclusion, subgroup analyses in recent cardiovascular RCTs were reported with several shortcomings, such as a lack of pre-specification, and testing of a large number of subgroups, without the use of the statistically appropriate test for interaction. Reporting of subgroup analysis needs to be substantially improved in cardiovascular RCTs, since emphasis in these secondary results may mislead treatment decisions for particular groups of patients.

**Table 3.** Suggestions to appropriately perform and interpret subgroup analysis.

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<th>Specification</th>
<th>Analysis</th>
<th>Interpretation</th>
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<td>Specify a limited number of subgroups in advance, with a clear rationale.</td>
<td>Use statistical interaction tests in the full RCT population.</td>
<td>a. Be sceptical if subgroups were not pre-specified, not biologically plausible or no interaction tests were applied.</td>
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<td>b. Interpret in context, e.g. look at prior findings, and independent confirmation.</td>
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<td>c. See subgroup analysis as a hypothesis-generating exercise to stimulate further research.</td>
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<td>d. Put emphasis on overall results, which may be considered better estimates of treatment effects than the subgroup effects.</td>
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Subgroup analysis and covariate adjustment in randomized clinical trials of traumatic brain injury: A systematic review
ABSTRACT

Objective: Few randomized clinical trials (RCTs) in the field of traumatic brain injury (TBI) have shown a significant treatment benefit. We aimed to critically review the uses of two types of secondary analyses, covariate adjustment and subgroup analysis, which may be common in TBI trials.

Methods: We performed a systematic review of therapeutic phase III RCTs, including acute, adult, moderate-to-severe TBI patients. Glasgow Outcome Scale (GOS) at ≥3 months as outcome, and ≥50 patients per arm were required. We compared the actual reporting of covariate adjustment and subgroup analyses with the CONSORT (Consolidated Standards of Reporting Trials) recommendations. Likewise, we reviewed six protocols of large multicenter RCTs, and compared planned and reported subgroups.

Results: We identified 18 RCTs (n= 6439). Sixteen trials used GOS at 6 months as outcome. Five RCTs reported covariate adjustment. The number of covariates was limited (≤5), most frequently including age. Many covariates were outcome predictors. Four RCTs reported only adjusted treatment effects as the main efficacy parameter. Eleven RCTs reported subgroup analyses. Several subgroup factors (≤7, mainly outcome predictors) and outcomes (≤4) were included. The highest total number of subgroups was fifteen, and only three RCTs completely pre-specified subgroups. Notably, 10 out of 11 RCTs performed inappropriate separate subgroup analyses. Five out of 11 RCTs gave subgroups the same emphasis as the overall effect. Reported subgroup analyses were insufficiently described, and clearly differed from those planned in the protocol.

Conclusions: The reported covariate adjustment and subgroup analyses from TBI trials had several methodological shortcomings. Appropriate performance and reporting of covariate adjustment and subgroup analysis should be considerably improved in future TBI trials, since interpretation of treatment benefits may be misleading otherwise.
Introduction

Acute traumatic brain injury (TBI) is a leading cause of premature death and disability and remains a major public health problem around the world. Brain injury management is primarily aimed at measures to prevent and limit the development of secondary brain damage. Many therapeutic randomized clinical trials (RCTs) have failed to demonstrate significant improvement in outcomes in patients with moderate and severe TBI. These failures have been attributed to many causes, including insufficient pre-clinical and initial clinical work-up, small sample size, inadequate use of the outcome measure, too optimistic expectations, ineffective therapies, inappropriate target mechanism, and heterogeneity of patients.

The heterogeneity of the TBI patients remains despite strict inclusion and exclusion criteria. Patient baseline characteristics, collected at entry to a RCT, give information on prognosis and type of injury, and reflect this heterogeneity. Proposals for dealing with heterogeneity in the design of RCTs include: stratified randomization, block randomization, inclusion of patients with similar types of injury, and targeting patients most likely to benefit from the treatment (e.g. exclude patients with very good and very bad prognosis). Other proposals have focused on the analysis of RCTs: covariate adjustment, and subgroup analysis.

The CONSORT (Consolidated Standards of Reporting Trials) statement includes recommendations to improve the analysis and reporting of covariate adjustment and subgroup analyses in RCTs. Recently, the misuse of baseline data, especially the overinterpretation of subgroup analyses, has been noted in general medicine RCT reports. It is likely that such misuse may have been more common in TBI trials because of the significant problems of heterogeneity. No formal evaluation of covariate adjustment and subgroup analysis in TBI trials has been performed so far.

We aimed to describe the appropriateness of reporting covariate adjustment and subgroup analysis in published phase III RCTs including acute, closed, and moderate to severe TBI adult patients, with a substantial sample size and with clinically relevant outcomes. We further reviewed a sample of the protocols of the largest multicenter TBI trials, in order to compare the concordance between planned and reported subgroup analyses.
Methods

RCT report search strategy

We searched MEDLINE (1966 to 1 April 2004), EMBASE (1974 to 1 April 2004), the Cochrane Controlled Trials Register and the Cochrane Database of Systematic Reviews (Cochrane Library, Issue 2, 19 April 2004) for RCTs in TBI. All searches used the key words traumatic brain injury or traumatic head injury or traumatic cranial injury in conjunction with each of the following words: severe, moderate, acute, treatment, randomized controlled trials, and randomized clinical trials. The searches were limited to RCTs in English, French, German and Spanish. We reviewed the bibliographies of relevant studies (RCTs and non-RCTs) to search for additional eligible RCTs. Only data accessible in peer-reviewed journals were included, and we were not masked with regard to authors or journal.

Inclusion and exclusion criteria of RCTs

We selected RCTs that met the inclusion and exclusion criteria (Box). One of us (A. V. H.) screened the titles and abstracts to exclude non-human studies and review articles, retrieved potentially relevant manuscripts for detailed evaluation, and selected publications compliant with the inclusion and exclusion criteria. Jointly with another of us (A. I. R. M.), both researchers reassessed inclusion and exclusion criteria. Reports that did not meet all these criteria were excluded. Differences were resolved by discussion until consensus was reached.

Data extraction

The eighteen eligible trials underwent data extraction from the full-text papers by one of us (A. V. H.) using a pre-designed extraction form. This form was previously used in another related review by two of the authors (A. V. H. and E. W. S.) and the information obtained was highly reproducible. Patient attributes measured before randomization were considered as baseline characteristics. The information retrieved included general information, such as sample size, number of centers, and primary outcome. Information on covariate adjustment included number of covariates, pre-specification, selection strategy, statistical method, primary use of covariate adjustment, and emphasis with respect to unadjusted analysis. Information on subgroup analyses included number of subgroup factors, number of subgroup outcomes, number of subgroup analyses (product of factors by outcomes), pre-specification, statistical method (interaction test or separate subgroup p value), and emphasis given to subgroups.
Inclusion criteria
a. Prospective, parallel-groups, phase III RCT with random assignment to either
   a new medication/intervention or placebo/best intervention available.
b. Main RCT report.
c. Patients with non-missile, closed, clinically diagnosed TBI.
d. Acute TBI presentation (<24 hours between injury and treatment).
e. Moderate or severe TBI (i.e. Glasgow Coma Scale [GCS] ≤ 12).
f. Primary outcome expressed as Glasgow Outcome Score (GOS) at ≥ 3 months.
g. Patients older than 15 years.
h. More than 50 patients per treatment arm.

Exclusion criteria
a. Phase II RCTs.
b. Mild TBI (GCS: 13 to 15).
c. Chronic TBI treatments (e.g. rehabilitation).
d. Pediatric TBI patients
e. Primary outcome other than GOS.

Box. Inclusion and exclusion criteria for the systematic review.

Methodological standards

The CONSORT statement established standards of trial reporting, based on a large amount of methodological and applied information regarding appropriate design and analysis of trials. This document proposed 22 items that should be reported in every RCT in order to allow the readers to judge the validity of the findings, and to be more confident when applying these findings in their practice. The CONSORT items 12, 15, and 18 refer to covariate adjustment and subgroup analysis. Covariate adjustment should use a limited number of covariates, and should clearly establish the reasons to choose covariates. Subgroup analysis should use a limited number of pre-specified subgroups, use interaction tests, and be considered a secondary analysis.

Definitions

An interaction test directly assesses differences between complimentary sub-
groups by studying treatment*subgroup factors. It involves one statistical test irrespective of the number of subgroups. In contrast, the separate subgroup p value method evaluates treatment effects in each complementary group independently. This is inappropriate from a methodological point of view.
Subgroups were pre-specified if they were clearly established in the methods part or if they were clearly labeled as pre-specified.

Subgroups were post-hoc if they were shown only in results and/or discussion or if they were clearly labeled as post-hoc. Emphasis on subgroups was classified as similar to the overall effect if subgroups were reported in the abstract or main conclusion of the paper. If the subgroups were only presented in the results and/or discussion, the overall effect had more emphasis.

**RCT Protocols**

We hypothesized that results on subgroup analyses might differ from subgroup analyses as specified in the protocol. Six protocols of some of the largest multi-center TBI trials were reviewed. We focused on the number of subgroup factors...
and outcomes, whether subgroups were pre-specified, and statistical method of subgroup analysis. Thus, we compared the planned subgroup analyses with the reported subgroup analyses, in order to evaluate their concordance and discrepancies.

Statistical analyses

Descriptive statistics included percentages and medians. The software used was EXCEL and SPSS 10.0 (SPSS Inc., Chicago, USA, 1999).

Results

General RCT characteristics

The systematic review of the literature identified 297 potentially relevant citations with titles and abstracts. We finally included 18 RCTs 3, 5, 12, 14, 15, 16, 20, 21, 22, 31, 34, 36, 41, 42, 45, 48, 49, 51 (Figure). All RCT reports were published in English, from 1981 to 2004 (Table 1). The number of patients included ranged between 100 and 1120 (median: 265), originating from 1 to 95 centers (median: 8) mainly from developed countries 34, 36.

Eleven trials investigated drugs, and they were published before the year 2000. The time of follow up ranged between 6 and 14 months (median 6 months). The primary end point was mainly GOS at 6 months (16 out of 18 trials), which was dichotomized in 9 trials. Notably, from six trials that yielded positive results 14, 16, 31, 48, 49, 51, five were single center studies, and used a therapy other than a drug—i.e. surgery, hypothermia, mannitol and hyperbaric oxygen 15, 31, 41.

Covariate adjustment

Five trials published before 1997 reported covariate adjustment 20, 22, 45, 48, 49 (Table 2). The number of covariates included ranged from one to five. Covariates from 2 trials were not clearly defined 45, 48. Age was the most commonly chosen covariate 22, 45, 48, 49. Most of the covariates were well-known outcome predictors (e.g. age, initial Glasgow Coma Scale [GCS], motor score, pupillary reactivity, and initial Computed Tomography [CT] abnormalities) but this reason was not clearly established in the RCT reports. Center was considered as a covariate in two older trials 20, 48, and imbalance in age and GCS was reported as the reason for adjustment in one trial 22. Logistic regression was the main method of adjustment in 3 trials 22, 45, 48. Four RCTs gave only adjusted results, and one RCT 22 reported adjusted and unadjusted results. In this trial, the unadjusted treatment
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<thead>
<tr>
<th>Author reference, year</th>
<th>Country*</th>
<th>Centers n (arms)</th>
<th>Treatment</th>
<th>Target population†</th>
<th>GOS‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive trials (n=6)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lu 31, 2003</td>
<td>CHN</td>
<td>1 230 (2)</td>
<td>Craniotomy</td>
<td>Severe</td>
<td>6m</td>
</tr>
<tr>
<td>Zhi 50, 2003</td>
<td>CHN</td>
<td>1 396 (2)</td>
<td>Hypothermia</td>
<td>Severe</td>
<td>6m</td>
</tr>
<tr>
<td>Cruz 16, 2002</td>
<td>BRA</td>
<td>1 141 (2)</td>
<td>Mannitol</td>
<td>Coma, Acute IPH</td>
<td>6m</td>
</tr>
<tr>
<td>Cruz 15, 2001</td>
<td>BRA</td>
<td>1 178 (2)</td>
<td>Mannitol</td>
<td>Coma, Acute SDH</td>
<td>6m</td>
</tr>
<tr>
<td>Harders 22, 1996</td>
<td>GER</td>
<td>21 123 (2)</td>
<td>Nimodipine</td>
<td>SAH</td>
<td>6m</td>
</tr>
<tr>
<td>Rockswold 40, 1992</td>
<td>USA</td>
<td>1 168 (2)</td>
<td>Hyperbaric O₂</td>
<td>Severe</td>
<td>12, 6, 18m</td>
</tr>
<tr>
<td>Negative trials (n=12)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cooper 14, 2004</td>
<td>AUS</td>
<td>12 226 (2)</td>
<td>Hypertonic saline</td>
<td>Severe, 6m (usual &amp; extended)</td>
<td></td>
</tr>
<tr>
<td>Clifton 12, 2001</td>
<td>USA</td>
<td>11 392 (2)</td>
<td>Hypothermia</td>
<td>Severe</td>
<td>6m</td>
</tr>
<tr>
<td>Morris 36, 1999</td>
<td>USA, ISR, EUR, CAN, AUS, ARG.</td>
<td>95 693 (2)</td>
<td>NMDA antagonist (Selfotel)</td>
<td>Severe</td>
<td>6m</td>
</tr>
<tr>
<td>Marshall 34, 1998</td>
<td>EUR, AUS, ISR.</td>
<td>50 1120 (2)</td>
<td>Tirilazad</td>
<td>Severe (85%), Moderate (15%)</td>
<td>6m</td>
</tr>
<tr>
<td>Young 48, 1996</td>
<td>USA</td>
<td>29 463 (3)</td>
<td>Pegorgotein</td>
<td>Severe</td>
<td>3m</td>
</tr>
<tr>
<td>Grumme 21, 1995</td>
<td>GER, AUT</td>
<td>9 396 (2)</td>
<td>Triamcinolone</td>
<td>Severe, Discharge &amp; 1y</td>
<td></td>
</tr>
<tr>
<td>European Study Group Nimodipine 44, 1994</td>
<td>EUR</td>
<td>21 852 (2)</td>
<td>Nimodipine</td>
<td>Severe, Not obeying commands</td>
<td>6m</td>
</tr>
<tr>
<td>Gaab 20, 1994</td>
<td>GER</td>
<td>10 300 (2)</td>
<td>Dexamethasone</td>
<td>Severe, Moderate</td>
<td>12m (modified)</td>
</tr>
<tr>
<td>Wolf 47, 1993</td>
<td>USA</td>
<td>2 149 (2)</td>
<td>Tromethamine</td>
<td>Severe</td>
<td>3, 6, 12m</td>
</tr>
<tr>
<td>Bailey 3, 1991</td>
<td>UK, FIN</td>
<td>6 351 (2)</td>
<td>Nimodipine</td>
<td>Not obeying commands</td>
<td>6m</td>
</tr>
<tr>
<td>Braakman 5, 1983</td>
<td>NED</td>
<td>2 161 (2)</td>
<td>Dexamethasone</td>
<td>Coma, Severe</td>
<td>6m &amp; Survival 1y</td>
</tr>
<tr>
<td>Saul 41, 1981</td>
<td>USA</td>
<td>1 100 (2)</td>
<td>Methylprednisolone</td>
<td>Severe</td>
<td>6m</td>
</tr>
</tbody>
</table>

*AUS: Australia; CHN: China; BRA: Brazil; USA: United States of America; ISR: Israel; EUR: Europe; GER: Germany; AUT: Austria; UK: United Kingdom; FIN: Finland; NED: Netherlands.
†Severe TBI: Glasgow Coma Score (GCS) <9; Moderate TBI: GCS 9 to 12; IPH: Intraparenchymal hemorrhage; SDH: Subdural hematoma; SAH: Subarachnoid hemorrhage.
‡GOS: Glasgow Outcome Scale; extended: GOSE, Glasgow Outcome Score Extended; modified: mGOS, Modified GOS; m: months; y: year.

Table 1. General characteristics of trial reports included in the review (n=18).
Subgroup analysis and covariate adjustment in traumatic brain injury trials

<table>
<thead>
<tr>
<th>Author *reference</th>
<th>Covariates included</th>
<th>Reason to include</th>
<th>Method used in covariate adjustment</th>
<th>Emphasis in results</th>
<th>Change in conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young 48, 1996</td>
<td>1 Age (&lt;45; ≥45)</td>
<td>Not given</td>
<td>Stratified Mantel Haenzel</td>
<td>Adjusted**</td>
<td>NA††</td>
</tr>
<tr>
<td>Harders 22, 1996</td>
<td>4 Age (continuous), GCS† at entry (≤12, &gt;12); amount of blood in initial CT (ordinal, 3); Fisher grade in initial CT (ordinal, 4)</td>
<td>Imbalance (age, GCS); rest not given</td>
<td>Logistic regression</td>
<td>Unadjusted</td>
<td>No</td>
</tr>
<tr>
<td>European Study Group Nimodipine 44, 1994</td>
<td>5 Age (ns‡); gender (ns), craniotomy (ns); pupilary reaction (ns); GCS motor responses (ns)</td>
<td>Not given</td>
<td>Logistic regression</td>
<td>Adjusted**</td>
<td>NA</td>
</tr>
<tr>
<td>Gaab 20, 1994</td>
<td>1 Center (categorical, 10)</td>
<td>Center</td>
<td>Stratified Mantel Haenzel</td>
<td>Adjusted**</td>
<td>NA</td>
</tr>
<tr>
<td>Wolf 11, 1993</td>
<td>5 Age (ns); GCS motor score (ns); strata of neurological insult (ns); elevated ICP§ (ns); center (categorical, 2)</td>
<td>Center; rest not given</td>
<td>Logistic regression</td>
<td>Adjusted**</td>
<td>NA</td>
</tr>
</tbody>
</table>

* Definition refers to the way they were considered in analyses: continuous, categorical or ordinal. In case of categorical or ordinal covariates, it is written the number of categories considered.
† GCS: Glasgow Coma Scale.
‡ ns: Non specified.
§ ICP: Intracranial pressure.
** Only adjusted effect given.
†† Not available.

Table 2. Covariate adjustment on five trial reports.

<table>
<thead>
<tr>
<th>Results of trial</th>
<th>TBI trials</th>
<th>Internal Medicine trials‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Covariate adjustment</td>
</tr>
<tr>
<td>Negative</td>
<td>12</td>
<td>4 (33%)†</td>
</tr>
<tr>
<td>Positive</td>
<td>6</td>
<td>1 (17%)</td>
</tr>
<tr>
<td>Total</td>
<td>18</td>
<td>5 (28%)</td>
</tr>
</tbody>
</table>

* No significant differences between positive and negative trials, and between TBI and internal medicine trials.
† Percentages are separated by topic (TBI or Internal Medicine), and correspond to: number of trials with the analyses / number of trials (n) in the same row.
‡ Internal Medicine includes: General Internal Medicine, Cardiology and Oncology (reference 26).

Table 3. Number of reported covariate adjustment and subgroup analyses in positive and negative trials: Comparison between traumatic brain injury and internal medicine trials*
<table>
<thead>
<tr>
<th>Author *reference</th>
<th>Subgroup factors</th>
<th>Subgroup outcomes</th>
<th>Total ¶</th>
<th>Pre-specified? **</th>
<th>Statistical method</th>
<th>Subgroup found? (n) ††</th>
<th>Emphasis in results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cooper 14, 2004</td>
<td>GCS</td>
<td>GOSE+6m</td>
<td>1</td>
<td>Yes</td>
<td>Separate test</td>
<td>No</td>
<td>Overall</td>
</tr>
<tr>
<td>Clifton 12, 2001</td>
<td>Age, GCS, compressed cisterns, surgical hematoma, initial hypothermia</td>
<td>Poor outcome‡, death, ICP&gt;30 mmHg</td>
<td>15</td>
<td>No</td>
<td>Separate test</td>
<td>Yes (2)</td>
<td>Overall</td>
</tr>
<tr>
<td>Morris 36, 1999</td>
<td>EDH*, SDH, IPH, GCS, secondary ischemic events</td>
<td>Favorable outcome‡, death</td>
<td>10</td>
<td>Yes</td>
<td>Separate test</td>
<td>No</td>
<td>Overall</td>
</tr>
<tr>
<td>Marshall 34, 1998</td>
<td>Gender, SAH, GCS.</td>
<td>Favorable outcome, death</td>
<td>6</td>
<td>Partially</td>
<td>Separate test</td>
<td>Yes(3)</td>
<td>Equal subgroup &amp; overall</td>
</tr>
<tr>
<td>Young 48, 1996</td>
<td>GCS</td>
<td>Good outcome‡, favorable outcome (3m &amp; 6m)</td>
<td>4</td>
<td>No</td>
<td>Separate test</td>
<td>No</td>
<td>Overall</td>
</tr>
<tr>
<td>Harders 22, 1996</td>
<td>GCS, amount of blood-CT, Fisher grade-CT</td>
<td>Favorable outcome</td>
<td>3</td>
<td>No</td>
<td>Separate test</td>
<td>No</td>
<td>Overall</td>
</tr>
<tr>
<td>Grumme 21, 1995</td>
<td>Age, focal lesions, GCS, EDH, SDH, admission &lt;1h, initial steroid treatment</td>
<td>GOS at discharge, GOS 1y</td>
<td>14</td>
<td>Partially</td>
<td>Separate test</td>
<td>Yes(1)</td>
<td>Equal subgroup &amp; overall</td>
</tr>
<tr>
<td>European Study Group Nimodipine 34, 1994</td>
<td>Brain damage, SAH, others (unknown)</td>
<td>Favorable outcome</td>
<td>&gt;2</td>
<td>Partially</td>
<td>Separate test</td>
<td>Yes(1)</td>
<td>Equal subgroup &amp; overall</td>
</tr>
<tr>
<td>Rockswold 40, 1992</td>
<td>GCS, mass lesion, contusion, pupillary reactivity</td>
<td>Favorable outcome, death (1y)</td>
<td>8</td>
<td>Partially</td>
<td>Separate test</td>
<td>Yes(2)</td>
<td>Equal subgroup &amp; overall</td>
</tr>
<tr>
<td>Bailey 3, 1991</td>
<td>Age, motor GCS, intracerebral lesion, motor response, others (unknown)</td>
<td>Favorable outcome, death</td>
<td>&gt;8</td>
<td>Partially</td>
<td>Interaction test</td>
<td>No</td>
<td>Overall</td>
</tr>
<tr>
<td>Braakman 5, 1983</td>
<td>Probability of survival§, center</td>
<td>Survival 1m &amp; 6m</td>
<td>4</td>
<td>Yes</td>
<td>Separate test</td>
<td>No</td>
<td>Equal subgroup &amp; overall</td>
</tr>
</tbody>
</table>

* EDH: Epidural hemorrhage.
† GOSE categories (8): dead, vegetative, lower severe disability, upper severe disability, lower moderate disability, upper moderate disability, lower good recovery, upper good recovery.
‡ GOS at 6 months, unless otherwise indicated. Categories (5): Poor outcome=severe disability, vegetative state and death; Favorable outcome=good recovery and moderate disability; Good outcome= Good recovery.
§ Probability of survival was calculated at admission, based on age, pupil reactivity to light and best motor response of the arms.
¶ Total number of subgroup analyses= number of factors * number of outcomes.
** Yes: Subgroups described in methods; No: Subgroups only described in results/discussion; Partially: some subgroups described in methods and some others only in results/discussion. †† n: number of significant (p<0.05) subgroups.

Table 4. Subgroup analyses in trial reports.
effect received more emphasis than the adjusted one, but it did not affect the overall conclusion. One positive trial reported a covariate adjusted treatment effect \(^{22}\) (Table 3).

**Subgroup analysis**

Eleven trials reported subgroup analyses \(^{3, 5, 12, 14, 21, 22, 34, 36, 41, 45, 49}\) (Table 4). The maximum number of subgroup factors was seven, including mainly GCS and mass lesions. The maximum number of subgroup outcomes was four, mainly favorable outcome of GOS at 6 months (both good recovery and moderate disability). Two trials did not report the complete number of subgroup factors \(^{3, 45}\). The highest total number of examined subgroups was fifteen \(^{12}\). Three trials did not report pre-specified subgroups \(^{12, 22, 49}\). Some of the trials reported partially pre-specified subgroups \(^{3, 21, 34, 41, 45}\). Ten out of 11 trials performed separate subgroup analyses, and only one performed the statistically appropriate interaction test \(^{3}\). Five trials found subgroup effects \(^{12, 21, 34, 41, 45}\), and five trials gave equal emphasis to the subgroup effects and overall effects \(^{5, 21, 34, 41, 45}\). Two positive trials reported subgroup analyses \(^{22, 41}\) (Table 3).

**Subgroup analysis in protocols and reports**

The protocols corresponded to six RCT reports \(^{3, 12, 34, 36, 45, 49}\) (Table 5). All six reported on subgroup effects, and the reported analyses clearly differed from those specified in the protocols. Two protocols did not define any subgroup factors, while they were considered in the reports \(^{3, 12}\). In the three protocols that pre-specified outcomes, these were also considered in the subgroup analyses \(^{34, 36, 45}\). Subgroup analyses were not pre-specified in three protocols \(^{3, 12, 49}\). When subgroup analyses were pre-specified in the protocols \(^{34, 36, 45}\), only one trial reported them as planned \(^{36}\). Finally, five trials reported separate subgroup tests, but protocols specified an interaction test, a combination of separate and interaction test, or nothing \(^{12, 34, 36, 45, 49}\). These findings supported our hypothesis that trial reports included different subgroups than those planned in the protocols.

**Discussion**

Many RCTs have been published in acute TBI, but most of these have failed to yield convincing treatment benefits \(^{18, 32, 33, 39, 40}\). Various explanations for these failures have been put forward: Most of the TBI trials have insufficient sample size, and are poorly designed to detect or refute treatment benefits \(^{17}\). Others have suggested that the hypothesized absolute treatment benefit was too large and too optimistic (e.g. 10-15%), that investigating a more modest absolute benefit (e.g. 5-8%) would be desirable, and that larger trials are necessary \(^{32, 39}\). The largest
phase III trial in our review had 1120 patients (34). Here, most of the patients had severe TBI (85%), and hence more than 20% of baseline risk of unfavorable outcome. Even, in this study, the power to find an absolute benefit of less than 8% was limited 17.

These disappointing results have led to an increased interest in subgroup
analyses, trying to identify more homogeneous subgroups who may benefit from the intervention. This stems from the realization that heterogeneity of patients is a major confounding factor in the design and analysis of TBI trials, and that heterogeneity is related to injury patterns and prognostic risk. Approaches for dealing with heterogeneity relate to both the design and analysis phases. In the design phase stratified randomization can be employed. Alternatively, treatment can be targeted to patients with a defined type of pathology or to patients with an intermediate prognosis, e.g. between 20 and 80% probability of unfavorable outcome. A reduction of the sample size of 30% may be achievable, for the same power as when the whole population is considered. In the analysis phase, covariate adjustment and subgroup analysis may be employed.

Covariate adjustment uses covariates in order to provide a more individual-oriented treatment effect, that is also corrected for imbalance. It increases power, and reduces the required sample size. Subgroup analysis assesses differences in treatment effect across different subpopulations of patients. Covariate adjustment and subgroup analysis are common in RCTs, but their reporting has shown many flaws in trials from general medicine journals, especially for subgroup analysis. The revised CONSORT statement recommended guidelines to improve the reporting of the RCTs, and facilitates informed judgments regarding the validity of the trials. We found that reporting of covariate adjustment and subgroup analysis in TBI clinical trials has several shortcomings. Further, reported subgroups differed substantially from those planned in the protocols.

Covariate adjustment was reported in trials that mainly had negative treatment benefits and were multicenter. Some papers have recommended using covariate adjustment in TBI trials, especially for prognostic factors. An appropriate small number of baseline characteristics were used in the trials, including age, GCS, pupilary reactivity, elevated intracranial pressure, CT abnormalities, gender, and center. Most of these baseline characteristics are known prognostic factors. Although covariates were appropriately few, the reasons to select these were not clearly stated. We also found that covariate definitions (i.e. dichotomized, ordinal or continuous) were insufficiently reported. We consider that covariate adjustment using a limited number of pre-specified, clearly defined prognostic factors is a valid procedure.

Age is the strongest predictor of unfavorable outcome in TBI, as demonstrated in data from epidemiological studies and RCTs. Age is continuously associated with unfavorable outcome, and should be used as a continuous variable in covariate adjustment. Motor GCS is another strong predictor, and should be
used as covariate \(^9, 32\). Indeed, adjusting for age and motor GCS could reduce the sample size by 25 to 30\% in TBI trials \(^9, 10\). Other severity characteristics (e.g. pupillary reactivity, CT severity, hypoxia, hypotension) may also be included \(^32\). Gender has not been suggested as a variable to adjust for \(^32\), and its potential predictive value could be related to its association with other strong predictors. Center/country also may be considered \(^10, 44\), because differences in patient baseline characteristics have been demonstrated across continents and regions \(^28\).

A moderate number of subgroup analyses were noted in TBI reports. Limiting the number of subgroups is strongly recommended, as this decreases problems arising from multiplicity and helps define valid statistical tests \(^50\). The subgroup factors were mainly predictors of unfavorable outcome \(^30, 35, 39\). TBI trials might focus on appropriate subgroups of patients, defined by predictors: age, gender, GCS, pupillary reactivity, hypotension, CT severity and SAH \(^10, 39\). Moreover, interaction tests are appropriate to assess differences between complementary subgroups. The separate subgroup p value method evaluates treatment effects in independent subgroups, which is inappropriate from a methodological point of view \(^1, 13\).

Remarkably, the reporting of subgroups in TBI trials had important methodological shortcomings \(^1, 2, 13, 50\): most trials reported partially or did not report pre-specified subgroups, used separate subgroup testing, and performed post-hoc subgroup analyses. Moreover, nearly half of the trials overemphasized any statistically significant effect found.

For example, the Tirilazad trial \(^34\) and the hyperbaric oxygen trial \(^41\) reported partially pre-specified subgroups, used separate analyses, and emphasized their subgroup findings. The former found a lower mortality in males, moderately head injured and non-SAH patients; the latter found lower mortality in severely head injured (GCS 4 to 6) and in patients with surgical mass lesions. However, without a good a priori rationale for subgroup differences, the overall treatment effect should provide a reasonable estimate for each subgroup of TBI patients, unless confirmatory evidence of treatment differences become available. These subgroups may be unreliable (i.e. based on small number of patients), should be considered exploratory, and should only serve to motivate further trials rather than drawing definite conclusions \(^13, 43\).

It can be argued that good or poor subgroup analysis reporting is not completely related to a good or poor practice in the analysis of TBI trials. It is clear that most physicians have only access to trial reports, and take decisions based on reports. Hence, the evaluation of reporting in TBI trials is worthwhile \(^46\). Moreover, the
CONSORT guidelines based their recommendations on papers dealing with design, conduct, analysis, and reporting of trials. These reporting guidelines may therefore include a part of good practice on trial analysis. However, it is also possible that an analysis plan may differ from a reported analysis. Results from Table 5 show that the most plausible explanation for poor subgroup analysis reporting is a poor analysis plan, especially for pre-specification of subgroups and statistical methods.

Differences in subgroup definitions between the TBI protocols and trial reports were substantial. We observed differences regarding subgroup factors, pre-specification, and method of analysis. This seems an indication of post-hoc analyses. Thus, the protocol stated a particular definition of subgroups, but the results only became statistically significant when an alternative definition of the subgroups was used. Further, post-hoc subgroups should be treated with skepticism, as they test data-derived hypotheses rather than hypotheses stated a priori. A recent paper found that trial reporting of outcomes was not only frequently incomplete, but also biased and inconsistent with protocols. Our results confirm the inconsistency and incompleteness of subgroup analyses between trials and protocols.

We have recently studied the reporting of covariate adjustment and subgroup analyses in high impact internal medicine (IM) journals (general medicine, cardiology and oncology). As shown in Table 3, TBI trials reported less covariate adjustment than IM trials, independently of their final result (positive or negative). Moreover, TBI trials adjusted for fewer covariates (≤5) than IM trials (mainly between 5 and 9). However, reasons to include covariates were poorly reported in TBI trials in comparison to IM trials (36 out of 44 reports). TBI and IM trials reported subgroup analyses in a similar frequency. However, negative TBI trials reported more subgroup than negative IM trials, and positive TBI trials reported fewer subgroups than IM trials. Moreover, TBI reports fully pre-specified subgroup analyses less commonly (3/11 vs. 22/47), and used interaction testing less frequently (1/11 vs. 20/47) than IM trials. This is an additional indication that TBI trials inappropriately reported subgroup analyses.

Future design of TBI trials should incorporate covariate adjustment for important predictors. Such an adjustment should be pre-specified in the trial protocol, including the coding of predictors. Alternatively, inclusion can be restricted to certain prognostic groups, defined by predictors. For example, patients with intermediate prognosis (20%-80% of favorable outcome) or patients with focal injury may be hypothesized to benefit from treatment. Such a targeting approach may decrease the sample size requirements by 30%. If subgroup effects are studied, the number of subgroups should be pre-specified with a clear rationale,
and should be analyzed with the appropriate test of interaction. Treatment effects can also be tested in a pre-specified subgroup within a TBI trial, such as the focal injury subgroup (‘confirmatory subgroup analysis’) \(^{38}\).

Our paper has some limitations. We did not include phase II TBI trials. However, we observed that most of them were small (n<100) and did not report relevant clinical outcomes (data not shown). We evaluated only reported results, and it is possible that there may be differences between the planned and the reported analysis. For subgroup analysis, we found clear discrepancies between protocols and reports. No evaluation was possible for covariate adjustment. It is also possible that investigators explored, for instance, more subgroups than those planned and reported. We could not evaluate this possibility. Finally, we used only a limited number of protocols.

In conclusion, reporting of covariate analyses and subgroup analyses in TBI clinical trials had several shortcomings, particularly for subgroup analyses. Likewise, reported subgroup analyses clearly differed from those planned in the protocols. The appropriate reporting of these secondary analyses should be considered in future TBI trials, since interpretation of treatment benefits may be misleading otherwise.

References

Clinical applications
Adjustment for strong predictors of outcome reduces sample size requirements by 25% in traumatic brain injury trials

4.1
ABSTRACT

**Purpose:** To quantify the potential reduction in sample size that can be achieved by adjustment for predictors of outcome in traumatic brain injury (TBI) trials.

**Methods:** We used individual patient data from eight therapeutic phase III randomized clinical trials (RCTs, n=6292) in moderate or severe TBI, and three TBI surveys (n=2238). The primary outcome was the dichotomized Glasgow Outcome Scale at six months (favorable/unfavorable). Baseline predictors of outcome considered were age, motor score, pupillary reactivity, CT classification, traumatic subarachnoid hemorrhage, hypoxia, hypotension, glycemia, and hemoglobin. We calculated the potential sample size reduction obtained by adjustment of a hypothetical treatment effect for one to seven predictors with logistic regression models.

**Results:** The distribution of predictors was more heterogeneous in surveys than in trials. Adjustment of the treatment effect for the strongest predictors (age, motor score and pupillary reactivity) yielded a reduction in sample size between 16% and 23% in RCTs, and between 28% and 35% in surveys. Adjustment for seven predictors yielded a reduction of about 25% in most studies: between 20% and 28% in RCTs, and between 32% and 39% in surveys.

**Conclusions:** A major reduction in sample size can be obtained with covariate adjustment in TBI trials. The design and analysis of future clinical trials should adjust for important predictors of outcome.
Introduction

Traumatic Brain Injury (TBI) is an important public health problem worldwide (Jennett, 1996; Masson 2000). Unfortunately the search for effective treatments has not been very successful to date because of limitations in clinical development programs and methodological weaknesses in phase III trials. Problems have included limited pre-clinical evaluation, inadequate sample sizes, insensitive outcome measures, over-optimistic expectations, ineffective therapies, inappropriate selection of patients, and heterogeneity of the patient population (Narayan et al., 2002; Doppenberg et al., 2004; Maas et al., 1999; Dickinson et al., 2000; Choi et al., 2002; Wilson, 2001).

Adjustment of the treatment effect for important predictors of outcome (‘covariates’) can increase the statistical power to identify an efficacious treatment or intervention in a randomized clinical trial (RCT) (Gail et al., 1984; Hauck et al., 1998; Steyerberg et al., 2000; Hernández et al., 2004; Hernández et al., in press a). Covariate adjustment also provides a more subject-specific treatment effect and corrects for any imbalance in measured patient characteristics. Many predictors of outcome are known, including age, Glasgow Coma Scale (GCS) motor score, pupillary reactivity, and computed tomography (CT) abnormalities (Maas et al., 1999). In spite of this, covariate adjustment is not a standard procedure in TBI trials (Hernández et al., in press b).

An adjusted analysis needs fewer patients than an unadjusted analysis for the same statistical power. Therefore, one way to quantify the increase in power with covariate adjustment is by calculation of the reduction in sample size (RSS) (Hernández et al., 2004; Hernández et al., in press a; Choi, 1998). A previous investigation to quantify the RSS was performed with data from a Medical College of Virginia TBI survey (Choi, 1998). Adjustment of the treatment effect for age and GCS motor score yielded a reduction in sample size of 30%. However, a survey population would be expected to be more heterogeneous than a typical RCT population, where strict inclusion and exclusion criteria are applied. Thus this previous study may have over-estimated the potential reduction achievable in the context of a RCT.

No further evaluation of covariate adjustment has been reported in TBI. As part of the work of the IMPACT (International Mission for Prognosis of Head Injury and Analysis of Clinical Trials) Group we aimed to quantify the RSS achievable by adjustment for predictors of outcome for TBI patients included in RCTs and in surveys.
Methods

RCTs and Surveys

IMPACT links researchers based in the Netherlands, the UK, and the USA in a project addressing methodological problems in the design and the analysis of TBI trials. We have access to individual data from eight large phase III RCTs (Tirilazad International [TINT], Tirilazad USA [TIUS], Selfotel, SAPHIR, PEGSOD, HIT-I, HIT-II, SKB) and three TBI surveys (TCDB, EBIC, UK4).

Outcome and predictors

The primary outcome was the Glasgow Outcome Scale (GOS) at 6 months, dichotomized as unfavorable (death, vegetative state, and severe disability) or favorable (moderate disability, and good recovery). Age is a strong predictor of outcome in moderate to severe TBI patients (Hukkelhoven et al., 2003), as are GCS motor score and pupillary reactivity (Choi, 1998; Mushkudiani et al., 2004). Most of these prognostic studies were performed before the general availability of CT scans. Hukkelhoven et al. (in press) recently developed a model including seven early accessible clinical features and CT abnormalities: age, GCS motor score, pupillary reactivity, Marshall CT classification, traumatic subarachnoid hemorrhage (tSAH), hypoxia, and hypotension. Other novel potential predictors that we secondarily considered in our analyses were biochemical values: hyperglycemia (Jeremitsky et al., 2005) and anemia (Ariza et al., 2004).

Imputation of missing data

We selected patients with complete data on outcome, age and motor score (including a ‘not testable’ category for the motor score). Further, only patients aged 14 years and above were included in this analysis. Some of the other potential predictors were incomplete (Table 1). The SAPHIR and SKB trials did not record pupillary reactivity. The Tirilazad trials had few missing values (<14% over 9 predictors). The PEGSOD trial did not record CT classification, hypoxia, and hypotension. Glycemia and hemoglobin were not available for the Selfotel and HIT-II trials, and the three surveys. We performed a two-stage single imputation technique where we estimated the expected values for the patients with missing covariate values based on correlations with other variables (Little, 1992). Values were randomly imputed to reflect the variability around the expected values using the aregImpute function in the Hmisc library of S-plus (Little, 2004).
<table>
<thead>
<tr>
<th>Predictors</th>
<th>TINT N=1118</th>
<th>TIUS N=1041</th>
<th>Selfotel N=409</th>
<th>SAPHIR N=919</th>
<th>PEGSOD N=1510</th>
<th>HIT-I N=350</th>
<th>SKB N=126</th>
<th>HIT-II N=819</th>
<th>UK4 N=812</th>
<th>TCDB N=604</th>
<th>EBIC N=822</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Motor score</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
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<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Pupils</td>
<td>93</td>
<td>95</td>
<td>97</td>
<td>0</td>
<td>97</td>
<td>98</td>
<td>0</td>
<td>98</td>
<td>90</td>
<td>100</td>
<td>94</td>
</tr>
<tr>
<td>CT class</td>
<td>99</td>
<td>99</td>
<td>100</td>
<td>99</td>
<td>100</td>
<td>73</td>
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<td>100</td>
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<td>tSAH</td>
<td>97</td>
<td>95</td>
<td>99</td>
<td>99</td>
<td>100</td>
<td>73</td>
<td>100</td>
<td>100</td>
<td>0</td>
<td>87</td>
<td>95</td>
</tr>
<tr>
<td>Hypoxia</td>
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<td>93</td>
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<td>67</td>
<td>0</td>
<td>98</td>
<td>100</td>
<td>99</td>
</tr>
<tr>
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<td>97</td>
<td>97</td>
<td>0</td>
<td>93</td>
<td>0</td>
<td>82</td>
<td>83</td>
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<td>99</td>
<td>100</td>
<td>99</td>
</tr>
<tr>
<td>Glucose</td>
<td>96</td>
<td>99</td>
<td>0</td>
<td>95</td>
<td>96</td>
<td>85</td>
<td>98</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>97</td>
<td>93</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Motor score: GCS motor score; Pupils: Pupillary reactivity; CT class: Marshall CT classification; tSAH: traumatic subarachnoid hemorrhage.

Table 1. Proportion of available predictors across studies.
Chapter 4.1

Prognostic Models

A reference model including only the treatment variable was used as the comparator for other models. Five increasingly complex logistic regression models were then used to quantify the RSS, with a treatment indicator being included in every model. The first regression model included age. Then GCS motor score was added, followed by pupillary reactivity to give the ‘Core model’. CT classification, tSAH, hypoxia, and hypotension were then added to give the ‘7-predictor model’, followed by glucose and hemoglobin to give the ‘Full model’. Each model was fitted for each of the studies.

Age, glucose and hemoglobin were treated as continuous variables, and the remainder as categorical variables: GCS motor score (5 categories – see Table 2), pupillary reactivity (3 categories – see Table 2); Marshall CT classification (Marshall et al., 1991) (3 categories: normal CT [I] /cisterns present –shift<5mm [II]; cisterns compressed or absent-shift<5mm [III] /shift>5mm [IV]; evacuated mass lesion [V] /non-evacuated mass lesion [VI]); tSAH (yes/no); hypoxia (yes/no); and hypotension (yes/no). The independent prognostic effects of the covariates were examined on the log-likelihood scale, providing chi-square ($\chi^2$) statistics.

Model performance was evaluated using the c-statistic and Nagelkerke’s $R^2$. The c-statistic quantifies the discrimination of the model, i.e. the ability to distinguish unfavorable from favorable outcome. For binary outcomes the c-statistic is identical to the area under the receiver operating characteristic (ROC) curve. The c-statistic lies between 0.5 and 1 and indicates better model discrimination if closer to 1 (Steyerberg et al., 2001). Nagelkerke’s $R^2$ measures the variability of the outcome explained by the model (i.e. the strength of association between the covariates and outcome). Nagelkerke’s $R^2$ ranges from 0 to 1, with larger values indicating a better fit (Nagelkerke, 1991). The full models included glucose and hemoglobin, which were totally missing in the Selfotel and HIT-II trials and in the three surveys (Table 1). Therefore, we showed performance measures up to the 7-predictor models across all trials and surveys.

Simulations

None of the RCTs included had demonstrated a significant treatment effect. We simulated a positive treatment effect that gave an unadjusted odds ratio (OR) of 0.57 (coefficient: -0.557, corresponding to an average absolute risk reduction of 10% in unfavorable outcome) (Machado et al., 1999). Fifty percent of the patients were randomly allocated to the hypothesized treatment. A new outcome variable
was generated per study and per simulation, based on the comparison of a random uniform distribution (from 0 to 1) and the probability of poor outcome. This probability was based on the combination of the predictors of the full model and the treatment effect. Each regression model was applied in turn for this outcome to compare estimates of treatment effect. One thousand simulations were run using the original sample size for each study.

Reduction in sample size

We calculated the RSS to express the gain in power for each of the adjusted models. The formula used was: $100 - 100\times[(\text{mean of Z score for reference model}) / (\text{mean of Z score for adjusted model})]^2$ (Hernández et al., 2004), where Z score is equal to the Wald statistic of the treatment effect coefficient. We only calculated RSS when data were available on the predictors included in the adjusted models (Table 1). Data on pupillary reactivity was not available in the SAPHIR and SKB trials, and the RSS was not calculated for their core models. Likewise, RSS was not calculated for the full models on trials or surveys with 100% of missings on biochemical values. We used S-plus 6 software (Insightful Inc, Seattle, WA).

Results

Predictors of outcome

Age, GCS motor score and pupillary reactivity were the strongest predictors of outcome and had a $\chi^2$ of around 400. Other important predictors were tSAH ($\chi^2=175$), CT classification ($\chi^2=102$), hypotension ($\chi^2=82$), and hypoxia ($\chi^2=30$). Glucose and hemoglobin were weaker predictors.

The three strongest predictors were distributed differently across the datasets (Table 2). Patients enrolled in TBI trials (median age [25th-75th percentile]: 30 [21-43]) were younger than patients enrolled in surveys (32 [22-53]). The UK4 and EBIC surveys had the oldest patients, and the TCDB survey the youngest.

A substantial proportion of patients from surveys had untestable GCS motor scores (n=375, 17%). However, a higher proportion of patients with GCS motor score $\geq 4$ was seen in trials (56%) in comparison with surveys (46%). A lower proportion of patients from trials had bilateral non-reactive pupils (21%) than patients from surveys (32%). Thus, patients from trials had lower risks of unfavorable outcome than patients from surveys (Table 2).
<table>
<thead>
<tr>
<th></th>
<th>TINT</th>
<th>TIUS</th>
<th>Selfotel</th>
<th>SAPHIR</th>
<th>PEGSOD</th>
<th>HIT-I</th>
<th>SKB</th>
<th>HIT-II</th>
<th>UK4</th>
<th>TCDB</th>
<th>EBIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>N= 1118</td>
<td>N= 1041</td>
<td>N= 409</td>
<td>N= 919</td>
<td>N= 1510</td>
<td>N= 350</td>
<td>N= 126</td>
<td>n= 819</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (Median, 25%-75%)</td>
<td>30 (21-45)</td>
<td>30 (23-41)</td>
<td>28 (21-43)</td>
<td>32 (23-47)</td>
<td>27 (20-38)</td>
<td>34 (21-47)</td>
<td>27 (20-39)</td>
<td>33 (22-49)</td>
<td>36 (22-55)</td>
<td>26 (21-40)</td>
<td>38 (24-59)</td>
</tr>
<tr>
<td>Motor score (n, %)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>No response/extension</td>
<td>141 (13)</td>
<td>152 (15)</td>
<td>55 (13)</td>
<td>264 (29)</td>
<td>655 (43)</td>
<td>163 (47)</td>
<td>56 (44)</td>
<td>280 (34)</td>
<td>200 (25)</td>
<td>243 (40)</td>
<td>230 (28)</td>
</tr>
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<td>Flexion abnormal</td>
<td>237 (21)</td>
<td>132 (13)</td>
<td>91 (22)</td>
<td>143 (16)</td>
<td>165 (11)</td>
<td>45 (13)</td>
<td>14 (11)</td>
<td>92 (11)</td>
<td>37 (5)</td>
<td>74 (12)</td>
<td>55 (7)</td>
</tr>
<tr>
<td>Flexion withdrawal</td>
<td>327 (29)</td>
<td>300 (29)</td>
<td>127 (31)</td>
<td>223 (24)</td>
<td>334 (22)</td>
<td>56 (16)</td>
<td>16 (13)</td>
<td>181 (22)</td>
<td>142 (17)</td>
<td>122 (20)</td>
<td>113 (14)</td>
</tr>
<tr>
<td>Localizes pain/obeys</td>
<td>413 (37)</td>
<td>457 (44)</td>
<td>136 (33)</td>
<td>286 (31)</td>
<td>356 (24)</td>
<td>77 (22)</td>
<td>23 (18)</td>
<td>207 (25)</td>
<td>232 (29)</td>
<td>134 (22)</td>
<td>281 (34)</td>
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<td>0</td>
<td>0</td>
<td>3 (.3)</td>
<td>0</td>
<td>9 (3)</td>
<td>17 (13)</td>
<td>59 (7)</td>
<td>201 (25)</td>
<td>31 (5)</td>
<td>143 (17)</td>
</tr>
<tr>
<td>Pupillary reactivity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Both responsive</td>
<td>813 (73)</td>
<td>709 (68)</td>
<td>316 (77)</td>
<td>612 (67)*</td>
<td>779 (52)</td>
<td>235 (67)</td>
<td>67 (53)*</td>
<td>583 (71)</td>
<td>445 (55)</td>
<td>300 (50)</td>
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</tr>
<tr>
<td>One unresponsive</td>
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<td>122 (12)</td>
<td>79 (19)</td>
<td>161 (18)*</td>
<td>160 (11)</td>
<td>51 (15)</td>
<td>35 (28)*</td>
<td>101 (12)</td>
<td>116 (14)</td>
<td>55 (9)</td>
<td>87 (11)</td>
</tr>
<tr>
<td>Both unresponsive</td>
<td>135 (12)</td>
<td>210 (20)</td>
<td>14 (3)</td>
<td>146 (16)*</td>
<td>571 (38)</td>
<td>64 (18)</td>
<td>24 (19)*</td>
<td>135 (16)</td>
<td>251 (31)</td>
<td>249 (41)</td>
<td>208 (25)</td>
</tr>
<tr>
<td>Unfavorable outcome</td>
<td>(n, %)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>456 (41)</td>
<td>395 (38)</td>
<td>177 (43)</td>
<td>378 (41)</td>
<td>774 (51)</td>
<td>171 (49)</td>
<td>70 (56)</td>
<td>328 (40)</td>
<td>518 (64)</td>
<td>393 (65)</td>
<td>422 (51)</td>
</tr>
</tbody>
</table>

* Imputed data

Table 2. Distribution of three main predictors and primary outcome across studies.
Table 3. Performance and reduction in sample size (RSS) for two logistic regression models across studies.

<table>
<thead>
<tr>
<th>Trials</th>
<th>TINT</th>
<th>TIUS</th>
<th>Selfotel</th>
<th>SAPHIR</th>
<th>PEGSOD</th>
<th>HIT-I</th>
<th>SKB</th>
<th>HIT-II</th>
<th>Surveys</th>
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<tbody>
<tr>
<td>Core model</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c-statistic</td>
<td>0.72</td>
<td>0.76</td>
<td>0.73</td>
<td>0.69</td>
<td>0.76</td>
<td>0.79</td>
<td>0.81</td>
<td>0.73</td>
<td>0.77</td>
</tr>
<tr>
<td>Nagelkerke-$R^2$</td>
<td>0.20</td>
<td>0.27</td>
<td>0.24</td>
<td>0.16</td>
<td>0.26</td>
<td>0.33</td>
<td>0.36</td>
<td>0.21</td>
<td>0.29</td>
</tr>
<tr>
<td>RSS (%)</td>
<td>16</td>
<td>22</td>
<td>18</td>
<td>16</td>
<td>23</td>
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<td>18</td>
<td>17</td>
<td>28</td>
</tr>
<tr>
<td>7-predictor model</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c-statistic</td>
<td>0.81</td>
<td>0.81</td>
<td>0.78</td>
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<td>0.84</td>
<td>0.84</td>
<td>0.80</td>
<td>0.82</td>
</tr>
<tr>
<td>Nagelkerke-$R^2$</td>
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<td>0.35</td>
<td>0.31</td>
<td>0.24</td>
<td>0.29</td>
<td>0.44</td>
<td>0.44</td>
<td>0.34</td>
<td>0.38</td>
</tr>
<tr>
<td>RSS (%)</td>
<td>24</td>
<td>27</td>
<td>24</td>
<td>20</td>
<td>25</td>
<td>28</td>
<td>24</td>
<td>24</td>
<td>32</td>
</tr>
</tbody>
</table>

Core model included age, motor score, and pupillary reactivity; 7-predictor model included age, motor score, pupillary reactivity, Marshall CT classification, tSAH, hypoxia, and hypotension.
Performance of the prognostic models

The performance of most models derived from surveys was better than for models derived from trials (Table 3). The c-statistics for the core model ranged between 0.69 and 0.82, and increased substantially in the 7-predictor model, ranging between 0.74 and 0.87. Likewise, Nagelkerke’s $R^2$ of the core model ranged between 16% and 39%, and between 24% and 51% for the 7-predictor model.

Reduction in sample size

The RSS for each model and across all studies is illustrated in Figure 1. We showed the RSS where data were available for the predictors included in the adjusted models. Adjustment of the treatment effect for age, motor score and pupillary reactivity yielded a RSS between 16% and 23% in trials, and between 28% and 35% in surveys (Table 3). Adjustment for seven predictors yielded even larger reductions: between 20% and 28% in trials, and between 32% and 39% in surveys. Further adjustment for 9 predictors (full model) increased the reductions in sample size limitedly (not shown). The positive relationship between both the c-statistic and Nagelkerke’s $R^2$ with the RSS is shown in Figures 2a and 2b for the core and 7-predictor models.

Discussion

A substantial reduction in the sample size requirements for TBI trials can be obtained with adjustment for important predictors. Adjustment of treatment effect for seven predictors (clinical, radiological and hypoxia) gave a reduction in sample size requirements between 20% and 28%. Adjustment for just three core clinical predictors showed a reduction between 16% and 23%. As expected, adjustment for predictors in population-based TBI surveys usually gave larger reductions in sample size requirements than trials.

The first formal attempt to explore the potential reduction in sample size with covariate adjustment in the context of clinical trials with dichotomous outcomes was made by Choi (1998). He simulated a trial from data of a registry of 555 patients of the Medical College of Virginia. The registry was divided into 2 independent treatment groups (A and B): group A retained its observed probability of favorable outcome, and group B was reconstructed by changing a proportion of patients (10%) from unfavorable to favorable outcome. A 30% reduction in
Adjustment for strong predictors in traumatic brain injury trials

**Figure 1.** Reduction in sample size across studies for different logistic regression models. For each trial/survey: the first column to the left represents the model with age adjustment, the column in the middle the core model, and the last column the full model. Larger reductions in sample size are achieved in surveys (UK4, TCDB and EBIC) than in trials. Motor denotes GCS motor score; Pupils: pupillary reactivity; CT: Marshall CT classification; tSAH: traumatic subarachnoid hemorrhage; Hypox: hypoxia; Hypot: hypotension; Hb: hemoglobin.

Sample size was found with adjustment for two strong predictors (age and GCS motor score).

The main concern with Choi’s procedure is that the change to outcomes of group B patients was rather artificial. In clinical practice, a patient in a vegetative state is less likely to move to a good recovery state than a patient with severe disability with a given treatment. An alternative approach was described by Machado et al. (1999). They incorporated a positive treatment effect (OR = 0.57) into a logistic model with 3 predictors (age, GCS motor score, and Marshall CT...
Figure 2. Relation between the reduction in the sample size, the c-statistic (Figure 2a), and Nagelkerke’s $R^2$ (Figure 2b). Empty and solid symbols represent values for the core model and 7-predictor model, respectively. A positive relationship between the RSS and both the c-statistic and Nagelkerke’s $R^2$ is observed.
classification) to create a new outcome. Thus, this outcome incorporated information from predictors, and patients with better prognosis had a greater chance of moving from an unfavorable to a favorable outcome in comparison to patients with a worse prognosis. We followed the latter approach, but found that Choi’s approach gave very similar results (data not shown).

In our simulations the core model (age, GCS motor score, pupillary reactivity) achieved good discrimination, which improved with the inclusion of more covariates. This is consistent with findings that it is possible to make better predictions of GOS outcome with more predictors (Maas et al., 1999; Machado et al., 1999). Using the same seven predictors as in Hukkelhoven et al. (in press), improved the predictive ability of the core model substantially, but a further extension with glucose and hemoglobin yielded only minor added value.

A similar pattern was observed in the RSS calculations. A larger RSS was observed when the 7-predictor model was used in comparison to the 3-predictor model. Reductions in sample size of approximately 20% with the core model and around 24% with the full model in TBI trials are greater than those obtained in trials of other fields in medicine. For instance, adjustment for 17 predictors of 30-day mortality in patients with acute myocardial infarction included in the GUSTO-I trial reduced the sample size requirements by only 15% (Steyerberg et al., 2000).

Other approaches to achieve a RSS have been suggested. Machado et al. (1999) used data from the EBIC survey, and defined models on different TBI prognostic groups, based on three predictors. They quantified the power that could be achieved when the analysis was targeted to some prognostic groups (e.g. defined by clinical or radiological characteristics), and when different treatment effects were defined for different prognostic groups (e.g. treatment benefit only in patients with intermediate prognosis). For instance, for a moderate/severe TBI population and with a uniform treatment effect, a trial with 344 patients with intermediate prognosis per arm had the same 90% power as a trial with 500 unselected patients per arm—that is, the sample size could be reduced by 31% with no decrease in the power.

More recently, Murray et al. (2005) proposed another approach to analyze TBI trials with ordered outcomes (such as GOS), called the ‘sliding dichotomy’. Using data from the Tirilazad International and Tirilazad USA trials, this approach increased the treatment OR from 1.38 to 1.71, and increased the statistical power to detect a significant treatment effect. These increases in power are equivalent to halving the trial sample size in a conventional analysis. Another approach is to use a proportional odds model. A formal comparison of these approaches to
quantify their benefits is required.

Our work has several limitations. First, information was incomplete for seven of the nine predictors, particularly glucose and hemoglobin. However, it was possible to replace missing values using a well-accepted imputation technique based on correlations with other variables (Little, 1992). Second, the RSS may vary in other trials according to their inclusion criteria. More or less restrictive criteria will produce less or more heterogeneous trial populations, respectively. Trials with more homogeneous patients may have a more limited benefit from covariate adjustment. Mega-trials, such as CRASH (n=10008), have considerable heterogeneity (CRASH trial collaborators, 2004, 2005). It is expected that covariate adjustment might yield a substantial RSS, although completeness of data for predictors may be of concern. Third, we used trials conducted between 1984 and 1997, and more recent trials may contain more or less heterogeneous populations. Finally, further work should indicate the incremental benefit to the RSS for the combination of the covariate adjustment with newer analysis approaches that exploit the ordinal nature of the outcome, such as the sliding dichotomy (Murray et al., 2005).

In conclusion, adjustment of the treatment effect for seven strong predictors yielded a reduction in sample size requirements by 25% in TBI trials, whilst adjustment for the three strongest predictors achieved a reduction of sample size of about 20%. Covariate adjustment for strong predictors should be incorporated in the design and analysis of future TBI trials.

References


myocardial infarction: should we adjust for baseline characteristics? Am. Heart J. 139, 745-751.


Effects of platelet glycoprotein IIb/IIIa receptor blockers in non-ST-segment elevation acute coronary syndromes: Benefit and harm in different age subgroups.

4.2
ABSTRACT

Purpose
To investigate whether the effects of platelet glycoprotein (GP) IIb/IIIa receptor blockers in patients with non-ST-elevation acute coronary syndromes (NSTE-ACS) depend on patient age.

Methods
An individual data meta-analysis of 6 trials (PRISM, PRISM-PLUS, PARAGON-A, PURSUIT, PARAGON-B, GUSTO4-ACS; n=31,402) was performed. Patients were randomized to a GP IIb/IIIa receptor blocker or placebo/control. We applied multivariable logistic regression analyses to evaluate the drug effects on death or non-fatal MI at 30 days, as well as on major bleeding, by age subgroups (<60, 60-69, 70-79, ≥80 years). We quantified the reduction of death or MI as number needed to treat (NNT), and the increase of major bleeding as number needed to harm (NNH) across age subgroups.

Results
Overall, 11,155 (35%) patients were <60, 9,727 (31%) were 60-69, 8,468 (27%) were 70-79, and 2,049 (7%) were ≥80 years-old. The relative benefit of GP IIb/IIIa receptor blockers did not differ significantly (p=0.5) across age subgroups (odds ratio [95% CI] for death or MI: 0.86 [0.74-0.99], 0.90 [0.80-1.02], 0.97 [0.86-1.10], 0.90 [0.73-1.16]; overall 0.91 [0.86-0.99]). Odds ratios (95% CIs) for major bleeding were 1.9 (1.3-2.8), 1.9 (1.4-2.7), 1.6 (1.2-2.1), and 2.5 (1.5-4.1), respectively. The overall NNT was 105, and the overall NNH was 90. The oldest patients had larger absolute increases in major bleeding, but also had the largest absolute reductions of death or MI. Patients ≥80 years had a half of the NNT and a third of the NNH in comparison with patients <60 years.

Conclusions
In patients with NSTE-ACS, the relative reduction of death or non-fatal MI with GP IIb/IIIa receptor blockers was independent of patient age. Larger absolute outcome reductions were seen in the elderly, but with a higher risk of major bleeding. Thus, a close monitoring of these patients is warranted.
**Introduction**

Platelet glycoprotein (GP) IIb/IIIa receptor blockers decrease the risk of death or non-fatal myocardial infarction (MI) at 30 days in patients with non-ST elevation acute coronary syndromes (NSTE-ACS) who are not routinely scheduled for early revascularization \(^1\)-\(^4\). Age is an important risk factor for these patients, and if the relative benefits of effective interventions are the same across age groups, physicians should treat the elderly even more aggressively than the younger, since the absolute benefit may be larger \(^5\). However, in clinical practice, the utilization of GP IIb/IIIa receptor blockers is lower among elderly patients \(^6\).

Elderly patients may be undertreated because of several reasons: they were underrepresented or excluded from randomized clinical trials (RCTs), clinicians may believe that benefits in younger may not generalize to the elderly, or they may be worried about harmful effects in elderly patients \(^5\). Researchers have argued that the benefit of GP IIb/IIIa receptor blockers is greater in younger patients \(^7\), similar in old and younger patients \(^8\), or greater in older patients given their higher baseline risk \(^5\), \(^9\).

Yet, it is difficult to determine how the efficacy of GP IIb/IIIa receptor blockers varies among age subgroups because most trials are not large enough to provide a reliable answer. Individual ACS trials have been inconclusive or even conflicting regarding the presence or absence of relative differences in drug effects across ages \(^10\)-\(^15\). Usually, the patient population was only split in two age groups (e.g. <65 years, \(\geq 65\) years) \(^11\), \(^13\)-\(^15\), and different primary endpoints were considered. An evaluation of the drug effects across age groups in a meta-analysis using individual data can better define its relative and absolute efficacies in older vs. younger patients.

One more issue is relevant in the interpretation of the effects of GP IIb/IIIa receptor blockers by age groups. The incorporation of harmful major bleeding rates in the evaluation of effects should be considered to further understand the net drug effectiveness across age strata \(^5\), \(^9\), \(^16\).

We investigated whether the relative effects of GP IIb/IIIa receptor blockers were consistent across age subgroups in non-ST-segment elevation ACS patients. Further, we evaluated whether the absolute benefits and harms differed across age subgroups.
Methods

Trial selection

A meta-analysis of individual patient data was performed, including trials reported since 1990 with the following characteristics: randomization of patients with NSTE-ACS, comparison of a GP IIb/IIIa receptor blocker with placebo or control therapy, no-recommendation for early (<48h) coronary revascularization during study-drug infusion, and enrolment of at least 1000 patients. Six trials met the inclusion criteria -PRISM, PRISM-PLUS, PARAGON-A, PURSUIT, PARAGON-B, and GUSTO IV-ACS- with a total of 31,402 patients. Details of the trial designs are available elsewhere.

Patient baseline characteristics

An electronic database consisting of data from individual patients in all eligible trials was available. These data were checked for completeness, for internal consistency of patients’ records, and for consistency with the published reports. For this analysis, baseline characteristics regarded as important predictors of the outcome for which information was almost complete (i.e. less than 1% missing) were age, gender, diabetes, smoking, previous myocardial infarction [MI], previous heart failure [HF], previous coronary artery bypass surgery (CABG), previous percutaneous coronary intervention (PCI), and ST-segment depression. Other important predictors had more than 20% of missing data: blood pressure and heart rate were not recorded in the GUSTO IV-ACS trial (n=7800, 25%); and baseline creatine kinase MB (CK-MB) was missing in 7469 patients (24%) across different trials. Blood pressure, heart rate and CK-MB were used in addition to the other predictors in secondary analyses that yielded largely similar results.

Endpoints

For this analysis, the primary efficacy endpoint was defined a priori as the composite of death of any cause or non-fatal MI at 30 days. MI was part of the composite outcome of all trials. The MI definitions had subtle differences across trials regarding the CK-MB threshold. However, all trials had pre-specified definitions of MI. Secondary endpoints were: death; non-fatal MI; coronary artery bypass graft (CABG); percutaneous coronary intervention (PCI); and CABG or PCI. The primary harm endpoint was major bleeding within 30 days. Individual trial definitions of major bleeding had also at most subtle differences, and trial-specific definitions were retained.
Efficacy analysis by age

We divided the patient data into four subgroups according to age: <60, 60-69, 70-79, and ≥80 years old. The decision to group patients in these intervals was made a priori, and was based on decade intervals of common clinical use. The choice of other cut-off points (e.g. quartiles) yielded similar results (not shown). Relative differences between GP IIb/IIIa receptor blockers and placebo/control on the primary endpoint by age subgroups were assessed, within each trial and across all trials. Logistic regression models were used, and odds ratios (OR) and corresponding 95% confidence intervals (95% CI) were calculated. To evaluate GP IIb/IIIa receptor blocker effect modification by age in each individual trial and in all trials, interaction tests were used. These tests also evaluated heterogeneity of effects across trials. The effects of GP IIb/IIIa receptor blockers and the interactions were adjusted for the previously described predictors, for trial, and for potential differences in age-related trends between trials. These effects were combined using random effects calculations. Heterogeneity of interactions across trials was evaluated with the random effects inverse variance model (with trial being the random effect).

Benefit and harm of GP IIb/IIIa receptor blockers by age subgroups

We performed analyses that incorporated the relation among the baseline risk (eBR, proportion of patients in the placebo/control group with the primary efficacy endpoint), the efficacy Odds Ratio (eOR), and the respective number needed to treat [NNT]. The calculation of NNT was done using eBR and eOR, with the formula: \[\frac{1-eBR(1-eOR)}{eBR(1-eBR)(1-eOR)}\] 22. The NNT is the number of patients who need to be treated in order to prevent one additional death or non-fatal MI. It is the inverse of the absolute risk reduction (ARR). Further, we looked at the relation among the baseline proportion of the primary harm endpoint in the placebo/control group (hBR), the harm Odds Ratio (hOR), and the respective number needed to harm [NNH]. The NNH was calculated using hBR and hOR, with the formula: \(\frac{hBR(hOR-1)+1}{hBR(1-hBR)(hOR-1)}\) 22. The NNH is the number of patients who need to be treated in order to cause one major bleeding. It is the inverse of the absolute risk increase (ARI). The NNT and NNH calculations were done overall and by age subgroups.
Role of the funding source

The trials included in this analysis were sponsored by several pharmaceutical companies, which are mentioned in the main trial reports 10-15, and in the acknowledgements. This study was designed, conducted, and interpreted independently of the sponsors. These had the right to review the manuscript, but not censor the findings. No separate industrial grant was obtained for this investigation.

Results

Age subgroups and predictors

Overall, 11,155 (35%) patients were < 60, 9,727 (31%) were 60-69, 8,468 (27%) were 70-79, and 2,049 (7%) were ≥ 80 years-old. Baseline characteristics across age subgroups are shown in Table 1. The proportion of women and of patients with a history of diabetes, MI or HF, and ST depression increased with age. Further, patients ≥80 years had lower proportions of previous revascularization procedures than younger patients. The proportion of patients older than 70 years ranged between 30% in the PURSUIT and PRISM trials and 40% in the GUSTO IV-ACS trial.

Endpoints at 30 days by age subgroups

The overall adjusted relative reduction in the odds of death or MI at 30 days was 9% (OR 0.91; 95% CI [0.85-0.99]). There was no difference in the relative benefit of GP IIb/IIIa receptor blockers across age subgroups (p for interaction = 0.5) and this was true also for secondary efficacy endpoints (Table 2). Interestingly, the ratio of non-fatal MI over death decreased with increasing age. The overall adjusted relative increase in the odds of major bleeding was 83% (OR 1.83 [1.5-2.2]). This was especially high for patients ≥80 years (OR 2.5 [1.5-4.1]), but there were no significant differences across ages (p for interaction=0.3) (Table 2).

Benefit of GP IIb/IIIa receptor blockers per trial by age subgroups

With regard to the incidence of death or non-fatal MI, two trials showed significantly different relative effects across age subgroups, but in opposite directions (Table 3). The PRISM trial patients had a clear gradient of GP IIb/IIIa receptor blocker effect across ages: older patients had larger odds reductions than younger ones (p for interaction=0.01). Conversely, younger PURSUIT patients had larger
Benefit and harm of GP IIb/IIIa receptor blockers in NSTEMI across age subgroups

<table>
<thead>
<tr>
<th></th>
<th>&lt;60 years (n=11,155)</th>
<th>60-69 years (n=9,727)</th>
<th>70-79 years (n=8,468)</th>
<th>≥80 years (n=2,049)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>8275 (74)</td>
<td>6274 (65)</td>
<td>4841 (57)</td>
<td>997 (49)</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1771 (16)</td>
<td>2360 (24)</td>
<td>2269 (27)</td>
<td>461 (23)</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Never</td>
<td>3931 (35)</td>
<td>3439 (36)</td>
<td>3269 (39)</td>
<td>861 (42)</td>
</tr>
<tr>
<td>Former</td>
<td>3144 (28)</td>
<td>3537 (37)</td>
<td>3133 (37)</td>
<td>621 (31)</td>
</tr>
<tr>
<td>Current</td>
<td>4036 (36)</td>
<td>2709 (28)</td>
<td>2015 (24)</td>
<td>552 (27)</td>
</tr>
<tr>
<td>Previous MI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3164 (28)</td>
<td>3445 (36)</td>
<td>3162 (37)</td>
<td>877 (43)</td>
</tr>
<tr>
<td>Previous HF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>578 (5)</td>
<td>962 (10)</td>
<td>1191 (14)</td>
<td>437 (21)</td>
</tr>
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<td>Previous CABG</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1088 (10)</td>
<td>1305 (13)</td>
<td>1194 (14)</td>
<td>185 (9)</td>
</tr>
<tr>
<td>Previous PCI</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1454 (13)</td>
<td>1251 (13)</td>
<td>956 (11)</td>
<td>162 (8)</td>
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<tr>
<td>ST depression</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>5096 (46)</td>
<td>5475 (57)</td>
<td>5441 (65)</td>
<td>1403 (69)</td>
</tr>
<tr>
<td>Trial</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRISM</td>
<td>1274 (11)</td>
<td>1005 (10)</td>
<td>781 (9)</td>
<td>172 (8)</td>
</tr>
<tr>
<td>PRISMIPLUS</td>
<td>693 (6)</td>
<td>603 (6)</td>
<td>495 (6)</td>
<td>124 (6)</td>
</tr>
<tr>
<td>PARAGON-A</td>
<td>737 (7)</td>
<td>728 (8)</td>
<td>631 (8)</td>
<td>183 (9)</td>
</tr>
<tr>
<td>PURSUIT</td>
<td>4082 (37)</td>
<td>3553 (37)</td>
<td>2763 (33)</td>
<td>550 (27)</td>
</tr>
<tr>
<td>PARAGON-B</td>
<td>1976 (18)</td>
<td>1513 (16)</td>
<td>1374 (16)</td>
<td>362 (18)</td>
</tr>
<tr>
<td>GUSTO4-ACS</td>
<td>2393 (21)</td>
<td>2325 (24)</td>
<td>2424 (29)</td>
<td>658 (32)</td>
</tr>
</tbody>
</table>

MI denotes myocardial infarction, HF: heart failure, CABG: coronary artery bypass graft, PCI: percutaneous coronary intervention, y: years. Differences among age subgroups were highly significant (p<0.001).

Table 1. Patient characteristics by age subgroups.

odds reductions than the older ones (p for interaction=0.03). The interactions between GP IIb/IIIa receptor blockers and age subgroup were heterogeneous across trials (p=0.002).

Benefit and harm of GP IIb/IIIa receptor blocker across age subgroups

The absolute risk of death or MI at 30 days correlated with age, varying from 8% in the youngest (<60 years) to 21% in the oldest group (≥80 years). Major bleeding at 30 days also correlated with age, from 0.8% in the youngest to 2.3% in the oldest. For the overall relative reduction in the odds of death or MI of 9%,
### Table 2. Treatment effect on various endpoints at 30 days according to age subgroups.

<table>
<thead>
<tr>
<th></th>
<th>&lt;60y (n=11,155)</th>
<th>60-69y (n=9,727)</th>
<th>70-79y (n=8,468)</th>
<th>≥80y (n=2,049)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events % OR* (95% CI)</td>
<td>Events % OR* (95% CI)</td>
<td>Events % OR* (95% CI)</td>
<td>Events % OR* (95% CI)</td>
</tr>
<tr>
<td><strong>Death†</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GP IIb/IIIa</td>
<td>70 1.1 0.86</td>
<td>165 2.9 0.98</td>
<td>281 5.6 0.91</td>
<td>115 9.5 0.90</td>
</tr>
<tr>
<td>Placebo/Control</td>
<td>58 1.2 (0.61-1.23)</td>
<td>124 3.0 (0.77-1.24)</td>
<td>215 6.2 (0.75-1.09)</td>
<td>88 10.5 (0.67-1.21)</td>
</tr>
<tr>
<td><strong>Nonfatal MI‡</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GP IIb/IIIa</td>
<td>372 5.7 0.83</td>
<td>428 7.6 0.85</td>
<td>437 8.8 1.02</td>
<td>112 9.3 0.91</td>
</tr>
<tr>
<td>Placebo/Control</td>
<td>316 6.8 (0.72-0.97)</td>
<td>365 8.8 (0.74-0.99)</td>
<td>299 8.6 (0.87-1.19)</td>
<td>85 10.1 (0.68-1.23)</td>
</tr>
<tr>
<td><strong>Death or MI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GP IIb/IIIa</td>
<td>442 6.8 0.86</td>
<td>593 10.6 0.90</td>
<td>718 14.4 0.97</td>
<td>227 18.8 0.90</td>
</tr>
<tr>
<td>Placebo/Control</td>
<td>374 8.0 (0.74-0.99)</td>
<td>489 11.9 (0.80-1.02)</td>
<td>514 14.8 (0.86-1.10)</td>
<td>173 20.5 (0.73-1.16)</td>
</tr>
<tr>
<td><strong>CABG</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GP IIb/IIIa</td>
<td>828 12.7 1.00</td>
<td>931 16.6 0.92</td>
<td>860 17.2 0.99</td>
<td>102 8.5 1.07</td>
</tr>
<tr>
<td>Placebo/Control</td>
<td>590 12.7 (0.90-1.13)</td>
<td>732 17.7 (0.83-1.03)</td>
<td>603 17.3 (0.88-1.11)</td>
<td>67 8.0 (0.77-1.47)</td>
</tr>
<tr>
<td><strong>PCI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GP IIb/IIIa</td>
<td>1839 28.3 0.92</td>
<td>1369 24.4 1.02</td>
<td>894 17.9 0.89</td>
<td>171 14.2 0.90</td>
</tr>
<tr>
<td>Placebo/Control</td>
<td>1404 30.1 (0.84-0.99)</td>
<td>991 24.0 (0.93-1.12)</td>
<td>684 19.7 (0.80-1.00)</td>
<td>131 15.6 (0.70-1.15)</td>
</tr>
<tr>
<td><strong>CABG or PCI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GP IIb/IIIa</td>
<td>2618 40.3 0.93</td>
<td>2264 40.4 0.97</td>
<td>1721 34.5 0.93</td>
<td>268 22.2 0.93</td>
</tr>
<tr>
<td>Placebo/Control</td>
<td>1960 42.1 (0.86-1.00)</td>
<td>1699 40.8 (0.89-1.05)</td>
<td>1258 36.2 (0.85-1.02)</td>
<td>197 23.4 (0.76-1.15)</td>
</tr>
<tr>
<td><strong>Major bleeding</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GP IIb/IIIa</td>
<td>90 1.5 1.90</td>
<td>118 2.3 1.94</td>
<td>174 3.8 1.58</td>
<td>63 5.7 2.46</td>
</tr>
<tr>
<td>Placebo/Control</td>
<td>35 0.8 (1.28-2.81)</td>
<td>46 1.1 (1.38-2.74)</td>
<td>80 2.3 (1.21-2.07)</td>
<td>19 2.3 (1.46-4.14)</td>
</tr>
</tbody>
</table>

* Odds ratio of treatment effect between GP IIb/IIIa and Placebo/Control, GP IIb/IIIa denotes platelet glycoprotein IIb/IIIa receptor blockers; †Death within 30 days; ‡ Non-fatal myocardial infarction in patients who survived at least 30 days. Number of patients per age group: <60 y: GP 6496, Placebo/control 4659; 60-69 y: GP 5602, Placebo/control 4125; 70-79 y: GP 4991, Placebo/control 3477; ≥80 y: GP: 1207, Placebo/control: 842.
### Table 3

Treatment effects on death or MI at 30 days according to age subgroups, by trial and overall.

<table>
<thead>
<tr>
<th>Age Subgroup</th>
<th>PRISM N=3,232</th>
<th>PRISMLPLUS N=1,915</th>
<th>PARAGON-A N=2,282</th>
<th>PURSUIT N=10,948</th>
<th>PARAGON-B N=5,225</th>
<th>GUSTO IV-ACS N=7,800</th>
<th>TOTAL* N=31,402</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt;60 years OR (95% CI)</td>
<td>1.13 (0.66-1.96)</td>
<td>0.98 (0.54-1.78)</td>
<td>1.65 (0.83-3.30)</td>
<td>0.72 (0.59-0.88)</td>
<td>0.90 (0.64-1.27)</td>
<td>1.01 (0.65-1.55)</td>
<td>0.86 (0.74-0.99)</td>
</tr>
<tr>
<td>Age 60-69 years OR (95% CI)</td>
<td>0.86 (0.53-1.38)</td>
<td>0.58 (0.35-0.96)</td>
<td>0.87 (0.55-1.39)</td>
<td>0.93 (0.77-1.20)</td>
<td>0.81 (0.59-1.12)</td>
<td>1.19 (0.85-1.67)</td>
<td>0.90 (0.80-1.02)</td>
</tr>
<tr>
<td>Age 70-79 years OR (95% CI)</td>
<td>0.63 (0.36-1.09)</td>
<td>1.02 (0.61-1.70)</td>
<td>0.83 (0.53-1.31)</td>
<td>0.91 (0.76-1.11)</td>
<td>1.11 (0.82-1.50)</td>
<td>1.15 (0.88-1.50)</td>
<td>0.97 (0.86-1.01)</td>
</tr>
<tr>
<td>Age ≥80 years OR (95% CI)</td>
<td>0.45 (0.19-1.07)</td>
<td>0.94 (0.39-2.27)</td>
<td>0.82 (0.37-1.81)</td>
<td>1.27 (0.87-1.86)</td>
<td>0.84 (0.48-1.47)</td>
<td>0.80 (0.52-1.22)</td>
<td>0.90 (0.73-1.16)</td>
</tr>
<tr>
<td>All subgroups, adjusted for predictors†</td>
<td>0.80 (0.60-1.06)</td>
<td>0.83 (0.62-1.11)</td>
<td>0.95 (0.72-1.25)</td>
<td>0.88 (0.79-0.98)</td>
<td>0.92 (0.78-1.10)</td>
<td>1.07 (0.90-1.27)</td>
<td>0.91 (0.86-0.99)</td>
</tr>
</tbody>
</table>

| Age by GP IIb/IIIa Interaction (p)‡ | 0.01 (0.01) | 0.77 (0.77) | 0.15 (0.15) | 0.03 (0.03) | 0.92 (0.92) | 0.52 (0.52) | 0.15 (0.15) |

* Odds ratios of each age subgroup adjusted for trial.
† Predictors included: age, gender, diabetes, smoking, previous MI, previous heart failure, previous CABG, previous PTCA, ST depression.
‡ Odds ratios adjusted for predictors, and age trend. The interactions age by GP IIb/IIIa are significantly different among trials. p: p-value.
the NNT was 105. For the overall relative increase in the odds of major bleeding of 83%, the NNH was 90.

The oldest patients had the largest absolute reductions of death or MI, but also had larger absolute increases in major bleeding. Patients younger than 70 years had higher NNTs and NNHs (149 and 163 for those younger than 60 years, and 105 and 110 for those between 60 and 69 years) than those older than 70 years (87 and 55 for those between 70 and 79 years, and 67 and 56 for those older than 80 years). The Figure shows the absolute event rate difference between GP IIb/IIIa receptor blocker and placebo/control arms across age subgroups. We noted a rather larger harm in patients ≥70 years and a somewhat variable benefit across all age subgroups.

**Figure.** Absolute event rate differences between treatment arms (GP IIb/IIIa vs. placebo/control) by age subgroups in beneficial (death or myocardial infarction) and harmful (major bleeding) endpoints. GP IIb/IIIa denotes platelet glycoprotein IIb/IIIa receptor blockers.
Discussion

In patients with ACS without ST elevation, the relative reduction in the odds of death or MI at 30 days with GP IIb/IIIa receptor blockers was largely independent of age. The oldest patients had about 3-fold the baseline risk of the youngest ones, not only for death or MI, but also for major bleeding. In the oldest patients, the use of GP IIb/IIIa receptor blockers yielded larger absolute reductions of death/MI, but also larger absolute increases in major bleeding rates in comparison with the youngest patients.

This meta-analysis had more statistical power than individual trials to explore how the GP IIb/IIIa receptor blocker effects vary by age. Individual trials did not report these effects in detail across similar age subgroups, and they analyzed different endpoints. Previous analyses of the age effects in single trials have yielded inconclusive results. Only the PURSUIT and GUSTO IV-ACS reported the same primary endpoint as we used in this paper. Also, these analyses did not adjust for important predictors of the primary endpoint. We found that the PRISM and the PURSUIT trials showed significant differential relative effects of GP IIb/IIIa receptor blockers across ages, but differences were in the opposite direction. We do not fully understand this phenomenon. We speculate that it could be related to the doses used as well as the duration of the study drug infusion. This might have resulted in different levels of platelet inhibition in the PRISM trial (where the dose was later shown to produce suboptimal platelet inhibition in young patients) as compared to the PURSUIT trial (where the dose was not adjusted for older age or modest renal impairment), which might have had different consequences in younger and older patients.

The effects of other antithrombotics have been evaluated in elderly patients with unstable angina or NSTE-ACS. The low molecular weight heparin enoxaparin, compared with unfractionated heparin, appeared to have greater relative and absolute benefit in patients aged 65 years and older, as compared with younger patients. When comparing clopidogrel plus aspirin to aspirin alone, there was a consistent 20% relative reduction in cardiovascular death, myocardial infarction, or stroke in both elderly and younger patients. For GP IIb/IIIa receptor blockers, we found an equivalent relative benefit across age subgroups, which translated into a greater absolute benefit in older in comparison with younger patients.

Most trials, meta-analyses, and systematic reviews have neglected the contribution of major bleeding rates in the evaluation of the net GP IIb/IIIa receptor blocker effectiveness across age subgroups in NSTE-ACS patients. Elderly patients have higher absolute risks of major bleeding. Therefore, the interpretation of the overall GP IIb/IIIa receptor blocker efficacy needs to
incorporate this harm. We should acknowledge that death or non-fatal MI and major bleeding do not have the same utility, and therefore are not comparable events. Determining the relative weights of these events is largely subjective. A recent review identified that the weight of a major bleeding related to a drug in the context of an acute coronary syndrome was 0.87, in comparison with the weight of death, which was equal to zero. In order to describe the relative gain in primary efficacy end points by age subgroups, we defined a ratio of reduction of non-fatal MIs to reduction of deaths. For instance, a ratio higher than 1 shows a larger benefit in reduction of non-fatal MIs in comparison to reduction of deaths. Given that the ratio of non-fatal MI to death decreased with increased age, the use of GP IIb/IIIa receptor blockers in the oldest likely aborted more deaths than non-fatal MIs.

An appropriate dosing of GP IIb/IIIa receptor blockers is a requisite to obtain a higher benefit and a lower harm in elderly NSTE-ACS patients. The CRUSADE registry demonstrated that GP IIb/IIIa receptor blockers were underutilized and mis-dosed in elderly patients, who are at higher risk for adverse cardiac events. An essential factor that increases the risk of major bleeding in elderly patients is low renal function, which is associated with higher serum levels of GP IIb/IIIa receptor blockers. Doses used in early trials were more aggressive than currently recommended doses, which are adjusted for renal dysfunction. Thus, elderly NSTE-ACS patients should receive adequate doses of GP IIb/IIIa receptor blockers to obtain the expected clinical benefit, and these doses should be adjusted for their level of renal function to avoid major bleeding events.

A recent decision analysis evaluated the efficacy of an unspecified potential drug on survival in patients with MI and unstable angina, and included serious adverse events (fatal complications) as an element of the evaluation of benefit-risk balance by age-related baseline risks. The authors used a registry database, and a hard primary endpoint (mortality at 1 year). The estimate of effectiveness was larger than in our randomized data (relative risk reduction 25%, absolute risk reduction 2%), and the registry population was more heterogeneous in risk (baseline risk of 2.3% in the youngest vs. 27% in the oldest). They defined a threshold beyond which the treatment benefit would be outclassed by the treatment harm, and found that the fatal complication rate would have to be sevenfold greater in the oldest compared with the youngest age group to outweigh the survival benefits associated with treatment. These results need to be interpreted cautiously given that most major events in these patients do not lead to death. Moreover, retrospective observational data may sometimes inflate estimates of treatment efficacy.

Some limitations should be acknowledged. First, even with over 30,000 ran-
domized patients, subtle age interactions could have been missed, especially for rare events such as death. We did not see any age interactions for death based on the available data (not reported) and the clinical significance of subtle interactions is debatable. Second, a substantial amount of missing values for a few important predictors (blood pressure, heart rate, CK-MB) limited some possibilities of adjusted analysis. However, the results with imputed data yielded similar conclusions (not shown). Third, additional research into the appropriate weighting of events is needed, that can allow a more direct comparison between benefits and harms.

A series of nuances should be considered in interpreting these results. The trials included broad populations of patients with ACS. Through analysis of subgroups, it seems evident that higher risk patients, such as those with positive troponins, diabetes, and perhaps ST segment depression, achieve the greatest benefit. Further, it is likely that patients treated with the aggressive revascularization strategy achieve more benefit than those treated with the conservative strategy. The trials themselves were heterogeneous, as GUSTO IV-ACS showed no benefit and perhaps a detriment of abciximab, and PURSUIT used a very liberal definition of myocardial infarction that minimized the differences between eptifibatide and placebo. Finally, the category of major bleeding overestimates risk relative to the risk of blood transfusion, which is a more direct measure of risk and occurs less frequently (Mahaffey KW et al., Circulation, in press). The EARLY ACS trial is enrolling patients without age limits, it is testing whether the benefit of antithrombotic drugs is similar between elderly and young patients, and it is also addressing each of the above issues \(^{35}\). Allowing for these caveats, our analysis provides estimates for NNTs and NNHs by age subgroups that may be used in clinical decision making for the use of GP IIb/IIIa receptor blockers in NSTE-ACS patients.

In conclusion, the relative risk reduction of death or MI with GP IIb/IIIa receptor blocker is independent of age in patients with non-ST-elevation acute coronary syndromes. Larger absolute reductions of death or MI were observed in the oldest in comparison with the youngest patients, as well as larger absolute increases in major bleeding rates. Attention should be given to optimizing the benefit to elderly patients without increasing bleeding, by ensuring that doses adjusted for renal function are given. Moreover, elderly patients should be monitored more intensively.
Acknowledgements

The data included in this subgroup meta-analysis were provided by Merck Inc, White House Station, NJ, USA (sponsor of the PRISM and PRISM-PLUS trials); Hoffman La-Roche, Basel, Switzerland (sponsor of PARAGON-A and PARAGON-B trials); COR Therapeutics Inc, San Francisco, CA, USA, and Schering-Plough Inc, Kenilworth, NJ, USA (sponsors of the PURSUIT trial); and Centocor Inc, Malvern, PA, USA (sponsor of the GUSTO IV-ACS trial). Dr. Adrián V. Hernández received support from the Netherlands Organization for Scientific Research (ZON/MW 908-02-117).

References

26. Vorchheimer DA, Badimon JJ, Fuster V. Platelet glycoprotein IIb/IIIa receptor
Predictors of stroke within 30 days in patients with non-ST-segment elevation acute coronary syndromes
Chapter 4.3

ABSTRACT

Purpose
Stroke is an uncommon but serious complication in patients with non-ST-segment elevation acute coronary syndromes (NSTE-ACS). We studied baseline patient characteristics that predict the development of stroke at 30 days.

Methods
We pooled data from 6 trials (n=31402) that randomized NSTE-ACS patients either to platelet glycoprotein (GP) IIb/IIIa receptor blockers or placebo/control. Potential predictors of stroke included treatment, and demographic and clinical characteristics. We quantified predictors using univariable and multivariable logistic regression models, and their performance was evaluated with calibration (Hosmer-Lemeshow test) and discrimination (c-statistic).

Results
We found 228 (0.7%) all-cause strokes: 155 (0.5%) non-hemorrhagic, 20 (0.06%) hemorrhagic, and 53 without CT confirmation. Patients with any type of stroke had a 30-day mortality of 25%. Randomization to GP IIb/IIIa receptor blockers was not significantly associated with all-cause stroke (OR [95% CI] 1.08 [0.83 – 1.41]. Older age (OR per increase of 10 years 1.5 [1.3-1.7]), prior stroke (2.1 [1.4-3.1]) and elevated heart rate (per increase of 10 beats 1.1 [1.0-1.2]) were the strongest predictors of 30-day all-cause stroke. Similar predictors were found for non-hemorrhagic and hemorrhagic strokes. Secondary predictors of all-cause stroke included smoking, previous myocardial infarction, diabetes and hypertension. The multivariable model to predict all-cause stroke was well calibrated, but the discriminative power was only moderate (c-statistic 0.69 [0.65 – 0.72]).

Conclusions
Stroke is a rare complication occurring early after NSTE-ACS, but is associated with high mortality. We found no evidence that GP IIb/IIIa receptor blockers increase stroke risks. There were few clinical characteristics that predicted a higher stroke risk. Thus, incident strokes in NSTE-ACS patients remain largely unexplained.
Introduction

The non-ST-segment elevation acute coronary syndrome (NSTE-ACS) is a heterogeneous disease. Risk stratification is essential for predicting prognosis, planning treatment strategy, and providing information to patients and relatives. Previous papers in patients with NSTE-ACS have evaluated the predictors associated with a range of clinical outcomes at 30 days or 6 months, such as death, cardiovascular death, and cardiovascular death or myocardial infarction (MI).

Stroke is an uncommon but severe event in patients presenting with NSTE-ACS. Analyses with a few events in the PURSUIT trial found several clinical predictors of non-hemorrhagic stroke at 30 days. These patients are also at increased risk for hemorrhagic strokes from polypharmacy anticoagulation. However, the confirmation of the importance of these predictors of stroke with a larger number of patients and events is desirable.

We aimed to identify baseline clinical and demographic patient characteristics that predict the development of all-cause, non-hemorrhagic and hemorrhagic strokes within 30 days. We analyzed 31,387 patients with NSTE-ACS from 6 large international trials. Moreover, we evaluated whether the use of GP IIb/IIIa receptor blockers was associated with an increased risk of stroke.

Methods

Clinical trials

We used individual patient data from 6 trials (PRISM, PRISM-PLUS, PARAGON-A, PURSUIT, PARAGON-B, and GUSTO IV-ACS). These trials were reported since 1990 with the following characteristics: randomization of patients with NSTE-ACS, comparison of platelet glycoprotein (GP) IIb/IIIa receptor blockers with placebo or control therapy, no-recommendation for early (<48h) coronary revascularization during study-drug infusion, and enrolment of at least 1000 patients. A total of 31,402 patients participated in these trials. Details of the trial designs are available elsewhere.

Potential predictors

An electronic database consisting of data from individual patients in all eligible trials was available. These data were checked for completeness, for internal
consistency of patients’ records, and for consistency with the published reports. For this analysis, we used available baseline demographic and clinical characteristics regarded as potential predictors of stroke. Those with almost complete information (<1% of missing values) included age, gender, smoking, weight, and prior history all the following: hypertension, diabetes, stroke, MI, heart failure, angina pectoris, coronary artery bypass surgery (CABG), percutaneous coronary intervention (PCI), and use of aspirin. Two variables had 2% of missing values: history of hypercholesterolemia, and ST-depression at baseline.

Other variables had more than 20% of missing data: race, heart rate, blood pressure (systolic and diastolic), and prior use of beta blockers, ACE inhibitors, nitrates and calcium antagonists. Blood pressure and heart rate were not recorded in the GUSTO IV-ACS trial (n=7800); baseline creatine kinase MB (CK-MB) was missing in 7469 patients across different trials. Predictors with more than 20% of missing were imputed using the EM (estimated mean) procedure in SPSS (SPSS Inc., Chicago IL, USA, 1999). Atrial fibrillation and creatinine clearance were not available. The body mass index could not be calculated (i.e. no height was available) and it was not included in the analysis. The use of GP IIb/IIIa receptor blockers was also included as a potential predictor of stroke.

Outcomes

For this analysis, the primary outcomes defined a priori were all-cause stroke, non-hemorrhagic stroke, and hemorrhagic stroke within 30 days of the index ACS. Non-hemorrhagic and hemorrhagic strokes needed CT confirmation. All-cause stroke was missing for 12 patients. Non-hemorrhagic stroke was missing in 7434 patients, and hemorrhagic stroke was missing in 7474 patients. No formal attempt to impute these outcomes was done.

Statistical analysis

Univariable logistic regression models were used to evaluate the association between each potential predictor and the outcome. The predictive weight of each variable was expressed as a $\chi^2$ statistic, which was calculated on the $-2$ log likelihood scale. The higher the number, the more important the predictor; a $\chi^2$ exceeding 3.84 corresponds to $p<0.05$ for a predictor with 1 degree of freedom. All predictors were entered in a multivariable logistic regression model without further selection to properly evaluate their predictive effects while adjusting for the effects of each other predictor.
The performance of the multivariable models was studied with respect to discrimination and calibration. Discrimination refers to the ability to distinguish a stroke from no stroke. It was quantified by a measure of concordance, the c-statistic. For binary outcomes the c-statistic is identical to the area under the receiver operating characteristic (ROC) curve. The c-statistic lies between 0.5 and 1, and is better if closer to one \(^{15}\). Since the apparent c-statistic is optimistic with low numbers of events, we used a standard bootstrapping procedure to correct the estimates \(^{14,15}\). Calibration refers to whether the predicted risks agree with the observed risk frequencies. Calibration was measured with the Hosmer-Lemeshow goodness-of-fit test \(^{16}\). Analyses were performed in SPSS 10.0 and S-PLUS 2000 (Insightful Inc, Seattle WA, USA).

**Results**

*Patient characteristics*

We found 228 (0.7%) all-cause strokes in the study population: 155 (0.5%) were non-hemorrhagic, 20 (0.06%) hemorrhagic, and 53 (0.2%) without CT confirmation. Older patients, those with a prior stroke, prior MI, diabetes, hypertension, and patients with elevated heart rate had higher risks of all-cause and non-hemorrhagic strokes (Table 1). Smoking was not clearly related with the stroke incidence. Patients with previous PTCA were at lower risk to develop any stroke. Less clear associations were seen in hemorrhagic strokes, probably due to small numbers.

A high proportion of patients who suffered a stroke died: 56 (25%) of those with all-cause stroke, 27 (17%) of those with non-hemorrhagic stroke and 13 (65%) of those with hemorrhagic stroke. The difference in mortality between non-hemorrhagic and hemorrhagic strokes was highly statistically different (p<0.001). No clear relation was observed between predictors and death in patients who suffered any type of stroke (Table 1).

*Predictors of stroke*

The use of GP IIb/IIIa receptor blockers was not associated with a higher incidence of all-cause (OR [95% CI] 1.08 [0.83-1.41]), non-hemorrhagic (1.06 [0.77-1.47]), and hemorrhagic (1.70 [0.65-4.45]) strokes.

The strongest univariable predictors of all-cause stroke were older age
Chapter 4.3

(χ²=69), prior stroke (χ²=19), prior MI (χ²=12), hypertension (χ²=10), elevated heart rate (χ²=9), lighter weight (χ²=9), diabetes (χ²=8), and smoking (χ²=6). The associations are shown in Table 2. No interactions between predictors were statistically significant. The three most important predictors were older age (OR [95% CI] per 10 years: 1.5 [1.3-1.7]), prior stroke (2.1 [1.4-3.1]), and elevated heart rate (per 10 beats: 1.1 [1.0-1.2]). Multivariable predictors with relatively minor effects included smoking, prior MI, diabetes mellitus and hypertension.

The strongest univariable predictors of non-hemorrhagic stroke were older age (χ²=38), prior stroke (χ²=18), elevated heart rate (χ²=9), prior MI (χ²=7), and diabetes (χ²=7). Lighter weight (χ²=4), and hypertension (χ²=3) had minor importance. The three most important predictors of non-hemorrhagic stroke had

<table>
<thead>
<tr>
<th>Predictor</th>
<th>All-cause strokes n=228</th>
<th>Non-hemorrhagic strokes n=155</th>
<th>Hemorrhagic strokes n=20</th>
</tr>
</thead>
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<tr>
<td>Age*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;70 y</td>
<td>20874  98 (0.5)  20 (20)</td>
<td>15836  69 (0.4)  10 (15)</td>
<td>15822  6 (0.03)  4 (67)</td>
</tr>
<tr>
<td>≥70 y</td>
<td>10513 130 (1.2) 36 (28)</td>
<td>8132  86 (1.1) 17 (20)</td>
<td>8108 14 (0.17)  9 (64)</td>
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<td>Prior stroke*</td>
<td></td>
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</tr>
<tr>
<td>No</td>
<td>29890 201 (0.7) 50 (25)</td>
<td>22777 134 (0.6) 24 (18)</td>
<td>23744 16 (0.07) 10 (63)</td>
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<td>Yes</td>
<td>1446  27 (1.9)  6 (22)</td>
<td>1141  21 (1.8)  3 (14)</td>
<td>1134  4 (0.35)  3 (75)</td>
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<td>Heart rate</td>
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<td>&lt;75</td>
<td>16807 104 (0.6) 18 (17)</td>
<td>12577 70 (0.6) 11 (16)</td>
<td>12564 10 (0.08)  5 (50)</td>
</tr>
<tr>
<td>≥75</td>
<td>14580 124 (0.9) 23 (19)</td>
<td>11391 85 (0.7) 10 (12)</td>
<td>11364 10 (0.09)  8 (80)</td>
</tr>
<tr>
<td>Smoking</td>
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<td></td>
<td></td>
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<tr>
<td>Never</td>
<td>11499  68 (0.6) 15 (22)</td>
<td>9516  55 (0.6)  8 (15)</td>
<td>9511  7 (0.07)  4 (57)</td>
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<tr>
<td>Former</td>
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<td>7577  55 (0.7) 10 (18)</td>
<td>7557  6 (0.08)  4 (67)</td>
</tr>
<tr>
<td>Current</td>
<td>9307   68 (0.7) 20 (29)</td>
<td>6768  44 (0.7)  9 (20)</td>
<td>6753  7 (0.10)  5 (71)</td>
</tr>
<tr>
<td>Prior MI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>20648 125 (0.6) 31 (25)</td>
<td>16345 90 (0.6) 14 (16)</td>
<td>16317 14 (0.09)  9 (64)</td>
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<tr>
<td>Yes</td>
<td>10646 103 (1.0) 25 (24)</td>
<td>7531  65 (0.9) 13 (20)</td>
<td>7519  6 (0.08)  4 (67)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>24488 159 (0.6) 43 (27)</td>
<td>18612 106 (0.6) 18 (17)</td>
<td>18590 16 (0.08) 11 (69)</td>
</tr>
<tr>
<td>Yes</td>
<td>6860  68 (1.0) 12 (18)</td>
<td>5317  49 (0.9)  9 (18)</td>
<td>5299  4 (0.08)  2 (50)</td>
</tr>
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<td>Hypertension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>14417  81 (0.6) 21 (26)</td>
<td>10908 60 (0.6) 11 (18)</td>
<td>10891  7 (0.06)  5 (71)</td>
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<td>Yes</td>
<td>16935 147 (0.9) 35 (24)</td>
<td>13025 95 (0.7) 16 (17)</td>
<td>13002 13 (0.09)  8 (62)</td>
</tr>
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<td>GP IIb/IIIa RB ‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>13097  91 (0.7) 21 (23)</td>
<td>9928  62 (0.6)  9 (15)</td>
<td>9908  6 (0.06)  2 (33)</td>
</tr>
<tr>
<td>Yes</td>
<td>18290 137 (0.8) 35 (26)</td>
<td>14040 93 (0.7) 18 (19)</td>
<td>14020 14 (0.09) 11 (79)</td>
</tr>
</tbody>
</table>

* P<0.001 for the comparison between categories
† Deaths within 30 days. The percentage refers to the number of deaths in patients who suffered a stroke
‡ Denotes platelet glycoprotein IIb/IIIa receptor blocker

Table 1: Distribution of patient baseline characteristics across stroke types (all-cause, non-hemorrhagic, and hemorrhagic).
Table 2: Univariate and multivariate OR (95% CI) of predictors of stroke in NSTE-ACS patients.

<table>
<thead>
<tr>
<th>Predictors</th>
<th>All-cause strokes</th>
<th>Non-hemorrhagic strokes</th>
<th>Hemorrhagic strokes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Univariable</td>
<td>Multivariable</td>
<td>Univariable</td>
</tr>
<tr>
<td><strong>Main</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (per 10 years)</td>
<td>1.68 (1.48-1.91)</td>
<td>1.51 (1.31-1.74)</td>
<td>1.59 (1.37-1.86)</td>
</tr>
<tr>
<td>Prior stroke</td>
<td>2.81 (1.87-4.21)</td>
<td>2.06 (1.36-3.12)</td>
<td>3.17 (1.99-5.04)</td>
</tr>
<tr>
<td>Heart rate (per 10 beats)</td>
<td>1.11 (1.05-1.19)</td>
<td>1.11 (1.04-1.18)</td>
<td>1.13 (1.05-1.20)</td>
</tr>
<tr>
<td><strong>Secondary</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Former</td>
<td>1.48 (1.08-2.03)</td>
<td>1.45 (1.05-2.02)</td>
<td>1.26 (0.86-1.83)</td>
</tr>
<tr>
<td>Current</td>
<td>1.24 (0.88-1.73)</td>
<td>1.37 (0.98-1.95)</td>
<td>1.13 (0.76-1.67)</td>
</tr>
<tr>
<td>Prior MI</td>
<td>1.60 (1.23-2.08)</td>
<td>1.32 (0.99-1.77)</td>
<td>1.57 (1.14-2.16)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.53 (1.15-2.04)</td>
<td>1.26 (0.93-1.69)</td>
<td>1.62 (1.16-2.28)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.55 (1.18-2.03)</td>
<td>1.21 (0.91-1.61)</td>
<td>1.32 (0.96-1.84)</td>
</tr>
</tbody>
</table>
comparable associations as those described for all-cause stroke. For hemorrhagic strokes, the strongest univariable predictors were older age ($\chi^2=12$), prior stroke ($\chi^2=8$), and lighter weight ($\chi^2=5$). Similarly, the three most important predictors were those of the non-hemorrhagic strokes (Table 2).

**Performance of predictive models**

The calibration of the predictive model of all-cause stroke was good (Hosmer-Lemeshow test 10.4, $p=0.24$), but the discriminative power of this model was moderate ($c$-statistic [95% CI]: 0.69 [0.65-0.72]). Although the calibration of the predictive models of non-hemorrhagic and hemorrhagic strokes was good, the discriminative power was either moderate ($c$-statistic 0.67 [0.63-0.71]) or poor ($c$-statistic 0.58 [0.54-0.63]), respectively.

**Discussion**

Stroke occurred in 0.7% of patients within 30 days of presenting with NSTE-ACS. Two thirds of the strokes were non-hemorrhagic. Older age, prior stroke and elevated heart rate were the strongest predictors of all-cause, non-hemorrhagic, and hemorrhagic strokes. However, the discriminative power of these predictors was moderate, and especially poor for hemorrhagic strokes. Thus, it is difficult to accurately predict the incidence of stroke in this population.

The incidence of 30-day all-cause stroke in our patients is comparable to the incidence in similar populations: 0.8% in the GUSTO-IIb trial 17, and 0.5% in the OPUS-TIMI 16 trial 18. However, in clinical practice the incidence of 30-day all-cause stroke may be larger, because the in-hospital incidence already reaches 0.7% 19. In a Spanish nationwide registry (DESCARTES) the incidence of 30-day all-cause stroke was 0.9% (95% CI 0.4-1.3%) 20. For comparison, the incidence of 30-day all-cause stroke in patients with ST-segment elevation-ACS (STE-ACS) treated with thrombolitics was 1.4% (between 1.2% and 1.6%) in the GUSTO-I trial 21, and 0.8% in nine trials from a meta-analysis 22. The VALIANT registry, including both NSTE- and STE-ACS patients, had 1.5% in-hospital strokes 23. The proportion of hemorrhagic strokes was around 50% of the total number of strokes in the GUSTO-I trial 21, and 13% in the meta-analysis 22. Strokes in NSTE-ACS patients were associated with a high mortality rate (25%), which is lower than that observed in STE-ACS patients (41%) 21.

Importantly, the use of GP IIb/IIIa receptor blockers was not clearly associated with an increased incidence of all-cause stroke, non-hemorrhagic stroke or
hemorrhagic stroke. However, it should be recognized that the conclusion about
the effect of GP IIb/IIIa receptor blockers on hemorrhagic strokes has substantial
uncertainty, given the low numbers of events available and, hence, the limited
power of the statistical analysis. The low frequency of hemorrhagic stroke in
the overall population, coupled with lack of clear evidence of increased risk,
provides reassurance that fear of intracranial hemorrhage should not be a reason
to avoid these drugs. However, when patients receive these drugs on top of
more aggressive antithrombotic therapy, the incidence of hemorrhagic strokes
increases, as in patients with STE-ACS who received thrombolytics 24. In our
NSTE-ACS patients, predictors associated with the incidence of hemorrhagic
stroke were similar to those associated with non-hemorrhagic stroke. In contrast,
STE-ACS patients who take oral anticoagulation before admission, with less than
70 kg, and older than 65 years were at increased risk of hemorrhagic stroke.

Stroke has only been studied as an outcome in a secondary analysis of the
PURSUIT trial 6. Sixty-six non-hemorrhagic strokes in 9461 NSTE-ACS patients
were studied. Hemorrhagic strokes were not studied. The strongest predictors
were higher heart rate, older age, prior anterior MI, prior stroke or transient
ischemic attack, and diabetes mellitus. Our analysis of 6 trials with a sample size
of 31,387 patients increased the number of events and the power to find predictors
of any type and all-cause stroke. However, the number of hemorrhagic strokes
was still limited.

Age was an important predictor of non-hemorrhagic stroke in the PURSUIT
trial 6, and the GUSTO-I trial 25. In our analysis, age was the strongest predictor of
all-cause, non-hemorrhagic, and hemorrhagic strokes, and its relative importance
was slightly higher than the results of the PURSUIT trial. Elderly patients
probably have a higher risk of stroke due to multiple co-morbidities associated
with older age, such as atrial fibrillation, hypertension, physical inactivity, and
asymptomatic carotid stenosis 26.

Prior stroke has been described as a predictor of stroke in the OPUS-TIMI
16 trial 27. In this trial, the proportion of 10-month all-cause stroke was 2.9%
in 1,173 patients with prior extra-cardiac vascular disease (peripheral + stroke
+ transient ischemic attack [TIA]) in comparison with 1.1% in 9108 patients
without prior extra-cardiac vascular disease. In the PURSUIT trial and in the
GUSTO-I trial 25 prior stroke was analyzed in conjunction of prior TIA, and this
combined predictor was important. Prior stroke may be a marker of underlying
cardiac, carotid or cerebral vascular disease in ACS patients.

Elevated heart rate was very important in the PURSUIT trial 6, and in the
GUSTO-I trial 25. An explanation for the association between elevated heart rate
and stroke is not clear. The heart rate may correlate with larger infarctions that predispose patients to a higher likelihood of atrial arrhythmia and left ventricular thrombi. Heart rate is strongly associated with the presentation of atrial fibrillation in patients with NSTE-ACS. Atrial fibrillation is a common complication of these patients, occurring in 6.4% of patients enrolled. Moreover, an elevated baseline heart rate may simply be an expression of a prior atrial fibrillation. Unfortunately, our dataset did not provide information over prior or incident atrial fibrillation. Finally, a high heart rate may be an expression of a decompensated heart failure, related to the extent of the MI. Heart failure on admission has been described as an independent predictor of in-hospital all-cause stroke in the VALIANT registry.

Diabetes and prior MI were important predictors of stroke in the PURSUIT trial, but not in our analysis. Diabetes has a known association with a widespread atherosclerosis, and prior MI is associated with the formation of mural thrombus and emboli. Finally, lighter weight was weakly associated with hemorrhagic stroke. This was probably related to doses of GP IIb/IIIa receptor blockers and anticoagulants that were not reduced in lighter patients, and especially for the elderly.

Our study has some limitations. We had about 7500 patients with missing values for the non-hemorrhagic and hemorrhagic stroke outcomes. The number of non-hemorrhagic strokes was still larger (n=155) than the largest previously published (n=66). However, the number of hemorrhagic strokes was small (n=20), and this limited the conclusions about the predictors of hemorrhagic stroke. We imputed several patient characteristics. Of them, only heart rate remained as strong predictor, as was demonstrated previously.

In conclusion, stroke is an infrequent but serious early complication of patients with NSTE-ACS. Mortality is high, especially for hemorrhagic strokes. Platelet GP IIb/IIIa receptor blockers were not significantly associated with any type of stroke. Three main predictors of stroke were older age, prior stroke and elevated heart rate. Since the discriminative ability of these patient characteristics was at best moderate, it is difficult to predict which ACS patients will suffer a stroke.
References


General Discussion
General discussion and conclusions

5.1
This thesis describes theoretical and practical aspects of covariate adjustment and subgroup analysis in randomized clinical trials (RCTs) with heterogeneous populations, with special interest in traumatic brain injury and acute coronary syndrome trials. In this chapter, we mention some theoretical aspects of covariate adjustment and subgroup analysis. Subsequently, use, reporting, and interpretation of covariate adjustment and subgroup analysis in recently published RCTs, and the practical application of these aspects in traumatic brain injury and acute coronary syndrome trials are discussed in the light of the theory. Finally, some general recommendations are formulated.

Summary answers to the research questions

**Question 1: Which are the pros and the cons of adjustment of the treatment effect in RCTs for baseline covariates?**

**Answer:** Covariate adjustment increases the power to detect a significant treatment effect, and reduces the sample size requirements. This reduction in sample size is directly related to the strength of the adjusted predictors, and it is independent of the treatment effect and sample size of the trial. When time-to-event outcomes are considered, this reduction in sample size is independent of the censoring level. Adjustment for imbalance yields a very limited gain in the reduction of sample size.

**Question 2: How well are covariate adjustment and subgroup analysis used, reported and interpreted in current internal medicine, oncology, cardiology, and neurosurgery trials?**

**Answer:** Covariate adjustment was used as primary analysis in about 50% of trials, and few predictive covariates were utilized. Subgroup analysis was used in over 50% of trials, but the appropriate interactions tests were underutilized. Moreover, a minority of subgroup analyses were pre-specified, and an overemphasis on results of subgroups was common.

**Question 3: How much can the adjustment for important predictors of unfavorable outcome decrease the requirements in sample size in TBI trials?**

**Answer:** Adjustment for seven strong predictors of 6-month unfavourable Glasgow Outcome Scale reduced the sample size requirements by 25% in TBI trials. Adjustment for the three strongest predictors reduced the sample size requirements by 20%.
**Question 4: Are the effects of GP IIb/IIIa receptor blockers similar in the young and the elderly in a meta-analysis of non-ST-segment elevation acute coronary syndrome trials?**

**Answer:** In an individual data subgroup meta-analysis of 6 large trials, GP IIb/IIIa receptor blockers had similar relative beneficial effects in old and young patients with NSTE-ACS. Absolute beneficial effects in old patients were larger than in young patients, given a higher baseline risk. However, these beneficial effects in the elderly were outweighed by a higher risk of major bleeding.

**Question 5: Which subgroups of patients are at higher risk to develop a stroke after a non-ST-segment elevation acute coronary syndrome?**

**Answer:** Patients who are old, with a prior stroke and with a high heart rate are at higher risk of stroke after sustaining a NSTE-ACS. GP IIb/IIIa receptor blockers did not increase the risk of any type of stroke.

**Research Question 1: Simulations using covariate adjustment**

Covariate adjustment provides a more individual-oriented treatment effect estimates, corrects for chance imbalance in baseline characteristics, and increases the power to detect an important treatment benefit. We performed simulation studies with dichotomous outcomes. In chapter 2.1, we showed that adjustment for a strong covariate (either pre-specified or tested) in logistic regression models led to a more beneficial treatment effect, with larger variability (i.e. broader confidence intervals) in direct relation to the strength of the covariate. However, the overall result was a gain in power. When we only adjusted when covariates were imbalanced, the gain in power was very limited. Moreover, we obtained a conservative type I error when the adjustment was performed due to imbalance, which is explained by the fact that adjusting for imbalances constrains the outcome variability between treatment groups.

In practical situations (Odds Ratio [OR] of the covariate between 2 and 5), a reduction in sample size between 3% and 14% was obtained with an outcome incidence of 50% and a covariate prevalence of 50%. The reduction was independent of the treatment effect and sample size, and makes it an attractive summary measure to express the benefit of covariate adjustment. We did not present calculations for covariate adjusted sample sizes in the RCT design phase. To quantify any anticipated sample gains, we would need to specify covariate effects and covariate distributions. We would have to meet these assumptions to achieve
the calculated power. We advised to perform unadjusted sample calculations, which need fewer assumptions. However, reductions of sample size of about 10% can be expected when adjusting for one known strong covariate.

In chapter 2.2, we applied the same methodology in simulated RCTs with time-to-event outcomes, analyzed with the Cox proportional hazards model. The power to detect the treatment effect was higher when covariates were pre-specified and/or predictive of the outcome. The type I error was usually at the nominal level. The reduction in sample size for a covariate Hazard Ratio (HR) between 2 and 5 ranged between 15% and 44% (covariate prevalence of 50%) and between 4% and 12% (covariate prevalence 10%). The reduction was independent of the treatment effect and sample size. Importantly, this measure was also independent of the censoring level. We should notice that the RSS were not directly comparable between a RCT with dichotomous outcomes and a RCT with time-to-event outcomes. When a covariate prevalence of 50% and no censoring were settled, a given value of HR corresponded to a higher OR (OR=HR*p2/p1, where p2 was the survival in the covariate group with the best prognosis, and p1 the survival with the covariate with the worst prognosis). Thus, a reduction of 16% was achieved with adjustment for a moderately predictive covariate (HR=2), and a reduction of 14% was obtained with adjustment for a highly predictive covariate (OR=5).

Research Question 2: Current reporting of covariate adjustment and subgroup analysis

When adequately reported, RCTs provide clinicians with valuable information that helps them to accept or reject treatments or interventions, and hence to improve their practice. The revised recommendations of the Consolidated Standards of Reporting Trials (CONSORT) statement highlighted the appropriate use and interpretation of covariate adjustment and subgroup analysis. Covariate adjustment should be performed for a limited number of covariates, and the reasons for their choice should be clearly stated. Likewise, only a limited number of pre-specified subgroup analyses should be performed, the appropriate interaction tests should be used, and subgroup analysis is to be considered as secondary analysis. Evaluation showed that the reporting of covariate adjustment and subgroup analysis in RCTs from the 80’s and 90’s often was inappropriate, such as inconsistencies in the use of covariate adjustment, underuse of tests of interactions, and overinterpretation of subgroup analyses.

We evaluated the reporting of covariate adjustment and subgroup analysis in RCTs from high impact factor medical journals, in general internal medicine (n=46), cardiology (n=21) and oncology (n=17) journals, published in an arbitrary
3-month period at the end of 2002. In chapter 3.1, it is described that covariate adjustment was used as primary analysis by only 50% of the RCTs, and predictive covariates were mainly used. Over 50% of RCTs used subgroup analysis, and about 20% used the appropriate interaction tests. Remarkably, 25% of the RCTs overemphasized the subgroup results. The reporting of covariate adjustment has improved in comparison to previous reports in the last two decades. However, the reporting of subgroup analysis has not improved. Therefore, subgroup analysis had major shortcomings that may have resulted in incorrect medical decisions.

Then, we focused on the reporting of subgroup analysis in 63 therapeutic cardiovascular RCTs published in 2002 and 2004, in the same cardiology journals chosen for the previous evaluation, with a median of 500 patients (Chapter 3.2). The number of trials in this clinical area has increased dramatically in the last 20 years: from 5410 in the period 1980-1989 to 14845 in the period 1990-2000. The interest to explore treatment effects in subgroups has also increased, due to the heterogeneity of these patients respect to their clinical outcome. Thus, many analyses have been done to look at differential treatment effects in groups such as elderly patients, female patients, diabetic patients, severe patients with acute coronary syndromes, heart failure, hypertension, hypercholesterolemia and stroke.

All 39 RCTs that reported subgroup analysis were not powered to detect subgroup effects, and 26 RCTs reported more than 5 subgroups. Fourteen trials reported fully pre-specified subgroups, only 11 RCTs used the appropriate tests of interaction, and 15 overemphasized the subgroup results. These results were worse than those from the assessment of RCTs as detailed in Chapter 3.1. A prior assessment of reporting of subgroup analysis was published. Here, large cardiovascular trials (n>1000 patients) published between 1980 and 1997 had similar shortcomings as we found in smaller and more recent trials. However, subgroup analysis in larger trials have more power to detect true subgroups than the smaller trials. Many physicians and cardiologists may misinterpret the results, and can use a harmful treatment in a “wrong” subgroup of patients, or even worse, can withhold a beneficial treatment in the “right” subgroup of patients.

Finally, we studied the reporting of covariate adjustment and subgroup analysis in 18 traumatic brain injury trials (Chapter 3.3). This is another clinical area with substantial interest in these methods due to the heterogeneity of patients, and negative results of the therapeutic trials. Five of the RCTs reported covariate adjustment, and 4 of them used the adjusted effect as main efficacy parameter. They correctly used few covariates, which mainly were predictors. Eleven RCTs reported subgroup analyses, but only 3 were completely pre-specified, 1 used the
appropriate interaction testing, and 5 gave the subgroup results a similar emphasis as the overall results. These mistakes in the reporting of subgroup analysis may have been planned, or may have been driven by the results (post-hoc analyses) \(^{13}\). We had the opportunity to evaluate the correspondence between subgroup analysis planning and reporting for 6 protocols-trials combinations. The correspondence was poor, and this seems an indication of post-hoc analyses. The results of post-hoc subgroup analyses should be treated with skepticism, as they are data driven rather than stated a priori \(^{14}\). A better translation of the CONSORT recommendations on appropriate reporting of covariate adjustment and subgroup analysis can improve the understanding of clinicians about the findings in trials with heterogeneous populations.

**Research Questions 3, 4, and 5: Clinical applications**

We focused in two clinical areas: traumatic brain injury \(^{15}\), and non-ST-segment elevation acute coronary syndromes \(^{16}\).

*Reduction in sample size with covariate adjustment for strong predictors in TBI trials*

Most of the trials of patients with moderate or severe traumatic brain injury have not demonstrated the efficacy of treatments or interventions \(^{17}\). One of the explanations to this failure has been the reduced sample sizes of previously reported trials \(^{18}\). It seems unrealistic to increase the sample size of explanatory TBI trials due to financial and administrative constraints. One way to achieve a smaller sample size is to adjust for important predictors of the clinical outcome. RSSs were calculated in 8 trials of moderate to severe TBI, with sample sizes ranging from 126 to 1118 (Chapter 4.1). We sequentially adjusted for 1 to 9 strong predictors (clinical, radiological, biochemical) of a 6-month dichotomous Glasgow Outcome Scale.

We found that the adjustment for the 3 strongest predictors (age, motor score and pupils) yielded RSS between 16% and 23%, and adjustment for 9 strong predictors yielded RSS between 23% and 30%. Adjustment for 7 strong predictors gave similar results to adjustment for 9 predictors. These RSS were smaller than the ones in the context of TBI registries, which have less restrictive inclusion criteria and hence is expected to have more heterogeneous populations. These results highlighted the importance of the adjustment for strong predictors, and it is valuable tool in the analysis phase of new TBI trials. However, other more sophisticated methods (e.g. sliding dichotomy or proportional odds models) \(^{19}\).
may reduce the sample size requirements even more. A reduction in sample size of 25% can be expected when adjusting for a group of known strong predictors.

**Platelet glycoprotein IIb/IIIa receptor blocker effects in elderly patients with non-ST-segment elevation acute coronary syndromes**

We performed a individual data subgroup meta-analysis of 6 large international trials, with a total of 31402 patients, to try to overcome the underrepresentation of the elderly in previous trials, and increase the power to find more reliable subgroup effects 20 (see Chapter 4.2). The appropriate interactions tests were used, and age subgroup effects were combined using random effects models 21. The relative GP IIb/IIIa effects were similar across age subgroups, and, consequently, the absolute drug effects were larger in the elderly. This is related to the fact that elderly patients have a larger baseline risk than younger patients, and therefore receive a larger benefit from this drug 22. However, elderly patients had larger major bleeding rates than younger patients. These results are more reliable than subgroup effects in each individual trial, and we studied a large number of elderly patients (n=2049). Likewise, harmful major bleeding complications have to be remembered when the decision to use these drugs is taken, and a close monitoring of these patients is warranted.

**Subgroups of patients at higher risk of stroke after a non-ST-segment elevation acute coronary syndrome**

We used the large meta-analysis database, with 155 non-hemorrhagic stroke and 228 all-cause strokes (Chapter 4.3). Elderly patients, with a prior stroke and elevated heart rate were at the highest risk to develop any type of stroke. The other previously reported predictors were not found in our analysis, and this is probably an indication of the selection of non-predictors when few events were available. Use of GP IIb/IIIa receptor blockers was not related to the presentation of any type of stroke. Although the model was well calibrated, the discriminative power of these 3 predictors was moderate (c-statistic 0.70). Thus, the prediction of stroke is difficult. We did not study long-term outcomes, and this can change the chosen predictors, and the performance of the models.

**Recommendations for appropriate analysis of RCTs**

Information about the appropriate analysis of RCTs with covariate adjustment and subgroup analysis in patients with heterogeneous populations is limited.
We summarize our recommendations, based on the literature and the papers presented in this thesis (Tables 1 and 2).

Subgroup analyses should be pre-specified. Limitation to a small number of subgroups is desirable. This minimizes multiple testing and false-positive

<table>
<thead>
<tr>
<th>Table 1: Recommendations for Covariate Adjustment</th>
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<tbody>
<tr>
<td>a. Specify the adjustment for few strong predictors in advance.</td>
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<td>b. If no predictors are known, specify that you will test a limited number of them, and adjust if one or more are predictive.</td>
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<tr>
<td>c. Adjust for imbalances in covariates only when these covariates are predictors of the outcome.</td>
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<tr>
<td>d. Define in advance the type of model to be used.</td>
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<td>e. Define the importance of the adjusted treatment effect in relation to the unadjusted effect (primary or secondary).</td>
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<tr>
<td>f. Perform usual unadjusted sample size calculations in the design phase. A 10% of reduction in sample size can be expected when adjusting for one strong covariate, and a 25% when adjusting for a group of strong covariates.</td>
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<th>Table 2: Recommendations for Subgroup Analysis</th>
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<tr>
<td><strong>Specification</strong></td>
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<tr>
<td>a. Specify a limited number of subgroups in advance</td>
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<tr>
<td>b. Detail the rationale of the chosen subgroups.</td>
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<tr>
<td><strong>Analysis</strong></td>
</tr>
<tr>
<td>a. Use statistical interaction tests</td>
</tr>
<tr>
<td>b. Avoid performing analysis of the treatment effect within small subgroups of patients (‘separate subgroup analysis’).</td>
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<tr>
<td><strong>Interpretation</strong></td>
</tr>
<tr>
<td>a. Be sceptical if subgroups were not pre-specified, not biologically plausible, or no interaction tests were applied.</td>
</tr>
<tr>
<td>b. Evaluate previous reports for similar findings, and work on independent confirmation such as subgroup meta-analysis.</td>
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<tr>
<td>c. Subgroup analyses are mostly hypotheses-generating exercises to stimulate further research.</td>
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<tr>
<td>d. Keep emphasis on the overall results.</td>
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subgroup effects. Subgroups should have a clear biological or pathophysiological rationale, and the appropriate interaction tests should be used. Subgroups must be confirmed independently to be more reliable. When possible, a subgroup meta-analysis increases the power to detect subgroup effects. Finally, subgroup analysis only generates new hypotheses to be tested. Thus, the overall trial result is the best estimate of the treatment effect.

Conclusions

1. Covariate analysis is a valuable method to obtain more individual-oriented treatment effects. Covariate analysis allows a substantial gain in the power to demonstrate a significant treatment effect, and reduces the sample size requirements.
2. Covariate analysis is recommended in the analysis of RCTs when predictors are scientifically established. If predictors are not known, testing for them and adjustment for significant predictors are recommended.
3. A reduction of sample size of 10% can be expected when adjusting for one strong predictor, and a reduction of 25% can be expected when adjusting for a group of strong predictors. Adjustment for moderate predictors yields reductions in sample size about 5%.
4. Subgroup analysis generates hypotheses to test in further trials, and rarely provides definitive answers about subgroup effects. Its reporting is poor in current clinical trials, in different clinical and surgical medical fields.
5. A full pre-specification of subgroups, the use of interactions tests, and the consideration as secondary analysis may improve the sceptical vision of subgroup analysis.
6. Subgroup meta-analysis of trials improves the power to detect differential subgroup effects, and should be recommended when individual patient data of trials are available.
References

Summary/Samenvatting/
Resumen

5.2
Summary

Randomized clinical trials (RCTs) are essential to evaluate the usefulness of treatments and interventions, and clearly influence clinical practice. Trials are often performed in heterogeneous populations, such as patients with traumatic brain injury (TBI), acute coronary syndromes (ACS), stroke and cancer. Patients are heterogeneous regarding to their characteristics, such as age, gender, or disease severity. Heterogeneity may produce imbalance in randomized groups with respect to prognosis, and may dilute the beneficial effect of treatments in some subgroups of patients.

However, heterogeneity of patients offers some solutions to deal with these problems. Covariate adjustment and subgroup analysis are two methods used in the analysis phase of the trials. Covariate adjustment leads to adjusted estimates of treatment effects that relate to the “average” patient with a certain risk profile. It corrects for imbalance, and increases the statistical power to detect significant treatment effects. Subgroup analysis assesses differences in treatment effect across different subpopulations of patients.

We aimed to know which are the pros and cons of adjustment of the treatment effect for baseline characteristics in trials with dichotomous outcomes, to know how well are used, reported and interpreted both covariate adjustment and subgroup analysis in current clinical trials, and to apply these methods in trials performed in heterogeneous patient populations. We wanted to know how much can adjustment for important predictors decrease the sample size in TBI trials, whether the effects of glycoprotein IIb/IIIa receptor blockers were similar in the young and elderly patients with ACS, and which subgroups of patients were at higher risk to develop a stroke after an ACS.

Part 2 focuses on simulations studies to quantify the gain in power and the reduction in sample size requirements with the use of covariate adjustment in trials with dichotomous outcomes. In Chapter 2.1 we showed that adjustment for a strong covariate (pre-specified or tested) in logistic regression models led to a more extreme estimate of the treatment effect, and a gain in power. With a strong covariate (OR between 2 and 5), adjustment yielded a reduction in sample size between 3% and 14%. This reduction was independent of the treatment effect and sample size, and it was an attractive summary measure to express the benefit of covariate adjustment. When we adjusted for covariates that were imbalanced, the gain in power and the reduction in sample size was very limited. In Chapter 2.2 we applied the same methodology in simulation that considered time-to-event outcomes, analyzed with the Cox proportional hazards model. The statistical power to detect a significant treatment effect was higher than without
adjustment. Reductions in sample size were between 15% and 44% when adjustment was made for strong covariates (HR between 2 and 5), and lower when lower covariate prevalences were considered. The reduction in sample size was independent of treatment effect, sample size and censoring level.

**Part 3** focuses on use, reporting and interpretation of covariate adjustment and subgroup analysis in internal medicine, oncology, cardiology and neurosurgery trials. In **Chapter 3.1** we evaluated internal medicine, cardiology and oncology trials published in 2002. Covariate adjustment was used in 50% of trials, and predictive covariates were used. Subgroup analysis was also used in 50% of trials. However, only 20% used the appropriate interaction tests, and 25% overemphasized the subgroup results. Subgroup analysis hence had major shortcomings that may be translated onto incorrect medical decisions. **Chapter 3.2** describes the situation of subgroup analysis in cardiovascular trials from 2002 and 2004. The interest in subgroup analysis in this field has increased dramatically in the last 20 years. Thirty-nine out of 63 trials reported subgroup analysis. Only 14 reported fully pre-specified subgroups, 11 used interaction tests, and 15 overemphasized the subgroup findings. The results were worse than those reported in chapter 3.1. Thus, many cardiologists may misinterpret the results of these subgroups, and can use a harmful treatment in “wrong” patients, and withhold a beneficial treatment in “right” patients. In **Chapter 3.3** we evaluated covariate adjustment and subgroup analysis in 18 TBI trials. Five trials used covariate adjustment, and correctly used few predictors. Eleven trials reported subgroup analysis, but only 3 fully pre-specified the subgroups, one used interactions testing, and 5 emphasized the results. We also evaluated whether these shortcomings in subgroup analysis were planned or were data-driven, by analyzing 6 available protocols of 6 trials. The correspondence was poor, and seems an indication of post-hoc analyses. Overall, the use, reporting and interpretation of covariate adjustment seems appropriate, but subgroup analysis have evident shortcomings.

**Part 4** focuses on clinical applications of covariate adjustment and subgroup analysis in trials performed in two heterogeneous patient populations, such as TBI and ACS. In **Chapter 4.1** we evaluated the reduction in sample size that could be obtained when adjusting for strong predictors of unfavorable outcome in 8 TBI trials. We found that adjustment for the three strongest predictors yielded a reduction in sample size of 20%, and adjustment for the seven strongest predictors a reduction of 25%. For comparison, adjustment in TBI surveys, with more heterogeneous populations, yielded a larger reduction in sample size (reaching 40%). Adjustment for predictors is a valuable tool in the analysis phase of TBI trials. **Chapter 4.1** describes a subgroup meta-analysis of 6 large trials, which evaluated whether the effect of glycoprotein IIb/IIIa receptor blockers were similar between young and elderly patients with non-ST-segment-elevation
(NSTE) ACS. The relative beneficial effects of the drug were similar across age subgroups, and the absolute beneficial effects were larger in the elderly. This was due to a higher baseline risk of elderly patients. However, elderly patients had a higher absolute risk of major bleedings. Thus, these drugs are useful in the elderly as well as in the young, and the higher risk of bleeding warrants a careful close monitoring in the elderly. Finally, in Chapter 4.3 we analyzed which subgroups of patients were at higher risk to develop a stroke after a NSTE-ACS. We found that patients with older age, with a prior stroke and with high heart rates were at increased risk of any type of stroke. Other previously described high-risk subgroups of patients (e.g. diabetics, hypertensive) were not at higher risk in our analysis. However, the model built with those 3 predictors had a moderate discrimination, making the prediction of stroke difficult.

Finally, in Part 5 we put the main findings on perspective, and general recommendations for an appropriate use, reporting and interpretation of covariate adjustment and subgroup analysis are given. We conclude that covariate adjustment is a valuable method to obtain more individual-oriented treatment effects in trials, and substantial reductions in sample size requirements can be obtained when adjusting for predictors. Covariate adjustment should be recommended for future trials in heterogeneous populations. Subgroup analysis is commonly performed in current trials, but important shortcomings were found. Full pre-specification, use of interaction tests, and recognition of its secondary importance are essential to improve the sceptical vision on subgroup analysis. Subgroup meta-analysis substantially improves the power to detect subgroup effects across trials, and should be recommended as a standard procedure when individual data are available.
Samenvatting

Gerandomiseerde, klinische trials (RCT’s) zijn zeer belangrijk voor onderzoek naar het nut van behandelingen en interventies en hebben veel invloed op de klinische praktijk. Trials worden vaak gedaan in heterogene populaties, zoals bijvoorbeeld patiënten met traumatisch hersenletsel (traumatic brain injury, TBI), acuut coronair syndroom (ACS), beroerte of kanker. De kenmerken van deze patiënten, zoals leeftijd, geslacht en ernst van de aandoening, zijn heterogeen. Deze heterogeniteit kan in gerandomiseerde groepen prognostische onbalans met zich meebrengen, waardoor het gunstige effect van een behandeling in sommige subgroepen van patiënten verwatert.

Er zijn verschillende oplossingen voor het probleem van de heterogeniteit van patiënten. De volgende twee methoden worden toegepast in de analysefase van trials: correctie voor covariabelen en subgroepanalyse. Correctie voor covariabelen leidt tot een aangepaste schatting van het behandeleffect voor een “gemiddelde” patiënt met een bepaald risicoprofiel. De onbalans wordt gecorrigeerd en het statistisch onderscheidingsvermogen (de power) voor het vaststellen van een significant behandel-effect wordt groter. Bij subgroepanalyse worden de verschillen in behandel-effect tussen verschillende subpopulaties van patiënten onderzocht.

We wilden onderzoeken welke voor- en nadelen correctie voor baseline kenmerken heeft op het behandel-effect in trials met dichotome uitkomstmaten, en in hoeverre correctie voor covariabelen en subgroepanalyse in de huidige klinische trials juist worden toegepast, beschreven en geïnterpreteerd. Tenslotte wilden we beide methoden toepassen in trials in heterogene patiëntengroepen: we wilden met name weten welke invloed correctie voor belangrijke voorspellers heeft op de steekproefomvang in trials naar TBI; of glycoproteïne-IIb/IIIa-receptorblockers in jonge en oudere patiënten met ACS een vergelijkbaar effect hebben; en welke subgroepen van patiënten na een ACS een hoger risico op een beroerte hebben.

In deel 2 worden enkele simulatiestudies beschreven waarin voor trials met een dichotome uitkomstmaat de verandering in de power en de vereiste steekproefomvang door correctie voor covariabelen gemeten werd. In hoofdstuk 2.1 laten we met behulp van logistische regressiemodellen zien dat correctie voor een sterke covariabele (vooraf bepaald of na toetsing) een extremere schatting van het behandel-effect en een grotere power met zich meebrengt. Correctie voor een sterke covariabele (OR tussen 2 en 5) resulteerde in een 3-14% kleinere steekproef. Deze reductie was onafhankelijk van het behandel-effect en de steekproefomvang, en bleek een geschikte samenvattende maat om de voordelen van correctie voor covariabelen in uit te drukken. Correctie voor ongebalanceerde
covariabelen had slechts een beperkte invloed op de power en de steekproefomvang. In hoofdstuk 2.2 pasten we met behulp van Cox-regressieanalyse dezelfde methode toe in een simulatie met time-to-event uitkomstmaten. De statistische power om een significant behandeleffect aan te tonen was groter met correctie dan zonder correctie. Wanneer voor sterke covariabelen (HR tussen 2 en 5) werd gecorrigeerd, nam de steekproefomvang met 15-44% af; deze reductie was minder wanneer voor laagprevalente covariabelen werd gecorrigeerd. De mate van reductie van de steekproefomvang was onafhankelijk van het behandeleffect, de steekproefomvang en het niveau van censurering.

Deel 3 gaat in op de toepassing, de beschrijving en de interpretatie van correctie voor covariabelen en subgroepanalyse in interne, oncologische, cardiológische en neurochirurgische trials. In hoofdstuk 3.1 evalueerden we de in 2002 gepubliceerde interne, oncologische en cardiológische trials. In 50% van de trials werd correctie voor covariabelen toegepast en gebruik gemaakt van voorspellende variabelen. In de andere helft van de trials werd subgroepanalyse toegepast. In slechts 20% echter werd een geschikte toets voor interactie gebruikt en in 25% werden de resultaten voor de subgroepen teveel benadrukt. Subgroepanalyse heeft dus belangrijke tekortkomingen die tot verkeerde medische beslissingen kunnen leiden. Hoofdstuk 3.2 beschrijft de toepassing van subgroepanalyse in cardiovasculaire trials in de periode van 2002 tot 2004. In de laatste twintig jaar is de belangstelling voor subgroepanalyse in dit veld drastisch toegenomen. In 39 van de 63 trials bleek subgroepanalyse te zijn gebruikt. In slechts 14 trials was sprake van vooraf bepaalde subgroepen en in 11 trials vond toetsing voor interactie plaats; in 15 trials werden de resultaten voor de subgroepen teveel benadrukt. Deze bevindingen waren slechter dan die in hoofdstuk 3.1. Cardiologen kunnen op deze manier de resultaten voor de subgroepen fout interpreteren en de “verkeerde” patiënten een schadelijke behandeling geven, terwijl de “goede” patiënten een gunstige behandeling onthouden wordt. In hoofdstuk 3.3 onderzochten we correctie voor covariabelen en subgroepanalyse in 18 trials naar TBI. Vijf trials pasten correctie voor covariabelen toe en gebruikten - terecht - weinig voorspellers. Elf trials pasten subgroepanalyse toe, maar in slechts 3 trials waren de subgroepen vooraf bepaald en in 1 trial vond toetsing voor interactie plaats. In 5 trials kregen de resultaten voor de subgroepen teveel nadruk. We bekeken ook de onderzoeksprotocollen die voor 6 trials beschikbaar waren om na te gaan of de tekortkomingen in de subgroepanalyse gepland waren of door de data waren ingegeven. De inhoud was mager en kan een reden zijn geweest voor post hoc analyses. Correctie voor covariabelen wordt in het algemeen correct toegepast, beschreven en geïnterpreteerd, maar subgroepanalysen hebben duidelijke beperkingen.

Deel 4 gaat in op de klinische toepassing van correctie voor covariabelen
en subgroepanalyse in trials in twee heterogene patiëntenpopulaties met TBI en ACS. In **hoofdstuk 4.1** onderzochten we de reductie van de steekproefomvang in 8 trials naar TBI door te corrigeren voor sterke voorspellers van een ongunstige uitkomst. We vonden dat correctie voor de 3 sterkste voorspellers tot een 20% kleinere steekproef leidde; bij correctie voor de 7 sterkste voorspellers was deze reductie 25%. Ter vergelijking: correctie in onderzoeken naar TBI, in heterogene populaties, leidde tot een grotere reductie van de steekproefomvang (tot 40%). Correctie voor voorspellers is een bruikbare methode in de analysefase van trials naar TBI. **Hoofdstuk 4.2** beschrijft een meta-analyse op subgroepniveau van 6 grote trials waarin het effect van glycoproteïne-IIb/IIIa-receptorblockers vergeleken werd bij jonge en bij oudere patiënten met ACS zonder elevatie van het ST-segment (NSTE-ACS). Relatief gezien waren de gunstige effecten van het geneesmiddel hetzelfde in de twee leeftijdsgroepen. Absoluut gezien waren de gunstige effecten het grootst bij oudere patiënten; dit had te maken met een hoger absolutum basisrisico. Oudere patiënten hadden echter ook een hoger absoluut risico op ernstige bloedingen. Dit houdt in dat dit middel bij zowel oudere als jongere patiënten nuttig is, maar dat oudere patiënten zorgvuldig in de gaten moeten worden gehouden vanwege het hogere risico op bloedingen. In **hoofdstuk 4.3** onderzochten we tenslotte subgroepen van patiënten met een hoger risico op een beroerte na NSTE-ACS. We vonden dat oudere patiënten, patiënten met een eerdere beroerte en patiënten met een snellere hartslag een verhoogd risico op een beroerte hadden. Andere eerder beschreven subgroepen van patiënten met een verhoogd risico (bijvoorbeeld patiënten met diabetes of hypertensie) hadden in onze analyse geen verhoogd risico. Het model met 3 voorspellers had echter een matig onderscheidend vermogen, waardoor het moeilijk was om een beroerte te voorspellen.

**In deel 5** plaatsen we de belangrijkste bevindingen in een breder perspectief en doen we algemene aanbevelingen voor een juiste toepassing, beschrijving en interpretatie van correctie voor covariabelen en subgroepanalyse. Wij concluderen dat correctie voor covariabelen in trials een bruikbare methode is voor het vaststellen van een meer op het individu gericht behandeleffect, en dat de steekproefomvang substantieel gereduceerd kan worden door te corrigeren voor voorspellers. Voor toekomstige trials in heterogene populaties is correctie voor covariabelen aan te bevelen. In huidige trials wordt vaak subgroepanalyse toegepast, maar deze schiet vaak tekort. Uitsluitend bepaling vooraf, toetsing voor interactie en onderkenning van het ondergeschikte belang zijn essentieel om de sceptische kijk op subgroepanalysen te verbeteren. Meta-analyse op subgroepniveau van verschillende trials vergroot de power om het effect in subgroepen te meten en is aan te bevelen als standaard procedure wanneer individuele gegevens beschikbaar zijn.
Resumen

Los estudios clínicos randomizados (RCTs) son esenciales para evaluar la utilidad de tratamientos e intervenciones, y claramente influencian la práctica clínica. Estos estudios son frecuentemente hechos en poblaciones heterogéneas, tales como pacientes con daño cerebral traumático (TBI), síndromes coronarios agudos (ACS), enfermedad cerebrovascular, y cáncer. Estos pacientes son heterogéneos respecto a algunas de sus características, tales como edad, género o severidad de enfermedad. La heterogeneidad puede producir imbalance en los grupos randomizados con respecto a pronóstico, y puede diluir el efecto beneficioso de los tratamientos en algunos subgrupos de pacientes.

Sin embargo, la heterogeneidad de pacientes ofrece algunas soluciones para lidiar con estos problemas. El ajuste de covariables y el análisis de subgrupos son dos métodos usados en la fase de análisis de los estudios clínicos. El ajuste de covariables produce estimaciones ajustadas de los efectos de tratamiento que se relacionan al “paciente promedio” con un cierto perfil de riesgo. Además corrige para imbalance e incrementa el poder estadístico para detectar efectos de tratamiento significativos. El análisis de subgrupos evalúa las diferencias en los efectos de tratamiento a través de diferentes subpoblaciones de pacientes.

Nos propusimos conocer cuáles son los pros y los contras del ajuste del efecto del tratamiento para características basales de los pacientes en estudios clínicos con resultados dicotómicos; conocer cuán bien son usados, reportados e interpretados el ajuste de covariables y el análisis de subgrupos en estudios clínicos actuales; y, aplicar estos métodos en estudios clínicos con poblaciones heterogéneas. Quisimos conocer cuánto puede el ajuste para predictores importantes disminuir el tamaño de muestra en estudios clínicos en TBI, si los efectos de los bloqueadores del receptor de glicoproteína IIb/IIIa son similares en jóvenes y ancianos con ACS, y cuáles subgrupos de pacientes están en mayor riesgo de desarrollar enfermedad cerebrovascular luego de un ACS.

En la Parte 2 presentamos estudios de simulación para cuantificar el incremento del poder estadístico y la reducción del tamaño de muestra que se obtienen con el uso del ajuste de covariables en estudios clínicos con resultados dicotómicos. En el Capítulo 2.1 mostramos que el ajuste para una covariable fuerte (pre-especificada o probada) en modelos de regresión logística produjo un estimado del efecto del tratamiento más extremo, y un incremento en el poder estadístico. Con una covariable fuerte (OR entre 2 y 5) el ajuste produjo una reducción del tamaño de muestra entre 3% y 14%. Esta reducción fue independiente del la fuerza del efecto del tratamiento y del tamaño de muestra, y fue una medida resumen atractiva para expresar el beneficio obtenido con el ajuste de covariables. Cuando
ajustamos para covariables que tuvieron imbalance, el incremento del poder estadístico y la reducción del tamaño de muestra fue limitado. En el Capítulo 2.2 aplicamos la misma metodología en un estudio de simulación que consideró resultados tiempo-a-evento, analizado con el modelo de hazards proporcionales de Cox. El poder estadístico para detectar un efecto de tratamiento significativo fue mayor que sin ajuste. Las reducciones en el tamaño de muestra fueron entre 15% y 44% cuando el ajuste fue hecho para covariables fuertes (HR entre 2 y 5), y menores cuando las prevalencias de las variables fueron mas pequeñas. La reducción del tamaño de muestra fue independiente del efecto del tratamiento, del tamaño de muestra y el nivel de censura.

La Parte 3 se enfoca en el uso, reporte e interpretación del ajuste de covariables y del análisis de subgrupos en estudios clínicos de medicina interna, oncología, cardiología y neurocirugía. En el Capítulo 3.1 evaluamos estudios clínicos de medicina interna, cardiología y oncología publicados en el 2002. El ajuste de covariables fue usado en el 50% de los estudios clínicos, y las covariables predictivas fueron usadas. El análisis de subgrupos fue usado en el 50% de los estudios. Sin embargo, solo 20% usó las apropiadas pruebas de interacción, y 25% sobreenfatizó los resultados obtenidos en los subgrupos. Por lo tanto, el análisis de subgrupos pudo importantes deficiencias que pueden ser traducidas en decisiones médicas incorrectas. El Capítulo 3.2 describe la situación del análisis de subgrupos en estudios clínicos cardiovasculares publicados en 2002 y 2004. El interés en el análisis de subgrupos en este campo medico se ha incrementado dramáticamente en los últimos 20 años. Treinta y nueve de los 63 estudios reportaron análisis de subgrupos. Sólo 14 reportaron subgrupos completamente pre-especificados, 11 usaron las pruebas de interacción, y 15 sobreenfatizaron los hallazgos de los subgrupos. Estos resultados fueron peores que los reportados en el Capítulo 3.1. Así, muchos cardiólogos pueden malinterpretar los resultados de estos subgrupos, y pueden usar un tratamiento dañino en pacientes “equivocados”, y pueden restringir su uso en pacientes “correctos”. En el Capítulo 3.3 evaluamos el ajuste de covariables y el análisis de subgrupos en 18 estudios clínicos en TBI. Cinco estudios usaron el ajuste de covariables, y usaron correctamente pocos predictores. Once estudios reportaron análisis de subgrupos, pero solamente tres los pre-especificaron completamente, uno usó pruebas de interacción y cinco enfatizaron los resultados. También evaluamos si estas deficiencias en el análisis de subgrupos fueron planeadas or fueron basadas en los datos, al analizar 6 protocolos y 6 estudios disponibles. La correspondencia entre éstos fue pobre, y parece indicar la presencia de análisis post-hoc. En conjunto, el uso, reporte e interpretación del ajuste de covariables parece adecuado, pero el análisis de subgrupos tiene deficiencias evidentes.

La Parte 4 se centra en las aplicaciones clínicas del ajuste de covariables y del
análisis de subgrupos en estudios clínicos realizados en poblaciones con pacientes heterogéneos, tales como TBI y ACS. En el Capítulo 4.1 evaluamos la reducción del tamaño de muestra que podría ser obtenida cuando se ajusta para predictores importantes de resultado desfavorable en 8 estudios de TBI. Encontramos que el ajuste para los 3 predictores más fuertes produjo una reducción del tamaño de muestra del 20%, y que el ajuste para los 7 predictores más fuertes una reducción del 25%. En comparación, el ajuste de covariables en registros de TBI, con más poblaciones heterogéneas, proporcionaron una reducción mayor del tamaño de muestra (alrededor del 40%). El ajuste para predictores es una herramienta útil en la fase de análisis de estudios clínicos en TBI. El Capítulo 4.2 describe un meta-análisis de subgrupos de 6 grandes estudios clínicos, los cuales evaluaron si los efectos de los bloqueadores del receptor de glicoproteína IIb/IIIa fueron similares entre pacientes jóvenes y ancianos con ACS sin elevación del segmento ST (NSTE-ACS). Los efectos benéficos relativos de estos fármacos fueron similares a través de los subgrupos de edad, y los efectos benéficos absolutos fueron mayores en los ancianos. Esto se debió a que los ancianos tuvieron un riesgo basal más alto que el de los jóvenes. Sin embargo, los pacientes ancianos tuvieron un riesgo absoluto mayor de sangrados significativos. Así, estos fármacos son útiles en los ancianos y en los jóvenes, y el mayor riesgo de sangrado significativo garantiza un monitoreo cuidadoso en los ancianos. Finalmente, en el Capítulo 4.3 analizamos cuáles subgrupos de pacientes tuvieron un mayor riesgo de desarrollar enfermedad cerebrovascular luego de un NSTE-ACS. Encontramos que los pacientes ancianos, con una enfermedad cerebrovascular previa y con frecuencias cardíacas altas tuvieron mayor riesgo para desarrollar cualquier tipo de enfermedad cerebrovascular. Otros grupos de alto riesgo previamente descritos (por ejemplo, diabéticos, hipertensos) no estuvieron en alto riesgo en nuestro análisis. Sin embargo, el modelo construido con aquellos 3 predictores tuvo una moderada discriminación, haciendo difícil la predicción de la enfermedad cerebrovascular en estos pacientes.

Por último, en la Parte 5 pusimos los principales resultados en perspectiva, y presentamos recomendaciones generales para un uso, reporte e interpretación apropiadas del ajuste de covariables y del análisis de subgrupos. Concluimos que el ajuste de covariables es un método valioso para obtener efectos de tratamiento más individualizados en los estudios clínicos, y que reducciones substanciales en los requerimientos de tamaños de muestra pueden ser obtenidos cuando se ajusta para predictores. El ajuste de covariables debería ser recomendado para estudios clínicos futuros que incluyan poblaciones heterogéneas. El análisis de subgrupos es frecuentemente realizado en estudios clínicos actuales, pero con deficiencias importantes. La pre-especificación de los subgrupos, el uso de las pruebas de interacción, y el reconocimiento de su papel secundario son esenciales para mejoras la vision escéptica que se tiene de este tipo de análisis. El meta-análisis de
subgrupos mejora substancialmente el poder estadístico para detectar efectos en subgrupos a través de estudios clínicos, y debería ser recomendada como un procedimiento estándar cuando están disponibles datos individuales de pacientes.
Epilogue
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Curriculum Vitae

Adrián V. Hernández Díaz was born on March 9, 1973 in Lima, Peru. He graduated with honours from the high school (Colegio Salesiano de Lima) in 1989. He began his studies of medicine in 1990, and obtained his medical degree (M.D.) with honours in 1998 at the San Fernando Medical School, Universidad Nacional Mayor de San Marcos, Lima. During his time at the medical school, he was assistant teacher at the Department of Anatomy (supervisor: Dr. María Meza). He did a Residency Training in Internal Medicine between June 1999 and August 2001 at the HIV/AIDS Unit, First Service of Internal Medicine, Guillermo Almenara General Hospital, Lima (Head: Prof. Dr. Raúl Salazar Castro). He then received a scholarship from the Netherlands Organization for International Co-operation (NUFFIC) in 2001 to perform a Master of Sciences (MSc) in Clinical Epidemiology at the Netherlands Institute for Health Sciences [NIHES] (Tutor: Dr. Ewout W. Steyerberg). After his MSc. graduation in June 2002, he became research fellow at the Center for Clinical Decision Sciences, Department of Public Health, Erasmus MC Rotterdam, where he started the work described in this thesis (Promotor: Prof. Dr. Dik Habbema; Co-promotor: Dr. Ewout Steyerberg). This work was performed in close collaboration with the Thoraxcenter, Department of Cardiology (Dr. Eric Boersma), and the Department of Neurosurgery (Dr. Andrew Maas), both at Erasmus MC. He was finalist of the Young Investigators Award in Population Sciences during the 2004 European Society of Cardiology Conference, 31 August- 3 September, Munich, Germany, for his work on subgroup analysis in therapeutic cardiovascular trials. He was awarded with the best oral presentation during the 2005 Congress of the Brazilian Society of Tropical Medicine, 6-10 March, Florianópolis, Brazil, for his collaborative work on diagnosis of cerebral toxoplasmosis in AIDS patients. He is member of the Editorial Board of the PanAmerican Journal of Infectology since June 2005. In July 2005, he began his Residency Training in Pulmonary Medicine at the Department of Pneumology, Hospital General Universitario 12 de Octubre, Madrid, Spain (Head: Prof. Dr. Pedro Martín Escribano).
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