Do high-risk patients benefit from off-pump coronary artery bypass grafting to a larger extent?

Evidence from an ecological analysis of randomized trials

Running head: High-risk patients in off-pump surgery

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Abstract

Background

It is commonly believed that especially high-risk patients benefit from off-pump coronary artery bypass (OPCAB) grafting. However, analyses from several registries give different results. A common shortcoming of all those analyses is the fact that they concentrate on evidence from non-randomized trials.

Methods

In an ecological analysis, we included all randomized trials comparing the on- and off-pump technique from the most recent systematic review of Møller et al. By means of logistic regression we investigated if the effect of off-pump surgery on mortality, myocardial infarction, and atrial fibrillation is modified across the range of the three risk factors age, proportion of females and ejection fraction.

Results

Fifty-six studies with a total population of 5,171 patients reported on at least one risk factor and one outcome. We found no effect modification of the off-pump effect by age, the proportion of females, or ejection fraction.

Comment

Our ecological analysis of more than 5,000 patients from 56 randomized trials found no indication that OPCAB is more beneficial in high-risk patients. As every ecological analysis is prone to ecological bias, a definite answer on the benefit of the off-pump technique in high-risk patients can only be given by meta-analyses using individual patient data.

Introduction

It is commonly believed that especially high-risk patients benefit from off-pump coronary artery bypass (OPCAB) grafting. As early as 2005, the International Society for Minimally Invasive Cardiothoracic Surgery (ISMICS) issued a consensus statement stating that OPCAB should be considered in patients with an EuroSCORE greater than 5, age greater than 75, diabetes, renal failure, left ventricular dysfunction, left main disease, and in patients undergoing reoperation [1]. Later reviews corroborated these recommendations [2-4]. However, in our review of 35 propensity score analyses [5], we found very similar odds ratios (OR) in standard (OR 0.68 [95% CI: 0.60; 0.77]) and high-risk groups (OR 0.71 [0.66, 0.78]) in a pooled analysis for eleven short-term outcomes. A common shortcoming of all those analyses is the fact that they mostly concentrate on evidence from non-randomized trials, where treatment assignment might be biased by patient characteristics. We report here on an ecological analysis of the possible modification of the OPCAB treatment effect through risk factors. The study is exclusively based on data from randomized trials (RCTs).

Material and Methods

We included all RCTs from the most recent general systematic review of Møller et al. [6]. One of us (OK) read all studies in full text and extracted mean or median age, proportion of females, and ejection fraction. In cases where the ejection fraction was only given in categories with percentages, we assumed values evenly distributed in categories and calculated the median value from the reported figures. For all analyses, we equated means to medians to describe the average value of the respective distribution.

The risk factors age, proportion of females and ejection fraction were chosen because the Møller paper [6] suggests that the respective data are available in the majority of studies. In terms of outcomes, we concentrated on the three short-term results mortality, myocardial infarction, and atrial fibrillation. The former two were chosen because of their clinical relevance, the latter one because of its non-sparse occurrence, thus providing sufficient power for analysis. Finally, information on risk factors and outcomes were also compared to our own database of RCTs [7].

To visualize associations between outcomes and risk factors, we drew scatter plots of treatment effect (measured as relative risks) versus the average value of the risk factor from each study. To assess the modifying effect of a risk factor on the treatment effect, we calculated - similarly to Puskas et al. [4] - logistic regression models. These included the respective outcome (mortality, myocardial infarction, or atrial fibrillation) as the dependent variable. The binary variable treatment (off-pump vs. on-pump), the respective risk factor (average age, proportion of females, or ejection fraction) on a continuous scale, and the interaction of both served as independent variables. The latter interaction assesses our main hypothesis of interest, because it measures if treatment effects vary across the range of values of the respective risk factor. Additionally, our logistic regression models included a random study effect to account for the correlation of patients within the respective study. Moreover, to interpret treatment effects as relative risks and not as odds ratios, we used a log link function (instead of the standard logit link function). To facilitate interpretation, we estimated the treatment effect for a set of a priori values of the respective risk factor and included these data in the scatter plots. Finally, for each combination of risk factor and outcome, we calculated an additional logistic model without reference to the respective risk factor. This latter model gives the standard estimate for the treatment effect (assumed to be constant over the whole range of risk factors) and can be used for comparisons.

It should be noted that while all these models use outcome and treatment information on each individual patient (easily derived from the respective study's four-fold table), the value of the respective risk factor (for example age) is not available for individual patients. Instead, the average value from the respective study is used. By definition, this approach makes our study an ecological one.

All estimates are given with their 95% confidence intervals; statistical analyses were conducted with SAS®, 9.2. (SAS Institute Inc., Cary, NC, USA).

Results

Fifty-six studies with a total population of 5,171 patients reported on at least one risk factor and one outcome. Information on average age, proportion of females and ejection fraction was available in 55, 54, and 42 studies, respectively. The distribution of the average values of risk factors is depicted in Table 1. In terms of outcomes, information on mortality, myocardial infarction, and atrial fibrillation was available in 56, 44, and 29 studies, respectively. Figures 1a) to c) show the scatter plots for each combination of risk factor and outcome. As seen in the graphs, there is no effect modification by age or the proportion of females for any of the outcomes: Graphs are more or less parallel to the x-axis, indicating a constant off-pump effect across the available range of the risk factor. As expected from previous results, there is some evidence of an effect modification by EF: Smaller EF values are associated with a larger superiority of the off-pump technique.

Comment

Our ecological analysis of more than 5,000 patients from 56 randomized trials found no indication that OPCAB is more beneficial in high-risk patients. This finding is in line with our observation of similar effects in high-risk and standard populations from 35 propensity score analyses [5], but contradicts the findings of others.

Several reasons could explain the observed differences. While Puskas [4] had access to risk factor data for individual patients, we had to resort to aggregated risk factor data. It is well known that such ecological analyses are prone to the so-called “ecological fallacy”, which can occur when associations that exist on an aggregate level do not represent the true association on an individual level [8]. While this is a serious limitation of our analysis, we can also point out a definite strength: While Puskas had to rely on single-center non-randomized data, we were able to include information from nearly all of the RCTs conducted worldwide up to now.

The populations actually included are another potential reason for differences. Registries and observational studies include the entire spectrum of patients treated during the observational period, i.e. both the “healthiest” and the “sickest” patients. Randomized off-pump studies, however, continue to include healthier populations. This can be exemplified by analyzing the risk factors of patients in the RCTs: The highest median age from a single study was 70 years and the median age over all studies was 63 years. In contrast, in 2008 more than 40% of all cardiac surgical patients in Germany were older than 70 years [9]. That is, although our study covers a wide range of values for the respective outcomes, it can provide only limited evidence for the groups of highest risk at the edge of the distributions.

A definitive answer to the question under study can only be given by an individual-data-based meta-analysis that collects individual data from as many RCTs as possible. We are aware of one attempt of such an analysis from a Dutch group which was reported as a poster abstract and as “work in progress” [10]. The group collected individual 9 RCTs with >100 patients in 2004. Unfortunately, no further analyses from this data set were published. Those types of analyses and RCTs specifically designed to recruit high risk groups such as the GOPCABE Study (German Off Pump Coronary Artery Bypass in Elderly Study; ClinicalTrials.gov number: NCT00719667) will finally answer the question we were asking in the title of this manuscript.

Disclosure statement

There was no external funding for this study. Both authors had full control of the design of the study, methods used, outcome parameters, analysis of data and production of the written report.

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Table 1: Distribution of risk factors (average values) in the 56 RCTs under study.

Risk factor	**N**	**Median**	**(Min, Q1, Q3, Max)**
Age (years)	55	63.0	48.3, 61.3, 64.5, 70.0
Proportion female (%)	53	21.1	10.0, 16.0, 25.0, 39.2
EF (%)	42	63.8	47.8, 56.1, 67.4, 75.0

Figure legend:

Scatter plots for each combination of risk factor (average age, proportion of females and ejection fraction) and outcome (mortality, myocardial infarction, and atrial fibrillation). Each plot gives four pieces of information. First, each circle represents a single study with its average value of the risk factor on the x-axis and the relative risk for off-pump surgery on the y-axis. Each circle area is proportional to the overall number of patients in the respective study. For plotting the circles (but not for statistical analysis), studies with no event in one or both treatment arms were corrected by the 0.5-continuity correction.

Second, the black line gives the relative risk of the respective outcome with off-pump treatment depending on its value for the respective risk factor. These lines are allowed to vary across the range of the risk factor, indicating a potential effect modification of the off-pump effect. Third, light grey lines depict the off-pump effect (with its 95% confidence interval) as calculated from a model that assumes a constant treatment effect across the range of the risk factor. Fourth, the given p-value stems from the test on the interaction of treatment and risk factor and can be interpreted as a test for no effect modification of the risk factor.

Figure 1a: Scatter plot for the risk factor age

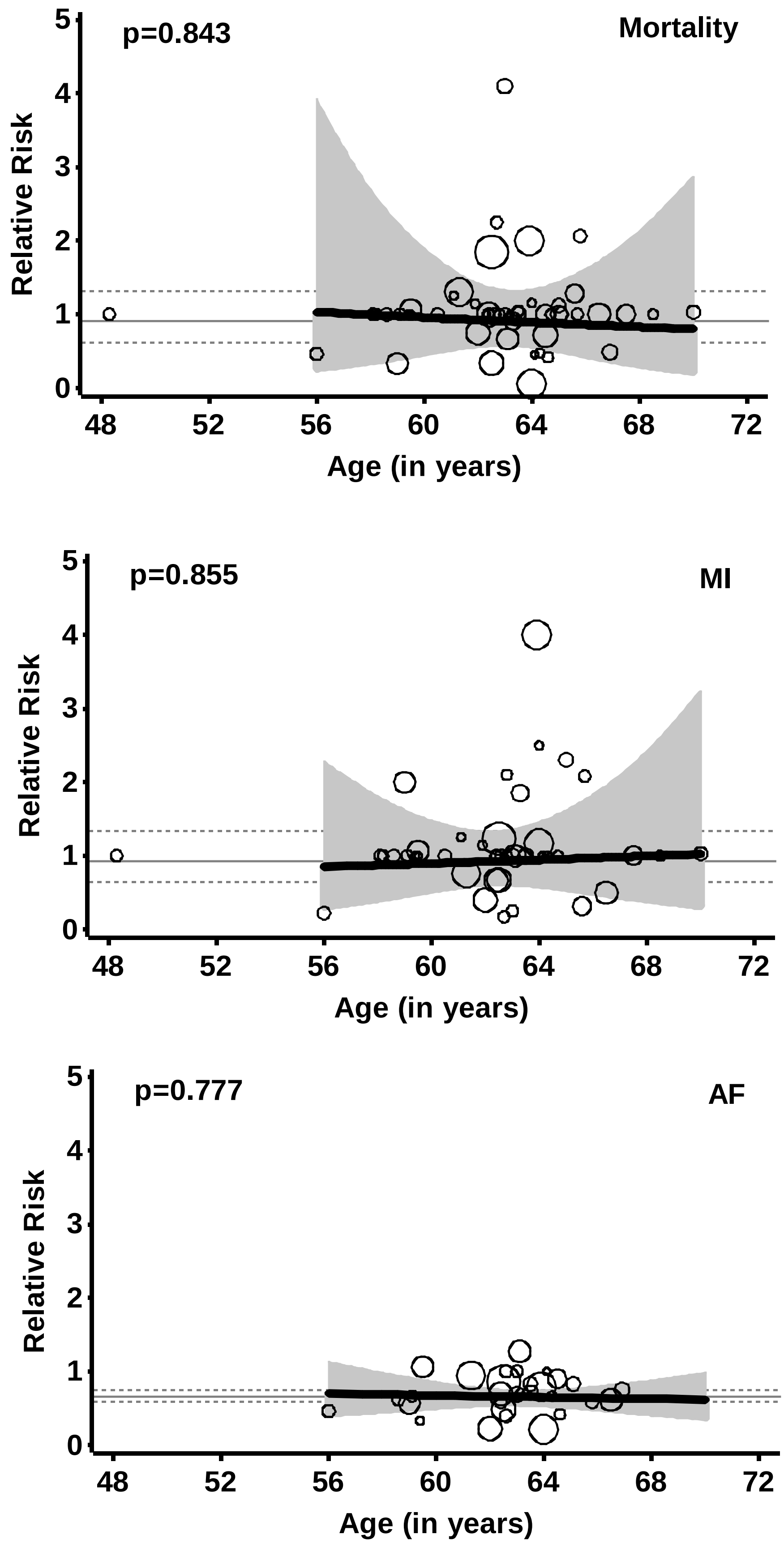

Figure 1b: Scatter plot for the risk factor proportion of females

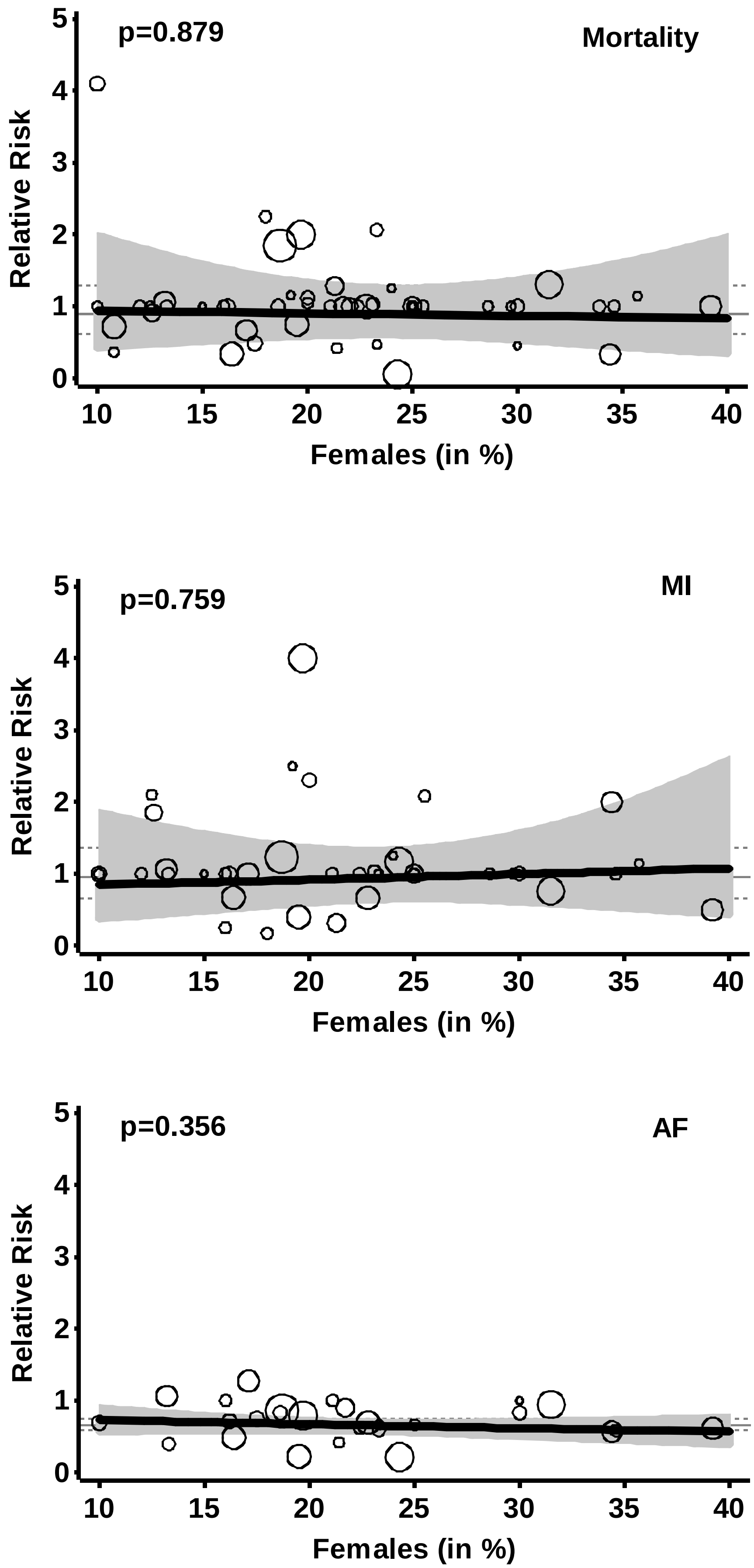

Figure 1c: Scatter plot for the risk factor EF