Clampless Off-Pump Versus Conventional Coronary Artery Revascularization
A Propensity Score Analysis of 788 Patients

Jochen Börgemann, MD; Kavous Hakim, MD; André Renner, MD; Amin Parsa, MD; Anas Aboud, MD; Tobias Becker; Marc Masshoff, MD; Armin Zittermann, PhD; Jan Fritz Gummert, MD; Oliver Kuss, PhD

Background—This study aimed to assess if clampless off-pump coronary artery bypass grafting (CABG) decreases risk-adjusted mortality, stroke rate, and morbidity in unselected patients in comparison to conventional CABG.

Methods and Results—Between July 2009 and November 2010, data of 1282 consecutive patients undergoing isolated CABG were prospectively recorded. In 30.8% (n=395), clampless off-pump revascularization was used, either with the PAS-Port automated central venous anastomosis system (n=310) or as total arterial revascularization without central anastomoses (n=85). Propensity score (PS) matching was performed based on 15 preoperative risk variables to correct for selection bias. In-hospital mortality and stroke rate as primary end point, as well as major complications and follow-up outcome of clampless off-pump (lessOPCAB) and conventional CABG (cCABG) were compared in 394 matched patient pairs (total: 788 patients). The clampless off-pump technique decreased the in-hospital rate of death (odds ratio, 0.25; 95% confidence interval, 0.05–1.18, \( P=0.080 \)) and stroke (odds ratio, 0.36; 95% confidence interval, 0.13–0.99, \( P=0.048 \)) significantly. Complications such as low cardiac output syndrome, prolonged ventilation and rethoracotomy were also reduced by lessOPCAB. Over a 2-year follow-up period overall survival, cerebrovascular and major adverse event rate were significantly lower in the lessOPCAB group, while the repeat revascularization rate was comparable.

Conclusions—In a retrospective PS-matched analysis, clampless off-pump CABG lowers mortality, stroke rate and other morbidity in an unselected group of patients with coronary artery disease. (Circulation. 2012;126[suppl 1]:S176–S182.)

Key Words: coronary artery bypass grafting ■ off-pump surgery ■ clampless ■ aortic manipulation ■ anastomotic device

Off-pump coronary artery revascularization remains hotly debated since it was introduced in the mid-90s. A working group of the American Heart Association in 2005 could not show any definitive advantage of either off-pump or conventional revascularization.1 Numerous risk-adjusted observational studies and meta-analyses did, however, demonstrate advantages of off-pump surgery. In these studies, off-pump surgery was superior in terms of hard end points such as death or stroke, and with respect to numerous surrogate end points and resource utilization.2,3 This holds particularly true for older patients4 and for patients with significant comorbidities.5 Meta-analyses of randomized studies confirm these advantages only to some extent.3,6 Two meta-analyses of randomized studies demonstrated a significant benefit of OPCAB in terms of stroke rates.7,8 The stroke incidence is reported to be in the range of 1% to 3% in the above-mentioned meta-analyses. Perioperative stroke is a devastating complication. Patients who suffer a perioperative stroke have a six-fold increased risk of developing respiratory failure and their lethality is six-fold higher.9 In on- and off-pump surgery, aortic manipulation is associated with higher rates of neurological events.10–12 By in situ mammary artery grafting, optionally combined with arterial Y- and T-grafts, and by fashioning central anastomoses with an automatic anastomotic devices, like the PAS-Port system,13 aortic manipulation can be completely avoided or minimized. Both techniques obviate aortic clamping altogether. To achieve utmost neuroprotection, we made an incremental transition to clampless off-pump revascularization during the past 2 years and report on our results in comparison to conventional revascularization with extracorporeal circulation and cardioplegic cardiac arrest. To the best of our
knowledge, this is the largest series of patients in whom the PAS-Port system was used in conjunction with the clampless technique.

Methods

Patients

Between July 2009 and November 2010, a total of 1282 patients underwent isolated coronary revascularization at our institution. Data were prospectively collected and entered into a database. Conventional coronary artery bypass grafting (cCABG) with extracorporeal circulation (ECC) and cardioplegic arrest was used in 69.2% (n=887) of patients, 30.8% (n=395) underwent clampless off-pump revascularization (lessOPCAB). Surgeons chose which method to use. All lessOPCAB procedures were performed by surgeons who used the off-pump approach in more than 80% of their cases.

Surgical Techniques

The heart was exposed through a median sternotomy. Our flexible approach to lessOPCAB included either complete arterial revascularization (n=85) with in situ mammary artery grafts, arterial Y- and T-grafts with both mammary arteries or the radial artery, or central vein graft anastomoses with the PAS-Port system (Cardica Inc, Redwood City, CA) (n=310). Central vein graft anastomoses were completed before the peripheral anastomoses. Partial aortic clamping was never used. Target vessels were immobilized with the Octopus Stabilizer (Medtronic GmbH, Meerbusch, Germany). When needed, exposure was facilitated by pericardial traction sutures. After incising the coronary arteries, 1- to 3-mm shunts (Medtronic GmbH, Meerbusch, Germany) maintained native coronary flow while completing the anastomoses. Patients were fully heparinized (target ACT ≥300 seconds) and mean arterial pressure was kept at a minimum of 60 mm Hg throughout the procedure.

A standardized protocol was followed for conventional revascularization (cCABG): After heparinization (target ACT ≥450 seconds) and aortic cannulation, a dual-stage venous cannula was placed. The ECC system comprised a roller pump (Maquet, Rastatt, Germany), a membrane oxygenator (Quadrox-i Adult, Maquet, Rastatt, Germany), and a tubing system (Romedic, Münchenberg, Germany). After aortic cross-clamping, warm Calafiore cardioplegic solution was instilled via the aortic root. Central anastomoses were constructed under partial clamping. After weaning from ECC, protamine was administered to antagonize the heparin effect.

When there was no postoperative hemorrhage, patients in the lessOPCAB and the cCABG groups received 500 mg of acetylsalicylic acid (ASA) plus high-molecular weight heparin intravenously, aiming for an aPTT of 40 to 60 seconds. On the first postoperative day, all patients were placed on 100 mg ASA orally plus weight-adjusted subcutaneous low-molecular weight heparin. Patients with central vein graft anastomoses completed with the PAS-Port device were additionally placed on 75 mg of daily oral clopidogrel for 6 months. Any preoperative ASA and/or clopidogrel regimen was continued without interruption in both groups.

Preoperative Patient Characteristics

The following preoperative variables were recorded for each patient: age, sex, body mass index (BMI), left main stenosis ≥50%, left ventricular ejection fraction (LVEF), any preoperative myocardial infarction, treated hypertension, diabetes mellitus, chronic obstructive pulmonary disease (COPD), renal failure (requiring dialysis or creatinine ≥200 mg/dL), preoperative stroke, peripheral arterial occlusive disease (PAOD) stage II or higher, number of previous cardiac surgical procedures, category (elective, urgent, emergent, last resort), and preoperative intra-aortic balloon pump (IABP) support. All 15 variables were incorporated into the propensity score model for risk-adjustment.

Categorical and Continuous Outcomes

Primary end points were death before hospital discharge and new stroke. Additional categorical outcomes were perioperative myocardial infarction (ST-segment anomalies and/or new Q waves) associated with significant troponin I elevation, low-output syndrome [cardiac index ≤2.0 L/(min×m^2 body surface area)], postoperative IABP support, artificial ventilation for ≥24 hours, new indication for postoperative dialysis, rethoracotomy, and revascularized myocardial territories (LAD, OM, RCA). Continuous outcomes were number of peripheral anastomoses, total units of packed red blood cells transfused, operative time, hours on the ventilator, days in intensive care, and duration of hospitalization.

Follow-Up

Follow-up data were reported on a standardized form completed by either the patients or by their general practitioners. We added missing data by conducting phone interviews. We defined four follow-up end points: time to death, time to death or stroke, time to a major event (death, stroke, or myocardial infarction), and time to re-revascularization (PCI or reoperation). For the combined end points, we defined the censoring time as the minimum of censoring times across end points, for time to re-revascularization we considered death a censoring event.

Statistical Analysis

Because of nonrandomized group assignment, we performed a matched propensity score (PS) analysis14 to assess treatment effects. A logistic regression model including all the covariates from Table 1 was used to estimate the PS. The fit of this model was checked with the Hosmer-Lemeshow test and the first two diagnostics proposed by Rubin.15 Following recommendations in the current literature, 1:1 matching was performed with the logit-transformed PS. For this, an optimal-matching algorithm with a caliper width of 0.2 standard deviations of the linear predictor was used. Balance of risk factors was judged by standardized differences.16 A rule of thumb suggests that the balance is satisfactory when the standardized difference is less than 10%. To measure the treatment effect, we calculated odds ratios for binary and differences of means for continuous end points. For the follow-up end points, we used methods of survival analysis. We give Kaplan-Meier plots for each end point, accompanied by an estimate of the hazard ratio from a Cox regression model. All analyses adjusted for PS pair matching by using conditional methods, that is, conditional logistic regression, linear mixed models and stratified Cox models for binary, continuous, and survival end points, respectively. Parameter estimates are given with their 95% confidence intervals and the probability value of the respective test testing for a zero treatment effect. For the follow-up end points we also performed a sensitivity analysis by calculating Cox regression models with all confounders from Table 1 as covariates. These analyses used the whole sample of 1282 patients, and can be compared with the follow-up results from the PS-matched subsample. All calculations were performed with SAS 9.2 (SAS Institute Inc, Cary, NC).

Results

Table 1 summarizes the preoperative patient variables before and after creating matched pairs. Between July 2009 and November 2010, a total of 1282 patients underwent isolated coronary revascularization, 887 (69.2%) with cCABG and 395 (30.8%) with lessOPCAB. Propensity score adjusted matching resulted in 394 pairs not differing in terms of their preoperative risk factors; all standardized differences were below 10%. The propensity score model showed an extraordinary goodness of fit (Hosmer-Lemeshow test: P=0.78), and distributions of the estimated propensity scores in both treatment groups were extremely similar: differences in PS means (Rubin’s first diagnostic) were 0.02% and the ratio of PS variances (Rubin’s second diagnostic) was 0.993.

Table 2 depicts the results for the categorical and continuous outcomes of the matched subgroups. Benefits of les-
sOPCAB were found for the primary end points lethality and stroke rate. Combining both end points reveals a 3.7-fold risk of death or stroke associated with conventional surgery (95% confidence interval [CI], 1.5–9.0).

The rates of low-output syndrome and rethoracotomy are significantly reduced. There was also a trend toward artificial ventilation being less frequent after lessOPCAB. Significant improvements were found for all continuous outcomes except for duration of hospitalization. The table also shows the difference between means (DBM) as a quantitative measure for differences between groups. Contrary to other authors, we found a minimally smaller number of peripheral anastomoses with conventional surgery, and no differences in the frequency of revascularization of the 3 coronary artery beds.

The Figure depicts the Kaplan-Meier analyses for the follow-up. Mean follow-up was 492 days (range, 2–867). As can be seen in Table 3, there were 13 deaths in the off-pump and 27 deaths in the on-pump group (hazard ratio [HR], 0.39; 95% CI, 0.19–0.80; P=0.010) in the PS matched subsample. Both the primary combined end point of death or stroke (HR, 0.58; 95% CI, 0.34–1.00; P=0.050) and MACCE (HR, 0.62; 95% CI, 0.37–1.02, P=0.061) differed significantly between groups for the follow-up period. No difference between groups was found with respect to re-revascularization rates (HR, 0.74; 95% CI, 0.40–1.38; P=0.345).

Table 3 also gives the results of the sensitivity analysis for the follow-up outcomes in the complete sample (n=1282). The results of these Cox models are remarkably similar to those from the PS-matched subsample.

**Discussion**

This propensity score analysis shows that clampless OPCAB lowers lethality and the rates of perioperative stroke and other complications in comparison to conventional revascularization. Numerous retrospective and randomized studies support this finding. In a recent meta-analysis of PS-adjusted studies on 123 137 patients, we demonstrated that off-pump surgery significantly lowers mortality and stroke rate (OR [95% CI]: 0.69 [0.60–0.75], 0.42 [0.33–0.54], respectively). Observational studies published by Mishra, Racz, and Mack revealed similar results. In addition, the most recent meta-analysis of randomized studies on a total of 8961 patients showed a 30% reduction of the relative stroke risk in the
off-pump group.7 Perioperative stroke prolongs duration of artificial ventilation, stay in intensive care and total hospital stay, but is most detrimental to cardiac surgical patients because of the associated lethality increase.9–20 These facts are corroborated by our study: after a perioperative stroke, lethality plus stroke, in-hospital death, they needed 93 [95% CI: 19–167] extra days in intensive care unit. The underlying mechanisms emerged as the only independent risk factor for stroke.11

Emmert et al12 compared on-pump with off-pump surgery and off-pump with partial clamping with clampless off-pump surgery (using the HEARTSTRING device). An off-pump no-touch TAR group served as gold standard. The stroke rate in the on-pump group was the same as that of the off-pump with partial clamping group (2.4% and 2.3%) and there was no difference between the clampless HEARTSTRING and the no-touch TAR groups (0.7% and 0.8%).12 The latter two studies support the concept that avoiding aortic manipulation lowers the neurological event rate in off-pump surgery, a hypothesis supported by 2 additional observations: First, a study using transcranial Doppler ultrasonography in off-pump patients showed significantly more solid microemboli with partial clamping than in 2 patient groups who underwent clampless surgery with the use of an automated device for constructing proximal anastomoses.21 The second observation relates to the chronologic distribution of strokes22: Strokes occur on the average on the second postoperative day after on-pump and on the 4th postoperative day after off-pump procedures. The earlier occurrence supports the hypothesis that strokes have intraoperative causes including micro- and macro-embolization, whereas strokes that happen at a later time are more likely due to coagulation disorders or atrial

### Table 2. Primary End Points and Categorical and Continuous Outcomes After Propensity Score Matching

<table>
<thead>
<tr>
<th></th>
<th>lessOPCAB (n = 394)</th>
<th>cCABG (n = 394)</th>
<th>OR [95% CI]</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Categorical outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lethality, n (%)</td>
<td>2 (0.5)</td>
<td>8 (2.0)</td>
<td>0.25 [0.05–1.18]</td>
<td>0.080</td>
</tr>
<tr>
<td>Stroke, n (%)</td>
<td>5 (1.3)</td>
<td>14 (3.6)</td>
<td>0.36 [0.13–0.99]</td>
<td>0.048</td>
</tr>
<tr>
<td>Combined primary endpoints: lethality plus stroke, n (%)</td>
<td>6 (1.5)</td>
<td>22 (5.6)</td>
<td>0.27 [0.11–0.67]</td>
<td>0.005</td>
</tr>
<tr>
<td>Perioperative Myocardial infarction, n (%)</td>
<td>3 (0.8)</td>
<td>6 (1.5)</td>
<td>0.50 [0.13–2.00]</td>
<td>0.327</td>
</tr>
<tr>
<td>Low output syndrome, n (%)</td>
<td>17 (4.3)</td>
<td>31 (7.9)</td>
<td>0.53 [0.29–0.98]</td>
<td>0.042</td>
</tr>
<tr>
<td>Postoperative IABP, n (%)</td>
<td>11 (2.8)</td>
<td>16 (4.1)</td>
<td>0.67 [0.30–1.48]</td>
<td>0.321</td>
</tr>
<tr>
<td>Artificial ventilation ≥24 h, n (%)</td>
<td>22 (5.6)</td>
<td>35 (8.9)</td>
<td>0.62 [0.36–1.06]</td>
<td>0.083</td>
</tr>
<tr>
<td>New-onset dialysis, n (%)</td>
<td>9 (2.3)</td>
<td>16 (4.1)</td>
<td>0.56 [0.25–1.27]</td>
<td>0.167</td>
</tr>
<tr>
<td>Rethoracotomy, n (%)</td>
<td>9 (2.3)</td>
<td>26 (6.6)</td>
<td>0.35 [0.16–0.74]</td>
<td>0.006</td>
</tr>
<tr>
<td>LAD territory grafting, n (%)</td>
<td>379 (96.2)</td>
<td>379 (96.2)</td>
<td>1.00 [0.49–2.05]</td>
<td>1.000</td>
</tr>
<tr>
<td>OM territory grafting, n (%)</td>
<td>288 (73.1)</td>
<td>284 (72.1)</td>
<td>1.06 [0.77–1.45]</td>
<td>0.744</td>
</tr>
<tr>
<td>RCA territory grafting, n (%)</td>
<td>234 (59.4)</td>
<td>207 (52.5)</td>
<td>1.32 [1.00–1.75]</td>
<td>0.054</td>
</tr>
<tr>
<td><strong>Continuous outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral anastomoses, n</td>
<td>2.7±0.8</td>
<td>2.6±0.8</td>
<td>−0.1 [−0.2 to 0.0]</td>
<td>0.019</td>
</tr>
<tr>
<td>Units of PRBCs transfused, n</td>
<td>4.1±3.8</td>
<td>6.5±10.3</td>
<td>2.3 [1.2–3.5]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Operative time, min</td>
<td>174.8±38.0</td>
<td>179.6±47.1</td>
<td>4.8 [−1.2 to 10.7]</td>
<td>0.119</td>
</tr>
<tr>
<td>Duration of artificial ventilation, h</td>
<td>14.5±38.2</td>
<td>25.7±89.7</td>
<td>11.1 [1.5–20.8]</td>
<td>0.024</td>
</tr>
<tr>
<td>Duration of stay in the intensive care unit, d</td>
<td>1.8±2.9</td>
<td>2.5±5.3</td>
<td>0.8 [0.2–1.3]</td>
<td>0.013</td>
</tr>
<tr>
<td>Duration of hospitalization, d</td>
<td>12.3±7.2</td>
<td>12.3±5.5</td>
<td>0.0 [−0.9 to 0.8]</td>
<td>0.954</td>
</tr>
</tbody>
</table>

**DBM** indicates difference between means; OR, odds ratio; LAD, left anterior descending coronary artery; OM, obtuse marginal branch; RCA, right coronary artery.
fibrillation. With the PAS-Port system, we were able to bring the relative stroke risk down by 60% in the clampless group. Safety and satisfactory midterm patency rates of central anastomoses constructed with this system were demonstrated in a randomized study. The numbers of bypass grafts per patient as well as the frequency of revascularization for the coronary beds were indistinguishable between the lessOP-CAB and cCABG group in our study.

In addition to lower lethality and stroke rates, we found additional advantages of the clampless off-pump technique: Perioperative complications such as low-output syndrome, rethoracotomy rate and resource utilization were significantly decreased, findings supported by risk-adjusted observational studies. The results of these analyses contradict, at least in part, published randomized studies and meta-analyses of these studies. The latter did not reveal group differences with respect to the hard end points lethality, low-output syndrome, respiratory and renal failure. Whether risk-adjusted observational studies or randomized, controlled trials (RCTs) are superior in providing the clearest conclusions on true treatment value is currently under debate: Randomization can control known and unknown risk factors, ensuring complete internal validity. Disadvantages of RCTs include patient selection, that is, they do not represent the typical day-to-day patient population, and have insufficient power for detecting differences between infrequent events. Observational studies, on the other hand, represent large unselected populations with high external validity, but are limited because they are based on statistical models designed for risk-adjustment, which cannot correct for all possible confounders. It is commonly believed that such population differences between observational studies and RCTs are the reason for apparent differences between treatment effects. Interestingly enough, we actually found similar treatment effects, for example, effects independent of the study type, after meta-matching patients of 28 PS-adjusted with those of 51 randomized off-pump studies. Overcoming the shortcomings of RCTs, however, requires off-pump RCTs in populations with higher risks and thereby both higher event rates and stronger treatment effects on the chosen end points. The risk factors in our PS matched population (1) are not very different from those of the total population (“all comers”) (Table 1) and (2) define a high-risk group as compared with patients typically studied in RCTs.

In summary, our risk-adjusted study confirms that clampless off-pump surgery, either by means of complete arterial revascularization or with central anastomoses fashioned with an anastomotic device, significantly lowers stroke rate and lethality in comparison to conventional revascularization. In light of today’s increasingly older patient populations with

![Figure](http://circ.ahajournals.org/)

**Figure.** Estimated probability of freedom from death (A), freedom from death or stroke (B), freedom from MACCE (death, stroke, or myocardial infarction, C), and freedom from re-revascularization (D). **Black lines** indicates clampless off-pump; **gray lines**, conventional coronary artery bypass grafting; HR, hazard ratio.
more comorbidities, clampless off-pump surgery should become the preferred approach.

**Study Limitations**

This study has limitations which require further discussion: In 80% of patients in the clampless off-pump group, the PAS-Port system was used to fashion the proximal vein graft anastomoses. Such anastomoses are supported by a stent. In addition to ASA, patients in this group were also put on clopidogrel for 6 months. Risk adjusted observational studies on patients who received clopidogrel after CABG have demonstrated that in patients status post myocardial infarction, clopidogrel lowers mortality, rate of myocardial infarction, and risk of stroke.27 Contrary to these findings, 2 RCTs comparing the use of ASA plus placebo versus ASA plus clopidogrel post CABG failed to demonstrate differences between the rate of major cardiovascular events or occluded grafts.28,29 Another RCT on 249 patients showed a significantly better vein graft patency rate in the clopidogrel group after 3 months.30 Although we did not find that the re-revascularization rates differed between groups, we cannot completely rule out that some of the study results in the clampless off-pump might not have been affected by the use of clopidogrel. Controlled studies are needed to further investigate the role of ASA and clopidogrel in the perioperative phase. Independent of this, future studies need to take all adjuvant pharmacological treatment into account to enable appropriate adjustments when analyzing follow-up data.

That all procedures in this study were performed by surgeons highly experienced in off-pump revascularization could be considered another limitation. One could therefore question the degree to which the study results can be generalized. The significant impact of surgeon volume on outcome has been demonstrated for cardiovascular procedures in general31 as well as for on-pump CABG.32 Current publications show that surgeon volume also affects outcome in off-pump surgery as illustrated by the results published by LaPar et al,33 who clearly demonstrated the impact of surgeon volume on mortality after off-pump CABG: The threshold was 50 procedures per year. In our study, all clampless off-pump as well as all on-pump procedures were performed by very experienced surgeons (case load 200 per year). Off-pump procedures were only performed by surgeons who used this challenging technique in 80% of their CABG cases. Therefore, the surgeon who performed a case is no longer a large confounding factor, that is, the interaction of surgical expertise with the respective technique is minimized. Distorted results secondary to inexperienced surgeons performing the cases are a common concern.34 We aimed to minimize this factor in our study.

**Acknowledgments**

The authors thank A. Kempa-Haupt, C. Schmidtke-Busse, and B. Peters for their excellent assistance and data collection.

**Disclosures**

None.

**References**

1. Sellke FW, DiMaio JM, Caplan LR, Ferguson TB, Gardner TJ, Hiratzka LF, Isselbacher EM, Lytle BW, Mack MJ, Murkin JM, Robbins RC. Comparing on-pump and off-pump coronary artery bypass grafting: numerous studies but few conclusions: a scientific statement from the American Heart Association council on cardiovascular surgery and anesthesia in collaboration with the interdisciplinary working group on...
Clampless Off-Pump Versus Conventional Coronary Artery Revascularization: A Propensity Score Analysis of 788 Patients
Jochen Börgermann, Kavous Hakim, André Renner, Amin Parsa, Anas Aboud, Tobias Becker, Marc Masshoff, Armin Zittermann, Jan Fritz Gummert and Oliver Kuss

_Circulation_. 2012;126:S176-S182
doi: 10.1161/CIRCULATIONAHA.111.084285

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2012 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/126/11_suppl_1/S176

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org//subscriptions/