p = 0.0177) after TAVI in patients with severe than nonsevere MAC. However, no significant difference in mortality was observed at 5 years (6 patients [35%] vs 7 patients [23%], HR 2.63, 95% CI 0.87 to 7.93, p = 0.084) likely owing to few surviving patients (Figure 1).

There is growing evidence that MAC is because of progressive atherosclerotic calcification and shares the traditional coronary artery disease risk factors.[1,5] Although echocardiography is the most common imaging modality to diagnose MAC, it lacks reproducible objective measures for classification and quantitation.[6] Both echocardiography and CT are prone to artifacts, but CT offers the ability to identify important landmarks, quantify MAC and its extension into the myocardium and onto the leaflets, and measure predicted left ventricular outflow tract area after implantation of a heart valve prosthesis.

Our study demonstrates a comprehensive MAC quantification score that is predictive of all-cause mortality in patients with symptomatic severe aortic valve stenosis who underwent TAVI that overcoming the current limitation of echocardiogram and the current calcium scoring system with maximum grading of >400 Hounsfield units (grade 4). This is a pilot study with small sample size and further validation with a larger patient cohort is needed and it is unknown whether the increased mortality associated with MAC would be reduced by valve-in-MAC procedures. Our MAC score is designed to quantitatively measure the total burden of MAC and its distribution. Thus, different from the Guerrero MAC score, which accurately predicts valve embolization risk for valve-in-MAC procedures.[2]

In conclusion, this study provides further evidence that total MAC burden is useful in risk stratification of patients with severe MAC who underwent TAVI.

### Disclosures

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1. Abramowitz Y, Kazuno Y, Chakravarty T, Kawamori H, Maeno Y, Anderson D, Allison Z, Mangat G, Cheng W, Gopal A, Jilaihawi H, Mack MJ, Makkar RR. Concomitant mitral annular calcification and severe aortic stenosis: prevalence, characteristics and outcome following transcatheter aortic valve replacement. *Eur Heart J* 2017;38:1194–1203.
2. Guerrero M, Wang DD, Pursnani A, Eleid M, Khalique O, Urena M, Salinger M, Kodali S, Kaptzan T, Lewis B, Kato N, Cajigas HM, Wendler O, Holzhey D, Pershad A, Witzke C, Alnasser S, Tang GHL, Grubb K, Reisman M, Blanke P, Leipsic J, Williamson E, Pellikka PA, Pislaru S, Crestanello J, Himbert D, Vahanian A, Webb J, Hahn RT, Leon M, George I, Bapat V, O'Neill W, Rihal C. A cardiac computed tomography-based score to categorize mitral annular calcium severity and predict valve embolization. *JACC Cardiovasc Imaging* 2020;13:1945–1957.
3. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol* 1990;15:827–832.
4. Barasch E, Gottdiener JS, Larsen EKM, Chaves PHM, Newman AB, Manolio TA. Clinical significance of calcification of the fibrous skeleton of the heart and aortosclerosis in community dwelling elderly. The cardiovascular health study (CHS). *Am Heart J* 2006;151:39–47.
5. Allison MA, Cheung P, Criqui MH, Langer RD, Wright CM. Mitral and aortic annular calcification are highly associated with systemic calcified atherosclerosis. *Circulation* 2006;113:861–866.
6. Silbiger JJ. Mitral annular calcification and calcific mitral stenosis: role of echocardiography in hemodynamic assessment and management. *J Am Soc Echocardiogr* 2021;34:923–931.

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### Effect on Morbidity and Mortality of Direct Oral Anticoagulants in Patients With COVID-19

The COVID-19 pandemic has caused millions of cases and deaths, resulting in a public health emergency. It is well established that 1 of the complications of infections in critically ill patients is disseminated intravascular coagulation. This complication is driven by the activation of multiple systemic coagulation and inflammatory responses.[1] From the beginning of the pandemic, early reports from Wuhan showed that patients with COVID-19 experienced abnormal coagulation, demonstrated by abnormal prothrombin time and partial thrombin time and elevated D-dimer.[1] Furthermore, several studies showed that patients with COVID-19 with high D-dimer had worse outcomes and severe clinical courses.[2] Presently, venous thromboembolism (VTE) prophylaxis is recommended for all patients with COVID-19 who are admitted to the hospital.[1] Consequently, it was very important to establish whether oral preparation of VTE prophylaxis can prevent severe and fatal COVID-19 outcomes among patients with COVID-19. The following databases: PubMed, ScienceDirect, Google Scholar, and medRxiv were searched up to September 16 2021, using "COVID-19" and "oral anticoagulation" and their related medical subject headings terms. Studies were included if they were cohort or case control in design, included patients with COVID-19, compared between patients on direct oral anticoagulants (DOACs) before COVID-19 diagnosis and control group in terms of COVID-19 severity and mortality, and adjusted for confounding variables. The exposure of interest was the use of DOACs before COVID-19 infection regardless of the type of the used DOACs and the outcome of interest was COVID-19 severity and mortality. COVID-19 mortality was defined as death and COVID-19 severity was defined as mechanical ventilation and intensive care unit (ICU) admission. The quality of the included studies was assessed using the Newcastle-Ottawa scale for observational studies. The adjusted odds ratio (OR) and adjusted hazard ratio (HR) and its related 95% confidence interval (95% CI) were pooled using the random effects model using Meta XL, version 5.3 (EpiGear International, Queensland, Australia). Cochran Q heterogeneity test and $I^2$ statistic were performed to estimate the heterogeneity. The search yielded 3,474 articles; after deduplication and applying the inclusion criteria, 5 articles[3–6] were included in the data

extraction (Figure 1). The total number of patients with COVID-19 in the included articles was 148,027. Of them, 70.5% (104,429/148,031) were previous DOAC users and the rest were controls. The quality of all of the included studies was good (9/9). Furthermore, 0.4% (400/104,429) of patients taking DOAC developed severe or fatal COVID-19 infection. In comparison, 4.9% (2,126/43,602) of controls developed severe or fatal COVID-19 infection. The analysis of the HRs showed that DOAC use was significantly associated with reduced risk of COVID-19 severity and mortality (HR 0.69, 95% CI 0.57 to 0.84; Figure 2) and the heterogeneity of this model was insignificant ($I^2 = 0\%$, $p = 0.52$). In the OR model, DOAC use was significantly associated with a reduced risk of COVID-19 severity and mortality (OR 0.50, 95% CI 0.33 to 0.76; Figure 3) and the heterogeneity of this model was insignificant ($I^2 = 0\%$, $p = 0.69$). Our analysis models revealed that patients who used DOACs before COVID-19 infection had a significant reduction by 50% and 31% in the risk of ICU admission, mechanical ventilation, and death because of COVID-19. This result was similar across all of the included studies except 1.[3] It was well established that COVID-19 increases the risk for both arterial and venous thrombosis. Several studies showed that patients in the ICU with COVID-19 had higher incidence of VTE compared with matched patients in the ICU who were COVID-19-negative.[7] Similarly, patients with acute respiratory distress syndrome because of COVID-19 experienced more VTE than their counterparts who had acute respiratory distress syndrome but were COVID-19 negative.[8] Consequently, it was important to conduct studies that assess the benefits and risks of the use of anticoagulants. A large cohort study showed that patients with COVID-19 who received prophylactic anticoagulants had lower 30-day mortality with no increase in the risk for bleeding compared with patients who did not receive prophylactic anticoagulants.[9] In contrast, the ACTIV (Accelerating COVID-19 Therapeutic Interventions) trial did not support using anticoagulants agents in treating nonhospitalized patients with COVID-19.[10] Yet,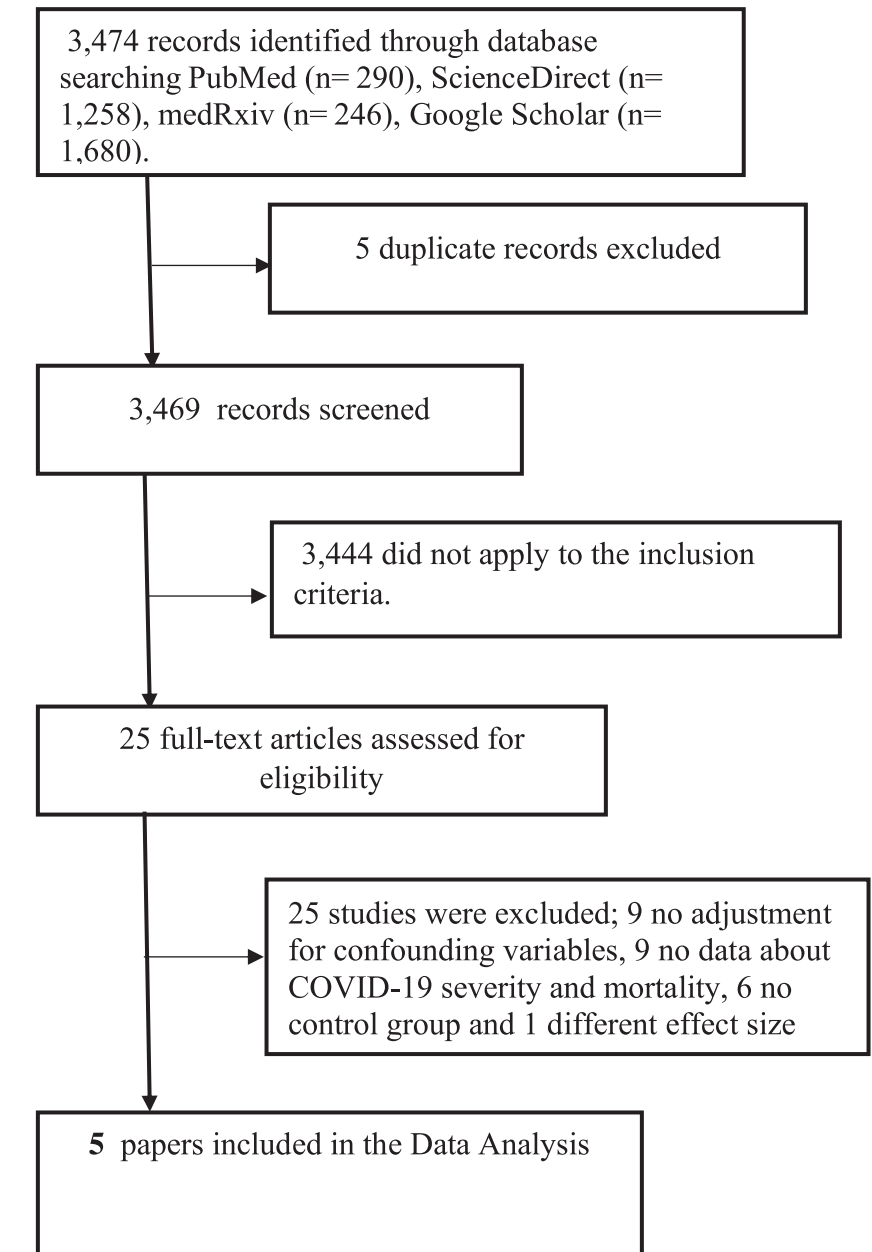 the trial did not recruit patients with elevated risk for thromboembolic events or deaths and therefore was underpowered to assess the effect of anticoagulants on patients with COVID-19. This indicates that using anticoagulants among patients with COVID-19 should be considered according to the clinical picture. Accordingly, the relative impact of anticoagulants could be enhanced using the CHADS score which is a nonspecific tool but shown to be prognostic in patients with COVID-19.[11] Because our meta-analysis included data from a large number of patients with COVID-19 who use DOACs, taken from 5 studies, and all of them were adjusted extensively for multiple potential confounding factors—the findings can be considered reliable. Our findings suggest a reduction in COVID-19 mortality and severity among patients with COVID-19 with previous use of DOACs. This supports the evidence that VTE is a very important prognostic factor among patients with COVID-19. Also, this substantiates the benefits of DOAC use in improving the outcomes of several diseases. However, much is left to be determined about which dose of DOAC is the most beneficial and when to start the therapy among patients with COVID-19. This
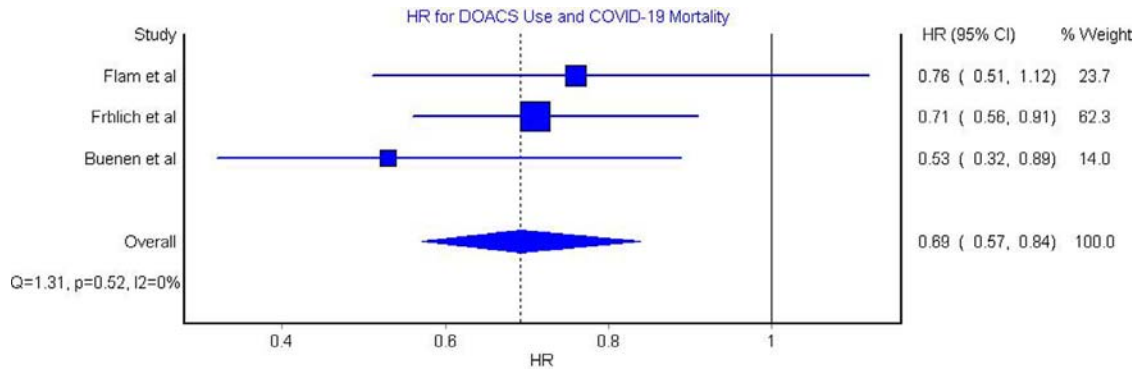


Figure 1. Flow chart

Figure 2.  Hazard Ratio for the Association between DOACS use and COVID-19 Severity and Mortality.
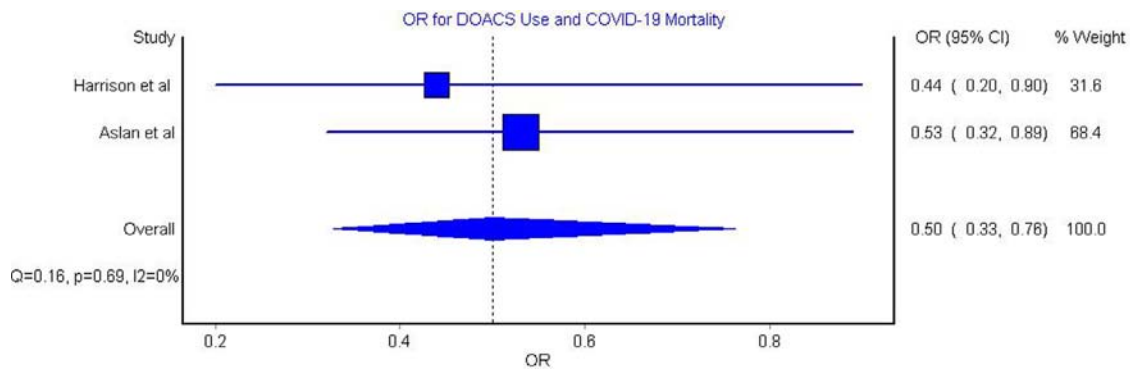


Figure 3.  Odds Ratio for the Association between DOACS use and COVID-19 Severity and Mortality.

necessitates the need for more data from well-designed prospective studies and clinical trials to support our results.

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1. Connors JM, Levy JH. COVID-19 and its implications for thrombosis and anticoagulation. *Blood* 2020;135:2033–2040.
2. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H, Cao B. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study [published correction appears in *Lancet* 2020;395:1038] [published correction appears in *Lancet* 2020;395:1038]. *Lancet* 2020;395:1054–1062.
3. Flam B, Wintzell V, Ludvigsson JF, Mårtensson J, Pasternak B. Direct oral anticoagulant use and risk of severe COVID-19. *J Intern Med* 2021;289:411–419.
4. Harrison RF, Forte K, Buscher MG Jr, Chess A, Patel A, Moylan T, Mize CH, Werdmann M, Ferrigno R. The association of preinfection daily oral anticoagulation use and all-cause in hospital mortality from novel coronavirus 2019 at 21 days: a retrospective cohort study. *Crit Care Explor* 2021;3:e0324.
5. Buenen AG, Sinkeldam M, Maas ML, Verdonschot M, Wever PC. Prior use of anticoagulation is associated with a better survival in COVID-19. *J Thromb Thrombolysis* 2021;52:1207–1211.
6. Aslan B, Akyüz A, Işık F, Çap M, İnci Ü, Kaya İ, Karahan MZ, Aktan A, Bilge Ö, Özbek M, Altıntaş B, Boyraz B. The effect of chronic DOAC treatment on clinical outcomes of hospitalized patients with COVID-19. *Int J Clin Pract* 2021;75:e14467.
7. Klok FA, Kruip MJHA, van der Meer NJM, Arbous MS, Gommers DAMPJ, Kant KM, Kaptein FHJ, van Paassen J, Stals MAM, Huisman MV, Endeman H. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res* 2020;191:145–147.
8. Helms J, Tacquard C, Severac F, Leonard-Lorant I, Ohana M, Delabranche X, Merdji H, Clere-Jehl R, Schenck M, Fagot Gandet F, Fafi-Kremer S, Castelain V, Schneider F, Grunebaum L, Anglés-Cano E, Sattler L, Mertes PM, Meziani F, CRICS TRIGGER-SEP Group (Clinical Research in Intensive Care and Sepsis Trial Group for Global Evaluation and Research in Sepsis). High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. *Intensive Care Med* 2020;46:1089–1098.
9. Rentsch CT, Beckman JA, Tomlinson L, Gellad WF, Alcorn C, Kidwai-Khan F, Skanderson M, Brittain E, King JT Jr, Ho YL, Eden S, Kundu S, Lann MF, Greevy RA Jr, Ho PM, Heidenreich PA, Jacobson DA, Douglas IJ, Tate JP, Evans SJW, Atkins D, Justice AC, Freiberg MS. Early initiation of prophylactic anticoagulation for prevention of coronavirus disease 2019 mortality in patients admitted to hospital in the United States: cohort study. *BMJ* 2021;372:n311.
10. Connors JM, Brooks MM, Sciurba FC, Krishnan JA, Bledsoe JR, Kindzelski A, Baucom AL, Kirwan BA, Eng H, Martin D, Zaharris E, Everett B, Castro L, Shapiro NL, Lin JY, Hou PC, Pepine CJ, Handberg E, Haight DO, Wilson JW, Majercik S, Fu Z, Zhong Y, Venugopal V, Beach S, Wisniewski S, Ridker PM, ACTIV-4B Investigators. Effect of antithrombotic therapy on clinical outcomes in outpatients with clinically stable symptomatic COVID-19: the ACTIV-4B randomized clinical trial. *JAMA* 2021;326:1703–1712.
11. Ruocco G, McCullough PA, Tecson KM, Mancone M, De Ferrari GM, D'Ascenzo F, De Rosa FG, Paggi A, Forleo G, Secco GG, Pistis G, Monticone S, Vicenzi M, Rota I, Blasi F, Pugliese F, Fedele F, Palazzuoli A. Mortality risk assessment using CHA(2)DS

(2)-VASc scores in patients hospitalized with coronavirus disease 2019 infection. *Am J Cardiol* 2020;137:111–117.

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## Characteristics, Acute Results, and Prognostic Impact of Percutaneous Coronary Interventions in Spontaneous Coronary Artery Dissection (from the Prospective Spanish Registry on SCAD [SR-SCAD])

A conservative management strategy, without percutaneous coronary intervention (PCI), has been recommended as the standard treatment in patients with spontaneous coronary artery dissection (SCAD).[1,2] However, in special scenarios (unstable patients or lesions causing a compromised coronary flow), PCI seems to be a more reasonable option. Nevertheless, no pure prospective information is available focusing on the analysis of the acute results and long-term outcomes of PCI in this challenging scenario.

The Spanish Registry on SCAD (NCT03607981) prospectively included cases of SCAD from 34 university hospitals.[3] From June 2015 to December 2020, a total of 429 patients were included. After core laboratory angiographic analysis at the coordinator center, 40 patients were excluded. Finally, 389 patients (441 narrowings) were included in this study. All events (major adverse cardiac or cerebrovascular event [MACCE]) were adjudicated by a blinded Clinical Events Committee. Eighty-eight percent of patients were women, with a median age of 53 years (interquartile range [IQR] 47 to 60). A non−ST-segment elevation myocardial infarction (54%) was the most frequent clinical presentation. On angiography, the left anterior descending coronary artery was most frequently affected (44%), with lesions predominantly involving distal territories (38%) or secondary branches (54%). A long intramural hematoma (IMH), type 2 lesion of the angiographic classification of Saw et al,[4] was the most frequent angiographic pattern (61%). Twenty-six percent of the lesions had an initial reduced thrombolysis in myocardial infarction (TIMI) flow (0 to 1). Most patients were initially managed conservatively, with only 84 patients (22%) who underwent PCI as initial strategy. When these 2 initial strategies were compared, no differences were observed regarding gender, age, and distribution of risk factors. However, patients that required PCI presented more frequently as ST-segment elevation myocardial infarction (58% vs 35%, p <0.001), with lesions affecting more frequently proximal segments (29% vs 9%, p <0.001) or the left main (8% vs 0.7%, p <0.001). A type 2 IMH angiographic pattern was less frequently seen in patients who underwent PCI (45% vs 66%, p <0.001). In contrast, patients who underwent PCI presented more severe lesions (diameter stenosis 89 ± 18% vs 76 ± 20%, p <0.001) with worse coronary flow (TIMI 0 to 1, 51% vs 21%, p <0.001). The main reason for the operator to perform PCI was the presence of an initial TIMI 0 to 1 flow (36%), followed by the presence of ongoing ischemia (33%) and proximal coronary segment involvement (27%). The most frequently applied strategy was drug-eluting stent implantation (66%), followed by plain balloon angioplasty (13%) or bioresorbable scaffold implantation (11%). The median number of devices implanted was 2 (IQR 1 to 2). Regarding the impact of PCI on coronary flow, a worsening of distal coronary flow related to the procedure was infrequent (only 2% showed a reduction in final TIMI flow). Importantly, however, an improvement in coronary flow compared with baseline ≥1 TIMI grade was achieved in 50% of the cases, and 78% of the cases without a change in flow corresponded to patients with initial TIMI 3 flow. Conventional PCI success (final TIMI flow 2 to 3 and residual stenosis <30% after stent implantation or <50% after balloon angioplasty) was obtained in 54% of the cases, but PCI success according to "flow criterion" (improvement in TIMI flow ≥1 grade with final TIMI flow 2 to 3) was 84%. In 37% of the cases, there were complications related to PCI, including the extension of the SCAD after stent implantation (19%), after passage of the intracoronary wire (9%) or after balloon dilatation (2%); iatrogenic dissections (6%), loss of a side branch ≥1.5 mm (4%), or coronary perforation (2%). After PCI, visible residual angiographic dissection flaps or IMH images persisted at the distal vessel in 62% of the cases.

Despite the described higher-risk clinical profile and the high rate of PCI-related complications, no significant differences in a predefined in-hospital MACCE (all-cause death, nonfatal reinfarction, unplanned revascularization, or stroke) were found between groups (9% vs 5%, p = 0.1599). Similarly, from prospectively collected data from 355 patients who completed a follow-up ≥6 months, no differences in MACCE were found at late follow-up (median time 29 months, IQR 17 to 38) (17% vs 12%, p = 0.2510) (Figure 1).
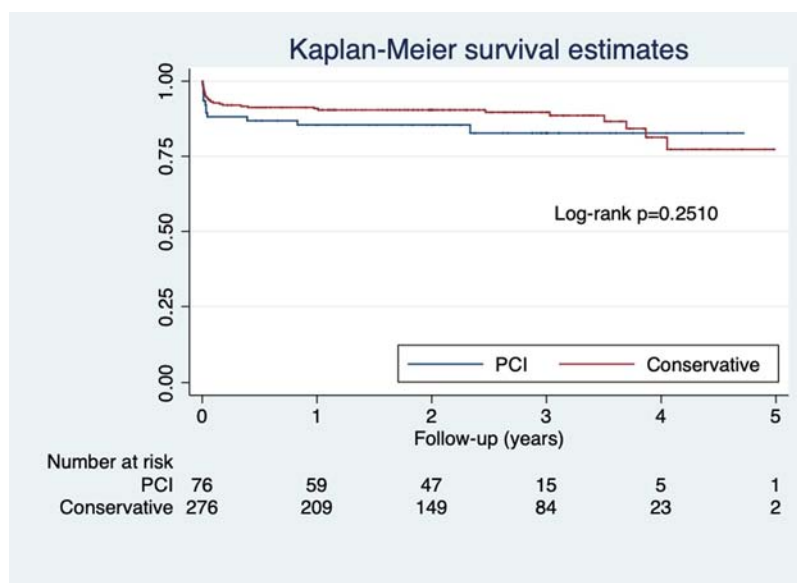


Figure 1. MACCE-free survival curves estimated by the Kaplan−Meier method according to the initial treatment strategy (PCI vs conservative management).