Angioplasty Guided by Intravascular Ultrasound: Meta-Analysis of Randomized Clinical Trials

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Abstract

Background: The impact of intravascular ultrasound (IVUS) use on stenting has shown inconclusive results.

Objective: Systematic review and meta-analysis of the impact of IVUS on stenting regarding the clinical and angiographic evolution.

Methods: A search was performed in Medline/Pubmed, CENTRAL, Embase, Lilacs, Scopus and Web of Science databases. It included randomized clinical trials (RCTs) that evaluated the implantation of stents guided by IVUS, compared with those using angiography alone (ANGIO). The minimum follow-up duration was six months and the following outcomes were assessed: thrombosis, mortality, myocardial infarction, percutaneous and surgical revascularization, major adverse cardiovascular events (MACE) and restenosis. The binary outcomes were presented considering the number of events in each group; the estimates were generated by a random effects model, considering Mantel-Haenszel statistics as weighting agent and magnitude of effect for the relative risk (RR) with its respective 95% confidence interval (95%CI). Higgins I^2 test was used to quantify the consistency between the results of each study.

Results: A total of 2,689 articles were evaluated, including 8 RCTs. There was a 27% reduction in angiographic restenosis (RR: 0.73, 95% CI: 0.54-0.97, I^2 = 51%) and statistically significant reduction in the rates of percutaneous revascularization and overall (RR: 0.88; 95% CI: 0.51 to 1.53, I^2 = 61%, RR: 0.73, 95% CI: 0.54 to 0.99, I^2 = 55%), with no statistical difference in surgical revascularization (RR: 0.95, 95%CI: 0.52-1.74, I^2 = 0%) in favor of IVUS vs. ANGIO. There were no differences regarding the other outcomes in the comparison between the two strategies.

Conclusion: Angioplasty with stenting guided by IVUS decreases the rates of restenosis and revascularization, with no impact on MACE, acute myocardial infarction, mortality or thrombosis outcomes. (Arq Bras Cardiol. 2013;101(2):106-116)

Keywords: Heart Failure; Angioplasty; Coronary Artery Disease / ultrasonography; Randomized Controlled Trials as Topic; Meta-Analysis.

Introduction

The intravascular ultrasound (IVUS) is an invasive access technique that allows the dynamic acquisition of tomographic imaging, *in vivo*, of the vascular lumen and wall, being considered one of the best invasive imaging methods for the analysis of characteristics (qualitative and quantitative) of coronary atherosclerosis[1,2].

In theory, the use of IVUS could improve the long-term results of angioplasty with stent implantation. These better results derive from at least three factors: the confirmation that there is no significant residual stenosis or that artery dissection did not occur; definite identification and removal of the calcified plaque that limits stent expansion; visualization of an optimal luminal gain.

Studies that evaluated the potential benefit of percutaneous procedures guided by IVUS, when compared with those that used only angiography (ANGIO) in reducing restenosis, were inconclusive in demonstrating greater efficacy[3-9].

In addition, more recent data suggests that the use of IVUS can prevent thrombosis of drug-eluting stents[10].

Performing percutaneous interventions for the implantation of drug-eluting stents guided by IVUS, which allow the identification and subsequent treatment of risk factors for in-stent restenosis, as well as for early thrombosis, remains a controversial issue when compared to the performance of percutaneous interventions guided by ANGIO.

In the last decade, several randomized studies investigated the routine use of IVUS in stent implantation; however, the results have been inconclusive[3-9].

In this study, we evaluated the impact of the routine use of IVUS in stenting through a systematic review with meta-analysis, regarding the clinical and angiographic evolution.

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Manuscript received October 28, 2012, revised manuscript November 24, 2012, accepted march 06, 2013

DOI: 10.5935/abc.20130131

Method

This study followed the guidelines for performing systematic reviews proposed by the Cochrane Collaboration, as well as other recommendations for systematic reviews[11-13].

We focused on randomized controlled trials (RCTs) that compared coronary angioplasties with stenting using IVUS, with angioplasties guided by angiography only (ANGIO), with a follow-up period of at least six months.

The following outcomes were assessed: thrombosis, mortality, acute myocardial infarction (AMI), percutaneous and surgical revascularization, restenosis and major adverse cardiovascular events (MACE), according to the definition of each study. Despite minor variations on the definition of MACE, most studies defined them as the combined endpoint of mortality (AMI) and the need for any other revascularization procedure during follow-up. Whenever possible, and when reported by the studies, clinical outcomes that comprised the combined endpoint were evaluated individually.

Article search was carried out comprehensively in the following electronic databases: Medline / Pubmed, CENTRAL, Embase, Lilacs, Scopus and Web of Science. There was no language restriction and the databases were searched from the date of availability up to November 2010. Previous reviews were consulted for identification and possible addition of other relevant studies.

The strategies were designed, whenever possible, using the controlled vocabulary of subject key words (Mesh / Medline, Emtree / Embase and DeCs / BVS). In addition, we used Word text words, synonyms and syntaxes combined with the Boolean operators "OR" for addition and "AND" for list of terms. The subject key words of the MESH / Medline strategy were sensitized by the addition of the "entry terms".

The main terms used in the search were: "Ultrasonography", "Ultrasonography, Interventional", "Coronary Artery Disease", "Angioplasty", "Coronary Angiography", "Coronary Angiography, transluminal percutaneous" and their equivalent in Portuguese language.

The filter used for the identification of randomized clinical trials only was prepared by Cochrane, with high sensitivity.

The sum of the database article search totaled 2,689 articles. Initially, 518 references were excluded, as they were in duplicate. The remaining 2,171 references had their eligibility confirmed by reading titles and abstracts (when available).

Two independent reviewers performed the selection. Articles suggestive of inclusion or that did not have an Abstract, but had suggestive titles, went to the next step of eligibility assessment through full-text reading.

At this phase, 57 articles had their eligibility assessed by reading the article in full-text form and guided by a standardized clinical record. When articles were excluded, the reasons for exclusion were recorded. Eight articles were selected for data extraction (Figure 1).

Statistical analysis was performed in two steps using the Metaview module of the Review Manager software program (RevMan 2000), created by Cochrane Collaboration[11]. At the first step, the descriptive analysis of baseline characteristics of patients was performed, as well as definitions of outcomes and interventions used. The binary outcomes were obtained considering the number of events in each group. For binary outcomes, the estimates were generated by a random effects model, considering Mantel-Haenszel statistics as weighting agent and the magnitude of effect for the relative risk (RR) with its respective 95% confidence interval (95%CI).

To quantify the consistency between the results of each study, we used the test of inconsistency (I2) of Higgins.

The evaluation of the study quality involved an adequate random allocation sequence, blinding of investigators, blinding of participants, blinding of outcomes and use of intention-to-treat analysis.

The results were reported as "yes" "no", "unclear" and "not reported" and a qualitative assessment of the table generated by this information was performed. The quality of evidence generated by the meta-analysis for each outcome was assessed using the program GRADE profiler release 3.2.

For each outcome, the quality of evidence was evaluated by observing five aspects: (1) limitation of the study design; (2) consistency of results; (3) direct evidence; (4) precision; (5) potential publication bias.

Results

The results are shown and discussed in the tables and charts of meta-analyses. The characteristics of the included studies are shown in Table 1.

The mortality outcome was assessed in all studies[6,7,9,14-18]. It was observed that IVUS-guided angioplasty were associated with a non-significant increase of 54% in mortality due to all causes: RR: 1.54, 95% CI: 0.85-2.78, I2 = 0 % (Figure 2). The quality of evidence evaluated by Grade was moderate, due to the fact that the effect estimates varied more than 25% between studies.

Seven articles[6,7,14-18] assessed the AMI outcome. As not all the articles precisely defined the type of AMI, we chose in this study to describe the overall results, including those AMI with and without Q-wave. The performance of IVUS-guided angioplasty was associated with a nonsignificant reduction of 27% in AMI (RR: 0.73; 95%CI: 0.43–1.16; I2=12%) (Figure 3).

The quality of evidence evaluated by Grade was low because the effect estimates varied more than 25% between studies and the study with the highest weight in the meta-analysis showed an opposite trend of effects, when compared to the other included studies, therefore generating inconsistency.

It was not possible to analyze the outcomes using target-lesion revascularization (TLR) and target-vessel revascularization (TVR) terminology, because definitions varied between studies. Furthermore, some studies indicated results in which the decrease in the number of revascularizations was highly significant, but without specifying whether the revascularization was surgical or percutaneous, as well as in which artery it was performed. Thus, we chose a more generic analysis, specified by type of intervention/procedure. Revascularization procedure was considered as the outcome, either surgical or by angioplasty.

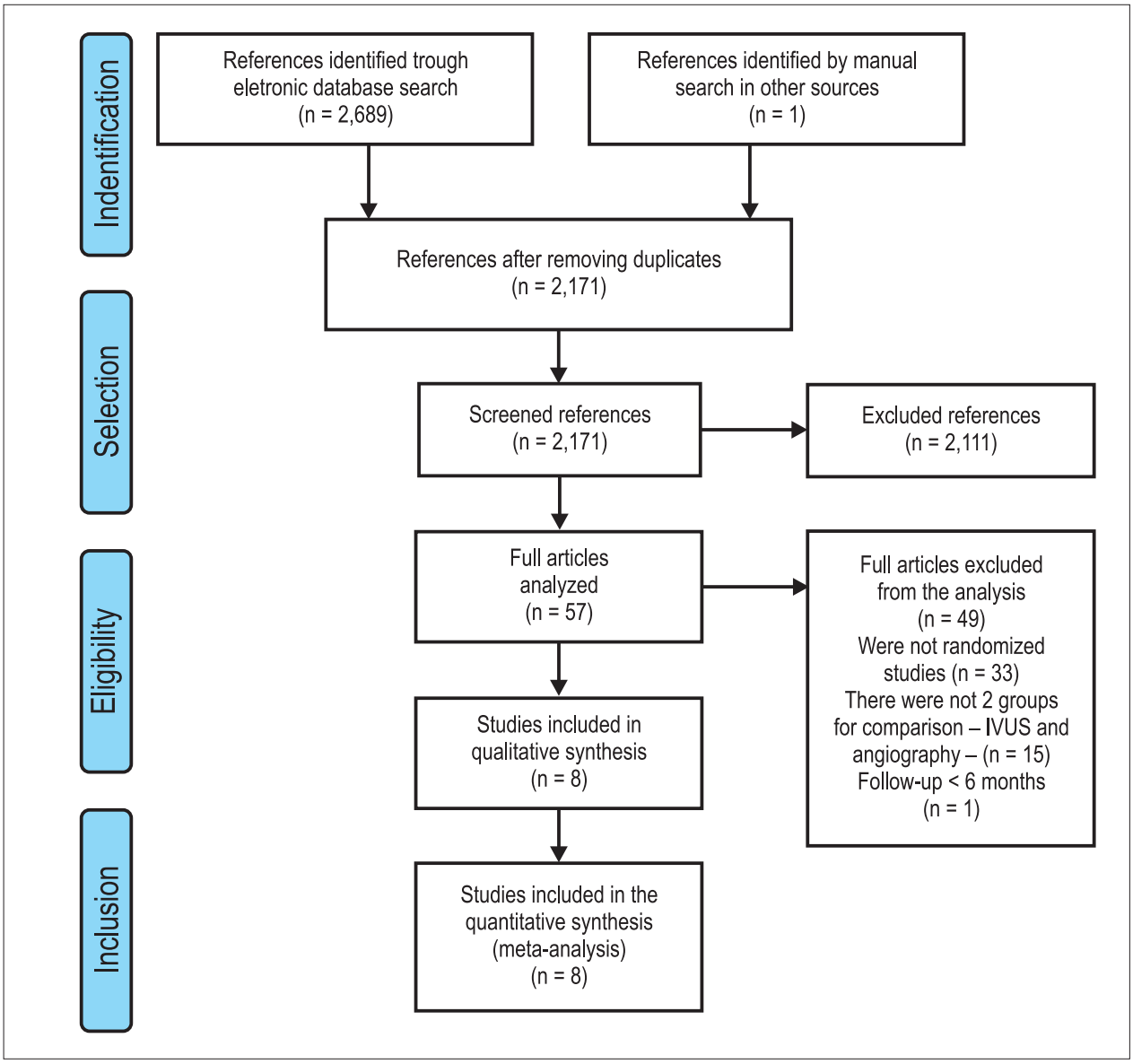

Figure 1 - *Flowchart of included studies.*

There was a statistically significant reduction of 27% in the number of revascularizations in angioplasty guided by IVUS group (RR: 0.73, 95%CI: 0.54-0.99, I2 = 55%). There was also a non-significant reduction of revascularizations by angioplasty in the IVUS group (RR: 0.88, 95% CI: 0.51-1.53, I2 = 61% (Figure 4).

The quality of evidence evaluated by Grade was moderate because the confidence intervals did not completely overlap between studies.

MACE were reported in seven studies[6,7,14-18], with the AVID study also including the clinical outcome of stent thrombosis, which was not included in the others.

There was a non-significant reduction in MACE of 14% in the group with IVUS-guided angioplasty (RR: 0.86, 95%CI: 0.70-1.07, I2 = 55%) (Figure 5).

The quality of evidence evaluated by Grade was moderate because the confidence intervals did not completely overlap between studies.

Two studies[15,16] reported the thrombosis outcome. IVUS-guided angioplasty was associated with a nonsignificant reduction of 10% in cases of thrombosis (RR: 0.90, 95% CI: 0.37-2.22, I2 = 0%) (Figure 6).

The quality of evidence evaluated by Grade was low because the two studies that reported this outcome showed opposite trends of effect measurement and only two studies reported data for this outcome.

Six studies[6,7,9,14,17,18] reported the angiographic restenosis outcome. We detected a nonsignificant reduction of 27% in angiographic restenosis in the group with IVUS-guided angioplasty (RR: 0.73, 95%CI: 0.54-0.97, I2 = 51%) (Figure 7).

Table 1 – Characteristics of included studies regarding population, stent type and time of follow-up

Study, year	Patients(n) IVUS/Angio	Population	Stent	Time of follow-up	MACE Definition	Clinical events reported
Schiele et al[9], 1998	79/76	Patients with CAD who had ischemia in one or more native vessels with > 70% stenosis in the target lesion, who underwent PTCA followed by stenting	Palmaz-Schatz, AVE MicroStent, NIR Scimed, Freedom Global Therapeutic	6 months	Not evaluated	Death , angiographic restenosis
Frey et al[14], 2000	121/148	Patients undergoing elective or urgency angioplasty or primary angioplasty in vessel with diameter from 2.2 to 4.6 mm	Provisional stent: Palmaz-Schatz	Angiographic: 6 months; Clinical: 24 months	Death, AMI, new angioplasty, surgical revascularization	MACE, death, AMI, angiographic restenosis, TLR
Mudra et al[6], 2001	273/275	Patients with angina or ischemia documented in lesion < 25 mm in length treated with 1 or 2 stents in artery with diameter > 2.5 mm	JJIS double spiral bridge, Power Grip, Crown stent or NIR	Angiographic: 6 months. Clinical: 12 months	Death, AMI, nova angioplasty, Surgical revascularization	Death, AMI, new angioplasty, surgical revascularization. MACE, angiographic restenosis
Gaster et al[17], 2003	54/54	Male patients with stable angina with *de novo* lesions in native coronary arteries with indication for PTCA	Not reported	Angiographic: 6 months, Clinical: 60 months	Death, AMI, new angioplasty, surgical revascularization	Death, AMI, new angioplasty, surgical revascularization. MACE, angiographic restenosis, TLR
Oemrawsingh et al[7], 2003	73/71	Patients undergoing elective PTCA in *de novo* lesions > 20 mm in length in native arteries that allowed stent placement with > 3 mm in diameter	AVE GFX-XL (Medtronic/AVE)	Angiographic and clinical: 6 months.	Death, AMI, TLR	MACE, death, AMI, TLR, angiographic restenosis
Gil et al[18], 2007	83/80	Patients with stable angina, with 1 or 2 *de novo* lesions, with reference vessel diameter > 2.75 mm and length > 25 mm	Not reported	6 months	Death, AMI, any new revascularization	MACE, death, AMI, TLR, TVR, angiographic restenosis
Russo et al[16], 2009	369/375	Patients selected for elective PTCA in native arteries or bypass grafts, who could receive one or more stents, with distal reference vessel diameter > 2.5 mm	Palmaz-Schatz, SCIMED NIR, Cordis Crown, AVE MicroStent II, ACS Rx MultiLink	12 months	Death, AMI, TLR	MACE, death, AMI, TLR, surgical revascularization
Jakabcin et al[15], 2010	105/105	Patients with complex lesions or type B2 and C lesions according to AHA, proximal lesions in the left anterior descending artery, trunk lesions, reference vessel with diameter < 2.5 mm, lesions > 20 mm in length, in-stent restenosis , insulin-dependent diabetic patients and acute coronary syndromes	Drug-eluting stents	18 months	Death, AMI, TLR	MACE, death, AMI, TLR, stent thrombosis

IVUS: intravascular ultrasound; Angio: angiography-guided stenting; PTCA: percutaneous transluminal coronary angioplasty, MACE: major adverse cardiac events, AMI: acute myocardial infarction; TLR: target lesion revascularization, TVR: target vessel revascularization.

Discussion

This meta-analysis demonstrated that angioplasty with stenting guided by IVUS, when compared with those without IVUS, are associated with a significant reduction in the need for new revascularizations and occurrence of angiographic restenosis, also showing a nonsignificant reduction in MACE, myocardial infarction and stent thrombosis outcomes. However, they were associated with a non-significant increase in mortality from all causes.

The evaluation of the restenosis outcome was performed in six studies[6,7,9,14,17,18]. The occurrence of angiographic restenosis was lower in the group with IVUS-guided angioplasty in five of these studies. The reduction in restenosis ranged from 64%[18] to 18%[14].

Suboptimal stent expansion resulted in reduced cross-sectional stent area observed at IVUS, being one of the most important predictors of restenosis after bare-metal stent implantation[19].

Considering these findings, several studies have assessed whether the routine use of IVUS during stent implantation would result in clinical benefit, thus leading to the reduction of in-stent restenosis rate.

The first of these studies was a multicenter study that compared angioplasty guided by IVUS or ANGIO. The benefit of using IVUS was observed in the early phase of the study, when the group that used IVUS had a higher post-dilatation when using larger balloons (restenosis at six months was 9.2% vs. 22%, $p = 0.04$). However, there was no difference in angiographic restenosis at six months, in the late phase of the study, when an approach with lower post-dilation was used due to the changes in the definition of optimal stent expansion (22% vs. 23.7%, $p = 1.0$). Despite being a non-randomized observational study, it demonstrated for the first time that stenting guided by IVUS could result in a strategy that would improve patient outcome[3].

Then, several small prospective studies indicated the superiority of the IVUS-guided angioplasty over angioplasty guided by ANGIO, with a reduced restenosis rate at the six-month follow-up.

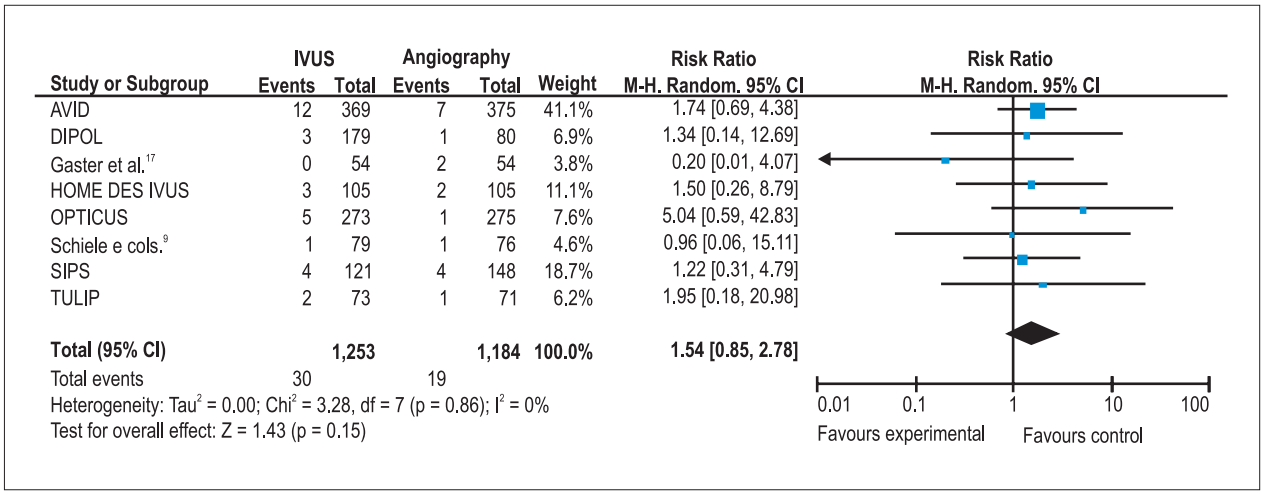

Figure 2 - *Meta-analysis of angioplasties guided or not by IVUS, on the death outcome, with inclusion of all studies.*

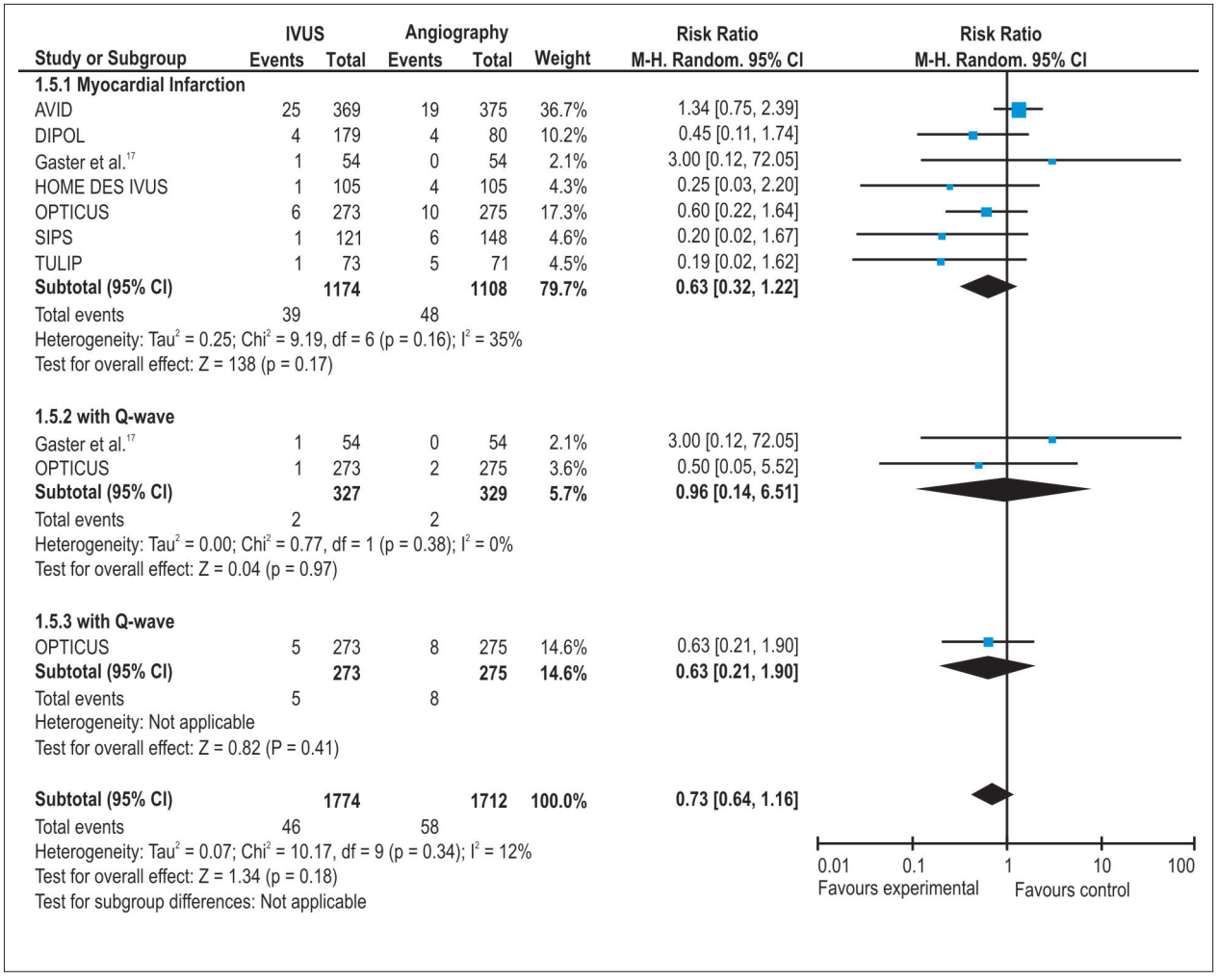

Figure 3 - *Meta-analysis of angioplasties guided or not by IVUS, on the acute myocardial infarction outcome, with inclusion of seven studies.*

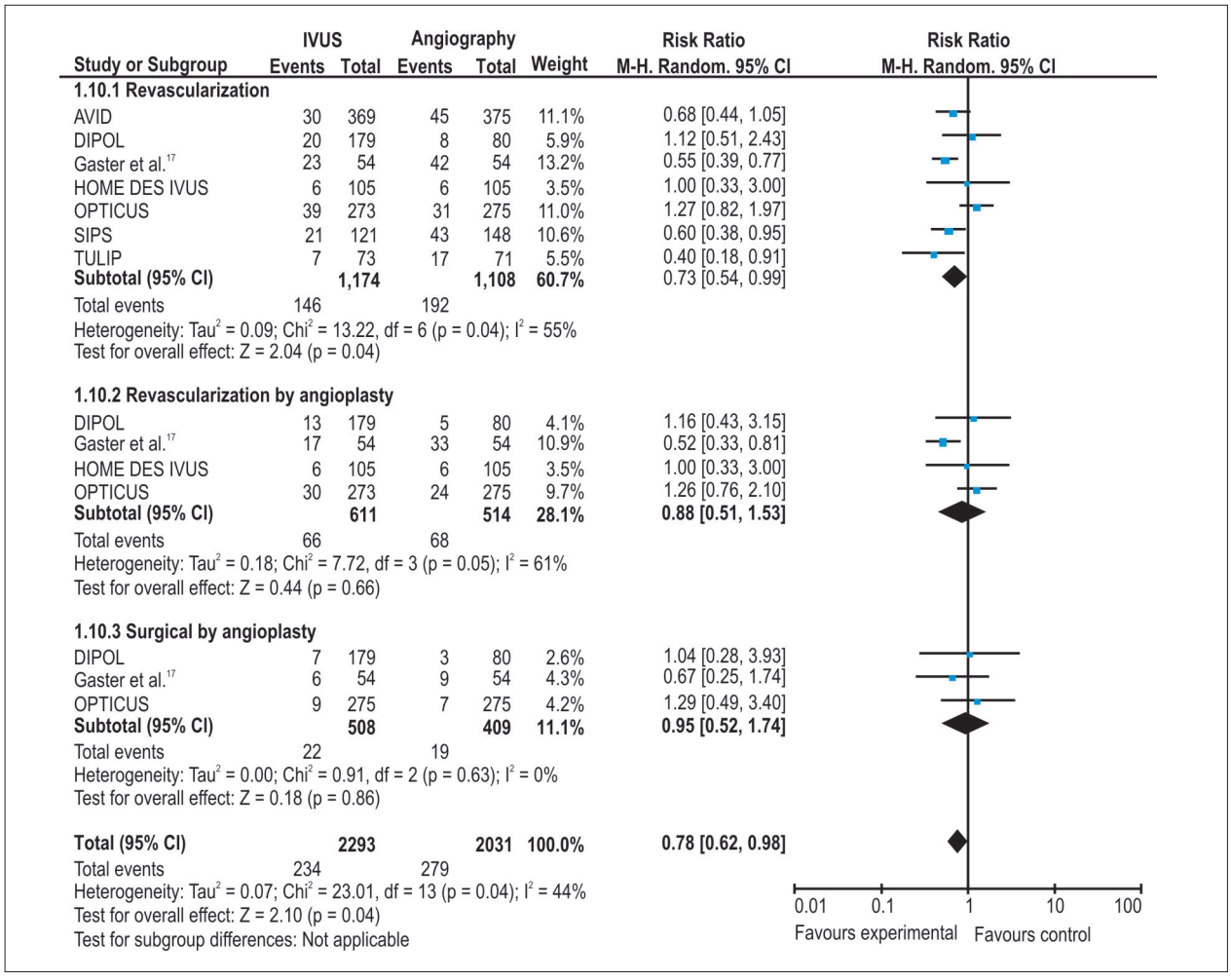

Figure 4 - *Meta-analysis of angioplasties guided or not by IVUS, on the revascularization outcome, with inclusion of seven studies.*

The RESIST (REStenosis after IVUS-guided Stenting) study was the first randomized study to investigate the impact of IVUS on the evolution of patients undergoing ANGIO. Although it analyzed only 155 patients, the study reported a tendency to a lower rate of restenosis at the six-month follow-up in the group that underwent angioplasty guided by IVUS[9].

These results were also observed by Blasini et al[4], who showed a significant reduction in the rate of restenosis at the six-month follow-up of patients that used IVUS (20.9% vs. 29.9%, p = 0.03), with the difference being particularly important in the group that met criteria for optimal stent release, when compared to those that did not meet these criteria (13.6% vs. 28.3%, p = 0.04)[4].

The OPTICUS (OPTimization with IVUS to reduce stent restenosis) study was the largest randomized study to evaluate the use of IVUS to reduce the rate of in-stent restenosis. The primary study objective was the rate of in-stent restenosis, the lowest luminal diameter and percent of stenosis at the six-month follow-up. The secondary objective was the rate of MACE at six and twelve months of follow-up. No difference was observed in any of the objectives between the two groups, suggesting the non-superiority of IVUS use in stenting[6].

The TULIP (The Thrombocyte activity evaluation and effects of Ultrasound guidance in Long Intracoronary stent Placement) study[7] randomly compared stent implantation guided by IVUS or ANGIO in long lesions (> 20 mm). Benefits were observed in the IVUS-guided group, which was considered at high risk for in-stent restenosis. In general, these studies did not clearly report that the routine use of IVUS in stenting was able to reduce in-stent restenosis rates.

These results are probably related to certain factors observed in these studies, such as the role of high-pressure insufflation to prevent inadequate stent expansion (which is related to restenosis), which was gradually incorporated into clinical practice, thus reducing potential IVUS benefits.

Drug-eluting stents are superior to bare-metal ones regarding restenosis rates and subsequent revascularization procedures[8,20].

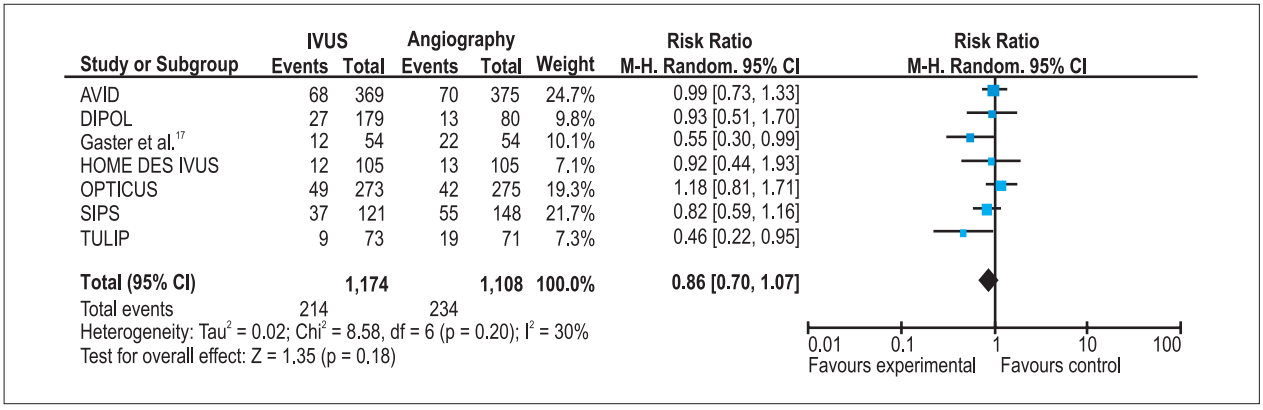

Figure 5 - *Meta-analysis of angioplasties guided or not by IVUS, on the MACE outcome, with inclusion of seven studies.*

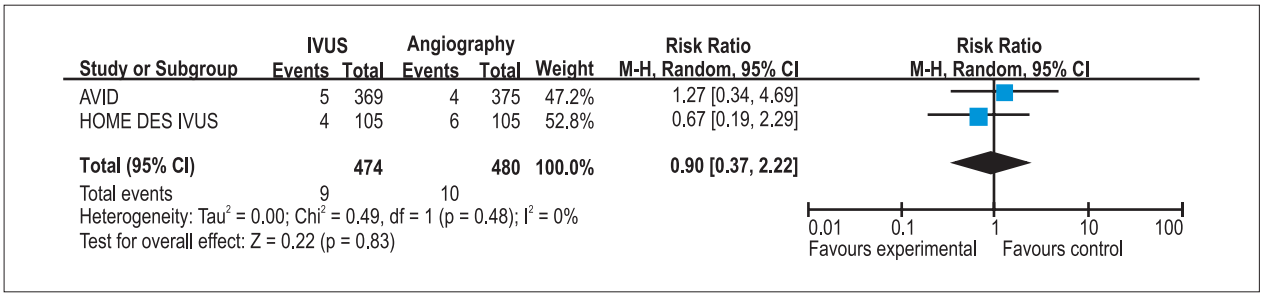

Figure 6 - *Meta-analysis of angioplasties guided or not by IVUS, on the thrombosis outcome, with inclusion of two studies*

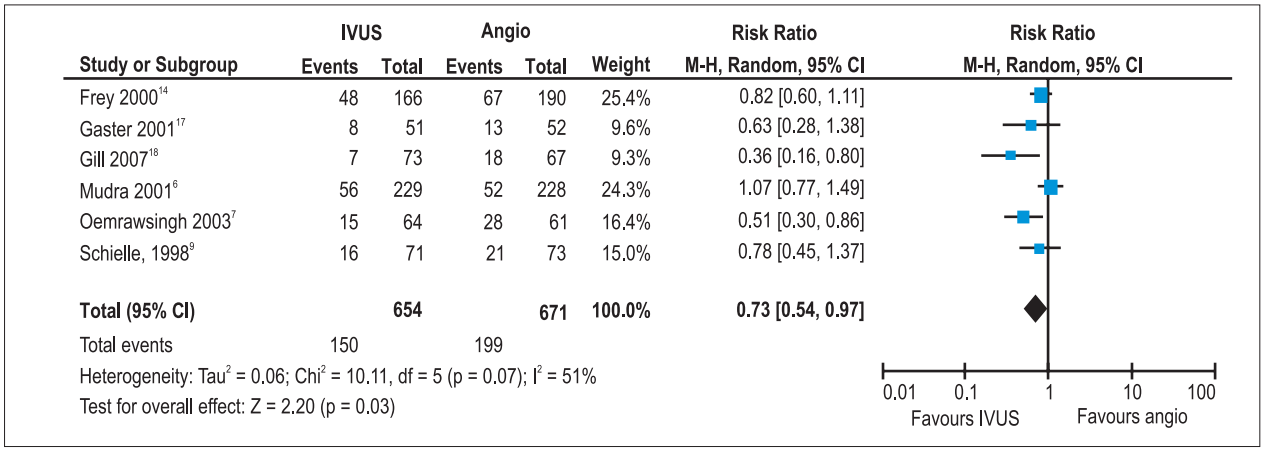

Figure 7 - *Meta-analysis of angioplasties guided or not by IVUS, on the restenosis outcome, with inclusion of six studies. Angio: angiography.*

Despite these advantages, restenosis has not been eliminated and TLR rates reach 10% within two years of evolution[19]. The increased use of drug-eluting stents in patients with more severe and complex lesions has resulted in a significant increase in restenosis rates, greater than that observed in randomized trials[21].

Given the encouraging results observed with the performance of IVUS-guided angioplasty with bare-metal stents, studies were designed to evaluate its role in angioplasties using drug-eluting stents.

Inadequate stent expansion has been reported as the predominant mechanism of restenosis in drug-eluting stents. With the suppression of myointimal proliferation achieved with drug-eluting stents, inadequate stent expansion became the main mechanism in the occurrence of restenosis[22].

In a study of 499 patients (543 lesions), followed by six months with angiographic control after drug-eluting stent implantation, the minimum stent area after the procedure and stent length at the IVUS were predictors for restenosis of DES[23].

The cutoff points that determined restenosis were a minimum stent area of 5.5 mm and length of 40 mm.

Similar results were observed in a study that used IVUS for DES implantation and assessed 33 lesions with 26 intra-stent restenosis, showing a minimum stent area of 5.0 mm in 67% of restenosis cases[24].

In another study that used IVUS for DES implantation, 82% of restenosis cases showed a minimum post-procedural area < 5 mm, also showing cross-sectional areas < 3 and 4 mm[25].

These studies suggest an association between a minimum cross-sectional stent area and occurrence of restenosis. Moreover, the higher the minimum cross-sectional area after the procedure, the lower the occurrence of restenosis.

The lack of adequate lesion coverage may also contribute to restenosis of drug-eluting stents. In a substudy of the SIRIUS study, the edges of 167 stents were studied, and 18 edge stenoses were identified during an eight-month angiographic follow-up, suggesting that inadequate plaque coverage may determine stent edge stenosis, which could be prevented by using IVUS[26].

The result of this meta-analysis is consistent with a meta-analysis performed by Casella et al[27], who detected a significant reduction of 19% in the angiographic restenosis outcome.

The revascularization outcome evaluation was performed in seven studies[6,7,14-18], and showed a significant reduction of 27% in the need for revascularization in the IVUS group, when analyzing together angioplasty or surgical revascularization.

The occurrence of revascularization was significantly lower in the group with IVUS-guided angioplasty in five of these studies. This reduction ranged from 60%[7] to 32%[16], and remained when considering only revascularizations with angioplasty, whereas in the surgical revascularization group there were fewer procedures in the IVUS group, but without statistical significance.

The evaluation of the new revascularization outcome among several studies shows some difficulties:

1st. It must to be expressed regarding the vessel that was revascularized and not another blocked vessel;

2nd. It is necessary to differentiate between percutaneous and surgical revascularization.

This occurs with revascularization because some studies show results in which the decrease in the number of revascularizations is highly significant, without specifying whether it is percutaneous or surgical and in which artery it was performed.

Revascularization was considered as clinical necessity or need for revascularization procedure, either surgical or by angioplasty. It was not possible to analyze outcomes using the TLR and TVR terminology, because definitions varied between studies. Thus, a more generic analysis was chose, specified by type of intervention / procedure.

The results of this study are consistent with those found in another meta-analysis[27], which showed a significant reduction relevant to the need for revascularization in the group with IVUS-guided angioplasty, mainly the reduction of revascularizations by angioplasty.

There was a non-significant decrease of the outcomes: myocardial infarction, MACE and stent thrombosis in the group with IVUS-guided angioplasty.

The definition of MACE varies from study to study, but in most of them it is a combination of death, nonfatal AMI, and TVR. Some studies, however, include new revascularization by angioplasty or surgical revascularization and subacute stent thrombosis.

A recent meta-analysis[27] showed a significant reduction in MACE (18.7% vs. 15%, p < 0.03) in favor of the group submitted to IVUS. This difference was primarily due to the reduction of in TVR observed in the IVUS group.

These results are consistent with those found in the present study, which detected a 14% MACE reduction in the IVUS group. Although TVR rates were not specifically determined, a significant decrease in new revascularizations, both by angioplasty and surgical revascularizations, of 27% in the IVUS group, contributed to this reduction in MACE.

Two studies[15,16] evaluated the outcome of stent thrombosis with nonsignificant reduction of 10% in favor of the IVUS group. This result is consistent with those of Casella et al[27], who observed nonsignificant reduction of 12% of subacute thrombosis in the IVUS group. The subacute stent thrombosis was an initial limitation to stent implantation, with an incidence of 10-15%[28,29]. The use of dual antiplatelet therapy and high-pressure stent implantation reduced the rate of thrombotic events after angioplasty to 0.9 %[30].

The first study using IVUS to evaluate subacute stent thrombosis observed that a smaller lumen and post-procedure dissection were independent predictors for this outcome in univariate and multivariate analysis, respectively[31].

A multicenter registry was performed to evaluate the role of IVUS in predicting stent thrombosis when compared to angiography. This study included patients who had stent thrombosis after angioplasty guided by IVUS.

At least one abnormal finding observed by IVUS (bad stent placement, dissection, thrombus or inadequate expansion) was present in 94% of 53 patients studied. Angiographic changes were present in only 32% of patients. These findings suggest that the use of IVUS was superior to angiography during angioplasty with implantation of stents[32]. However, there has been no study evaluating whether the routine use of IVUS decreases the rates of stent thrombosis.

In a recent registry, when evaluating patients undergoing angioplasty with implantation of drug-eluting stents, patients who underwent IVUS-guided angioplasty were compared with those guided by ANGIO. There was a significant reduction in sub-acute thrombosis (0.5% vs. 1.4%, p < 0.045), as well as at the end of the twelve-month follow-up (0.7% vs. 2%, p < 0.014) in the group that used IVUS[10].

There have been few studies evaluating IVUS findings in patients with late stent thrombosis. The late stent thrombosis mechanisms are multifactorial and the findings observed during the procedure do not correlate with late events. A case-control study showed a high prevalence of bad stent placement in patients with late thrombosis (> 12 months)[33].

The incidence of incomplete stent apposition was 77% in late thrombosis and 12% in the control group ($p < 0.001$). Although the association between bad stent placement and late thrombosis remains controversial, the use of IVUS during angioplasty may prevent bad stent placement, which would reduce late stent thrombosis.

Our data are consistent with two recent meta-analyses: the one performed by Parise et al[34], with similar results, differing only regarding the benefit observed in the use of IVUS in reducing the incidence of MACE (OR 0.72, 95% CI: 0.52-0.99), which was not demonstrated in this analysis. As for the meta-analysis performed by Sbruzzi et al[35], the results of this study are similar.

Conclusion

The use of IVUS when performing angioplasty compared with angioplasty guided by quantitative ANGIO, shows a statistically significant decrease in the need for new revascularization and angiographic restenosis.

Its use is not associated with a statistically significant difference in mortality, thrombosis, myocardial infarction and MACE outcomes when compared to angioplasty with stenting performed without IVUS.

There were no clear clinical benefits regarding the routine use of IVUS to guide the performance of angioplasties with stent implantation.

The definitive confirmation of the data presented here requires the performance of randomized clinical trials in a new scenario of drug-eluting stents and use of potent antiplatelet strategies after stenting.

Author contributions

Conception and design of the research: Figueiredo Neto JA, Nogueira IAL, Berwanger O; Acquisition of data and Analysis and interpretation of the data: Figueiredo Neto JA, Nogueira IAL, Figueiro MF, Buehler AM; Statistical analysis: Figueiro MF, Buehler AM, Berwanger O; Obtaining funding: Figueiredo Neto JA, Nogueira IAL; Writing of the manuscript: Figueiredo Neto JA; Critical revision of the manuscript for intellectual content: Figueiredo Neto JA, Figueiro MF, Buehler AM, Berwanger O.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

This study was funded by MCT, CNPq, CT-Saúde, SCT1E and DECIT.

Study Association

This study is not associated with any post-graduation program.

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