Balloon angioplasty versus stenting for pulmonary vein stenosis after pulmonary vein isolation for atrial fibrillation: A meta-analysis

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ABSTRACT

Background: The incidence of pulmonary vein stenosis (PVS) as complication after pulmonary vein isolation (PVI) for atrial fibrillation (AF) has decreased in the last decade. However, as PVI for AF is becoming more prevalent, the incidence remains considerable in absolute terms. The purpose of this meta-analysis is to investigate the optimal approach for management of PVS after PVI for AF.

Methods and results: We searched electronic scientific databases for studies comparing plain balloon angioplasty (BA) versus stenting for PVS after PVI for AF. Aggregate data were pooled to perform a meta-analysis. The primary and secondary outcomes were restenosis requiring repeated intervention and procedure-related complications, respectively.

A total of 4 studies, treating 315 PVS in 188 patients (BA, $n = 171$ versus stent, $n = 144$ PVS) were considered. After a median follow-up of 32 months, the overall incidence of restenosis was 46%. A percutaneous therapy with BA was associated with a higher risk for restenosis requiring repeat intervention compared to stent (risk ratio — RR, 95% confidence interval [95% CI] = 2.18 [1.64–2.89], $p < 0.001$). Procedure-related complications were comparable between BA and stent (RR [95% CI] = 0.96 [0.19–4.96], $p = 0.96$). The time to diagnosis of PVS after PVI for AF did not modify the treatment effect for the primary outcome with BA versus stent (p for interaction = 0.16).

Conclusions: In patients presenting PVS after PVI for AF, a percutaneous therapy with BA is associated with higher risk for restenosis requiring repeat intervention as compared to stent. These percutaneous therapies display comparable safety.

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1. Introduction

Iatrogenic pulmonary vein stenosis (PVS) remains a highly morbid complication of pulmonary vein isolation (PVI) for atrial fibrillation (AF). The earliest ablation procedures reported a prevalence of PVS as high as 42% [1]. Despite the iterations of current ablation techniques, the incidence of PVS in the current practice ranges between 0.29 and 19% [2–5], depending on ablation strategies, diagnostic imaging modalities, and operators' experience. Patients with high-degree PVS warrant prompt diagnosis and timely management to prevent pulmonary vein occlusion and lung parenchymal damage. However, the lack of awareness of this procedural complication coupled with the paucity of data reporting the optimal therapeutic strategy for this complication has resulted in heterogeneous interventional approaches and controversial results.

Currently, a percutaneous dilation with plain balloon angioplasty (BA) of the narrowed pulmonary vein represents the first-line therapy for symptomatic PVS after PVI for AF. However, despite that this therapy has been associated with acceptable acute and short-term results, the vessel re-narrowing occurs between 44% and 70% of cases [6–8]. The widespread adoption and the favorable outcomes of stent-based strategies to dilate stenosed vascular segments calls into question whether BA alone still represents the therapy of choice for patients with PVS after PVI for AF. However, available data on efficacy and safety of BA versus stent in this clinical setting is inconclusive.

Against this background, we performed a meta-analysis of studies investigating the outcomes of BA versus stent in patients suffering from PVS after PVI for AF.

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2. Methods

2.1. Search strategy and selection criteria

Scientific databases (Ovid, Medline, PubMed, CENTRAL) and relevant websites (www.clinicaltrialresults.org, www.escardio.org) were searched from inception to April 2017 for studies comparing BA versus stent as percutaneous therapy for PVS after PVI for AF. The full search strategy is reported in Supplemental Table 1. The following key words and the corresponding Medical Subject Heading (MeSH) terms were used: "pulmonary vein stenosis", "catheter ablation", "atrial fibrillation", "pulmonary vein isolation", "pulmonary balloon angioplasty", and "pulmonary stenting". The reference list of all eligible items was checked for identification of further relevant studies. Duplicated data were excluded.

To be included, studies should have data regarding the assessment of patency of pulmonary veins after index PVI for AF and a follow-up length ≥ 6 months. Studies of revascularization therapies for PVS after PVI for AF other than BA or stent, those including congenital PVS or PVS after procedures other than PVI for AF were ineligible for the current study.

2.2. Data collection and quality assessment

Eligible studies were extracted at the title or abstract level by two authors (AB, GvO) with divergences resolved with a third author (TI). Freedom from bias was evaluated for each study by the same investigators, in accordance with the Cochrane Collaboration method [9].

2.3. Outcome variables and definitions

The primary outcome of this report was restenosis requiring repeat intervention. The secondary outcome consisted of major procedure-related complications including: death, major adverse cardiac and cerebrovascular events (MACCE), major in-hospital complications requiring additional therapy and/or prolonged hospitalization (i.e. major bleeding or vascular complication, cardiac tamponade). These outcomes were evaluated according to definitions of the original protocols at the longest follow-up available.

At the time of index intervention patients were given intravenous heparin to achieve an activated clotting time of 250–300 s. Two studies provided data regarding ancillary therapy after revascularization. Neumann et al. [13] prescribed coumarin derivatives, aspirin and clopidogrel for the first 3 months after revascularization. Fender et al. [14] prescribed coumarin derivatives and clopidogrel (600 mg loading and 75 mg maintenance dose).

2.4. Statistical analysis

Statistical analysis was performed using the Review Manager Version 5.1 (RevMan; The Cochrane Collaboration, Copenhagen, Denmark) software package.

Distribution of patients and study characteristics were presented as counts (proportions) or mean (standard deviation). Risk ratio (RR, for categorical variables) and weighted mean difference (WMD, for continuous variables) with inherent 95% confidence intervals [95% CI] served as summary statistics for comparison of BA versus stent. The Mantel–Haenszel random effects model (DerSimonian and Laird) was used to calculate pooled RR for categorical variables, whilst the inverse variance random effects model served to calculate pooled mean difference for continuous variables. Visual inspection of funnel plot asymmetry was performed to address for possible small-study effect. Random effects model was checked against fixed effects to avoid influence of small studies. In case of variability of risk estimates between the fixed- and random-effects model, this latter was selected as the most conservative option. The Breslow-Day chi^2 test and the I^2 statistic were used to test heterogeneity across the studies: I^2 values of <25%, 25–50% or >50% indicated low, moderate or high heterogeneity [9], whilst the restricted maximum likelihood method (Tau^2) tested between-study heterogeneity.

Using a chi^2 test for subgroup by treatment interaction, we investigated whether the time interval between the most recent PVI for AF and the percutaneous treatment of PVS was associated with the risk estimate for primary outcome. Finally, an influence analysis, in which meta-analysis estimates are computed omitting one study at time, was performed for the primary outcome. The study was performed in compliance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement [10].

3. Results

3.1. Eligible studies

The process of study selection is summarized in Supplemental Fig. 1. Four studies (two retrospective [11,12] and two prospective studies [13,14]) – all with full-length manuscripts – were included in the meta-analysis. The main characteristics of these studies are reported in Supplemental Table 2. Each study enrolled patients with at least 70% stenosis in a pulmonary vein at non-invasive evaluation after PVI for AF. PVI was obtained by virtue of radiofrequency energy in the overwhelming majority of participants, with a negligible proportion of AF-patients undergoing cryoballoon ablation [14]. The imaging protocols to diagnose PVS after PVI for AF were slightly different. All studies but one [7] assessed the diagnosis of PVS by contrasted-enhanced spiral computed tomography (CT) scans in those patients complaining symptoms, mainly dyspnea and hemoptysis. Conversely, Neumann et al. [7] performed routine magnetic resonance imaging at 3 months in all AF-patients receiving PVI, regardless of the presence of symptoms. A fairly high proportion of patients received quantitative lung perfusion scans, though perfusion studies were not systematically performed. In all cases, the diagnosis of PVS was confirmed at invasive angiography. Main exclusion criterion was the evidence of complete pulmonary vein occlusion at invasive angiography. One study [14] reported that 6% of pulmonary veins presenting severely stenosed at CT-scans displayed <50% narrowing at invasive angiography and were not treated.

Procedural aspects were described in detail in all studies. Briefly, a right heart hemodynamic monitoring and a selective pulmonary angiography were systematically performed to visualize the venous anatomy before trans-septal puncture, especially in cases presenting as occlusions at CT-scans. In all studies, a standard predilation with an appropriately sized balloon-catheter (balloon-to-vein ratio ranging between 1:1 and 1.5:1) was performed and lesions were gradually dilated up to a final diameter of ≥7 mm. In two studies [11,14], drug-eluting stents (4 mm in diameter) were used in cases where a larger luminal diameter could not be achieved despite multiple balloon inflations. In all studies but one [12], stenting was used as a bail-out strategy in cases presenting significant (>50%) vessel recoil after predilation with BA or obstructive intimal flap. Conversely, default stenting was performed in all cases presenting restenosis after previous BA. In 6 cases the stent dislodged after deployment and could be retrieved without complications. Data regarding antiplatelet therapy after revascularization was available for 66% of patients. Endpoints definitions and follow-up characteristics among original studies are provided in Supplemental Table 3.

3.2. Outcomes

A total of 188 patients were included in the studies selected, with 315 PVS treated with BA ($n = 171$) or stent ($n = 144$). Patients' characteristics and frequency of clinical signs and symptoms are reported in Table 1. Clinical symptoms suggestive for PVS after PCI for AF occurred after a mean period of 6 months after the last PVI procedure. The median follow-up available for this analysis was to 32 months.

Table 1
Main clinical characteristics of patients treated with either BA or stenting included in the meta-analysis.

Study	Patients n	Mean age (years)	Males (%)	Frequency of clinical signs/symptoms			Severe PVS treated, n
				Dyspnea (%)	Hemoptysis (%)	Asymptomatic (%)	
Fender et al. [14,15]	113	50	77	67	27	0	178
Neumann et al. [13]	12	58	70	77	8	17	15
Prieto et al. [12]	44	53	70	88	23	7	80
Qureshi et al. [11]	19	51	N/R	95	63	0	37

BA: balloon angioplasty; PVS: pulmonary vein stenosis; N/R: not reported.