

Synopsis of Most Relevant Articles on Cardiac Arrhythmias

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Comparison of Left Bundle Branch and His Bundle Pacing in Bradycardia Patients*

Recently, left bundle branch pacing (LBBP), initially reported by Huang et al., has emerged as a potential alternative conduction system pacing approach to His bundle pacing (HBP). Compared with HBP, LBBP can achieve similar paced QRS durations and acute success rates, stable lower pacing thresholds, and better sensing of ventricular activation (R-waves). The study aimed to compare pacing and electrophysiological parameters between HBP and LBBP in many consecutive patients undergoing physiologic pacing for bradycardia indications. Consecutive patients who underwent pacemaker implantation with conduction system pacing were enrolled in this observational study at Fuwai hospital from January 2018 to April 2019. All patients had symptomatic bradycardia and were indicated for pacing therapy. HBP was performed using the 4-F active fixation non lumen lead (Select Secure 3830, 69 cm, Medtronic, Minneapolis, Minnesota) delivered through a fixed curve sheath (C315His, Medtronic). If an acceptable His bundle capture threshold ≤ 2.5 V/1.0 ms could not be achieved after 20 min of fluoroscopy, then the lead was placed in the RV mid-septum. Patients were classified as failed HBP implantation and were excluded from further analyses. LBBP was performed using the Select Secure 3830 lead and C315HIS sheath (Medtronic); pace mapping through the lead's tip was used to find the optimal pacing sites. Once the paced ECG QRS morphology in lead V1 showed a "W" configuration with a mid-notch or paced QRS duration (QRSd) < 145 ms, then the pacing lead was advanced with approximately 5 to 6 clockwise rotations. There were 251 patients included in the study. HBP was attempted in 125 patients, and LBBP was attempted in 126 patients. The cardiac pacing indication included sick sinus syndrome (SSS) with intact AV conduction (51.4%) and AV block (64.1%), including 15.5% of patients with both pacing indications. The implantation success rate of permanent HBP was 87.2% (109 of 125): selective HBP was achieved in 41.3% of patients with nonselective HBP in the remaining 58.7% of patients. In the LBBP group, successful LBBP was achieved in 115 (91.3%) of 126 patients: selective LBBP in 73 patients (63.5%) and nonselective LBBP in 42 patients (36.5%). The implantation success rates were similar for the HBP and LBBP groups (87.2% vs. 91.3%, $p = 0.298$). However, the mean procedure (78 ± 36 min vs. 54 ± 24 min, $p < 0.001$) and fluoroscopy durations (12 ± 5 min vs. 5 ± 2.8 min, $p < 0.001$) were significantly longer in the HBP group compared with the LBBP group. LBBP had a significantly lower capture threshold (0.6 ± 0.2 V vs. 1.3 ± 0.6 V; $p < 0.001$) and larger sensed R-wave amplitude (12.5 ± 9.0 mV vs. 2.8 ± 3.0 mV, $p < 0.001$) compared with HBP. The capture threshold for LBBP remained significantly lower than for HBP (0.63 ± 0.19 vs. 1.36 ± 0.83 at 0.4 ms pulse width; $p < 0.001$). In the HBP group, 8 patients (7.3%) had capture thresholds > 3.0 V/0.4 ms at 3-month follow-up compared with none for LBBP ($p = 0.003$). Moreover, 4 HBP patients (3.7%) developed an increase in capture

threshold of >1 V at 3-month follow-up and none with LBBP. The results showed that among patients with a bradycardia indication for pacing therapy, compared with HBP, LBBP resulted in similar paced QRSd and implantation success rates, whereas there were shorter procedural and fluoroscopy durations. LBBP had a significantly lower pacing threshold and higher R-wave amplitude at implantation and during 3-month follow-up compared with HBP. Finally, the capture threshold was more stable in LBBP than HBP during follow-up. The authors conclude that further studies are needed to evaluate the long-term safety and clinical outcomes in a broad patient population for these two conduction system pacing modalities to establish the role of LBBP in clinical practice.

*Hua W, Fan X, Li X, et al. Comparison of Left Bundle Branch and His Bundle Pacing in Bradycardia Patients. *Clinical Electrophysiology*, 2020; 6(10):1291-9. <https://doi.org/10.1016/j.jacep.2020.05.008>

Cryoballoon Ablation of Atrial Fibrillation in Octogenarians*

The management of AF in the geriatric population is associated with several challenges, including multiple comorbidities, increased toxicity of antiarrhythmic drugs (AAD), an increased risk of complications from invasive procedures and an increased risk of stroke and bleeding complication secondary to anticoagulation use. In this case series, the authors report an institutional experience with second-generation cryoballoon-based PVI in octogenarian patients. The study participants were non-consecutively included and derived from an institutional review board-approved, a prospectively populated clinical database of AF ablation patients. The cohort comprised 15 patients between 80 and 88 years of age who underwent cryoballoon AF ablation between 2012 and 2019. The mean patient age was 83 ± 3 years and 60% of the patients were men. Of the 15 patients, 13 (87%) presented with paroxysmal AF (PAF) and two (13%) had long-standing persistent AF (PsAF). The mean time since AF was first diagnosed was 8.9 ± 8.2 years. Mean CHA₂DS₂-VASc score and HASBLED scores were 4.2 ± 1.7 and 2.4 ± 0.8 , respectively. Mean LA diameter was 4.5 ± 1.2 cm. During a mean follow-up duration of 15.8 months (range 6–60 months), AF recurred in three patients. The freedom from AF recurrence was 80% and 70% at 6 and 12 months of follow-up, respectively. Thirteen of the 15 patients reported a significant reduction in symptoms and AF burden associated with improved quality of life following catheter ablation. Compared to the previous study of cryoballoon ablation in patients over the age of 80, this report's lower success rate could result from the inclusion of the patients with long-standing PsAF, higher CHA₂DS₂-VASc score, and greater LA diameter. Previous studies have reported that these factors are associated with a low success rate of the ablation procedure. The authors conclude that, with limited sample size, cryoballoon AF ablation appears to be a safe and effective strategy for treating octogenarians with symptomatic AF refractory to AAD therapy. The findings require validation by prospective randomized studies with larger sample sizes.

*Akhtar T, Berger R, Marine JE, et al. Cryoballoon Ablation of Atrial Fibrillation in Octogenarians. *Arrhythmia & Electrophysiology Review* 2020;9(2):104–8. <https://doi.org/10.15420/aer.2020.18>

Initial and Long-Term Antithrombotic Therapy After Left Atrial Appendage Closure with the Watchman*

Percutaneous left atrial appendage (LAA) closure is increasingly used as an alternative to oral anticoagulation (OAC) for stroke prevention in patients with non-valvular atrial fibrillation. The WATCHMAN occluder (Boston Scientific, Natick, MA, USA) is the only LAA closure device compared against warfarin in randomized controlled trials. Patients undergoing LAA closure in the real world have mostly relative or absolute contraindications against OAC due to an increased bleeding risk, even for a short period. This makes post-implant antithrombotic management difficult. The initially recommended therapy of warfarin plus aspirin for 45 days followed by dual antiplatelet therapy (DAPT) for 6 months (more aggressive

antithrombotic therapy in the initial phase until endothelialization of the LAA occluder) and aspirin lifelong after that frequently not possible to perform. A subanalysis was performed using data of the EWOLUTION registry to address this issue, which assessed patients undergoing WATCHMAN implantation in a real-world population. Various antithrombotic therapies chosen depending on the patients' risk were evaluated regarding ischaemic and bleeding events during a follow-up period of 2 years. For this sub-analysis, all patients were included in successful WATCHMAN implantation and known medication after the LAA closure procedure. Adverse events were assessed at implant, during post-procedural hospital course and at follow-up, which was performed according to each center's standard up to 2 years following the procedure. Primary outcome measures were a composite ischaemic endpoint consisting of stroke, TIA, systemic embolism and device thrombus, and a bleeding endpoint defined as major bleeding, including fatal and life-threatening bleeding. From October 2013 until May 2015, 1025 patients from 13 countries at 47 institutions were enrolled in the EWOLUTION study. The WATCHMAN device was successfully implanted in 1005 patients, which corresponds to a technical success rate of 98%. For the initial period, the leading antithrombotic regimen chosen was DAPT followed by oral anticoagulation—41% non-vitamin K antagonists and 59% vitamin K antagonists ([N]OAC)—single antiplatelet therapy (SAPT) and no antithrombotic medication at all. Patients receiving OAC were younger and had rather fewer comorbidities compared to the other groups. Consequently, the calculated stroke risk using the CHA₂DS₂-VASc score was lower in the OAC group. History of major bleeding and particularly the history of hemorrhagic stroke was observed more frequently in subjects taking antiplatelet or no therapy. Consequently, the HAS-BLED score was higher in the SAPT and no therapy groups. For assessing different antithrombotic therapies in the initial phase, OAC was compared to the widely used management using DAPT and the minimalistic regimen consisting of SAPT or no therapy. No differences were found between these groups concerning the composite ischaemic endpoint consisting of stroke, TIA, systemic embolism, and device thrombus. Major bleeding complications were similarly rare in the OAC and DAPT cohort. A significantly higher rate was observed in patients receiving SAPT or no therapy. For the assessment of the long-term therapy, a total of 748 patients with known medication status were available. Only a minimal number of subjects received OAC as a long-term treatment (n= 22) due to ischaemic complications and residual major peri-device leaks >5 mm. Therefore, those patients were excluded from the long-term analysis and the treatment strategies consisting of DAPT, SAPT, or no therapy were analyzed in the second period, respectively. SAPT was used, for the most part, followed by DAPT and no therapy. No significant differences were observed between the groups regarding the ischaemic endpoint. No differences were seen for device thrombus at the early nor the late period within the different treatment groups. In contrast to the PROTECT-AF and PREVAIL trial, most patients following WATCHMAN LAA closure in the real world outside the USA received antiplatelet therapy in the initial phase—mostly DAPT—instead of OAC. Dual antiplatelet therapy, SAPT, and no antiplatelet therapy were not associated with an increased risk for ischaemic events in the initial period after LAA closure compared to OAC in the present trial, despite a higher risk based on a higher CHA₂DS₂-VASc Score. A small but considerable number of patients received no antiplatelet therapy after LAA closure for the long term. This population showed a similar low ischaemic and bleeding event rate than SAPT and DAPT during the 2-year follow-up. A common strategy in the present study was, to begin with, DAPT instead of OAC initially after LAA closure. The analysis showed that reducing anticoagulation to SAPT or no therapy even directly after LAA closure is possible when high-risk bleeding criteria are present. That approach was used in 13% of the patients. The rate of the composite of ischaemic stroke, TIA, systemic embolism, and device thrombus was 3.9% for the first six months. The initially increased rate of major bleeding in the SAPT/no therapy group, which was as high as 7.4%, could be potentially explained by the multi-morbid condition of the patients and several other patient characteristics triggering an increased bleeding risk such as the history of major bleeding in 41% and history of intracranial bleeding in 38%. This increased bleeding risk was most likely the main reason to use a reduced antithrombotic regimen in these patients. The default regimen for the long-term treatment was SAPT used in 65% of the population, followed by DAPT in 24% of the cases. Only 7% received DAPT at the final 2-year follow-up, indicating that DAPT was administered for an extended duration and was reduced to mainly SAPT at some point during follow-up as shown in an EWOLUTION subanalysis from Bergmann et al. Eight percent received no antithrombotic therapy at all as long-term management. The event rate of both the ischaemic and bleeding endpoint was similar in patients without therapy compared to those under SAPT or DAPT

despite higher bleeding and ischaemic risk. The reason why those patients receiving SAPT and no therapy in the second period did not have an increased rate of bleeding during long-term follow-up compared to the initial SAPT/no therapy group may be a result of the medication switch. The SAPT group in the second period consisted mainly of patients who had DAPT as an initial regimen. These subjects were characterized by a considerably lower bleeding risk, which probably impacted the rate of major bleedings. Furthermore, patients under SAPT in the initial period were switched to no therapy in the second period. This reduced regimen may have decreased bleeding events during long-term follow-up. The authors conclude that all studied antithrombotic strategies showed similarly low event rates for the composite ischaemic endpoint of stroke, TIA, systemic embolism, or device thrombus. Therefore, the study provided evidence supporting the possibility of a minimal or even no antithrombotic regimen after LAA closure in selected patients with high bleeding risk. This approach should be tested in prospective randomized trials.

*Ledwoch J, Sievert K, Boersma LVA, et al. Initial and long-term antithrombotic therapy after left atrial appendage closure with the WATCHMAN. *Europace*, 2020;22(7) 0, 1036-43. <https://doi.org/10.1093/europace/euaa074>

Rivaroxaban in Patients with Atrial Fibrillation and a Bioprosthetic Mitral Valve

Patients with atrial fibrillation and a bioprosthetic mitral valve require long-term anticoagulation, but questions remain about the most effective therapeutic strategy. Recommendations for the use of vitamin K antagonists in patients with bioprosthetic valves are guided by limited evidence from randomized trials. The efficacy and safety of direct oral anticoagulants in patients with atrial fibrillation and a bioprosthetic mitral valve are based on subgroup analyses of pivotal trials of apixaban and edoxaban that included a total of 31 and 131 patients, respectively, and on the findings of a pilot trial of dabigatran that enrolled 27 patients. The authors conducted the Rivaroxaban for Valvular Heart Disease and Atrial Fibrillation (RIVER) trial to assess rivaroxaban's efficacy and safety compared with warfarin in patients with atrial fibrillation and a bioprosthetic mitral valve. This multicenter trial had a randomized, noninferiority, open-label design with blinded adjudication of outcomes, as led by an academic steering committee. Patients included in the trial were adults (≥ 18 years of age) who had permanent, paroxysmal, or persistent atrial fibrillation or flutter and a bioprosthetic mitral valve and who were receiving (or planning to receive) oral anticoagulation for thromboembolism prophylaxis. Patients were eligible for inclusion in the trial at any time at least 48 hours after undergoing mitral-valve surgery. The main exclusion criteria were a contraindication to either rivaroxaban or warfarin, an extremely high risk of bleeding, transient atrial fibrillation caused by surgery, and mechanical valves' placement. Eligible patients were randomly assigned to receive rivaroxaban or warfarin in a 1:1 ratio in permuted blocks of variable size that were stratified according to the site using a central concealed, Web-based, automated randomization system. Patients were assigned to receive oral rivaroxaban at a dose of 20 mg once daily; those with a calculated creatinine clearance of 30 to 49 ml per minute per 1.73 m² of the body-surface area received a reduced dose of 15 mg once daily. In patients assigned to receive warfarin, the dose was adjusted to maintain a target international normalized ratio (INR) of 2.0 to 3.0. The INR was measured at least every four weeks. In the warfarin group, the method of Rosendaal et al.¹² was used to calculate the overall time that INR values fell within the therapeutic range. The primary outcome was a composite of death, major cardiovascular events, or major bleeding at 12 months. Major cardiovascular events were stroke, transient ischemic attack (TIA), valve thrombosis, systemic embolism not related to the central nervous system (CNS), or hospitalization for heart failure. The key secondary efficacy outcome was a composite of death from cardiovascular causes or thromboembolic events (stroke, TIA, deep venous thrombosis, pulmonary embolism, valve thrombosis, or systemic embolism not related to the CNS). Safety outcomes were bleeding events (major, clinically relevant nonmajor, minor, and total). Bleeding events were classified according to the ROCKET AF trial criteria (main analysis for safety) and the criteria of the Thrombolysis in Myocardial Infarction (TIMI) and Bleeding Academic Research Consortium (BARC). From April 14, 2016, through July 22, 2019, a total of 1005 patients were enrolled and randomly

assigned to receive either rivaroxaban (500 patients) or warfarin (505 patients). Twelve-month data were missing owing to a loss of follow-up for six patients (0.6%). The median age was 59.3 years; 60.4% of the patients were women. Of the trial patients, 60.7% had hypertension, 38.8% had heart failure, and 15.4% had a history of stroke or TIA. A total of 95.6% of the patients had atrial fibrillation, and 4.3% had atrial flutter. The mean (\pm SD) risk score for stroke from atrial fibrillation was 2.6 ± 1.4 on the CHA₂DS₂-VASc scale. The interval between mitral-valve surgery and randomization was less than three months for 18.8% of the patients, between 3 months and less than one year for 16.8%, between 1 year and less than five years for 32.2%, and five years or more for 30.6%; data were missing for 1.6% of the patients. Patients in the warfarin group had an INR in the therapeutic range (2.0 to 3.0) for a median of 65.5% (interquartile range, 51.3 to 70.5) of the time. The mean time until a primary-outcome event was 347.5 days in the rivaroxaban group and 340.1 days in the warfarin group (restricted mean survival time – RMST difference, 7.4 days; 95% confidence interval [CI], -1.4 to 16.3; $P < 0.001$ for noninferiority and $P = 0.10$ for superiority). In the as-treated analysis, the meantime until a primary-outcome event was 350.1 days in the rivaroxaban group and 339.6 days in the warfarin group (RMST difference, 10.5 days; 95% CI, 1.9 to 19.1); in the per-protocol analysis, the time until the event was 356.7 days and 347.1 days, respectively (RMST difference, 9.6 days; 95% CI, 2.2 to 16.9). At 12 months, the composite secondary outcome of death from cardiovascular causes or thromboembolic events occurred in 17 patients (3.4%) in the rivaroxaban group and 26 (5.1%) in the warfarin group (hazard ratio, 0.65; 95% CI, 0.35 to 1.20) (Table 2). The total stroke incidence was 0.6% in the rivaroxaban group and 2.4% in the warfarin group (hazard ratio, 0.25; 95% CI, 0.07 to 0.88). Valve thrombosis occurred in 5 patients in the rivaroxaban group and 3 in the warfarin group (1.0% vs. 0.6%). Other secondary efficacy outcomes were not significantly different in the two groups. Results of analyses using RMST calculations for secondary efficacy outcomes were consistent with the time-to-event analyses. Concerning bleeding events at 12 months, major bleeding occurred in 7 patients (1.4%) in the rivaroxaban group and in 13 (2.6%) in the warfarin group (hazard ratio, 0.54; 95% CI, 0.21 to 1.35). The incidence of clinically relevant nonmajor bleeding was similar in the rivaroxaban and warfarin groups (4.8% and 4.6%, respectively). There were no reported intracranial bleeding events in the rivaroxaban group and 5 (1.0%) in the warfarin group. Similarly, the incidence of fatal bleeding was 0% in the rivaroxaban group and 0.4% in the warfarin group. In the trial, those who received rivaroxaban for one year were free of a composite primary outcome of death, major cardiovascular events, or major bleeding for a mean of 7.4 days longer than their counterparts who received warfarin. The confidence interval for the primary analysis may have excluded an effect size of more than 1.4 days free from events favoring

warfarin, which showed the noninferiority effect of rivaroxaban in this clinical setting. Secondary efficacy outcomes were generally similar in the two groups; total stroke incidence was 0.6% with rivaroxaban and 2.4% with warfarin. The incidence of valve thrombosis was very low and similar in the two groups, as were incidences of bleeding (including major, nonmajor clinically relevant, and total events). The authors conclude that in patients with atrial fibrillation and a bioprosthetic mitral valve, rivaroxaban was non-inferior to warfarin to the meantime until the occurrence of major clinical events.

*Guimarães HP, Lopes RD, Barros e Silva PGM. Rivaroxaban in Patients with Atrial Fibrillation and a Bioprosthetic Mitral Valve. *New England Journal of Medicine*, 2020;383:2117-26. <https://doi.org/10.1056/NEJMoa2029603>