Valvular Heart Disease

Clinical Impact of Persistent Left Bundle-Branch Block After Transcatheter Aortic Valve Implantation With CoreValve Revalving System

Luca Testa, MD, PhD; Azeem Latib, MD; Federico De Marco, MD; Marco De Carlo, MD; Mauro Agnifili, MD; Roberto Adriano Latini, MD; Anna Sonia Petronio, MD; Federica Ettori, MD; Arnaldo Poli, MD; Stefano De Servi, MD; Angelo Ramondo, MD; Massimo Napodano, MD; Silvio Klugmann, MD; Gian Paolo Ussia, MD; Corrado Tamburino, MD; Nedy Brambilla, MD; Antonio Colombo, MD; Francesco Bedogni, MD

Background—Conduction disturbances are relatively common after transcatheter aortic valve implantation. Previous data demonstrated an adverse impact of persistent left bundle-branch block (LBBB) after surgical aortic valve replacement. It is unclear whether new-onset LBBB may also impact the prognosis of patients after transcatheter aortic valve implantation.

Methods and Results—Among 1060 patients treated with a CoreValve Revalving System transcatheter aortic valve implantation between October 2007 and April 2011 in high-volume centers in Italy, we analyzed those without LBBB or pacemaker at admission (879 patients [82.9%]). We further excluded those who underwent permanent pacemaker implantation within 48 hours after the procedure (61 patients [7%]), for a final study population of 818 patients. Among them, 224 patients (group A; 27.4%) developed a persistent LBBB and the remaining 594 (group B; 72.6%) did not. Clinical characteristics were similar between groups. A low implantation was significantly more frequent in group A (15% versus 9.8%, P=0.02). No patients were censored before 1 year (median follow-up period 438 days, interquartile range 174–798 days). Survival analyses and inherent log-rank tests showed that LBBB was not associated with higher all-cause mortality, cardiac mortality, or hospitalization for heart failure at 30 days or 1 year. At 30 days, but not at 1 year, group A had a significantly higher rate of pacemaker implantation.

Conclusions—In this registry of high-volume centers, persistent LBBB after CoreValve Revalving System transcatheter aortic valve implantation showed no effect on hard end points. On the other hand, LBBB was associated with a higher short-term rate of pacemaker implantation. (Circulation. 2013;127:1300-1307.)

Key Words: aortic valve ■ bioprosthesis ■ cardiac pacemaker, artificial ■ left bundle-branch block ■ prognosis

Transcatheter aortic valve implantation (TAVI) is now recognized as a valid option in patients with severe aortic stenosis deemed at high or prohibitive risk for conventional surgical aortic replacement.1,2 Recent publication of several national registries contributed significantly to the understanding of possible factors associated with or predictive of adverse prognosis.3–6 Some of these factors, such as older age, critical preoperative state, renal failure, and the presence of multiple comorbidities, are common predictors of adverse outcome even after surgical aortic valve replacement.5–7

Clinical Perspective on p 1307

The development of a persistent left bundle-branch block (LBBB) has been recognized as a predictor of mortality at 1 year in patients undergoing surgical aortic valve replacement.8 Although definitive explanations are lacking, it has been hypothesized that this effect could be a consequence of subsequent impaired left ventricle contractility, dysynchrony, worsened mitral regurgitation, and higher risk of progression to complete atrioventricular (AV) block and sudden death.9 Whether this specific conduction disturbance could have an ominous impact in patients undergoing TAVI is still unclear, because limited data have specifically focused on this topic so far. We thus sought to evaluate, in a multicenter registry of patients treated
in high-volume centers, the prognostic significance of persistent LBBB after TAVI with the CoreValve Revalving System (CRS).

Methods

Study Design and Patient Population

From June 2007 to April 2011, a total of 1060 consecutive patients were treated with the third-generation 18-F CRS device in high-volume centers in Italy. We specifically focused on those without LBBB or a permanent pacemaker at admission (879 patients [82.9%]). We further excluded those who underwent permanent pacemaker implantation within 48 hours after the procedure (61 patients [7%]), for a final study population of 818 patients (Figure 1). We chose a temporal window of 48 hours because a temporary pacemaker was conventionally left in place for this time period to prevent the consequences of advanced AV block.

Clinical follow-up was scheduled for all patients at 1, 6, and 12 months and then yearly. Patients were followed up by means of outpatient clinics or regular contact with general practitioners. In the case of hospitalization in a different hospital from that of the index procedure, colleagues were contacted directly to collect information, or the patient was transferred. In all cases, an ECG was required as part of the follow-up plan. Local institutional ethics committees approved the study protocol. All patients had severe symptomatic aortic stenosis with a valve area <1 cm². Eligibility for TAVI was established at each center based on the consensus of a local multidisciplinary heart team that included clinical cardiologists, cardiac surgeons, and cardiac anesthesiologists.

Written informed consent was obtained in all cases. Enrolled patients were divided into 2 groups: Patients who did not develop an LBBB or who developed a transient LBBB, that is, not present at discharge (group A), and patients with persistent LBBB at discharge (group B).

Device and Procedure

The CoreValve prosthesis consists of a trileaflet biological valve sewn into a self-expanding nitinol frame. The choice of general anesthesia, local anesthesia, or mild sedation was made by the heart team during the preoperative meeting. Arterial access (femoral, left or right subclavian) and percutaneous puncture or surgical exposure were also determined on the basis of the panel of preoperative imaging tests that included in most cases both angiography and computed tomography scan. For percutaneous femoral access, hemostasis was achieved by means of a Prostar XL 10 (Abbott Vascular, Abbott Park, IL) in the study population. Numbers at discharge are subsets of the groups after procedure. CRS-TAVI indicates transcatheter aortic valve implantation with the CoreValve Revalving System; LBBB, left bundle-branch block; PM, pacemaker; pts, patients; and w/o, without.

Results

After the procedure, the majority of patients were managed in an intensive care unit or coronary care unit with continuous ECG monitoring for at least 1 day. In all cases, a temporary pacemaker was left in place for at least 48 hours after TAVI as a backup for paroxysmal or persistent advanced AV block. Those patients with early (up to 48 hours after TAVI) advanced AV block underwent pacemaker implantation and were thus excluded from the final study population. In the cardiology ward, patients were monitored with telemetry until their discharge. An ECG was printed and added to the chart, as a source document, at least daily.

All patients received acetylsalicylic acid (≥100 mg before the procedure and lifelong), as well as clopidogrel (300 mg bolus plus 75 mg/d for 3–6 months unless prolonged administration was required because of previous coronary intervention with drug-eluting stents). During the intervention, unfractionated heparin 100 UI/kg was administered to achieve an activated clotting time of 200 to 250 seconds for the duration of the procedure. In the case of concomitant coronary disease, percutaneous intervention was performed before TAVI. All of the TAVI-related end points in the study, such as overall mortality, cardiac mortality, and hospitalization for heart failure, were defined according to the definitions of the Valve Academic Research Consortium.

Statistical Analysis

Continuous variables with normal distribution are presented as mean±SD and compared by Student unpaired t test for comparisons between groups and Student paired t test for within-group comparisons. Variables that did not follow a normal distribution were compared with a Mann-Whitney test for comparisons between groups and a Wilcoxon signed rank test for within-group comparisons. Categorical variables are presented as counts and percentages and were compared by χ² or Fisher exact tests, as appropriate. The cumulative incidences of clinical events at follow-up were assessed by the Kaplan-Meier method and log-rank test. A 2-way ANOVA for repeated measures with interaction was used to compare changes in left ventricular ejection fraction, end-diastolic volume, end-systolic volume, and peak transaortic gradient at different time points between groups.

All probability values reported are 2-sided, and P<0.05 was considered significant. All data were processed with the Statistical Package for Social Sciences, version 18 (SPSS, Chicago, IL).

Among the 818 patients who did not undergo permanent pacemaker implantation within the first 48 hours after TAVI, 354 (43.3%) developed new-onset LBBB after the procedure, but the LBBB persisted in only 184 (52%) of them at discharge, which means that this conduction disturbance was transient in almost half of the cases. On the other hand, among the 464 patients who did not develop LBBB immediately after the procedure, a very small percentage (40 patients [8.6%]) showed LBBB at discharge. Thus, 224 patients overall developed persistent LBBB after TAVI (group A; 27.4%) and 594 patients (group B; 72.6%) did not. These percentages were consistent at 30 days (Figure 2), that is, patients with LBBB at discharge were the same as those with LBBB at 30 days, and no new-onset LBBB was observed at 1 month.

No patients were censored before 1 year, with a median follow-up period of 438 days (interquartile range 174–798 days). Baseline and procedural features of the 2 groups are shown in Tables 1 and 2.

In group A, the widening of the QRS was remarkable, reaching a mean duration of 142 ms (range 130–155 ms). In the same group, a higher rate of low implantation, defined as a distance >8 mm between the lower edge of the noncoronary cusp and the lower edge of the CRS frame, was observed.
Overall Mortality and Cardiac Mortality
At 30 days, 45 patients had died (5.5%; Table 3). No significant differences were observed between the 2 groups (overall mortality: 5.8% versus 5.4%, \(P=0.62\); cardiac mortality: 1.8% versus 2.4%, \(P=0.58\)).

At 1-year follow-up (mean follow-up of 266±248 days, median 180 days), 159 patients had died (19.4%). Overall mortality was 18.7% versus 19.7% (\(P=0.12\)), whereas cardiac mortality was 8.9% versus 9.1% (\(P=0.74\); Table 3). In absolute terms, patients who developed a persistent LBBB had slightly lower overall and cardiac mortality, although this was not statistically significant (Figure 3).

Rate of Pacemaker Implantation
At 30 days, patients with a persistent LBBB (group A) had a significantly higher rate of pacemaker implantation (4.9% in group A versus 2% in group B, \(P=0.02\)). At 1 year, this difference was no longer significant (18.3% in group A versus 17% in group B, \(P=0.6\)).

Within the first 30 days, pacemaker implantation was performed for a diagnosis of advanced AV block in 95% (group A) and 96% (group B) of the cases. At 1 year, the reason for pacemaker implantation was advanced AV block in 78% and 80% of the cases, respectively. In the remaining cases, a pacemaker was implanted to treat symptomatic bradycardia, syncope, and atrial fibrillation with a low ventricular rate. No significant differences in terms of the diagnosis that led to pacemaker implantation were observed between groups at either time point.

Rate of Hospitalization for Heart Failure and New York Heart Association Functional Class
At 30 days, as well as at 1-year follow-up, the rate of hospitalization for heart failure was consistent between the 2 groups (Table 3), as was the overall improvement in New York Heart Association functional class (Figure 4).

Echocardiographic Data
Echocardiographic data were available in 100% of the cases at baseline. At discharge, these percentages were 95% and 96%, respectively. At 1-month, 6-month, and 1-year follow-up, data were available for 80%, 65%, and 40% of group A patients and 70%, 55%, and 45% of group B patients, respectively. Figure 5 shows the comparison among the 2 groups with respect to left ventricular ejection fraction (Figure 5A), end-diastolic volume (Figure 5B), end-systolic volume (Figure 5C), and mean transaortic peak gradient (Figure 5D).

In both groups, transaortic peak gradient was significantly lower after TAVI, and from discharge to 1-year follow-up, it did not change significantly (\(P=0.36\) and \(P=0.51\)). No difference was detected between the groups. Left ventricular ejection fraction, end-diastolic volume, and end-systolic volume were not statistically significant between the 2 groups at either time point.
did not significantly change over time within either group, and no differences were observed between groups.

**Discussion**

A new-onset LBBB after CRS TAVI is a relatively frequent finding, occurring in up to 43% of the cases in the present large multicenter registry. This percentage decreased at discharge to 27.3% and remained stable at 30 days. Overall mortality and cardiac mortality were comparable between patients with and without a persistent LBBB at 30 days and at 1-year follow-up. Likewise, the rate of hospitalization for heart failure and the improvement in New York Heart Association class were similar. The presence of a persistent LBBB was associated with a higher rate of pacemaker implantation at 30 days. On the other hand, after we censored events that occurred within 30 days, the 1-year rate was equivalent between patients with and without persistent LBBB.

The pathophysiology of new-onset LBBB after TAVI is unclear. The porcine pericardial valve of the CRS is mounted in a self-expandable nitinol frame. Compression exerted by the CRS frame on the interventricular membranous septum, which is contiguous with the atrioventricular node and the left bundle branch, may cause inflammation and subsequent edema. This mechanism has been postulated as responsible for the impaired function of the atrioventricular node, the His Bundle, and its branches (Figure 6). Low implantation depth was more frequent among those who developed an LBBB, thus corroborating the compression/inflammation pathophysiological hypothesis. This phenomenon is different from what may occur after surgical aortic valve replacement.

**Table 2. Procedural Data**

<table>
<thead>
<tr>
<th></th>
<th>LBBB (n=224)</th>
<th>No LBBB (n=594)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedure time, min</td>
<td>77±34</td>
<td>75±38</td>
<td>0.23</td>
</tr>
<tr>
<td>Arterial access</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Femoral</td>
<td>201 (89.7)</td>
<td>522 (87.9)</td>
<td></td>
</tr>
<tr>
<td>Subclavian</td>
<td>22 (9.8)</td>
<td>71 (11.9)</td>
<td></td>
</tr>
<tr>
<td>Anesthesia</td>
<td></td>
<td></td>
<td>0.93</td>
</tr>
<tr>
<td>General</td>
<td>62 (27.7)</td>
<td>170 (28.6)</td>
<td></td>
</tr>
<tr>
<td>Local</td>
<td>162 (72.3)</td>
<td>424 (71.4)</td>
<td></td>
</tr>
<tr>
<td>Hemostasis, 0–1</td>
<td>45/55</td>
<td>42/58</td>
<td>0.44</td>
</tr>
<tr>
<td>Surgical</td>
<td>40 (17.9)</td>
<td>95 (16.0)</td>
<td></td>
</tr>
<tr>
<td>Percutaneous</td>
<td>184 (82.1)</td>
<td>499 (84.0)</td>
<td></td>
</tr>
<tr>
<td>Size 29/26, n</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postprocedural paravalvular leak</td>
<td>0–1</td>
<td>173 (77.2)</td>
<td>427 (71.9)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>47 (20.9)</td>
<td>142 (23.9)</td>
</tr>
<tr>
<td></td>
<td>3–4</td>
<td>4 (1.8)</td>
<td>25 (4.2)</td>
</tr>
<tr>
<td></td>
<td>Postdilation</td>
<td>20 (8.9)</td>
<td>59 (9.9)</td>
</tr>
<tr>
<td></td>
<td>“Valve-in-valve”</td>
<td>8 (3.6)</td>
<td>19 (3.2)</td>
</tr>
<tr>
<td></td>
<td>Device success</td>
<td>215 (95.9)</td>
<td>574 (96.6)</td>
</tr>
<tr>
<td></td>
<td>Procedural success</td>
<td>221 (98.7)</td>
<td>588 (98.9)</td>
</tr>
<tr>
<td></td>
<td>Low implant*</td>
<td>33 (14.7)</td>
<td>58 (9.8)</td>
</tr>
<tr>
<td></td>
<td>Conversion to open heart surgery</td>
<td>6 (2.7)</td>
<td>16 (2.7)</td>
</tr>
<tr>
<td></td>
<td>Major access site complications</td>
<td>6 (2.7)</td>
<td>14 (2.4)</td>
</tr>
<tr>
<td></td>
<td>Cardiac tamponade</td>
<td>5 (2.2)</td>
<td>12 (2.0)</td>
</tr>
</tbody>
</table>

Values are n (%) or mean±SD unless otherwise indicated. LBBB indicates left bundle-branch block. *Defined as distance between the lower edge of the noncoronary cusp and the lower edge of the frame >8 mm.

**Table 3. Clinical Events at 30 Days and 1 Year**

<table>
<thead>
<tr>
<th></th>
<th>LBBB (n=224)</th>
<th>No LBBB (n=594)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-Day follow-up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall mortality</td>
<td>13 (5.8)</td>
<td>32 (5.4)</td>
<td>0.62</td>
</tr>
<tr>
<td>Cardiac mortality</td>
<td>4 (1.8)</td>
<td>14 (2.4)</td>
<td>0.58</td>
</tr>
<tr>
<td>PM implantation</td>
<td>11 (4.9)</td>
<td>12 (2.0)</td>
<td>0.02</td>
</tr>
<tr>
<td>NYHA class I or II</td>
<td>197 (87.9)</td>
<td>516 (86.9)</td>
<td>0.86</td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>4 (1.8)</td>
<td>11 (1.8)</td>
<td>0.77</td>
</tr>
<tr>
<td>1-Year follow-up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall mortality</td>
<td>42 (18.7)</td>
<td>117 (19.7)</td>
<td>0.1</td>
</tr>
<tr>
<td>Cardiac mortality</td>
<td>20 (8.9)</td>
<td>54 (9.1)</td>
<td>0.7</td>
</tr>
<tr>
<td>PM implantation</td>
<td>41 (18.3)</td>
<td>101 (17.0)</td>
<td>0.6</td>
</tr>
<tr>
<td>NYHA class I or II</td>
<td>179 (79.9)</td>
<td>499 (84.0)</td>
<td>0.08</td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>17 (7.6)</td>
<td>47 (7.9)</td>
<td>0.7</td>
</tr>
</tbody>
</table>

Values are n (%). LBBB indicates left bundle-branch block; NYHA, New York Heart Association; and PM, pacemaker.

His Bundle, and its branches (Figure 6). Low implantation depth was more frequent among those who developed an LBBB, thus corroborating the compression/inflammation pathophysiological hypothesis. This phenomenon is different from what may occur after surgical aortic valve replacement.
that is, surgical trauma, ischemia, dissecting hematomas, and extending calcifications or granulomas, although it leads to the same conduction disturbance.

New-onset LBBB worsens 1-year survival after surgical aortic valve replacement. Possible explanations may be related to the fact that LBBB itself induces intraventricular and interventricular asynchrony, abnormal left ventricular diastolic filling patterns, and impairment of left ventricular systolic performance. Moreover, LBBB heightens the risk of life-threatening ventricular arrhythmias and sudden death. Given these premises, the high percentage of new-onset LBBB after TAVI spurred interest into whether this conduction disturbance could be associated with a worse prognosis after transcatheter procedures. The present data, from the largest registry to specifically evaluate this question, suggest that new-onset LBBB after TAVI is not associated with a worse prognosis. These findings are consistent with those from a previous report in which the development of an LBBB was not associated with adverse outcomes. On the other hand, another recent publication reporting on a smaller population of patients treated by TAVI with either the CRS or Edwards Sapien valve actually suggested a negative prognostic impact or even a neutralization of the benefit of TAVI when a new LBBB developed.

Another point that needs to be taken into account is the very high baseline risk of morbidity and mortality of this specific subset of patients. It could be postulated that the true effect of new-onset LBBB may be attenuated by the stronger impact of other negative predictors. Specifically, factors such as periprocedural complications, comorbidities, or paravalvular leak may exert a negative impact on early and late outcomes during follow-up, thus overshadowing the role of LBBB at 30 days. These factors have been investigated elsewhere.

As for the increased short-term risk of pacemaker implantation, the role of new-onset LBBB remains unclear. We hypothesize that the presence of LBBB might have an impact exclusively on acute and early risk of progression to advanced AV block but not on late risk. This assumption would be consistent with the compression/inflammation mechanism, which would increase inflammation, compression, and edema of the interventricular septum early after the procedure. As compression decreases and the inflammation disappears, the risk of progression to advanced AV block declines. Indeed, limited data are available about pacemaker dependency during follow-up in patients implanted with a pacemaker after TAVI. Nevertheless, it seems reasonable to advocate that patients presenting with new-onset LBBB require close monitoring in the early post-TAVI period, and a routine Holter ECG to detect paroxysmal advanced AV block or life-threatening arrhythmias should be considered. On the other hand, conventional echocardiography and tissue Doppler imaging

Figure 4. New York Heart Association (NYHA) functional class at admission (A), discharge (B), and last follow-up (C). LBBB indicates left bundle-branch block.
techniques offer the potential for a detailed clarification of the effects of LBBB on cardiac contraction.22–24

Study Limitations
This was a very large multicenter registry. There was no randomization, and differences in local experience could have added bias to the present results. In particular, a percentage of patients were excluded from the final population as a consequence of pacemaker implantation early after TAVI, during the time window of temporary pacing. A clear retrospective diagnosis leading to pacemaker implantation was not possible at that early phase. Our finding of an overall 10% rate of pacemaker implantation at 1 month (7% within the first 48 hours and a further 3% within the first month) seems low compared with that of Tamburino et al,6 who reported a rate of ≈16%. This difference may be related to the fact that all patients with preexisting LBBB, that is, a subgroup at higher risk for progression to advanced AV block, were excluded from the final population of the present study. Registries are typically limited in their ability to measure end points beyond survival and can be misleading if data monitoring is less than accurate; however, the present data were collected in a nationwide registry and monitored extensively. Moreover, this database since inception has included the first few centers in Italy in which the TAVI experience reached a high-volume level, which means that any impact of a learning curve is unlikely or at least homogeneously shared across enrolling centers. There was no central adjudication of events; however, Valve Academic Research Consortium definitions were adopted to standardize results. There was no selection bias, a common flaw of study registries, because every single patient was included in the registry from participating centers, and the rate of clinical follow-up was quite high.

At 1-year follow-up, echocardiographic data were available for <50% of the cases. As in any other large real-world multicenter registry, the standardization and collection of echocardiographic follow-ups was complicated by local logistical issues. However, the rates of complete echocardiographic follow-up in the present study were consistent with those observed in other national registries.

Conclusions
TAVI is a relatively new therapeutic option for patients at high or even prohibitive risk for conventional surgical aortic valve replacement. Its availability triggered a paradigm change in the management of these patients by fulfilling a true and unmet clinical need. Intense research in this field is aimed at delineating which factors worsen or ameliorate
outcomes, as well as the preventive or therapeutic approaches that consequently are required. Unlike traditional surgical aortic valve replacement, new-onset LBBB after TAVI does not negatively affect 30-day or 1-year survival. Nevertheless, new-onset LBBB appears to be associated with a higher short-term risk of pacemaker implantation, albeit in the multifaceted risk scenario of conduction disturbances after TAVI.

Disclosures

Drs Bedogni, Ussia, Petronio, and Ramondo are TAVI medical proc-
tors for Medtronic. Dr Latib serves on a Medtronic Advisory Board. However, Medtronic had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. The other authors report no conflicts.

References


---

**CLINICAL PERSPECTIVE**

A new-onset left bundle-branch block (LBBB) after surgical aortic valve replacement is associated with a worse prognosis. Of note, a new LBBB is quite frequent in patients undergoing transcatheter aortic valve implantation by means of the CoreValve Revalving system. Whether this conduction disturbance could have an ominous impact is still unclear. In this large multicenter registry, we observed a new-onset LBBB in >40% of the patients after the procedure. This percentage decreased at discharge to 27%. Patients who had an LBBB at discharge also had the LBBB at 30 days. On the other hand, at 30-day follow-up, no new LBBBs were observed among patients without LBBB at discharge. A new-onset LBBB was not associated with higher all-cause mortality, cardiac mortality, or hospitalization for heart failure at 30 days and at 1 year. At 30 days, but not at 1 year, patients presenting with a new-onset LBBB had a significantly higher rate of pacemaker implantation. From a clinical perspective, we found no evidence of any correlation between the development of LBBB and an increased risk of major adverse events. Nevertheless, these data highlight the need for closer follow-up of patients who develop an LBBB after transcatheter aortic valve implantation by means of the CoreValve Revalving system, because they are prone to develop arrhythmias that require permanent pacing.
Clinical Impact of Persistent Left Bundle-Branch Block After Transcatheter Aortic Valve Implantation With CoreValve Revalving System
Luca Testa, Azeem Latib, Federico De Marco, Marco De Carlo, Mauro Agnifili, Roberto Adriano Latini, Anna Sonia Petronio, Federica Ettori, Arnaldo Poli, Stefano De Servi, Angelo Ramondo, Massimo Napodano, Silvio Klugmann, Gian Paolo Ussia, Corrado Tamburino, Nedy Brambilla, Antonio Colombo and Francesco Bedogni

_Circulation_. 2013;127:1300-1307; originally published online February 26, 2013;
doi: 10.1161/CIRCULATIONAHA.112.001099
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2013 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/127/12/1300

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/