Association of Long vs Standard Detection Intervals for Implantable Cardioverter-Defibrillators With Hospitalizations and Costs

The role of implantable cardioverter-defibrillators (ICDs) in reducing sudden and overall mortality is established. Recently, an ICD programming strategy that allows delayed detection of arrhythmias was shown to reduce unnecessary and inappropriate therapies.2,3

In this exploratory analysis of the Avoid Delivering Therapies for Non-sustained Arrhythmias in ICD Patients III (ADVANCE III) trial, we assessed the association of programming a long-detection interval on hospitalizations, length of stay (LOS) in the hospital, and costs.

Methods | The ADVANCE III study design has been published.4 Briefly, at 94 international centers between 2008 and 2010, 1902 patients receiving their first ICD were randomized to a long-detection interval group (the number of intervals to detect arrhythmias was programmed at 30 of 40) or a standard interval group (18 of 24 intervals). Patients were blinded to assignment. In both groups, antitachycardia pacing during capacitor charge was activated. Patients were followed up every 3 months for 1 year.

Each institutional review board approved the study and written informed consent was obtained from each participant. Diagnosis, delivered therapies, recovery, and discharge dates for hospitalizations related to each adverse event were requested in the case report forms. An independent committee reviewed all events, querying the center in case of unclear information.

The economic effect was a prespecified secondary outcome. Overall and cardiovascular hospitalization rates, time to first hospitalization, and LOS in the hospital were exploratory outcomes. To account for different follow-up durations, the number of hospitalizations and LOS were adjusted by considering the total number of patient-years and estimating annual incidence rates. Time to first event curves were generated using the Kaplan-Meier method and survival distributions were compared by the log-rank test.

Table. Rates of Hospitalizations, Length of Stay (LOS), and Mean Cost per Patient-Year

<table>
<thead>
<tr>
<th>Exposure Time/Patient-Year</th>
<th>No. of Hospitalizations</th>
<th>No. of Patients</th>
<th>Rate/100 Patient-Years (95% CI)</th>
<th>IRR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall hospitalizations</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard interval</td>
<td>904</td>
<td>473</td>
<td>302</td>
<td>52.3 (47.7-57.3)</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Long-detection interval</td>
<td>895</td>
<td>392</td>
<td>244</td>
<td>43.8 (39.6-48.4)</td>
<td>0.84 (0.73-0.96)</td>
</tr>
<tr>
<td>Cardiovascular hospitalizations</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard interval</td>
<td>904</td>
<td>364</td>
<td>238</td>
<td>40.3 (36.2-44.6)</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Long-detection interval</td>
<td>895</td>
<td>293</td>
<td>193</td>
<td>32.7 (29.1-36.7)</td>
<td>0.81 (0.69-0.95)</td>
</tr>
<tr>
<td>Overall hospital LOS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard interval</td>
<td>904</td>
<td>4246</td>
<td>302</td>
<td>470 (456-484)</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Long-detection interval</td>
<td>895</td>
<td>3647</td>
<td>244</td>
<td>407 (394-421)</td>
<td>0.87 (0.83-0.91)</td>
</tr>
<tr>
<td>Cardiovascular hospital LOS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard interval</td>
<td>904</td>
<td>3326</td>
<td>238</td>
<td>368 (356-381)</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Long-detection interval</td>
<td>895</td>
<td>2665</td>
<td>193</td>
<td>298 (287-309)</td>
<td>0.81 (0.77-0.85)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mean Cost/Patient-Year (95% CI), $</th>
<th>Mean Cost Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall hospitalizations</td>
<td></td>
</tr>
<tr>
<td>Standard interval</td>
<td>904</td>
</tr>
<tr>
<td>Long-detection interval</td>
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<tr>
<td>Cardiovascular hospitalizations</td>
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<tr>
<td>Standard interval</td>
<td>904</td>
</tr>
<tr>
<td>Long-detection interval</td>
<td>895</td>
</tr>
</tbody>
</table>

Abbreviation: IRR, incidence rate ratio.

* Exposure time considered in this analysis differs from that in eTable 2 in Gasparini et al5 because of different definitions of exposure time (from enrollment to last scheduled visit vs last known date). Loss to follow-up was limited (17/95 [1.8%] in the standard interval group and 20/948 [2.1%] in the long-detection interval group). In 44/473 (9.3%) patients in the standard interval group and 39/392 (9.9%) cases in the long-detection interval group, data on hospital LOS was missing. The median hospital LOS (7 days in both groups) was used to impute those missing values.
The International Classification of Diseases, Ninth Revision, Clinical Modification, codes were used to assign the proper diagnosis related group (and cost) for each hospitalization. Cost per patient-year was presented as mean and 95% confidence interval and was adjusted for the total number of patient-years. A mean cost ratio was performed to compare costs between groups. Stata version 12.0 (StataCorp) was used, and a 2-sided probability value of ≤.05 was used for declaring statistical significance.

**Results** | Of 1902 patients randomized, the 948 in the long-detection interval and 954 in the standard interval groups presented similar demographics as previously described.² During 12 months of follow-up, 546 patients reported 865 overall hospitalizations (473 hospitalizations in 302 patients in the standard interval group and 392 hospitalizations in 244 patients in the long-detection interval group) (Table).

The long-detection interval group was associated with a longer time to the first overall hospitalization (hazard ratio, 0.81 [95% CI, 0.68-0.95]; P = .01) and cardiovascular hospitalization (hazard ratio, 0.81 [95% CI, 0.67-0.98]; P = .03) compared with the standard interval group (Figure), and reductions in overall hospitalization rate (52.3 [95% CI, 47.7-57.3] vs 43.8 [95% CI, 39.6-48.4], respectively, per 100 patient-years; incidence rate ratio, 0.84 [95% CI, 0.73-0.96]; P = .005) and LOS (470 [95% CI, 456-484] vs 407 [95% CI, 394-421] per 100 patient-years; incidence rate ratio, 0.87 [95% CI, 0.83-0.91]; P < .001), without difference in mortality.²

Similar results were found for cardiovascular hospitalization rates and LOS (Table). The long-detection interval group was also associated with a mean reduction of $299 per patient-year for overall hospitalizations and $329 per patient-year for cardiovascular hospitalizations compared with the standard interval group (Table).

**Discussion** | These exploratory analyses of the ADVANCE III trial found that a programming strategy combining a long-detection interval and antitachycardia pacing during charging was associated with an increase in the time to first hospitalization and reductions in hospitalization rate, LOS, and the cost per patient-year compared with standard interval programming. The reduction in all-cause hospitalizations was mainly driven by the reduction in cardiovascular hospitalizations (P = .004). This result is consistent with the RELEVANT trial,³ which in contrast enrolled only patients with nonischemic cardiomyopathy treated with cardiac resynchronization therapy defibrillators.

As a limitation, costs were estimated, not directly collected, and follow-up was limited to 1 year. These favorable results for resource use complement the demonstrated clinical effectiveness of the long-detection interval strategy and come without additional costs for the hospitals or patients.

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**Administrative, technical, or material support:** Manotta.

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COMMENT & RESPONSE

Age-Adjusted D-Dimer Cutoff Levels and Pulmonary Embolism

To the Editor The study by Dr Righini and colleagues1 validated the use of an age-adjusted D-dimer cutoff level to rule out pulmonary embolism. The 6 different D-dimer assays used in the study were demonstrated to be equivalent in a previous meta-analysis.2 Nevertheless, we noticed that there was a significant difference among the assays in the proportion of negative results, considering both standard and age-adjusted D-dimer cutoff levels.

This variability may be the result of different characteristics of patients in each subgroup, such as age distribution, or the different diagnostic accuracy of the assays, thus reducing the reliability of the results. Further information about the patients in the different subgroups could be helpful for solving this issue.

However, considering both the variability and that the upper 95% confidence limit of most of the assays’ failure rates was near or included 3% (upper confidence limit of <3% was prespecified to validate the cutoff), most assays would not be appropriate for clinical use.

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In Reply Mr Colombo and colleagues asked whether all D-dimer assays perform equally when using the age-adjusted D-dimer cutoff to rule out pulmonary embolism or whether different patient characteristics could explain the variability in the proportion of patients with negative D-dimer levels.

We favor the latter hypothesis. There were important differences in patient characteristics across assay subgroups. For example, mean age varied from 58 years in the VIDAS D-Dimer Exclusion group to 67 years in the Tina-quant D-Dimer group.

The proportion of patients with cancer varied from 5% in the VIDAS D-Dimer Exclusion group to 16% in the Innovance D-Dimer group. The proportion of patients with a history of venous thromboembolism was 7.5% in the Liestat D-Dimer group vs 15.7% in the Tina-quant D-Dimer group.

Our study did not have sufficient power to provide narrow confidence intervals around the estimates of the 3-month thromboembolic risk for each individual D-dimer assay; only the VIDAS D-Dimer Exclusion assay had a failure rate upper confidence limit of less than 3%.

However, we believe that the generalizability of our findings is also supported by the large amount of previous retrospective data using many different D-dimer tests.1,2

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