Long-term clinical effects of ventricular pacing reduction with a changeover mode to minimize ventricular pacing in a general pacemaker population

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Aim
Right ventricular pacing (VP) has been hypothesized to increase the risk in heart failure (HF) and atrial fibrillation (AF). The ANSWER study evaluated, whether an AAI-DDD changeover mode to minimize VP (SafeR) improves outcome compared with DDD in a general dual-chamber pacemaker population.

Methods and results
ANSWER was a randomized controlled multicentre trial assessing SafeR vs. standard DDD in sinus node disease (SND) or AV block (AVB) patients. After a 1-month run-in period, they were randomized (1 : 1) and followed for 3 years. Pre-specified co-primary end-points were VP and the composite of hospitalization for HF, AF, or cardioversion. Pre-specified secondary end-points were cardiac death or HF hospitalizations and cardiovascular hospitalizations. ANSWER enrolled 650 patients (52.0% SND, 48% AVB) at 43 European centres and randomized in SafeR (n = 314) or DDD (n = 318). The SafeR mode showed a significant decrease in VP compared with DDD (11.5 vs. 93.6%, P < 0.0001 at 3 years). Deaths and syncope did not differ between randomization arms. No significant difference between groups [HR = 0.78; 95% CI (0.48–1.25); P = 0.30] was found in the time to event of the co-primary composite of hospitalization for HF, AF, or cardioversion, nor in the individual components. SafeR showed a 51% risk reduction (RR) in experiencing cardiac death or HF hospitalization [HR = 0.49; 95% CI (0.27–0.90); P = 0.02] and 30% RR in experiencing cardiovascular hospitalizations [HR = 0.70; 95% CI (0.49–1.00); P = 0.05].

Conclusion
SafeR safely and significantly reduced VP in a general pacemaker population though had no effect on hospitalization for HF, AF, or cardioversion, when compared with DDD.

Keywords
Dual-chamber pacing • Minimization of ventricular pacing • Heart failure • Atrial fibrillation • Randomized controlled trial • SafeR

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Introduction

The risk in experiencing adverse cardiac outcomes due to ventricular pacing (VP) with dual-chamber pacemakers is well established. Ventricular pacing modifies left ventricular (LV) contraction by generating an electrical activation sequence resembling a left bundle branch block. The resulting dyssynchrony is associated with LV remodelling, reduced ejection fraction (EF), and increased risk in heart failure (HF) and death in patients with already depressed LVEF. A secondary analysis from the mode selection trial (MOST) established the hypothesis that also pacemaker patients with preserved LVEF may develop HF depending on the prevalence of right VP. Accordingly, a number of different pacing algorithms have been developed that reduce the degree of VP in the atrio-ventricular (AV) sequential pacing mode (DDD). Such systems have been shown in clinical studies to reduce the risk in developing atrial fibrillation (AF), mainly in patients with sinus node disease (SN). The SafeR algorithm (Sorin CRM, Clamart, France) was developed to individually adapt to a patient’s varying AV conduction and to combine the benefits of single-chamber atrial pacing (AAI) with the safety of DDD pacing. Several randomized trials have previously confirmed the efficient VP prevention and safety of the algorithm in selected populations. In the SafeR study, SafeR reduced VP over 1 year in selected patients with preserved or minimally impaired AV conduction compared with DDD. However, in patients with conventional indication to pacemaker, including AV block (AVB), long-term data on the impact of SafeR on the risk in developing adverse cardiac outcomes, including developing HF or AF, is undetermined.

Methods

Study design

The ANSWER study was an investigator-initiated, prospective, randomized, single-blind, controlled, parallel-design, European, multicentre (43 centres) trial. Patients aged ≥18 years were included if they had a pacemaker indication and had received a dual-chamber pacemaker equipped with the SafeR mode less than a month prior to enrolment. The pacemaker indication was based on the diagnosis of SN, second degree intermittent AVB, or third degree intermittent or permanent AVB. Patients were excluded if they had permanent AF, sustained ventricular arrhythmias, congenital complete heart block, or vasovagal syncope. The study was conducted in accordance with the declaration of Helsinki and Good Clinical Practice. The protocol was approved by the local ethics committees.

Devices implanted and randomization

SafeR-enabled pacemakers were used (Symphony 2550 device or REPLY DR, Sorin CRM SAS). The SafeR dual-chamber pacemaker mode has been designed to privilege intrinsic AV activation, while continuously monitoring spontaneous AV conduction and delivering right VP only temporarily, and only in case of demonstrated lasting long PR or repetitively lacking intrinsic ventricular activation. This changeover pacing mode commutes between single-chamber atrial (AAI) pacing and dual-chamber pacing (DDD) and has previously been described in detail. The selection of atrial (bipolar configuration required) and right VP leads was left to the implanters’ discretion. All devices implanted were CE marked at the beginning of the study.

At implant, all pacemakers were programmed to SafeR for 1 month. Subsequently, patients were randomized in a 1:1 fashion to the SafeR mode (SafeR group) or to a conventional dual-chamber pacing mode (DDD) with a nominal AV delay (155 ms after a sensed atrial event, 220 ms after a paced atrial event, dynamic shortening with increasing heart rate) as preferred settings (control group).

Follow-up and study end-points

Follow-up visits were scheduled after enrolment before hospital discharge, at 1 month (randomization visit), at 6, 12, 18, 24, and 36 months (termination visit). At each visit, the device memory was interrogated.

ANSWER had a co-primary technical end-point, the percentage of VP at 1 year, and a co-primary clinical end-point, a composite of hospitalization for HF, AF, or cardioversion at 3 years. Pre-specified secondary end-points comprised the percentage of VP at 3 years, the individual components of the co-primary composite end-point, hospitalization for HF or cardiac death, and CV hospitalization (defined as hospitalization for major cardiovascular event, HF, AF, cardioversion, ventricular tachycardia, and cardiac death, occurring at hospital). The comparison of the hospital stay during these cardiovascular hospitalizations was performed as an ancillary analysis.

Collection and adjudication of adverse events

The assessment relied on the site investigators notification of any serious adverse event (AE) and all device-related AE. The site investigators were supported in the detection of events by study monitors. All these events were reported on specific AE forms and had to be transferred to the study manager as soon as possible and no later than five working days after detection. The AE forms included information on the time course, symptoms, treatment modalities, and diagnosis. All events were blindly reviewed and categorized by the Study Steering Committee during regular meetings. The events, including deaths, were adjudicated and classified as serious (Y/N), protocol-related (Y/N), device-related (Y/N), procedure-related (Y/N), hospitalization (Y/N), AF-related (Y/N), HF-related (Y/N), cardioversion (Y/N), other cardiovascular event (Y/N), clinical (non-cardiovascular) event (Y/N), syncope (Y/N). In syncpe patients with unclear clinical presentation, the device memory was also reviewed with the aim to identify a correlation with asystolic pauses during AAI-DDD commutations, and to check for possible ventricular tachyarrhythmias induced by changeover episodes. If deemed necessary, additional information was requested from the study sites.

Data on percentage of VP were ascertained from device memories. Changes of the programming mode, retrieved from case report forms and implant files, were also reviewed by the Steering Committee.

Sample size and statistical methods

The trial was designed to detect the effects for both co-primary end-points. The sample size calculation was thus based on the 1-year assumed rate of VP and the 3-years expected incidence of the composite of hospitalization for HF, AF, or cardioversion. Under the assumption of (i) per cent of VP of 30.7% in the control group and 7.1% in the SafeR group, with a common standard deviation of 34%; (ii) frequency of the composite end-point of 20% in the control group and 10% in the SafeR group, corresponding to a difference of 10% With a statistical power...
of 90% and a type 1 error of 0.025 (two-sided), we estimated the sample size to 45 and 532 patients in total, respectively, for the cumulative percent of VP (co-primary technical end-point at 1 year) and for hospitalization for HF, AF, or cardioversion (co-primary composite end-point at 3 year). Therefore, the sizing was based on the sample size of 532 patients. The rate of loss to follow-up was estimated at 20%, and we therefore planned to enroll 440 patients in total.

The co-primary technical end-point on the percentage of VP was calculated on the intention-to-treat (ITT) population with at least one implant file; and analysed using the Last Observation Carried Forward imputation method. The number of patients with missing data for whom the last observation needed to be carried forward is reported. The co-primary composite end-point was analysed based on a Kaplan–Meier analysis, with patients dropping out censored at the time of their last observation. A Bonferroni correction was applied to both co-primary end-points and a P-value of 0.025 was set as the significance limit for both co-primary end-points. Each of the co-primary end-points had to be significant at the 0.025 level in order to reach the primary end-point. All secondary end-points were carried out on the ITT population and considered statistically significant at a P-value of 0.05. All of them though were considered exploratory.

The co-primary technical end-point on the percentage of VP was analysed by the Mann–Whitney U-test. The co-primary composite end-point (hospitalization for HF, AF, and cardioversion) was analysed by Kaplan–Meier curves and rates per 100 person/year for description, log-rank test for comparisons, Cox model with calculation of hazard ratio (HR) and 95% CI for quantifying the effect. The end-point of the duration of hospitalization for cardiovascular event was analysed using a 0 inflated negative binomial regression.

For non-normally distributed data, median values and inter-quartile ranges are presented for hospitalization for cardiovascular event was analysed using a 0 inflated negative binomial regression.

Likewise both individual components of the co-primary composite end-point showed no significant difference between randomization arms, although for the HF component a numerical reduction tended to favour SafeR (hospitalization for HF: HR = 0.58; 95% CI: 0.31–1.09; P = 0.09; Figure 2B); hospitalization for AF or cardioversion did not significantly differ between randomization groups (HR = 0.78; 95% CI: 0.48–1.25; P = 0.30; Figure 2A).

Safety
No differences in the occurrence of death and device- or procedure-related events were observed between treatment groups (Table 2). None of the syncopal events reported was considered device-related, and no pro-arrhythmic effects of changeover episodes were documented.

Discussion
ANSWER investigated VP prevention and long-term clinical outcomes of an AAI–DDD changeover mode designed to minimize VP (SafeR™) in a typical patient population indicated to conventional cardiac pacing, as shown by an equal proportion of included patients presenting with either SND and/or AVB. The study met the co-primary technical end-point; it showed that VP was significantly reduced as well, whereas the algorithm safely provided mandatory VP in those with permanent AVB. Importantly, the percentage of VP increased over time, which reflects
progressive AV conduction disease. In contrast, the co-primary clinical end-point, represented by a combination of hospitalization for HF or AF or cardioversion, did not significantly differ between the randomization groups, nor were the individual end-point components significantly different in the DDD vs. SafeR group.

Dual-chamber pacing implies a trade-off between the paced restoration of a reasonable heart rate and undesired pacing-induced cardiac dyssynchrony. But it is sometimes difficult to decide, when pacing is actually required, and when it is more appropriate to avoid pacing. This is particularly true for patients with intermittent AVB and in those with a prolonged PR interval. In these patients, re-establishing a favourable AV sequence by VP with best possible transmitral LV filling may be offset by pacing-induced LV impairment; and vice versa, preserving prolonged intrinsic AV conduction may prevent pacing-related dysynchrony, but may in turn produce undesirably fused transmitral filling.

A secondary analysis of a large pacemaker study to compare DDD vs. VVI in SND14 founded the hypothesis that VP favours clinical HF despite a fairly preserved LVEF.5 Another smaller randomized study2 showed that in SND with normal AV conduction DDD with short or long AV delay was associated with more AF compared with AAI. The impairment of LV haemodynamics by right VP15 was hypothesized to be responsible for the observed adverse effects. Modifiers of right VP adverse effects can likely be seen in the global LV systolic function and the presence of an unpaced bundle branch block (BBB). Patients with depressed LVEF may particularly be harmed by pacing-induced dysynchrony and require biventricular pacing in case of AVB, 4,16 whereas those with BBB and already compromised electromechanical activation may experience less of a disadvantage by right VP.17–19

Several large studies, conducted in highly selected populations, investigated the effect (AF-related and HF-related outcome) of different device-based pacing strategies to prevent VP.6,20–22 The SAVEPACe study,6 conducted in patients with SND and preserved intrinsic AV conduction, evaluated a mixture of VP prevention programming compared with DDD with a high percentage of...

### Table 1  Baseline characteristics of the study population

| Clinical characteristics | Enrolled (n = 650) | SafeR group (n = 314) | DDD group (n = 318) |
|--------------------------|-------------------|----------------------|---------------------|
| Age, mean ± SD, years    | 72.4 ± 11.2       | 71.8 ± 12.2          | 72.9 ± 9.8          |
| Male gender, n (%)       | 358 (55.2)        | 182 (58.0)           | 169 (53.1)          |
| Heart disease, n (%)     |                   |                      |                     |
| Coronary artery disease  | 183 (28.2)        | 87 (27.7)            | 91 (28.6)           |
| Dilated cardiomyopathy   | 31 (4.8)          | 15 (4.8)             | 13 (4.1)            |
| Valvular disease (%)     | 84 (12.9)         | 37 (11.8)            | 44 (13.8)           |
| Comorbidities, n (%)     |                   |                      |                     |
| Arterial hypertension    | 423 (65.1)        | 197 (62.7)           | 215 (67.6)          |
| COPD                     | 32 (4.9)          | 13 (4.1)             | 17 (5.3)            |
| Diabetes                 | 140 (21.5)        | 68 (21.7)            | 68 (21.4)           |
| Sinus node disease       | 336 (52.0)        | 167 (53.5)           | 160 (50.5)          |
| AV block                 | 310 (48.0)        | 145 (46.5)           | 157 (49.5)          |
| Intermittent AV block    | 270 (41.8)        | 127 (40.7)           | 136 (42.9)          |
| Permanent AV block       | 40 (6.2)          | 18 (5.8)             | 21 (6.6)            |
| Symptoms of HF           |                   |                      |                     |
| None, n (%)              | 202 (32.0)        | 103 (33.7)           | 91 (29.4)           |
| NYHA I/II/III/IV, %      | 43.0/50.7/5.8/0.5 | 41.9/53.7/3.9/0.5    | 44.5/48.6/4.5/0.5   |
| LVEF, mean ± SD, %       | 58.3 ± 8.7        | 58.6 ± 9.1           | 58.2 ± 8.3          |
| ECG parameters           |                   |                      |                     |
| LBBB, n (%)              | 64 (11.1)         | 29 (10.4)            | 31 (11.1)           |
| LAHB, n (%)              | 52 (8.7)          | 29 (9.9)             | 23 (7.9)            |
| LPHB, n (%)              | 1 (0.2)           | 1 (0.4)              | 0 (0)               |
| AR, mean ± SD, ms        | 214.0 ± 58.2      | 207.1 ± 55.9         | 219.8 ± 60.2        |
| PR, mean ± SD, ms        | 191.4 ± 45.2      | 189.6 ± 47.1         | 191.8 ± 43.6        |
| Arrhythmias history, n (%)|                   |                      |                     |
| Atrial arrhythmiasb      | 248 (38.2)        | 116 (37.1)           | 125 (39.3)          |
| Ventricular arrhythmias  | 16 (2.5)          | 2 (0.6)              | 13 (4.1)            |

AR, atrial-paced—ventricle-sensed interval; AV block, atrio-ventricular block; COPD, chronic obstructive pulmonary disease; HF, heart failure; LAHB, left anterior hemi-block; LBBB, left bundle branch block; LPHB, left posterior hemi-block; LVEF, left ventricular ejection fraction determined by echocardiography; NYHA, New York Heart Association; SD, standard deviation; PR, atrial—sensed—ventricle-sensed interval.

a Determined on SND and AVBI patients only.
b Atrial fibrillation, flutter, or tachycardia.
Figure 1 CONSORT flow diagram.

Figure 2  (A) Freedom from hospitalization for heart failure, atrial fibrillation or cardioversion. (B) Freedom from hospitalization for heart failure. (C) Freedom from hospitalization for atrial fibrillation or cardioversion.
VP; it demonstrated a prolonged time to persistent AF by VP prevention. In contrast, three recently published large pacemaker trials\textsuperscript{20–22} fell short of confirming a significant clinical advantage through VP prevention. The DANPACE trial\textsuperscript{20} randomized 1415 SND patients to AAIR vs. DDDR and adapted the AV programming in the DDDR group to the baseline PR interval. This trial showed no differences in mortality or HF and a disadvantage of AAIR vs. DDD. The PREFER-MVP study\textsuperscript{21} randomized 605 patients without permanent AVB after pulse generator replacement to VP prevention by the managed ventricular pacing (MVP) mode, vs. DDD. This trial failed to demonstrate a difference in cardiovascular hospitalizations over 2 years. In a similar manner, MINERVA\textsuperscript{22} study which enrolled patients with bradycardia (mainly with SND and previous atrial tachyarrhythmias) and compared DDDR with the MVP mode with and without preventive atrial pacing algorithms (DDDRP), demonstrated successful prevention of permanent AF by DDDRP in this specific population, but showed no effect of VP prevention on AF progression, death, or cardiovascular hospitalization. Thus, findings of the ANSWER study are well in line with those of most recent trials that appear to collectively contradict the earlier SAVEPACe results\textsuperscript{6} with regard to the AF end-point. It must be kept in mind, however, that SAVEPACe demonstrated a prolonged time to persistent AF by VP prevention, but did not either show a difference in AF-related hospitalizations, HF, or death. When comparing these trials, the heterogeneous end-points, different VP prevention methods, and importantly different study populations must be considered.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure3.png}
\caption{(A) Freedom from hospitalization for heart failure or cardiac death. (B) Freedom from cardiovascular hospitalization.}
\end{figure}

\begin{table}[h]
\centering
\caption{Number of patients with death, device, or procedure-related events and syncope}
\begin{tabular}{llllll}
\hline
 & Overall (n = 650) & BR (n = 18) & SafeR (n = 314) & DDD (n = 318) & P-value \\
\hline
Deaths (%) & & & & & \\
All causes death & 58 (8.9) & 2 (0.3) & 26 (8.3) & 30 (9.4) & 0.61 \\
Cardiac death & 17 (2.6) & 1 (0.2) & 5 (1.6) & 11 (3.5) & 0.14 \\
Device or procedure-related adverse events (%) & & & & & \\
All device or procedure-related events & 28 (4.3) & 14 (2.1) & 6 (1.9) & 8 (2.5) & 0.61 \\
Lead dislodgment & 10 (1.5) & 6 (0.9) & 0 & 4 (1.3) & 0.12 \\
Lead fracture & 1 (0.2) & 0 & 0 & 1 (0.3) & 1.00 \\
Pocket hematoma & 4 (0.6) & 4 (0.6) & 0 & 0 & - \\
Pocket infection & 7 (1.1) & 3 (0.5) & 2 (0.6) & 2 (0.6) & 1.00 \\
Pocket erosion & 1 (0.2) & 0 & 1 (0.3%) & 0 & 0.50 \\
Pacing mode intolerance & 5 (0.8) & 2 (0.3) & 3 (1.0) & 1 (0.3) & 0.37 \\
Syncope & & & & & \\
Syncope & 16 (2.5) & 2 (0.3) & 5 (1.6) & 9 (2.8) & 0.42 \\
\hline
\end{tabular}
\begin{flushleft}
Results are presented as number of patients (% of patients).
A same patient could experience an event before and after randomization.
BR, before randomization.
\end{flushleft}
\end{table}
The ANSWER study further expands current knowledge because it included AVB patients (6% even with complete permanent AVB) who have not been previously considered. The SafeR changeover mode has safely been applied to a broader pacemaker population indicated for conventional pacing. No pro-arrhythmic adverse effects of SafeR have been observed, whereas the induction of ventricular tachycardia has been described as a rare side-effect of the AAI-to-DDD commutation pattern used by the MVP mode. All-cause mortality, cardiac mortality, and syncope were not significantly different between SafeR and DDD, but deaths and syncopal events occurred numerically less frequently in the SafeR group, which supports the view that this pacemaker mode is safe.

Interestingly, the components of the ANSWER co-primary composite end-point appeared to come out differently, despite both being non-significant. The survival curves for the AF end-point were superimposed, whereas the HF component showed a trend favouring SafeR. The favourable effect of SafeR-mediated VP prevention on HF outcomes, however, warrants further investigation, as the combined clinical secondary outcome of cardiac death or HF hospitalization differed in favour of the SafeR group, and a borderline significant reduction in cardiovascular hospitalizations and shorter duration of hospital stay for these hospitalizations was observed.

Additional favourable effects of the demonstrated VP prevention in AVB patients are the possibly diminished need for biventricular pacing in those with paroxysmal AVB (but otherwise normal PR) and reduced LVEF and improved device longevity by reduced energy consumption.

**Study limitations**

The ANSWER study and the co-primary clinical end-point have been designed in 2006–07 based on available knowledge, before the heterogeneous SAVEPACe6 and DANPACE21 results had been published. The pacemaker memory stores paced and sensed events, but the extent of fused or pseudo-fused pacing, which is likely to be unequal in both randomization groups, cannot be retrieved from the counters. One-fifth of the ANSWER population had LBBB or other types of BBB. This may have extenuated the effects of VP prevention. The occurrence of the primary end-point was lower than predicted by the sample size calculation, which limits the statistical power. Because ANSWER study was a single-blinded study, a possible influence, yet likely marginal, of the investigators’ knowledge of the treatment arm on clinical outcome components cannot be ruled out with certainty. Although many of the cardiac deaths in the study occurred in the hospital following an HF hospitalization, it must be said that the classification of causes of death is generally associated with significant uncertainty.

**Conclusions**

The SafeR pacemaker mode significantly reduced VP compared with DDD in a broad population clinically indicated to dual-chamber pacemaker, regardless of the primary electrical disease (SNR or AVB). The risk in experiencing hospitalization for HF or AF/AFL cardioversion was not significantly reduced by SafeR vs. DDD. Secondary end-point results warrant further investigation of SafeR-mediated prevention of HF.
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