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Heparin dosing in uninterrupted anticoagulation with dabigatran vs. warfarin in atrial fibrillation ablation: RE-CIRCUIT study

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Aims To describe heparin dosing requirements in patients who underwent catheter ablation of atrial fibrillation with uninterrupted anticoagulation using dabigatran etexilate (dabigatran) or warfarin to attain therapeutic activated clotting time (ACT) in the RE-CIRCUIT® study. The RE-CIRCUIT study showed significantly fewer major bleeding events in the dabigatran vs. warfarin treatment group. Unfractionated heparin was administered during the procedure to maintain ACT >300 s.

Methods and results Patients were randomly assigned to dabigatran 150 mg bid or international normalized ratio-adjusted warfarin. Ablation was performed with uninterrupted anticoagulation and continued for 8 weeks after the procedure. Heparin was administered after placement of femoral sheaths before or immediately after transseptal puncture. Ablation was performed in 635 patients (dabigatran, 317; warfarin, 318); data were available from 396 patients administered heparin (dabigatran, 191; warfarin, 205). Most frequent time window from last dose of study drug to septal puncture was 0 to <4 h in the dabigatran (41.3%) and 16 to <24 h in the warfarin arms (44.7%). Overall mean (standard deviation) heparin dose was similar between the dabigatran and warfarin groups [12 402 (10 721) vs. 11 910 (8359) IU, respectively]. Heparin dosing requirement to reach therapeutic ACT was lowest when time from last dose of dabigatran to septal puncture was 0 to <4 h.

Conclusion Patients treated with dabigatran required a similar amount of unfractionated heparin as those treated with warfarin to achieve an ACT of >300 s during ablation. More heparin units were required when the time from the last dose of dabigatran to septal puncture increased.

Keywords Atrial fibrillation • Anticoagulation • Catheter ablation • Dabigatran • Heparin dosing • Warfarin

Introduction

Catheter ablation is a widely used and effective interventional treatment for atrial fibrillation (AF).[1–4] However, periprocedural stroke or transient ischaemic attack and cardiac tamponade are serious complications associated with the ablation procedure.[1] Periprocedural management of anticoagulation in patients undergoing ablation is critical to limit these complications.[1] In patients with

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What's new?

- Previous evidence suggests that during atrial fibrillation ablation, heparin dose requirements differ in patients receiving non-vitamin K antagonist oral anticoagulant compared with vitamin K antagonists (VKAs).
- In this *post hoc* analysis of the RE-CIRCUIT study, the heparin dosing requirement was similar between the dabigatran and warfarin arms, thereby contrasting with results of the VENTURE-AF study, in which the average total heparin dose was higher in the rivaroxaban vs. VKA arm.
- The present analysis demonstrated that the closer the septal puncture was to the last anticoagulant dose, the lower the heparin requirement was to achieve the desired activated clotting time (ACT).
- This study also suggests that the heparin units required to reach the desired ACT may be affected by the time from the last preprocedural dose of dabigatran.

planned catheter ablation of AF, oral anticoagulation with a vitamin K antagonist (VKA) or non-vitamin K antagonist oral anticoagulant (NOAC) should be continued during the procedure, maintaining effective anticoagulation, and should be continued for at least 8 weeks afterwards.[3] Uninterrupted VKA during the ablation procedure has a lower risk of periprocedural bleeding and stroke than interrupted VKA and bridging with low molecular weight heparin.[5,6] In addition, the RE-CIRCUIT study observed a lower risk of bleeding with uninterrupted anticoagulation with dabigatran etexilate (dabigatran) compared with warfarin in patients undergoing catheter ablation for paroxysmal or persistent AF.[7]

According to current guidelines, catheter ablation of symptomatic AF is a Class I or II recommendation depending on previous antiarrhythmic treatment and AF type.[1–3] According to the Heart Rhythm Society, the European Heart Rhythm Association, the European Cardiac Arrhythmia Society, the Asia Pacific Heart Rhythm Society, and the Latin American Society of Cardiac Stimulation and Electrophysiology (Sociedad Latinoamericana de Estimulación Cardíaca y Electrofisiología) expert consensus statement, performing the ablation procedure without interruption of warfarin or dabigatran is a Class I recommendation.[4] The current guidelines also recommend systemic anticoagulation with heparin during the ablation procedure to maintain an activated clotting time (ACT) of more than 300 s to reduce the risk of thromboembolic events associated with the ablation procedure.[1,4] Previous guidelines suggested that a loading dose of 100 U/kg heparin be administered, followed by heparin infusion at 10 IU/kg/h in order to achieve ACT >300 s.[8] The current guidelines do not recommend which heparin to use (e.g. unfractionated heparin, or low molecular weight heparin) or the dosage regimen to achieve ACT >300 s, with the suggestion that ACT levels be checked every 10–15 min until >300 s, and then every 15–30 min for the remainder of the procedure.[1,4] According to a European Heart Rhythm Association survey, the first loading dose of heparin was given after a transseptal puncture in the majority of centres (69.4%).[9]

Dabigatran can prolong activated partial thromboplastin time (aPTT) and ACT in a dose-dependent manner.[10] Previous evidence suggests that heparin dose requirements differ in patients receiving NOACs compared with VKAs. A single-centre Japanese study that assessed the differences in ACT and initial heparin dosing in patients receiving NOACs and warfarin showed the need for a higher initial bolus heparin dose for NOACs compared with warfarin (120–130 U/kg vs. 100 U/kg).[11] A limited number of other single-centre studies that examined the heparin[7] (two studies evaluated unfractionated heparin[12,13]) requirements and ACTs associated with NOACs and warfarin showed that NOACs require a higher dose of heparin and more time to reach the target ACT compared with uninterrupted warfarin.[12–14]

In the RE-CIRCUIT trial, the rate of bleeding events was significantly lower with dabigatran compared with warfarin (risk difference −5.3%, 95% confidence interval −8.4 to −2.2; $P < 0.001$).[7] In this *post hoc* analysis of the RE-CIRCUIT data, we evaluated the differences in heparin dosing between the dabigatran and warfarin treatment groups.

Table 1 ACT (ablation set)

	Dabigatran	Warfarin	Total
Patients ablated, *n*	317	318	635
Individual mean ACT			
N	312	308	620
Mean (SD), s	330 (81.0)	342 (74.0)	336 (77.8)
ACT categories			
Maintained >300 s, *n* (%)	101 (31.9)	96 (30.2)	197 (31.0)
Dropped ≤300 s, *n* (%)	213 (67.2)	213 (67.0)	426 (67.1)
Missing, *n* (%)	3 (0.9)	9 (2.8)	12 (1.9)

ACT, activated clotting time; SD, standard deviation.

Methods

Study design

RE-CIRCUIT was a prospective, randomized, open-label, blinded adjudicated-endpoint, multicentre, controlled study in patients scheduled for catheter ablation for paroxysmal or persistent AF (NCT02348723). The complete study design, methodology, and primary results were published previously.[7,15] In brief, eligible patients were randomly assigned to anticoagulation with dabigatran 150 mg bid or international normalized ratio-adjusted warfarin. Ablation was performed with uninterrupted anticoagulation, which was continued for 2 months after the procedure.[7] Unfractionated heparin was administered after placing femoral sheaths before or immediately after a transseptal puncture during AF ablation procedures. For the duration of the procedure when catheters were in the left atrium, it was recommended that weight-adjusted boluses of heparin should be adjusted to achieve and maintain an ACT >300 s. Investigators were instructed to measure ACT within 15 min after the administration of the bolus dose, and every 20 min subsequently.

The first post-procedural dose of dabigatran was administered in the evening of the procedure at the scheduled dosing time, with a minimum delay of 3 h after removal of the sheath and achievement of haemostasis. In this *post hoc* analysis, we compared heparin dosing, and the relationship between ACT, heparin dosing, and the time elapsed from morning administration of the study drug to transseptal puncture in the dabigatran and warfarin treatment groups. The study was performed in accordance with

Table 2 Baseline demographic and clinical characteristics in patients receiving heparin (ablation set)

	Dabigatran 150 mg, bid (*N* = 191)	Warfarin (*N* = 205)	Total (*N* = 396)
Age (years), mean (SD)	59.0 (10.0)	59.4 (10.1)	59.2 (10.1)
Male sex, *n* (%)	136 (71.2)	152 (74.1)	288 (72.7)
Mean BMI (kg/m^2)	28.1 (6.2)	28.3 (5.8)	28.2 (6.0)
CHA_2DS_2-VASc score, mean (SD)	1.9 (1.2)	2.1 (1.3)	2.0 (1.3)
Activated clotting time			
Patients analysed, *n*	188	196	384
Mean (SD), s	332 (52.6)	340 (71.9)	336 (63.2)
Medical history, *n* (%)			
CHF	20 (10.5)	23 (11.2)	43 (10.9)
LVD	13 (6.8)	11 (5.4)	24 (6.1)
CAD	14 (7.3)	29 (14.1)	43 (10.9)
PCI	6 (3.1)	10 (4.9)	16 (4.0)
Previous MI	4 (2.1)	7 (3.4)	11 (2.8)
Hypertension	100 (52.4)	115 (56.1)	215 (54.3)
Previous stroke	8 (4.2)	5 (2.4)	13 (3.3)
Previous major bleeding or predisposition	0 (0.0)	1 (1.0)	2 (0.5)
Previous GI bleeding, ulcerative GI disease or gastritis	14 (7.3)	14 (6.8)	28 (7.1)
Renal disease	6 (3.1)	9 (4.4)	15 (3.8)
Diabetes mellitus	15 (7.9)	18 (8.8)	33 (8.3)
AF, *n* (%)			
Paroxysmal	128 (67.0)	137 (66.8)	265 (66.9)
Persistent	52 (27.2)	54 (26.3)	106 (26.8)
Long-standing persistent	11 (5.8)	14 (6.8)	25 (6.3)
Baseline medication use, *n* (%)	184 (96.3)	198 (96.6)	382 (96.5)
VKA	48 (25.1)	55 (26.8)	103 (26.0)
Dabigatran	32 (16.8)	26 (12.7)	58 (14.6)
Rivaroxaban	18 (9.4)	15 (7.3)	33 (8.3)
Apixaban	14 (7.3)	18 (8.8)	32 (8.1)
Edoxaban	2 (1.0)	0 (0.0)	2 (0.5)
NSAIDs	35 (18.3)	42 (20.5)	77 (19.4)
PPIs	46 (24.1)	48 (23.4)	94 (23.7)
Statins	56 (29.3)	60 (29.3)	116 (29.3)
Beta-blockers	108 (56.5)	123 (60.0)	231 (58.3)

AF, atrial fibrillation; BMI, body mass index; CAD, coronary artery disease; CHF, congestive heart failure; GI, gastrointestinal; LVD, left ventricular dysfunction; MI, myocardial infarction; NSAIDS, non-steroidal anti-inflammatory drugs; PCI, percutaneous coronary intervention; PPI, proton pump inhibitors; SD, standard deviation; VKA, vitamin K antagonists.

the provisions of the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice Guidelines.[16,17] The study protocol and procedures were approved by the relevant institutional review boards and ethics committees.

Consent

All patients provided written informed consent before entering the study.

Statistical analysis

Heparin doses administered and ACT values in both treatment groups are presented descriptively.

Results

Study population

A total of 635 patients were administered at least one dose of the study drug and underwent the ablation procedure (dabigatran, 317; warfarin, 318 patients).[7] In this randomized trial, baseline demographic and clinical characteristics were well balanced between the treatment groups. The mean age of patients was 59.2 years overall, and the mean CHA_2DS_2-VASc score was 2.0 in the dabigatran and 2.2 in warfarin treatment groups. Mean ACT during the ablation was similar between the dabigatran and warfarin groups (330 and 342 s, respectively), as was the percentage of patients who maintained a

Table 3 Heparin dose requirements in patients with ACT <300 vs ≥300 s (ablation set)

	Dabigatran 150 mg, bid		Warfarin		Total	
	N	Heparin dose (IU), mean (SD)	*N*	Heparin dose (IU), mean (SD)	*N*	Heparin dose (IU), mean (SD)
Overall	191	12 402 (10 721)	205	11 910 (8359)	396	12 147 (9562)
First ACT						
<300 s	80	14 822 (13 743)	89	13 485 (9634)	169	14 118 (11 742)
≥300 s	108	10 699 (7534)	107	10 864 (7289)	215	10 781 (7396)
Maximum ACT						
<300 s	13	7554 (3269)	16	7381 (2828)	29	7459 (2979)
≥300 s	175	12 817 (11 067)	180	12 469 (8727)	355	12 641 (9937)
Minimum ACT						
<300 s	126	13 956 (12 401)	136	12 501 (8963)	262	13 201 (10 758)
≥300 s	62	9399 (5264)	60	11 042 (7363)	122	10 207 (6410)
Mean ACT						
<300 s	54	12 358 (9046)	46	10 026 (7154)	100	11 285 (8273)
≥300 s	134	12 492 (11 450)	150	12 676 (8816)	284	12 589 (10 127)
ACT missing	3	9167 (3884)	9	8778 (1889)	12	8875 (2317)

ACT, activated clotting time; SD, standard deviation.

Table 4 ACT and heparin dose according to the time from the last preprocedural dabigatran administration to septal puncture (ablation set[a])

	Time from dabigatran dose to septal puncture				
	0 to <4 h	4 to <8 h	≥8 h	NR	Total
N	79	74	33	5	191
Median heparin dose (IU)	9500	10 167	10 000	9008	10 000
First ACT					
0 to <100 s, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
100 to <200 s, *n* (%)	12 (15.2)	11 (14.9)	10 (30.3)	0 (0.0)	33 (17.3)
200 to <300 s, *n* (%)	19 (24.1)	19 (25.7)	8 (24.2)	1 (20.0)	47 (24.6)
≥300 s, *n* (%)	47 (59.5)	44 (59.5)	15 (45.5)	2 (40.0)	108 (56.5)
Missing, *n* (%)	1 (1.3)	0 (0.0)	0 (0.0)	2 (40.0)	3 (1.6)
Mean ACT					
0 to <100 s, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
100 to<200 s, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
200 to <300 s, *n* (%)	19 (24.1)	21 (28.4)	14 (42.4)	0 (0.0)	54 (28.3)
≥300 s, *n* (%)	59 (74.7)	53 (71.6)	19 (57.6)	3 (60.0)	134 (70.2)
Missing, *n* (%)	1 (1.3)	0 (0.0)	0 (0.0)	2 (40.0)	3 (1.6)

[a]Restricted to patients with documented heparin dosing.
ACT, activated clotting time; NR, not reported.

therapeutic ACT >300 s during ablation between these treatment groups (31.9% and 30.2%, respectively) (*Table 1*).

Heparin dose

Data on heparin doses on the day of ablation were available from 396 patients (dabigatran, 191; warfarin, 205), with baseline demographic and clinical characteristics well balanced between treatment groups (*Table 2*). Of the 396 patients who received heparin, almost three quarters were male (72.7%), and the mean age was 59.2 years. The mean CHA_2DS_2-VASc score was 1.9 and 2.1 in the dabigatran and warfarin groups, respectively. Almost twice as many patients receiving warfarin had coronary artery disease vs. those

Table 5 ACT and heparin dose according to the time from the last preprocedural warfarin administration to septal puncture (ablation set[a])

	Time from warfarin dose to septal puncture				
	0 to <4 h	4 to <8 h	≥8 h	NR	Total
N	13	18	160	14	205
Median heparin dose, IU	8000	8833	10 000	8500	10 000
First ACT					
0 to <100 s, *n* (%)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.5)
100 to <200 s, *n* (%)	0 (0.0)	2 (11.1)	30 (18.8)	3 (21.4)	35 (17.1)
200 to <300 s, *n* (%)	4 (30.8)	5 (27.8)	44 (27.5)	0 (0.0)	53 (25.9)
≥300 s, *n* (%)	9 (69.2)	11 (61.1)	84 (52.5)	3 (21.4)	107 (52.2)
Missing, *n* (%)	0 (0.0)	0 (0.0)	1 (0.6)	8 (57.1)	9 (4.4)
Mean ACT					
0 to <100 s, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
100 to <200 s, *n* (%)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.5)
200 to <300 s, *n* (%)	3 (23.1)	5 (27.8)	36 (22.5)	1 (7.1)	45 (22.0)
≥300 s, *n* (%)	10 (76.9)	13 (72.2)	122 (76.3)	5 (35.7)	150 (73.2)
Missing, *n* (%)	0 (0.0)	0 (0.0)	1 (0.6)	8 (57.1)	9 (4.4)

[a]Restricted to patients with documented heparin dosing.
ACT, activated clotting time; NR, not reported.

receiving dabigatran (14.1% vs 7.3%), while twice as many patients receiving dabigatran had a prior stroke vs. those receiving warfarin (4.2% vs. 2.4%).The overall heparin dose on the day of the ablation was similar between the dabigatran and warfarin groups [mean (standard deviation, SD) 12 402 (10 721) vs. 11 910 (8359) IU, respectively] (*Table 3*). Heparin dosing tended to be lower in patients with a first or minimum ACT measurement of ≥300 s vs. <300 s for all patients; mean (SD) heparin dose for first ACT <300 s vs. ≥300 s was 14 118 (11 742) IU vs. 10 781 (7396) IU, and for minimum ACT <300 s vs. ≥300 s it was 13 201 (10 758) IU vs. 10 207 (6410) IU, respectively. In addition, mean (SD) heparin dosing also tended to be lower in patients who did not achieve ACT ≥300 s [7459 (2979) IU] compared with those who did [12 641 (9937) IU] (*Table 3*). The mean (SD) number of ACT measurements per patient (for those receiving heparin) was 5.2 (3.3) for dabigatran and 4.9 (3.5) for warfarin.

Time from preprocedural oral anticoagulant dosing

The most frequent time window from the last preprocedural dose of the study drug to septal puncture was 0 to <4 h in the dabigatran arm (41.3%) and 16 to <24 h in the warfarin arm (44.7%). *Table 4* shows ACT according to the time from the last preprocedural dose of dabigatran; the first ACT was ≥300 s for the majority of patients (56.5%). Similarly, the first ACT was ≥300 s for the majority of the patients in the warfarin treatment group (52.2%) (*Table 5*). As would be expected, the lowest doses of heparin required to reach therapeutic ACT were given within 0 to <4 h of the last preprocedural dose of dabigatran and warfarin (median 9500 IU and 8000 IU, respectively) (*Tables 4* and *5*).

Discussion

In this analysis of the RE-CIRCUIT study in patients with documented heparin use, the heparin dosing requirement was similar between the dabigatran and warfarin arms. However, the RE-CIRCUIT data contrast with the results of the VENTURE-AF study, in which the average total heparin dose in patients undergoing catheter ablation for AF was higher in the rivaroxaban arm (once-daily dose) than in the VKA arm (13 871 vs. 10 964 units; $P < 0.001$).[18] The mean ACT level attained was also lower in the rivaroxaban arm vs. the VKA arm (302 vs. 332 s; $P < 0.001$).[18] The difference in heparin dosing between dabigatran and rivaroxaban may be attributed to their different modes of action. As a direct thrombin inhibitor, dabigatran can modify ACT and aPTT, whereas therapeutic doses of the factor Xa inhibitor rivaroxaban do not affect ACT or aPTT. Thus, patients treated with rivaroxaban require higher doses of heparin to maintain ACT.[19] Furthermore, in the RE-CIRCUIT study, the last dose of dabigatran was given very close to the ablation procedure, whereas patients in the rivaroxaban study took their last dose of rivaroxaban the evening before the day of the ablation procedure. The number of patients maintaining an ACT >300 s during ablation was low (~30%), suggesting that physicians may have been more conservative with heparin administration in the context of uninterrupted oral anticoagulant. However, the heparin requirement in the present study is comparable to that reported in a retrospective cohort study from a prospective AF ablation registry, the average heparin dose required to reach therapeutic ACT was 12 900 units in dabigatran-treated patients.[20]

Intraprocedural ACT and heparin requirements were evaluated in 184 patients treated with dabigatran or warfarin (one dose of

dabigatran was withheld for 70 patients, two doses of dabigatran and warfarin were withheld for 63 and 51 patients, respectively). Patients receiving dabigatran who withheld one or two doses before the procedure had higher intraprocedural heparin requirements (mean ± SD 225.2 ± 64.4 U/kg and 239.0 ± 65.0 U/kg, respectively) compared with warfarin (164.9 ± 36.1 U/kg; $P < 0.001$) to achieve an ACT ≥350 s.[12] These results support the concept mentioned above that, for patients for whom an uninterrupted dabigatran anticoagulation strategy has been decided, the heparin requirements may be similar to a comparable uninterrupted anticoagulation strategy with warfarin, owing to the ability of dabigatran to affect ACT in a dose-dependent manner.[10]

This *post hoc* analysis of RE-CIRCUIT showed that the closer the septal puncture was to the last anticoagulant dose, the lower the heparin requirement was to achieve the desired ACT. Limitations of the current analysis include the small sample size with documented heparin dosing, and the inherent shortcomings of *post hoc* analyses.

Conclusions

The data from the RE-CIRCUIT study showed that patients treated with dabigatran 150 mg bid required a similar amount of heparin as those treated with international normalized ratio-adjusted warfarin, and similar ACT was achieved in the treatment groups. It also suggests that the heparin units required to reach the desired ACT may be affected by the time from the last preprocedural dose of dabigatran.

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Safety and usefulness of a second Micra transcatheter pacemaker implantation after battery depletion

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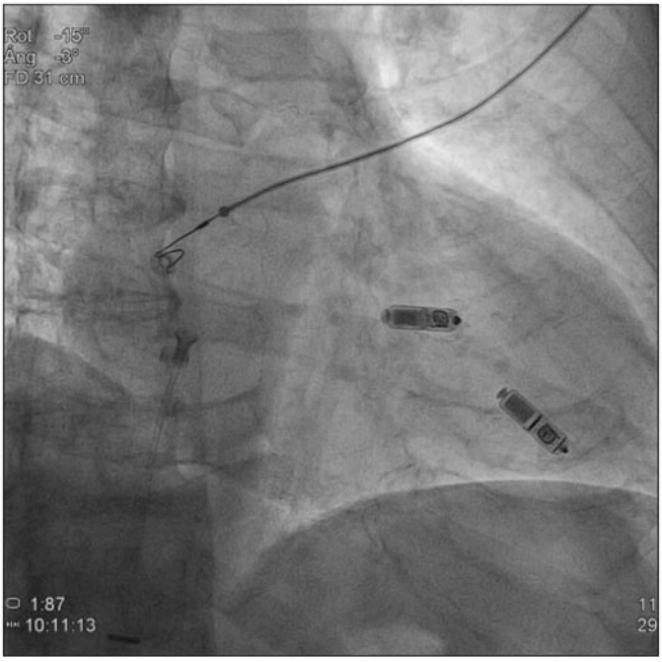
Techniques to manage the end of life of the Micra transcatheter pacing system (Medtronic Micra TPS) are not well standardized. It has been suggested that the best option is to leave the old device in the heart and implant a new one. Nevertheless, to date no double implant has successfully been reported in humans.

We present the case of a 78-year-old man who had reached the elective replacement time of the pacemaker after having received a Micra TPS in 2014 due to atrioventricular block. Reasons for early battery depletion were high right ventricular pacing threshold and 100% right ventricle (RV) pacing. A new Micra TPS was implanted through right femoral vein access. The new pacemaker was placed in the mid-septum of the RV, distant from the first pacemaker (*Figure*). The parameters of the new device (sensing, impedance, and threshold) were achieving within acceptable limits. No interactions were observed between the two devices. An echocardiography ruled out a negative impact of RV function by the implantation of the two devices. To our knowledge, this study is the first successful case of multiple implants of a Micra TPS with correct sensing and capture and no negative effects on RV function.



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