



Shorter RSPV cryoapplications result in less phrenic nerve injury and similar 1-year freedom from atrial fibrillation

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Abstract

Background: In the 123-study, we prospectively assessed, in a randomized fashion, the minimal cryoballoon application time necessary to achieve pulmonary vein (PV) isolation (PVI) in patients with paroxysmal atrial fibrillation (AF) with the aim to reduce complications by shortening the application duration. The first results of this study demonstrated that shortened cryoballoon applications (<2 minutes) resulted in less phrenic nerve injury (PNI) without compromising acute isolation efficacy for the right PVs. We now report the 1-year follow-up results regarding safety and efficacy of shorter cryoballoon applications.

Methods: A total of 222 patients with AF were randomized to two applications of 1 min “short,” 2 min “medium,” or 3 min “long” duration, 74 per group. Recurrence of AF and PV reconnection at 1-year follow-up were assessed.

Results: The overall 1-year freedom from AF was 79% and did not differ significantly between the short, medium, and long application groups (77%, 74%, and 85% for short, medium, and long application groups, respectively; $P = 0.07$). In 30 patients, a redo PVI procedure was performed. For all four PVs, there was no significant difference in reconnection between the three groups. Reconnection was most common in the left superior PV (57%). The right superior PV (RSPV) showed significantly less reconnection (17%) compared to the other PVs.

Conclusions: Shortening cryoballoon applications of the RSPV to <2 minutes results in less PNI, while acute success and 1-year freedom from AF are not compromised. Therefore, shorter cryoballoon applications (especially) in the RSPV could be used to reduce PNI.

KEYWORDS

atrial fibrillation, cryoballoon, phrenic nerve injury, pulmonary vein isolation, safety

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1 | INTRODUCTION

Since the recognition that pulmonary vein (PV) ectopy can trigger atrial fibrillation (AF), PV isolation (PVI) has become the cornerstone for nonpharmaceutical treatment of AF. The continuous improvement of ablation techniques has made catheter ablation, including cryoablation, the first-line therapy worldwide.^{1,2} When compared to radiofrequency (RF), cryoballoon-based PVI is characterized by steeper learning curves, faster and more reproducible procedures, and has documented noninferiority in terms of safety and efficacy.^{3,4} Cryoballoon has even been suggested to be the most advantageous choice in first-time PVI.⁵

Duration and dosing continue to be the topic of highest interest in cryoballoon PVI. Not only to achieve the best possible results in terms of efficacy but also in terms of safety. The optimal duration of cryoapplications is a ratio between acceptable efficacy and safety. Especially phrenic nerve injury (PNI) is a common complication and reducing PNI with cryoballoon PVI is of utmost importance.⁶⁻⁹ In current clinical practice, the duration of cryoapplications differs widely from 180 to 240 seconds.^{10,11}

In the 123-study,¹² we prospectively assessed, in a randomized fashion, the minimal cryoballoon application duration necessary to achieve PVI, with the aim to reduce procedural complications. The first results indicated that application duration reduction for the right PVs, less than 2 minutes, resulted in less PNI with similar acute isolation success.¹²

Here, we present the 1-year follow-up results of the 123-study in terms of freedom from AF and the insights gained from redo procedures considering safety and efficacy.

2 | METHODS

The study design and the initial PVI procedure of the 123-study have been described in detail previously.¹² Patients received two applications of 1 (short), 2 (medium), or 3 (long) minutes, after reaching maximal N₂O cooling flow, in all four PVs. A total of 222 consecutive patients with paroxysmal AF were enrolled: 74 per group. Cryoballoon applications were performed using a double-walled cryoballoon (Arctic Front Advance™ [n = 208] or Arctic Front Advanced ST™ [n = 14], Medtronic Inc., MN, USA). Quality of PV occlusion was visualized by contrast administration during fluoroscopy and scored on a semiquantitative scale with grades 1 to 4. An occlusion of 4 was aimed for in every application. The operators were not blinded for the application duration.

The Achieve™ mapping catheter was inserted through the inner lumen of the balloon to assess PV signals before, during, and after every application and to guide the positioning of the balloon. During cryoablation of the right-sided PVs, the right phrenic nerve was continuously stimulated by pacing from the superior caval vein or the right subclavian vein. In case of a diminished diaphragm excursion during cryotherapy, the application was stopped immediately using the double-stop technique.¹³ If a premature termination caused by dimin-

ished diaphragm excursion had to be performed, this was qualified as “PNI.”

2.1 | Group definition

Primary successful PV isolation was defined as isolation of that particular PV, proven by an entrance and exit block, after two applications. The primary success group represents the patients in which all PVs were successfully isolated after the designated application duration. Analysis of this group represents the success after 2 × 1, 2 × 2, or 2 × 3 minutes of ablation after reaching maximal N₂O freezing flow.

The entire patient group can be seen as the intention-to-treat group. Representing a “real-world group” in which, depending on the randomization, a shortened application duration was used for the first two applications. If these applications were not sufficient for isolation, supplementary applications were applied to assure complete isolation for all the PVs. The number and duration of these supplementary application(s) were determined by the operating physician. The analysis of this group represents whether starting with shorter applications could be used to prevent complications reaching the same efficacy level.

2.2 | Follow-up

All patients were scheduled for outpatient clinic visits at 3, 6, and 12 months post-PVI. A 7-day holter ECG (Vitaphone GmbH, Mannheim, Germany) capable of autodetecting AF or a 48-hour regular holter ECG was recorded at 3, 6, and 12 months post-PVI.

2.3 | Redo PVI procedure

After confirmation of AF recurrence lasting >30 seconds, patients were offered a redo procedure. In the redo procedure, isolation was assessed and reconduction gaps were ablated using RF. Atrial geometry was constructed using either CARTO® (Biosense Webster, CA, USA) or NavX™ mapping systems (St Jude Medical, St Paul, MN, USA). Reconduction was assessed using a spiral catheter (Lasso®, Biosense Webster) for every PV. In PVs with identified reconduction, RF was applied until isolation was achieved.

2.4 | Statistical analysis

The study was designed to assess three noninferiority hypotheses comparing the different groups (short, medium, long) independent of each other. Prior to the study, a noninferiority margin of 10% was determined and a power calculation that assumes success was performed. Based on this calculation, a total of 222 patients (3* 74) were enrolled. Data analysis was performed using SPSS (version 22). Continuous variables are summarized by mean ± standard deviation for normally distributed variables or median with interquartile ranges for nonnormally

TABLE 1 Patient and procedural characteristics

	Total (n = 222)	Short group (n = 74)	Medium group (n = 74)	Long group (n = 74)	P-value
Age (years)	58 ± 9	58 ± 10	59 ± 9	57 ± 9	.40
Gender (male,%)	143 (64)	46 (62)	47 (64)	50 (68)	.78
CHA ₂ DS ₂ VASC score	1.2 ± 1.1	1.3 ± 1.2	1.2 ± 1.2	1.0 ± 1.0	.34
EHRA class	2.4 ± 0.5	2.4 ± 0.5	2.4 ± 0.5	2.4 ± 0.6	.90
Duration of one application (s) (median [IQR])	163 [107-219]	105 [101-108]	164 [160-168]	224 [219-226]	<.001 ^a
Procedure time (hh:mm)	1:28 ± 0:24	1:22 ± 0:23	1:29 ± 0:27	1:32 ± 0:20	.04 ^b

Data are expressed in mean ± SD or n(%) unless stated otherwise.

^aSignificant between all groups.

^bSignificant between short and long group.

distributed variables. Categorical variables are expressed as numbers and percentages. Statistical differences for continuous normally distributed variables were analyzed using Analysis of Variance (ANOVA) for three groups. In case the ANOVA showed significant differences, post hoc tests according to the method of Tukey's honestly significant differences were performed. For nonnormally distributed variables, the Kruskal-Wallis test was used to test for differences between the three groups with post hoc Mann-Whitney U tests using Bonferroni-Holm correction. Statistical differences between the groups for categorical variables were analyzed using chi-square or Fisher exact tests, as appropriate. In case significant differences between categorical variables were observed, post hoc tests according to Bonferroni-Holm were performed.

3 | RESULTS

Between July 2014 and August 2017, a total of 222 patients, 74 patients in each group, were enrolled and had follow-up until August 2018. There were no significant differences between the baseline patient characteristics for the three groups (Table 1).¹² Significant differences in procedural characteristics were found for application duration and total procedure duration. PNI incidence was reduced from 6.8% and 6.5% in the long and medium group to 1.7% in the short group (Figure 1).¹² Three patients were lost to follow-up. One patient withdrew consent, and two patients died before reaching the 1-year follow-up point. One patient died 254 days postprocedure of a metastasized sigmoid carcinoma and the other patient died 299 days postprocedure without a specific cause of death found at autopsy. The former had symptomatic recurrence of AF during follow-up.

3.1 | Freedom from AF

One hundred seventy three out of 220 (79%) patients were free from recurrence of AF (Figure 2A). There was no significant difference between the three randomization groups for recurrence of AF ($P = .07$).

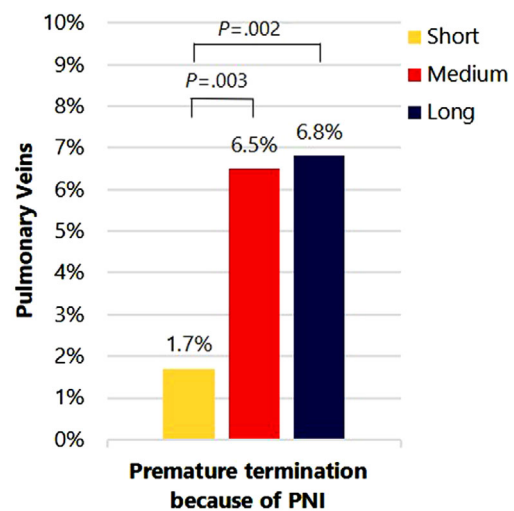


FIGURE 1 Percentage of pulmonary veins in which applications were prematurely terminated because of phrenic nerve injury (PNI) (from Molenaar et al¹²) [Color figure can be viewed at wileyonlinelibrary.com]

In the initial PVI, all PVs were primarily successful isolated in 128/220 (58%) patients (Figure 2B). Differences in numbers of primary successful patients per randomization group were significant for short (45%) versus medium (66%) ($P = .01$) and short versus long (64%) ($P = .03$). As shown in the first results, these differences were significant for the left PVs but not for the right PVs. The right superior PV (RSPV) showed a primary success percentage of > 90% for all randomization groups (figure 3 in Molenaar et al¹²). The freedom from AF in the 128 primary successful patients was 84% and there was no significant difference ($P = .08$) between the randomization groups in the primary successful patients either (Figure 2C).

3.2 | Redo PVI procedure

In 17/47 patients with recurrence of AF, no redo procedure was performed. These patients experienced a significant reduction in AF

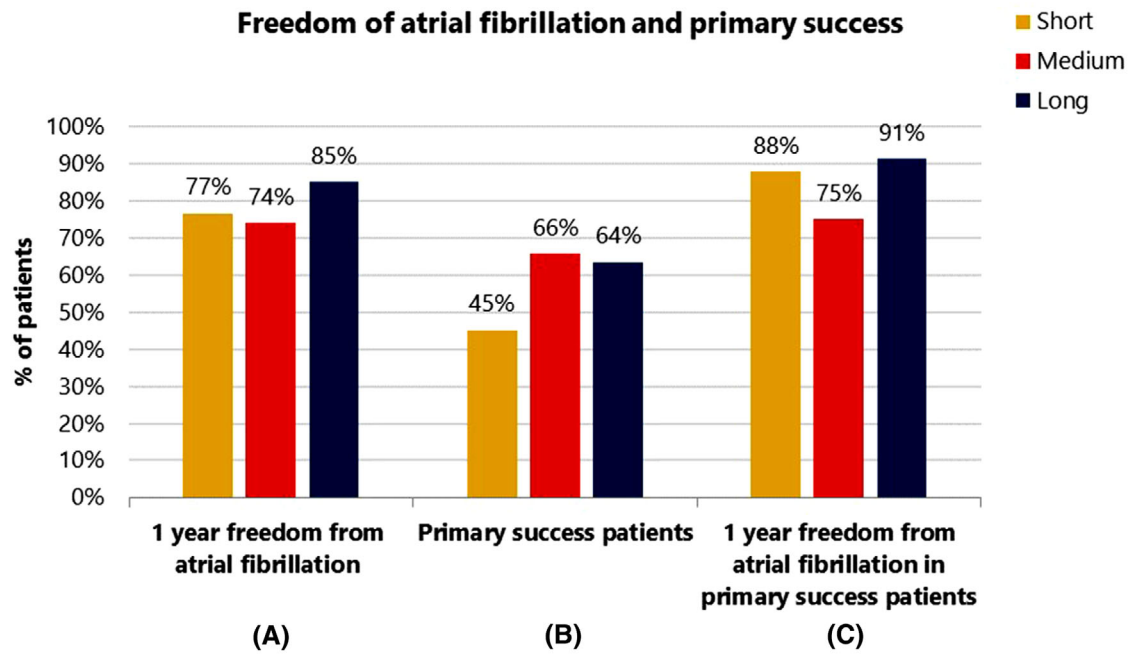


FIGURE 2 Distribution of patients over randomization-groups: (A) 1-year freedom of atrial fibrillation (in all patients, intention to treat group), (B) primary success patients (= all PV's primarily successful isolated in initial procedure), and (C) 1-year freedom of atrial fibrillation in primary success patients [Color figure can be viewed at wileyonlinelibrary.com]

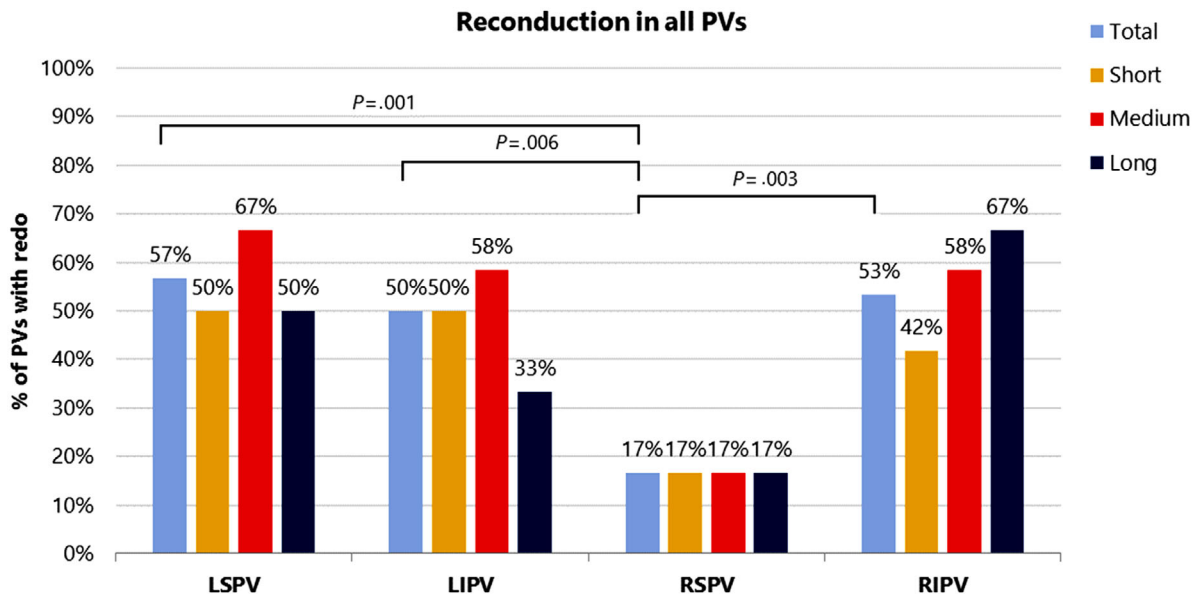


FIGURE 3 Recurrence distribution per PV for all patients Overall (= total) Per randomization group (short, medium, long) Abbreviations: LS, left superior; PV, pulmonary vein; RI, right inferior; RS, right superior [Color figure can be viewed at wileyonlinelibrary.com]

burden following the initial PVI, with or without medical treatment, so that they renounced a redo procedure. In 30 patients, 12 in the short and medium group and 6 in the long group, a redo PVI procedure was performed. In three patients (10%), all PVs showed durable isolations. Reconduction was found in one PV in eight (27%) patients, in two PVs

in 13 (43%) patients, and in three PVs in five (17%) patients, and in one patient (3%), all PVs showed reconduction.

For all PVs, as well as the subgroup of PVs in which isolation was primarily successful, most reconduction was found in the left superior PV (LSPV) (17/30 57% all PV group, 15/25 60% primary

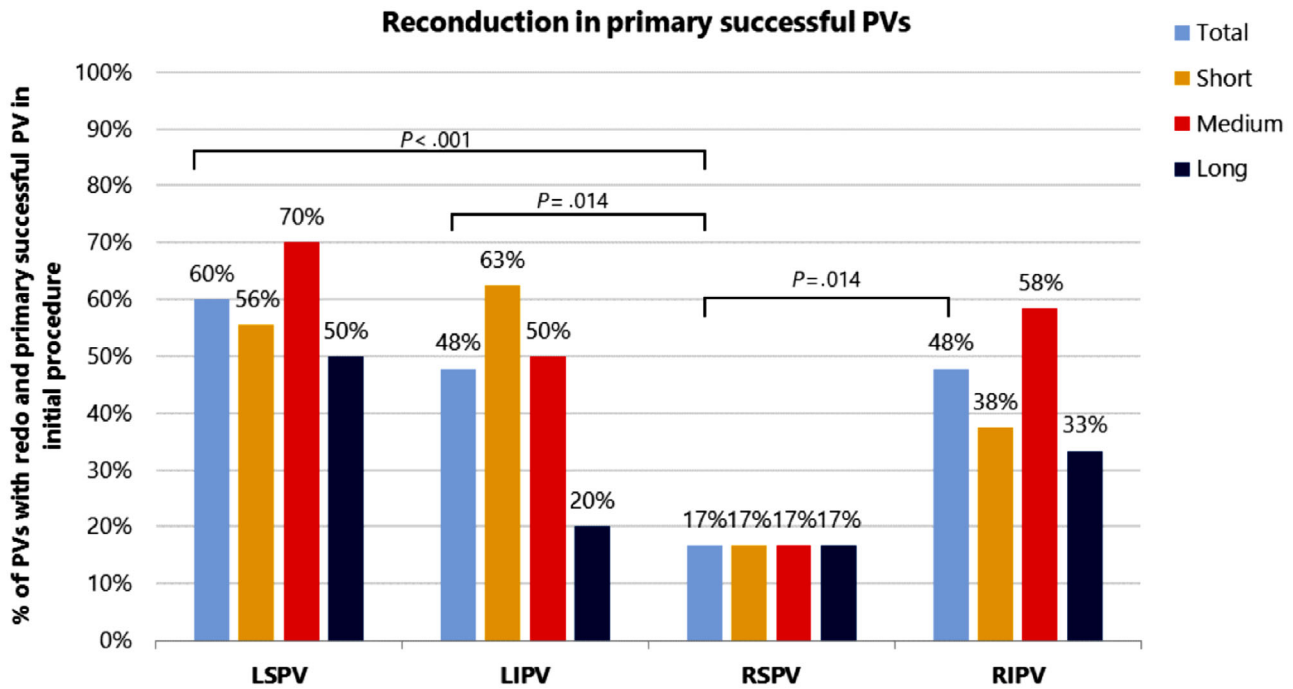


FIGURE 4 Recurrence distribution per PV for primary successful PV group Overall (total, group of primarily successful isolated PV's in initial procedure) Per randomization group (short, medium, long) Abbreviations: LI, left inferior; LS, left superior; PV, pulmonary vein; RI, right inferior; RS, right superior [Color figure can be viewed at wileyonlinelibrary.com]

successful PV group). The RSPV (5/30, 17%) showed significantly less reconduction compared to all other PVs (Figures 3 and 4, total bar). A subanalysis comparing reconduction in all four separate PVs showed no significant differences between the three randomization groups in the intention to treat PV group (Figure 3, short-medium-and-large bars) as well as the primary successful PV group (Figure 4, short-medium-and-large bars).

4 | DISCUSSION

The 123-study was designed to assess the minimal cryoballoon application duration for PVI while improving safety. Patients were randomized to three different groups comparing standard to reduced application durations, resulting in application durations of 105 [101-108] seconds for the short group, 164 [160-168] seconds for the medium group, and 224 [219-226] seconds for the long group. The purpose of the study was to find an optimal freezing duration preserving efficacy and improving safety (especially) by avoiding PNI. The first results of the 123-study demonstrated that the incidence of PNI was successfully reduced by using shorter cryoapplications.

The follow-up results show (a) similar 1-year freedom from AF for the short, medium, and long duration groups in both the primary successful patients as well as the entire (intention to treat) patient group. Isolation assessment in redo procedures show that (b) the RSPV had significantly less reconduction compared to all other PVs. (c) For all four

PVs, reconduction appeared independent of the previously applied duration of cryoapplications.

4.1 | Application duration and freedom from AF

This follow-up analysis shows a 1-year freedom from AF success rate of about 80%, which is in accordance with success rates reported earlier.^{3,14,15} The success rates for 1-year freedom from AF did not differ significantly between the randomization groups, indicating that 1-year efficacy is not impaired by shortening application duration. However, a trend toward higher 1-year freedom from AF for the "long" group was found in the entire patient group. Similar results were seen in the CIRCA-DOSE study, the only other study performed prospectively in a randomized fashion comparing the standard to new dosing protocols. In that study, 2 versus 4 minutes application duration showed a 73% versus 78% efficacy after 12 months.¹⁶

4.2 | Reconduction per randomization group

The per-PV-analysis indicated that shortening the cryoablation duration does not affect the reconduction rate in the individual PVs. However, a trend toward more durable lesions was noted in the "long" group for the LSPV, LIPV, and right inferior PV (RIPV) (Figure 4). The 123 study was powered for noninferiority of primary successful isolated

PVs between the three application duration groups.¹² However, the study may not have enough power for the secondary analysis in which we compared the recurrence rate. Although the absolute success in three groups were relatively different, 77%, 74%, and 85% for short, medium, and long application groups, this was not statistically significant ($P = .07$). Therefore, not finding a significant P value should be interpreted with caution. This is even more the case for the redo PVI procedure, which was performed in 30 patients. However, we can conclude that the numerical reconnection of the RSPV was the same (17% for all groups). Hence, we focused on shortening RSPV application, and not RIPV applications, to prevent from PNI. Recently, Chen et al published comparable results where a freeze duration of 240 versus 180 seconds was associated with significantly increased lesion durability, particularly at the left-sided PVs.¹⁷ Here, the low number of PVs per group in our study should be considered. Assessment of larger redo cohorts is needed to confirm these results.

4.3 | Reconnection per PV

Isolation assessment in redo procedures showed that the LSPV had the most and RSPV the least reconnections, significantly less when compared to all three other PVs. The reconnection per PV after second-generation cryoballoon PVI showed mixed results in earlier studies. One study demonstrated that the RSPV is most prone to reconnection, and in other studies, the RIPV showed most reconnections, attributed to the challenging anatomy of the RIPV in terms of occlusion.¹⁸⁻²⁰ A recent study by Martins et al reported reconnection rates around 20% in the left PVs and around 30% in the right PVs.²¹ With patient numbers in the mentioned studies ranging from around 18 to 66, our study with 30 patients is comparable. A retrospective study by Heeger et al with 192 patients found no differences in reconnection rate per PV.²² The different dosing protocols adopted in these studies may have accounted for differences in outcome.

4.4 | Phrenic nerve injury

The first results of the 123-study showed an important reduction in PNI incidence from 6.8% and 6.5% in the long and medium group to 1.7% in the short group.¹² Although the number of primary successful patients differed between the randomization groups (Figure 2B), the RSPV showed an acute success rate of 92% that was similar to acute success rates for medium and long randomization groups. Hence, application duration reduction toward short applications (105 [101-108] seconds) for the RSPV resulted in less PNI and did not impair acute isolation.¹² The current results show that 1-year success with shorter cryoapplications for the RSPV is not impaired either justifying a shortened application duration in the RSPV to prevent from PNI. This adds to the growing awareness that all four PVs should be assessed separately regarding PV isolation and to find the parameters to predict lesion durability.²³

5 | CONCLUSION

Shortening cryoballoon application duration of the RSPV to less than 2 minutes results in less PNI, while acute success (PVI) as well as 1-year success (freedom from AF) was not compromised. Therefore cryoballoon application duration for the RSPV could be shortened to prevent PNI.

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DISCLOSURES

The authors declare no conflict of interest.

CONFLICTS OF INTEREST

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