CJC Open 6 (2024) 893–900

Original Article

Exploring Patient Viewpoints to Optimize Implementation of a Biological Therapy for Atrial Fibrillation Prevention

Chloé Smith, MD,[a] Manoj M. Lalu, MD, PhD,[b,c,d] and Darryl R. Davis, MD[a,b]

[a] Division of Cardiology, Department of Medicine, University of Ottawa Heart Institute, University of Ottawa, Ottawa, Ontario, Canada

[b] Department of Cellular and Molecular Medicine, University of Ottawa, Ottawa, Ontario, Canada

[c] Department of Anesthesiology and Pain Medicine, University of Ottawa, The Ottawa Hospital, Ottawa, Ontario, Canada

[d] Regenerative Medicine and Clinical Epidemiology Programs, Ottawa Hospital Research Institute, Ottawa, Ontario, Canada

ABSTRACT

Background: Embracing patient viewpoints can enhance the translation of novel therapeutics to clinical settings. This study evaluated the acceptability of using extracellular vesicles (EVs) as a biological therapy for preventing postoperative atrial fibrillation (AF), through engagement with patients, providing insights into their attitudes and information needs.

Methods: Patients participated in prerecorded presentations, virtual focus groups, and surveys to assess their perspectives on EV therapy and determine the factors influencing their acceptance of the intervention.

Results: Participants with postoperative AF experienced prolonged intensive care unit and hospital stays, compared to those of patients with normal heart rhythm. Prior to the presentation, a number of participants were unfamiliar with postoperative AF and biological

RÉSUMÉ

Contexte : Adopter le point de vue des patients permet de faciliter l'introduction de nouveaux traitements en milieu clinique. Cette étude visait à évaluer l'acceptabilité des vésicules extracellulaires comme traitement biologique dans la prévention de la fibrillation auriculaire postopératoire en favorisant un rapprochement avec les patients, en comprenant leurs attitudes et leurs besoins d'information.

Méthodologie : Les patients ont assisté à des présentations préenregistrées, ont participé à des groupes de discussion virtuels et ont rempli des questionnaires. L'objectif était d'évaluer leur point de vue sur les vésicules extracellulaires et de déterminer les facteurs influençant l'acceptation de l'intervention.

Résultats : Les participants atteints de fibrillation auriculaire postopératoire sont restés plus longtemps à l'unité des soins intensifs et à l'hôpital par comparaison aux patients ayant un rythme cardiaque

The landscape of cardiovascular disease treatment is evolving with the emergence of novel biological therapies. Among these promising advancements, RNA interference has demonstrated its efficacy as a therapeutic agent for hypertension,[1] and antibodies have shown safety in efforts to deplete cardiac amyloid.[2] Additionally, stem cell–based interventions have shown promise in enhancing cardiac function for individuals with Duchenne muscular dystrophy.[3] As these therapies continue to develop, exploring patient perspectives that may influence their willingness to embrace a novel therapy becomes crucial. Considerations relating to these new biological treatments remain relatively unexplored, but their successful translation hinges on their acceptance by patients. All progress may be rendered futile if patients ultimately reject treatments due to unforeseen factors. Simple modifications of study design to incorporate patients concerns hold the potential to exert profound effects on patients' eagerness to adopt and embrace innovative therapies.

In this study, we recruited patients to evaluate the acceptability of extracellular vesicles (EVs) as a biological therapy to prevent postoperative atrial fibrillation (AF). EVs are a new, promising therapy for cardiovascular disease that is gaining increased attention in the preclinical literature.[4] EVs are lipid-enclosed microparticles that naturally are created and released from many, if not all, cells of the body. EVs merge with neighbouring cells to alter function. The protein and transcriptional cargo within EVs are characteristic of their producer cell and define the inductive effect on neighboring cells.[5,6] In the treatment of AF, EVs offer an alternative to standard therapies by targeting the proinflammatory substrate that results from cardiac surgery and increases vulnerability to AF.[7,8] Recently, we demonstrated that EVs produced by heart-derived cells are anti-inflammatory and antifibrotic.[5] When injected into the atria at the time of open chest surgery, EVs prevent AF by reducing inflammation and fibrosis.[9]

Received for publication January 24, 2024. Accepted April 10, 2024.

Corresponding author: Dr Darryl R. Davis, University of Ottawa Heart Institute, H3214, 40 Ruskin Street, Ottawa, Ontario K1Y 4W7, Canada. Tel.: +1-613- 696-7298; fax: +1-613-696-7136

E-mail: ddavis@ottawaheart.ca

See page 898 for disclosure information.

https://doi.org/10.1016/j.cjco.2024.04.003

therapies. However, postpresentation and post–focus group activities resulted in enhanced understanding of the research, with high levels of comprehension reported by all participants. The level of acceptance of EV therapy tended to increase, with a majority expressing willingness to participate in clinical trials and accept the therapy. The focus groups identified and addressed common questions regarding the potential risks and side effects of EVs, their source, dosing, utility for patients with preexisting AF, and the risk of human immunodeficiency virus (HIV) contraction or allergic reactions.

Conclusions: The study highlights the importance of providing education, involving the patient's circle of care, and addressing patient concerns, to promote acceptance of therapies such as EV therapy for postoperative AF.

Clinical Trial Registration: NCT05032495.

normal. Avant la présentation, un certain nombre de participants ne connaissaient pas la fibrillation auriculaire postopératoire et les traitements biologiques. Cependant, après la présentation et le groupe de discussion, les participants ont pu mieux comprendre la recherche, et tous ont indiqué un niveau de compréhension élevé. Le degré d'acceptation des vésicules extracellulaires avait tendance à augmenter. En effet, la majorité des patients se disait prête à participer à des essais cliniques et à accepter le traitement. Les groupes de discussion ont relevé et abordé des questions communes concernant les risques et effets secondaires des vésicules extracellulaires, leur source, leur dose, leur utilité pour les patients présentant une fibrillation auriculaire préexistante et le risque d'infection par le virus de l'immunodéficience humaine (VIH) ou de réactions allergiques.

Conclusions : L'étude souligne l'importance de l'éducation, de la participation du réseau de soins du patient et de la prise en compte des préoccupations du patient pour favoriser l'acceptation de traitements comme les vésicules extracellulaires pour la fibrillation auriculaire postopératoire.

Enregistrement de l'essai clinique : NCT05032495.

Work is ongoing in parallel to develop this new approach for clinical translation.

By using EVs as a symbolic prototype, we hope to gain insight into patient attitudes toward biological cardiovascular interventions, particularly those designed to prevent AF after surgery. Among various promising preclinical therapies, EVs were chosen, backed by compelling reasons, as the primary focus, due to their suitability. First, the prevalence of this disease is substantial, with a million patients in North America undergoing cardiac surgery annually,[10] half of whom will experience AF after the procedure.[11-21] This condition significantly impacts patient care, as 90% of patients exhibit symptoms such as palpitations, fatigue, and light-headedness, with 15% being hemodynamically unstable. Additionally, AF elevates the risk of in-hospital stroke[13,22-27] and other complications,[28] leading to a doubling of hospital mortality, according to retrospective studies (7.4% vs 3.4%).[23] Unsurprisingly, postoperative AF also prolongs hospital stays and increases hospitalization costs.[11,13,16,22,24,29-31] The well-defined patient population, comprised of individuals undergoing surgery and those with confirmed AF, offers unique perspectives that can significantly influence the design of preclinical or clinical trials. Lastly, effective treatment to prevent postoperative AF is lacking. Despite the widespread usage of amiodarone or sotalol with additional ion-channel blocking effects, these drugs do not offer any benefit, compared to beta blockers.[32,33] Other approaches, such as steroids or anti-inflammatories, have shown potential benefits in small trials, but results have been inconsistent, with limited uptake due to adverse effects.[34-39]

In this study, we recruited patient partners who are awaiting surgery and those who have already undergone surgery. This unique approach allowed us to compare individuals who had experienced AF with those who did not. To assess their perspectives on EV therapy and understand the factors influencing their acceptance of the intervention, patients will participate in prerecorded presentations, virtual focus groups, and surveys. We hypothesize that patients awaiting surgery, and those who have undergone surgery without experiencing AF, may not be fully aware of the risk of postoperative AF, which could influence their interest in receiving an investigational therapy. Conversely, patients who have undergone surgery and did experience AF may be more receptive to EV therapy as a preventive measure. Additionally, we sought patient perspectives that could help optimize the design and implementation of clinical, and possibly preclinical, studies. To the best of our knowledge, this study marks the first endeavor to engage patients early in the cardiovascular research discovery process. We envision that this approach could have an impactful influence on research, even at a preclinical stage.

Materials and Methods

Recruitment

Patient partners were recruited to inform and guide the research process from study onset to completion. This clinical trial was approved by the University of Ottawa Research Ethics Board (20210710-01H) and was registered on ClinicalTrials.gov (Identifier: NCT05032495). The research team partnered with the University of Ottawa Heart Institute Patient Engagement in Research Advisory Council and surgical collaborators, to approach interested individuals with lived experience of a heart disease, with some who had undergone cardiac surgery. Participants were provided with sufficient background on the objectives of the project and a terms-of-reference document outlining team member roles and responsibilities.

Participants (10 men and 12 women) were divided into 3 groups. The first group included cardiac surgery patients who did not experience postoperative AF (n = 10); the second consisted of cardiac surgery patients who did experience postoperative AF (n = 6); and the third included cardiac patients who were scheduled for future cardiac surgery (n = 6).

A member of the research team initially called and explained the study. Participants were given time to review the information before being asked to give their consent. After

providing verbal consent, the participants communicated with the research team mainly via e-mail, and provided written consent.

Inclusion and exclusion criteria

All participants were recruited from the University of Ottawa Heart Institute patient partner volunteer database. These volunteers have a current or past affiliation with the institute, direct experience as patients or caregivers, availability for active participation, and a commitment to contributing to the cardiovascular community. Patients were excluded if they were unable to complete an electronic survey and/or participate in a virtual focus group. This group included patients who did not have a computer or Internet access, patients who needed translation services, patients who were illiterate, and patients who had trouble understanding or producing speech and required special support, including the use of assistive devices.

Study design and procedures

Two surveys were conducted to gather data from the participants—one before and one after they watched a prerecorded presentation and engaged in a virtual focus group. The first survey aimed to collect demographic information, as well as insights into prior experiences and opinions. The second survey was utilized to evaluate the acceptability of the intervention among participants and identify the most effective method of explaining the intervention. Both surveys were available in English and French (see Supplemental Appendices S1 and S2). We adapted and refined these surveys based on our previous publications,[40,41] and we incorporated feedback from laboratory staff and patient-engagement researchers, with the final versions being approved by the University of Ottawa Research Ethics Board.

Participants were invited to watch a standardized 37-minute prerecorded video presentation, which covered various topics, including an explanation of AF pathogenesis, risk factors, incidence, consequences, EV therapy biogenesis and role, as well as preclinical research data (see Video 1; view video online). The video was developed using expert content, clinical experience, materials available in the clinic, public literature, and feedback from colleagues specializing in cardiac nursing, surgery, and electrophysiology.[42,43] To facilitate discussion using nominal group techniques, a virtual focus group was conducted using the Zoom for Healthcare platform, ensuring privacy.[44-46] Four focus groups were organized, with each group consisting of 4-9 participants. The duration of each focus-group session was 60-90 minutes. Ahead of the focus group, discussion topics were provided to the participants to allow them to review and prepare questions, as well as consult with their caregivers. The discussion topics explored their understanding of AF, their perspectives on EV therapy, and potential research questions for further investigation. During this session, participants individually generated ideas on the feasibility, safety, and efficacy of EV-based therapy, followed by round-robin sharing, concept clarification, and confidential voting on the acceptability of EV therapy as a preventive measure. Throughout the focus group, questions and concerns were addressed and recorded by the moderator as anonymized written comments. We applied the "theoretical framework of acceptability" to assess various dimensions of healthcare intervention acceptability, using changes in patients' willingness to undergo intramyocardial exosome injections for AF prevention, measured via surveys conducted before and after the educational session, as our primary indicator.[47,48]

Statistical analysis

All statistical tests and graphical depictions of data are defined within the figure legends for the respective data panels (GraphPad Prism 9.5, GraphPad, La Jolla, CA). All data are presented as mean ± standard deviation. To determine if differences existed within groups, data were analyzed using an ordinary 1-way analysis of variance; if such differences existed, Šídák's multiple-comparisons test was used to determine the group(s) with the difference(s). In all cases, the normality of variances was confirmed prior to further post hoc testing, using Bartlett's test. Differences in categorical measures were analyzed using the N−1 χ^2 test. A final value of $P \leq 0.05$ was considered significant for all analyses.

Results

As shown in Table 1, the mean age was similar among the 3 groups (68 ± 7 years, P = not significant), with an equal distribution of individuals that self-identified as female vs male. All 22 participants completed the first survey, watched

Table 1. Patient demographics

Characteristic	Postsurgery with AF (n = 10)	Postsurgery without AF (n = 6)	Awaiting surgery (n = 6)	P
Age, y, mean ± SD	67 ± 7	69 ± 7	69 ± 8	0.83
Gender,female	67	33	57	0.45
Coronary artery disease	40	50	86	0.09
Valvular disease	30	33	50	0.34
Aortic disease	30	0	17	0.04
Congenital heart disease	10	33	0	0.51
Coronary artery bypass graft	40	50	N/A	0.15
Valve repair	22	33	N/A	0.55
Aortic repair	40	33	N/A	0.06
Completed survey 1	100	100	100	1.00
Watched presentation	100	100	100	1.00
Participated in focus group	100	100	100	1.00
Completed survey 2	90	100	83	

Values are %, unless otherwise indicated.
AF, atrial fibrillation; N/A, not available; SD, standard deviation.

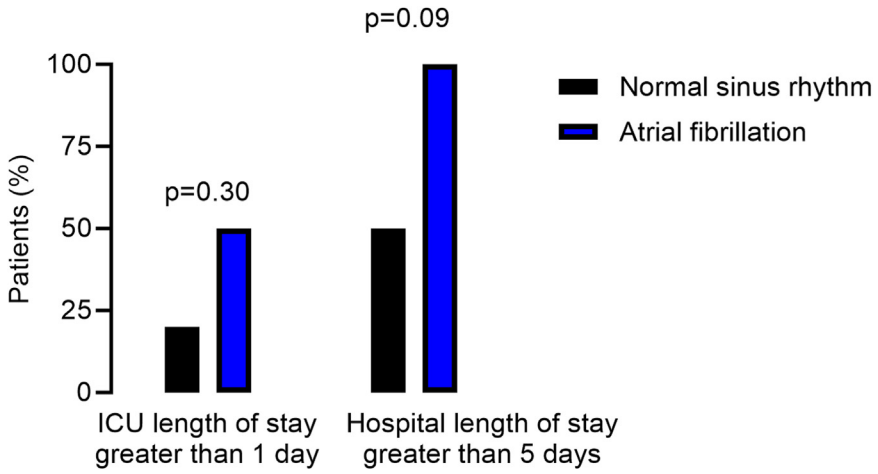

Figure 1. Influence of postoperative atrial fibrillation on intensive care unit (ICU) and overall hospital length of stay. Length of stay data from patients who experienced atrial fibrillation after surgery (n = 6) and patients who maintained normal sinus rhythm after surgery (n = 10) was analyzed using Fisher's exact test.

the presentation, and actively participated in the focus group. Although 2 participants did not complete the second survey, their input still was included in the analysis of pre-presentation and focus-group data.

Intensive care unit (ICU) and total hospital stays were analyzed for participants who had undergone cardiac surgery, as shown in Figure 1. Consistent with several clinical series,[11,13,16,22,24,29-31] participants who experienced post-operative AF tended to have longer ICU and total hospital stays, compared to those of participants that maintained normal sinus rhythm after the operation. Specifically, 50% of participants with postoperative AF stayed in the ICU for > 1 day, whereas only 20% of participants with normal heart rhythm stayed for the same duration (Fisher's exact test $P = 0.30$). Furthermore, all participants with postoperative AF had hospital stays > 5 days, whereas 50% of participants with normal rhythm after surgery had hospitals stays lasting < 5 days after surgery (Fisher's exact test $P = 0.09$).

The results from the pre-presentation surveys are presented in Figure 2A (Supplemental Appendix S1). Prior to watching the presentation, 33% of participants were unfamiliar with AF, and the prospect of AF occurring after surgery. A total of

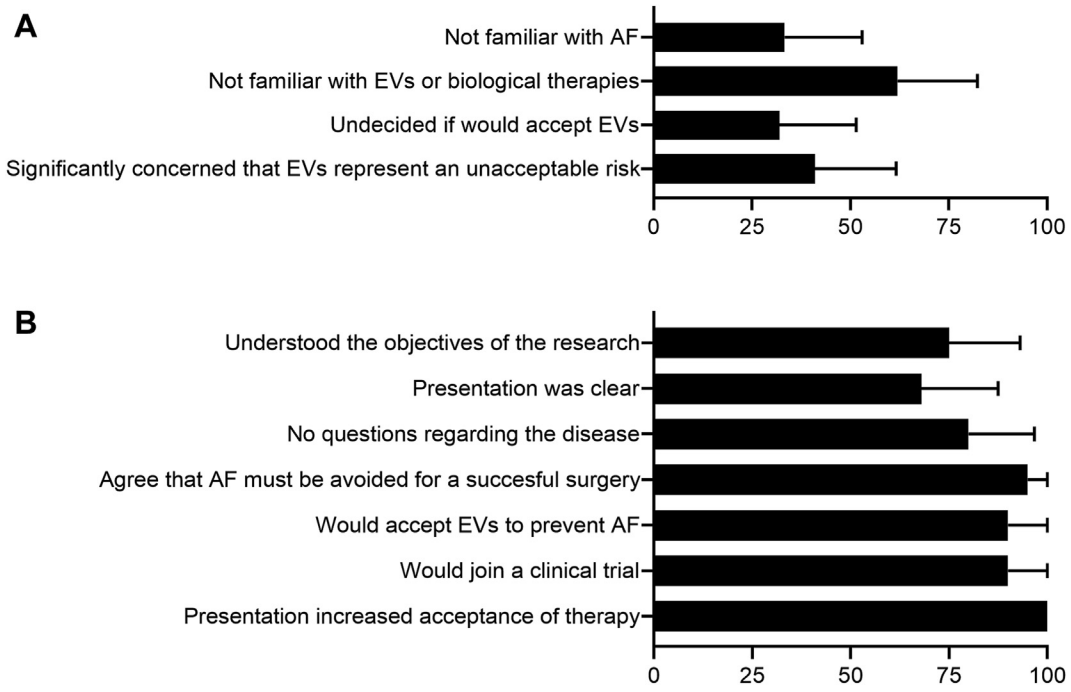

Figure 2. Patient knowledge and opinions regarding atrial fibrillation (AF) after cardiac surgery and the use of a biological therapy (extracellular vesicles [EVs]) to prevent postoperative AF. (**A**) Outcome of the initial survey from all patient partners. (**B**) Outcome from the second survey performed after watching a standardized video presentation and a virtual focus group. Data are presented as mean and 95% confidence intervals.

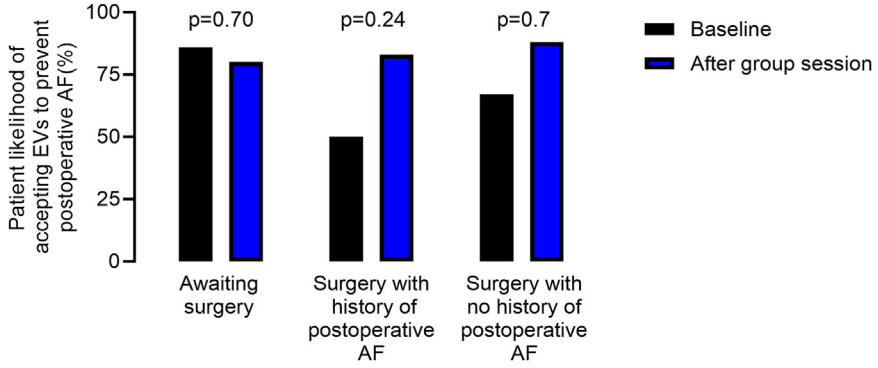

Figure 3. Influence of patient experience and educational sessions on the likelihood of accepting a biological therapy (extracellular vesicles [EVs]) to prevent postoperative atrial fibrillation (AF) was analyzed using the N−1 χ^2 test.

62% of participants had no knowledge of biological therapies. When the possibility of using EVs to reduce the incidence of postoperative AF was suggested, 32% of participants were undecided and required additional information, and 41% expressed significant concerns.

Postpresentation and focus-group opinions were captured in a second survey (Supplemental Appendix S2) and are displayed in Figure 2B. All participants (100%) reported a full understanding of the research presented, with 90% finding the presentation to be clear. Additionally, 95% of the participants believed that postoperative AF should be avoided for successful surgery. In terms of acceptance, 67% of participants expressed willingness to participate in a clinical trial, 80% stated their willingness to accept EV therapy without further questions, and 75% indicated that the presentation had increased their acceptance of EV therapy.

The acceptance of EV therapy for postoperative AF was evaluated before and after the presentation and focus group, categorized by participant groups, as shown in Figure 3. The acceptance rates varied among the different research groups. Prior to the presentation, 86% of participants awaiting surgery, 50% of participants with postoperative AF, and 67% of participants with normal rhythm postsurgery expressed their willingness to accept EV therapy to prevent postoperative AF. Following the presentation and focus groups, the acceptability rates remained high for all 3 groups, with 80% acceptance for the preoperative group, 83% for the postoperative AF group, and 88% for the postoperative normal-rhythm group. Notably, the largest trend in acceptance rates, before and after the presentation and focus group, was observed in participants who had experienced AF postoperatively.

During the focus groups, the 5 most frequently asked questions were identified and addressed (Table 2). These questions included the potential risks and side effects of EV therapy, the source of EVs, the dosing of EVs, the utility of EVs for patients already diagnosed with AF, and the risk of contracting human immunodeficiency virus (HIV) or experiencing allergic reactions associated with EV therapy. These questions were discussed thoroughly during the focus groups and will be addressed when explaining the therapy to interested patients.

Table 2. Top 5 issues regarding the use of a biological therapy to prevent postoperative atrial fibrillation

1. Risks and side effects of the biological therapy
2. Source of the biological therapy
3. Dosing of the biological therapy
4. Potential utility of the biological for other indications
5. Risk of contracting communicable diseases or experiencing an allergic reaction

Discussion

In this study, patient partners proved to be instrumental in determining the most effective way to communicate complex information to the general public to ensure informed consent. One recurring theme throughout this study was the participants' desire for education on therapies. Although time constraints may limit the ability to provide in-depth explanations for emergency cardiac surgeries, offering information after the surgery can empower patients and enhance their sense of control over their health outcomes. Also, involving the patient's circle of care in therapy discussions is important, as the influence of its members can shape the patient's perspective significantly and reduce the level of misinformation gathered by patients. Survey data revealed that, except for patients who had previously experienced AF, many patients had limited familiarity with AF or biological therapies prior to the presentation and focus group. The majority of participants expressed in the initial survey that, although they did not fully understand the therapy and had significant concerns, they would still accept it based on their trust in their doctors. However, they also expressed a desire for more information regarding their own medical care. The responses to the video presentation were generally positive. Despite initial apprehension relating to perception of EV therapy as experimental and intimidating, participants felt more comfortable accepting the therapy and participating in a clinical trial after gaining a better understanding of the consequences of AF, the therapy's mechanism of action, preclinical research results, and similar studies involving EV therapies. Participants suggested that the video should be shown to all future trial participants before they undergo treatment, as it effectively explained the therapy's benefits and risks.

Initial participant acceptance of the therapy varied, depending on their previous experiences, with participants

who had experienced postoperative AF exhibiting the lowest level of acceptance. This result may be attributed to such patients' higher rates of complications, such as increased ICU and hospital stays, infections, sternum reconstruction, acute respiratory distress syndrome, and pleural effusions. Challenging postsurgery experiences could make patients less receptive to receiving preventive therapy for a problem that may not manifest. However, after being informed through the presentation and focus group, participants who had experienced AF showed the largest increase in acceptance level in the postpresentation surveys. Following the presentation and focus group, all participants displayed high and comparable levels of acceptance of the therapy, indicating that being well informed influenced their level of acceptance.

Participants played a vital role in informing the development of the initial early-phase clinical trial. Their insights could be incorporated into animal models before human trials are conducted. For example, if all focus group participants expressed reluctance toward injection administration of EVs, the use of spray administration in animal models could be considered. Frequently asked questions and voiced concerns identified during the focus groups could be addressed in the presentation, to alleviate patient anxiety.

Participants also provided valuable advice for improving the presentation. Their suggestions included the following: incorporate more graphs; keep the presentation simple, to provide reassurance instead of inducing fear; shorten the duration, to maintain attention; add subtitles for hearing-impaired patients; translate the content into other languages (particularly French); and consider color combinations that are accessible for individuals with color blindness. These recommendations hold value for the presentation of future therapies as well.

Incorporating insights from patient partners should be a priority for identifying knowledge gaps and understanding patient attitudes in any study that precedes a clinical trial. Given the novel nature of using cell-derived therapeutics, identifying and addressing potential barriers to adoption and acceptance of EV therapy is crucial, as perceived by the patient panel, during the clinical trial preparation phase. Survey data demonstrated that patients had a better understanding of the risks and benefits of EV therapy for postoperative AF after the presentation. With the therapy progressing along the translational pipeline, establishing a long-term relationship with our patient partners is desirable. Future patient-partner activities may involve reviewing the clinical trial consent form to ensure clarity for the general public, developing educational materials, and raising awareness about potential applications for other forms of AF. Encouraging discussions and questions from a diverse patient-partner group proves beneficial both for the research team's preparation and for patient comfort during the transition to a clinical setting.

Our approach is inherently quite time-consuming, thereby limiting the number of patients we could include in the study. Given that we identified patients from the University of Ottawa Heart Institute Patient Engagement Database, we were limited to those who self-selected as providing ongoing research permission to contact, and self-identified as within the realm of cardiac surgery. They then had to be willing to commit to engaging in reviewing a video, 2 surveys, and an encounter group. This small sample size inherently limited the power of all statical analyses performed. However, the information gleaned from this process is valuable and can be used to identify issues for future studies.

How this resource- and time-consuming process should be integrated into regular clinical research is an interesting question. One practical example could involve incorporating patient-engagement activities into the standard protocol for clinical trials, such as including patient advisory boards or focus groups to provide ongoing feedback on study design and implementation. Additionally, leveraging digital platforms and telehealth services can facilitate remote participation and increase accessibility for patients. Another approach could be to establish partnerships with patient-advocacy organizations, to identify and recruit patients for research participation, as well as to disseminate study findings to the broader patient community. Ultimately, integrating patient engagement into clinical research requires a proactive and collaborative approach that prioritizes the perspectives and needs of patients, which we hope will lead to more patient-centred and impactful research outcomes.

Ethics Statement

Institutional review board approval was obtained at the participating institution, and patients provided informed consent for their study participation.

Patient Consent

The authors confirm that patient consent forms have been obtained for this article.

Funding Sources

This work was supported by the Canadian Institutes of Health Research (Project Grant 410103) and the Natural Sciences and Engineering Research Council of Canada (CHRPJ 549626−20).

Disclosures

D.R.D. is inventor for a patent application submitted regarding extracellular vesicle treatment of atrial fibrillation (US patent filing number 63/278,518, Compositions of human heart derived extracellular vesicles and uses thereof). The other authors have no conflicts of interest to disclose.

References

1. Desai AS, Webb DJ, Taubel J, et al. Zilebesiran, an RNA interference therapeutic agent for hypertension. N Engl J Med 2023;389:228-38.
2. Garcia-Pavia P, aus dem Siepen F, Donal E, et al. Phase 1 trial of antibody NI006 for depletion of cardiac transthyretin amyloid. N Engl J Med 2023;389:239-50.
3. McDonald CM, Marbán E, Hendrix S, et al. Repeated intravenous cardiosphere-derived cell therapy in late-stage Duchenne muscular dystrophy (HOPE-2): a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. Lancet 2022;399:1049-58.
4. Marban E. The secret life of exosomes: what bees can teach us about next-generation therapeutics. J Am Coll Cardiol 2018;71:193-200.

5. Vaka R, Parent S, Risha Y, et al. Extracellular vesicle microRNA and protein cargo profiling in three clinical-grade stem cell products reveals key functional pathways. Mol Ther Nucleic Acids 2023;32:80-3.

6. Vaka R, Khan S, Ye B, et al. Direct comparison of different therapeutic cell types susceptibility to inflammatory cytokines associated with COVID-19 acute lung injury. Stem Cell Res Ther 2022;13:20.

7. McRae C, Kapoor A, Kanda P, Hibbert B, Davis DR. Systematic review of biological therapies for atrial fibrillation. Heart Rhythm 2019;16:1399-407.

8. Seo C, Michie C, Hibbert B, Davis DR. Systematic review of pre-clinical therapies for post-operative atrial fibrillation. PLoS One 2020;15:e0241643.

9. Parent S, Vaka R, Risha Y, et al. Prevention of atrial fibrillation after open chest surgery with extracellular vesicle therapy. JCI Insight 2023;8:e163297.

10. i Research. How many cardiac surgeries are performed each year? — New study by iData Research Vol 2023. iData Research, 2021. Available at: https://idataresearch.com/over-900000-cardiac-surgeries-performed-every-year-in-the-united-states/. Accessed April 12, 2024.

11. Aranki SF, Shaw DP, Adams DH, et al. Predictors of atrial fibrillation after coronary artery surgery. Current trends and impact on hospital resources. Circulation 1996;94:390-7.

12. Mathew JP, Parks R, Savino JS, et al. Atrial fibrillation following coronary artery bypass graft surgery: predictors, outcomes, and resource utilization. MultiCenter Study of Perioperative Ischemia Research Group. JAMA 1996;276:300-6.

13. Almassi GH, Schowalter T, Nicolosi AC, et al. Atrial fibrillation after cardiac surgery: a major morbid event? Ann Surg 1997;226:501-11. discussion 511-03.

14. Kowey PR, Stebbins D, Igidbashian L, et al. Clinical outcome of patients who develop PAF after CABG surgery. Pacing Clin Electrophysiol 2001;24:191-3.

15. Soucier RJ, Mirza S, Abordo MG, et al. Predictors of conversion of atrial fibrillation after cardiac operation in the absence of class I or III antiarrhythmic medications. Ann Thorac Surg 2001;72:694-7. discussion 697-8.

16. Hravnak M, Hoffman LA, Saul MI, Zullo TG, Whitman GR. Resource utilization related to atrial fibrillation after coronary artery bypass grafting. Am J Crit Care 2002;11:228-38.

17. Mathew JP, Fontes ML, Tudor IC, et al. A multicenter risk index for atrial fibrillation after cardiac surgery. JAMA 2004;291:1720-9.

18. Izhar U, Ad N, Rudis E, et al. When should we discontinue antiarrhythmic therapy for atrial fibrillation after coronary artery bypass grafting? A prospective randomized study. J Thorac Cardiovasc Surg 2005;129:401-6.

19. Ahlsson A, Fengsrud E, Bodin L, Englund A. Postoperative atrial fibrillation in patients undergoing aortocoronary bypass surgery carries an eightfold risk of future atrial fibrillation and a doubled cardiovascular mortality. Eur J Cardiothorac Surg 2010;37:1353-9.

20. Steinberg BA, Zhao Y, He X, et al. Management of postoperative atrial fibrillation and subsequent outcomes in contemporary patients undergoing cardiac surgery: insights from the Society of Thoracic Surgeons CAPS-Care Atrial Fibrillation Registry. Clin Cardiol 2014;37:7-13.

21. Melduni RM, Schaff HV, Bailey KR, et al. Implications of new-onset atrial fibrillation after cardiac surgery on long-term prognosis: a community-based study. Am Heart J 2015;170:659-68.

22. Creswell LL, Schuessler RB, Rosenbloom M, Cox JL. Hazards of postoperative atrial arrhythmias. Ann Thorac Surg 1993;56:539-49.

23. Villareal RP, Hariharan R, Liu BC, et al. Postoperative atrial fibrillation and mortality after coronary artery bypass surgery. J Am Coll Cardiol 2004;43:742-8.

24. Stamou SC, Dangas G, Hill PC, et al. Atrial fibrillation after beating heart surgery. Am J Cardiol 2000;86:64-7.

25. Reed GL 3rd, Singer DE, Picard EH, DeSanctis RW. Stroke following coronary-artery bypass surgery. A case-control estimate of the risk from carotid bruits. N Engl J Med 1988;319:1246-50.

26. Lahtinen J, Biancari F, Salmela E, et al. Postoperative atrial fibrillation is a major cause of stroke after on-pump coronary artery bypass surgery. Ann Thorac Surg 2004;77:1241-4.

27. Akintoye E, Sellke F, Marchioli R, Tavazzi L, Mozaffarian D. Factors associated with postoperative atrial fibrillation and other adverse events after cardiac surgery. J Thorac Cardiovasc Surg 2018;155:242-251.e210.

28. Saxena A, Dinh DT, Smith JA, et al. Usefulness of postoperative atrial fibrillation as an independent predictor for worse early and late outcomes after isolated coronary artery bypass grafting (multicenter Australian study of 19,497 patients). Am J Cardiol 2012;109:219-25.

29. Kosmidou I, Chen S, Kappetein AP, et al. New-onset atrial fibrillation after PCI or CABG for left main disease: the EXCEL trial. J Am Coll Cardiol 2018;71:739-48.

30. Crystal E, Connolly SJ, Sleik K, Ginger TJ, Yusuf S. Interventions on prevention of postoperative atrial fibrillation in patients undergoing heart surgery: a meta-analysis. Circulation 2002;106:75-80.

31. Kim MH, Deeb GM, Morady F, et al. Effect of postoperative atrial fibrillation on length of stay after cardiac surgery (The Postoperative Atrial Fibrillation in Cardiac Surgery Study [PACS(2)]. Am J Cardiol 2001;87:881-5.

32. Burgess DC, Kilborn MJ, Keech AC. Interventions for prevention of post-operative atrial fibrillation and its complications after cardiac surgery: a meta-analysis. Eur Heart J 2006;27:2846-57.

33. Kerin NZ, Jacob S. The efficacy of sotalol in preventing postoperative atrial fibrillation: a meta-analysis. Am J Med 2011;124:875.e1-9.

34. Ho KM, Tan JA. Benefits and risks of corticosteroid prophylaxis in adult cardiac surgery: a dose-response meta-analysis. Circulation 2009;119:1853-66.

35. Dieleman JM, van Paassen J, van Dijk D, et al. Prophylactic corticosteroids for cardiopulmonary bypass in adults. Cochrane Database Syst Rev 2011:CD005566.

36. Whitlock RP, Devereaux PJ, Teoh KH, et al. Methylprednisolone in patients undergoing cardiopulmonary bypass (SIRS): a randomised, double-blind, placebo-controlled trial. Lancet 2015;386:1243-53.

37. Imazio M, Brucato A, Ferrazzi P, et al. Colchicine reduces postoperative atrial fibrillation: results of the Colchicine for the Prevention of the Postpericardiotomy Syndrome (COPPS) atrial fibrillation substudy. Circulation 2011;124:2290-5.

38. Imazio M, Brucato A, Ferrazzi P, et al. Colchicine for prevention of postpericardiotomy syndrome and postoperative atrial fibrillation: the COPPS-2 randomized clinical trial. JAMA 2014;312:1016-23.

39. Horbach SJ, Lopes RD, da CGJC, et al. Naproxen as prophylaxis against atrial fibrillation after cardiac surgery: the NAFARM randomized trial. Am J Med 2011;124:1036-42.

40. Lalu MM, Richards D, Foster M, et al. Protocol for co-producing a framework and integrated resource platform for engaging patients in laboratory-based research. Res Involv Engagem 2024;10:25.

41. Fox G, Lalu MM, Sabloff T, et al. Recognizing patient partner contributions to health research: a systematic review of reported practices. Res Involv Engagem 2023;9:80.

42. Shea JB, Sears SF. A patient's guide to living with atrial fibrillation. Circulation 2008;117:e340-3.

43. Baman JR, Passman RS. Atrial fibrillation. JAMA 2021;325:2218.

44. McMillan SS, King M, Tully MP. How to use the nominal group and Delphi techniques. Int J Clin Pharm 2016;38:655-62.

45. Jones J, Hunter D. Consensus methods for medical and health services research. BMJ 1995;311:376-80.

46. Black N, Murphy M, Lamping D, et al. Consensus development methods: a review of best practice in creating clinical guidelines. J Health Serv Res Policy 1999;4:236-48.

47. Sekhon M, Cartwright M, Francis JJ. Acceptability of healthcare interventions: an overview of reviews and development of a theoretical framework. BMC Health Serv Res 2017;17:88.

48. Sekhon M, Cartwright M, Francis JJ. Acceptability of health care interventions: a theoretical framework and proposed research agenda. Br J Health Psychol 2018;23:519-31.

Supplementary Material

To access the supplementary material accompanying this article, visit *CJC Open* at https://www.cjcopen.ca/ and at https://doi.org/10.1016/j.cjco.2024.04.003.