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An mHealth intervention to improve nurses' atrial fibrillation and anticoagulation knowledge and practice: the EVICOAG study.

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1

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Declaration of Conflicting Interests

The authors declare that there is no conflict of interest.

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Ethical Approval

Approval to conduct the study was obtained from each relevant hospital's human research ethics committee (HREC ref no: LNR/16/POWH/176) and the university's human research ethics committee (ETH16-0390). The results reported conform to the Revised Standards for Quality Improvement Reporting Excellence (SQUIRE 2.0)¹ and the principles outlined in the Declaration of Helsinki.

Abstract

Background: There is a need to improve cardiovascular nurses' knowledge and practices related to stroke prevention, atrial fibrillation (AF) and anticoagulation therapy.

Aim(s): To evaluate the efficacy of EVICOAG - a novel mHealth, smartphone-based, spaced-learning intervention on nurses' knowledge of AF and anticoagulation.

Methods: Nurses employed in 4 clinical specialties (neuroscience, stroke, rehabilitation, cardiology) across 3 hospitals were invited to participate. In this quasi-experimental study, 12 case-based AF and anticoagulation learning scenarios (hosted via an mHealth platform) were delivered to participants' smartphones over a 6-week period (July-December 2016) using a spaced timing algorithm. Electronic surveys to assess awareness and knowledge were administered pre (T1) and post (T2) intervention.

Results: From seventy-four participants recruited to T1, 40 completed T2. There was a 54% mean improvement in knowledge levels post-intervention. The largest improvement was achieved in domains related to medication interaction and stroke and bleeding risk assessment. Post-

intervention, those who completed T2 were significantly more likely to use CHAD₂DS₂VASc (2.5% vs. 37.5%) and HAS-BLED (2.5% vs. 35%) tools to assess stroke and bleeding risk, respectively (p < 0.01).

Conclusion: The EVICOAG intervention improved nurses' knowledge of AF and anticoagulation, and influenced their uptake and use of stroke and bleeding risk assessment tools in clinical practice. Future research should focus on whether a similar intervention might improve patient-centred outcomes such as patients' knowledge of their condition and therapies, medication adherence, time in therapeutic range and quality of life.

Keywords: atrial fibrillation; anticoagulation; thromboprophylaxis; stroke; knowledge; nursing practice; mHealth.

Introduction

Atrial fibrillation (AF) is the most common heart rhythm disorder, with an estimated global prevalence of 33.5 million individuals in 2010 ². Although its management has been steadily improving, AF remains a major cause of stroke, heart failure, and cardiovascular morbidity. Ischaemic strokes are the most commonly feared adverse events among those with AF, reflecting the overall 3-5 fold increase in stroke risk among individuals with AF ³. While AF presents a significant burden to individuals and health care systems, many AF-related strokes remain very preventable. The problem is three-fold. To optimise stroke prevention in this population, there is a need for: (i) improved identification (screening) and diagnosis, (ii) thromboprophylaxis optimisation, and (iii) increasing the quality control of anticoagulation (long term).⁴

Nurses are well positioned throughout primary and acute care settings to address these challenges and improve stroke prevention efforts. However, the findings from our recent survey, conducted in Australia, indicate that, while there is a strong opportunity for nurse involvement in stroke prevention/management for AF patients, nurses currently demonstrate poor knowledge and practice in this area ⁵. Nurses make significant contributions to the management of AF, including informal and formal patient counselling regarding AF related therapies. ^{6,7} Though, there is need for greater nurse involvement and engagement in supporting patients with shared decision- making around anticoagulation for stroke prevention. ^{4,8} This requires nurses to be proficient and confident in assessing patients for stroke and bleeding risk using the CHA₂DS₂-VASc and HAS-BLED tools ⁹ Yet, to date, nurses report a lack of awareness and confidence in using these instruments, consequentially they are somewhat underused in clinical practice. A survey published by the research team in 2016 revealed nurses' knowledge deficits, particularly regarding interactions between anticoagulants and other drugs, lifestyle factors, and diet. Hence, there is a need to improve nurses' knowledge and practices related to medication—management and decision-making around anticoagulation for stroke prevention in patients with AF. ¹⁰

Objective

The objective of this study was to evaluate the efficacy of a theory driven QStream[™] based, spaced-learning intervention (EVICOAG) on nurses' knowledge of AF and anticoagulation, and their clinical use of stroke and bleeding risk assessment tools.

Methods

Study design and setting

A quasi-experimental pre-test (T1) /post-test (T2) pilot study was conducted in three Australian acute care hospitals in metropolitan Sydney (New South Wales), Australia.

Participants

All registered nurses working in 4 clinical specialties (neuroscience, stroke, rehabilitation, cardiology), and employed for more than 14 hours per week within in-patient wards at 3 hospitals, were invited to participate between July and December 2016. A cut off of 14 hours was selected to engage part-time and full-time nurses working more than two days per week. Eligible nurses were provided with written and verbal information about the study, and their written consent to participate obtained.

Ethical considerations

Approval to conduct the study was obtained from each relevant hospital's human research ethics committee (HREC ref no: LNR/16/POWH/176) and the university's human research ethics committee (ETH16-0390). The results reported conform to the Revised Standards for Quality Improvement Reporting Excellence (SQUIRE 2.0)¹ and the principles outlined in the Declaration of Helsinki.

Description of intervention

Spaced learning

Spaced learning is an evidence-based pedagogy that has been shown, in numerous separate randomised controlled trials to increase clinicians' knowledge and change behaviours¹¹⁻¹³. This form of educational intervention involves a 'push notification' of brief clinical case scenarios to participants from an online platform (QStream™) directly to their email or smartphone device. A small number (2-3) of case studies are delivered every second day. Upon answering a question, a participant's performance is benchmarked against their peers' de-identified responses, and they are provided with concise feedback linked to credible, evidence-based resources (e.g., journal articles, clinical practice guidelines).

QStream™

In our study, spaced learning was delivered via QStream[™], an internet based, subscription-free (free for participants) platform developed by the Harvard Medical School. QStream[™] has been shown across several clinical trials to improve knowledge retention, aid lasting translation to clinical practice, and help improvements in patient outcomes ^{14,15}. The movement towards innovative QStream[™] mobile solutions has been driven by findings from several clinical trials demonstrating that it can improve knowledge retention, aid lasting translation to clinical practice, and help provide I improvements in patient outcomes ^{14,15}. It serves as a means of achieving higher quality and safety of patient care above traditional knowledge reinforcement methods such as inservice education or reminders.

EVICOAG

EVICOAG, an QStream[™]-based online learning module, comprises 12 case-based AF and anticoagulation learning scenarios. The 12 key topic areas were identified as priority areas for improvement from an earlier survey, conducted by the research team.¹⁰ This novel intervention

combines: (i) authentic case based anticoagulation learning scenarios; (2) real-time audit and feedback; and (3) online links to evidence-based decision supports (stroke and bleeding risk assessment tools, and international clinical management guidelines). The intervention is delivered directly to consenting participants' email and is accessible from their desktop computer or smart phone. Participants using smart phones receive pop-up notifications (by default). The EVICOAG module was developed by an interdisciplinary expert panel including nurses and pharmacists. This process included the development of unique case studies. Case studies focussing on the following key topic areas pertinent to anticoagulant therapy use and management in persons with AF: (1) non-steroidal anti-inflammatory (NSAID) medicines interactions; (2) antibiotic medicines interactions; (3) bleeding risk assessment; (4) stroke risk assessment; (5) treatment optimisation; (6) epistaxis management; (7) the role of aspirin in stroke prevention for AF; (8) reversal agents for novel oral anticoagulants (NOACs); (9) renal monitoring for NOACs; (10) ECG assessment for AF; (11) shared decision-making; and (12) adherence and persistence with anticoagulation therapy.

Answers to the case scenarios were informed and supported by the best evidence available in open access format to participants at the time of completing the module. Open access format was selected to remove any pay-wall access barrier for participants to review the evidence base once completed. Participants were given a short introduction (oral presentation to the nurse participants at each hospital site) about the study and assisted by the study nurse to download the application to their smartphone device/desktop computer after completing the first (T1) electronic survey (directly after enrolment into the study).

Automated delivery of the twelve case scenarios via the QStream[™] platform followed a standardised spaced algorithm: (i) two questions per delivery, every two days; (ii) questions answered incorrectly are repeated after seven days, and questions answered correctly are repeated after thirteen days; (iii) two consecutive correct answers are required to retire a question, and a maximum of three attempts

are provided before retiring a question. An example of an EVICOAG case study, and response is provided in *figure 1*.

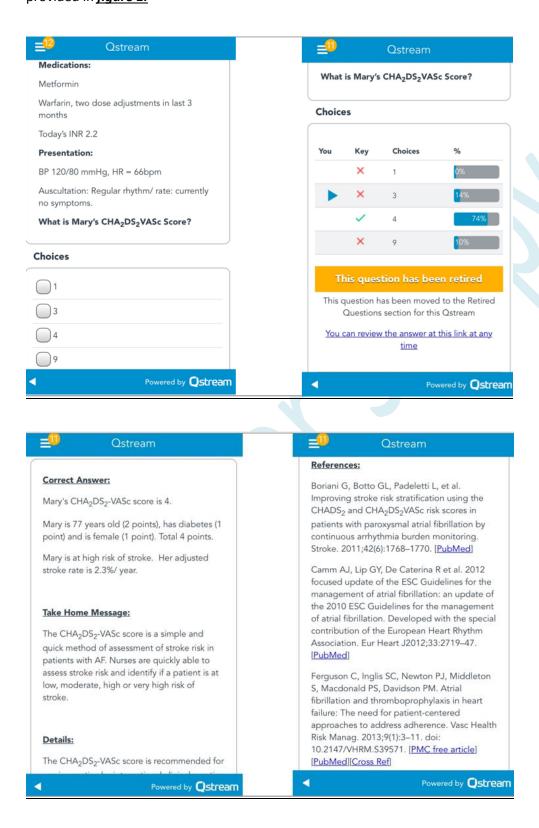


Figure 1: Example of EVICOAG Case Study

Procedure

Nurses completed an online pre-survey (T1) delivered via Survey Monkey[™] platform to ascertain there: (i) basic demographics; (ii) clinical experience in caring for patients; (iii) practice patterns in relation to clinical decision making for anticoagulation; (iv) perceived barriers to anticoagulation in clinical practice; (v) provision of choice of therapy in patients; and (vi) nurses' level of knowledge of anticoagulation.

The survey was adapted from a previous survey developed by Oterhals et al (2014)¹⁶ and used by Ferguson et al (2016) a to assess knowledge and practices of cardiovascular nurses in Australia and New Zealand in relation to AF and anticoagulation.¹⁰ The original questionnaire was reported as demonstrating good face validity. The survey assessed key criteria in relation to knowledge relating to anticoagulation and practice patterns. Some additional questions were included after consultation of the interdisciplinary advisory panel and extensive review of the literature.

Participants were then enrolled into the EVICOAG (QStream[™]) module. This delivered 12 case-scenarios related to AF and anticoagulation via the online application over a period of 6 weeks. Following completion of this online module, participants were asked to undertake an online post-intervention survey (T2) using Survey Monkey[™] to evaluate the efficacy of the QStream[™] intervention in relation to AF anticoagulation related knowledge.

Data collection

Survey data was collected at two time points over the 6-week study period:

- Time 1 (baseline) (T1): Immediately prior to the online module (intervention) commencing.
- Time 2 (T2): Immediately following completion of the intervention.

Data were extracted via the QStream™ platform upon completion of the intervention.

Data analysis

Data that were generated from the electronic surveys and were exported into a SPSS. Descriptive analyses were used to describe the sample and responses to study variables. Data are reported as number (percentages) unless otherwise stated. For electronic survey data, student's t-tests were used to determine whether there was a significant difference between the two groups. A p value of < 0.05 was deemed to be statistically significant. Knowledge proficiency scores were calculated based on the percentage of correct responses for initial (baseline knowledge proficiency score) and post intervention knowledge proficiency scores. For each clinical specialty group (stroke, neuroscience, cardiovascular and rehabilitation) the knowledge proficiency scores were calculated based on the percentage of correct responses at baseline and post intervention. Knowledge improvement represents the relative percentage increase in the knowledge proficiency scores.

Results

Baseline data (T1)

The participant recruitment flow is outlined in **Figure 2**. A total of 89 participants consented to participate in the study; of this 74 completed the baseline survey (T1) and were included in the final analyses. The majority of participants were ≥ 25 years old (42%; 56/74), female (82%; 61/74), practicing as registered nurses following Bachelor's degree qualifications (70%; 52/74), worked at the Site 1 (45%; 33/74) and working in the rehabilitation specialty (27%; 20/74). While 35% (26/74) had >10 years' experience in clinical practice, approximately 52% (39/74) had worked less than 3 years in their current specialty and 57% (42/74) had worked less than 3 years in their current department. Previous participation in topic-relevant educational programs ranged from 17-38% across four topics (AF, stroke risk, anticoagulation and health behaviour modification). Only 54% (n= 40) of participants completed the post-intervention evaluation survey (T2) (**Refer to table 1**).

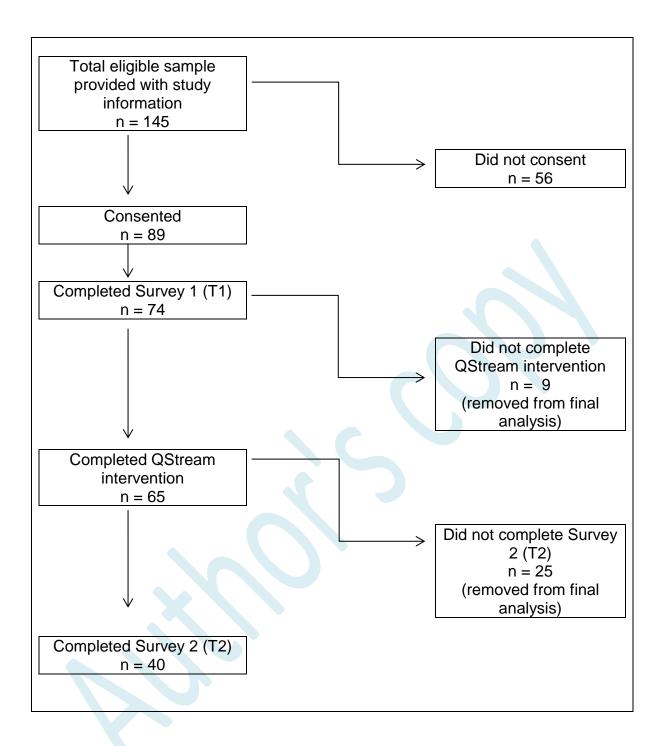


Figure 2: Participant Recruitment Flow Chart

Table 1: Baseline sample characteristics and demographics

Demographic	Result (%) (n/total n)
Sex	
Female	82% (61/74)
Male	18% (13/74)
Age	
Under 25	12% (9/74)
25-35	42% (31/74)
35-45	34% (25/74)
45-55	5% (4/74)
55-65	5% (4/74)
65 and over	1% (1/74)
Hospital Site	
A	28% (21/74)
В	45% (33/74)
С	27% (20/74)
Specialty	
Neuroscience	25% (18/74)
Acute Stroke	22% (16/74)
Cardiology/ Cardiothoracic	26% (19/74)
Rehabilitation	27% (20/74)
Highest level of education	
Nursing training	4% (3/74)
Bachelor degree	70% (52/74)
Graduate certificate	12% (9/74)
Graduate diploma	5% (4/74)
Masters degree	8% (6/74)
PhD	0%
Current position	
Enrolled Nurse	5% (4/74)
New Graduate Registered Nurse	7% (5/74)
Registered Nurse	68% (50/74)
Clinical Nurse Specialist	7% (5/74)
Clinical Nurse Educator	3% (2/74)
Nurse Educator	3% (2/74)
Nurse Unit Manager	3% (2/74)
Clinical Nurse Consultant	4% (3/74)
Nurse Practitioner	1% (1/74)
Advanced Practice (above RN)	21% (15/74)
Years worked in clinical practice	
<3 years	28% (21/74)
4-5 years	11% (8/74)
6-10 years	26% (19/74)
> 10 years	35% (26/74)
Years worked in current specialty	

<3 years	52% (39/74)
4-5 years	10% (7/74)
6-10 years	14% (10/74)
> 10 years	20% (15/74)
Missing	4% (3/74)
Years worked in current department	
<3 years	57% (42/74)
4-5 years	9% (7/74)
6-10 years	16% (12/74)
> 10 years	18% (13/74)
Participation in previous education	Attendance %
program	
Atrial fibrillation	29% (21/73)
Stroke risk	38% (28/73)
Anticoagulation	25% (25/73)
Health behaviour modification	17% (12/70)

Survey findings

Almost one third of participants felt that nurses had no specific role in anticoagulation management in clinical practice. The majority reported that they were not directly involved in multidisciplinary team discussions regarding treatment decision-making around anticoagulation for patients with AF. The CHA₂DS₂-VASc and HAS-BLED tools to assess stroke and bleeding risk were highly underutilised; 93-95% of participants reported that they did not use these tools. The full pre- and post-test survey results are presented in **Table 2**.

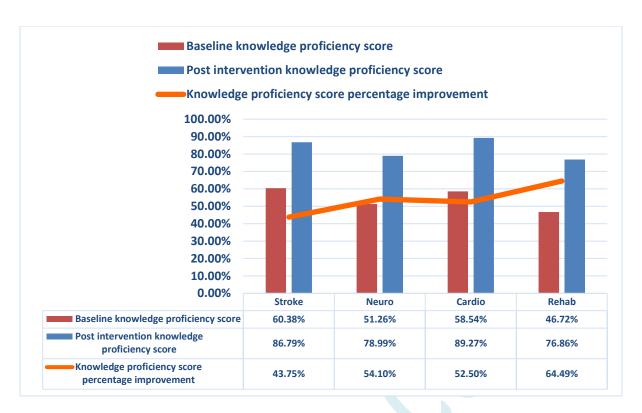
Table 2: Pre- and post-test survey results

	T1 n (%)	T2 n (%)	P value
Clinical experience			
Cared for a patient with AF who has experienced an intracranial haemorrhage whilst receiving	40/74 (54%)	-	N/A
anticoagulation Cared for a patient with known AF who has experienced a stroke whilst	38/72 (52%)	-	N/A
not receiving anticoagulation No involvement in multidisciplinary team discussions when making treatment decisions	47/74 (64%)	-	N/A
Practice patterns			
The risk of stroke vs. the risk of bleeding is clearly articulated to patients prior to commencing	43/72 (58%)	39/47 (83%)	p = 0.00045
anticoagulation Unsure of whether to advocate for thromboprophylaxis or not when	22/74 (31%)	4/47 (9%)	p = 0.00049
involved in team decisions Did not know enough about the risk and benefits of various anticoagulants	40/73 (55%)	8/46 (17%)	p = < 0.0001
Quality decision making			
Took time to understand patients views of the risk and benefits of anticoagulation	43/74 (58%)	35/47 (74%)	P = 0.0747

Disagreed with the statement that "Patients are were well-informed	20/74 (27%)	4/47 (9%)	P = 0.0163
about the risks and benefits of			
anticoagulation at time of	12/74/170/\	2/47/40/	D 0.0224
commencement"	12/74 (17%)	2/47 (4%)	P = 0.0324
Disagreed with the statement that			
"Patients received comprehensive	A /72 /70/\	10/47 (40%)	P = < 0.0001
education about anticoagulation	4/73 (7%)	19/47 (40%)	P = < 0.0001
prior to discharge" Used CHADS ₂ or CHA ₂ DS ₂ -VASc to	4/74 (5%)	18/47 (38%)	P = < 0.0001
stratify stroke risk	4,74 (370)	10/47 (50/0)	1 - 10.0001
Used HAS-BLED to stratify stroke	26/74 (35%)	32/47 (68%)	P = 0.0004
risk	20,7 . (00,70)	<i>32,</i> (<i>32,12</i>)	. 0.000
Use of shared decision making to			
explain risks and benefits of			
anticoagulation to patients			
Nurses' role			
Counsel patients regarding	21/74 (62%)	39/47 (83%)	P = 0.0143
adherence to the drug regimen			
Teach about drugs, how to take	46/74 (62%)	23/47 (49%)	P = 0.1610
them and side-effects			
Advise patients on dosing warfarin	36/74 (49%)	35/47 (75%)	P = 0.0048
based on INR results			
Do not have a specific role	46/74 (28%)	6/47 (13%)	P = 0.0539

CHA₂DS₂-VASc- Score for Atrial Fibrillation Stroke Risk; **HASBLED**- Hypertension, Abnormal liver/ renal function, Stroke, Bleeding, Labile INRs, Elderly >65, Drugs or Alcohol; **OAC**- Oral Anticoagulation; P<0.05 was considered statistically significant.

Post-intervention, those who completed T2 reported significant improvements in the use of the CHA_2DS_2 -VASc (2.5% to 37.5%) and HAS-BLED (2.5% to 35%) tools to assess stroke and bleeding risk (p< 0.01). Overall, knowledge proficiency scores also improved by 54% post-intervention (**Figure 3**). Rehabilitation nurses demonstrated the greatest improvement with a 64% increase in overall knowledge scores post-intervention. The largest improvement was observed in knowledge domains focused on medication interactions and risk assessment (**Appendix 1**).



<u>Figure 3: Knowledge proficiency score improvement by clinical specialty pre- and post- QStream intervention</u>

Appendix 1: Case study proficiency heat map

Based on % of correct responses by topic and team	Rehab	Neuro	Cardio	Stroke	Average
Initial Level					
Case Scenario 5 (Ibuprofen Interaction)	10%	27%	18%	11%	16%
Case Scenario 2 (Bleeding Risk Assessment)	27%	17%	12%	50%	25%
Case Scenario 4 (Treatment Optimisation)	32%	36%	24%	56%	34%
Case Scenario 11 (Epistaxis Management)	31%	29%	65%	25%	42%
Case Scenario 6 (Antibiotic Interaction)	15%	55%	71%	56%	46%
Case Scenario 8 (Role of Aspirin)	35%	50%	53%	50%	46%
Case Scenario 9 (Reversal Agents)	65%	29%	41%	38%	47%
Case Scenario 7 (Renal Monitoring in NOACS)	56%	40%	65%	56%	56%
Case Scenario 3 (AF- ECG Assessment)	50%	83%	94%	89%	75%
Case Scenario 1 (Stroke Risk Assessment)	73%	71%	72%	91%	75%
Case Scenario 10 (Shared Decision Making)	88%	100%	88%	100%	92%
Case Scenario 12 (Persistence & Adherence)	100%	86%	100%	100%	98%
Average	47%	51%	59%	60%	53%

Rehab	Neuro	Cardio	Stroke	Average
Kenas	itcuio	curuio	Stroke	Average
76%	64%	88%	67%	76%
59%	75%	65%	60%	64%
68%	73%	71%	100%	75%
88%	86%	88%	88%	88%
60%	82%	88%	78%	75%
59%	50%	94%	88%	73%
94%	86%	94%	100%	94%
83%	80%	100%	89%	89%
77%	83%	100%	89%	87%
77%	86%	89%	91%	85%
94%	100%	94%	100%	96%
100%	100%	100%	100%	100%
77%	79%	89%	87%	83%
	59% 68% 88% 60% 59% 94% 83% 77% 94% 100%	76% 64% 59% 75% 68% 73% 88% 86% 60% 82% 59% 50% 94% 86% 83% 80% 77% 83% 77% 86% 94% 100% 100% 100%	76% 64% 88% 59% 75% 65% 68% 73% 71% 88% 86% 88% 60% 82% 88% 59% 50% 94% 94% 86% 94% 83% 80% 100% 77% 83% 100% 77% 86% 89% 94% 100% 94% 100% 100% 100%	76% 64% 88% 67% 59% 75% 65% 60% 68% 73% 71% 100% 88% 86% 88% 88% 60% 82% 88% 78% 59% 50% 94% 88% 94% 86% 94% 100% 83% 80% 100% 89% 77% 83% 100% 89% 77% 86% 89% 91% 94% 100% 94% 100% 100% 100% 100% 100%

Colour Legend; – Graded colour scale (Poor- excellent range)

Dark Red (0-25%); Light Red (26-60%); Yellow (61-80%); Light Green (81-95%); Dark Green (96-100%).

Satisfaction with the QStream™ learning module

Participants who completed the T2 survey were asked to rate satisfaction regarding content clarity and ease of navigation within the learning module. Overall, the majority (41/47; 87%) were satisfied or very satisfied with the learning module, 42/47 (89%) were satisfied or very satisfied with content clarity, and 41/47 (87%) found the tool easy or very easy to navigate.

In the feedback, participants identified that the most valuable parts of the learning module were the: authentic and contemporary nature of the case studies, repeated nature of the module, links to evidence-based resources, ease of use, and accessibility of the app based education.

Discussion

The major findings from this study show that the EVICOAG intervention improved nurses' knowledge of AF and anticoagulation, and improved the use of stroke and bleeding risk assessment tools. Embedding evidence-based learning applications throughout clinical education curricula offers the potential to address the evidence-treatment gaps in AF and anticoagulation. This form of novel online education, known as spaced-learning, takes advantage of two phenomena - the space and testing effects. Within the health care setting, online spaced-learning methods have proven effective in improving long-term retention of knowledge and generating meaningful behaviour changes in practice ^{14,15,17-19}. While this study focused on the effectiveness of the EVICOAG spaced-learning on nurses' knowledge of AF and anticoagulation, further research would be warranted to tailor this type of intervention to the patient and caregiver level. QStream™ spaced-learning was shown to be effective in the self-management of patients with diabetes [4], to our knowledge there have been no

known studies to date within an AF population. This is especially important as patients and caregivers play a significant role in AF thromboprophylaxis management ^{20,21}.

Given the ubiquitous nature of smartphone devices, QStream™ type modules offer an ideal means of ensuring current evidence-based findings are disseminated to targeted end-users in a timely and effective manner. There is scope for professional organisations to credential nurses on AF and anticoagulation (e.g Stroke Society of Australia & New Zealand, Australasian Cardiovascular Nursing College, Cardiac Society of Australia & New Zealand). Additionally, this level of online educational connectedness, allows various health care professionals to access information at a time that is convenient and geographically unconfined.

In recent years, there have been a proliferation of health education 'apps' to support patients with cardiovascular disease.²² Examples include the recently launched ESC 'AF Manager' app and the Health Buddies app²². The 'AF Manager' app is a high quality educational resource and platform for patients with AF. A component of this app is the educational resource for patients with AF, including information about AF, stroke risk and treatment options and lifestyle considerations.²³

Whilst improving nurses' knowledge and practice with regards to AF is critical, there is need for increasing knowledge in patients with AF and their informal caregivers. Improvements in patients' knowledge may increase knowledge of their condition and related therapies, adherence to therapy, improved self-care and overall quality of anticoagulation. Further, not all apps are high quality and it is important that all cardiovascular nurses are adept in appraising and recommending apps for patients with cardiovascular disease. There is scope to develop cardiovascular nurses' skills and expertise in the appraisal of high quality, credible apps.²⁴

Limitations

This research showed improvements in nurses' knowledge of AF and anticoagulation therapy and modest improvements in the utilisation of the CHA₂DS₂-VASc and HAS-BLED tool to stratify stroke and bleeding risks in patients with AF. It also demonstrated the feasibility and acceptability of an evidence-based education intervention across multiple sites. However, the lack of control group and participant selection bias is a major limitation of this pilot study. The response rate of 69% (n=74) of those eligible to participate who completed the baseline survey is modest, as is the 88% (n=65) completion of the learning module for those who enrolled in the study. It was unfortunate that only 54% (n=40) who enrolled in the study completed the T2 survey, this being a major limitation of this study. Further, whilst there was rigor in the approach applied to ensure that the electronic survey addressed the contents of the learning module. It should be noted that the knowledge survey was not a validated instrument. Whilst assessment of patient level outcomes (including clinical documentation of stroke risk) was not within the scope of this study, however this may be valuable to examine in future studies.

Conclusions and Implications

The EVICOAG QStream[™] intervention improved nurses' knowledge of AF and anticoagulation, and influenced their uptake and use of stroke and bleeding risk assessment tools in clinical practice. There is scope to upscale this intervention and for credentialing of cardiovascular nurses in AF and anticoagulation management. It is recommended that nurses undertake regular training and education on all aspects of AF and anticoagulation care. It is important that cardiovascular nurses are well informed on the latest evidence and practice in relation to AF. Smartphone applications can support learning through enhanced access to resource materials. Future research should focus on whether a similar theory-driven, mHealth intervention may improve patient-centred outcomes such as patients' knowledge of their condition and therapies, medication adherence and time in therapeutic range.

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