Warfarin—Is Self-Care the Best Care?

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In an era of non-vitamin K antagonist (VKA) oral anticoagulants, there has been relatively little research focused on redefining current warfarin management services. Warfarin has been in use for over 60 years, and is still the mainstay of treatment for people requiring anticoagulation with advanced chronic kidney disease, antiphospholipid syndrome, rheumatic mitral valve disease, or artificial heart valves. Rather than absolute international normalized ratio (INR) values, the quality of warfarin management is measured by the time in therapeutic range (TTR), with a therapeutic target INR of 2.0 to 3.0 (rather than lower INR targets[1]). This is directly related to treatment success (thromboembolism prevention) and safety (bleeding prevention).[2,3] Data from the GARFIELD-AF registry on 9,934 people taking warfarin for atrial fibrillation (AF) revealed a significant association between a TTR <65% and an increased risk of stroke/systemic embolism (hazard ratio [HR]: 2.55, 95% confidence interval [CI]: 1.61–4.03) and major bleeding (HR: 1.54, 95% CI: 1.04–2.26) during 1-year follow-up.[2]

Indeed, contemporary guidelines define optimal management as a TTR >70% within a therapeutic range of INR 2.0 to 3.0,[4,5] and the practice of aiming for a lower target INR range should be discouraged given the risks of worse outcomes.[6] Nonetheless, there is often suboptimal management of people on warfarin requiring long-term anticoagulant therapy. Mean TTR was reported as 55% for the people included in the GARFIELD-AF registry.[2] This finding was corroborated in a nationwide Danish study which reported that only 1,691 (35.4%) had a TTR ≥70% 6 months after VKA initiation. Amongst these, only 513 (55.7%) had a TTR ≥70% after 12 months,[7] highlighting the need for warfarin management services to be improved. Currently, service provision varies nationally and internationally, with different levels of engagement and access to warfarin self-testing or self-management. Given that warfarin treatment is complex and multifactorial, there will never be a "one management strategy fits all" approach to warfarin care because health care systems vary.

In the current issue of *Thrombosis & Haemostasis*, Dhippayom et al[8] performed a systematic review and network meta-analysis of randomized controlled trials (RCTs) that investigated the effect of warfarin self-care on anticoagulant control (TTR and proportion of INR in range [PINRR]) and clinical outcomes (all-cause mortality, major bleeding, and thromboembolic events). Utilizing robust methodology (following Cochrane Collaboration and PRISMA guidelines), 16 RCTs were identified including 5,895 participants (mean age range: 31–73 years, 81.9% male). Studies were categorized by type of self-care intervention following a TIP (theme, intensity and provider) framework previously developed by the authors (►**Fig. 1**).[8] Seven types of self-care interventions are described under two main categories of self-testing (high intensity [>1/week] via an e-Health platform [PST/High/e-Health], high intensity [>1/week] with health care professional involvement [PST/High/HCP], low intensity [<1/week] with health care professional involvement [PST/Low/HCP]), or self-management (high intensity [>1/week] with unaided self-dosing [PSM/High/patient]; high intensity [>1/week] with self-dosing aided by an e-Health platform [PSM/High/e-Health]; low intensity [<1/week] with unaided self-dosing [PSM/Low/Patient], flexible with unaided self-dosing [PSM/Flex/Patient]).[8]

Modest improvements in TTR were found in PST/High/e-Health (mean difference [MD]: 5.65%, 95% CI: 0.04–11.26) and PSM/High/Patient groups (MD: 7.67%, 95% CI: 0.26–15.08) when compared with usual care.[8] The risk of

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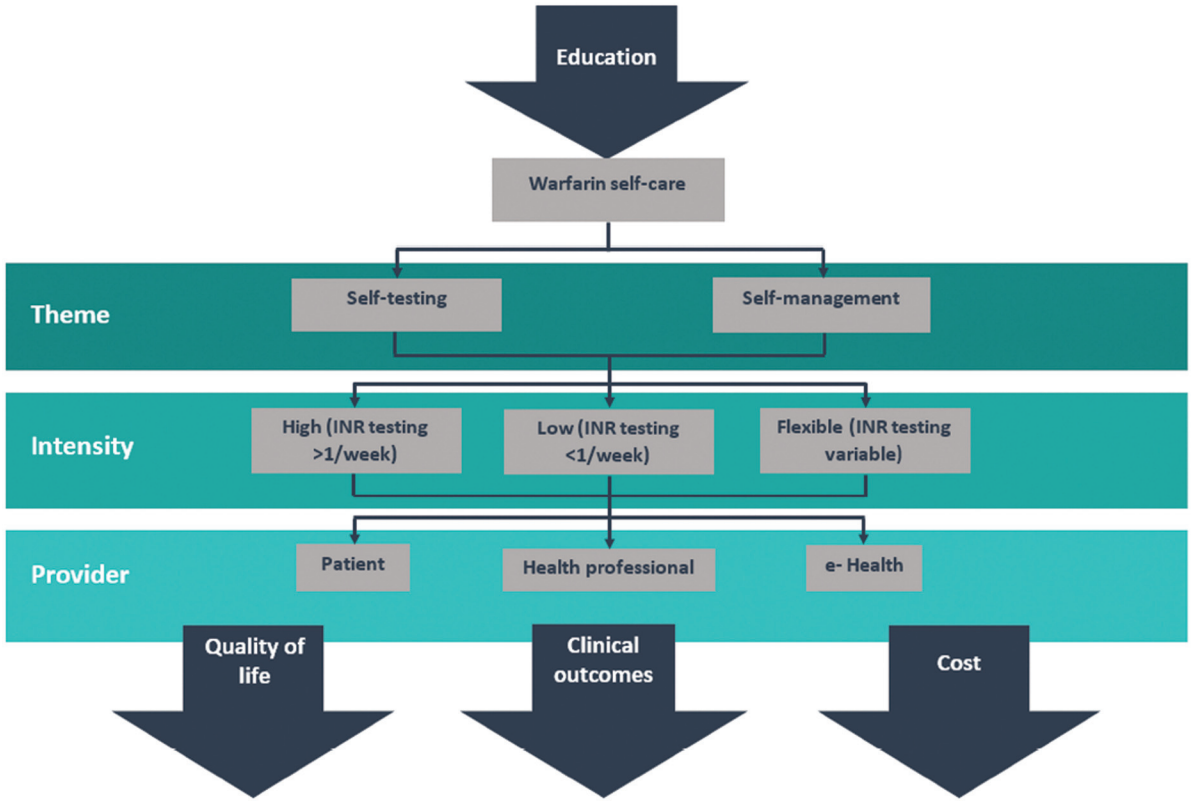

Fig. 1 Components of warfarin self-care strategies for studies to report on following the TIP (theme, intensity and provider) framework and relevant outcomes.

thromboembolic events was significantly lower with implementation of flexible self-management and unaided self-dosing (PSM/Flex/Patient) compared with high-intensity self-management with self-dosing aided by an e-Health platform (PSM/High/e-Health: relative risk [RR]: 0.39, 95% CI: 0.20–0.77) or usual care (RR: 0.38, 95% CI: 0.17–0.88).[8] However, this effect was nullified when a sensitivity analysis was performed to exclude a study that evaluated thromboembolic events in a high-risk subgroup (post-mechanical heart valve surgery).[8] There was no significant difference amongst any of the self-care interventions for other outcomes including PINRR, all-cause mortality, or major bleeding events. Based on these findings, Dhippayom et al recommend high-intensity warfarin self-care to maintain TTR.[8]

The authors should be commended on providing a detailed synthesis of the latest RCT evidence on warfarin self-care at a time when this is recommended to support remote patient management during the COVID-19 pandemic.[9] The use of a novel TIP framework to classify studies under seven types of self-care strategies highlights the complexity of these interventions, but this limited the number of direct comparisons for outcomes in meta-analyses. Furthermore, results for comparisons of clinical outcomes require cautious interpretation because of low statistical power.

Dhippayom et al[8] contextualize their findings with those of three previously published systematic reviews on warfarin self-care. Sharma et al[10] also found self-testing to be associated with a modest increase in TTR when compared with usual care (weighted MD: 4.4%, 95% CI: 1.71–7.18) after pooling results from five studies of 3,522 people (1,728 self-testing, 1,794 usual care) with mixed indications for VKA. There were no improvements reported for self-management strategies.[10] A Cochrane review of 28 RCTs (8,950 participants) evaluated the effect of self-testing/self-management (compared with usual care) on the same clinical outcomes.[11] Pooled estimates showed a reduction in thromboembolic events with self-testing (RR: 0.69, 95% CI: 0.49–0.97) and self-management (RR: 0.47, 95% CI: 0.31–0.70), a reduction in all-cause mortality with self-management only (RR: 0.55, 95% CI: 0.36- 0.84), and no effect of either self-testing or self-management on major bleeding.[11] Another meta-analysis reported a lower risk of mortality (odds ratio [OR]: 0.74, 95% CI: 0.63–0.87) and thromboembolism (OR: 0.58, 95% CI: 0.45–0.75) in people self-testing or self-managing when compared with usual care, with no difference in the risk of major bleeding or percentage of TTR.[12]

When studies report on TTR, it is important to assess the extent to which baseline characteristics of the study population may be responsible for changes observed. The SAMe-TT_2R_2 score may help to discriminate people who are likely to achieve a TTR >65% based on gender, medical history, smoking history, concomitant medications, race and age.[13] If a study population has favorable characteristics to suggest they will achieve an optimal TTR (SAMe-TT_2R_2 score between 0 and 2), this may partially explain any observed improvements.[13]

The effect of self-care strategies on patient quality of life and health care expenditure should also be considered.[14] A study by Sølvik et al[15] reported that warfarin self-management improved patient's self-reported general management satisfaction and self-efficacy, as well as a reduction in daily hassles, psychological distress, and strained social network. However, the study suffered from high attrition rates; 2-year follow-up quality-of-life assessments were only completed by 61.1% of participants.[15] This attrition may reflect difficulty in managing and sustaining warfarin self-management, and raises the potential of study bias. Another study reported that health-related quality of life was independent of TTR,[16] highlighting the need for quality of life to be included as a separate outcome in warfarin self-care studies. One cost-effectiveness study modeled VKA therapy self-testing/self-management compared with usual care over 10 years.[17] Using pooled estimates of clinical effectiveness, the study concluded that both self-care strategies appeared cost-effective but further studies are needed to evaluate long-term clinical outcomes.[17] Irrespective of cost, warfarin self-care will not be suitable for everyone.

People who want to self-test or self-manage must receive appropriate training. It would be beneficial for training to encompass educational interventions for VKA therapy that have shown to improve TTR. Further research is needed to identify these interventions; a Cochrane review on the impact of education and behavioral interventions was unable to draw any firm conclusions about the effect of educational interventions on TTR in AF patients receiving VKA due to the small number of studies and diversity of interventions.[18] The results of one on-going prospective RCT investigating the effect of education on TTR, clinical outcomes and quality of life will add to the evidence base.[19]

In summary, access to warfarin self-care will vary according to the local health service provision. Currently, there are extensive criteria to meet before a person qualifies as suitable for self-testing or self-management, and self-testing devices often have to be funded by the patient. While research shows promise that these strategies can improve clinical outcomes and quality of life, there are concerns about cost-effectiveness. To identify a standardized self-care model, studies need to provide detailed descriptions of self-care strategies that cover education and training, frequency of INR testing and care providers, and report on clinical outcomes (TTR, all-cause mortality, thromboembolic and major bleeding events), quality of life, and cost-effectiveness.

Conflict of Interest

L.A.R. has no conflicts of interest to declare. P.E.P owns four shares in AstraZeneca PLC and has received honoraria and/or travel reimbursement for events sponsored by AKCEA, Amgen, AMRYT, Link Medical, Napp, and Sanofi; D.A.L. has received investigator-initiated educational grants from Bristol-Myers Squibb (BMS) and Boehringer Ingelheim; speaker for Boehringer Ingelheim, Bayer, and BMS/Pfizer; and consultant for Boehringer Ingelheim, Bayer, BMS/Pfizer, and Daiichi-Sankyo.

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