MEDINFO 2019: Health and Wellbeing e-Networks for All
L. Ohno-Machado and B. Séroussi (Eds.)

doi:10.3233/SHTI190327

Effects of Computerized Guideline-Oriented Clinical Decision Support System on Antithrombotic Therapy in Patients with Atrial Fibrillation: A Systematic Review and Meta-Analysis

Ryota Sakurai[a], Kazuhiko Ohe[b]

[a] School of Medicine, International University of Health and Welfare, Chiba, Japan,
[b]Department of Biomedical Informatics, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

Abstract

A systematic review and meta-analysis was conducted to investigate the effects of computerized guideline-oriented clinical decision support system (CDSS) on antithrombotic therapy in patients with atrial fibrillation. PubMed, the Cochrane Library, and Web of Science were queried. Four studies were included in this meta-analysis. The proportion of appropriate antithrombotic therapy in accordance with clinical guidelines was significantly higher in the CDSS group than in the control group (risk ratio (RR): 1.03, 95% confidence interval (CI): 1.01 to 1.04, P = 0.004). Although the incidence of thromboembolic events was similar between the two groups (RR: 1.12, 95% CI: 0.88 to 1.42, P = 0.357), the incidence of major bleeding tended to be lower in the CDSS group compared with the control group (RR: 0.79, 95% CI: 0.61 to 1.01, P = 0.063). Computerized guideline-oriented CDSS may be effective for appropriate antithrombotic therapy as compared with control in patients with atrial fibrillation.

Keywords:

Computers, Decision Support Systems, Clinical, Atrial Fibrillation

Introduction

Atrial fibrillation is one of the most common cardiac rhythm disturbances and well-known as a strong risk factor of ischaemic stroke. Patients with atrial fibrillation are approximately five times more likely to have an ischaemic stroke compared to those without atrial fibrillation through all ages [1]. Accordingly, the prevention of ischaemic stroke in patients with atrial fibrillation is of great importance. Since the prevalence for atrial fibrillation has doubled in the last decade [2], more physicians have been involved in the treatment of atrial fibrillation, regardless of their specialties. As a result, especially in general or primary care, the need for clinical guidelines has been increasing. However, although antithrombotic therapy in accordance with clinical guidelines improves clinical outcomes as compared to undertreatment in high-risk patients for ischaemic stroke with atrial fibrillation [3], guideline-oriented antithrombotic therapy is underused [4-6]. Therefore, treatment adherence to clinical guidelines may be critical for care in patients with atrial fibrillation.

A computer-based clinical decision support system (CDSS) is thought to have the potential to improve clinical outcomes in patients with chronic diseases in the era of widespread electronic health record systems [7]. In this context, computerised CDSS, in conjunction with clinical guidelines, is expected to have a synergistic effect for management of atrial fibrillation, and the development of such CDSS will have a powerful impact on daily practice, especially for non-cardiology specialists. However, it has not been well characterized whether this type of CDSS is effective for atrial fibrillation, especially regarding appropriate prescription of antithrombotic agents according to clinical guidelines. To test the hypothesis that computerized CDSS implemented clinical guidelines improves appropriate antithrombotic therapy for atrial fibrillation in clinical practice, we conducted a systematic review and meta-analysis of clinical trials that compared computerized guideline-oriented CDSS with control.

Methods

Search Strategy and Eligibility Criteria

PubMed, the Cochrane Library, and Web of Science were queried for articles of any language from inception to November 2018. The search terms included “clinical,” “decision,” “support,” “system,” “atrial,” and “fibrillation.” For PubMed, the search details were ("decision support systems, clinical"[MeSH Terms] OR ("decision"[All Fields] AND "support"[All Fields] AND "systems"[All Fields] AND "clinical"[All Fields]) OR "clinical decision support systems"[All Fields] OR ("clinical"[All Fields] AND "decision"[All Fields] AND "support"[All Fields] AND "system"[All Fields]) OR "clinical decision support system"[All Fields]) AND ("atrial fibrillation"[MeSH Terms] OR ("atrial"[All Fields] AND "fibrillation"[All Fields]) OR "atrial fibrillation"[All Fields]). The same terms or relevant studies were also queried on the website of the U.S. National Institute of Health and relevant reviews. To increase internal validity, only randomized controlled trials were included in our study. The primary endpoint of our interest was the proportion of appropriate antithrombotic therapy in accordance with clinical guidelines. We also investigated the impact of CDSS on the incidence of systemic thromboembolic events, such as stroke, transient ischaemic attack or other thromboembolism, and major bleeding as clinical outcomes. If multiple follow-up reports existed in the same study, the outcomes during the longest follow-up period were analyzed. To investigate the usefulness of CDSS for physicians in daily practice, regardless of familiarity with care for atrial fibrillation, the inclusion criterion were the studies comparing the computerized guideline-oriented CDSS, defined as any that provide clinical support automatically generated by a computer according to clinical guidelines, with no CDSS. The exclusion criteria were the studies of CDSS not for physicians (nurses, patients, etc.) or not guideline-oriented CDSS.

Statistical Analysis

A random-effects model was performed to estimate the pooled risk ratio (RR). We chose RR, not odds ratio, since only randomized controlled trials were included and the proportion of appropriate antithrombotic therapy would be expected not so low as approximaled by odds ratio. The I^2 statistics and the Cochran's Q test were conducted to assess homogeneity among each study to confirm internal validity [8]. The possibility of publication bias was assessed visually at first by a funnel plot for asymmetry plotting of the standard error of log RR against the log RR. In addition, the Duval and Tweedie's trim and fill procedure would be conducted to estimate the possible impact of unpublished studies on the pooled estimate. A 2-sided P value of < 0.05 was considered to be statistically significant. In cases of the assessment of homogeneity, however, a 2-sided P value of < 0.10, instead of 0.05, was considered to be statistically significant [9]. If an I^2 statistic value was $> 50\%$, we also considered the results among each study as heterogeneous [10]. All analyses were performed using STATA 11.2 (Stata Corp., College Station, Texas, USA).

Results

Study Selection and Characteristics of Studies

This study was conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses as much as possible [11]. Figure 1 shows a flow chart of study selection. After excluding articles on basis of title and abstract screening, we further excluded 2 studies due to no endpoints of our interest and another study due to not being guideline-oriented. As a result, 18,646 patients (10,313 patients assigned to the CDSS group and 8,333 to the control group) in 4 studies were included in this meta-analysis [12-15].

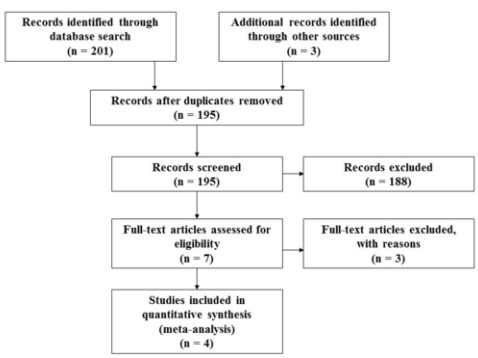

Figure 1– Flow Chart of Study Selection

The characteristics of studies are summarized in Table 1. All studies were performed as a cluster randomized controlled trial in outpatients. The follow-up period ranged from 8 months to 2.2 years. The targets of intervention were primary care physicians or general practitioners.

Pooled Estimates

Figure 2 shows the pooled estimate for the primary endpoint. Homogeneity was not rejected across individual studies by either the I^2 statistics or the Cochran's Q test ($I^2 = 0.0\%$ or P = 0.396).

Author (year)	Number of pts*	Follow up	Target	Clinical GL
Eckman, et al. (2016)	801:692	1 year	Primary care physician	2014 ACC/AHA/HRS GL for AF
Arts, et al. (2017)	522:259	8 months	GP	2013 Dutch GP GL for AF
Karlsson, et al. (2018)	7861:6156	1 year	Primary care physician	2012 ESC focused updated GLs for the management of AF
van Doorn, et al. (2018)	1129:1226	2.2 years	GP	2013 Dutch GP GL for AF

Table 1– Characteristics of Studies

ACC = American College of Cardiology; AF = atrial fibrillation; AHA = American Heart Association; ESC = European Society of Cardiology; GL = guideline; GP = general practitioner; HRS = Heart Rhythm Society; pts = patients.

* clinical decision support system:control.

The proportion of appropriate antithrombotic therapy was significantly higher in the CDSS group (from 55% to 85%) compared with the control group (from 50% to 84%, RR: 1.03, 95% confidence interval (CI): 1.01 to 1.04, P = 0.004).

Figures 3 and 4 show the pooled estimates for clinical outcomes. Homogeneity was also not rejected across individual studies by either the I^2 statistics or the Cochran's Q test ($I^2 = 38.2\%$ or P = 0.203 for thromboembolic events, and $I^2 = 0.0\%$ or P = 0.456 for major bleeding, respectively). Although the incidence of thromboembolic events was similar between the 2 groups (RR: 1.12, 95% CI: 0.88 to 1.42, P = 0.357), the incidence of major bleeding tended to be lower in the CDSS group compared with the control group (RR: 0.79, 95% CI: 0.61 to 1.01, P = 0.063).

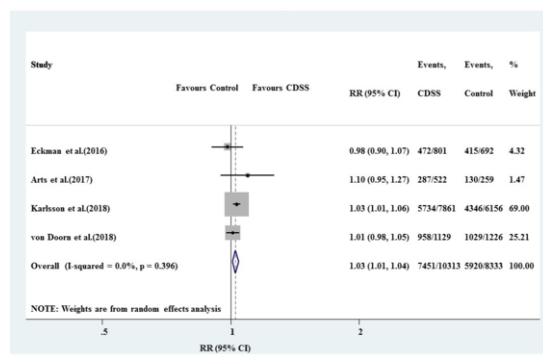

Figure 2– Forest Plot for the Proportion of Appropriate Antithrombotic Therapy

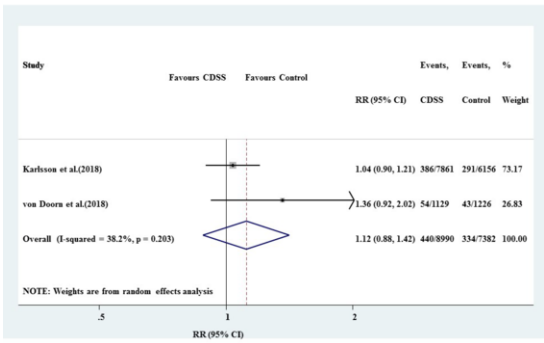

Figure 3– Forest Plot for the Incidence of Thromboembolic Events

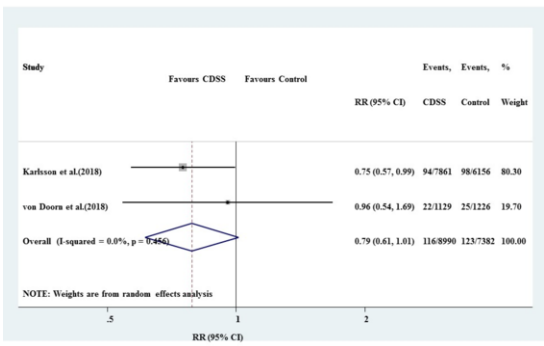

Figure 4– Forest Plot for the Incidence of Major Bleeding

Publication Bias

A funnel plot seemed asymmetric, especially for the incidence of thromboembolic events and major bleeding. Therefore, we conducted the Duval and Tweedie's trim and fill procedure, and the possible impact of an unpublished study favorable for control was suggested for the incidence of thromboembolic events and major bleeding, but not for the proportion of adherence to guidelines (Figures 5, 6, and 7).

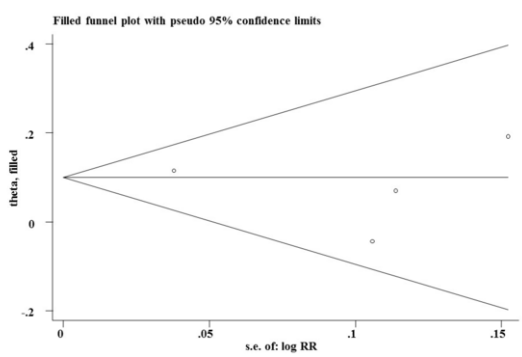

Figure 5– The Duval and Tweedie's Trim and Fill Procedure for the Proportion of Appropriate Antithrombotic Therapy

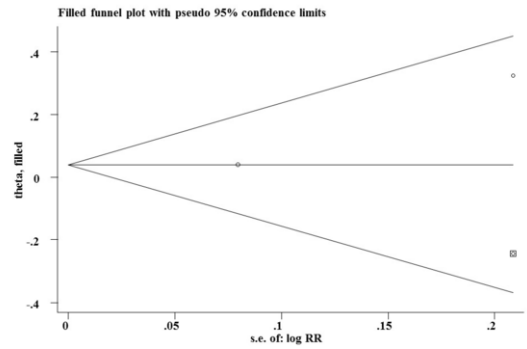

Figure 6– The Duval and Tweedie's Trim and Fill Procedure for the Incidence of Thromboembolic Events

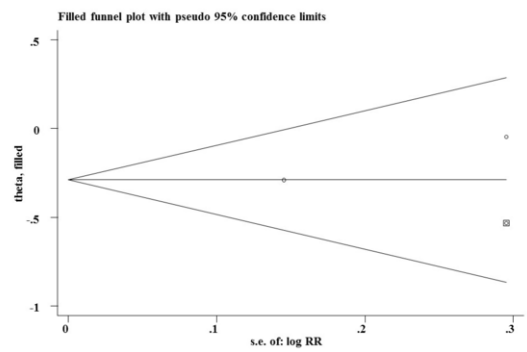

Figure 7– The Duval and Tweedie's Trim and Fill Procedure for the Incidence of Major Bleeding

Discussion

In this meta-analysis, computerized guideline-oriented CDSS demonstrated more favorable effects on the proportion of appropriate antithrombotic therapy as compared with control. Surprisingly, although the incidence of thromboembolic events was similar between the two groups, the incidence of major bleeding tended to be lower in the CDSS group than in the control group. Due to inclusion of only randomized controlled trials, heterogeneity among each study was not observed in any endpoints. To the best of our knowledge, this study reports favorable effects of computerized CDSS on guideline adherence in patients with atrial fibrillation by meta-analysis.

In real-world management of patients with atrial fibrillation, physicians must consider the risks of not only thromboembolic events, but also bleeding. There are several clinical guidelines incorporating some risk scores for stratifying patients, including the $CHADS_2$ or the CHA_2DS_2-VASc score for stroke risk, and the HAS-BLED, the RIETE, or the ATRIA score for bleeding risk. These clinical guidelines generally have numerous pages and are very complicated. In addition, patients with atrial fibrillation frequently have other cardiac diseases or comorbidities, such as coronary artery disease, valvular heart disease, hypertension, heart failure, thyroid dysfunction, and so on [2, 16]. In such complex clinical situations, especially in general or primary care practices, physicians may be extremely

troubled in making decisions by themselves. Accordingly, computerized guideline-oriented CDSS is helpful for non-cardiology specialists to deal with these situations, which may improve clinical outcomes in patients with atrial fibrillation. In fact, most studies included in this meta-analysis took bleeding risk into consideration as well as stroke risk [12-14], and this kind of CDSS may play an important role in decreasing the incidence of major bleeding, even with the similar incidence of thromboembolic events.

On the other hand, despite statistical significance, the range of the proportion of appropriate antithrombotic therapy varied from 55% to 85% in the CDSS group. From the viewpoint of physicians who use CDSS, the difficulties of handling computerized CDSS may be critical for adherence to clinical guidelines. Possible reasons for lower adherence to guidelines include a separate, nonintegrated CDSS apart from natural flow of patient care, requiring the click of a mouse to access information, too many tasks and too much information at once, and too many alert notifications contributing to alert fatigue [12-15]. To facilitate the use of CDSS and further increase adherence to guidelines, therefore, it is tremendously important for system developers to create and provide a fully integrated, simple, and user-friendly computerized guideline-oriented CDSS that is easily accessed by any physician within the limited time as part of clinical workflow, according to some standards or guidelines, e.g. ISO/IEC 25010 [17-19].

There may be several possible limitations in the present study. First, the number of studies included was relatively small in terms of a meta-analysis, partially due to possible publication bias. Therefore, the results, especially regarding the incidence of clinical outcomes, may not be conclusive. Second, the patient population may not be the same across individual studies. Therefore, we used a random-effects model instead of a fixed-effects model to calculate more conservative pooled estimate, although heterogeneity was suggested by neither the I^2 statistics nor the Cochran's Q test. Third, even an increased high internal validity, an external validity may be relatively low in a meta-analysis of randomized controlled trials with strict inclusion and exclusion criteria. Therefore, a real-world data such as registry may also be needed to validate our findings. Finally, due to the existence of several clinical guidelines, the quality of guidelines may not be the same. However, almost all guidelines are based on the $CHADS_2$ or the CHA_2DS_2-VASc score to recommend the treatment.

Conclusions

In this meta-analysis, computerized guideline-oriented CDSS is associated with more appropriate antithrombotic therapy in patients with atrial fibrillation as compared with control. To achieve further improvement of adherence to guidelines and clinical outcomes, it seems that the development of a fully integrated, simple, and user-friendly computerized CDSS in accordance with some standards or guidelines such as ISO/IEC 25010 would be more effective.

Acknowledgements

The authors thank Heidi N. Bonneau for her editorial review of this manuscript. The authors have nothing to disclose regarding this study.

References

[1] P.A. Wolf, R.D. Abbott, and W.B. Kannel, Atrial fibrillation as an independent risk factor for stroke: the Framingham Study, *Stroke* **22** (1991), 983-988.

[2] M. Zoni-Berisso, F. Lercari, T. Carazza, and S. Domenicucci, Epidemiology of atrial fibrillation: European perspective, *Clin Epidemiol* **6** (2014), 213-220.

[3] R. Nieuwlaat, S.B. Olsson, G.Y. Lip, A.J. Camm, G. Breithardt, A. Capucci, J.G. Meeder, M.H. Prins, S. Levy, and H.J. Crijns, Guideline-adherent antithrombotic treatment is associated with improved outcomes compared with undertreatment in high-risk patients with atrial fibrillation. The Euro Heart Survey on Atrial Fibrillation, *Am Heart J* **153** (2007), 1006-1012.

[4] I.M. Ogilvie, N. Newton, S.A. Welner, W. Cowell, and G.Y. Lip, Underuse of oral anticoagulants in atrial fibrillation: a systematic review, *Am J Med* **123** (2010), 638-645 e634.

[5] H. Gamra, J. Murin, C.E. Chiang, L. Naditch-Brule, S. Brette, and P.G. Steg, Use of antithrombotics in atrial fibrillation in Africa, Europe, Asia and South America: insights from the International RealiseAF Survey, *Arch Cardiovasc Dis* **107** (2014), 77-87.

[6] J.C. Hsu, T.M. Maddox, K.F. Kennedy, D.F. Katz, L.N. Marzec, S.A. Lubitz, A.K. Gehi, M.P. Turakhia, and G.M. Marcus, Oral Anticoagulant Therapy Prescription in Patients With Atrial Fibrillation Across the Spectrum of Stroke Risk: Insights From the NCDR PINNACLE Registry, *JAMA Cardiol* **1** (2016), 55-62.

[7] D.L. Hunt, R.B. Haynes, S.E. Hanna, and K. Smith, Effects of computer-based clinical decision support systems on physician performance and patient outcomes: a systematic review, *JAMA* **280** (1998), 1339-1346.

[8] J.P. Higgins and S.G. Thompson, Quantifying heterogeneity in a meta-analysis, *Statistics in medicine* **21** (2002), 1539-1558.

[9] J.A. Sterne, D. Gavaghan, and M. Egger, Publication and related bias in meta-analysis: power of statistical tests and prevalence in the literature, *Journal of clinical epidemiology* **53** (2000), 1119-1129.

[10] J.P. Higgins, S.G. Thompson, J.J. Deeks, and D.G. Altman, Measuring inconsistency in meta-analyses, *BMJ* **327** (2003), 557-560.

[11] A. Liberati, D.G. Altman, J. Tetzlaff, C. Mulrow, P.C. Gotzsche, J.P. Ioannidis, M. Clarke, P.J. Devereaux, J. Kleijnen, and D. Moher, The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration, *BMJ* **339** (2009), b2700.

[12] M.H. Eckman, G.Y. Lip, R.E. Wise, B. Speer, M. Sullivan, N. Walker, B. Kissela, M.L. Flaherty, D. Kleindorfer, P. Baker, R. Ireton, D. Hoskins, B.M. Harnett, C. Aguilar, A.C. Leonard, L. Arduser, D. Steen, A. Costea, and J. Kues, Impact of an Atrial Fibrillation Decision Support Tool on thromboprophylaxis for atrial fibrillation, *Am Heart J* **176** (2016), 17-27.

[13] D.L. Arts, A. Abu-Hanna, S.K. Medlock, and H.C. van Weert, Effectiveness and usage of a decision support system to improve stroke prevention in general practice: A cluster randomized controlled trial, *PLoS One* **12** (2017), e0170974.

[14] L.O. Karlsson, S. Nilsson, M. Bang, L. Nilsson, E. Charitakis, and M. Janzon, A clinical decision support tool for improving adherence to guidelines on anticoagulant therapy in patients with atrial fibrillation at risk of stroke: A cluster-randomized trial in a Swedish primary care

setting (the CDS-AF study), *PLoS Med* **15** (2018), e1002528.
[15] S. van Doorn, F.H. Rutten, C.M. O'Flynn, R. Oudega, A.W. Hoes, K.G.M. Moons, and G.J. Geersing, Effectiveness of CHA2DS2-VASc based decision support on stroke prevention in atrial fibrillation: A cluster randomised trial in general practice, *Int J Cardiol* **273** (2018), 123-129.
[16] P.L. Hess, S. Kim, J.P. Piccini, L.A. Allen, J.E. Ansell, P. Chang, J.V. Freeman, B.J. Gersh, P.R. Kowey, K.W. Mahaffey, L. Thomas, E.D. Peterson, and G.C. Fonarow, Use of evidence-based cardiac prevention therapy among outpatients with atrial fibrillation, *Am J Med* **126** (2013), 625-632 e621.
[17] N.B. de Oliveira and H.H. Peres, Evaluation of a system of electronic documentation for the nursing process, *NI 2012 : 11th International Congress on Nursing Informatics, June 23-27, 2012, Montreal, Canada. International Congress in Nursing Informatics* **2012** (2012), 312.
[18] L.A. Virginio, Jr. and I.L. Ricarte, Identification of Patient Safety Risks Associated with Electronic Health Records: A Software Quality Perspective, *Studies in health technology and informatics* **216** (2015), 55-59.
[19] A. Idri, M. Bachiri, and J.L. Fernandez-Aleman, A Framework for Evaluating the Software Product Quality of Pregnancy Monitoring Mobile Personal Health Records, *Journal of medical systems* **40** (2016), 50.

Address for correspondence

Ryota Sakurai, MD, PhD, MPH. Prefer to be contacted by email.
School of Medicine, International University of Health and Welfare
4‐2 Kozunomori, Narita City, Chiba 286‐8686, Japan.
Email: yoshimune-tky@umin.ac.jp
Phone: +81-476-20-7701
Fax: +81-476-20-7702