Treatments for stroke prevention in atrial fibrillation: A network meta-analysis and indirect comparisons versus dabigatran etexilate

Neil S. Roskell; Gregory Y. H. Lip; Herbert Noack; Andreas Clemens; Jonathan M. Plumb

1RTI Health Solutions, Williams House, Manchester Science Park, Lloyd Street North, Manchester, UK; 2University of Birmingham, Centre for Cardiovascular Sciences, City Hospital, Birmingham, UK; 3Boehringer Ingelheim GmbH, Binger Strasse, Ingelheim am Rhein, Germany

Summary Patients with atrial fibrillation at moderate to high risk of stroke are not always anticoagulated despite a lack of contraindications to vitamin K antagonists (VKAs) like warfarin. These patients are treated with aspirin, aspirin-clopidogrel combination therapy or even receive no thromboprophylaxis. The oral direct thrombin inhibitor, dabigatran etexilate 150 mg BID and 110 mg BID, might represent an alternative for these patients; however, no head-to-head clinical trial data exist versus these alternative treatments. A network meta-analysis (NMA) was performed to indirectly compare dabigatran etexilate with antiplatelets and placebo. Compared with placebo, dabigatran etexilate 150 mg BID was estimated to significantly reduce the risk of any stroke (ischaemic and haemorrhagic) by 75% (relative risk [RR] 0.25; 95% confidence interval [CI] 0.12–0.51), ischaemic stroke by 77% (RR 0.23; 95% CI 0.14–0.38), systemic embolism by 83% (RR 0.17; 95% CI 0.05–0.50) and mortality by 36% (RR 0.64; 95% CI 0.45–0.91). Dabigatran etexilate 150 mg BID was estimated to significantly reduce the risk of any stroke compared with aspirin monotherapy by 63% (RR 0.37; 95% CI 0.20–0.69) and aspirin plus clopidogrel by 61% (RR 0.39; 95% CI 0.21–0.72). Trends toward reduced risk with both dabigatran etexilate regimens were found for most clinical outcomes. Relative risk estimates of dabigatran etexilate versus adjusted-dose VKAs within the NMA were consistent with results from the head-to-head randomised trial of these two strategies. Indirect evidence suggests treatment with dabigatran etexilate offers benefit for the prevention of stroke, systemic embolism and mortality over antiplatelets and placebo. There was no indication of increased intracranial or extracranial haemorrhage with dabigatran etexilate compared to antiplatelet agents.

Keywords Anticoagulation, atrial fibrillation, dabigatran, meta-analysis, stroke, thrombosis

Introduction Atrial fibrillation (AF) is a leading cause of ischaemic stroke and systemic embolism (1). Stroke in AF patients is associated with greater mortality and morbidity and costlier medical care than stroke patients without AF (2–4); consequently, long-term anticoagulation with vitamin K antagonists (VKAs, e.g. warfarin) currently represents the mainstay of AF patient management. However, the variable pharmacokinetic profile and multiple drug-drug and drug-food interactions associated with VKAs make frequent dose adjustment necessary to ensure that the international normalised ratio (INR) remains within the therapeutic range of 2.0 to 3.0 (5). INRs falling below the recommended range increase the risk of ischaemic stroke, while INRs above 3.0 increase the risk of potentially disabling major bleeds like intracranial haemorrhage. The limitations of VKA therapy have constrained prescribing, so that many VKA-eligible patients with AF receive only aspirin, aspirin-clopidogrel combination therapy or no stroke prophylaxis (6, 7). Aspirin prevents fewer ischaemic strokes than VKA, hence it is recommended as an alternative to VKA only in low-risk patients or in those with contraindications. Consequently, an unmet medical need exists for an oral anticoagulant with improved efficacy and safety (8).

Dabigatran etexilate is an oral direct thrombin inhibitor, which is administered in a fixed dose of either 150 mg or 110 mg twice daily (BID) and does not require anticoagulation monitoring. The phase 3 study results for dabigatran etexilate (RE-LY) have recently been reported (9, 10), whereby the AF patients treated with dabigatran etexilate had a lower rate for the primary endpoint of stroke and systemic embolism than those receiving adjusted-dose warfarin (1.11% per year of 150 mg BID; relative risk [RR] 0.65; 95% confidence in-
tential [CI] 0.52–0.81, and 1.54% per year of 110 mg BID; RR 0.90; 95% CI 0.74–1.10, vs. 1.71% per year with adjusted-dose warfarin), and a significantly lower rate of intracranial haemorrhage (0.32% per year for 150 mg BID; RR 0.41; 95% CI 0.28–0.60, and 0.23% per year for 110 mg BID; RR 0.30; 95% CI 0.19–0.45, vs. 0.76% per year with warfarin). Thus, dabigatran etexilate 150 mg BID and 110 mg BID might represent alternatives to the non-VKA strategies, such as antiplatelet drugs or no treatment; however, no head-to-head clinical trial data exist for dabigatran etexilate versus such options.

The objectives of this study were to perform a systematic literature review and network meta-analysis (NMA) to synthesise the efficacy and safety data of treatments frequently used in the prevention of stroke and systemic embolism in AF patients. This paper extends previous meta-analyses by using indirect treatment comparisons and incorporates recently published trial data (11–13). For the presentation of findings, the dabigatran etexilate perspective was taken since directly assessing the efficacy and safety of dabigatran etexilate versus aspirin (with and without clopidogrel) and placebo in a clinical trial would be unethical in a patient population suitable for anticoagulation given the existing evidence base. This approach presents results that are suitable to inform cost-effectiveness analyses comparing dabigatran etexilate with thromboprophylactic treatment options for which no head-to-head trials have been performed (14).

Methods

Search process

A systematic literature review was performed according to the Quality of Reporting of Meta-analyses (QUOROM) statement (15). The following electronic databases were searched: (i) The Cochrane Library including the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, and the Database of Abstracts of Reviews of Effectiveness; (ii) MEDLINE and MEDLINE In-Process; (iii) EMBASE; and (iv) BIOSIS. No restrictions were applied on publication dates and all searches were completed in August 2009. Search terms included combinations of free text and medical subject headings (MeSH). We used three sets of terms: health condition of interest, interventions, and study type. Appropriate terms were combined and iterative searches using other relevant terms and concepts were performed. Reference lists from relevant systematic reviews and meta-analyses were searched for further studies. Where appropriate, non-English language publications that met the inclusion criteria were translated into English and considered in the full-text review.

Inclusion/exclusion criteria

Study type included only randomised controlled trials and excluded phase 1 studies, non-randomised studies, short-term phase 2 studies, single-arm studies, study reviews, letters, and comment articles. The population/disease condition of interest included patients with AF being treated for the prevention of stroke. Eligible trials had to include at least one of the following active interventions: adjusted-dose VKA, fixed low-dose warfarin with or without aspirin, aspirin monotherapy, aspirin plus clopidogrel, indobufen, idraparinux, triflusal, ximelagatran, and dabigatran etexilate. The two dabigatran etexilate doses, 110 mg BID and 150 mg BID, were considered separately. Inclusion or exclusion of studies was performed by two researchers, and differences of opinion were resolved in discussion with a third researcher. The Jadad scale was used to assess the quality of the clinical trials (16). Trials scoring 2 or less were excluded from the meta-analysis.

Outcomes

Outcomes included: (all) stroke, ischaemic stroke, systemic embolism, all-cause mortality, intracranial haemorrhage (excluding haemorrhagic stroke), extracranial haemorrhage (major bleeds), and acute myocardial infarction. Transient ischaemic attack (TIA), minor bleeds, “any bleeds”, and adverse events like dyspepsia were not included due to inconsistent definitions, recording, and/or adjudication across studies. Fatal or disabling strokes and pulmonary embolism were considered for analysis but were not included due to low event counts and/or inconsistent reporting. We attempted to analyse haemorrhagic stroke, but the lack of data and low event counts led to unreliable results. We have included the underlying trial data for this outcome in the online appendix (see Supplementary Table 1, available at www.thrombosis-online.com).

Statistical analyses

A mixed log-binomial model was separately fit for each outcome to estimate relative risks and confidence intervals. The model included a fixed treatment effect, a random study effect and fixed effect for mean length of follow-up (centred on its mean). Mean patient age and gender were also individually explored for potential covariate significance; however, both were excluded. The generic statistical model can be written as:

\[
\log(p_{ij}) = t_i + s_j + b*x_{ij}
\]

where \(y_{ij}\) and \(n_{ij}\) are the number of events and number of patients, respectively, on treatment \(i\) and in study \(j\). We assume that:

- \(s_j\) is the random effect to account for outcomes within trial \(j\) being correlated,
- \(x_{ij}\) is length of follow-up and
- \(t_i\) is the logarithm of overall event probability for treatment \(i\) at the mean follow-up.

The models were fit using PROC GLIMMIX provided in SAS version 9.2. PROC GLIMMIX is a new procedure within SAS that is suitable for NMA and offers an alternative to the traditional WinBUGs software approach (17). Number needed to treat (NNT) es-
timates for benefit or harm of active treatments versus placebo were derived using the treatment estimates, standard errors and covariance estimates from the models. NNT is calculated as the reciprocal of the difference in risks between the treatments and an NNT of \( \infty \) indicates no treatment difference (18).

This paper focuses on the analysis results between dabigatran etexilate and relevant treatment options (RTO) according to current treatment guidelines (adjusted-dose VKA, aspirin monotherapy, and aspirin plus clopidogrel) (5). We included the comparison with placebo to enable the full treatment effects for dabigatran etexilate to be estimated.

**Sensitivity analyses**

Three sensitivity analyses were performed to explore the dependence of analysis results on trial inclusion/exclusion criteria.

**Sensitivity Analysis 1: INR analysis**

The primary analyses included all trials that contained any form of adjusted-dose VKA regardless of the target INR. This sensitivity analysis investigated whether including only the trials with the currently recommended target INR of 2.0 to 3.0 in the adjusted-dose VKA arm had any impact on the results.

**Sensitivity Analysis 2: ACTIVE A analysis**

The primary analyses excluded trial data that recruited only patients who were ineligible for anticoagulation. One important trial (ACTIVE A) with over 7,000 patients studying aspirin plus clopidogrel versus aspirin monotherapy was therefore excluded (19). This sensitivity analysis investigated whether including the ACTIVE A trial would have affected the results.

**Sensitivity Analysis 3: RTO analysis**

The primary analyses included trial data from large, historically important trials (e.g. from trials including medications not approved or infrequently used for stroke prevention). In this RTO sensitivity analysis, the primary analyses were repeated to include only trials that contained at least two of the following treatments: dabigatran etexilate 110 mg BID, dabigatran etexilate 150 mg BID, adjusted-dose VKA (any INR range), aspirin plus clopidogrel, aspirin monotherapy, and placebo.

**Results**

**Search results**

A total of 1,486 titles (Medline = 342; The Cochrane Library = 228, EMBASE = 818, BIOSIS = 98) were retrieved. After removing duplicates and applying inclusion and exclusion criteria, 26 articles for 24 trials were retained and abstracted (AFASAK 2 [20, 21] and SPAF II [22, 23] were reported over two publications) (Fig. 1). A further three trial articles with a Jadad score of 2 or less were excluded leaving 21 trials included in the analyses (24–26). A total of 20 trials were included in the primary analyses (9, 10, 20–23, 27–43), and one further (ACTIVE A) (19) was added in a sensitivity analysis. The network of studies and abstracted data included in the meta-analyses are presented in an online appendix (see Suppl. Fig. 1 and Table 1, respectively, available at www.thrombosis-online.com).

**Evidence base**

Table 1 presents the number of trial arms that were included in the primary analyses for each of the outcomes. The non-RTO trial arms included fixed low-dose warfarin, fixed low-dose warfarin plus aspirin, idraparinux, indobufen, triflusal, and ximelagatran. Since all 20 trials included in the primary meta-analysis included adjusted-dose VKA, the network for the analyses was centred on adjusted-dose VKA, and all indirect comparisons used adjusted-dose VKA as the linked common comparator. Table 2 summarises key characteristics of the RTOs from the trials in the primary meta-analysis. Of the 20 trials, the mean length of follow-up ranged from 10 to 42 months. Mean age and gender varied among

<table>
<thead>
<tr>
<th>Table 1: Number of trials included for each treatment by outcome.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcome</strong></td>
</tr>
<tr>
<td>---------------------</td>
</tr>
<tr>
<td>All stroke</td>
</tr>
<tr>
<td>Ischaemic stroke</td>
</tr>
<tr>
<td>Systemic embolism</td>
</tr>
<tr>
<td>Mortality</td>
</tr>
<tr>
<td>Intracranial haemorrhage</td>
</tr>
<tr>
<td>Extracranial haemorrhage</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
</tr>
</tbody>
</table>

BID, twice daily; RTO, relevant treatment options; VKA, vitamin K antagonists.
studies, but the mean age and gender distribution for each treatment was similar across the trials.

Data on target INR and time spent within the target range revealed that 12 of the 20 trials (RE-LY, 1 aspirin-plus-clopidogrel trial, 3 aspirin monotherapy trials, and 8 non-RTO trials) had the currently recommended target INR of between 2.0 and 3.0, while the other eight trials had different target INRs. In the eight trials with different target INRs, the lower end of the range of target INR was between 1.4 and 2.8 and the upper end was between 2.7 and 4.5. The year of publication for the eight trials where target INR was not 2.0–3.0 ranged from 1989 to 1999, whilst the year of publication for the 12 trials with target INR 2.0–3.0 ranged from 1991 to 2009, eight of which were published in 2003 or later. Average time spent in the INR range was 65% for the 20 trials and 64% for the 12 trials with a target INR of 2.0–3.0.

Table 2: Trial characteristics/demographics.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo</th>
<th>Aspirin monotherapy</th>
<th>Aspirin plus clopidogrel</th>
<th>Adjusted-dose VKA</th>
<th>Dabigatran etexilate 150 mg BID</th>
<th>Dabigatran etexilate 110 mg BID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean follow-up months</td>
<td>22 (15–28)</td>
<td>30 (12–42)</td>
<td>15 (11–42)</td>
<td>20 (11–42)</td>
<td>24 (11–42)</td>
<td>24 (11–42)</td>
</tr>
<tr>
<td>Mean age in years</td>
<td>67.6 (66.0–70.0)</td>
<td>74.9 (70.0–82.6)</td>
<td>70.2 (65.0–83.5)</td>
<td>71.5 (65.0–83.5)</td>
<td>71.5 (N/A)</td>
<td>71.4 (N/A)</td>
</tr>
<tr>
<td>Percentage males</td>
<td>70 (54–100)</td>
<td>60 (48–70)</td>
<td>67 (39–100)</td>
<td>65 (39–100)</td>
<td>63 (N/A)</td>
<td>64 (N/A)</td>
</tr>
</tbody>
</table>

BID, twice daily; VKA, vitamin K antagonists; N/A, not applicable is shown where the data is based on one single study.
Results of the primary NMA (Fig. 2) and sensitivity analyses (see Suppl. Table 2, available at www.thrombosis-online.com) for dabigatran etexilate 150 mg BID were all broadly consistent. For the comparison of dabigatran etexilate versus adjusted-dose VKA, most point estimates observed in the RELY trial were similar to those estimated in the NMAs, with generally wider 95% CIs in the NMAs due to the addition of indirect comparisons. For five of the six outcomes where placebo data were available, dabigatran etex-
Roskell et al. Dabigatran etexilate for stroke prevention

Placebo had an estimated 44% lower risk of extracranial haemorrhage compared with dabigatran etexilate 150 mg BID (RR 1.80), but the 95% CI (0.28 to 11.38) was wide. For all stroke, ischaemic stroke, systemic embolism, mortality, and acute myo-

Figure 3: Meta-analysis of dabigatran etexilate 110 mg BID versus placebo, aspirin monotherapy, aspirin plus clopidogrel, and adjusted-dose vitamin K antagonists. The plot shows the relative risk and 95% confidence interval of each outcome with dabigatran etexilate 110 mg BID versus comparators estimated from the network meta-analyses and, for comparison, the RE-LY trial.

© Schattauer 2010
cardiac infarction (AMI), dabigatran etexilate 150 mg BID had an estimated lower risk than active treatment with antiplatelet drugs. The comparison versus aspirin monotherapy was statistically significant in favour of dabigatran etexilate 150 mg BID for all stroke (RR 0.37; 95% CI 0.20–0.69) and ischaemic stroke (RR 0.48; 95% CI 0.27–0.84). The comparison versus aspirin plus clopidogrel was statistically significant in favour of dabigatran etexilate 150 mg BID for all stroke (RR 0.39; 95% CI 0.21–0.72), ischaemic stroke (RR 0.37; 95% CI 0.23–0.61) and systemic embolism (RR 0.21; 95% CI 0.07–0.61). There were no other statistically significant findings when comparing dabigatran etexilate 150 mg BID with antiplatelet drugs, and the relative risks were all close to unity for intracranial haemorrhage, and extracranial haemorrhage.

RR for dabigatran etexilate 110 mg BID

The results of the primary NMA (Fig. 3) and sensitivity analyses (see Suppl. Table 3, available at www.thrombosis-online.com) for dabigatran etexilate 110 mg BID, were similar to the findings for dabigatran etexilate 150 mg BID and are generally consistent across all analyses. For five of the six outcomes where placebo data were available, dabigatran etexilate 110 mg BID had a lower risk of the event than placebo; of these, all stroke (RR 0.35; 95% CI 0.17–0.71), ischaemic stroke (RR 0.33; 95% CI 0.21–0.54), systemic embolism (RR 0.19; 95% CI 0.06–0.57) and mortality (RR 0.66; 95% CI 0.47–0.93) outcomes were statistically significant. As for the dabigatran etexilate 150 mg BID comparison, placebo had an estimated 37% lower risk of extracranial haemorrhage compared with dabigatran etexilate 110 mg BID (RR 1.58), but the confidence interval (0.25 to 10.02) was wide. For all stroke, ischaemic

Figure 4: NNT to show benefit with active treatments over placebo. The plot shows the NNT point estimates and 95% confidence intervals derived from the network meta-analyses. The scale was chosen to display symmetric confidence intervals for NNT; however, the displayed width of confidence intervals on this scale should not be translated into precision of estimation.
stroke, systemic embolism, mortality, intracranial haemorrhage, extracranial haemorrhage and AMI, dabigatran etexilate 110 mg BID had an estimated lower risk than active treatment with antiplatelet drugs. In the primary analysis, for the comparison with aspirin monotherapy, only the all stroke outcome was statistically significant in favour of dabigatran etexilate 110 mg BID (RR 0.52; 95% CI 0.28–0.96); however, including the results from the ACTIVE A study lead to additional statistically significant differences in both the ischaemic stroke and systemic embolism outcomes. The comparisons of aspirin plus clopidogrel were statistically significant for ischaemic stroke (RR 0.54; 95% CI 0.33–0.87) and systemic embolism (RR 0.24; 95% CI 0.08–0.70); all stroke was borderline statistically significant (RR 0.55; 95% CI 0.30–1.00).

NNT estimates

Figures 4 and 5 present results of the NNT analysis for the active treatments compared with placebo. One stroke of any type will be avoided for every 16 (150 mg BID) or 18 (110 mg BID) patients treated with dabigatran etexilate compared with patients receiving no stroke prophylaxis. Compared with no stroke prophylaxis, one additional extracranial haemorrhage will be experienced for every 71 (150 mg BID) or 97 (110 mg BID) patients treated with dabigatran etexilate.

Discussion

In this analysis, we show that when compared with placebo, dabigatran etexilate was estimated to provide a reduction in risk up to 75% for any stroke, up to 77% for ischaemic stroke, up to 83% for systemic embolism, and up to 36% for all-cause death. When compared with aspirin plus clopidogrel and aspirin monotherapy, use of dabigatran etexilate was estimated to provide reduction in risk up to 63% for any stroke, 63% for ischaemic stroke, and up to 79% for systemic embolism. As well as those statistically significant risk reductions, consistent trends toward reduced risk with dabigatran etexilate were found for most of the other clinical outcomes, except for extracranial haemorrhage. The risk of AMI does not increase with dabigatran etexilate treatment.

The RE-LY trial compared two doses of dabigatran etexilate with adjusted-dose warfarin, the current standard of care for stroke prevention in AF patients at risk of thromboembolic complications (9, 10). Head-to-head clinical trials provide the highest level of evidence and therefore are the primary source for comparative efficacy and safety assessments of these two treatment options. However, not all eligible patients are currently receiving adjusted-dose warfarin and may receive antiplatelet therapy or no treatment at all to prevent thromboembolic events (6, 7).

The point estimates of the relative risks resulting from the trial analysis and the NMAs were largely consistent and, as expected, confidence intervals from the RE-LY trial were narrower than the NMAs confidence intervals. Moreover, the results of the ACTIVE A sensitivity analyses are also broadly consistent with the recently presented findings of the AVERROES study of apixaban and aspirin in patients deemed unsuitable for anticoagulation with warfarin (44). In addition, to the described sensitivity analyses, we repeated the analyses using the traditional methods in WinBUGs and found very similar point estimates, suggesting PROC GLIMMIX is a valid option for these types of analyses. Furthermore, of the three trials excluded from the primary analysis due to a Jadad score of under three, only one trial potentially contributed any data to our outcomes of interest. Repeating the primary analyses including this extra trial made no difference to the results or conclusions of our study.

Limitations

As with any meta-analysis, several limitations are worth discussing. Differences in inclusion and exclusion criteria, patient population, data collection methods, and definitions of outcomes and their adjudication are a source of persisting heterogeneity in any meta-analysis. The definition of intracranial haemorrhage was especially heterogeneous and findings for this outcome therefore should be interpreted with caution. Dyspepsia was excluded from
the meta-analysis for similar reasons; however, in the RELY study the proportion of patients reporting dyspepsia (defined as the composite of the coding terms: abdominal pain upper, abdominal pain, abdominal discomfort, and dyspepsia) was significantly higher than with warfarin. Given the scarcity of data, the power to detect a treatment by covariate interaction is quite limited leaving us with two options; either accept the heterogeneity which is already accounted for in the wide confidence intervals, or live without any quantitative comparison of new oral anticoagulants since placebo or aspirin-controlled studies are no longer ethical given the current evidence base. That said, Cooper et al. have attempted to formally assess heterogeneity in a previous indirect comparison of stroke prevention studies concluding that the portion of patients with a history of stroke or TIA might also impact this type of analysis as in the older studies this percentage within the AF population was more varying (45). No statistical adjustments were made for multiple comparisons within these meta-analyses. Finally, we have included ‘historical’ trials which were conducted nearly two decades ago, during which time the clinical management of stroke risk factors has improved leading to declining stroke rates (46). In these early trials, <10% of patients screened were ultimately randomised, raising issues on generalisability – in contrast to more contemporary trials (e.g. RE-LY) where 89% of those screened were randomised. Given that eight of the 12 studies included in the INR sensitivity analysis were published in 2003 or later, these results could be considered a proxy for both a historical data analysis and an analysis separating variations in history of stroke/TIA, the results of which effectively mirror those of the primary analysis.

Conclusions

In conclusion, there is indirect evidence that treatment with dabigatran etexilate reduces the risk of stroke, systemic embolism, and mortality compared with aspirin plus clopidogrel, aspirin alone, and placebo, in patients with atrial fibrillation. Moreover, there is no indication of increased bleeding with dabigatran etexilate compared to the antplatelet therapies, as evidenced by the relative risk estimates for intracranial haemorrhage and extracranial haemorrhage. These results are largely consistent throughout the primary analysis and all conducted sensitivity analyses.

Acknowledgements

The authors thank Dr. Brigitta Monz, Boehringer Ingelheim, for her contributions regarding the NNT analyses, discussion of the results and review of previous drafts of this manuscript, Dr. Jiamin Wang, RTI Health Solutions, for his help developing the NMA statistical methodology, and Paul Robinson, health economist at Boehringer Ingelheim, for his contributions regarding the design of the study.

Disclosures

N. S. Roskell was a paid consultant to Boehringer Ingelheim for this project. G. Y. H. Lip has received funding for research, educational symposia, consultancy, and lecturing from different manufacturers of drugs used for stroke prevention in atrial fibrillation and the treatment of thrombosis, including Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, Daichii-Sankyo, Merck, and Sanofi-Aventis. He has served on the Executive Steering Committee for phase 2 and 3 clinical trials with new oral anticoagulant drugs for atrial fibrillation and acute coronary syndromes. A. Clemens, H. Noack and J. M. Plumb are paid employees of Boehringer Ingelheim.

References

5. Fuster V, et al.; American College of Cardiology/American Heart Association Task Force on Practice Guidelines; European Society of Cardiology Committee for Practice Guidelines; European Heart Rhythm Association; Heart Rhythm Society.


