Control of Anticoagulation Therapy in Patients with Atrial Fibrillation Treated with Warfarin: A Study from the Chinese Atrial Fibrillation Registry

Hai-Feng Liang
Xin Du
Ying-Chun Zhou
Xiao-Yi Yang
Shi-Jun Xia
Jian-Zeng Dong
Gregory Y.H. Lip*
Chang-Sheng Ma

Corresponding Author:
Chang-Sheng Ma, e-mail: chshma@vip.sina.com

Background:
Several factors determine the efficacy of warfarin anticoagulation in patients with non-valvular atrial fibrillation (NVAF). This study aimed to use data from the Chinese Atrial Fibrillation Registry study to assess the control of anticoagulation therapy in Chinese patients with NVAF treated with warfarin.

Material/Methods:
From the Chinese Atrial Fibrillation Registry study the anticoagulant use and dosing, the time in therapeutic range (TTR) of the international normalized ratio (INR), and standard deviation of the observed INR values (SDINR), and their influencing factors were evaluated.

Results:
The median INR and SDINR were 2.04 (IQR 1.71–2.41) and 0.50 (IQR, 0.35–0.69), respectively. The median TTR was 51.7% (IQR, 30.6–70.1%) and only 25.1% had a TTR ≥70%. Age was ≥70 years (OR, 0.72; 95% CI, 0.55–0.94; P=0.015), bleeding history (OR 0.48; 95% CI, 0.23–0.89; P=0.029), the use of a single drug (OR, 0.62; 95% CI, 0.42–0.92; P=0.016), more than drug (OR, 0.60; 95% CI, 0.41–0.88; P=0.009), and lack of assessment of bleeding risk (OR, 0.72; 95% CI, 0.54–0.97; P=0.033) were associated with TTR <70% (INR 2.0–3.0). Coronary heart disease (CHD) and peripheral artery disease (PAD) (OR, 0.69; 95% CI, 0.52–0.90; P=0.007) and diabetes mellitus (OR, 0.79; 95% CI, 0.62–0.99; P=0.044) were associated with increased variability in INR (SDINR ≥0.5).

Conclusions:
In Chinese patients with NVAF, warfarin anticoagulation was associated with lower TTR and less stable anticoagulation than in current guidelines, and risk factors for reduced safety and efficacy were identified.

MeSH Keywords: Anticoagulants • Atrial Fibrillation • Quality Control • Warfarin

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Background

The vitamin K antagonists that include warfarin are highly effective for the prevention of stroke in patients with atrial fibrillation (AF) [1]. An appropriate degree of anticoagulant and maintenance of stable anticoagulation are important in balancing the benefits of warfarin in the prevention of stroke and in avoiding the risk of bleeding [2]. It is has been assumed that Asian populations are at a higher risk of bleeding when treated with warfarin [3]. The Chinese Atrial Fibrillation Registry study is a hospital-based, multicenter, prospective registry study, that includes real-world data of approximately 20,000 patients with AF [4]. An international normalized ratio (INR) target range of 2.0–3.0 is recommended by the Chinese Atrial Fibrillation Registry management guidelines [4], and an INR range of 1.6–2.6 has been recommended for patients with AF who are ≥70 years old by the Japanese Circulation Society [5,6].

In China, there are limited data on the degree of anticoagulation required in real-world clinical practice and on the factors that influence the effectiveness of anticoagulation. In this study, we identified patients with nonvalvular atrial fibrillation (NVAF) taking long-term warfarin therapy from the Chinese Atrial Fibrillation Registry study. Quality of anticoagulation control as reflected by time in therapeutic range (TTR) of the international normalized ratio (INR) and anticoagulation stability, or the standard deviation of INR (SDINR), were evaluated [7,8]. Factors associated with TTR ≥70% and anticoagulation stability were also analyzed. This study aimed to use data from the Chinese Atrial Fibrillation Registry study to assess the control of anticoagulation therapy in Chinese patients with NVAF treated with warfarin.

Material and Methods

Study population

The Chinese Atrial Fibrillation Registry study is a prospective, multicenter, hospital-based, ongoing registry study of patients with atrial fibrillation (AF) in Beijing, China [4]. Thirty-one tertiary and non-tertiary hospitals in Beijing that treated patients with AF were included in the study [9]. Each patient signed an informed consent before enrolment. We extracted the data of patients with AF treated with warfarin from the Chinese Atrial Fibrillation Registry study from August 1, 2011, to June 30, 2016 [4]. Exclusion criteria included age <18 years, rheumatic valvular disease, others diseases with life expectancy <6 months, with anticoagulation therapy other than warfarin, number of INR values ≤5, the maximal interval between two successive INR values >90 days and follow-up period of more than six months. The INR values of the first six weeks of the patients who had recently commenced treatment with warfarin were excluded.

Data collection

Relevant information about warfarin treatment, including the date of starting and stopping warfarin, and all INR values during the time period were collected. To minimize missing data, INR values from the hospital information system (HIS) of participating hospitals were extracted and integrated with those from Chinese Atrial Fibrillation Registry database.

Baseline information included demographic characteristics including age, gender, history of smoking, alcohol consumption, comorbidities that included hypertension, diabetes mellitus, heart failure, stroke, transient ischemic attack (TIA), thromboembolism, peripheral artery disease (PAD), bleeding history, and coronary heart disease (CHD), was collected. Patients who were followed up in the third month, sixth month, and every six months after that. Data were collected on the use of anti-platelet agents and other concomitant drugs, including arrhythmic drugs, drugs to control ventricular rate, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and statins.

Ethics

This study was approved by the Beijing Anzhen Hospital Ethics Committee (No. D11110700300000) on June 10, 2011.

Quality of anticoagulation control and stability of warfarin

The time in the different therapeutic range of INR (TTR) was calculated using the Rosendaal method [10]. TTR ≥70% was considered as high-quality INR control according to the European Society of Cardiology (ESC) guidelines [7]. The distribution of TTR and INR reflected the quality of anticoagulation control in the warfarin-treated patients. Anticoagulation stability was assessed using the standard deviation (SD) of observed INR values (SDINR) of each participating patient [8]. In this study, SDINR <median (0.5) was considered as high anticoagulation stability.

Definitions

A score for bleeding risk was derived from the Atrial Fibrillation Effect on Quality-of-life (AFEQT) score [11]. The risk of bleeding was scored on a 1–7 Likert scale (ranging from 1, not at all, to 7, extremely). We defined 1–2, 3, and 4–7 as low, moderate, and high levels of bleeding risk, respectively. The risk of stroke for each patient was evaluated using the CHADS-VASc score, which included congestive heart failure, hypertension, diabetes mellitus, vascular disease including coronary heart disease (CHD) or peripheral arterial disease (PAD), female gender, and age between 64–75 years contributed 1 point and 2 points each for stroke, TIA, thromboembolism history and age ≥75 years [12–14].
HAS-BLED was used as a scoring system for bleeding risk with 1 point (range, 0–9) assigned for the presence of each of the following: old age, hypertension, abnormal liver or renal function, a previous stroke, a history of bleeding, unstable INRs, concomitant drugs or alcohol excess [15]. A HAS-BLED score of ≥3 indicated an increased risk of bleeding [15].

SAME-TT, Rs2 score was calculated using the factors of female gender, age (<60 years), medical history, with at least two of the following: hypertension, diabetes mellitus, CHD, PAD, congestive heart failure, stroke history, pulmonary disease, hepatic or renal disease. Treatment, with interacting drugs such as amiodarone, contributed 1 point respectively and 2 points each for current tobacco use and race (non-Caucasian) [16].

Statistical analysis

Continuous variables were reported as the mean ± standard deviation (SD), or the median (IQR 25–75%), and categorical variables as n (%). A multivariate logistic regression model was constructed to identify the associated factors independently associated with the degree of anticoagulation and stability. In the model, we adjusted age, gender, history of stroke, TIA, thromboembolism, history of bleeding, history of myocardial infarction, known CHD or PAD, diabetes mellitus, hypertension, congestive heart failure, anemia, combined platelet agents, current smoking, current drinking, bleeding risk score, combination medication, CHA2DS2-VASc score and HAS-BLED score. Data were analyzed using SAS version 9.2 software. P<0.05 was considered to be statistically significant.

Results

A total of 1,895 eligible patients with a mean age of 66.78±9.60 years (56.5% were men) who were treated with warfarin were included in this study. Only 24.8% of patients with non-valvular atrial fibrillation (NVAF) in the Chinese Atrial Fibrillation Registry met the inclusion criteria for this study. The patient inclusion process for this study is shown in Figure 1. Baseline characteristics of the included patients are shown in Table 1.

Distribution of the international normalized ratio (INR) values

We collected 29,335 international normalized ratio (INR) values during a median follow-up time of 1,094 days (IQR, 729–1,609 days). The median interval of INR testing was 29 days (IQR, 23–38 days). The number of INR tests for each patient ranged from 5–114, with a median of 9 (IQR, 6–18). INR values ranged from 0.69–19.85, with a median of 2.04 (range, 1.7–2.4). The density distribution of INRs is shown in Figure 2.
Factors associated with anticoagulation intensity and stability

Multivariate logistic regression showed that for INR target range of 2.0–3.0, age ≥70 years, history of bleeding, low bleeding risk score, and concomitant drugs were independently associated with a TTR <70%. When the INR target range was 1.6–2.6, these factors were no longer significantly related to the TTR (Table 2). Multivariate logistic regression analysis showed that a history of myocardial infarction, CHD, PAD, and diabetes mellitus resulted in worse INR stability (SD$_{INR}$ ≥0.5) (Table 3).

**Discussion**

This study used data from the Chinese Atrial Fibrillation Registry study to assess the control of anticoagulation therapy in patients with non-valvular atrial fibrillation (NVAF) treated with warfarin. The distribution of the international normalized ratio (INR) values and the mean time in therapeutic range (TTR) showed that the quality of anticoagulation control was generally suboptimal. Also, for the INR target range of 2.0–3.0, age ≥70 years, history of bleeding, low bleeding risk score, and concomitant drugs were independently associated with a TTR <70%. The variability in INR was significantly associated with a history of coronary heart disease (CHD), peripheral arterial disease (PAD), and diabetes mellitus.

From this study, warfarin anticoagulation intensity was shifted towards lower INR ranges, with a median INR of 2.04, and the median time distribution proportion of INR <2 was more than 40%, compared with an INR >3 (less than 1%), the mean time distribution proportion were 44.90% and 5.07%. In the ROCKET AF trial, the mean time distribution proportion under the INR range <2 and >3 accounted for 29.1% and 15.7%, respectively [2]. Time distribution proportion of INR had the same tendency to each subgroup whether categorized by age, gender, history of stroke or transient ischemic attack (TIA), pulmonary embolism, bleeding history, CHA$_2$DS$_2$-VASc score, or HAS-BLED score, suggesting that the status of anticoagulation intensity that was shifted to left did not vary based on thromboembolic or bleeding risk. However, the CHA$_2$DS$_2$-VASc score and

### Table 1. Patient characteristics.

| Characteristics                        | Total (N=1895) |
|----------------------------------------|---------------|
| Age, (y)                               | 66.78±9.60    |
| Male                                   | 1071 (56.5)   |
| Current smoking*                       | 235/1886 (12.5)|
| Comorbidities                          |               |
| Congestive heart failure               | 287 (15.1)    |
| Hypertension                           | 1331 (70.2)   |
| Diabetes mellitus                      | 535 (28.2)    |
| Stroke/TIA/thromboembolism             | 456 (24.1)    |
| Anemia                                 | 60 (3.2)      |
| Prior MI/known CHD/PAD                 | 337 (17.8)    |
| Chronic kidney disease                 | 7 (0.4)       |
| Bleeding history                       | 109 (5.8)     |
| Medication                             |               |
| Antiplatelet agents                    | 334 (17.6)    |
| Antiarrhythmic drugs                   | 476 (25.1)    |
| Rate control drugs                     | 1210 (63.9)   |
| ACEI/ARB                               | 770 (40.6)    |
| Statin                                 | 785 (41.4)    |
| Score                                  |               |
| Bleeding risk                          | 3.11±1.00     |
| CHA$_2$DS$_2$-VASc score               | 3.09±1.71     |
| HAS-BLED score                         | 2.60±1.15     |
| SAME-TT2R2 score                       | 3.64±1.07     |

Data were indicated as mean ± standard deviation (SD) of the number (%); * N of total, 1886; N of age <70 years, 1068; N of age ≥70 years, 818. Angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs). TIA – transient ischemic attack; MI – myocardial infarction; CHD – coronary heart disease; PAD – peripheral artery disease.

**Figure 2.** Distribution of the international normalized ratio (INR) in 1,895 patients with non-valvular atrial fibrillation (NVAF) treated with warfarin. Density: frequency/distance=percent/0.1. IQR – interquartile range.
Figure 3. The comparison of the proportion of time of the international normalized ratio (INR) within subgroups, the HAS-BLED score, the CHA2DS2-VASc score, history of bleeding, stroke, transient ischemic attack (TIA), history of thromboembolism, gender, and age (p<0.05).

Table 2. Multivariate logistic regression analysis of factors associated with the time in therapeutic range (TTR) ≥70% with different international normalized ratio (INR) target ranges.

| Characteristics                  | INR Target ranges of 2.0–3.0 |            |            | INR Target range of 1.6-2.6 |            |
|----------------------------------|-----------------------------|------------|------------|-----------------------------|------------|
|                                  | n/N (%)                     | OR (95% CI) | P value    | n/N (%)                     | OR (95% CI) | P value    |
| Age ≥70 y                        | 177/822                     | 0.72       | (0.55–0.94) | 0.015                       | 473/822     | 0.93       | (0.73–1.17) | 0.531        |
| Male                             | 274/1071                    | 0.96       | (0.74–1.26) | 0.786                       | 654/1071    | 1.16       | (0.92–1.46) | 0.224        |
| Stroke/TIA/thromboembolism       | 115/456                     | 1.05       | (0.74–1.48) | 0.798                       | 274/456     | 1.14       | (0.84–1.56) | 0.393        |
| Bleeding history                 | 16/109                      | 0.48       | (0.23–0.89) | 0.029                       | 64/109      | 0.95       | (0.59–1.53) | 0.824        |
| Prior MI/known CHD/PAD           | 84/337                      | 1.16       | (0.84–1.57) | 0.361                       | 207/337     | 1.11       | (0.84–1.47) | 0.458        |
| Diabetes mellitus                | 137/535                     | 1.05       | (0.8–1.36)  | 0.737                       | 337/535     | 1.17       | (0.92–1.49) | 0.195        |
| Hypertension                     | 336/1331                    | 1.27       | (0.93–1.75) | 0.13                        | 775/1331    | 0.95       | (0.72–1.25) | 0.704        |
| Congestive heart failure         | 60/287                      | 0.83       | (0.58–1.17) | 0.285                       | 174/287     | 1.11       | (0.83–1.51) | 0.483        |
| Anemia                           | 14/60                       | 0.97       | (0.48–1.84) | 0.931                       | 30/60       | 0.68       | (0.39–1.2)  | 0.184        |
| Combined platelet agents         | 82/334                      | 1.07       | (0.73–1.55) | 0.739                       | 195/334     | 1.07       | (0.77–1.5)  | 0.675        |
| Current smoking                  | 67/336                      | 1.08       | (0.74–1.56) | 0.679                       | 137/235     | 0.81       | (0.58–1.15) | 0.236        |
| Current drinking                 | 93/235                      | 1.11       | (0.76–1.59) | 0.603                       | 209/336     | 1.27       | (0.91–1.77) | 0.165        |
| Bleeding risk score ≥3           | 81/373                      | 0.72       | (0.54–0.97) | 0.033                       | 220/373     | 0.97       | (0.75–1.26) | 0.834        |
| Bleeding risk score >3           | 95/395                      | 0.82       | (0.62–1.09) | 0.178                       | 226/395     | 0.91       | (0.71–1.17) | 0.456        |
| *Concomitant drugs (n=1)         | 128/527                     | 0.62       | (0.42–0.92) | 0.016                       | 327/527     | 1.24       | (0.86–1.79) | 0.243        |
| *Concomitant drugs (n=2)         | 284/1169                    | 0.64       | (0.41–0.88) | 0.009                       | 680/1169    | 0.93       | (0.65–1.32) | 0.694        |
| CHA2DS2-VASc score ≥2            | 376/1536                    | 1.05       | (0.71–1.55) | 0.806                       | 907/1536    | 1.09       | (0.77–1.53) | 0.639        |
| **HAS-BLED score ≥2              | 132/554                     | 0.95       | (0.64–1.43) | 0.821                       | 319/554     | 0.85       | (0.6–1.22)  | 0.379        |

* Concomitant drugs include antiarrhythmic drugs, ventricular rate control drugs, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and statins. ** Excluding labile INR. Total number=1895. Total number of TTR ≥70%=475 (INR range, 2.0–3.0). Total number of TTR ≥70%=1123 (INR range, 1.6–2.6). TIA – transient ischemic attack; MI – myocardial infarction; CHD – coronary heart disease; PAD – peripheral artery disease.
HAS-BLED scores were not associated with the degree of anticoagulation. Physicians do not often treat patients based on their risk [17–19]. Notably, the median INR in our study was 2.04, which was close to the recommended INR target range of 1.6–2.6 for patient age \(\geq 70\) years by the Japanese Circulation Society [5,6], although guidelines from China recommend the INR target range should be 2.0–3.0. The optimal INR range for warfarin use is debated in Asian populations because of the limited evidence from controlled studies [20]. It has been believed that Asian patients have an increased risk of hemorrhage because of race, genetics, and lifestyle differences [21]. Therefore, both physicians and patients appear more concerned about bleeding risk related to warfarin anticoagulation and aim for lower INR ranges. However, the TTR is a stronger determinant of bleeding risk than the INR values [22,23].

In this study, multivariate logistic regression analysis showed that age \(\geq 70\) years and bleeding history were independent risk factors associated with TTR. Reduced concern regarding the risk of bleeding may increase the compliance with and the effectiveness of anticoagulation. Therefore, patients undergoing warfarin anticoagulation therapy require education and support to improve their compliance with optimal anticoagulation therapy. Concomitant drug use is also independently associated with TTR, and is probably related to the interaction of various drugs in the body.

As this study showed, the standard deviation (SD) of observed INR values \(SD_{INR}\) is an important index of the INR variability, reflecting INR fluctuations, either outside or within the therapeutic window. The variability of INR is an important factor associated with the anticoagulation effects of warfarin, which is related directly to prognosis in patients on warfarin therapy [8,24,25]. In this study, INR fluctuation was associated with the patient history of CHD, PAD, and diabetes mellitus, which suggested these comorbidities significantly impacted the stability of anticoagulation. Attention to these comorbidities as part of a holistic and integrated approach to the management of AF would improve clinical outcomes [26–28].

The results of the present study showed that the quality of anticoagulation control using warfarin was suboptimal and this was associated with several factors that included age, comorbidities, concomitant drugs, and the attitudes of the physician and patient. It has been assumed that the stability of warfarin anticoagulation in Asian patients is worse than in European patients.

| Characteristics                          | n/N(%) | OR (95% CI) | P value |
|-----------------------------------------|--------|-------------|---------|
| Age \(\geq 70\) y                       | 424/822| 1.08 (0.85–1.36) | 0.541   |
| Male                                    | 533/1071| 1.12 (0.89–1.41) | 0.342   |
| Stroke/TIA/TE                           | 229/456| 1.20 (0.88–1.62) | 0.244   |
| Bleeding history                        | 54/109 | 0.98 (0.61–1.58) | 0.946   |
| Prior MI/known CHD/PAD                  | 141/337| 0.69 (0.52–0.90) | 0.007   |
| Diabetes mellitus                       | 242/535| 0.79 (0.62–0.99) | 0.041   |
| Hypertension                            | 661/1331| 1.23 (0.94–1.62) | 0.135   |
| Congestive heart failure                | 124/287| 0.88 (0.66–1.18) | 0.404   |
| Anemia                                  | 26/60 | 0.97 (0.55–1.7) | 0.908   |
| Combined antiplatelet agents            | 152/334| 1.05 (0.76–1.46) | 0.765   |
| Current smoking                         | 121/336| 1.25 (0.89–1.75) | 0.196   |
| Current drinking                        | 158/235| 0.87 (0.63–1.2) | 0.39    |
| Bleeding risk score \(<3\)              | 177/373| 0.86 (0.66–1.1) | 0.223   |
| *Concomitant drug (n=1)                 | 203/395| 1.03 (0.8–1.32) | 0.817   |
| *Concomitant drugs (n\(\geq2\))        | 269/527| 0.79 (0.55–1.13) | 0.204   |
| CHA2DS2 –VASc score \(\geq2\)           | 564/1169| 0.84 (0.59–1.2)| 0.341   |
| **HAS-BLED score \(>2\)                | 755/1536| 1.05 (0.75–1.48) | 0.772   |

* Concomitant drugs include antiarrhythmic drugs, ventricular rate control drugs, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and statins. ** Excluding labile INR. Total number of \(SD_{INR}\)<0.5=940. TIA – transient ischemic attack; MI – myocardial infarction; CHD – coronary heart disease; PAD – peripheral artery disease.
and American patients [21]. The use of a clinical score helped to identify patients with AF who were less likely to do well on warfarin and included the SAMe-TT\textsubscript{2} score, which in non-Caucasians was assigned 2 points [16]. Those patients with a SAMe-TT\textsubscript{2} score $\geq 2$ may require additional methods to improve the effects of anticoagulation, such as more frequent INR checks, education, and counseling [29].

Whether vitamin K antagonists or new oral anticoagulants (NOACs) are used, medication adherence is central to the prevention of thromboembolism. Although the use of NOACs is increasing, patients with valvular heart diseases and a high proportion of patients with non-valvular AF will still be on warfarin in China. Therefore, a multidisciplinary approach, including education of healthcare professionals, implementation of local guidelines, multidisciplinary medical care programs, and healthcare system support are needed to improve the quality of anticoagulant control [30,31].

This study had several limitations. First, Chinese patients with AF on long-term warfarin were identified from the Chinese Atrial Fibrillation Registry study [4]. It may be difficult to apply the findings from this study to other regions of China, as the Chinese Atrial Fibrillation Registry study mainly registered patients from Beijing. We identified patients with NVAF undergoing long-term warfarin therapy, and therefore, the patients included in this study had good compliance with their medication. Study indices that included warfarin use and discontinuation rates also are important factors reflecting the quality of warfarin anticoagulation, but these factors were not recorded in this study, but have been previously reported in other studies [32,33].

Supplement Table 1. Variability of anticoagulation intensity.

| Characteristics | SDINR Median (25–75%) | p-Value |
|-----------------|----------------------|---------|
| **Age**         |                      |         |
| <70y            | 0.52 (0.37–0.68)     | P=0.082 |
| $\geq$70y       | 0.49 (0.36–0.65)     |         |
| **Gender**      |                      |         |
| Male            | 0.50 (0.36–0.66)     | P= 0.607|
| Female          | 0.50 (0.37–0.68)     |         |
| **Stroke/TIA/thromboembolism** | | |
| Yes             | 0.50 (0.36–0.66)     | P= 0.740|
| No              | 0.50 (0.37–0.67)     |         |
| **Bleeding history** | | |
| Yes             | 0.50 (0.40–0.67)     | P=0.926 |
| No              | 0.50 (0.36–0.67)     |         |

Conclusions

This study aimed to use data from the Chinese Atrial Fibrillation Registry study to assess the control of anticoagulation therapy in Chinese patients with non-valvular atrial fibrillation (NVAF) treated with warfarin. The study findings showed that the quality of warfarin anticoagulation in Chinese patients with NVAF was generally lower than that recommended in current clinical guidelines. Increased age, a history of bleeding, concomitant drug therapies, and insufficient attention to bleeding risk were associated with reduced time in the therapeutic range (TTR) of the international normalized ratio (INR). A previous history of coronary heart disease (CHD), peripheral arterial disease (PAD), and diabetes mellitus were factors associated with reduced stability of anticoagulation.

Conflict of interest

Dr. Chang-Sheng Ma has received honoraria from Bristol-Myers Squibb (BMS), Pfizer, Johnson & Johnson, Boehringer Ingelheim (BI), and Bayer for giving lectures. Dr. Jian-Zeng Dong also received honoraria from Johnson & Johnson for giving lectures. Dr. Gregory Y.H. Lip is a Consultant for Bayer/Janssen, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Novartis, Verseon, and Daiichi-Sankyo, and is a speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, and Daiichi-Sankyo. No fees were directly received personally regarding this study.
