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## **Use of the SAME-TT<sub>2</sub>R<sub>2</sub> score to predict anticoagulation control in atrial fibrillation and venous thromboembolism patients receiving vitamin K antagonists**

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1 **Use of the SAME-TT<sub>2</sub>R<sub>2</sub> score to predict anticoagulation control in atrial fibrillation and venous**  
2 **thromboembolism patients treated with vitamin K antagonists: A review**

3

4 **Running head:** The SAME-TT<sub>2</sub>R<sub>2</sub> score: a review

5

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32

33 **Abstract**

34 Identifying patients who are likely to achieve and maintain a therapeutic INR when prescribed a  
35 vitamin K antagonist (VKA) for stroke prevention in atrial fibrillation (AF) and venous  
36 thromboembolism (VTE) is challenging. The SAME-TT<sub>2</sub>R<sub>2</sub> score was developed based on common  
37 clinical factors that can highlight patients who may be unable to achieve and maintain good  
38 anticoagulation control and for whom a ‘trial of warfarin’ would be inadvisable. This review  
39 summarises the main published prospective and retrospective studies that have validated the SAME-  
40 TT<sub>2</sub>R<sub>2</sub> score in AF and VTE patients treated with a VKA and how the SAME-TT<sub>2</sub>R<sub>2</sub> score could aid  
41 clinical decision-making; 19 studies were included. Taken together validation studies suggest that the  
42 SAME-TT<sub>2</sub>R<sub>2</sub> score is able to predict good or poor anticoagulation control among AF and VTE  
43 patients, although data on VTE patients are limited (3 studies). The available evidence suggests that  
44 the SAME-TT<sub>2</sub>R<sub>2</sub> score may be a useful tool to aid clinical decision-making for oral anticoagulants  
45 (OAC) in AF and VTE patients.

46

47 **Keywords:** SAME-TT<sub>2</sub>R<sub>2</sub> score; atrial fibrillation; venous thromboembolism; vitamin K antagonist;  
48 decision-making; oral anticoagulation

49

## 50 **Introduction**

51 For decades, vitamin K antagonists (VKA, e.g., warfarin) have been the cornerstone of stroke  
52 prevention in atrial fibrillation (AF) and prevention of venous thromboembolism (VTE).<sup>1</sup> However,  
53 VKA efficacy and safety requires achievement of an international normalised ratio (INR) between  
54 2.0-3.0. Achieving this target INR alone is an inadequate measure of the therapeutic efficacy of  
55 VKA.<sup>1</sup>

56

57 Time in therapeutic range (TTR) is one measure that summarises INR control over time. TTR  
58 is an important and independent predictor of thromboembolic and bleeding outcomes in AF patients  
59 on VKA.<sup>2,3</sup> An average individual TTR $\geq$ 65% is recommended by NICE guidelines,<sup>1</sup> while European  
60 guidelines<sup>4</sup> recommend TTR $\geq$ 70% to maximize effectiveness and safety of VKAs.

61

62 However, identifying patients who are likely to achieve and maintain a therapeutic INR is  
63 more difficult. Based on common clinical factors that influence INR and anticoagulation control in  
64 everyday clinical practice, a clinical scoring system, the SAME-TT<sub>2</sub>R<sub>2</sub> score<sup>5</sup> (**Table 1**) was developed  
65 in 2013 to identify risk factors highlighting those patients who may be unable to achieve/maintain  
66 good anticoagulation control and for whom a ‘trial of warfarin’ would be inadvisable. The frequency  
67 of INR measurements are not factored-in (or intended to be). This score assigns 1 point each to female  
68 sex, age <60 years, history of  $\geq$ 2 co-morbidities (hypertension, diabetes mellitus, coronary artery  
69 disease or myocardial infarction, peripheral artery disease, congestive heart failure, previous stroke,  
70 pulmonary, hepatic, or renal disease) and treatment with drugs interacting with VKA (e.g.,  
71 amiodarone) and 2 points each for current/recent tobacco use (within 2-years) and non-white  
72 ethnicity<sup>5</sup> (**Table 1**). The score can be used to aid decision-making by identifying those patients who  
73 would probably do well on VKA (achieving a high TTR,  $\geq$ 65%) or conversely, those would need  
74 additional interventions to achieve good INR control or to be started on/switched to a non-VKA oral  
75 anticoagulant (NOAC). The current review summarises studies which have assessed and/or validated  
76 the SAME-TT<sub>2</sub>R<sub>2</sub> score in patients treated with VKA for AF or VTE.

77

## 78 **Methods**

79 A comprehensive structured literature search was performed using MEDLINE and EMBASE from  
80 2013 until February 2017; the SAME-TT<sub>2</sub>R<sub>2</sub> score was first published in 2013. The search strategy  
81 included keywords and MeSH terms relating to AF, deep vein thrombosis, VTE, stroke prevention,  
82 warfarin, VKAs, oral anticoagulant, inception cohort, adverse effect, poor control, INR and SAME-  
83 TT<sub>2</sub>R<sub>2</sub> score (without MeSH term) individually and in combination. Primary published research  
84 articles and abstracts on prospective or retrospective studies validating the SAME-TT<sub>2</sub>R<sub>2</sub> score were  
85 included. Studies that did not provide comparative outcomes, information on follow-up time, or were  
86 not published in English language were excluded. Manual search of citations was also performed, and  
87 discussion with content experts was undertaken to identify any other relevant studies (**Figure 1**).

88

## 89 **Results**

90 Searches identified 166 citations. After removal of duplicates and screening of titles and abstracts, 24  
91 full-text articles were assessed for eligibility and 19 studies were included (see **Figure 1**). Current  
92 studies assessing the SAME-TT<sub>2</sub>R<sub>2</sub> score are summarised in **Table 2** and baseline patient  
93 characteristics of these cohorts in **Table 3**. With the exception of three<sup>6-8</sup> all were performed in AF  
94 patients.<sup>2,5,9-22</sup> Most studies (n=11)<sup>5-7,11,14,17,19-22</sup> were performed prospectively, with follow-up duration  
95 ranging from six-months<sup>17</sup> to 4.7 years.<sup>15</sup> The number of participants included in VTE cohorts ranged  
96 from 135<sup>6</sup> to 1943<sup>8</sup> and between 104<sup>14</sup> to 8120<sup>21</sup> in studies on AF patients.

97 Fourteen studies were performed in European populations,<sup>5-7,9-12,14,17-22</sup> two in Asian  
98 populations,<sup>15, 16</sup>(with one reporting a target INR 2.0-3.0<sup>15</sup>) and two in North American populations.<sup>8,</sup>

99 <sup>13</sup> Proietti et al<sup>11</sup> studied a mixed indication clinical trial cohort including patients from Europe, Asia  
100 and Australasia.

101 Most studies were performed in elderly (mean/median age ranging from 61-76 years) white-  
102 Western populations, mainly using warfarin (13 studies)<sup>5-11,13,15,16,19-21</sup> as the OAC of choice. Most  
103 patients had multiple comorbidities with hypertension the most common, except for the study by Lip  
104 et al<sup>21</sup> where congestive heart failure was most prevalent. All studies reported a low prevalence of

105 smoking status and use of amiodarone for rhythm-control, with the exception of the original  
106 derivation study; 35% of patients used amiodarone.<sup>21</sup> As the SAME-TT<sub>2</sub>R<sub>2</sub> score categories increase,  
107 the mean TTR of their study population decreases, except for one study by Domelo-Rodriguez<sup>6</sup> which  
108 showed the opposite relationship (Figure 2).

109 Five studies<sup>8,12,13,15,18</sup> investigated the relationship between components included in the  
110 SAME-TT<sub>2</sub>R<sub>2</sub> score and TTR. Three studies<sup>12,13,18</sup> showed that female sex was associated with poor  
111 anticoagulation control; one<sup>18</sup> showed that having  $\geq 2$  comorbidities was related to poor TTR and one<sup>13</sup>  
112 showed that black ethnicity (as well as NYHA IV) was associated with poorer anticoagulation control.  
113 Chan et al<sup>15</sup> also reported that having heart failure and diabetes mellitus independently predicts poor  
114 anticoagulation control.

115 Eight studies<sup>2,5,7-9,12,18, 21</sup> reported the predictive ability of the SAME-TT<sub>2</sub>R<sub>2</sub> score using c-  
116 statistics (**Figure 3**). Taken together these validation studies suggest that the SAME-TT<sub>2</sub>R<sub>2</sub> score is  
117 able to predict good or poor anticoagulation control among AF patients better than chance, with c-  
118 statistics ranging from 0.56<sup>12</sup> to 0.72;<sup>5</sup> the evidence is less robust in VTE patients (c-statistic 0.52-  
119 0.65).<sup>7,8</sup>

120 Eight studies<sup>11,15,18,20-22</sup> also examined if the SAME-TT<sub>2</sub>R<sub>2</sub> score could discriminate AF  
121 patients with clinical events. Five<sup>11,15,18,21,22</sup> demonstrated some positive associations for SAME-TT<sub>2</sub>R<sub>2</sub>  
122 score predicting clinical events, with c-statistics ranging from 0.55<sup>21</sup> to 0.62<sup>22</sup> (**Table 4**). Another  
123 study,<sup>8</sup> also examined if the SAME-TT<sub>2</sub>R<sub>2</sub> score was associated with clinical outcomes, in particular  
124 recurrent VTE and International Society on Thrombosis and Haemostasis (ISTH) major bleeding rates  
125 in a VTE cohort; patients with a score  $> 2$  had more overall adverse event rates (composite of recurrent  
126 VTE and ISTH major bleeding) than those with a score of 0-2 (7.9 vs. 4.5 overall adverse event  
127 rates/100 patient-years respectively).<sup>8</sup>

128

## 129 **Discussion**

130 This review of studies assessing and validating the SAME-TT<sub>2</sub>R<sub>2</sub> score extends and updates a previous  
131 narrative review<sup>23</sup> with the addition of validation studies in VTE populations<sup>6, 7</sup> and validations in  
132 Asian AF populations.<sup>15,16</sup> Overall, eight studies<sup>2,5,7-9,12,18,21</sup> suggest that the SAME-TT<sub>2</sub>R<sub>2</sub> score is able

133 to modestly predict quality of anticoagulation control in AF patients receiving VKA therapy, with c-  
134 statistics ranging from 0.56<sup>12</sup> to 0.72.<sup>5</sup> Many risk scores based on clinical factors such as CHADS<sub>2</sub>,  
135 CHA<sub>2</sub>DS<sub>2</sub>-VASc, Killip and TIMI scores show broadly similar modest c-indexes (approx. 0.6) when  
136 used to predict patients categorised at ‘high risk’ who actually sustain clinical events.<sup>24,25</sup>

137         The original purpose of developing the SAME-TT<sub>2</sub>R<sub>2</sub> score was to produce a simple clinical  
138 schema which could be used routinely in everyday practice to help assess the likelihood of an AF  
139 patient being able to achieve and maintain good anticoagulation control on VKA therapy, using  
140 patient-related clinical parameters which are readily available. The availability of NOACs worldwide  
141 has resulted in increased usage due to their advantages. These include faster onset-of-action (average  
142 maximum effect approximately three hours after intake<sup>26</sup> compared to VKA (onset 36-72 hours)),  
143 greater reduction in stroke/systemic embolism (+19% compared to VKA<sup>4</sup>), avoidance of INR  
144 monitoring with NOACs,<sup>27</sup> and absence of achieving/maintaining adequate TTR (as with warfarin).  
145 Achieving a therapeutic INR can take 2-4 weeks and often longer.<sup>3</sup> After termination of study drug in  
146 the NOAC trials, of those patients switching to warfarin, <40% achieved a therapeutic INR within 15  
147 days, and <80% after 30 days;<sup>28</sup> more strokes occurred during that period in the patients who went  
148 from study drug to VKA than from VKA to VKA.<sup>28,29</sup> This strongly argues for using NOACs over  
149 VKAs where possible, however, VKAs are still widely used globally and will not disappear from use  
150 especially for AF patients with severe renal impairment, moderate to severe mitral stenosis or  
151 mechanical heart valves.<sup>4</sup>

152         In addition, in low- and middle-income countries where cost plays an important role in  
153 options available for OAC treatment VKA is still the first-line antithrombotic agent of choice,  
154 therefore the SAME-TT<sub>2</sub>R<sub>2</sub> score will remain an important decision-making tool, currently and in the  
155 future, to guide physicians choice of anticoagulant treatment.<sup>30</sup> Most validation studies included in  
156 this review demonstrated good predictive ability except two<sup>6,19</sup> which demonstrate that the SAME-  
157 TT<sub>2</sub>R<sub>2</sub> score was unable to predict anticoagulation control well in their populations. Although both  
158 studies were prospective, results should be interpreted with care as both included small numbers of  
159 participants (135<sup>6</sup> and 180<sup>19</sup> respectively) and thus may not be adequately powered to test the  
160 predictive ability of the SAME-TT<sub>2</sub>R<sub>2</sub> score in regard to anticoagulation control.



161

162 **Importance of good anticoagulation control**

163 Achieving good anticoagulation control (TTR $\geq$ 65-70%) as recommended by guidelines<sup>1,4</sup> is  
164 essential for managing AF and VTE patients treated with VKA. Numerous studies have demonstrated  
165 that a high TTR translates into lower risk of stroke and bleeding.<sup>31-35</sup> A systematic review  
166 demonstrated that a 7% and 12% improvement in TTR can lead to a reduction in major bleeding and  
167 thromboembolic events, respectively, by 1 event per 100 patient years.<sup>34</sup> A real-world study<sup>32</sup> of  
168 27,458 warfarin-treated AF patients ( $\geq$ 3 INR measurements), showed that in patients with good  
169 anticoagulation control (TTR  $\geq$ 70%), stroke risk was reduced to 79% compared to patients with poor  
170 INR control (TTR  $\leq$ 30%). However, achieving and maintaining a therapeutic INR can be difficult to  
171 accomplish and therefore, NOACs are preferred to VKA in the majority of patients requiring OAC  
172 initiation.<sup>4</sup>

173

174

175 **SAMe-TT<sub>2</sub>R<sub>2</sub> score and clinical events**

176 Evident in most studies included in this review,<sup>2,5,7,9-18,20-22</sup> increasing SAMe-TT<sub>2</sub>R<sub>2</sub> score  
177 demonstrated poorer TTR values which might also translate into poorer clinical outcomes. This can be  
178 evidenced by studies that showed the SAMe-TT<sub>2</sub>R<sub>2</sub> score relating to severe bleeding<sup>22</sup> and major  
179 bleeding (defined by the Bleeding Academic Research Consortium),<sup>21</sup> stroke/TE,<sup>21</sup> adverse  
180 cardiovascular events<sup>22</sup> and death<sup>21, 22</sup> during follow-up. In an observational study performed in 911  
181 Spanish AF patients, the SAMe-TT<sub>2</sub>R<sub>2</sub> score also successfully predicted the composite outcome of  
182 major bleeding, TE complications and death.<sup>18</sup> A Chinese study also demonstrated that a SAMe-  
183 TT<sub>2</sub>R<sub>2</sub> score of  $\leq$ 2 vs. SAMe-TT<sub>2</sub>R<sub>2</sub> of 3 vs. SAMe-TT<sub>2</sub>R<sub>2</sub>  $\geq$ 4 is associated with lower annual stroke  
184 risk (3.49%/year vs. 4.56% per year vs. 6.41%/year, respectively).<sup>15</sup>

185

186

187 **Impact of different methods of calculating TTR**

188 Fauchier and colleagues<sup>36</sup> have raised concern about the different methods used to calculate  
189 TTR, whether to use TTR based on the Rosendaal method, percentage of INRs in range (PINRR)  
190 (traditional method) or percentage of visits in range on a given date (cross-sectional method), as these  
191 methods are not interchangeable. In this review, 17 studies<sup>2,5-17,19,20,22</sup> reported TTR using the  
192 Rosendaal method, only one<sup>18</sup> calculated time in therapeutic range according to PINRR, while the  
193 other reported 'labile INR' as their measure of anticoagulation control.<sup>21</sup> Currently there is no  
194 evidence on the optimal method of calculating percentage of INR in range, as each method has its  
195 own unique strengths and weaknesses.<sup>37</sup> While TTR via the Rosendaal method calculates the exact  
196 percentage of days the INR falls within range, its calculation is more complex than the others and is  
197 based on linear extrapolation. In contrast, calculating TTR via the PINRR method is simpler as it only  
198 looks at the number of INRs that fall within the therapeutic range divided by the total number of INR  
199 tests undertaken. However, the PINRR method does not take into account the actual number of days  
200 of anticoagulant treatment and thus might underestimate control in patients with inconsistent INR  
201 monitoring, patients who have temporarily discontinued therapy and patients with a long gaps  
202 between each INR test, in contrast to the Rosendaal method where these factors will be accounted for,  
203 resulting in a lower TTR.

204

### 205 **Factors affecting anticoagulation control**

206 In this review, only 5 studies<sup>8,12,13,15,18</sup> investigated the relationship of individual components  
207 of the SAME-TT<sub>2</sub>R<sub>2</sub> score with the quality of anticoagulation control. Among these female sex<sup>12,13,18</sup>,  
208 >2 comorbidities,<sup>18</sup> heart failure and diabetes mellitus<sup>15</sup> (individually) and black ethnicity<sup>5</sup> were  
209 associated with poor TTR control, however no studies found any association between age <60 years  
210 and smoking with poor TTR.

211 It is interesting to speculate how some elements of the SAME-TT<sub>2</sub>R<sub>2</sub> score could influence  
212 anticoagulation control. Some studies<sup>38,39</sup> investigating predictors of TTR have demonstrated that  
213 women have poorer anticoagulation control compared to men (translating into poorer outcomes),  
214 although the precise mechanism remains unclear.<sup>5</sup> Similarly, women are known to be at higher risk of  
215 AF-related stroke irrespective of warfarin use.<sup>40,41</sup> Tobacco use within 2 years scores 2-points in the

216 SAME-TT<sub>2</sub>R<sub>2</sub> score, however most validation studies reported low prevalence of smoking (6.3%-30%)  
217 except in the external validation study by Apostolakis et al<sup>5</sup> (49% reported as smoker/ex-smoker  
218 (within 2 years)). How smoking can influence anticoagulation control is unclear but it may reflect less  
219 interest in maintaining good health which may translate into poorer adherence to oral anticoagulants,  
220 thus resulting in poor TTR.<sup>5</sup>

221 The original SAME-TT<sub>2</sub>R<sub>2</sub> score publication suggested that patients who are younger and  
222 have more comorbidities probably have adherence issues with VKA therapy which are reflected by  
223 poor TTR<sup>3</sup>. In terms of non-white ethnicity, some studies have shown that African-Americans and  
224 Hispanics have poorer anticoagulation control compared to whites and suggest that this may be due to  
225 various reasons including socioeconomic status, poor understanding of therapy, adherence issues,  
226 genetic predisposition, etc.<sup>42,43</sup> However, these aspects need to be further investigated as studies in  
227 these areas are lacking.

228 Another editorial<sup>44</sup> suggests that other factors, not currently within the SAME-TT<sub>2</sub>R<sub>2</sub> score,  
229 could be included in the assessment of anticoagulation control, such as distance from home to  
230 anticoagulation clinic, which could be the main reason preventing patients attending for regular  
231 follow-up. There is clearly the need for a large prospective randomised trial to evaluate the impact of  
232 SAME-TT<sub>2</sub>R<sub>2</sub> score-guided therapy with VKA or NOAC not only in relation to anticoagulation  
233 control (TTR) but also towards clinical outcomes (stroke and bleeding), which would formalise its  
234 utility in clinical practice. Hence, where patients have chosen VKA over a NOAC for stroke  
235 prevention or treatment of VTE or where NOACs are contraindicated but a high SAME-TT<sub>2</sub>R<sub>2</sub> score  
236 (>2) is present, perhaps more frequent follow-up visits and reviews, educational interventions and  
237 counselling<sup>45</sup> may be required to ensure that INRs are within the therapeutic range in order to achieve  
238 the best outcomes and minimise treatment complications.

239

## 240 **Limitations**

241 The main limitation of the included studies is study design; none utilised a randomised controlled trial  
242 design and most were performed in white populations. Given that one of the risk factors for poorer

243 anticoagulation control is ethnicity, SAME-TT<sub>2</sub>R<sub>2</sub> score in these populations is automatically worse  
244 compared to non-whites; thus a lower score predicts better control of VKA therapy. Thus, future  
245 studies need to ascertain whether the threshold of the SAME-TT<sub>2</sub>R<sub>2</sub> score used to indicate probability  
246 of poorer anticoagulation control (SAME-TT<sub>2</sub>R<sub>2</sub> score  $\geq 2$ ) needs to be modified in non-white  
247 populations so that the SAME-TT<sub>2</sub>R<sub>2</sub> score is applicable globally. In addition, only three studies have  
248 validated the SAME-TT<sub>2</sub>R<sub>2</sub> score in VTE cohorts to date, hence more studies are needed specifically  
249 in VTE cohorts to enhance its applicability in these patients. Lastly, only 8 studies reported the c-  
250 statistic to quantify the predictive ability of the SAME-TT<sub>2</sub>R<sub>2</sub> score.

251

## 252 **Conclusions**

253 Making decisions when choosing OAC therapy can be challenging. The available evidence suggests  
254 that the SAME-TT<sub>2</sub>R<sub>2</sub> score is a useful tool to aid decision-making for OAC in AF (and VTE) patients  
255 and adequately predicts those who are likely to be able/unable to achieve and maintain good INR  
256 control.

257

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**Table 1:** The SAME-TT<sub>2</sub>R<sub>2</sub> score

	<b>Component</b>	<b>Score</b>
	<b>S</b> Sex (female)	1
	<b>A</b> Age (<60 years)	1
	<b>Me</b> Medical history <sup>†</sup>	1
	<b>T</b> Treatment (interacting drugs, e.g., amiodarone)	1
	<b>T</b> Tobacco use (within 2-years)	2
	<b>R</b> Race (non-white ethnicity)	2
	<b>Maximum total score</b>	<b>8</b>

<sup>†</sup>≥2 of the following: hypertension, diabetes mellitus, coronary artery disease/myocardial infarction, peripheral arterial disease, congestive heart failure, previous stroke, pulmonary, hepatic, or renal disease.

**Table 2:** Studies assessing the SAME-TT<sub>2</sub>R<sub>2</sub> score in atrial fibrillation and venous thromboembolism cohorts

	<b>a. Study design b. Mean follow-up c. Method INR monitoring</b>	<b>Population a. Number b. Mean (SD)/median (IQR) age (range, years) c. Race/ethnicity d. OAC used</b>	<b>SAME-TT<sub>2</sub>R<sub>2</sub> score distribution (%); mean TTR (%) ± SD</b>	<b>Percentage of patients with dichotomised TTR (%)</b>
<b>Pivatto Junior<sup>9</sup> 2017 Brazil</b>	a. Retrospective b. 1 year c. Hospital OAC clinic	a. 263 AF b. 71.2 (64.1-78.5) c. White d. 97.3% Warfarin	0-1: 138 (52.5); 69.2 ≥2: 125 (47.5); 56.3	-
<b>Kataruka<sup>8</sup> 2017 USA</b>	a. Retrospective b. Median 0.56 years ± 1.13 c. Hospital OAC clinic	a. 1943 VTE b. 61.8 (15.7) c. White d. Warfarin	0-1: 665; 57±21 2: 432; 55±22 >2: 846; 50±23	TTR<60:57.6
<b>Bernaitis<sup>16</sup> 2016 Singapore</b>	a. Retrospective b. - c. Hospital	a. 1137 AF b. 71 (63-77) c. Asian d. Warfarin	0-1:0 2: 339; 63.2±34.1 >2:798; 55.8±34.1	-
<b>Chan<sup>15</sup> 2016 Hong Kong</b>	a. Retrospective b. 4.7 ± 3.6 years c. Hospital	a. 1428 NVAF b. 76.2 (8.7) c. Chinese d. Warfarin	2: 22(14.3); 70 <sup>†</sup> 3: 80 (51.9); 70 4: 41 (26.6); 70 5: 7 (4.5); 70 6: 4 (2.6); 70	TTR≥70: 11 TTR<70: 89
<b>Demelo-Rodriguez<sup>6</sup> 2016 Spain</b>	a. Prospective b. 72,668 patient-years c. Primary care	a. 135 VTE b. Median 66 <sup>#</sup> c. White d. Warfarin	0-1:91; 64.7±19.5 ≥2: 44; 66 ±20.5	-
<b>Gorzalak-Pabis<sup>14</sup> 2016 Poland</b>	a. Prospective b. - c. Hospital	a. 104 AF with cognitive impairment b. 75 (10) c. White d. 61% Acenocoumarol	0-1: 64±26 ≥2: 50±28	-

<b>Lip<sup>13</sup> 2016 USA</b>	a. Prospective b. 438 days c. Trial setting	a. 229 AF b. 66.7 (11) c. 80.3% White d. Warfarin	0-1:0.571±0.22 ≥2: 0.498±0.24	-
<b>Lobos-Bejarano<sup>12</sup> 2016 Spain</b>	a. Retrospective b. >12 months c. Primary care	a. 1524 NVAF b. 77.4 (8.7) c. White d. 94.8% Acenocoumarol	0-1: 69.6% ± 17.4 ≥2: 66.6% ± 18.5	TTR≥65: 60.6 TTR<65: 39.4
<b>Palareti<sup>7</sup> 2016 Spain</b>	a. Prospective b. 998 patient-years c. Hospital OAC clinic	a. 1308 VTE b. 68(51-78) c. White d. Warfarin	0-1: 916 (70); 61±22 ≥2: 392 (30); 56±23	TTR≥65: 50.4 TTR<65: 49.6
<b>Proietti<sup>11</sup> 2016 Europe, Asia, Australasia</b>	a. Prospective b. Median 563 days c. Trial setting	a. 3665 AF b. 72(66-77) c. Mixed‡ d. Warfarin	0-2: 2914 (80.4); 69.05 (55.63-79.89) >2: 710 (19.6); 66.55 (52.83-77.46)	TTR>70: 46.9 TTR≤70: 53.1
<b>Szymanski<sup>10</sup> 2016 Poland</b>	a. Retrospective b. - c. Hospital	a. 211 AF b. 57.1 (10.2) c. White d. 75.4% warfarin	0-1: 114 (54); 52.3 ≥2: 97 (46); 51.3	TTR>70: 25.2 TTR≤70: 74.8
<b>Abumuaileq<sup>18</sup> 2015 Spain</b>	a. Retrospective b. 10 months c. Hospital OAC clinic	a. 911 NVAF b. 73 (11) c. White d. 93% Acenocoumarol	0-1:672 (74); 59±18 <sup>¶</sup> ≥2: 239 (26); 54±19 <sup>¶</sup>	PINRR>65:39 PINRR≤65:61
<b>Roldán<sup>44</sup> 2015 Spain</b>	a. Prospective b. 6 months c. Hospital OAC clinic	a. 459 NVAF b. 76 (70-82) c. White d. Acenocoumarol	<2: 253 (55); 67±18 ≥2: 206 (44.8); 61±16	TTR>65:54 TTR≤65:46
<b>Ruiz-Ortiz<sup>2</sup> 2015 Spain</b>	a. Retrospective b. Median 27 months c. Cardiology clinic	a. 1056 NVAF b. 73.6 (9.8) c. White d. Acenocoumarol	0-1:613 (58); 65.6±26.2 ≥2: 443 (42); 61.3±25.3	TTR≥65:52.7 TTR≥65:47.3

<b>Gallego<sup>22</sup> 2014 Spain</b>	a. Prospective b. Median 952 days c. Hospital OAC clinic	a. 972 NVAF b. 76 (70-82) c. White d. Acenocoumarol	0-1:431 (44); 79.67 ±19.46 ≥2: 332 (34); 78.4 ± 20.28 >2:208 (21); 74.25 ± 20.24	-
<b>Lip<sup>21</sup> 2014 France</b>	a. Prospective b. 1016±1018 days c. Clinicians -hospital	a. 8120 AF b. 70 (15) c. White d. Warfarin	0-1: 4504 (55); 77(1.7) <sup>§</sup> ≥2: 2252 (28); 52(2.3) <sup>§</sup> >2:1364 (17); 43(3.2) <sup>§</sup>	-
<b>Poli<sup>20</sup> 2014 Italy</b>	a. Prospective b. 4.6 years c. Hospital OAC clinic	a. 1089 AF b. 75 (30-94) c. White d. Warfarin	0-1:624 (57); 72.3 ± 15.3 2: 288 (26); 72.0 ± 15.6 >2:177 (16); 68.2 ±16.4	-
<b>Skov<sup>19</sup> 2014 Denmark</b>	a. Prospective b. 1 year c. Hospital OAC clinic	a. 182 AF b. 70.2 <sup>#</sup> c. White d. Warfarin	0-1:105 (58); 76 ≥2: 77 (42); 76	-
<b>Apostolakis<sup>5</sup> 2013 United Kingdom</b>	a. Retrospective and prospective b. 3.5 years c. Clinical trial (internal-validation)/Hospital OAC clinic (external-validation)	a. 1305 AF b. 69(8)/74(10) c. 8.7%, 19.3 % non-white (internal/external-validation) d. Warfarin	(Internal/External validation) 0: 242 (19); 0.66±0.16/0.7±0.13 1: 413 (32); 0.65±0.18/0.66±0.17 2: 303 (23); 0.63±0.17/0.66±0.16 3:185 (14); 0.59±0.22/0.65±0.17	<b>Internal validation</b> TTR>70:35.7 TTR≤70:64.3 <b>External validation</b> TTR>70:44.1 TTR≤70:55.9

AF: atrial fibrillation; CV: cardiovascular; INR: international normalised ratio; IQR: interquartile range; Max: maximum; MI: myocardial infarction; NVAF: non-valvular atrial fibrillation; OAC: oral anticoagulant/anticoagulation; ROC: area under curve; SD: standard deviation; SAME-TT<sub>2</sub>R<sub>2</sub> score: sex (female), age (<60 years, medical history (≥2 of the following: hypertension, diabetes, coronary artery disease or myocardial infarction, peripheral arterial disease, congestive heart failure, previous stroke, pulmonary, hepatic, or renal disease), treatment with interacting drugs (e.g. amiodarone[all 1 point], current tobacco use and race (non-white) [2 points]); TTR: time to therapeutic; TE: thromboembolism; VTE: venous thromboembolism

†TTR presented as ≥70% and <70% not mean TTR; ‡mixed population: White, Black, Asian, other; §number of patients with labile INR, (%); ¶PINRR % (mean ± SD); # no SD or IQR reported; - not reported

**Table 3:** Baseline characteristics of studies assessing SAME-TT<sub>2</sub>R<sub>2</sub> score in AF and VTE cohorts

Patient characteristic, N (%)	Sex (female)	Age <60 y	Hypertension	Diabetes mellitus	Heart failure	Prior stroke/TIA	Peripheral arterial disease	Renal disease	Coronary artery disease	COPD	Current smoking habit	Previous bleeding	Treatment: Amiodarone
<b>PivattoJunior</b> <sup>9</sup>	113 (43.0)	41 (15.6)	231 (87.8)	108 (41.1)	149 (56.7)	96 (36.5)	25 (9.5)	7 (2.7)	76 (28.9)	36 (13.7)	37 (14.1)	24 (9.1)	26 (9.9)
<b>Kataruka</b> <sup>8</sup>	1017 (52.3)	1060 (54.6)	-	-	-	-	-	-	-	-	575 (29.6)	-	22 (1.1)
<b>Bernaitis</b> <sup>16</sup>	448 (39.4)	172 (15.1)	677 (59.5)	343 (30.2)	88 (7.7)	45 (4.0)	-	156 (13.7)	271 (23.8)	-	84 (7.4)	-	78 (6.9)
<b>Chan</b> <sup>15</sup>	671 (52.5)	48.0 (3.4)	922 (64.6)	387 (27.1)	367 (25.7)	496 (34.7)	102 (7.1)	2.9 (2.0)	407 (28.5)	-	71.0 (5.0)	-	94 (6.6)
<b>Demelo-Rodriguez</b> <sup>6</sup>	(50.4)	-	(51.9)	(18.5)	(3.7)	(5.2)	(3.0)	(15.6)	-	(17.0)	(18.5)	-	-
<b>Gorzalak-Pabis</b> <sup>14</sup>	63 (60.6)	-	92 (88.5)	30 (28.8)	72 (69.2)	15 (14.0)	-	-	-	-	20 (19.2)	-	8 (7.7)
<b>Lip</b> <sup>13</sup>	47 (20.5)	57 (24.9)	206 (90.0)	106 (46.3)	126 (55.0)	26 (11.4)/ 14 (6.1)	31 (13.5)	-	178 (77.7)	-	-	-	46 (20.1) <sup>#</sup>
<b>L-Bejarano</b> <sup>12</sup>	741 (48.6)	66 (4.3)	1223 (80.2)	473 (31.0)	392.0 (25.7)	209.0 (13.7)	99 (6.5)	92 (6.0)	286 (18.8)	-	100 (6.6)	134 (8.8)	100 (6.6)
<b>Palareti</b> <sup>7</sup>	698.0 (53.4)	446 (34.1)	678 (51.8)	107 (8.2)	36.0 (2.8)	66 (5.0)	54 (4.1)	73 (5.6)	99.0 (7.6)	-	134 (10.0)	-	15 (1.1)
<b>Proietti</b> <sup>11</sup>	1116 (30.5)	72 <sup>§</sup> (66-77)	2812 (76.7)	860 (23.5)	1372 (37.4)	753 (20.5)	-	-	1619 (44.2)	-	334 (9.1)	208 (5.7)	-
<b>Szymanski</b> <sup>10</sup>	79 (37.4)	108 (51.2)	-	27 (12.8)	8.0 (3.8)	16 (7.6)	-	-	-	-	31.0 (14.7)	-	17 (8.1)
<b>Abumuaileq</b> <sup>18</sup>	306 (33.6)	-	678 (74.4)	220 (24.1)	343 (37.7)	103 (11.3)	92 (10.1)	36 <sup>¶</sup> (4)	127 (13.9)	183 (20.1)	77 (8.5)	115 (12.6)	-
<b>Roldán</b> <sup>17</sup>	237 (53.0)	38 (8.0)	368 (80.0)	141 (31.0)	87 (19.0)	67 (15.0)	-	51 (11.0)	70 (15.0)	50 (11.0)	38 (8.0)	37 (8.0)	72 (16.0)
<b>Ruiz-Ortiz</b> <sup>2</sup>	443 (42.0)	-	884 (83.7)	321 (30.4)	235 (22.2)	150 (14.2)	-	153 (14.5)	215 (20.3)	176 (16.7)	76 (7.2)	56 (5.3) <sup>††</sup>	102 (9.7)

<b>Gallego<sup>22</sup></b>	494 (51.0)	66 (7.0)	796 (82.0)	249 (26.0)	350 (36.0)	182 (19.0)	-	94 (10.0)	182 (19.0)	-	136 (14.0)	79 (8.0)	-
<b>Lip<sup>21</sup></b>	3,129 (39)	-	3,405 (42.0)	1,244 (15.0)	4,466 (55.0)	674 (8.0)	-	734 (9.0)	2,434 (30.0)	870 (11.0)	1,053 (13.0)	-	1,670 (35.0)
<b>Poli<sup>20</sup></b>	412 (37.8)	61 (5.6)	745 (68.7)	216 (19.9)	268 (24.7)	313 (28.8)	143 (13.2)	-	239 (22.1)	-	181 (16.6)	-	200 (18.4)
<b>Skov<sup>19</sup></b>	54 (29.6)	23 (12.6)	-	-	-	-	-	-	-	-	41 (22.5)	-	27 (14.8)
<b>Apostolakis<sup>5†</sup></b>	382 (37.5)	147 (14.4)	692 (67.9)	200 (19.6)	197 (19.3)	130 (12.8)	57 (5.6)	53 (5.2)*‡	173 (17.0)§§	-	64.0 (6.3)	-	129 (12.7)
<b>Apostolakis<sup>5‡</sup></b>	157 (67.1)	30.0 (10.5)	234 (81.8)	64 (22.4)	45 (15.7)	30.0 (12.8)	8 (2.8)	2.0 (0.7)*‡	44 (15.4)§§	-	140 (49.0)	-	26 (9.1)

COPD: chronic obstructive pulmonary disease; eGFR: estimated glomerular filtration rate; MI: myocardial infarction; TIA: transient ischemic attack

†Internal validation; ‡external validation; §median age (IQR); ¶eGFR 30 ml/min/1.73m<sup>2</sup>; # antiarrhythmic; ††Major bleed; ‡‡ hepatic/renal disease; §§ history of MI



**Table 4:** Predictive ability (c-statistics) of SAME-TT<sub>2</sub>R<sub>2</sub> for anticoagulation control and clinical events

	Anticoagulation control, c-statistics (95% CI)	Clinical events, c-statistics (95% CI)
<b>PivattoJunior</b> <sup>9</sup>	TTR $\geq$ 65: 0.612 (0.544-0.681; p=0.002)	-
<b>Kataruka</b> <sup>8</sup>	TTR<60: 0.61(-) TTR<65: 0.65(-) TTR<70: 0.65 (-)	-
<b>Chan</b> <sup>15</sup>	-	Stroke: 0.54 (0.52-0.57)
<b>Lobos-Bejarano</b> <sup>12</sup>	TTR $\geq$ 65: 0.562 (0.533-0.592; p<0.001)	-
<b>Palareti</b> <sup>7</sup>	TTR<65: 0.52 (0.48-0.55; p:0.35)	-
<b>Abumuaileq</b> <sup>18</sup>	PINRR $\leq$ 70: 0.60 (0.56-0.64; p<0.001)	Composite major bleeding, thromboembolic complication or death: 0.57 (0.51-0.62)
<b>Ruiz-Ortiz</b> <sup>2</sup>	TTR $\geq$ 65: 0.57 (0.53-0.60; p<0.0005)	-
<b>Gallego</b> <sup>22</sup>	-	Adverse CV event: 0.62 (0.57-0.68; p<0.001) Bleeding: 0.55 (0.49-0.62; p=0.117) All-cause mortality: 0.62 (0.55-0.68; p<0.001)
<b>Lip</b> <sup>21</sup>	Labile INR: 0.589 (0.574-0.603)	Stroke/TE: 0.561 (0.547-0.575) Severe bleeding: 0.552 (0.537-0.566) Major BARC bleeding: 0.574 (0.560-0.589) Death: 0.544 (0.530-0.559)
<b>Apostolakis</b> <sup>5</sup>	TTR 31% internal 0.72 (0.64-0.795) TTR 36% external 0.70 (0.57-0.82)	-

BARC: Bleeding Academic Research Consortium; CV: cardiovascular; INR: international normalised ratio; PINRR: percentage of INR in range; TE: thromboembolism; TTR: time in therapeutic range; - not reported

**Figure legends:**

**Figure 1:** Selection of studies for inclusion – PRISMA flowchart

**Figure 2:** Mean TTR vs. SAMe-TT<sub>2</sub>R<sub>2</sub> categories in validation studies

Legend: SAMe-TT<sub>2</sub>R<sub>2</sub> categories: black= score 0-1; grey= score of 2; white= score >2

**Figure 3:** Predictive ability (c-statistics and 95% confidence intervals) of SAMe-TT<sub>2</sub>R<sub>2</sub> and anticoagulation control in validation studies