**Supplementary material**

**Table 1.** Clinical event rates of dabigatran 150 mg and vitamin K antagonists from the RE-LY trial (1−4).

|  |  |  |  |
| --- | --- | --- | --- |
|  | VKAs | Dabigatran | |
| %/y | %/y | RR |
| Major events |  |  |  |
| Stroke or systemic embolism | 1.71 | 1.11 | 0.65 |
| Stroke | 1.58 | 1.01 | 0.64 |
| Non-disabling stroke | 0.58 | 0.37 | 0.64 |
| Disabling or fatal stroke | 1.01 | 0.66 | 0.65 |
| Deaths | 4.13 | 3.64 | 0.88 |
| Vascular death | 2.69 | 2.28 | 0.85 |
| Non-vascular death | 1.44 | 1.36 | 0.94 |
|  |  |  |  |
| Thromboembolic events |  |  |  |
| Ischemic stroke | 1.21 | 0.92 | 0.76 |
| Transient ischemic attack (TIA) | 0.84 | 0.72 | 0.86 |
| Systemic embolism | 0.18 | 0.11 | 0.61 |
| Pulmonary embolism | 0.10 | 0.15 | 1.50 |
| Myocardial infarction | 0.64 | 0.81 | 1.27 |
|  |  |  |  |
| Hemorrhagic events |  |  |  |
| All hemorrhages | 18.37 | 16.56 | 0.90 |
| Major hemorrhage | 3.57 | 3.32 | 0.93 |
| Intracranial hemorrhage | 0.76 | 0.32 | 0.42 |
| Hemorrhagic stroke | 0.38 | 0.10 | 0.26 |
| Extracranial hemorrhage | 2.84 | 3.02 | 1.06 |
| Gastro-intestinal hemorrhage | 1.07 | 1.56 | 1.46 |
| Upper gastro-intestinal hemorrhage | 0.80 | 0.83 | 1.03 |
| Lower gastro-intestinal hemorrhage | 0.27 | 0.73 | 2.74 |
| Ear. nose. throat | 0.15 | 0.07 | 0.47 |
| Genitourinary | 0.13 | 0.13 | 1.00 |
| Intra-articular | 0.06 | 0.02 | 0.33 |
| Intraocular | 0.12 | 0.09 | 0.75 |
| Intrathoracic | 0.07 | 0.07 | 1.00 |
| Pericardial | 0.03 | 0.02 | 0.67 |
| Retroperitonial | 0.11 | 0.07 | 0.64 |
| Intramuscular/ intraspinal | 0.19 | 0.09 | 0.47 |
| Surgical | 0.59 | 0.40 | 0.68 |
| Not reported | 0.31 | 0.40 | 1.29 |
| Minor hemorrhage | 16.37 | 14.85 | 0.91 |
|  |  |  |  |
| Other |  |  |  |
| Dyspepsia | 5.80 | 11.30 | 1.95 |
| Hospitalization | 20.20 | 20.80 | 1.03 |
| Red cell transfusion | 1.93 | 2.10 | 1.09 |
|  |  |  |  |

**Table 2.** The relative risk of ischemic stroke, major hemorrhage and myocardial infarction of dabigatran (150 mg twice daily) versus vitamin K antagonists for different subgroups of the RE-LY study population.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Relative risk of dabigatran 150 mg BID vs. vitamin K antagonists | | | | | |
|  | Ischemic  stroke\* | | Major  hemorrhage | | Myocardial infarction | |
|  |  |  |  |  |  |  |
| All participants (1,2) | 0.76 |  | 0.93 |  | 1.27 |  |
| Age (3) |  |  |  |  |  |  |
| <75 years | 0.74 |  | 0.70 |  |  |  |
| ≥75 years | 0.78 |  | 1.17 |  |  |  |
| Gender |  |  |  |  |  |  |
| Male | 0.86 | (1) | 0.93 | (3) |  |  |
| Female | 0.66 | (1) | 0.93 | (3) |  |  |
| Ethnicity |  |  |  |  |  |  |
| Asian | 0.55 | (5) | 0.57 | (5) | 0.86 | (5) |
| European/ Arab | 0.88 | (1) | 1.00 | (5) | 1.32 | (5) |
| Other | 0.69 | † | 1.00 | (5) | 1.00 | (5) |
| Prior stroke/ TIA(6) |  |  |  |  |  |  |
| Yes | 1.00 |  | 1.00 |  | 1.59 |  |
| No | 0.66 |  | 0.90 |  | 1.19 |  |
| Prior MI/ CAD (7) |  |  |  |  |  |  |
| Yes | 0.88 |  | 0.94 |  | 1.32 |  |
| No | 0.69 |  | 0.92 |  | 1.18 |  |
| Diabetes mellitus (8) |  |  |  |  |  |  |
| Yes | 0.76 |  | 1.12 |  |  |  |
| No | 0.76 |  | 0.86 |  |  |  |
| Heart failure (9) |  |  |  |  |  |  |
| Yes | 0.88 |  | 0.79 |  |  |  |
| No | 0.71 |  | 0.98 |  |  |  |
| Hypertension (1) |  |  |  |  |  |  |
| Yes | 0.79 |  |  |  |  |  |
| No | 0.67 |  |  |  |  |  |
| CHADS2-score (10) |  |  |  |  |  |  |
| 0-1 | 0.70 |  | 0.74 |  |  |  |
| 2 | 0.71 |  | 0.92 |  |  |  |
| 3-6 | 0.81 |  | 1.05 |  |  |  |
| Renal function (11) |  |  |  |  |  |  |
| CC <50 ml/min | 0.66 |  | 1.00 |  |  |  |
| CC 50-79 ml/min | 0.80 |  | 0.91 |  |  |  |
| CC ≥80 ml/min | 0.79 |  | 0.84 |  |  |  |
| Level of INR control (12) |  |  |  |  |  |  |
| Centre’s TTR <57.1% | 0.67 |  | 0.71 |  |  |  |
| Centre’s TTR 57.1-65.5% | 0.59 |  | 0.81 |  |  |  |
| Centre’s TTR 65.5-72.6% | 0.81 |  | 1.12 |  |  |  |
| Centre’s TTR >72.6% | 1.09 |  | 1.16 |  |  |  |
|  |  |  |  |  |  |  |

Abbreviations: SE, systemic embolism; TTR, time in therapeutic range.

\* The risk for ischemic stroke for was not reported with respect to subgroups based on age, gender, prior MI, heart failure, renal function, and time in therapeutic range. However, the risk of stroke and systemic embolism for these subgroups was reported. The risk of ischemic stroke was calculated on the assumption that, for dabigatran 150 mg, 83% of stroke/ SE equals an ischemic stroke, while this is 71% for VKAs (1).

† Calculated on the basis of information provided in Connolly et al., 2009 (1), and Hori et al., 2013 (5).

**Table 3.** Questions to assess the relevance of economic modeling studies – developed by Caro et al. (13) – and explanation of why and how questions apply to studies on the cost-effectiveness of dabigatran as compared to vitamin K antagonists.

|  |  |  |  |
| --- | --- | --- | --- |
| **(Helper) Questions (13)** | **Applicability of the questions to economic modeling studies comparing dabigatran with VKAs** | **Questions applied to economic modeling studies comparing dabigatran with VKAs** | **Link to questionnaire** |
| **Is the population relevant?** | | | |
| Are demographics similar? | * The risk of ischemic stroke increases with age, and is higher for women (1;14). * The RR of ischemic stroke of DBG vs. VKAs is influenced by gender and ethnicity (1;5). * The RR of major hemorrhage of DBG vs. VKAs is influenced by age and ethnicity (3;5). | * Is the age of the cohort similar to the target population? | * Question 11 |
| * Is the share of women in the cohort similar to the target population? | * Question 12 |
| * Is the share of patients with an Asian ethnicity in the cohort similar to the target population? | * Question 13 |
| * Is the share of patients with an European ethnicity in the cohort similar to the target population? | * Question 14 |
| Are risk factors similar? | * The risk of ischemic stroke is higher in patients who suffered a prior stroke or TIA (6). * The risk of MI is higher in patients who suffered a prior MI (15). * The RR of ischemic stroke of DBG vs. VKAs is higher in patients with a prior stroke or TIA and/or MI (6). * The RR of MI of DBG vs. VKAs is higher in patients with prior stroke or TIA and/or MI (6). | * Is the share of patients with a prior stroke or TIA similar to the target population? | * Question 15 |
| * Is the share of patients with a prior MI similar to the target population? | * Question 16 |
| Are behaviors similar? | * DBG users have a higher rate of discontinuation than VKA users (1).Discontinuation of treatment is associated with at least one consultation to assess further options for anticoagulation. * Non-adherence impacts all health outcomes, and is higher in clinical practice than during trials (16). | * Is the rate of discontinuation in the model similar to clinical practice, and is discontinuation associated with at least one consultation? | * Question 17 |
| * Is the impact of non-adherence included in the data or sensitivity analyses? | * Question 18 |
| Is the medical condition similar? | *Following from the inclusion criteria, all studies assess the cost-effectiveness of dabigatran and VKAs in patients with atrial fibrillation.* | *None* | * Not applicable |

Abbreviations: DBG = dabigatran; GIH = gastrointestional hemorrhage; ICH = intracranial hemorrhage MI = myocardial infarction; nGI-ECH = non-gastrointestinal extracranial hemorrhage; INR = international normalized ratio; RR = relative risk; TIA = transient ischemic attack; TTR = time in therapeutic range; VKA = vitamin K antagonist.

|  |  |  |  |
| --- | --- | --- | --- |
| **(Helper) Questions (13)** | **Applicability of the questions to economic modeling studies comparing dabigatran with VKAs** | **Questions applied to economic modeling studies comparing dabigatran with VKAs** | **Link to questionnaire** |
| **Is the population relevant? (continued)** | |  |  |
| Are co-morbidities similar? | * The risk of ischemic stroke is higher in patient with hypertension (1). * The RR of ischemic stroke of DBG vs. VKAs is higher in patients with heart failure and/or hypertension, and lower in patients with renal impairment (CC<50 ml/min) (1;9;11). * The RR of major hemorrhage of DBG vs. VKAs is higher in patients with diabetes mellitus and/or in patients with renal impairment (CC<50 ml/min), and lower in patients with heart failure (8;9;11). | * Is the share of patients with diabetes mellitus similar to the target population? | * Question 19 |
| * Is the share of patients with heart failure similar to the target population? | * Question 20 |
| * Is the share of patients with hypertension similar to the target population? | * Question 21 |
| * Is the average renal function similar to the target population? | * Not applicable\* |
| **Are any critical interventions missing?** | |  |  |
| Does the analyzed intervention match the intervention of interest? | The intervention of interest is DBG in a dose of 150 mg 2 times daily. DBG 110 mg 2 times daily is not approved in the US. Therefore, DBG in sequential dosing (150 mg for patients aged < 75 and 110 mg for patients aged ≥ 75) is also not applicable to the US. | * Does cost-effectiveness of DBG pertain to a dose of 150 mg twice daily? | * Question 22 |
| Have all relevant comparators been considered? | Following from the inclusion criteria, all studies use VKAs as a comparator against DBG. The effectiveness of VKAs greatly depends on the time in therapeutic range (TTR). The mean TTR was 64.4% in the RE-LY trial, but is lower in US clinical practice, estimated to be ~55%, varying between 54% and 64% (17−19). | * Was the time in therapeutic range of VKAs similar to clinical practice? | * Question 23 |
| Does the background care in the model match yours? | * Patients visit a physician start of DBG, and often one month thereafter to assess tolerance of the drug. AHA/ ACC/ HRS guidelines advise a renal function test before starting DBG (20). * Patients with moderate renal impairment, and/or patients who are aged ≥ 75 years, require annual monitoring of renal function with DBG (20). | * Is the nature and frequency of monitoring with the start of DBG in line with US clinical guidelines (at least 2 visits and 1 renal function test in the first 2 months)? | * Question 24 |
| * Is the nature and frequency of monitoring of DBG in line with US clinical guidelines (annual monitoring of renal function in vulnerable patients)? | * Question 25 |

**Table 3.** Continued (1).

\* Information was lacking on the prevalence of renal impairment in the target population.

|  |  |  |  |
| --- | --- | --- | --- |
| **(Helper) Questions (13)** | **Applicability of the questions to economic modeling studies comparing dabigatran with VKAs** | **Questions applied to economic modeling studies comparing dabigatran with VKAs** | **Link to questionnaire** |
| **Are any critical interventions missing? (continued)** | |  |  |
| Does the background care in the model match yours (continued)? | * It is advised that patients undergo intensified monitoring with the start of VKAs (at least 4 physician or INR clinic visits in the first 2 months) before long-term follow-up (21). * Patients need regular INR monitoring with the use of VKAs. It is advised that patients with stable INR levels are monitored at least once every month (21). | * Is the nature and frequency of monitoring with the start of VKAs in line with US clinical guidelines (at least 4 visits to INR clinic or physician in the first 2 months)? | * Question 26 |
| * Is the nature and frequency of monitoring of VKAs in line with US clinical guidelines (is there at least 12 times INR monitoring per year)? | * Question 27 |
| **Are any relevant outcomes missing?** | |  |  |
| Are the health outcomes relevant? | * Relevant clinical events are: ischemic stroke, TIA, systemic embolism, pulmonary embolism, MI, ICH, major gastrointestinal hemorrhage (GIH), major non-gastrointestinal extracranial hemorrhage (nGI-ECH), minor hemorrhage, and dyspepsia (1−3). | * Is ischemic stroke taken into account as a separate clinical event? | * Question 1a |
| * Is TIA taken into account as a separate clinical event? | * Question 2 |
| * Is systemic embolism taken into account as a separate clinical event? | * Question 3 |
| * Is pulmonary embolism taken into account as a separate clinical event? | * Question 4 |
| * Is MI taken into account as a separate clinical event? | * Question 5a |
| * Is ICH taken into account as separate clinical event? | * Question 6a |
| * Is extracranial hemorrhage taken into account as a separate clinical event, and are GIH and nGI-ECH separated? | * Question 7 |
| * Is minor hemorrhage taken into account as a separate clinical event? | * Question 8 |
| * Is dyspepsia into account as a separate clinical event? | * Question 9a |

**Table 3.** Continued (2).

**Table 3.** Continued (3).

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **(Helper) Questions (13)** | | **Applicability of the questions to economic modeling studies comparing dabigatran with VKAs** | **Questions applied to economic modeling studies comparing dabigatran with VKAs** | **Link to questionnaire** |
| **Are any relevant outcomes missing (continued)?** | | |  |  |
| Are the health outcomes relevant (continued)? | * Some clinical events can cause permanent changes in the health status of patients (such as disability or chronic pain), that are associated with disutility or costs.   + Strokes (ischemic and hemorrhagic) can result in disability.   + Pulmonary embolism can cause ventricular dysfunction (22).   + MI can lead to heart failure (23).   + Dyspepsia is associated with discomfort/pain and the use of proton pump inhibitors (24). | | * Is ischemic stroke associated with a risk of permanent disutility? | * Question 1b |
| * Is ICH associated with a risk of permanent disutility? | * Question 5b |
| * Is MI (possibly) associated with permanent disutility? | * Question 6b |
| * Is dyspepsia associated with permanent disutility? | * Question 9b |
| Are the economic endpoints relevant? | For an economic modeling study to be more relevant for decision-makers, the costs for both clinical events and health states should be taken into account. | | * Are costs of the clinical event, as well as of the resulting health status, taken into account for ischemic stroke? | * Question 1c |
| * Are costs of the clinical event, as well as of the resulting health status, taken into account for ICH? | * Question 5c |
| * Are costs of the clinical event, as well as of the possible resulting health status, taken into account for MI? | * Question 6c |
| * Is the occurrence of dyspepsia associated with a physician visit, and a possible prescription of a proton pump inhibitor? | * Question 9c |
| **Is the context applicable?** | | |  |  |
| Is the geographic location and health care system similar? | | *The geographic location and health care system were not deemed relevant, as country-specific factors, such as monitoring and time in therapeutic range were already taken into account.* | *None* | * Not applicable |
| Is the time horizon applicable to your decision? | | Patients with atrial fibrillation need to receive lifelong anticoagulation treatment for the prevention of stroke. | * Are the patients in the modeled cohort assumed to receive DBG or VKAs for the remainder of their life? | * Question 10 |
| Is the analytic perspective appropriate to your decision problem? | | *The context in this systematic review is defined as a region (i.e. the US), not as a decision problem. It is therefore possible that a societal or funder perspective – e.g. private insurance, Medicare or Medicaid – was chosen,. However, one perspective was not considered to be more or less appropriate by us beforehand.* | *None* | * Not applicable |

**Table 4.** Overview of whether model-based economic evaluations on dabigatran vs. VKAs for the prevention of stroke in patients with AF in the United States are relevant with respect to different context-*dependent* factors (set against the context of the United States).

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | [18] | [19] | [20] | [21] | [22] | [23] |  | **(%)** |
| Is the study cohort comparable to the US target population?\* |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |
| *Baseline age* |  |  |  |  |  |  |  | 100 |
|  |  |  |  |  |  |  |  |  |
| *Women (%)* |  |  |  |  |  |  |  | 0 |
|  |  |  |  |  |  |  |  |  |
| *Patients from Asian origin (%)* |  |  |  |  |  |  |  | 0 |
|  |  |  |  |  |  |  |  |  |
| *Patients from European origin (%)* |  |  |  |  |  |  |  | 0 |
|  |  |  |  |  |  |  |  |  |
| *Patients with prior stroke/ TIA (%)* |  |  |  |  |  |  |  | 67 |
|  |  |  |  |  |  |  |  |  |
| *Patients with prior MI (%)* |  |  |  |  |  |  |  | 0 |
|  |  |  |  |  |  |  |  |  |
| *Rate/costs of drug discontinuation* |  |  |  |  |  |  |  | 0 |
|  |  |  |  |  |  |  |  |  |
| *Scenario with non-adherence* |  |  |  |  |  |  |  | 0 |
|  |  |  |  |  |  |  |  |  |
| *Patients with diabetes mellitus (%)* |  |  |  |  |  |  |  | 33 |
|  |  |  |  |  |  |  |  |  |
| *Patients with heart failure (%)* |  |  |  |  |  |  |  | 67 |
|  |  |  |  |  |  |  |  |  |
| *Patients with hypertension (%)* |  |  |  |  |  |  |  | 67 |
|  |  |  |  |  |  |  |  |  |
| Are the treatments comparable to the US context? |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |
| *Dabigatran, 150 mg bid* |  |  |  |  |  |  |  | 100 |
|  |  |  |  |  |  |  |  |  |
| *Time in therapeutic range of VKAs* |  |  |  |  |  |  |  | 17 |
|  |  |  |  |  |  |  |  |  |
| *Monitoring: start of dabigatran* |  |  |  |  |  |  |  | 17 |
|  |  |  |  |  |  |  |  |  |
| *Monitoring: dabigatran, continuous* |  |  |  |  |  |  |  | 50 |
|  |  |  |  |  |  |  |  |  |
| *Monitoring: start of VKAs* |  |  |  |  |  |  |  | 33 |
|  |  |  |  |  |  |  |  |  |
| *Monitoring: VKAs, continuous* |  |  |  |  |  |  |  | 83 |
|  |  |  |  |  |  |  |  |  |
| **% relevant per study** | 59 | 47 | 29 | 29 | 24 | 35 |  |  |

Abbreviations: MI, myocardial infarction; TIA, transient ischemic attack; VKA, vitamin K antagonist.

\* The share of patients with renal impairment was excluded, because data on this variable in the US population of AF patients was missing.

|  |  |
| --- | --- |
|  | Incorporated |
|  | Not (completely) incorporated |
|  | Unknown |

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