Health Technology Assessment (HTA)

Stakeholder Feedback: Oral anticoagulants for prevention of stroke and systemic embolism in people with non-valvular atrial fibrillation

Contents

Preface

This document details the authors' responses to stakeholder feedback on the protocol for an HTA on o*ral anticoagulants for the prevention of stroke and systemic embolism in people with non-valvular atrial fibrillation.*

The stakeholder feedback and corresponding author responses are detailed in tables. The tables are listed by stakeholder, in alphabetical order.

Where multiple stakeholders provided similar feedback, the authors have only provided a response to the first comment; subsequent comments instruct the reader to cite the original response.

1. Bayer (Schweiz) AG

Domain	Comment	Author response
1. Comments on research questions	1. The HTA protocol mentions the publication by Mueller et al. (2018) as one of the reasons to assess the benefits and harms of DOACs compared to VKAs. Mueller et al. conducted a nonrandomized observational study and found that "a VKA therapy seems to be more effective and safer than a NOAC therapy in a real-world cohort of German AF patients". In the observational period, DOACs were already the preferred standard therapy for NVAF. Only patients doing well on VKA remain on VKA, difficult NVAF patients were switched to or initiated on DOACs. Thus, there is a huge bias inherent to the Mueller et al. results since patients in the 2 cohorts are very different, with the challenging ones in the DOAC arm. 2. Randomized trials investigating DOACs vs VKAs clearly demonstrated a significant superiority of DOACs vs VKAs. Thus, all DOAC RCTs and the vast majority of publications conclude the opposite to the Mueller et al. publication.	Thank you for this feedback. It has been noted and will be considered during the evaluation of the evidence in the HTA phase.
2. Comments on PICO	1. Protocol states that "The term valvular NVAF is generally used to differentiate patients who do not have moderate/severe mitral stenosis or a mechanical prosthetic heart valve(s) from other patients who are considered to have valvular AF". However, valvular NVAF (= non valvular AF) is a contradiction in itself. Is this just a typo or lack of understanding? 2. 5.2 Intervention: Not all DOAC doses approved and used in Switzerland are listed 3. 5.3 Comparator: It is unclear why VKAa are treated as a class whereas DOACs as individual therapies. The 3 Xa-inhibitors have at least as much in common as warfarin, phenprocoumon and acenocoumarol and should be treated as a class too. 4. 5.4 Outcomes: Protocol states that "critical outcomes related to anticoagulant therapy for NVAF relate to ... embolic events related to inadequately treated NVAF (i.e. effectiveness outcomes)." How is "inadequately treated NVAF" defined and can data on such relatedness be extracted from data bases?	1. Per the European Society of Cardiology (2021) guidelines, the term "nonvalvular atrial fibrillation" is no longer recommended, as it does not imply the absence of valvular heart disease. Nonetheless, the project has been established using this terminology, as many relevant clinical trials refer to these terms. For the purpose of this review, we have further defined the population to capture contemporary evidence that does not use the term "NVAF". Nuance around the use of the term "NVAF" is described in section 3.0. 2. The doses listed for each DOAC reflect the eligible patient population outlined in the PICO criteria, per their approved use on Swissmedic, and limitations listed on the Spezialitätenliste. Dosages recommended for other indications (e.g. edoxaban 15mg, rivaroxaban 2.5mg/10mg) have not been included. 3. The grouping of the VKA class reflects the policy question, which aims to determine the safety and efficacy of individual DOACs. The safety and efficacy of individual VKAs is not in question. 4. "Inadequately treated NVAF" is not an inclusion criteria, but rather describes the direction of effect expected for "effectiveness outcomes". We put "effectiveness outcomes" in quotations because all outcomes are dichotomous events (except for health-related quality of life), which can be interpreted as either effectiveness (i.e. if the rate of

Domain	Comment	Author response
		negative events are reduced) or safety (i.e. if rate of negative events are increased).
3. Comments on databases and search strategy	1. See "research question" - only randomized studies can answer the research question. 2. There is a discrepancy between the executive summary (four databases) and the methods section (7.7.1: five databases) - How reliable is this protocol if there are discrepancies in critical aspects such as the number of databases to be included? 3. 4.1.3 "Unlike coumarin derivatives, there is no specific reversal agent (with the exception of idarucizumab for dabigatran) and patients with renal impairment are either ineligible for treatment or require dose reduction, noting that bleeding can be treated with unspecific methods, and DOAC antagonists are under development" - Please note that a specific reversal agent for apixaban and rivaroxaban has been approved by Swissmedic in December 2020? How can it be that such an important information was missed by the protocol responsible team?	1. The aim of the HTA is to investigate both efficacy (from RCT) and effectiveness (from NRSI). 2. Four databases are relevant to the systematic review of clinical outcomes. The 5th database (econlit) will only be searched for the evaluation of economic outcomes. We have made this clearer in the executive summary. 3. Thank you for this feedback, this section has been removed from the report to align with other comments from stakeholders.
4. Comments on data extraction, analysis and synthesis	1. Not clear how budget impact of VKA is measured. We have not seen any publication on the impact of the additional costs related to VKA therapy (INR etc) with real Swiss figures. Since there is no such publication, how will this be calculated and how reliable will this calculation be on the true budget impact of the VKA in Switzerland?	1. The budget impact of each intervention will be modelled by the HTA evaluators, not from existing publications. Very briefly, we estimate the size of the population and number of prescriptions (either using administrative data e.g. from COGE GmbH, SASIS, IMS/IQVIA, and/or through an epidemiological approach), and take relevant costs associated with the medications (per listed costs on the Spezialitätenliste) and outpatient and inpatient services related to the medication use (per the listed costs on TARMED and SwissDRG). The budget impact is modelled over a number of years, accounting for changes in the population and medication use over time, and reflecting different policy scenarios.

2. Boehringer-Ingelheim (Schweiz) GmbH

Domain	Comment	Author response
1. Comments on research questions	1. This HTA appears to be triggered by controversial evidence on safety and effectiveness of DOACs vs VKAs, derived from a single non-randomized retrospective study based on insurance claims of a non-representative population in Germany (Mueller et al.). The methods utilized by Mueller et al. are unclear and do not form a solid basis for the proposed HTA. Various analysis and randomized trials investigating DOACs vs. VKAs show a clear benefit of DOACs. 2. It is unclear how Switzerland specific social, ethical, and organizational benefits/harms of DOACs vs VKAs will be assessed. 3. Evidence derived from other countries may not be applicable to Switzerland.	1. The intent of the HTA is to evaluate both the efficacy (derived from RCTs) and effectiveness (derived from NRSI) of DOACs compared to VKAs. The protocol does not pre-empt the findings of the full evaluation. 2. Auxiliary domains (e.g. social, legal, ethical and organisational) are evaluated through literature review, and discussion with clinical experts around models of service delivery. 3. The applicability of all evidence included in the review, to the Swiss context, will be evaluated.
2. Comments on PICO	1. All-cause mortality needs to be stratified into other causes and NVAF-related death to allow differentiation between individual DOACs and VKAs. 2. VKAs should be assessed separately, just like the DOACs, and not as a treatment group. 3. It would be appropriate to use Swiss data in case real world evidence is included. 4. Adherence should be assessed for all medications, DOACs and VKAs, included in the HTA because it is an overall problem especially in long-term treatment. 5. The comparison of medical costs should include costs of subsequent treatment, AE management and treatment monitoring next to the direct costs of DOACs and VKAs. 6. The term “inadequately treated NVAF” should be defined.	1. Cardiovascular-related mortality has been added to the list of outcomes. 2. See response to comment ***1.2.3***. 3. Where Swiss-specific data is available from published sources, we will indeed include it. 4. Thank you for this comment. Adherence is included as an outcome for all interventions. 5. Thank you for this suggestion, these costs will indeed be considered during the HTA phase. 6. “Inadequately treated NVAF” is not an inclusion criteria, but rather describes the direction of effect expected for “effectiveness outcomes”. We put “effectiveness outcomes” in quotations because all outcomes are dichotomous events (except for health-related quality of life), which can be interpreted as either effectiveness (i.e. if the rate of negative events are reduced) or safety (i.e. if rate of negative events are increased).

Domain	Comment	Author response
3. Comments on databases and search strategy	1. SL-Dossier: Only RTC accepted, therefore only RTC should be considered for the HTA process, since HTA has potential consequences for SL-listing. 2. Which professionell criteria must the reviewers meet? (clinical, statistical/scientific expertise, publication record of reviewers) 3. Which are the exclusion criteria's applicable to the selection of evidence sources for economic outcomes. 4. In contrast to previous HTA protocols the systematic literature review (SLR) has not been performed yet. Stakeholders will not have the opportunity to comment on the SLR and included data. Valuable information/input may therefore be lost and the FOPH should make the protocol and SLR results available for stakeholder input.	1. For inclusion on the SL-list the best available evidence is evaluated, with RCTs as golden standard study design type. The list does not exclude other study design types, when RCTs are not available. 2. HTA evaluators are selected to be included on the HTA Framework Agreement through a competitive, open tender process. Evaluators are selected based on experience in conducting HTA reports, oral and written proficiency in English, knowledge and understanding of the Swiss healthcare system or another national healthcare system, national and international network of experts in the field, operational capacity, conflicts of interest, and other administrative criteria. 3. The full protocol for the health economic evaluation is developed during the HTA phase. The protocol presents a summary of the overall approach that is likely to be taken. 4. This comment has been addressed, per responses above.
4. Comments on data extraction, analysis and synthesis	1. It is not clear how budget impact of VKA is measured. There are no publications on the impact of the additional costs related to VKA therapy (INR etc) with real Swiss figures. How will this be calculated and how reliable will this calculation be on the true budget impact of the VKA? 2. Choice of cost effectiveness model or criteria driving selection of an existing model were not discussed. There are no Swiss specific utilities values and the source of utilities values for the cost effectiveness analysis should be addressed in the protocol. 3. It is unclear how different sources of evidence (RCT/NRSIs) will be weighted in the NMA and how the evidence will be ranked. Should the NMA include NRSIs, not only qualified NRSIs of acenocoumarol/phenprocoumon but also NRSIs on Warfarin will need to be considered. Furthermore, NRSIs without adjustment for confounders should be excluded from the NMA.	1. The budget impact of each intervention will be modelled by the HTA evaluators, not from existing publications. Very briefly, we estimate the size of the population (either using administrative data e.g. from COGE, SASIS, IMS/IQVIA, and/or through an epidemiological approach), and take relevant costs associated with the medications (i.e. from the Spezialitätenliste) and outpatient and inpatient services related to the medication use (e.g. per TARMED and SwissDRG). The budget impact is modelled over a number of years, accounting for changes in the population and medication use over time, and reflecting different policy scenarios. 2. These details are not requested by the FOPH during the HTA protocol phase. A separate economic protocol is developed during the HTA phase, establishing the parameters for the modelling approach. 3. As stated in the protocol, RCT and NRSI evidence will be evaluated separately, appraised for risk of bias using design-specific tools, and the overall findings will be evaluated separately using the GRADE approach. Warfarin will only be considered in the absence of evidence for acenocoumarol or phenprocoumon, in order to ensure the evidence is applicable to the Swiss context.

3. Bristol Myers Squibb and Pfizer

Domain	Comment	Author response
1. Comments on research questions	1. The policy question of this appraisal is based heavily on evidence from a German retrospective study which used data only until June 2014.[1] The evidence from this study is not in complete alignment with the myriad of other more recent real-world evidence (RWE) and clinical trial data which suggest superior efficacy and safety profiles of apixaban vs. VKAs.[2-6] In addition, contemporary guidelines which have assessed the current evidence base recommend DOACs as the first line treatment option for NVAF.[7] 2. Section 4.1.3 describes several disadvantages of DOACs to strengthen the rationale for this appraisal. We feel these critiques should not be generalized for all DOACs. One of the disadvantages discussed is the lack of reversal agents for DOACs except for dabigatran; however, andexanet alfa (Ondexxya™) is approved in Switzerland as a reversal agent for apixaban and rivaroxaban. Further, dose reduction or ineligibility for DOACs are linked to renal impairment; this is not true for apixaban, as renal impairment alone does not necessitate apixaban dose reduction. 3. Adherence issues with DOACs are identified as a key point in this appraisal; however, VKAs are also associated with adherence issues which can severely impact the time in therapeutic range (TTR) and therefore the efficacy of therapy.[8] Whilst the study by Ozaki *et al* cited in this protocol indicates less optimal adherence for DOACs[9], it did not evaluate adherence for warfarin. Thus, it is unclear how adherence compares between the two classes of anticoagulants. However, comparative persistence was evaluated and found to be greater for DOACs than warfarin, a conclusion supported by other recent studies which also found persistence to vary between DOACs, commonly in favor of apixaban.[10,11] In addition, the hypotheses from Ozaki *et al* that 'reduced monitoring with DOACs may be linked to reduced adherence' is speculative and not supported by evidence.[9] We feel the critiques put forward for DOACs to support the development of this appraisal are not all scientifically sound.	1. Issues relating to contemporary evidence and guidelines will be evaluated in the HTA phase of the project. 2. This section will be removed from the protocol. 3. Adherence (the extent to which a patient's behaviour, with medication, aligns with the agreed recommendations from the medical practitioner [Burnier, 2006]) is planned to be evaluated for both DOACs and VKAs. Persistence (the total amount of time from medication initiation to discontinuation [Burnier, 2006]) will be added as an outcome.
2. Comments on PICO	1. We fully support the decision to consider the evidence for each DOAC individually. We are also in agreement with the proposed approach to use warfarin as a surrogate for other VKAs given the paucity of high-quality comparative evidence for acenocoumarol and phenprocoumon. However, the analysis plan in the protocol is to consider RCTs for warfarin and non-RCT for	1. The choice to use warfarin as a surrogate for VKAs has only been approved due to the absence of evidence for drugs currently used in Switzerland (i.e. phenprocoumon and acenocoumarol). Where evidence for these drugs exists, evidence for warfarin will not be reported in order to ensure the evidence is applicable to the Swiss context.

Domain	Comment	Author response
	phenprocoumon and acenocoumarol; we do not feel it is suitable to use warfarin as a surrogate VKA in RCTs, but not in non-randomized studies. 2. It is unclear from the protocol how RCTs and non-randomized studies will be incorporated into the decision making. It would not be appropriate to aggregate data where drugs considered relevant to the decision problem are sometimes included and other times excluded. Further, RWE may be subject to considerable bias, due to differences in the patient population who would be considered to receive DOACs or VKAs, so that modelling of this data is inappropriate. 3. Given the suitability of warfarin as a surrogate for VKAs, an approach supported by an analogous German appraisal,12 and the abundance of RCT evidence for warfarin, we recommend using the highest quality evidence available to inform the treatment network and economic model.	2. NRSI and RCT evidence will be reported separately in the HTA; risk of bias will be evaluated using design-specific tools; all outcomes will be evaluated using the GRADE approach, considering different levels of evidence accordingly. 3. We note and thank you for your feedback regarding the use of NRSI evidence in the economic model. The design and inputs used for the economic model will be decided during the HTA phase.
3. Comments on databases and search strategy	1. Review of the proposed search strategies has identified a few potential flaws, including that Medical Subject Heading (MeSH) terms and drug synonyms have not been included in the search strategy. 2. It is expected that the number of hits across databases will be vast, so study design filters may be employed to increase the relevance of identified studies. 3. Additionally, it is useful to note where validated search strategies have been used. 4. Given the geographic relevance, French and German HTA bodies should also be considered during grey literature searches (Table 9). 5. Given there is uncertainty on the intended approach in this appraisal, we would like to see an additional opportunity for stakeholders to provide feedback when more detail on the SLR and the approach to analysis and synthesis of evidence is ready. We believe this is in keeping with recent FOPH appraisals where protocols were more developed at the stage of stakeholder engagement.	1. MeSH headings are captured by the 'text word' field (denoted as [tw]), which has been used in the search strategy for all search terms that need to be searched as both MeSH headings and keywords. 2. Thank you for this suggestion. We sometimes use study design filters to increase the specificity of our search results. In this case we decided a filters was not suitable, given the importance of capturing all relevant NRSI. We opted instead to not use filters, to ensure the search strategy is highly sensitive to all relevant RCT and NRSI evidence. 3. Search strings undergo critical appraisal by multiple members of the project team, and the draft search results are checked against known relevant studies to ensure the searches are sensitive. It is not possible to fully validate a search string before the searches are conducted, as to do this requires full knowledge of all relevant studies on the topic, which is, of course, the purpose of running the search in the first place. 4. We will expand the table to capture HTA agencies that are members of INAHTA. 5. Stakeholders are consulted during the HTA scoping/protocol phase, but no longer during the HTA phase. This change will be re-evaluated in 2022. It is not excluded that new modification to the HTA process are required. If this implies offering the stakeholders the possibility to make a second statement, following the finalization of the HTA report, this will be communicated to the stakeholders directly.
4. Comments on data extraction,	1. There is no clear plan given on the approach to evidence synthesis and modelling. In particular it is not clear how studies will be weighted in the NMA	1. As stated in the protocol, RCT and NRSI evidence will be evaluated separately, appraised for risk of bias using design-specific tools, and

Domain	Comment	Author response
analysis and synthesis	and how the evidence base will be ranked. It is essential that RCTs and non-randomized studies be synthesized separately, with a clear assessment of bias for each; particular scrutiny should be given to non-randomized studies given they are prone to bias. In addition, it is not clear how appropriate use of treatment that reflects best clinical practice will be considered. This is of particular relevance where VKAs are concerned and has been dealt with by previous appraisals in NVAF through scrutiny of the TTR of the cohort receiving VKA; lower values not reflecting best clinical practice are deemed to severely reduce the quality of the evidence.[7] In line with the recommendations above, restricting the evidence used in the NMA to RCTs would reduce uncertainty brought on by lower quality evidence. 2. It is not made clear in the protocol how organizational issues will be assessed. If there is a potential for VKA use to rise following the advice from this appraisal, it will be important to consider the cost and organizational implications that come with it, aligned with contemporary evidence that suggests there may be an overall healthcare cost increase where DOACs are displaced for VKAs.[13] The key considerations should include the increased requirements for frequent INR monitoring, which may increase the burden upon nursing staff, establish a requirement for additional doctor visits and pose a greater burden upon patients.[14] 3. It is also unclear from the protocol exactly how final guidance will be provided. We recommend that guidance should be provided for each individual DOAC being assessed, not for the drug class as a whole, due to the unique utility of each individual DOAC within the NVAF population.	the overall findings will be evaluated separately using the GRADE approach. The appropriateness of the evidence to the Swiss context will be evaluated through the application of the ESC guidelines, and discussion with Swiss clinical experts. 2. Thank you for your suggestions regarding the evaluation of organisational issues. These will be considered during the HTA phase when organisational issues are evaluated. Auxiliary domains (e.g. social, legal, ethical and organisational) are evaluated through literature review, and discussion with clinical experts around models of service delivery. 3. As stated in the protocol, each DOAC will be investigated individually.

4. Curafutura

Domain	Comment	Author response
1. Comments on research questions	Die Forschungsfrage ist verständlich und prägnant dargestellt.	Thank you for the feedback.
2. Comments on PICO	1. C: Comparator Wegen fehlender Evidenz aus RCT's für Acenocoumarol und Phenprocoumon wird das in der Schweiz für die Studienpopulation nicht zugelassene Warfarin herangezogen, das ebenfalls zu den Coumarinen gehört. Wie ändert sich das Resultat, würde man non-RCT's in die Evaluation einbeziehen? 2. O: Outcomes Clinical outcomes: - Listen von EMA und ESC wurden gekürzt im Hinblick auf die wichtigsten, für Patienten relevanten Outcomes. Was wurde warum nicht berücksichtigt? - Ergänzen mit „Manageability", d.h. wie gut können Blutungen, wenn sie auftreten, kontrolliert werden. - Adhärenz, Studienlage dazu? These: Intensives Monitoring auf Ebene Arzt und Patient führt bei Coumarinen zu höherer Adhärenz im Vergleich zu den DOACs. 3. Health economic outcomes: - Sicherstellen, dass Aufwand für Monitoring erfasst wird.	1. This will be a key outcome of the HTA, to compare and contrast the results from RCT and NRSI evidence. 2. There are practical limitations on the production of HTA reports. Not every outcome can be included, as there are time and resource limitations that need to be considered. In designing the PICO criteria, the evaluators identify standard outcome sets (where available), and discuss the most important clinical outcomes with clinical experts. Then, the draft outcomes list are peer reviewed by a panel of independent experts selected by the FOPH, and finally stakeholders are given the opportunity to provide input into the proposed outcomes. For this topic, the outcomes were selected based on their direct relevance as clinical endpoints, usefulness for informing the final outcome of the economic evaluation (i.e. QALYs), and concordance with international guidelines and standard outcome sets (e.g. ICHOM). 3. We will take this into consideration when the methods for the health economic evaluation are further developed during the HTA phase.
3. Comments on databases and search strategy	Die Methodik der Suchstrategie ist zeitgemäss und die Kriterien klar definiert. Sie ist kohärent mit den in Appendix A hinterlegten Suchkriterien (am Beispiel PubMed).	Thank you for the feedback.
4. Comments on data extraction, analysis and synthesis	Daten aus der Schweiz: Allenfalls könnten Nebenwirkungsmeldungen bei swissmedic von Interesse oder evtl. Blutungsdatenbanken eine Informationsquelle sein.	Noted, thank you for the suggestion.

5. Daiichi Sankyo (Schweiz) AG

Domain	Comment	Author response
1. Comments on research questions	In der HTA-Analyse werden die DOACS als Einzelsubstanzen separat betrachtet, welchem die Zulassungsinhaberin zustimmt. In der Studie von Paschke et. al 2020 wurde das Schlaganfall- und Blutungsrisiko unter DOAC- vs. Phenprocoumon-Therapie in Patienten mit AF (arterial fibrillation) verglichen. Es wurde für Edoxaban und Phenprocoumon ein ähnlich hohes Schlaganfallrisiko gezeigt (0.88; 0.74–1.05). Das Blutungsrisiko war bei Edoxaban verglichen mit Phenprocoumon niedriger 0.29; 0.17–0.51). Blutungen sind einer der Gründe, warum 10-40% der AF Patienten jährlich hospitalisiert werden. Mit einem geringeren Risiko für Blutungen können Hospitalisierungen verhindert und Kosten gespart werden.	Noted.
2. Comments on PICO	No comment.	N/A
3. Comments on databases and search strategy And 4. Comments on data extraction, analysis and synthesis	Bereits 2013 wurde die Studie von Plescher et. al zur Kosteneffektivität von Dabigatran in AF Patienten im Schweizer Kontext publiziert («Cost-effectiveness of dabigatran for stroke prevention in atrial fibrillation in Switzerland»). Dabigatran wurde im Vergleich zu VKA für kosteneffektiv befunden, da die höheren Medikamentenkosten von Dabigatran durch Einsparungen wegen fehlender INR- Monitorierung kompensiert werden. Auf Basis dieser Studie kann eine simple Abschätzung der Kosteneffektivität von Lixiana durchgeführt werden. Damals beliefen sich die Tagestherapiekosten (Publikumspreis) von Dabigatran auf durchschnittlich 4.00 CHF und jene von Marcoumar auf durchschnittlich 0.21 CHF. Unter der Annahme, dass sich alle weiteren Parameter bei Edoxaban und Dabigatran ähnlich verhalten, kann man mit den heutigen Preisen von Lixiana schlussfolgern, dass dieses heute ebenfalls kosteneffektiv ist: Tagestherapiekosten Lixiana (PP, Grosspackung): 2.79 CHF Tagestherapiekosten Marcoumar (PP, Grosspackung, Dosis 2.25mg/d): 0.15 CHF/d Die 2.79 CHF/d (Lixiana) entsprechen 70% der damaligen Kosten von 4.00 CHF/d (Dabigatran). Die 0.15 CHF/d (Marcoumar heute) entsprechen 71% der 0.21 CHF/d (Marcoumar Publikation 2013).	More sophisticated methods are required for the HTA, even if a new analysis was not to be undertaken. Clinical evidence specific to edoxaban would need to be included. Recent cost utility analyses from other settings have shown differences in cost effectiveness outcomes among the DOACs (although this is not the focus of this HTA). Assumptions used in Pletscher 2013 would need to be critically assessed for relevance to today's clinical practice setting. Nonetheless, it would be an existing evaluation(s) of edoxaban that would be considered if any translations of results to today's Swiss setting were to be made. Again, these would need to be critically assessed.

Domain	Comment	Author response
	Da Verhältnisse (Lixiana heute vs. Dabigatran 2013 und Marcoumar heute vs. Marcoumar 2013) gleich sind, kann geschlussfolgert werden, dass auch Lixiana als kosteneffektiv zu betrachten ist. Dieser einfache Vergleich wirft die Frage auf, ob die vom BAG geplante HTA-Analyse im Verhälnis zu ihren Kosten sinnvoll ist. Wir danken dem BAG für den Einbezug dieser Stellungnahme in das weitere Verfahren um diese HTA- Analyse.	

6. Interpharma

Domain	Comment	Author response
1. Comments on research questions	1. This HTA appears to be triggered by controversial evidence on safety and effectiveness of DOACs vs VKAs, derived from a single non-randomized retrospective study based on insurance claims of a non-representative population in Germany (Mueller et al.). The methods utilized by Mueller et al. are unclear and do not form a solid basis for the proposed HTA. In addition, other analysis and randomized studies are not in line with the findings of Muller et al. Randomized trials investigating DOACs vs. VKAs clearly demonstrate the benefit of DOACs over VKAs. 2. It is unclear how Switzerland specific social, ethical, and organizational benefits/harms of DOACs vs VKAs will be assessed. 3. Evidence derived from other countries may not be applicable to Switzerland.	1. See response to comment ***1.1.1***. 2. See response to comment ***2.1.2***. 3. See response to comment ***2.1.3***.
2. Comments on PICO	1. All cause mortality needs to be stratified into other causes and NVAF-related death to allow differentiation between individual DOACs and VKAs, if real world evidence are included, it would be appropriate to use Swiss data. 2. Adherence concerns both DOACs and VKAs, it should be considered uniformly for both DOACs and VKAs, and need to be assessed concomitantly with persistence. 3. Direct medical cost of DOACs vs. VKAs should include cost of subsequent treatment, AE management and treatment monitoring. 4. Not all DOAC doses approved/used in Switzerland are listed. 5. How is "inadequately treated NVAF" defined and can data on relatedness to clinical outcomes be extracted from data bases? 6. The proposed method can't provide a trustworthy answer to the research question, we consider the protocol as unbalanced and biased against DOACs.	1. Swiss data will of course be used where available. Cardiovascular-related mortality will be added as an outcome. 2. See response to comment ***3.1.3***. 3. Relevant costs for the economic model and budget impact analysis will be defined during the HTA phase, and will likely include the costs recommended. 4. See response to comment ***1.2.2***. 5. See response to comment ***1.2.4***. 6. Noted as opinion; the reported methods have been developed in accordance with international guidelines on evidence synthesis and evaluation, per the Cochrane Handbook of Systematic Reviews of Interventions, and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).
3. Comments on databases and search strategy	1. In contrast to previous HTA protocols the systematic literature review (SLR) has not been performed yet. Stakeholders will not have the opportunity to comment on the SLR and included data. Valuable information/input may therefore be lost and the FOPH should make the protocol and SLR results available for stakeholder input. 2. Currently, for SL-Dossier only RCTs are accepted, therefore only RCTs should be considered for the HTA process, since this has potential consequences on the SL-listing. 3. Criteria for the selection of reviewers remain unclear (clinical, statistical/scientific expertise, publication record of reviewers)	1. See response to comment ***2.3.4***. 2. See response to comment ***2.3.1***. 3. See response to comment ***2.3.2***. 4. See response to comment ***2.3.3***. 5. See response to comment ***1.3.3***. 6. See response to comment ***1.3.2***.

Domain	Comment	Author response
	4. Exclusion criteria applicable to the selection of evidence sources for economic outcomes are unclear. 5. The protocol ignores the fact that a specific reversal agent for apixaban and rivaroxaban was approved by Swissmedic in Dec. 2020. 6. There is a discrepancy between executive summary and methods section on the number of databases to be screened (4 versus 5).	
4. Comments on data extraction, analysis and synthesis	1. It is not clear how budget impact of VKA is measured. There are no publications on the impact of the additional costs related to VKA therapy (INR etc) with real Swiss figures. How will this be calculated and how reliable will this calculation be on the true budget impact of the VKA? 2. Choice of cost effectiveness model or criteria driving selection of an existing model were not discussed. There are no Swiss specific utilities values and the source of utilities values for the cost effectiveness analysis should be addressed in the protocol. It is unclear how different sources of evidence (RCT/NRSIs) will be weighted in the NMA and how the evidence will be ranked. The protocol of NMA should be made available to stakeholders. Should the NMA include NRSIs, not only qualified NRSIs of acenocoumarol/phenprocoumon but also NRSIs on Warfarin will need to be considered. 3. Furthermore, NRSIs without adjustment for confounders should be excluded from the NMA.	1. See response to comment ***1.4.1***. 2. See response to comment ***2.4.2***. 3. All relevant NRSI that meet the PICO criteria will be included, and the risk of bias due to confounding in each publication will be evaluated using the ROBINS-I tool, and used to weight the overall strength of evidence per the GRADE approach.

7. Santésuisse

Domain	Comment	Author response
1. Comments on research questions	The research question is clearly formulated - WZW comparison DOACs to VKAs. Chapter 6 lists the individual, subsumed questions for this. They cover the aspects to be investigated.	Thank you for the feedback.
2. Comments on PICO	1. The PICO criteria listed are comprehensive and cover the question in the correct direction. We support the inclusion of warfarin as an important comparator - comparable efficacy, approval is based on studies with comparison to warfarin. 2. It is important to assess the individual DOACs on their own and not only as a group, which is already planned. 3. Outcome criteria are based on international guidelines (EMA, ESC), which is reasonable. In addition to "bleeding" as the greatest safety aspect, side effects / risk factors should also be examined as a whole (currently only listed as "discontinuation rate") in order to identify further differences between individual substances, among others.	1. Thank you for the feedback. 2. Each individual DOAC is intended to be evaluated separately, as noted in the Protocol in section 7.1.5.1 Data synthesis. 3. “Discontinuation due to adverse events” has been replaced with “serious adverse events”.
3. Comments on databases and search strategy	1. The search strategy and study selection are comprehensibly described. In addition to the five databases mentioned, a search is also made for studies that have not been completed and may still be ongoing, which is very supportable. Important reviews should also be considered if they appear after the period under consideration. 2. When searching for studies, the third national language (Italian) should be taken into account - at least for the legal, social, ethical and organisational questions.	1. Thank you for the feedback. 2. We have added Italian in as an eligible language.
4. Comments on data extraction, analysis and synthesis	1. Data extraction, their analysis, the assessment of study quality and the data synthesis as a whole are described in detail and comprehensively. Among other things, the assessment of subgroups is important here, as a certain heterogeneity in the patient population can be assumed. 2. An independent evaluation of cost-effectiveness is very welcome so that the Swiss context can be adequately taken into account. It is also envisaged that the DOACs will be assessed individually (four ICERs), which is important. 3. Under budget impact analysis, only the Tarifpool should be considered directly, as the COGE GmbH database contains the data from the Tarifpool and there is a risk of errors at the interfaces (at least differences between those two databases should be carefully analysed).	1. Thank you for the feedback. 2. Each DOAC is intended to be assessed individually. 3. Noted.

8. Schweizerische Gesellschaft für Kardiologie (SGK)

Domain	Comment	Author response
1. Comments on research questions	1. Generell ist die Fragestellung kaum notwendig, die DOACs sind etabliert &sehr gut dokument. Die Forschungsfrage basierend auf einer Publikation in einem unbekannten Journal "Pragmatic and Observational Research" im 2018 überrascht. Die Validität der Daten dieser Analyse ist grundsätzlich in Frage zu stellen. In Bezug auf die Güte der Daten ist eine Analyse basierend auf "claims datasets" wie in der zitierten Publikation die niedrigste Qualitätsstufe (Hierarchie von der besten zur niedrigsten Datengüte: RCT und Metaanalysen von RCTs > prospektives Register > Retrospektives Register > Claims database study). Die Methodik der Analyse kann dabei korrekt sein (in diesem Falle propensity score matching), jedoch können systematische Unterschiede in der Patienten Population, welche unbekannt sind (unknown confounders) nicht eliminiert werden. 2. Als doch sehr erstaunliche Limitation der DOAC ist das fehlende Antidot bei den Xa-Hemmern erwähnt. Dies ist heute nicht mehr korrekt (Andexanet Alfa).	1. Thank you for this feedback. The issues surrounding differences in methodological quality of RCTs compared to NRSI will be considered during the evaluation. 2. See response to comment ***3.1.2***.
2. Comments on PICO	Es darf Skepsis geäussert werden, ob der CH HTA verlässliche und nützliche Zusatzinformationen zur vorhandenen Evidenz liefern kann: Umfassende Vorarbeit (BMJ http://dx.doi.org/10.1136/bmj.j5058) mit einer NMA mit >94'000 Patienten ist geleistet. Sie zeigt, dass die DOAC vgl. mit Warfarin das Schlaganfallrisiko/Mortalität reduzieren, sicherer sind als Warfarin und wahrscheinlich kosteneffektiv sind (basierend auf den knappen britischen Verhältnissen (NICE) mit willingness to pay von £20'000 - 30'000). Darauf basierend entschied auch NICE im April 2021. Vgl hämor. stroke cost!(https://www.nice.org.uk/guidance/ng196/evidence/g1-anticoagulant-therapy-for-stroke-prevention-in-people-with-atrial-fibrillation-pdf-9081923442; siehe 1.5.2), dass eine zusätzliche NICE Review mit niedriger Wahrscheinlichkeit Zusatzinformation zum BMJ paper bringen würde. Da CH Kostendaten trotzdem interessant wären, wäre ein limitierter Approach mit Fokus auf CH Kosten sinnvoll (CAVE: DOAC Patente laufen aus!) Da unter Punkt 2 nicht genügend Platz hier noch ein Kommentar zum PICO Bzgl. C: S.14: Es müsste Warfarin genommen werden (mit Acenocoumarol/Phenprocoumon nicht genügend Daten) Punkt O:	Noted. The HTA will aim to include existing reviews where possible, which may include the NICE review (we say “may” as study inclusion decisions are made after the systematic searches are conducted”). The key difference between the NICE review and the planned HTA is the inclusion of NRSI evidence to inform the real-world effectiveness of DOACs compared to VKAs. Stroke, bleeding and mortality are all included in the analysis. None of the outcomes are defined as primary endpoints, the order is coincidental, and does not represent the priority of the outcomes under investigation.

Domain	Comment	Author response
	Eine Antikoagulation bei Vorhofflimmern wird verordnet, um strokes (und dessen Folgen Lähmungen und kognitiver Abbau) zu verhindern. Dies sollte der primäre Efficacy endpoint sein im Vgl. zu VKA. Die Therapie sollte sicher sein, deshalb sollten major bleedings (mit den Komponenten ICB, kritische Blutungen, GI Blutungen) der primäre safety endpoint sein. Mortality ist bei der Therapie als Endpunkt auch zu analysieren, sollte jedoch nicht an oberster Stelle stehen (wie in der Table 3, S. 12 und in 7.1.4, S. 15)	
3. Comments on databases and search strategy	Die Datenbanken und Suchstrategien scheinen adäquat. Da eine Vielzahl von RCTs und Metaanalysen verfügbar sind, erscheint uns die Inklusion von NRSI nicht gerechtfertigt (wenn auch methodisch korrekt, dass erwähnt wird, dass diese einbezogen würden, falls keine NMA oder Metaanalysen von RCTs verfügbar). Generelle Bemerkungen zur Analyse: Aktuell gibt es die über die Jahre extrem gut dokumentierte, etablierte und akzeptierte DOAC Therapie. Eine Rückkehr zu den VKA ist angesichts der Datenlage, der Patienten- und ärztlichen Präferenz und -Akzeptanz, dem internationalen Standing sowie den div Kosten-und Nutzenanalysen in der Literatur undenkbar. Dazu zeigen sich schwer erklärbare Lücken (Verfügbarkeit und Bedeutung von Antagonisten). Deshalb stellt sich generell die Sinnfrage der aufwendigen Analyse.	The purpose of including NRSI is to evaluate differences between the trial-based efficacy and real-world effectiveness of DOACs compared to VKAs. We acknowledge there are methodological considerations around the use of NRSI, particularly around the possibility of confounding; these issues are evaluated through appraisal with NRSI-specific risk of bias tools, and are weighted in the overall findings using the GRADE approach.
4. Comments on data extraction, analysis and synthesis	Die Datenextraktion, Analyse udn Synthese erscheinen grundsätzlich korrekt.	Thank you for the feedback.

9. Schweizerische Hirnschlaggesellschaft (SHG)

Domain	Comment	Author response
1. Comments on research questions	1. We emphasize on the necessity of a specific subgroup analysis of patients with a history of stroke as outlined in 7.1.5.4. The risk/benefit and health economic outcomes may differ in this particularly vulnerable group with increased risk of intracranial haemorrhage (DOACs are known to particularly reduce the risk of intracranial haemorrhage compared to VKA) as well as increased risk of stroke recurrence and morbidity. 2. We also suggest to perform a specific subgroup analysis of patients with "silent/covert" strokes (i.e. vascular brain lesions visible on CT or MRI which did not manifest with a clinical event). This also has implications concerning neuro-cognitive outcomes and the burden of vascular dementia. 3. Page 13: The specific reversal agent Andexanet alfa is approved for reversal of rivaroxaban and apixaban	1. Thank you for the feedback, we acknowledge the importance of this subgroup, and note that it has already been listed as a subgroup for the clinical evaluation. 2. Sub-clinical events are not typically included as outcomes in HTA evaluations, as they are surrogate markers for patient-relevant outcomes such as health-related quality of life, or symptomatic stroke; it is more difficult to ascribe utility to surrogate end points, and their clinical relevance is more difficult to interpret. 3. See response to comment ***3.1.2***.
2. Comments on PICO	The PICO is clear and well defined. As mentioned above we would include (vascular) dementia/ cognitive impairment as a very important outcome variable.	Thank you for the feedback and suggestion. Cognitive impairment will be added to the list of outcomes as it is in line with recommendations from the International Consortium for Health Outcomes Measurements (ICHOM).
3. Comments on databases and search strategy	Data search and extraction strategy seems valid and adequate. No specific comment.	Thank you for the feedback.
4. Comments on data extraction, analysis and synthesis	We would like to refer to our initial comment on subgroup analysis for patients with a history of stroke/TIA and those with silent stroke. Moreover we would suggest including (vascular) dementia/ cognitive impairment as a very important outcome variable with potential impact on the overall vascular health burden.	See response to comment ***9.1.1***.

10. Schweizerische Neurologische Gesellschaft (SNG)

Domain	Comment	Author response
1. Comments on research questions	1. We emphasize on the necessity of a specific subgroup analysis of patients with a history of stroke as outlined in 7.1.5.4. The risk/benefit and health economic outcomes may differ in this particularly vulnerable group with increased risk of intracranial haemorrhage (DOACs are known to particularly reduce the risk of intracranial haemorrhage compared to VKA). 2. We also suggest to perform a specific subgroup analysis of patients with "silent/covert" strokes (i.e. vasular brain lesions visible on CT or MRI which did not manifest with a clinical event). 3. Page 13: The specific reversal agent Andexanet alfa is approved for reversal of rivaroxaban and apixaban	1. See response to comment ***9.1.1***. 2. See response to comment ***9.1.2***. 3. See response to comment ***3.1.2***.
2. Comments on PICO	The PICO is clear and well defined. No specific comments.	Thank you for the feedback.
3. Comments on databases and search strategy	Data search and extraction strategy seems valid and adequate. No specific comment.	Thank you for the feedback.
4. Comments on data extraction, analysis and synthesis	We would like to refer to our initial comment on subgroup analysis for patients with a history of stroke and those with silent stroke.	See response to comments ***9.1.1*** and ***9.1.2***.