Health Technology Assessment (HTA)

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

Preface

This document details the authors' responses to stakeholder feedback to the HTA report on oral 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.

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1. Alliance Bristol Myers Squibb and Pfizer

Domain	Comment	Author response
General comment on the HTA report:	1. The BMS and Pfizer team agree with the general outcomes of the assessment that DOACs are clinically effective and cost saving versus VKAs, which is aligned with analyses conducted in other countries. Although guidance is not issued for each DOAC individually, apixaban provides the most favourable cost-effectiveness outcomes. 2. However, BMS and Pfizer note that all DOACs are developed to prevent stroke and SE, as opposed to all-cause mortality. Therefore, emphasis should be put on those endpoints rather than all-cause mortality, which is not within the DOAC label and is subject to bias due to mortality resulting from other diseases too. 3. a. The HTA report includes non-approved doses for DOACs, including apixaban 2.5mg, edoxaban 30mg and dabigatran 110mg, which are not relevant to clinical practice in Switzerland and should be removed from the HTA report. b. The gastrointestinal (GI) bleeding analysis did not consider dabigatran and rivaroxaban 20mg.	1. Acknowledged 2. Agreed. The HTA reported SE and bleeding events as critical outcomes, not all-cause mortality. However, all-cause mortality is always needs to be assessed when reviewing mediations. No changes have been made to the report. 3. a. Apixaban 2.5 mg, Edoxaban 30 mg, and Dabigatran 110 mg, are listed on *SwissMedic* for the treatment of NVAF. Similarly, all medications and dosages are listed on the on the *Spezialitatenliste*. Amendments have been made to ***Table 10*** (***Section 7.2.5***) to clarify the different circumstance that aforementioned DOACs and dosages are used to treat NVAF. b. Amended, Dabigatran (110 mg and 150 mg) and Rivaroxaban 20 mg have been added GI bleeding.
Commentary on Efficacy, Effectiveness and Safety	1. The outcomes for apixaban on stroke and SE don't align with those observed from other relevant NMAs, incl. the NICE 2021 update, where evidence frequently favoured apixaban over other DOACs. It is incorrect to state that across all DOACs there was no difference in all stroke and SE compared to warfarin. 2. Notably, ARISTOTLE-J is included within the comparison, despite low patient numbers and limited relevance to Swiss setting. The heterogeneity (I2 = 40%) between Aristotle and Aristotle-J was moderate, while the power for heterogeneity test was low and p-value wasn't statistically significant. Given the small study size, few events in a small study such as ARISTOTLE-J can easily have a large impact. Hence, we disagree to combine ARISTOTLE-J with ARISTOTLE using a random effect model. A fixed effect model would increase the certainty of outcomes.	1. Drawing comparisons between DOACs was outside the scope of this HTA. This HTA focused on comparing individual DOACs to VKAs. The different findings between this HTA and the NICE 2021 update are due to the methodologies. This HTA used pairwise meta-analyses to compare individual DOACs to VKAs, whereas the NICE 2021 update used network meta-analyses (NMA) to compare DOACs to each other and VKAs. 2. Acknowledged. A random-effects model was used to account for variations between the two trials. For example, in the ARISTOTLE-J trial, the control-arm was open-label, and all trial centres were located in Japan exclusively. Whereas, in the ARISTOTLE trial both arms were double-blind, and the trials centres were located across 42 countries. 3. Amending

	3. Relevant observational studies (NAXOS, ARISTOPHANES, CARBOS E+ studies) haven't been included within the comparison, despite large sample size.	a. Acknowledged. NAXOS was excluded due to an incorrect comparator. The NRSI trial was conducted in France and the most popular VKA in France is fluindione. b. Acknowledged. ARISTOPHANES was excluded due to an incorrect comparator. The VKA used was warfarin. c. Amended. Hohnloser et al. 2018 (CARBOS E+ trial) has been added to the HTA report.
Commentary on health economic evaluation and budget impact analysis	1. It is acknowledged that DOAC use is likely to increase in the future. However, there is no rationale supporting an annual growth rate of 6% for patients receiving DOACs. Furthermore, some of the DOACs are close to patent-expiry which will result in a significant price decrease. It is unclear if and how payer costs for DOACs will increase. 2. Further, it is anticipated that the cost-effectiveness model is conservative, as the model does not consider the cost for managing the increased clinical events associated with VKA use. Additionally, it needs to be stated that the budget impact model approach chosen is not taking these full costs into account. Therefore, the conclusions from this analysis need to be interpreted with caution.	1. The assumed growth rate was based upon trends observed in IQVIA survey data over the period April 2019 to March 2022. An alternate rate of 0.8%, based on growth in the relative use of DOACs between the years Apr2020–Mar2021 and Apr2021–Mar2022 (again, as observed in IQVIA survey data), was used in sensitivity analysis. Adjustments have been made to ***Table 50*** in the HTA Report to ensure the source of the 6% rate is clear. Regarding the potential decrease in drug costs after patent expiry, a sensitivity analysis assuming a reduced unit cost for all DOACs (-20%) was included. 2. Acknowledged. A sentence stating that the model is conservative has been added into the limitation's discussion (***Section 11.3***). Regarding the BIA, it was limited to an exploration of the potential treatment costs of OACs under current policy conditions given there was no justification to model the potential financial implications of any policy changes. Again, a sentence has been added into the limitation's discussion (***Section 11.3***).

Commentary on ethical, social, legal and organizational aspects	1. The HTA report acknowledges no evidence to support adherence issues for DOACs but suggests that this is due to a lack of data, suggesting a challenge with how treatment effectiveness is monitored in practice. However, the report does not acknowledge evidence that VKAs are also associated with adherence issues which can severely impact the time in therapeutic range (TTR) and therefore the efficacy of therapy. Further, where adherence and persistence has been considered in comparison with VKAs, DOACs show improved adherence and increased persistence, particularly for apixaban. 2. The HTA report acknowledges the impact of INR monitoring costs, but not the burden on clinicians and patients. Further, the cost and time impact of reintroducing clinics to administer and monitor widespread VKA use are not assessed in the report.	1. Acknowledged. Social and organisational issues relating to INR monitoring are discussed in ***Section 9.*** 2. Acknowledged. Social and organisational issues relating to INR monitoring are discussed in ***Section 9.***
Commentary on the discussion and conclusions	1. The ARISTOTLE study was criticised in the HTA report as being at high risk of bias, and therefore low evidence, due to poor reporting of randomisation procedures. However, the protocol for ARISTOTLE is available as an appendix to Granger et al. clearly stating it will be double-dummy designed study with IVRS assigning each subject to one of the two treatment arms at time of randomisation and with the Randomization Center at BMS having access to the treatment allocation only. Further, the publication for ARISTOTLE was named in Drazen 2019. 2. NRSI results are reliant on two German studies. Ujeyl et al. used a larger database (30% vs 12.5% of population) and therefore analysed more patients but used data for 2010 to 2014, whereas Warkentin used data from 2014-2019. It is unclear whether only NVAF patients or a broader population were included in the Warkentin study. Exclusion of Warkentin from consideration could change results in favour of DOACs.	1. This HTA reported and referenced the risk of bias (RoB) assessment published in the NICE 2021 network meta-analysis. A *de novo* RoB was not conducted by the authors of this HTA. However, the ARISTOTLE trial has appropriately been assigned a high risk of selection bias, as it does not report the randomisation procedure used to allocate patients in sufficient detail. 2. Acknowledged. The population included in Warkentin et al. 2022 meets the NVAF population detailed in ***Section 5.1*** of the HTA report.

2. Bayer (Schweiz)

Domain	Comment	Author response
General comment on the HTA report:	1. Bayer ist im Allgemeinen mit dem HTA Report einverstanden und begrüsst, dass wissenschaftliche Limitationen klar beschrieben und respektiert wurden, insbesondere was den «indirekten Vergleich» der DOAKs angeht. 2. Die Liste der NRSI erscheint sehr kurz, Im Kontext zu den von Ihnen erwähnten Limitationen geht das aber so in Ordnung. 1. Bayer generally agrees with the HTA report and appreciates that scientific limitations have been clearly described and respected, especially with regard to the "indirect comparison" of the DOAKs. 2. The list of NRSIs seems very short, but in the context of the limitations you mentioned, that's fine.	1. Acknowledged 2. Acknowledged
Commentary on Efficacy, Effectiveness and Safety	1. Bayer teilt die Meinung der Autoren, dass die RCT-Daten einen signifikanten Nutzen der DOAKs vs. VKA zeigen, während die Interpretation der t.w. widersprüchlichen NRSI-Daten nicht konklusiv ist. Insbesondere nimmt Bayer auch die konsistent gute Beurteilung der «certainty of evidence» der Daten aus der ROCKET Studie zur Kenntnis, die bestätigt, dass der Einsatz von Rivaroxaban bei Patienten mit NVAF auf sehr solider Evidenz beruht. 2. Einige kleine Punkte im Report könnten noch korrigiert werden: - Seite 9 unter 5.1: The term valvular NVAF is generally used to differentiate patients. Am Anfang des Satzes sollte es heissen: The term NVAF is generally used… («valvular» löschen) - Seite 9 unter 5.2: apixaban 2.5–5 mg twice daily, dabigatran 110 mg or 150 mg twice daily… Aus Konsistenzgründen sollte es heissen: apixaban 2.5 mg or 5 mg twice daily («or» statt «– » wie bei allen anderen DOAKs in der Aufzählung) - Seite 46 letzter Bullet: Rivaroxaban 30 mg once daily… Korrekt wäre: 20 mg. 1. Bayer shares the authors' opinion that the RCT data show a significant benefit of the DOACs vs. VKA, while the interpretation of the t.w. conflicting NRSI data is not conclusive. In particular, Bayer also notes the consistently good assessment of the "certainty of evidence" of the	1. Acknowledged 2. a. Accepted, 'valvular' has been removed. b. Accepted, '—' has been replaced with 'or' c. Accepted '30 mg' has been replaced with '20 mg'

Domain	Comment	Author response
	data from the ROCKET study, which confirms that the use of rivaroxaban in patients with NVAF is based on very solid evidence. 2. A few small points in the report could still be corrected: a. Page 9 under 5.1: The term valvular NVAF is generally used to differentiate patients. At the beginning of the sentence it should read: The term NVAF is generally used… (delete «valvular») b. Page 9 under 5.2: apixaban 2.5–5 mg twice daily, dabigatran 110 mg or 150 mg twice daily… For reasons of consistency, it should read: apixaban 2.5 mg or 5 mg twice daily ("or" instead of "–" as with all other DOACs in the list) c. Page 46 last bullet: Rivaroxaban 30 mg once daily… Correct would be: 20 mg.	
Commentary on health economic evaluation and budget impact analysis	1. Bayer stimmt der auf den Schweizer Kontext bezogenen RCT-basierten Analyse zu, welche – in-line mit anderen HTA Analysen (z.B. NICE) – alle vier DOAKs gegenüber VKA besonders aufgrund des Mortalitäts-Benefits und der wegfallenden Monitoring-Kosten als kosten-sparend beurteilt. 2. Kleine Korrektur auf Seite 118 (unterste Zeile): of dabigatran) across… Sollte heissen: of rivaroxaban) across… 1. Bayer agrees with the RCT-based analysis related to the Swiss context, which - in-line with other HTA analyzes (e.g. NICE) - considers all four DOACs to be cost-effective compared to VKA, particularly due to the mortality benefit and the elimination of monitoring costs. judged sparingly. 2. Small correction on page 118 (bottom line): of dabigatran) across… Should read: of rivaroxaban) across…	1. Acknowledged 2. Accepted, 'dabigatran' has been replaced by 'rivaroxaban'
Commentary on ethical, social, legal and organizational aspects	Bayer nimmt die in diesem Abschnitt beschriebenen Analysen zustimmend zur Kenntnis und hat keine weiteren Kommentare dazu. Bayer acknowledges and has no further comments on the analyzes described in this section.	Acknowledged

Domain	Comment	Author response
Commentary on the discussion and conclusions	1. Bayer ist ebenfalls nicht überrascht über die Konsistenz der Schlussfolgerungen dieses HTA, des NICE-Reports sowie zahlreichen anderen Assessments basierend auf den NOAK-RCTs. 2. Da der Report mit der «Policy Question» beginnt könnte die Antwort auf diese ans Ende der Conclusion auf Seite 140 geschrieben werden (statt aktuell auf Seite 129): The clinical and economic evidence presented in this HTA did not provide justifications to model the financial implications of any policy changes (i.e. restriction of disinvestment from DOACs). 1. Bayer is also not surprised at the consistency of the conclusions of this HTA, the NICE report, and numerous other assessments based on the NOAK RCTs. 2. Since the report begins with the "Policy Question", the answer to this could be written at the end of the Conclusion on page 140 (instead of currently on page 129): The clinical and economic evidence presented in this HTA did not provide justifications to model the financial implications of any policy changes (i.e. restriction of disinvestment from DOACs).	1. Acknowledged 2. Amended. Sentence added in Conclusion (***Section 12***), and in the conclusion of the Executive Summary.

3. Curafutura (Sanitas Krankenversicherung AG)

Domain	Comment	Author response
General comment on the HTA report:	1. Die in Frage kommenden Wirkstoffe wurden einzeln evaluiert, trotz gleicher Wirkstoffklasse, was auch kleine Unterschiede v.a. im Risikoprofil aufzeigt. Der Komparator Warfarin wurde v.a. bei RCTs herangezogen, obwohl dieser in der CH nicht eingesetzt wird - er ist jedoch weltweit der am meisten eingesetzte VKA. VKAs untereinander sind jedoch vergleichbar, eine Verallgemeinerung ist daher ok. Die Aussagen aus diesem Bericht können daher für die Schweiz als gültig betrachtet werden. 2. Es wurde eine sehr gründliche und aufwendige Literaturrecherche betrieben. Das methodische Vorgehen wird detailliert beschrieben, es wurden 9 RCTs angeschaut, nur für den spez. Vergleich mit Phenprocoumon/Acenocoumarol wurden 9 weitere NRSIs herangezogen (mit Vorbehalt aufgrund möglicher Bias). 1. The active ingredients in question were evaluated individually, despite the same class of active ingredient, which also shows small differences, especially in the risk profile. The comparator warfarin was mainly used in RCTs, although it is not used in Switzerland - it is the most used VKA worldwide. However, VKAs are comparable with each other, so a generalization is ok. The statements from this report can therefore be regarded as valid for Switzerland. 2. A very thorough and extensive literature search was carried out. The methodological procedure is described in detail, 9 RCTs were looked at, only for the spec. A comparison with phenprocoumon/acenocoumarol included 9 other NRSIs (with reservations due to possible bias).	1. Acknowledged 2. Acknowledged
Commentary on Efficacy, Effectiveness and Safety	1. Es wurden die korrekten Endpunkte sowie die bekannten und relevanten Adverse Events untersucht. 2. Der Unterschied der Resultate bezüglich Mortalität bei den NRSIs je nach Studienendpunkt (HR oder RR) müsste klar genauer untersucht werden, ansonsten ist keine eindeutige Aussage möglich. Aus diesem Grund wurde auch kein Unterschied bei den Schlaganfällen und dem Embolie-Risiko ausgewiesen. 3. Trotz Klasseneffekt bei den DOACs nur für Endoxaban eine Reduktion der GI-Blutungen gefunden, somit sollte dieser WS wohl als der Sicherste gelten.	1. Acknowledged 2. Acknowledged 3. Acknowledged

	1. The correct endpoints as well as the known and relevant adverse events were examined. 2. The difference in the results regarding mortality in the NRSIs depending on the study endpoint (HR or RR) would have to be examined more closely, otherwise no clear statement is possible. For this reason, no difference was reported in terms of stroke and embolism risk. 3. Despite the class effect in the DOACs, a reduction in GI bleeding was only found for endoxaban, so this WS should probably be considered the safest.	
Commentary on health economic evaluation and budget impact analysis	Der Budget-Impact wird auf Grund der Zunahme der Bevölkerung und der Alterung zunehmen. Der überproportionale Anstieg der DOACs wird abgefedert durch die Abnahme der Monitoring-Kosten sowie Kosten für VKAs. --- The budget impact will increase due to population growth and aging. The disproportionate increase in DOACs is cushioned by the decrease in monitoring costs and costs for VKAs.	Acknowledged.
Commentary on ethical, social, legal and organizational aspects	1. Die ethischen Aspekte der DOAKs sind grundsätzliche Fragestellungen, die sich bei jeder medikamentösen Therapie stellen. Diese werden durch die Zulassungen (& klinischen Studien) beantwortet, welche nur Wirkstoffe mit positivem Nutzen-Risiko-Profil zur Verwendung zulassen. 2. einverstanden mit den gemachten Schlussfolgerungen. allenfalls wäre es sinnvoll, die DOACs untereinander in RCTs zu vergleichen, da hier uneinheitliche Ergebnisse vorliegen. Dies würde eine individuellere Nutzen-Risiko-Abwägung erlauben --- 1. The ethical aspects of DOACs are fundamental questions that arise with any drug therapy. These are answered by the approvals (& clinical studies), which only allow active ingredients with a positive benefit-risk profile to be used. 2. agree with the conclusions made. at best, it would make sense to compare the DOACs with each other in RCTs, since the results are inconsistent here. This would allow a more individual benefit-risk assessment	1. Acknowledged 2. Acknowledged. Between DOAC comparisons was outside the scope of this HTA.
Commentary on the discussion and conclusions	NR	NA

4. Daiichi Sankyo (Schweiz) AG

Domain	Comment	Author response
General comment on the HTA report:	Im Namen von Daiichi Sankyo (Schweiz) AG, Zulassungsinhaberin von Lixiana (Edoxaban), danken wir dem BAG für die Analyse und die Möglichkeit der Stellungnahme. On behalf of Daiichi Sankyo (Switzerland) AG, authorization holder of Lixiana (edoxaban), we would like to thank the FOPH for the analysis and the opportunity to comment.	Acknowledged
Commentary on Efficacy, Effectiveness and Safety	Nichts hinzuzufügen. Nothing to add.	NA
Commentary on health economic evaluation and budget impact analysis	Nichts hinzuzufügen. Nothing to add.	NA
Commentary on ethical, social, legal and organizational aspects	Nichts hinzuzufügen. Nothing to add.	NA
Commentary on the discussion and conclusions	Die Ergebnisse dieser HTA-Analyse unterstützten die Tatsache, dass Edoxaban seine WZW-Kriterien im Rahmen seiner Indikation und SL-Limitation nach wie vor vollumfänglich erfüllt. The results of this HTA analysis supported the fact that edoxaban still fully meets its WZW criteria within its indication and SL limitation.	Acknowledged

5. MEDA Pharma GmbH

Domain	Comment	Author response
General comment on the HTA report:	Wir danken Ihnen, dass wir als Zusassungsinhaberin die Gelegenheit zur Stellungnahme zum vorliegenden HTA-Bericht erhalten. Thank you for giving us, as the authorization holder, the opportunity to comment on this HTA report.	Acknowledged.
Commentary on Efficacy, Effectiveness and Safety	Interessant etwa die minimen Unterschiede betreffend kardiovaskulär bedingter Mortalität (RCT): Studie ARISTOTLE: 308 (DOAC) vs. 344 (VKA) Studie RE-LY: 289 (DOAC) vs. (317 (VKA) Studie ENGAGE: 527 (DOAC) vs. 611 (VKA) Studie ROCKET: 170 (DOAC) vs. 193 (VKA) (NRSI): Korenstra et al.: 0 (DOAC) vs. 4 (VKA) Sämtliche Untersuchungen zeigen diese nahe beieinanderliegenden Resultate zwischen DOAC und VKA, meist leicht favorabel zugunsten DOACs. Aber z.B. gastrointestinal bleeding in der Studie ENGAGE: 232 (DOAC) vs. 190 (VKA). Methodologisch ist insbesondere zu bemängeln, dass eine ausführliche Diskussion der klinischen Evidenz schlicht nicht durchgeführt wurde. Immerhin wurde im Executive Summary konstatiert, dass grossmehrheitlich keine einheitlichen Differenzen zwischen DOAC- und VKA-Therapiekonsequenzen existieren. Interesting, for example, are the minimal differences in cardiovascular mortality (RCT): Study ARISTOTLE: 308 (DOAC) vs. 344 (VKA) Study RE-LY: 289 (DOAC) vs. (317 (VKA) Study ENGAGE: 527 (DOAC) vs. 611 (VKA) Study ROCKET: 170 (DOAC) vs. 193 (VKA)	The clinical evidence was identified, analysed, and synthesised using a rigorous and transparent methodology. All evidence was examined and discussed in sufficient detail.

Domain	Comment	Author response
	(NRSI): Korenstra et al.: 0 (DOAC) vs. 4 (VKA) All investigations show these closely related results between DOAC and VKA, mostly slightly favorable in favor of DOACs. But e.g. gastrointestinal bleeding in the study ENGAGE: 232 (DOAC) vs. 190 (VKA). From a methodological point of view, it is particularly to be criticized that a detailed discussion of the clinical evidence was simply not carried out. Nevertheless, it was stated in the executive summary that the majority of the time there are no uniform differences between DOAC and VKA therapy consequences.	
Commentary on health economic evaluation and budget impact analysis	1. Die Analyse wurde teilweise mit konkreten Schweiz spezifischen Daten durchgeführt. Allerdings wurde mit sehr vielen, nicht verifizierten Annahmen gearbeitet. 2. Auch die Kosten des Monitorings wurden gar rudimentär dargestellt. So sind die meistens polymorbiden Patienten nicht spezifisch für den INR-Test in ärztlicher Behandlung. 3. Eine eigentliche Unterlassung ist das nicht nähere Erläutern zukünftiger Test-Formen: 4. "At-home INR self-testing could potentially reduce the cost and the intensity of clinician involvement in VKA therapy, but it is unclear how effective these tests are, how much they cost, or how widely available they are in Switzerland; therefore, they were not included in the economic evaluation." 5. Ohne solche Erhebung ist ein wesentlicher Teil der ökonomischen Analyse wertlos, und wollte man am aktuellen Vergütungs-Setting etwas ändern, müssten die Untersuchtung alternativer Testformen und die damit verbundenen (geringeren) Kosten evaluiert werden. 1. The analysis was partially carried out with concrete Switzerland-specific data. However, a large number of unverified assumptions were used.	1. Acknowledged. A summary of model assumptions, including commentary on the rationale behind each assumption, is provided in ***Table 119***, ***Appendix D***. It is difficult to respond to this comment in more detail given the 'unverified assumptions' referred to have not been specified. 2. Acknowledged. All economic models are simplifications of reality. We attempted to model INR monitoring costs for an average anticoagulated patient with NVAF. 3. Acknowledged. At home INR self-testing was briefly mentioned in ***Section 8.2.5.3.2.1*** and was further discussion in the organisation issues section (see ***Section 9.2.3.3***). 4. A further sentence has been added to the limitation's discussion (***Section 11.3***). 5. Acknowledged. Given uncertainty in how effective or how widely available these tests are they were not modelled. Nevertheless, scenario analyses on VKA monitoring costs were undertaken, including a scenario where the monitoring costs for patients on VKA were set equal to those for patients on DOAC.

Domain	Comment	Author response
	2. The costs of monitoring were also presented in a rudimentary way. Thus, the mostly polymorbid patients are not specific for the INR test in medical treatment. 3. An actual omission is not explaining future test forms in more detail: 4. "At-home INR self-testing could potentially reduce the cost and the intensity of clinician involvement in VKA therapy, but it is unclear how effective these tests are, how much they cost, or how widely available they are in Switzerland; therefore , they were not included in the economic evaluation." 5. Without such a survey, an essential part of the economic analysis is worthless, and if one wanted to change something in the current remuneration setting, the investigation of alternative test forms and the associated (lower) costs would have to be evaluated.	
Commentary on ethical, social, legal and organizational aspects	1. Das HTA zeigt hierzu keine kritischen "Findings". 2. Erwähnenswert folgende Conclusiones: 3. "Based on the lack of adherence and persistence data from NRSIs, there is a fundamental issue of how treatment effectiveness of DOACs is monitored in practice." 4. In relation to organisational impacts on practice, DOACs have fewer monitoring requirements compared to VKAs, which require INR testing approximately every 20 days. At-home INR testing could potentially reduce the cost and the intensity of clinician involvement in VKA therapy, but it is unclear how effective these tests are, how much they cost, or how available they are in Switzerland." 5. Es ist erstaunlich, dass die für das Schweizer Gesundheitswesen interessierenden Fragen nicht näher untersucht wurden, wohingegen die zusammengestellten Findings aus RCTs und NRSIs common global medical knowledge darstellen und keiner eingehenden Untersuchung bedurft hätten. --- 1. The HTA does not show any critical "findings". 2. The following conclusions are worth mentioning: a. "Based on the lack of adherence and persistence data from NRSIs, there is a fundamental issue of how treatment effectiveness of DOACs is monitored in practice." b. “In relation to organizational impacts on practice, DOACs have fewer monitoring requirements compared to VKAs, which require INR testing approximately every 20 days. At-home INR	1. Acknowledged. 2. Acknowledged. All RCT and NRSI evidence was limited to WHO mortality stratum A countries to ensure that the evidence was applicable the Swiss healthcare context. Furthermore, the HTA report followed the FOPH template.

Domain	Comment	Author response
	testing could potentially reduce the cost and the intensity of clinician involvement in VKA therapy, but it is unclear how effective these tests are, how much they cost, or how available they are in Switzerland." It is astonishing that the issues of interest to the Swiss healthcare system were not examined in more detail, whereas the findings compiled from RCTs and NRSIs represent common global medical knowledge and would not have required an in-depth investigation.	
Commentary on the discussion and conclusions	1. Viele Patienten die eine Phenprocoumon erhalten sind mit dieser Therapie gut eingestellt sind. 2. Die genaue Betrachtung der RCT- und der NRSI-Evidenz offenbart ein heterogenes Bild. 3. In einigen Untersuchungen offenbaren DOACs bessere Werte in anderen VKAs. Vielfach sind die Unterschiede minim. 4. Daher erachten wir es als wichtig, im Einzelfall den verschreibenden Ärzten bzw. den Patienten die Therapiewahl offenzulassen. 5. Bemerkenswert ist der Gehalt der Arbeit. Untersucht wurde - Sie gestatten diesen Kommentar - was medizinisch letztlich längst unbestritten war, wohingegen die konkreten relevanten Kostenfolgeanalysen im Schweizer System nicht näher untersucht worden sind. 6. Wir sehen uns als wichtiger Partner in der Antikoagulationstherapie und es ist uns wichtig die Versorgungssicherheit der Patienten zu gewährleisten. 7. Eine zusätzliche Preissenkung nach der vergangenen per 1.12.2021 (-12.568%) könnte unsere Existenz im Schweizer Markt gefährden. --- 1. Many patients receiving phenprocoumon are well controlled with this therapy. 2. A closer look at the RCT and NRSI evidence reveals a heterogeneous picture. 3. In some studies, DOACs reveal better values in other VKAs. The differences are often minimal. 4. We therefore consider it important to leave the choice of therapy open to the prescribing physicians or patients in individual cases. 5. The salary of the work is remarkable. What was examined - if you allow this comment - was ultimately medically undisputed for a long time,	1. Acknowledged. 2. Acknowledged. Heterogeneity was considered when interpreting the results. 3. Acknowledged. 4. Acknowledged. 5. The HTA was commissioned to determine if the potential increased effectiveness of DOACs offset the potential increased cost, when compared to VKA. The question was asked due to the results of a German observational study. The HTA does not just considered clinical outcomes (i.e. effectiveness and safety) but also economic outcomes. 6. Acknowledged. 7. Acknowledged.

Domain	Comment	Author response
	whereas the concrete relevant cost analysis in the Swiss system was not examined in more detail. 6. We see ourselves as an important partner in anticoagulant therapy and it is important to us to ensure the security of care for patients. 7. An additional price reduction after the previous one on December 1, 2021 (-12,568%) could endanger our existence in the Swiss market.	

6. Santésuisse

Domain	Comment	Author response
General comment on the HTA report:	The HTA report is very detailed and well structured. Methodology, results and discussion with conclusions are presented in a comprehensible way.	Acknowledged
Commentary on Efficacy, Effectiveness and Safety	In addition to randomised controlled trials (RCTs), NRSIs were also included and reviewed. The NRSI included are retrospective cohort studies with data from registries or clinical systems. Although these studies have a high to critical risk of bias, they provide an interesting insight into the use of medicines in everyday life, which may differ in terms of the closely defined patient population in the clinical trials. We therefore welcome the fact that these studies and the corresponding results were also addressed in the HTA report and compared with the RCTs.	Acknowledged
Commentary on health economic evaluation and budget impact analysis	The health economic evaluation and budget impact analysis can be reproduced. The results are plausible. santésuisse has no further comments.	Acknowledged
Commentary on ethical, social, legal and organizational aspects	1. From santésuisse's point of view, the relevant ethical, social, legal and organisational aspects are addressed. 2. In Chapter 10 (Additional issues), information on guidelines and on unpublished or ongoing studies is also presented. We consider this summery important and welcome it very much.	Acknowledged
Commentary on the discussion and conclusions	The discussion and conclusions are brief, but clear and comprehensible. In particular, the limitations addressed therein with regard to the evaluation in the areas of effectiveness and cost-effectiveness are well presented. We can follow the conclusions reached on the basis of the information presented here.	Acknowledged

7. Schweizerische Gesellschaft für Allgemeine Innere Medizin (SGAIM)

Domain	Comment	Author response
General comment on the HTA report:	1. Die SGAIM bedankt sich für die Möglichkeit einer Rückmeldung. 2. Die Ergebnisse des HTA "Orale Blutverdünner bei Vorhofflimmern" waren für die SGAIM in dieser Form zu erwarten, so dass sich aus unserer Sicht die Frage stellt, ob die Ergebnisse den Aufwand und die Kosten der Untersuchung rechtfertigen. Wie bitten dieses, bei zukünftigen HTAs zu berücksichtigen. 3. Aus hausärztlicher Sicht gibt es noch einen Punkt für Patienten/innen unter OAK zu beachten. Häufig handelt es sich um multimorbide Patienten, welche von der monatlichen Arztvisite neben der INR Kontrolle auch sonst profitieren, da der Termin auch genutzt wird, um auf akute Beschwerden zu reagieren sowie zur Monitorisierung der weiteren chronischen Krankheiten. --- 1. SGAIM thanks you for the opportunity to provide feedback. 2. The results of the HTA "Oral blood thinners in atrial fibrillation" were to be expected for the SGAIM in this form, so from our point of view the question arises as to whether the results justify the effort and costs of the examination. We ask that this be considered for future HTAs. 3. From the point of view of general practitioners, there is one more point for patients on OAC to bear in mind. These are often multimorbid patients, who also benefit from the monthly doctor's visit in addition to the INR check, since the appointment is also used to react to acute symptoms and to monitor other chronic diseases.	1. Acknowledged 2. The HTA was commissioned to determine if the potential increased effectiveness of DOACs offset the potential increased cost, when compared to VKA. The question was asked due to the results of a German observational study. The HTA does not just considered clinical outcomes (i.e. effectiveness and safety) but also economic outcomes. 3. Acknowledged. The scope of the HTA was limited to patients with NVAF. A potential subgroup analysis to review the impact of co-morbidities was included, however it was not performed due to limited data (trials <10). A sentence on how this may impact the economic analysis has been added into the limitations' discussion (***Section 11.3***).
Commentary on Efficacy, Effectiveness and Safety	Keine. --- None.	NA
Commentary on health economic evaluation and budget impact analysis	Keine. --- None.	NA

Domain	Comment	Author response
Commentary on ethical, social, legal and organizational aspects	Keine. None.	NA
Commentary on the discussion and conclusions	Keine. None.	NA

8. SGH-SSH/Working Party Hemostasis

Domain	Comment	Author response
General comment on the HTA report:	1. Members of the Working Party Hemostasis of SGH-SSH have reviewed the above named HTA report. In summary, they have come to the conclusion that setting, results, and conclusions of the report are sound. 2. There is, however, a remark: it is to our understanding quite clear how effective tests for monitoring VKA are, and how their cost and availability in Switzerland is (see Executive summary – last line before Conclusions). There is even a well-established program for the self-monitoring of anticoagulation with vitamin K antagonists in Switzerland (www.coagulationcare.ch).	1. Acknowledged 2. Acknowledged, the importance of VKA is reflected throughout the report.
Commentary on Efficacy, Effectiveness and Safety	NR	NA
Commentary on health economic evaluation and budget impact analysis	NR	NA
Commentary on ethical, social, legal and organizational aspects	NR	NA
Commentary on the discussion and conclusions	NR	NA

9. Société Médicale du Valais / Walliser Ärztegesellschaft

Domain	Comment	Author response
General comment on the HTA report:	Nous nous permettons de vous transmettre la prise de position du groupement des cardiologues Valaisans à ce sujet: "Cette évaluation confirme le rapport coût/efficacité favorable d'un traitement par ACOD. De plus cette stratégie est en ligne avec les recommandations des sociétés spécialisées américaines et européennes. Par conséquent, le groupement des cardiologues valaisans soutient leur utilisation comme anticoagulants de première ligne pour les patients atteints de fibrillation auriculaire, en tenant compte du risque thrombo-embolique individuel." We allow ourselves to send you the position of the group of Valais cardiologists on this subject: "This evaluation confirms the favorable cost-effectiveness ratio of treatment with ACOD. Moreover, this strategy is in line with the recommendations of specialized American and European companies. Therefore, the group of Valais cardiologists supports their use as first-line anticoagulants for patients with atrial fibrillation, taking into account the individual thromboembolic risk."	Acknowledged
Commentary on Efficacy, Effectiveness and Safety	NR	NA
Commentary on health economic evaluation and budget impact analysis	NR	NA

Commentary on ethical, social, legal and organizational aspects	NR	NA
Commentary on the discussion and conclusions	NR	NA