Consolidated Stakeholder Feedback HTA Short-Report

Dual Antiplatelet Therapy following Percutaneous Coronary Interventions

Stakeholders **1. santésuisse, die Schweizer Krankenversicherer** **2. Médecins Fribourg – Ärztinnen und Ärzte Freiburg** **3. Schweizerische Gesellschaft für Kardiologie** **4. Working Party Hemostasis der Schweizerischen Gesellschaft für Hämatologie**	
Allgemeiner Kommentar zum Kurzbericht	
1	Der Kurzbericht ist übersichtlich aufgebaut und adressiert die relevanten Fragen. Der Bericht basiert auf einem im Jahr 2019 erschienen HTA aus Kanada zum gleichen Thema (Studien publiziert bis Ende 2017 / anfangs 2018). Die klinische Evidenz wird übersichtlich dargestellt. Die Subgruppenanalysen sind sehr hilfreich. Inwiefern relevante Studien seit anfangs 2018 zur Thematik publiziert wurden, wäre zusätzlich zu prüfen. A search for additional RCTs published between the publication of the CADTH report and the writing of this report, using the same selection criteria, did not retrieve new unique RCTs. Aufgefallen ist der Ausschluss von Patienten mit hohem Blutungsrisiko in den selektionierten Studien. Wie vermerkt wird, braucht es hier mehr Evidenz und diese Fragestellung sollte im Auge behalten werden.

	Acknowledged. No amendment needed. Das ökonomische Modell sollte zumindest im Anhang ausführlicher erläutert werden. Damit liessen sich die Resultate besser nachvollziehen. Die ökonomische Beurteilung basiert auf den kanadischen Gegebenheiten. Der Einbezug der Schweizer Rahmenbedingungen ist zu prüfen. For the sake of completeness the original CADHTH report will be attached to this short-report. Details regarding the economic model are to be found there. It's beyond the scope of this short-report to conduct a Swiss economic evaluation. Unklar bleiben auch die weiteren Schritte im Hinblick auf die Vergütung der Leistung durch die OKP. This HTA short-report evaluates the available data. The FOPH HTA-Section does not ***appraise*** the findings. The FOPH HTA-Section operates as an independent entity within the FOPH and is **not involved** in decision-making. Other FOPH Sections and responsible Federal Commissions appraise the findings and formulate a recommendation. The final decision regarding reimbursement lies within the field of the Federal Office of Home-Affairs.
2	Nous sommes convaincus par les différentes conclusions des études citées, d'autant que les cohortes impliquent de très grands volumes de patients. Il nous semble donc raisonnable éthiquement et économiquement de proposer une extension au delà de 12 mois la prescription d'une double antiaggrégation plaquettaire (aspirine à faible dose et inhibiteurs des récepteur P2Y12) chez des patients choisis, avec un risque de resténose après pose de stents coronariens, pour autant que les patients avec hauts risques hémorragiques en soient exclus. Effectivement, comme cela est souligné dans le rapport, en Suisse, contrairement au Canada, le générique du Clopidogrel est très souvent utilisé, donc les coûts en seront d'autant plus faibles. Nous rejoignons donc l'avis des différentes associations internationales de spécialistes en cardiologie. Acknowledged. No amendment needed.

3	The synopsis of the document is a clear and well structured summary of the findings of the analysis and of its relevant implications from both a clinical as well as cost-effectiveness standpoint in the swiss environment. It has several strengths and few limitations, the latter mainly coming from the intrinsic shortcomings with which data were gathered and analyzed in the HTA report published by the Canadian Agency for Drugs and Technologies in Health (i.e. subgroup analysis, see below comments). Among the strengths, the origin of this analysis is clearly acknowledged as well as the granularity in discussing how the findings may or may not apply to the current practice in Switzerland. In addition, the critical appraisal of the cost-effectiveness analysis is highly welcome considering that it is mainly based on simulations more than actual outcome data as well acknowledging that the type of implanted stent may be a treatment modifier. The conclusions seem entirely justifiable. Ackowledged. No amendment needed.
4	This HTA short report was redacted by the Swiss FOPH (Dr G van Haasteren, PhD) based on a 2019 report from the Canadian Agency for Drugs and Technology in Health (CADTH). Optimal duration of double antiplatelet treatment (DAPT) following percutaneous coronary intervention is debated. Original studies evaluated 12 month DAPT. DAPT for up to 12 months duration is considered "standard duration". DAPT for up to 6 months is considered “short duration”. DAPT for longer than 12 months is considered "prolonged duration". Treatment duration can also be categorized as "limited in time" vs. "life-long". Short durations of DAPT are associated with lower rates of bleeding. Prolonged duration of DAPT is associated with reduced recurrence of cardiovascular events. The combined effect on bleeding related death, cardiovascular death, non-cardiac death and all-cause mortality are debated. Acknowledged. No amendment needed.
Kommentar zu Forschungsfrage und PICO	
1	Die Forschungsfragen adressieren die relevanten Punkte. Die Frage, ob eine Plättchenhemmung nach einer koronaren Implantation eines Stents auch länger als 12 Monate durchgeführt werden soll, ist relevant. Dabei

	sollte im Hinblick auf die Beurteilung der Zweckmässigkeit der Leistung diese Schwelle von 12 Monaten medizinisch hergeleitet werden. Die PICO-Fragen sind nachvollziehbar. Die Subgruppenanlyse ermöglicht eine differenzierte Analyse der Chancen und Risiken der Intervention. Es zeigt sich klar, dass die Intervention nur bei bestimmten Subgruppen zu eine positiven Behandlungsbilanz führt. Die Intervention sollte deshalb auf bestimmte Subgruppen limitiert werden. Acknowledged. No amendment needed.
2	Kein Feedback
3	The question being asked, i.e. what is the benefits and risks of extending DAPT duration beyond 6 to 12 months after PCI is a clinically relevant question both because it involves a large number of individuals in Switzerland and other developed countries as well as because of the large and not entirely consistent amount of clinical data. However, it does not reflect that fact that DAPT is not only a secondary prevention measure for patients who received prior stent implantation, rather a fully blown secondary prevention measure to improve outcome after an ACS, irrespective of whether patients were or were not treated with coronary stent insertion. The specific focus on prior PCI patients (instead of on patients with prior myocardial infarction at risk for recurrences) needs therefore to be justified. In this HTA the patient population, as defined in the PICO, consists of adult patients who have undergone PCI with any type of stent and who are receiving DAPT. The specification of this selected patient group was made and accepted as such, during the topic selection process proceeding the actual HTA phase. Therefore, it is beyond the scope of this short-report to include all ACS patients.
4	The policy question that the author raises is whether P2Y12 inhibitors (clopidogrel, prasugrel, ticagrelor) in combination with aspirin (acetylsalicylic acid) should be reimbursed beyond 12 months for patients who recently underwent PCI with drug eluting or bare metal stent insertion. The primary research question addresses clinical efficacy and safety of six to 12 months DAPT versus 12 months or more in the post PCI patient cohort and relevant subgroups (prior myocardial infarction, initial acute coronary syndrome at presentation, diabetic patients, varying age groups, smokers).

	The secondary research question regards cost-effectiveness for the above named patient population and the subgroups described. The policy question is pertinent. The research questions are concise. Cost-effectiveness is not discussed in detail for lack of data. Acknowledged. No amendment needed.
Kommentar zur Analyse / Synthese	
1	Die Strategie für die Literatursuche basiert auf relevant Quellen. Aktuellere Studien, publiziert nach 2018 oder auch aktuell laufende Studien wurden nicht berücksichtigt. Diese sind beispielsweise der Quelle "ClincalTrials.gov" zu entnehmen und sollten ergänzend ebenfalls berücksichtigt werden. Die klinischen Resultate sind nachvollziehbar. Die ökonomische Beurteilung zeigt nur kleine, kaum relevante Vorteile. Dabei wäre es hilfreich, wenn das ökonomische Modell zumindest im Anhang detailliert erläutert würde. Es wäre zudem angebracht, wenn das ökonomische Modell den Verhältnissen in Schweiz angepasst würde. A search for additional RCTs published between the publication of the CADTH report and the writing of this report, using the same selection criteria, did not retrieve new unique RCTs. Relevant ongoing RCTs are typically referred to when either lack of evidence or outdated data are serious limitations of the presented available evidence. Since neither of the two apply to the current data presentation, this line of research was not further followed. This topic was selected as short-report topic. This implies that no economic evaluation reflective of the Swiss payer perspective is conducted. However, we agree that an economic evaluation adapted to the Swiss conditions is likely to answer some open questions with respect to the cost-effectiveness and budget impact of prolonged DAPT on the Swiss healthcare expenditures. This being said, it is important to repeat that none of the economic findings presented in the CADTH report encompassed convincing evidence. It is unlikely that Swiss conditions would change the magnitude of possible benefits significantly.
2	Kein Feedback

3	The focus on prior PCI and the arbitrary threshold of at least 85% of patients receiving PCI excluded the PEGASUS trial, which is not only the largest but also the most important study in the space of prolonged DAPT. PEGASUS shows not only a reduction of myocardial infarction, but also a significant reduction of stroke risk and a trend towards lower cardiovascular mortality with ticagrelor-based extended DAPT. Meta-analyses including PEGASUS and restricting to patients with prior MI show a cardiovascular mortality benefit of prolonged DAPT. Moreover, this study clearly shows that prior stent implantation is not a treatment modifier. The subgroup analyses are largely questionable because only limited number studies contributed (e.g. diabetes) and superiority testing in each stratum more than interaction statistics is used. Only the DAPT trial used prasugrel selectively for patients receiving first generation DES. Hence, data on long-term use of prasugrel in current practice is absent. The PEGASUS-TIMI trial is indeed the only identified RCT to assess the benefits and harms of long-term ticagrelor use. The main reasons for excluding this trial are that not all included patients had undergone PCI before randomization, there is uncertainty about the proportion of participants who received a P2Y12 inhibitor prior to randomization, and the duration of potential DAPT before randomization is longer than the eligibility criteria for the present review. To acknowledge the relevance of this trial with respect to long-term ticagrelor use the CADTH report summarized the clinical data of this trial in a separate section of their report. In response to the stakeholders comment, and in line with the CADTH report, the findings of this single RCT will be briefly discussed in this short-report. Amendment needed. The limitations of the strength of evidence based on subgroup analyses is discussed in the ***Discussion*** section of this short-report. No amendment required.
4	The author summarizes relevant data that the Canadian working group had collected and discussed. The analysis and synthesis are structured, clear and correct. Key organisations have also formulated assessments for DAPT duration. In 2016 the American College of Cardiologists (ACC) recommended DAPT for PCI in the context of stable coronary artery disease and in the context of acute coronary syndromes on a class of recommendation (COR) / level of evidence (LOE) I A for up to 6 months and 12 months respectively. In 2017 the European Society of Cardiology (ESC) issued very similar

	recommendations with the similar COE/LOE. Both organisations defined reasons for curtailed and prolonged durations of DAPT. These reasons were based on patient-related (bleeding diathesis), intervention-related (bioresorbable vascular scaffold vs other stents) and medication-related factors (Clopidogrel vs other P2Y12). Treatment prolongations had COR/LOE >= II A. Acknowledged. No amendment needed.
Kommentar zu Diskussion und Schlussfolgerungen	
1	Die Diskussion kann nachvollzogen werden. Es hat sich gezeigt, dass diejenigen Patienten mit hohem Blutungsrisiko ausgeschlossen wurden. Dies ist ein relevanter Punkt. Damit ein relevantes Gesamtbild hinsichtlich der Wirkung der Intervention entsteht, sollte diese Gruppe ebenfalls berücksichtigt werden. Es wird empfohlen diese Lücke zu schliessen. Die Schlussfolgerungen können nachvollzogen werden. Die entsprechende Intervention ist nur bei bestimmten Subgruppen in Betracht zu ziehen. Vor allem die schweren Blutungen sind dabei im Auge zu behalten. Die Intervention ist nur mit geringen ökonomischen Vorteilen verbunden. Dabei basiert diese Beurteilung auf den Verhältnissen in Kanada. Deshalb ist in Betracht zu ziehen, dieses ökonomische Modell auf die Verhältnisse in der Schweiz zu übertragen. Eine unlimitierte Vergütung dualer Plättchenhemmung nach koronarer Implantation von Stents wird abgelehnt. Die Risiken von Blutungen und anderen Ereignissen sind relevant. An economic evaluation from the perspective of the Swiss payer is beyond the scope of this short-report. It is also beyond the scope of this HTA short-report to evaluate other subpopulations than included in the CADTH report. However, the FOPH acknowledges the relevance of studying this group of at-risk patients further. An additional analysis of research focussed on this subpopulation and prolonged DAPT may indeed complement the findings of the presented report. Given the ethical restrictions of conducting research with this at-risk group of patients may, however, limit the quantity and quality of the available evidence.
2	Kein Feedback

3	The conclusions are justifiable based on the data but we suggest removing the specific considerations on subgroup analysis based on the comments above. The limitations of the strength of evidence based on subgroup analyses is discussed in the ***Discussion*** section of this short-report. For the sake of completeness the FOPH sees no reason to remove the subpopulation analyses. There is no data assessing the trade-off between risks and benefits for prasugrel in patients receiving contemporary stents. Hence, this option should probably be restricted to patients who cannot tolerate clopidogrel or ticagrelor. The predominance of studies enrolling patients who received clopidogrel as P2Y12 inhibitor, limits the generalizability of the findings of this review. This limitation is discussed in the ***Discussion*** section of the report. More unique prasugrel- and ticagrelor-focussed trials are needed before conclusions can be drawn regarding the benefits and risks of these two P2Y12 inhibitors as components of prolonged DAPT after PCI. The small sentence referring to the possible use of the DAPT score seems not justified considering that this score works only in patients having received first generation DES which are no longer in use in Switzerland. Instead, the routine assessment of the bleeding risk, e.g. with the use of the PRECISE DAPT score, as suggested by guidelines, should be more promoted. Recent data suggests that risk stratification based on bleeding risk is much more effective in identifying responders to prolonged DAPOT than ischemic risk per se. The information regarding risk stratification tools will be adjusted accordingly. Amendment needed.
4	The author summarizes that all-cause mortality is not significantly different in PCI patients with more than 12 months of DAPT vs 6-12 months of DAPT. The same holds true for cardiovascular death. Extending DAPT beyond 12 months was associated with reduced risk of myocardial infarction and stent thrombosis while the risk of bleeding was increased. There is a recent meta-analysis (Yin et al. BMJ 2019; 365:2222) indicating that >12 month of DAPT is associated with more death and bleeding related events compared to shorter DAPT, thus providing a strong rationale for further studies that are to define the subgroups, which may benefit from prolonged DAPT.

	In view of current evidence the WPH concludes that for "PCI patients" as a group, limited duration DAPT is indicated. For subgroups the decision to prolong DAPT beyond 12 months should be based on current data, individualisation, and patient preference. Acknowledged. No amendment needed.

Please insert more rows as required