HTA Report

Stakeholder feedback

Revascularisation versus optimal medical therapy (OMT) for the treatment of chronic coronary syndrome (CCS)

15.08.2023

Table of contents

1 Preface 3
2 List of invited stakeholders for consultation 3
3 List of stakeholders who submitted feedback 4
4 Stakeholder feedback 5
4.1 General comments regarding the HTA report 5
4.2 Comments on efficacy, effectiveness, and safety 7
4.3 Comments regarding on health economics evaluation and budget impact analysis 10
4.4 Comments on ethical, social, legal, and organizational aspects 13
4.5 Comments on the discussion and conclusions 14

1 Preface

According to the predefined HTA process which can be consulted on www.bag.admin.ch/hta, the FOPH conducts a stakeholder consultation on the HTA report. A stakeholder consultation was held from 8 February 2023 to 8 March 2023 for the HTA report on "**Revascularisation versus optimal medical therapy (OMT) for the treatment of chronic coronary syndrome (CCS)**". The report was submitted to stakeholders, such as health insurance associations, patient organisations, healthcare professional associations, professional societies, industry associations or other interested parties. Stakeholders were notified of the report 20 working days in advance and were given 20 working days to comment on the report.

This document details the authors' responses to stakeholder feedback on the HTA report on "**Revascularisation versus optimal medical therapy (OMT) for the treatment of chronic coronary syndrome (CCS)**". The stakeholder feedback and corresponding author responses are detailed in tables. The tables are listed by comment boxes and stakeholder, in alphabetical order. Where multiple stakeholders provided similar feedback, the authors have only provided a response to the first comment; for subsequent comments the reader is referred to the original response.

2 List of invited stakeholders for consultation

The following stakeholder have been invited on 8 February 2023 to submit feedback regarding the HTA report:

ACSI - Associazione dei consumatrici e consumatori della Svizzera Italiana

BSV - Bundesamt für Sozialversicherung, Invalidenversicherung

curafutura - Die innovativen Krankenversicherer

DVSP - Dachverband Schweizerischer Patientenstellen

FMH - Verbindung der Schweizer Ärztinnen und Ärzte

FRC - Fédération romande des consommateurs

GDK - Schweizerische Konferenz der kantonalen Gesundheitsdirektorinnen und -direktoren

GSASA - Schweizerischer Verein der Amts- und Spitalapotheker

H+ - Die Spitäler der Schweiz

Intergenerika - Swiss Generics and Biosimilars

Interpharma - Verband der forschenden pharmazeutischen Firmen der Schweiz

Konsumentenforum

MTK - Medizinaltarif-Kommission

pharmaSuisse - Schweizerischer Apothekerverband

PUE - Preisüberwachung

SAMW - Schweizerische Akademie der Medizinischen Wissenschaften

santésuisse - Die Schweizer Krankenversicherer

SAPhW - Schweizerische Akademie der Pharmazeutischen Wissenschaften

SGAIM Schweiz. Gesellschaft allgemeine Innere Medizin

SBK - ASI - Schweizer Berufsverband der Pflegefachfrauen und Pflegefachmänner

Schweizerische Gesellschaft für Kardiologie

SGHC - SCHWEIZERISCHE GESELLSCHAFT FÜR HERZ- UND THORAKALE GEFÄSSCHIRURGIE

SGV - Schweizerische Gesellschaft der Vertrauens- und Versicherungsärzte

SKS - Stiftung für Konsumentenschutz

SPO - Patientenschutz

sQmh - Schweizerische Gesellschaft für Qualitätsmanagement im Gesundheitswesen

SVBG/FSAS - Schweizerischer Verband der Berufsorganisationen im Gesundheitswesen

Swiss Medtech

VIPS - Vereinigung Pharmafirmen in der Schweiz

3 List of stakeholders who submitted feedback

The following stakeholders have submitted feedback within the stakeholder consultation round:

Santésuisse - Die Schweizer Krankenversicherer

Swiss Medtech

Schweizerische Gesellschaft für Kardiologie (Swiss Society of Cardiology)

4 Stakeholder feedback

4.1 General comments regarding the HTA report

The following comments have been submitted by stakeholders regarding the general comments regarding the HTA report "Revascularisation versus optimal medical therapy (OMT) for the treatment of chronic coronary syndrome (CCS)".

Comment no.	Stakeholder	Stakeholder comment	Authors' response
1.1	Santésuisse	1. The HTA addresses a medically and economically relevant topic. Comprehensible description of pathology, diagnostics and treatment options of CCS. Clear research questions. 2. Detailed explanation of PICO as well as references to deviations from the HTA protocol. The comparator OMT is not further differentiated and assumed to be the same, which means that a potential influence of different OMT (or non-pharmacological lifestyle adjustment) cannot be excluded. 3. The deviations from the initial protocol are in principle understandable. However, a potential influence on the results cannot be excluded with certainty. Comprehensible study selection and analysis methodology. 4. The lack of consideration of systematic reviews and meta-analyses, which were included in the European and American guidelines, remains unclear. Different regulations compared to international guidelines require a strong evidence base.	1. No changes made. 2. The assumption made (due to lack of transparent study descriptions) is that OMT is the same and any variation in prescribing would be accounted for by randomisation of participants. Also, a random effects model was used to account for study variability. No changes made. 3. Regarding broadening the inclusion to earlier generation drug-eluting stents this was a necessity due to the lack of third generation RCT data, and is highlighted as a limitation of this HTA. No changes made. 4. Existing systematic reviews/meta-analyses were examined, however, due to their inclusion of trials outside of the designated WHO mortality stratum A countries, it was not possible to utilise the results. No changes made.
1.2	SwissMedtech	1. The heterogeneity of the CCS population has an impact on the assessment of potential treatment benefit as well as cost-effectiveness and budget impact which is not adequately addressed. This heterogeneity has been reflected in the clearly distinguished treatment pathways for PCI and CABG for different types of patients in the latest treatment guidelines, yet the current draft concludes on CCS as one homogenous population, which leads to the inconsistency noted with existing evidence reviews and guidelines. 2. We suggest that the evidence evaluation takes into account	1. Acknowledged; an attempt to address the fact that there is large variability within the CCS population has been made. However, the report authors do agree that this is a limitation of the analysis. Challenges in identifying baseline event rates for the target population are discussed in ***Section 8.3.2*** as well as in the limitations section (***Section 11.3***). Both the results section and conclusion summarise economic outcomes from a base case cohort and subgroups of higher-risk cohorts (informed by RCT populations). The conclusion notes the following: "*Given the complexities in treatment decision-making for*

		better the different patient populations and treatment pathways, eg by providing more emphasis on health economic modelling of real-world patient populations. We note that the clinical and economic evidence evaluation of "revascularization" as a separate treatment strategy is not meaningful and confusing, this should be at least taken into account clearly in the evidence conclusions for PCI and CAGB treatment.	*CCS, cost-effectiveness analysis stratified by patient subgroups is an area for further research.*" Detailed, patient-level data—needed to facilitate such a rigorous analysis—were not identified by the authors. 2. Acknowledged (no changes). The results and conclusion sections summarise economic outcomes from both a base case cohort and subgroups of higher risk cohorts. Results are also presented separately for PCI and CABG, as well as for a combined 'revascularisation' intervention. All analyses are presented; decision makers are free to decide which are most pertinent to them. The authors note that the alterations to the PICO were made during the HTA process to accommodate evidence reporting on a combined 'revascularisation' intervention. This was particularly important to ensure the ISCHEMIA RCT—identified as a key trial in the area during expert consultation—was captured in the analysis.
1.3	Swiss Society of Cardiology	1. Unfortunately, many of the previous comments of the Swiss Society of Cardiology released prior to executing this HTA and exchange was not possible, which actually makes our previous comments almost an alibi exercise. This includes but is not limited to not separating current devices (newer gen DES from BMS, that are NOT used since >1 decade in Switzerland), lack of inclusion of spontaneous MI, cardiovacular death and angina as endpoint (not only limited as part of QoL). 2. In PCI vs. OMT trials, a substantial proportion is undergoing cross over (25-85%), which increase the longer the follow-up is, which is neither considered in the methods, results nor conclusion/executive summary. All trials were investigating an INITIAL approach of revasc vs. OMT not revasc vs. OMT. The executive summary dose not reflect the result section, e.g. for PCI vs. OMT reduction in MACE and QoL were found but not reported. Generally, the HTA does not account for the high heterogeneity of CCS patients.	1. Separation and analysis of different DES was not possible due to how the data were reported in the published studies. This is an acknowledged limitation of the report. Outcome measures were primarily guided by the International Consortium for Health Outcomes Measurement (ICHOM). Cardiovascular death was not included, because this was captured under all-cause mortality; a more useful measure that also accounts for non-cardiac causes of death related to the procedure (e.g. due to infection, etc.). Myocardial infarct was included under MACE. Anginal frequency and anginal stability were indeed included in the report, as a measure of health-related quality of life. No changes made. 2. Limitations of the analysis methods used in the studies (i.e. ITT) have been added as a limitation in the discussion section. All included patients had CCS and were treated in comparable health contexts. Variation in populations were also considered in the

			GRADE tables when determining the certainty of the evidence.

4.2 Comments on efficacy, effectiveness, and safety

The following comments have been submitted by stakeholders regarding the efficacy, effective and safety section of the HTA report "Revascularisation versus optimal medical therapy (OMT) for the treatment of chronic coronary syndrome (CCS)".

Comment no.	Stakeholder	Stakeholder comment	Authors' response
2.1	Santésuisse	Interpretation of the results and answering the decision questions are made difficult by various limitations that are only partially discussed or considered in the evaluation: 1. High heterogeneity, inconsistency and contradictory results remain largely unexplained. 2. The transferability to Switzerland must be critically assessed. Relevant questions regarding comparability of population (e.g. risk factors, comorbidities), diagnostics, intervention (e.g. indication, criteria for therapy selection, reimbursement incentives, PCI technology / CABG procedure), comparator (e.g. comparability of OMT, lifestyle adjustment) remain largely unanswered. Individual PCI procedures (BMS, DES, balloon angioplasty, DEB) are not evaluated in a differentiated manner. 3. Data on stent generations are not considered. Efficacy and usefulness of modern DES (3rd generation) can only be assessed after completion of ongoing studies. Subgroup analyses are only performed to a limited extent.	1. Due to insufficient study data it was not possible to perform subgroup analyses to investigate heterogeneity. Attempts have been made in the report to explain why such inconsistency occurred. The report was constrained by the data and limited patient characteristics to derive clear reasons to explain such variability. No changes made. 2. There is no clear evidence that the participants in the trials are unrepresentative of the Swiss population. Only studies in the WHO stratum A were included to ensure a comparable healthcare context. Additionally, individual PCI (BMS, first, second & third generation DES) data were not reported in the trials and therefore could not be differentiated. No changes made. 3. No pairwise studies were available comparing third generation DES to OMT, and therefore due to lack of data it was not possible to compare latest generation stents to older technologies. No change made.
2.2	SwissMedtech	1. Improvement of angina symptoms and quality of life (QoL) has been noted as an important treatment objective for CCS patients in all recent treatment guidelines. QoL has been included as a relevant	1. The GRADE summary of findings only allows for 7 outcomes to be included for assessment and these were chosen ***a-priori***. As stated in the GRADE Handbook, outcomes as assessed as relevant to patients for decision making should be selected in order of their importance. The authors, with

		outcome in the review, yet the outcome reflecting best the treatment objectives in these patients, ie disease-specific quality of life including angina symptom evaluation, has not been considered as a prioritized outcome in the GRADE summary of findings table and in the conclusions. We therefore request that these outcomes receive more weight in the evidence evaluation and conclusion. 2. The risk of bias assessment assigns a high risk of bias for the ISCHEMIA Qol study, due to apparently the Qol analyses being only a post-hoc analyses. This seems to be incorrect as the study protocol did prespecify these analyses. As mentioned previously, the effects of completeness of revascularization are not considered; at least the obvious relation to endpoints (e.g., revascularization, hospitalization) .	consideration of the Swiss-patient/clinical perspective and review of evidence concerning patients' values and perspectives, selected the most appropriate outcomes for inclusion. As such, no changes will be made to the report to include additional outcomes to the GRADE assessment. 2. It was planned in the ISCHEMIA QoL study but not implemented because: "At the time of initial funding, plans called for all randomly assigned patients to complete a battery of QOL instruments before randomization and during follow-up. However, for administrative (site data collection burden) and budgetary reasons, that plan was altered early in the trial to require only a brief assessment of angina-related QoL in all randomly assigned patients and to collect the more comprehensive battery of QOL in a substudy". No changes made.
2.3	Swiss Society of Cardiology	1. Cardiovascular mortality has to be included in the relevant endpoints. ISCHEMIA-EXTEND (PMID 36335918) and a recently published comprehensive meta-analysis (PMID 34002203), have shown a signal of similar magnitude favoring PCI for the outcome of cardiovascular mortality. Disease specific outcomes are highly relevant in cardiovascular research, therefore such outcomes should have been also considered in this review. 2. It is unclear, why only few trials (7 RCTs) have been included compared to the contemporary landmark meta-analysis on the same topic published in 2021 (PMID 34002203), where 25 RCTs involving 19 806 patients (10 023 revascularisation and 9783 OMT). 3. As mentioned in our initial comment, angina is the primary aim of PCI in CCS and this outcome should make part of the evaluation (not only QoL). The ischemia QoL study was prespecified, low risk of bias, requires correction.	1. All-cause mortality was guided by the consensus on outcome measure reported by the International Consortium for Health Outcomes Measurement (ICHOM). All-cause mortality removes diagnosis bias, and variations in non-cardiac causes between treatment groups should be balanced due to randomisation. In addition, ICHOM recommends to use all-cause mortality instead of cardiac-mortality. No change made. (https://www.ahajournals.org/doi/10.1161/JAHA.115.001767#d5221154e1274_copied). 2. Existing systematic reviews /meta-analyses were examined but due to their inclusion of trials outside of the designated WHO mortality stratum A countries, it was not possible to utilise the results. No changes made. 3. Angina frequency and stability scores were used when reported from the SAQ questionnaire, as indicated by the ICHOM standard outcomes set; the ICHOM standard outcomes set preferentially includes patient-reported measures of health status. All patients had CCS and were treated in comparable health contexts. Also, variability of populations was considered in the GRADE tables when determining certainty of evidence. No changes made. 4. It was not possible to stratify the outcomes based on the generation of DES because the data reported in the trials only reported the findings as

		4. Considering trials over a time range of 2000 until nowadays for this condition and intervention is not appropriate, since the indexed interventions related to PCI have considerably evolved over the last 20 years. Mixed intervention of PCI with BMS, 1st gen DES and 2nd gen DES is scientifically inappropriate and leads to misleading conclusions, it is incorrect to state that trials do not declare type of stents used (5.1). In the Swiss context, 99% of the stents implanted in Switzerland (2019) are newer generation DES."Also this point was mentioned in our initial review and ignored. Analyses at least need stratification in this regard. 5. STICH is no CCS patient population but rather ischemic cardiomyopathy, thus methodologically not correltly identified. 6. Lack of as treated analysis is substantial limitation, important in view of substantial cross over ranging between 25-85%.	combined stents, without consideration for type of stent. No changes made. 5. All included patients had CCS and were treated in comparable health contexts. Variation in populations were also considered in the GRADE tables when determining the certainty of the evidence. No changes made. 6. The trialists analysed data using an intention-to-treat (ITT) approach and both ITT and per protocol methods have strengths and limitations. ITT maintains the advantage of randomisation – that the interventions groups do not differ at baseline regarding prognostic risk factors. However, the term ITT does not have a consistent definition and is used inconsistently in study reports and without detailed information commentary on how, or if this impacted results is limited. Discussion section has been amended.

4.3 Comments regarding the health economics evaluation and budget impact analysis

The following comments have been submitted by stakeholders regarding the health economics evaluation and budget impact analysis of the HTA report "Revascularisation versus optimal medical therapy (OMT) for the treatment of chronic coronary syndrome (CCS)".

Comment no.	Stakeholder	Stakeholder comment	Authors' response
3.1	Santésuisse	1. The results of the cost-benefit analysis showed unfavourable results (i.e. high ICERs or dominance) for PCI and CABG. These results are plausible from santésuisse's point of view. 2. In 2023, costs of around CHF 146.1 million are estimated to be borne by compulsory health insurance for CABG and PCI procedures for the treatment of CCS. The estimates are plausible from santésuisse's point of view.	1. Acknowledged. 2. Acknowledged.
3.2	SwissMedtech	1. The model seems too simplistic as post-event risks eg risk of secondary MIs or strokes are not considered. 2. A base case assumption of no treatment effect beyond 5 years for PCI, 10 years for CABG seems overly conservative. This assumption should be investigated through sensitivity analyses. The modelled population was defined according to ISCHEMIA which might only reflect 4% of the Swiss CCS patients. We recommend that analyses with higher risk populations defined from real-world data sets are undertaken and receive more weight as they are more reflective of the real risk profile of patients. 3. The current assumed growth in the number of PCI procedures until 2027 is based on historical data and is likely to be an overestimate considering latest Swiss data that show a stable number of PCI procedures over the last 5 years (Wagener et al J. Clin. Med. 2022). Long-term effects of patients on medication should consider the potential transition to an acute disease state(costs beyond OMT)	1. Acknowledged as a limitation. This limitation is already discussed within the HTA report, ***Section 11.3***. 2. Acknowledged. For PCI, no statistically significant benefits were observed for any MACE outcome at 5 years follow-up (significant effect observed on revascularisation up to 2 years). Some domains of the SAQ showed significant differences at 12 months, with no follow-up beyond this point. Scenario analyses extrapolating this benefit to 2 and 5 years were included in the HTA. Additional analyses including these alternate assumptions for change in HRQoL after PCI *and* including only significant RR estimates have been added. For CABG, statistically significant impacts on all MACE outcomes except stroke were present at the last observed follow-up. A scenario extrapolating these outcomes under the assumption of continuing treatment benefit beyond 5/10 years has been added. A similar scenario has been added for the revascularisation comparison also. Overall, this assumption appears to have minimal impact on cost-effectiveness outcomes.

			Concerns that the ISCHEMIA trial represents a highly selected lower-risk CCS population are acknowledged in the HTA (***Section 8.3.2.2.2***). Challenges in identifying baseline event rates for the target population present an issue and have been discussed in the limitations section (***Section 11.3***). The conclusion (***Section 12.2***) summarises results from both the base cases and subgroup analyses in higher-risk cohorts. 3. Acknowledged, and addressed with inclusion of additional scenario analyses, using data from the publication provided along with previous PCI surveys. These scenarios consider that the number of PCIs for CCS may be trending slightly downward. We note that the additional publication was published in December 2022, after the draft HTA was submitted. The BIA considers the potential cost of PCI and CABG procedures under current policy conditions and using a market share approach. No comparative scenario (e.g. based on a potential policy change) is defined. Given this, there wasn't a need to incorporate long-term disease-related costs for patients on OMT in the BIA.
3.3	Swiss Society of Cardiology	1. The analysis is based on ISCHEMIA, which clearly does not reflect Swiss patients (<10% meeting eligibility of ischemia). This analysis should be redone including more high risk patients or the limitation must be prominently acknowledged in conclusion. 2. The working group of interventional cardiology reports stable PCI numbers over the last 4 years were absolutely stable, which is not considered under 12.2. where an increase of >30 Mio is anticipated. 3. The current shift towards ambulatory care is neither quantified nor put into the model.	1. Acknowledged (no changes made). Concerns that the ISCHEMIA trial represents a highly selected lower-risk CCS population are raised in ***Section 8.3.2.2.2***; challenges in identifying the target population are an issue and have been discussed in the limitations section (***Section 11.3***). The highest level (RCT) data was used to inform the economic modelling. Moreover, the conclusion acknowledged (***Section 12.2***) this limitation -- "*given the complexities in treatment decision-making for CCS, cost-effectiveness analysis stratified by patient subgroups is an area for further research".* 2. Acknowledged, and addressed with inclusion of additional scenario analyses, using data from an additional publication along with previous PCI surveys. These

			scenarios consider that the number of PCIs for CCS may be trending downward. See above for details on the additional data source informing the scenarios. 3. The potential for PCI to be performed as an outpatient service is discussed in ***Section 8.3.1*** ('Findings: costs'). In the analyses, location of PCI provision effects cost estimates only; clinical evidence was not stratified by the setting in which PCI was performed. To inform the estimated cost of PCI used in the economic evaluation, the proportion performed in the outpatient setting was based on 2020 inpatient and TARMED claims for PCI (i.e. up-to-date real-world data). Potential future changes were not considered pertinent to the valuation of this model input. Given uncertainty (due to the derivation process), this model input was varied in sensitivity analysis (one-way DSA and PSA). Growth in relative use of outpatient PCI was however considered in the budget impact analysis, which seeks to estimate potential future costs to the health system. Further shifts toward outpatient care is relevant for such projections.

4.4 Comments on ethical, social, legal, and organizational aspects

The following comments have been submitted by stakeholders regarding the ethical, social, legal, and organizational sections of the HTA report "Revascularisation versus optimal medical therapy (OMT) for the treatment of chronic coronary syndrome (CCS)".

Comment no.	Stakeholder	Stakeholder comment	Authors' response
4.1	Santésuisse	1. The results on ethical, social and organisational aspects are mainly based on Anglo-Saxon studies (USA, UK, Aus) and are essentially shaped by the corresponding social systems and cultural areas. Selected aspects and findings are also likely to be relevant in Switzerland (e.g. socio-economic status, women, adherence). However, it can be assumed that the type and extent of the factors shown in Switzerland differ in part from the findings from Anglo-Saxon studies. Additional explanations on the possible transferability of the results to Switzerland would be useful. 2. The studies considered indicate that ethical, social and organisational problems can be contained through shared decision-making between patients and physicians. The authorities should draw more attention to these facts.	1. Agreed, the social issues such as culture distrust of health care providers and assumptions made by healthcare providers may not be relevant to a Swiss context. The text has been amended to acknowledge these differences. 2. Acknowledged.
4.2	SwissMedtech	We appreciate the report highlighting the importance of shared decision-making between patients and clinicians, which is is particularly important considering the complexity of this heterogeneous patient population and problems of adherence to medication in some patients. As outlined in the treatment guidelines, patients views on the potential benefits and risks and treatment preference should be an important factor in the treatment decisions. We suggest that this be considered more in the conclusions of the report.	Acknowledged. No change made, as the focus of the HTA is CABG, PCI and revascularisation further discussion of shared-decision making beyond that already covered in ***Section 9*** (ethical, legal, social and organisational issues) would not add anything new. No further change.
4.3	Swiss Society of Cardiology	None provided	NA

4.5 Comments on the discussion and conclusions

The following comments have been submitted by stakeholders regarding the discussion and conclusions of the HTA report "Revascularisation versus optimal medical therapy (OMT) for the treatment of chronic coronary syndrome (CCS)".

Comment no.	Stakeholder	Stakeholder comment	Authors' response
5.1	Santésuisse	1. The discussion of the results and conclusions is comparatively brief. They should be expanded, differentiated and deepened with regard to limitations and transferability to Switzerland. 2. Based on the health economic study, santésuisse proposes that PCI and CABG interventions be strictly limited. Corresponding adjustments should be made promptly in the corresponding ordinances. 3. It has been shown within the framework of the HTA that joint decision-making between patient and physician can improve the effect of the intervention. santésuisse proposes that appropriate measures be taken in this regard.	1. The results and conclusions were limited to WHO stratum to ensure comparable healthcare context, and that all issues are addressed in the applicability section. Additional comments have been added to the report in response to stakeholder feedback. 2. It is beyond scope of this HTA to comment on changes to the health insurance ordinances. The report suggests cost-effectiveness may be improved in cohorts with higher baseline events risks, but that the present HTA lacked comprehensive cost-effectiveness analyses stratified by patient subgroups. 3. Acknowledged. No change made.
5.2	SwissMedtech	4. We disagree with the conclusions on an evidence gap on 3rd generation DES (page 149), as DES' safety and efficacy has been established with the previous generation trials; the improved performance of 3rd generation DES has not been addressed. The current report's evidence conclusions are confusing as "revascularization" is looked at as a separate research question, in addition to PCI and CABG, with partly different conclusions (eg long-term data not favorable for PCI, favorable for revascularization). We request that these conflicting conclusions be resolved in the report, eg by incorporating evidence for revascularization in the conclusions on PCI and CABG. 5. The negative conclusions in the ex summary around PCI stating "no clear benefit …" is not in line with the favorable outcomes in the HTA (eg page 173 for PCI MACE, HRQOL, revascularization). We kindly request that the executive summary conclusion does not oversimplify and takes into	4. An evidence gap currently exists regarding additional benefits of 3rd generation DES and we cannot assume that older generation DES are comparable to 3rd generation unless there is a compelling reason to think so, such as the formulations/metallurgy being the same. As we don't have any data from the included studies specific to 3rd generation DES we cannot comment on any differential effects that may exist. No further change. Revascularization plus OMT is different from CABG plus OMT or PCI plus OMT, and as a result, it's not surprising that their outcomes differ. Revascularization combines two types of revascularization, which are not equivalent. The 5-year data for *revascularization* (PCI/CABG) showed favourable results for repeat revascularization and also for CABG, but not PCI. It's possible that a positive treatment effect occurred in the CABG participants within the revascularization group (i.e. CABG/PCI) that is significant enough to achieve significance without being diminished by

		account the whole range of outcomes reviewed.	the PCI treated participants. Therefore, there is no conflict between the results of revascularization and PCI. No change needed. 5. The text has been amended in the executive summary to consider short-term outcomes.
5.3	Swiss Society of Cardiology	1. The conclusions are based solely on the conventional statistical significance. Such interpretation can be misleading in this case. As shown in the main results (Figures 4, 5, and 6) in all shown meta-analyses the confidence intervals of the corresponding summary effects clearly lie on the left showing favoring results for any revascularization strategy. The conclusions should be revised accordingly. 2. Conclusions do not mention the substantial effect on angina, i.e. the key parameter for efficacy in PCI of stable CCS. Limitation to QoL is not acceptable, also conclusions need to extend to cardiovascular mortality and spontaneous MI. 3. Conclusions do not acknowledge lack of as treated analysis, this is highly relevant. 4. There is a disconnect between the conclusion in executive summary (no clear benefit of PCI) as compared to the positive outcomes in the results section (12.1.2.) including MACE, qOL and revasc. This is not reflecting a minority of outcomes. E-summary requires revision.	1. Only ***Figure 4*** (CABG) is significant, whereas ***Figure 5*** and ***6*** find no significant difference as the confidence intervals cross in line of no effect. No changes made. 2. The conclusions have been amended to state angina frequency. All-cause mortality has been reported and this captures cardiovascular mortality. MI was reported for CABG and the conclusions encompass MI for the other comparators. No further change made. 3. The trialists analysed data using an intention-to-treat (ITT) approach and both ITT and per protocol methods have strengths and limitations. ITT maintains the advantage of randomisation – that the interventions groups do not differ at baseline regarding prognostic risk factors. However, the term ITT does not have a consistent definition and is used inconsistently in study reports and without detailed information commentary on how, or if this impacted results is limited. Discussion section has been amended. 4. Angina frequency has been added to the discussion ***Section 12.1.2.*** The executive summary has been amended.