Prediction of mortality, bleeding, and ischaemic events in patients with cancer and acute coronary syndrome: a model development and validation study

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Brief title Risk prediction in cancer patients with acute coronary syndrome

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Summary

Background: Accurate assessment of mortality, bleeding, and atherothrombotic risk in cancer patients with acute coronary syndrome (ACS) could inform novel personalised treatment strategies, but no standardised tools for this purpose exist. We aimed to develop and validate a clinically applicable risk score for mortality, bleeding, and ischaemic events in cancer patients with ACS.

Methods: We analysed data of 1 017 759 patients with ACS from England, UK (n=815 170; 36 771 with cancer), Sweden (n=194 059; 10 262 with cancer), and Switzerland (n=8530; 203 with cancer) between Jan 1, 2004, and Aug 8, 2023. Machine learning models to predict 1) all-cause mortality, 2) major bleeding, and 3) ischaemic events, defined as a composite of cardiovascular death, myocardial infarction, and ischaemic stroke, were developed in cancer patients with ACS from England in a competing risks framework with a prediction horizon of 6 months. Final models (the ONCO-ACS score) were externally validated in geographically distinct held out datasets from the English Midlands, Sweden, and Switzerland.

Findings: Cancer patients with ACS were characterised by high rates of mortality (cumulative incidence 27·8% [95% CI 27·3%–28·3%]), major bleeding (7·3% [7·0%–7·5%]), and ischaemic events (16·1% [15·7%–16·4%]) and had a distinct risk profile. The ONCO-ACS score was informed by a single set of variables: tumour type, time since cancer diagnosis, metastatic disease, age, haemoglobin, heart rate, estimated glomerular filtration rate, body mass index, Killip class, cardiac arrest, and major bleed within six months. Accounting for traditional and cancer-related risk factors ONCO-ACS showed an area under the time-dependent receiver operating characteristic curve (tAUC at 6 months) of 0·84 (0·83–0·85) for all-cause mortality, of 0·70 (0·68–0·73) for major bleeding and of 0·79 (0·78–0·81) for ischaemic events upon internal validation. On external validation, ONCO-ACS achieved similar performance for all-cause mortality (Midlands tAUC at 6 months 0·84 [0·82–0·85], Sweden 0·80 [0·79–0·82], Switzerland 0·83 [0·76–0·91]), major bleeding (Midlands 0·70 [0·67–0·74], Sweden 0·67 [0·65–0·70], Switzerland 0·74 [0·57–0·91]), and ischaemic events (Midlands 0·76 [0·74–0·78], Sweden 0·70 [0·69–0·72], Switzerland 0·73 [0·61–0·86]). ONCO-ACS was well calibrated and decision curve analyses suggested favourable clinical utility. Applying ONCO-ACS to current guidelines suggests that most cancer patients with ACS qualify for invasive management and long dual antiplatelet therapy using clopidogrel.

Interpretation: The ONCO-ACS score provides a validated practical tool for predicting mortality, bleeding, and ischaemic risk in cancer patients with ACS. Combined assessment of competing outcome risks may facilitate balancing treatment benefits and harms.

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Research in context

Evidence before this study

The management of cancer patients with acute coronary syndrome (ACS) is challenging due to a complex interplay of total mortality, bleeding risk, and ischaemic risk. We systematically searched PubMed for studies published from database inception up to Jan 15, 2025, using the search terms: “acute coronary syndrome”, “myocardial infarction”, “cancer”, “malignancy”, “neoplasm”, and “malignant”, with no language restrictions. No articles were excluded. Cancer patients were systematically excluded from clinical trials and established risk stratification tools in ACS. Available risk scores do not account for cancer characteristics or for competing risks, which are particularly relevant due to high event rates in cancer patients with ACS. No risk classification system for cancer patients with ACS is currently available.

Added value of this study

We used nationwide ACS cohorts from England, Sweden, and Switzerland, including 1 017 759 patients, of whom 47 236 had cancer. Cancer patients with ACS were characterised by different clinical characteristics and a distinct risk profile. Leveraging a machine learning-based approach, we developed and externally validated, for the first time, a novel cancer-specific risk tool for mortality, bleeding, and ischaemic events after the ACS (the ONCO-ACS score). Based on 11 clinically available variables, the ONCO-ACS score simultaneously predicts the risk of multiple clinically relevant outcomes to support decision making. ONCO-ACS considers competing event risks and enables risk stratification of cancer patients with ACS. Risk groups were based on a cancer-free reference population to facilitate the contextualisation of existing clinical evidence and the design of future clinical trials in cancer patients with ACS.

Implications of all the available evidence

The ONCO-ACS score provides a validated, practical tool for predicting mortality, major bleeding and ischaemic events in cancer patients with ACS. In the context of a comprehensive clinical evaluation, this standardised tool may support personalised treatment decisions. Early risk stratification based on multiple competing risks can inform tailored strategies for interventional procedures and antithrombotic therapy in patients with cancer and ACS. The ONCO-ACS score may further guide the design of dedicated randomised controlled trials in cancer patients with ACS.

Introduction

The management of cancer patients with acute coronary syndrome (ACS) is challenging. Cancer-related tissue damage, a systemic pro-inflammatory state, concomitant coagulation disturbance and varying cancer-specific mortality lead to a complex interplay of overall mortality, bleeding risk, and ischaemic risk.[1-3] An ageing population and improved survival following a cancer diagnosis have resulted in increasing numbers of cancer patients presenting with ACS,[1,2,4] yet existing evidence to inform ACS management in these patients is sparse.

Cancer patients were systematically excluded from the development of current risk tools and from major randomised controlled trials in ACS.[1,2] This is reflected by poor performance of established risk stratification tools for patients with ACS and a history of cancer.[5] Emerging evidence supports that cancer patients with ACS display a distinct clinical phenotype characterised by frailty, high comorbidity burden, more extensive coronary artery disease, alongside oncological features. Importantly, outcomes in these patients are determined by both traditional and cancer-related factors. While timely myocardial revascularisation remains the cornerstone of care in ACS, an individual's cancer-related characteristics warrant careful consideration, particularly with respect to secondary prevention measures and antithrombotic therapy.

Optimal ACS management requires a balanced assessment of multiple competing risks. According to international guidelines,[1,2] individualised estimation of mortality, bleeding, and ischaemic event risks should guide the approach to invasive treatment, the type and duration of antithrombotic therapy, and potential adaptations in cancer therapy. However, currently there are no tools and no standardised risk classification systems available for this purpose.

Here, we sought to develop and externally validate a clinically useful risk score to predict all-cause mortality, major bleeding, and ischaemic events in cancer patients with ACS.

Methods

Study design

We used national health data from England, Sweden and Switzerland to create real-world ACS cohorts with information on cancer. Patients were stratified into individuals with a

current or previous cancer diagnosis within five years prior to presentation and individuals without (appendix pp 4, 20).[6,7]

Clinical characteristics, outcomes, and outcome-specific predictive importance of baseline variables were compared between patients with and without cancer in England (n = 815 170, appendix pp 14–18, 43–47). Clinically applicable prediction models for all-cause mortality, major bleeding, and ischaemic events (ONCO-ACS score) in cancer patients with ACS, informed by a single set of clinically available predictor variables, were developed in England with patients from the Midlands excluded (n = 31 193). Geographically distinct datasets from the English Midlands (n = 5578, external validation cohort 1) and from Sweden (n = 10 262, external validation cohort 2) were used for external validation. In addition, we externally validated all models in a cohort of cancer patients with ACS from Switzerland (n = 203, external validation cohort 3) with manual review of hospital case notes for cancer-specific variables and outcomes.

We included all cancer patients with ACS into risk model development and validation, regardless of whether they had undergone invasive management or not, given that many patients are not eligible for invasive treatment, and numerous treatment decisions that require balancing of bleeding risk and ischaemic risk precede the completion of invasive treatment in the clinical workflow.[8] Cancer diagnoses were defined according to the International Classification of Disease 10th revision (appendix p 23). Benign tumours, in-situ tumours, neoplasms of uncertain or unknown behaviour and non-melanoma skin neoplasms were not counted as cancer since they present distinct clinical considerations.

Participants

In England, we used multiple national health datasets within the framework of the Virtual Cardio-Oncology Research Initiative (VICORI), a whole-country cardio-oncology research platform from multisource electronic health records (appendix p 4).[9] We linked individual-level data across the Myocardial Ischaemia National Audit Project (MINAP),[10] the National Cancer Registration Dataset (NCRD),[9,11] the British Cardiovascular Intervention Society National Adult Percutaneous Coronary Interventions (BCIS NAPCI) dataset, the Hospital Episode Statistic (HES), and the Office for National Statistics (ONS, appendix p 4). Between Jan 1, 2005, and Mar 31, 2018, we included 815 170 patients with ACS (appendix p 4) aged >18 years presenting to one of 209 hospitals in England (appendix pp 9–11). Among these, 36 771 patients had current or previous cancer.

In Sweden, we linked data across the Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART),[12] the Swedish National Patient Registry (NPR), the National Cancer Registry (NCR), Statistics Sweden (SS), and the National Cause-of-Death Registry (NCDR). Between Jan 1, 2004, and Dec 31, 2014, there were 194 059 patients with ACS aged >18 years presenting to one of 80 hospitals in Sweden (appendix p 12). Among these, 10 262 patients had current or previous cancer.

In Switzerland, we used data from the prospective nationwide ACS registry (Acute Myocardial Infarction in Switzerland [AMIS] Plus, NCT01305785)[13] and from the prospective multicentre Special Programme University Medicine Acute Coronary Syndrome (SPUM-ACS) cohort (NCT01000701, appendix pp 5, 13),[14-16] including a total of 8 530 patients aged >18 years presenting with ACS to University Hospital Zurich and University Hospital Bern between Jan 1, 2005, and Aug 8, 2023. Among these, 203 patients had current or previous cancer. For all participants, data on sex were collected from medical records with two options available (male and female). Ethnicity was based on self-reported data in the UK and on country of birth in Sweden. No data on ethnicity were available in Switzerland.

Outcomes

Mortality of any cause at 6 months after admission for ACS, major bleeding at 6 months after admission for ACS, and ischaemic events, defined as the first occurrence of a composite of cardiovascular death, myocardial infarction and ischaemic stroke[17], at 6 months after admission for ACS are the primary outcomes of the respective ONCO-ACS prediction models. In England, clinical outcomes were obtained from the HES and the ONS (appendix pp 5, 25). In Sweden, outcomes were obtained from the NCDR and the NPR (appendix pp 5, 25). In AMIS Plus, events were ascertained through manual medical chart review using predefined variable definitions conducted by independent investigators who were not involved in data analysis. In SPUM-ACS, events were recorded using pre-specified protocols and confirmed by an independent event adjudication committee (appendix pp 5, 25).

Development of prediction models

We leveraged a machine learning approach to capture potential complex non-linear relationships between baseline characteristics and outcomes. We used eXtreme Gradient Boosting (XGB), a well-established and widely-used tree-based ensemble learning algorithm for all prediction models.[14,18,19] For the prediction of major bleeding and ischaemic events,

non-bleeding-related mortality and non-ischaemia-related mortality were treated as competing risks, respectively (appendix p 5).[20]

Candidate predictors were extracted based on clinical considerations and evidence from the clinical, epidemiological, and prediction model literature (appendix pp 23–24). To evaluate the importance of individual variables and the risk distribution in patients with and without cancer, prediction models for each outcome were separately trained in patients with and without cancer using all traditional predictor variables (ie, variables not specific to cancer) as model features (appendix, pp 43–47). In cancer patients, additional models were trained with the inclusion of cancer-specific predictor variables. The importance of individual model features was assessed using the Shapley additive explanations (SHAP) approach (appendix pp 48–49). A SHAP value indicates how much a single feature contributes to the difference between actual prediction and mean prediction, considering its interaction with other features, given the current set of feature values. For validation of the SHAP approach, we used the XGB built-in Gain metric (appendix p 6).

Based on variable importance for the three score endpoints and clinical considerations, we used a single set of 11 predictor variables at admission (tumour type, time since cancer diagnosis, metastatic disease, age, haemoglobin, heart rate, estimated glomerular filtration rate, body mass index, Killip class, cardiac arrest, and major bleed within six months prior to admission) for all final prediction models (appendix p 5). The performance of the final models was evaluated on internal and external validation cohorts. Sample size considerations and further information on model development are summarised in the appendix (pp 5, 21–22).

Performance and external validation

We assessed various aspects of model performance. Discrimination was evaluated using the time-dependent area under the receiver operating characteristic curve (tAUC) at 6 months. The tAUC ranges from 0·5 to 1, with a value of 1 meaning perfect separation between individuals who had the event and those who did not. Calibration was evaluated by constructing smoothed calibration curves and by calculating the calibration slope, adjusting for competing risks where appropriate.[21,22] The calibration slope represents the dispersion of predicted risks and indicates whether they are overly extreme with an ideal value of 1.[21,22] To assess the specificity of the major bleeding model and the ischaemic event model for the respective outcome, observed probabilities of both outcomes were plotted as a function of each, predicted bleeding risk and predicted ischaemic risk. Clinical utility was evaluated

using decision curve analyses (appendix p 6). This approach implicitly accounts for both discrimination and calibration and extends the model evaluation to consider the ramifications on clinical decision making.[20]

External validation of model performance was conducted in regions not involved in the development process to evaluate geographical transportability (appendix, pp 6, 41). We did several subgroup analyses to assess the sensitivity of the models with respect to different population characteristics including sex, ethnicity, age, ACS type, tumour type, and evidence of active cancer (appendix p 6). Given the evolution of medical treatment over time, we assessed model performance across different time periods to evaluate temporal transportability (appendix, pp 6, 41). These analyses were done in validation cohort 1 due to its comparably high ethnical diversity and long overall observation period. For benchmarking, we compared the ONCO-ACS mortality model to the established Global Registry of Acute Coronary Events (GRACE) score for 6-month mortality[23], the ONCO-ACS major bleeding model to the PRECISE-DAPT score,[24] and the ONCO-ACS ischaemia model to the Patterns of Non-Adherence to Anti-Platelet Regimen In Stented Patients (PARIS) score for atherothrombotic events,[25] and assessed the improvement in risk discrimination and reclassification by calculating 1) the difference in tAUC (delta tAUC) at 6 months, 2) the integrated discrimination improvement (IDI) index, and 3) the continuous net reclassification improvement (NRI), each suggesting improved performance if values are positive (appendix pp 6–7).

Risk groups

As there is no established risk classification system for cancer patients with ACS, we grouped all cancer patients based on their predicted risk compared to patients without cancer. This approach facilitates the interpretation of predicted risks in the context of existing clinical evidence on ACS management that primarily derives from patients without cancer. Respective cutoffs were obtained from the risk distribution in the non-cancer population and absolute values are provided in the appendix (p 7). Patients were categorised into a low risk (≤33th percentile of risk in the non-cancer population), a moderate risk (>33th to ≤66th percentile of risk in the non-cancer population), a high risk (>66th to ≤90th percentile of risk in the non-cancer population), and a very high risk (>90th percentile of risk in the non-cancer population) group (appendix p 7). We calculated the competing risks-adjusted cumulative incidence functions of each outcome according to risk group. We used flexible parametric models and Fine-Gray subdistribution hazards regression models to estimate the unadjusted

hazard ratios (HRs) for mortality and subdistribution hazard ratios (SHRs) for bleeding and ischaemic events across risk groups with the respective low risk group serving as reference. We also explored a potential influence of risk group status on the observed association between treatment variables (ie, percutaneous coronary intervention [PCI] and dual antiplatelet therapy [DAPT] prescription at discharge) and clinical outcomes using multivariable-adjusted flexible parametric models (appendix p 7).

Impact on treatment stratification

We estimated the potential implications of the ONCO-ACS prediction models for clinical treatment stratification by applying the newly derived risk classification to current guideline recommendations.[1,2] To this end, we used the final prediction models to calculate the proportion of patients with 1) 6-month mortality risk ≤50%, for whom invasive management is recommended, 2) very high bleeding risk (>9%), in whom a short DAPT duration may be considered after PCI, and 3) low bleeding risk and very high ischaemic risk, in whom potent P2Y12 receptor inhibitors instead of clopidogrel may be considered for DAPT after PCI.[1,2] To demonstrate the use of ONCO-ACS, we provide patient examples that highlight how clinical characteristics contribute to the individual risk profile and potential treatment considerations.

Statistical analysis

A detailed description of the statistical analyses is presented in the appendix (pp 4–8). Continuous variables are presented as median and interquartile range (IQR) or mean and standard deviation (SD), as appropriate. Categorical data are shown as counts and valid percentages. Predictive analyses were conducted using multiply imputed data (10 imputations) and results were pooled using Rubin's rules (appendix p 8). Multiple imputation models were separately employed in each study cohort, as appropriate. To evaluate a potential impact of the imputation on the results, sensitivity analyses using complete cases were performed (appendix pp 26, 34–35). Data reporting follows the principles outlined by the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis Artificial Intelligence (TRIPOD AI) statement and the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement (appendix pp 63–66). All p values and CIs are two-tailed. Results were deemed statistically significant at a p <0·05. Data were analysed in R software version 4.3 or later. A calculator for the ONCO-ACS score, incorporating 11 widely available clinical variables, will be made available online [please add this link as a margin note: www.onco-acs.com](appendix pp 8, 40, 42).

Ethical approval was obtained from the respective institutional review boards and participant consent was obtained or waived in accordance with the prevailing local policy (appendix p 8).

Role of the funding source

This study was investigator-initiated. No sponsor played any role in the conception of the study, data collection, analysis, interpretation of the results, or writing of the manuscript. All authors had full access to the data and are responsible for the decision to submit for publication.

Results

A total of 1 017 759 patients with and without cancer presented with ACS to one of 291 involved hospitals between Jan 1, 2004, and Aug 8, 2023 (appendix pp 4, 41). Among these, there were 31 193 patients with cancer in the development cohort, 5578 patients with cancer in the English Midlands, 10 262 patients with cancer in Sweden, and 203 patients with cancer in Switzerland (tables 1–2). Cancer patients had different clinical characteristics and high rates of mortality (cumulative incidence 27·8% [95% CI 27·3%–28·3%]), major bleeding (7·3% [7·0%–7·5%]), and ischaemic events (16·1% [15·7%–16·4%]; appendix pp 14–19). The sex-specific, ethnic group-specific, age-specific, ACS type-specific, tumour type-specific, tumour activity-specific and period-specific cumulative incidence of mortality, major bleeding, and ischaemic events in cancer patients with ACS are summarised in the appendix (p 19).

The predictive importance of traditional risk factors differed between patients with and without cancer (appendix, pp 43–47). The newly developed ONCO-ACS score accounts for the cancer-specific importance of traditional risk factors and for cancer-related risk factors. The contribution of each score variable to the overall prediction varies by the predicted endpoint (figure 1; appendix pp 50–51).

ONCO-ACS showed a tAUC at 6 months of 0·84 (0·83–0·85) for all-cause mortality, 0·70 (0·68–0·73) for major bleeding, and 0·79 (0·78–0·81) for ischaemic events upon internal validation (appendix pp 27, 30, 52). On external validation, ONCO-ACS achieved similar performance for all-cause mortality (Midlands tAUC at 6 months 0·84 [0·82–0·85], Sweden 0·80 [0·79–0·82], Switzerland 0·83 [0·76–0·91]), major bleeding (Midlands 0·70 [0·67–0·74], Sweden 0·67 [0·65–0·70], Switzerland 0·74 [0·57–0·91]) and ischaemic events (Midlands 0·76 [0·74–0·78], Sweden 0·70 [0·69–0·72], Switzerland 0·73 [0·61–0·86];

appendix p 27). ONCO-ACS showed good alignment of observed and predicted risks across the entire spectrum of predicted risks (appendix pp 27, 53–55). Predicted risks of major bleeding were in good agreement with the observed risk of major bleeding but not with the observed risk of ischaemic events, and vice versa. This highlights that the predictions were specific to the respective endpoint (appendix p 62). Decision curve analyses suggested favourable clinical utility (appendix pp 56–61). ONCO-ACS provided helpful predictive performance across sex-, ethnic-, age-, ACS type-, tumour type-, and tumour activity-specific subgroups (appendix p 28). Model performance was stable across different periods of cohort entry (appendix p 29). The ONCO-ACS mortality model showed substantially improved performance for predicting mortality compared to the GRACE score across all validation cohorts (appendix p 33). Similarly, the ONCO-ACS bleeding and ischaemia models outperformed the PRECISE-DAPT score for predicting major bleeding at 6 months and the PARIS score for predicting ischaemic events at 6 months, respectively (appendix p 33). Decision curve analyses suggested higher net benefit of the ONCO-ACS score compared to the GRACE, PRECISE-DAPT and PARIS scores across the full range of clinically relevant decision thresholds (appendix pp 59–61).

ONCO-ACS classified 16 329/31 193 (52·3%) cancer patients with ACS as high or very high mortality risk, 19 683/31 193 (63·1%) as high or very high bleeding risk, and 19 220/31 193 (61·6%) as high or very high ischaemic risk, highlighting the increased vulnerability of this population. There was a progressive increase in events across risk groups for each endpoint (figure 2). The HRs of mortality were 7·0 (5·6–8·7) in the moderate risk group, 27·0 (21·6–33·6) in the high-risk group and 90·4 (72·2–113·2) in the very high-risk group compared to cancer patients in the low-risk group. The SHRs of bleeding and ischaemic events were 2·0 (1·4–2·8) and 3·1 (2·5–3·8) in the moderate risk group, 3·3 (2·3–4·7) and 5·8 (4·9–7·0) in the high-risk group and 7·8 (5·5–11·1) and 20·5 (17·2–24·3) in the very high-risk group, respectively.

Combined assessment of bleeding and ischaemic risk classified 1678/31 193 (5·4%) cancer patients with ACS as high or very high bleeding risk and low ischaemic risk suggesting particularly high potential benefit from a cautious approach to antithrombotic drug treatment (figure 3). In contrast, 1025/31 193 (3·3%) cancer patients with ACS were classified as high or very high ischaemic risk and low-bleeding risk suggesting potential benefit from intensive antithrombotic therapy. The strongest association of PCI with favourable outcomes at 6 months was observed in patients with low predicted mortality risk (p interaction < 0·0001,

appendix pp 36, 39). For DAPT, the strongest association with favourable outcomes was observed in patients with low predicted bleeding risk and very high predicted ischaemic risk (p interaction < 0·0001, appendix pp 37–39).

Applying ONCO-ACS-based risk estimates and cutoffs (figure 4) to current guidelines suggests that for 24 663/31 193 (79·1%) cancer patients with ACS invasive treatment is recommended, whereas in 6530/31 193 (20·9%) patients a conservative treatment strategy may be considered. Accounting for the predicted bleeding and ischaemic risk suggests that most patients with recommended invasive treatment may qualify for long DAPT using clopidogrel (figure 3).

Discussion

Heterogeneity in the ACS patient population has important implications for risk-stratified treatment. Here, we characterised the risk profile of cancer patients with ACS and developed a clinically applicable tool to support individualised decision-making on optimal management. Our results demonstrate that the relationship between clinical characteristics and outcomes differs between patients with and without cancer (appendix p 43–47).

Cancer-related systemic inflammation coupled with disturbances in the coagulation system induce a proatherogenic state while also promoting anticoagulant pathways, which leads to different levels of risk for ischaemic and bleeding events across cancer types (appendix p 19). The newly developed ONCO-ACS score enables accurate prediction of all-cause mortality, major bleeding, and ischaemic events, accounting for potential non-linear relationships and competing risks. This may help standardise outcome research and support more evidence-based risk assessment in routine clinical care. Using a single set of broadly available variables, ONCO-ACS reliably predicted multiple clinically relevant endpoints simultaneously. Thus, the score can be easily applied at the bedside through an online calculator.

External validation of ONCO-ACS on health data from multiple countries confirmed robust performance across regions, time periods, and population subgroups. Notably, our score outperformed established risk models that do not account for cancer.

In line with previous studies, cancer patients were older, had worse haemodynamics and decreased renal function, as well as higher rates of all-cause mortality, major bleeding, and ischaemic events.[26] The large proportion of cancer patients classified as high or very high risk of each score outcome highlights the unfavourable clinical phenotype of this vulnerable

patient population. Objective risk assessment based on ONCO-ACS could facilitate the interpretation of existing evidence on ACS management in the context of cancer and standardise guideline implementation. Translated into practice, our findings suggest that most cancer patients with ACS would qualify for invasive management and long DAPT using clopidogrel. In addition, the score may support the design of future clinical trials on the selection and timing of coronary revascularisation strategies, optimisation of antiplatelet therapy regimens, and adjustment of cancer treatment after ACS.

Benefits and harms of established pharmaco-interventional treatments depend on an individual's risk of adverse clinical outcomes. Patients with high or very high bleeding risk might benefit from a restrictive approach to antithrombotic therapy, especially when the ischaemic risk is low. In contrast, patients with high or very high ischaemic risk might benefit most from intensive secondary prevention, such as more aggressive antithrombotic therapy if the bleeding risk is low. Randomised trial evidence is required to determine the optimal risk thresholds for specific interventions.

In clinical practice, ONCO-ACS may help identify patients who benefit from conservative *vs* invasive management. Our results suggest the strongest association between PCI and favourable outcomes in patients with low mortality risk. Moreover, ONCO-ACS could facilitate the selection of acetylsalicylic acid (ASS) and clopidogrel *vs* ASS and potent P2Y12 receptor antagonist, guide the duration of DAPT, and inform the intensity of antiplatelet therapy in combination with oral anticoagulation. Additionally, the score may support individualised discussions with patients regarding the trade-offs between cardiovascular protection and bleeding risk, helping clinicians align treatment plans with patient preferences. Given the link between some cancer therapies and atherothrombotic events, ONCO-ACS may also support more personalised decisions on whether cancer therapy should be adjusted after ACS.[27] With current evidence on the management of cancer patients with ACS largely based on observational data, well-designed prospective research remains essential to substantiate treatment decisions in this vulnerable population.

Our study has several strengths. It is the largest study on risk assessment in cancer patients with ACS to date and includes multiple high-quality datasets. External validation of the score in cohorts from different countries reflected the geographical and sociocultural diversity of the population, enhancing the robustness of the results. Simultaneous prediction of mortality, bleeding, and ischaemic events from a single set of readily available clinical variables enhances the practical value of the score. In addition, ONCO-ACS is the first score for

patients with ACS accounting for cancer-specific risk factors. Finally, basing the definition of risk groups on a non-cancer population increases the comparability to prior evidence.

There are some limitations inherent to the involved cohorts. First, only a limited number of cancer-specific variables were available, and information on specific histological subtypes and marker profiles was lacking. Yet, in the context of large-scale ACS cohorts, our study is among the first and most comprehensive to account for key characteristics of cancer. Of note, histological and molecular subtyping might not be available in emergency situations and might reduce clinical applicability. Second, several non-cancer specific laboratory parameters such as platelet count could not be considered as they were not recorded across the involved cohorts. Nevertheless, the use of a limited number of readily available, standardised clinical variables facilitates further external validation efforts, provides high clinical applicability for physicians, and is less prone to overfitting the models to specific variables. Next, due to lack of information on cancer therapy, we could not evaluate model performance across different types of local and systemic cancer treatment regimens. However, we found good model performance in patients recruited in recent years. In addition, our study included cohorts from three European countries with a high proportion of White patients underlining the need for external validation of our findings in ethnically more diverse populations. Finally, the size of the Swiss cohort is limited. Yet, this cohort featured prospective external event adjudication and adds an additional layer of evidence supporting the predictive performance of the score.

In conclusion, the ONCO-ACS score is the first practical tool for comprehensive risk assessment in cancer patients with ACS. The score simultaneously predicts mortality, bleeding, and ischaemic events to help clinicians balance treatment benefits and harms. In the context of a comprehensive clinical evaluation, the ONCO-ACS risk score can support personalised treatment decisions on whether to pursue an invasive strategy, how to tailor DAPT intensity and duration, and when to adjust cancer therapy in the context of cardiovascular risk. Our study highlights the distinct clinical phenotype of cancer patients with ACS and may guide the design of clinical trials for this growing patient population. Further studies are warranted to provide randomised evidence on the clinical benefit of the ONCO-ACS score and assess its performance in other geographies.

Contributors

FAW and DA conceived the study. FAW, FT, JL, MAV, and DR performed data queries. VS and AG performed chart reviews and gathered data. FAW, FT, JL, PW and MAV were

involved in the data curation. FAW and MAV accessed, verified, and analysed the data. FAW, PW, and MAV generated descriptive summary statistics of patient baseline characteristics. FAW wrote the first draft of the manuscript. FAW, MAV, and MAS were involved in the visualisation of the results. FAW, SJ, DA and TFL jointly directed the study. All authors provided important intellectual input in the interpretation of the data, revisited the work critically, approved the final version of the manuscript to be published, and agreed to be accountable for the content and the decision to submit for publication.

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Declaration of interests

FAW has no conflicts of interest related to this manuscript but reports financial support from the Fund for Fostering Young Scientists at the University of Zurich, the European Society of Cardiology, the Swiss Society of Cardiology, the Swiss Heart Foundation, the Medical University of Graz, Amgen Switzerland, 4TEEN4 Pharmaceuticals GmbH, PAM Theragnostics GmbH and Sphingotec GmbH. Further, FAW has received support for attending meetings by 4TEEN4 Pharmaceuticals GmbH, PAM Theragnostics GmbH, the European Society of Cardiology, the Swiss Society of Cardiology, the Zurich Heart House – Foundation for Cardiovascular Research and the Critical Care Clinical Trialists Workshop, and has received support for biomarker measurement by Roche Diagnostics, 4TEEN4 Pharmaceuticals GmbH, PAM Theragnostics GmbH and Sphingotec GmbH, outside of the submitted work. FAW reports membership in the ESC Digital Cardiology & AI Committee and the Steering Committee of the Swiss National Registry of Myocardial Infarction. KWO is a National Institute of Health and Care Research (NIHR) Academic Clinical Fellow in Cardiology and funded by the NIHR (ACF-2021-11-007). MAS reports travel grants by Alphamed Fischer, Implantcast, ImplanTec, and PharmaMar, outside of the submitted work. EH received institutional grants by Pfizer, NovoNordisk, and Amgen, declares honoraria for lectures by Amgen, NovoNordisk, AstraZeneca and Bayer, has participated on the Data Safety Monitoring Board/Advisory Board of Amarin AB, NovoNordisk, Amgen, and Sanofi, is Chair of the Swedish Secondary Prevention Registry and has leadership roles in the National Coordinator DalCore: CAL301 DalGene and R1500-CL-1643; Aegis II/Perfuse,

outside of the submitted work. MS has received honoraria for lectures by Amgen, Boehringer Ingelheim, Novartis and NovoNordisk, and has participated in the Advisory Board for AstraZeneca. CW received honoraria for educational meetings by AstraZeneca and is the Clinical Lead of the Myocardial Ischaemia National Audit Project (MINAP) registry. CT received consulting fees by Biotronik, Medtronic, Microport and Philips, declares honoraria for lectures by AstraZeneca, Boehringer Ingelheim, and Novartis, and has received payment for expert testimony by Microport, outside of the submitted work. LR received grants from Abbott, Boston Scientific, Biotronik, Sanofi, Regeneron, Infraredx, and the Swiss National Science Foundation, reports consulting fees by Abbott, Amgen, Medtronic, NovoNordisk, Occlutech, and Sanofi, and has received honoraria for lectures by Abbott and Occlutech, outside of the submitted work. JD received grants by Alzheimer's Research UK (2022–2025) and British Heart Foundation (2019–2022), consulting fees by Amgen, AstraZeneca, Boehringer Ingelheim, Merck, Pfizer, Aegerion, Novartis, Sanofi, Takeda, NovoNordisk, and Bayer, and honoraria for lectures by Amgen, AstraZeneca, Boehringer Ingelheim, Merck, Pfizer, Aegerion, Novartis, Sanofi, Takeda, NovoNordisk, and Bayer, outside of the submitted work. SJ received research grants by Janssen, AstraZeneca, Amgen, BMS, Novo Nordisk, Edwards and Medtronic, and consulting fees by Medtronic, and declares participation on the Data Safety Monitoring Board/Advisory Board of New Amsterdam, outside of the submitted work. DA received research grants by Cancer Research UK and the British Heart Foundation for the submitted work, research grants by NIHR UK, Abbott Vascular and Heart Research UK, outside of the submitted work, has received royalties by Elsevier, holds patents (cardiac arrest device - EP3277337A1, heart failure shunt device – patent application number 2211616.4), is member of the Phoenix study (NCT05825417), member of the Advisory Board of Beat SCAD, and Chair of the ESC-EORP SCAD Registry. TFL has no conflicts of interest related to this manuscript, but received institutional educational and research grants from Abbott, Ablative Solutions, Amgen, AstraZeneca, Boehringer Ingelheim, Daichi Sankyo, Novartis, Sanofi, Servier and Vifor. TFL has received consulting fees by Daichi Sankyo, Philips, Pfizer and Ineeo Inc, and honoraria from Amgen, Dacadoo, Daichi Sankyo, GlaxoSmithKline, Firalis, Menarini Foundation, NeuroImmune and NovoNordisk, outside of the submitted work, and holds leadership positions at the European Society of Cardiology, the Swiss Heart Foundation, the Foundation for Cardiovascular Research—Zurich Heart House and the London Heart House, London, UK. The other authors report no conflicts of interest.

Data sharing

Due to data protection regulations related to the different study cohorts involved in this study the authors do not have authorisation to provide unrestricted data access. Requests for the data and additional documents including the analysis code related to the present study should be made to the corresponding author.

Figure legends

Figure 1: **Outcome-specific risk prediction by the ONCO-ACS score**

Variable importance according to mean (ie, aggregated across all patients) absolute Shapley (SHAP) value scaled to the variable with the highest value in the final prediction models depicted as radar plots (top) and predicted *vs* observed event probability for each score outcome (bottom) for (A) all-cause mortality, (B) major bleeding, and (C) ischaemic events at 6 months. Colour bands signify 95% confidence intervals. Radar plots are based on patients in the training dataset in the development cohort and calibration plots are based on data from external validation cohort 1. Untransformed mean absolute SHAP values are provided in the appendix (p 50). BMI=body mass index, eGFR=estimated glomerular filtration rate.

Figure 2: **Classification of mortality, bleeding, and ischaemic risk in cancer patients with ACS**

Cumulative incidence curves for all-cause mortality (A), major bleeding (B), and ischaemic events (C) at 6 months in low-risk, moderate risk, high-risk, and very high-risk groups. The number at risk is indicated. Complete follow-up was available in all participants. In (B) and (C), numbers in brackets indicate competing events. Results are based on patients in the development cohort. HR=hazard ratio, SHR=subdistribution hazard ratio, CI=confidence interval.

Figure 3: **Combined assessment of competing outcome risks**

(A) Risk classification according to combined assessment of bleeding and ischaemic risk. (B) Potential treatment stratification in cancer patients with ACS when applying ONCO-ACS-based risk assessment to current guideline recommendations.[1,2] Results are based on patients in the development cohort. Absolute patient counts per category are provided in the appendix (pp 31–32). DAPT=dual antiplatelet therapy.

Figure 4: **Illustrative patient examples**

(A) Example of a hypothetical 59-year-old patient with breast cancer, diagnosed 5 months ago, no evidence of metastatic disease, and the following clinical characteristics: BMI 26, heart rate 77 bpm, Killip class I, no cardiac arrest, negative history for prior bleed in past 6 months, eGFR 84 ml/min and haemoglobin levels of 12 g/dL. In comparison to the non-

cancer reference population, ONCO-ACS predicts low mortality risk and moderate bleeding and ischaemic risk in this patient. Thus, invasive treatment and long DAPT with clopidogrel may be considered.[1,2] (B) Example of a hypothetic 77-year-old patient diagnosed with metastatic lung cancer 9 months ago and the following clinical characteristics: BMI 24, heart rate 88 bpm, Killip class I, no cardiac arrest, negative history for prior bleed in past 6 months, eGFR 73 ml/min and haemoglobin levels of 10 g/dL. According to ONCO-ACS, mortality risk is very high compared to the non-cancer population, and ischaemic and bleeding risk are high. Therefore, a conservative treatment strategy may be considered.[1,2] (C) Example of a hypothetical 66-year-old patient diagnosed with bladder cancer 48 months ago, no evidence of metastatic disease, and the following clinical characteristics: BMI 22, heart rate 77 bpm, Killip class II, no cardiac arrest, positive history of prior bleed in past 6 months, eGFR 52 ml/min and haemoglobin levels of 11 g/dL. ONCO-ACS classifies this patient as having very high bleeding risk, very high ischaemic risk, and high mortality risk. Consequently, invasive treatment and short DAPT with clopidogrel may be considered.[1,2] Data are depicted as waterfall plot to explain the contribution of each feature value in a specific patient to the model prediction. Bars represent absolute increase (purple) or decrease (green) in predicted risk. BMI=body mass index, bpm=beats per minute, DAPT=dual antiplatelet therapy, eGFR=estimated glomerular filtration rate.

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	Development cohort (England w/o Midlands; *n* = 31 193)	Validation cohort 1 (English Midlands; *n* = 5578)	Validation cohort 2 (Sweden; *n* = 10 262)	Validation cohort 3 (Switzerland; *n* = 203)
Age, years	76 (68–82)	75 (68–81)	75 (68–82)	70 (63–77)
Sex				
Female	9769/31 121 (31·4%)	1653/5547 (29·8%)	2958/10 262 (28·8%)	39/203 (19·2%)
Male	21 352/31 121 (68·6%)	3894/5547 (70·2%)	7304/10 262 (71·2%)	164/203 (80·8%)
Ethnicity				
Asian	268/30 834 (0·9%)	42/5542 (0·8%)	98/10 261 (1·0%)	..
Black	732/30 834 (2·4%)	149/5542 (2·7%)	16/10 261 (0·2%)	..
Mixed	59/30 834 (0·2%)	12/5542 (0·2%)	15/10 261 (0·1%)	..
White	29 469/30 834 (95·6%)	5327/5542 (96·1%)	10 113/10 261 (98·6%)	..
Other	306/30 834 (1·0%)	12/5542 (0·2%)	19/10 261 (0·2%)	..
Haemodynamics				
Heart rate, beats per minute	80 (68–96)	79 (66–95)	78 (66–94)	78 (68–89)
Systolic blood pressure, mm Hg	136 (29)	136 (28)	145 (29)	127 (28)
Cardiac arrest	1690/31 193 (5·4%)	272/5578 (4·9%)	122/9295 (1·3%)	16/203 (7·9%)
Killip class				
I	10 064/13 582 (74·1%)	1609/2115 (76·1%)	8273/9725 (85·1%)	153/199 (76·9%)
II	2328/13 582 (17·1%)	336/2115 (15·9%)	1135/9725 (11·7%)	19/199 (9·5%)
III	944/13 582 (7·0%)	119/2115 (5·6%)	178/9725 (1·8%)	9/199 (4·5%)
IV	246/13 582 (1·8%)	51/2115 (2·4%)	139/9725 (1·4%)	18/199 (9·0%)
ST-segment deviation	14 622/29 913 (48·9%)	2937/5373 (54·7%)	5225/7501 (69·7%)	114/192 (59·4%)
Onset-to-door time, min	190 (103–508)	180 (99–464)	208 (100–570)	215 (112–540)
Cardiometabolic risk factors				
BMI, kg/m^2	26 (23–29)	26 (24–30)	26 (24–29)	27 (25–30)
Body surface area, m^{2*}	1·9 (0·2)	1·9 (0·2)	1·9 (0·2)	1·9 (0·2)
Diabetes	6654/30 010 (22·2%)	1215/5384 (22·6%)	2478/10 262 (24·1%)	48/200 (24·0%)
Dyslipidaemia[†]	8182/28 456 (28·8%)	1307/4650 (28·1%)	2718/10 176 (26·7%)	106/197 (53·8%)
Smoking status				
Never	11 099/28 162 (39·4%)	2058/5119 (40·2%)	4147/9221 (45·0%)	57/191 (29·8%)
Former	12 345/28 162 (43·8%)	2176/5119 (42·5%)	3713/9221 (40·3%)	88/191 (46·1%)
Current	4718/28162 (16·8%)	885/5119 (17·3%)	1361/9221 (14·8%)	46/191 (24·1%)
Tumour type				
Anus	131/31 193 (0·4%)	15/5578 (0·3%)	27/10 262 (0·3%)	2/203 (1·0%)
Bladder	1768/31 193 (5·7%)	308/5578 (5·5%)	767/10 262 (7·5%)	18/203 (8·9%)
Brain	92/31 193 (0·3%)	9/5578 (0·2%)	21/10 262 (0·2%)	3/203 (1·5%)
Breast	2995/31 193 (9·6%)	567/5578 (10·2%)	923/10 262 (9·0%)	9/203 (4·4%)
Cervix	110/31 193 (0·4%)	7/5578 (0·1%)	36/10 262 (0·4%)	0/203 (0·0%)
Colorectal	4386/31 193 (14·1%)	754/5578 (13·5%)	1341/10 262 (13·1%)	21/203 (10·3%)
Hodgkin lymphoma	147/31 193 (0·5%)	27/5578 (0·5%)	26/10 262 (0·3%)	4/203 (2·0%)
Kidney	1064/31 193 (3·4%)	186/5578 (3·3%)	239/10 262 (2·3%)	6/203 (3·0%)
Larynx	332/31 193 (1·1%)	63/5578 (1·1%)	59/10 262 (0·6%)	2/203 (1·0%)
Leukaemia	1033/31 193 (3·3%)	162/5578 (2·9%)	251/10 262 (2·4%)	10/203 (4·9%)
Liver	235/31 193 (0·8%)	30/5578 (0·5%)	46/10 262 (0·4%)	0/203 (0·0%)
Lung	2956/31 193 (9·5%)	469/5578 (8·4%)	417/10 262 (4·1%)	23/203 (11·3%)
Melanoma	1155/31 193 (3·7%)	201/5578 (3·6%)	488/10 262 (4·8%)	13/203 (6·4%)
Mesothelioma	152/31 193 (0·5%)	19/5578 (0·3%)	0/10 262 (0·0%)	0/203 (0·0%)
Myeloma	716/31 193 (2·3%)	127/5578 (2·3%)	141/10 262 (1·4%)	5/203 (2·5%)
Non-Hodgkin lymphoma	1310/31 193 (4·2%)	249/5578 (4·5%)	345/10 262 (3·4%)	11/203 (5·4%)
Oesophagus	582/31 193 (1·9%)	99/5578 (1·8%)	43/10 262 (0·4%)	6/203 (3·0%)
Ovary	355/31 193 (1·1%)	56/5578 (1·0%)	76/10 262 (0·7%)	2/203 (1·0%)
Pancreas	321/31 193 (1·0%)	42/5578 (0·8%)	59/10 262 (0·6%)	3/203 (1·5%)
Prostate	8024/31 193 (25·7%)	1554/5578 (27·9%)	3702/10 262 (36·1%)	46/203 (22·7%)
Small intestine	92/31 193 (0·3%)	18/5578 (0·3%)	34/10 262 (0·3%)	0/203 (0·0%)
Stomach	544/31 193 (1·7%)	92/5578 (1·6%)	87/10 262 (0·8%)	2/203 (1·0%)

Testis	83/31 193 (0·3%)	29/5578 (0·5%)	22/10 262 (0·2%)	3/203 (1·5%)
Thyroid	117/31 193 (0·4%)	19/5578 (0·3%)	47/10 262 (0·5%)	0/203 (0·0%)
Uterus	550/31 193 (1·8%)	126/5578 (2·3%)	240/10 262 (2·3%)	1/203 (0·5%)
Vulva	126/31 193 (0·4%)	28/5578 (0·5%)	34/10 262 (0·3%)	0/203 (0·0%)
Other	1817/31 193 (5·8%)	322/5578 (5·8%)	791/10 262 (7·7%)	13/203 (6·4%)
Time since tumour diagnosis, months	19 (6–38)	20 (7–39)	24 (10–41)	20 (5–37)
Metastatic disease	2747/14 302 (19·2%)	471/2424 (19·4%)	1256/7262 (17·3%)	31/203 (15·3%)
Clinical chemistry and haematology				
Haemoglobin, g/dL	12·3 (2·2)	12·5 (2·2)	13·1 (1·9)	12·6 (2·4)
Troponin elevation‡	28 133/29 489 (95·4%)	5119/5355 (95·6%)	9188/10 261 (89·6%)	163/165 (98·8%)
Estimated glomerular filtration rate, ml/min¶	66 (25)	69 (24)	60 (22)	76 (24)
Glucose, mmol/L	7·1 (6·0–9·3)	7·1 (6·0–9·4)	7.0 (5·9–9·0)	7·0 (5·9–9·2)
Total cholesterol, mmol/L	4·4 (3·6–5·4)	4·5 (3·7–5·4)	4.7 (4·0–5·6)	4·4 (3·6–5·4)
Medical history				
Heart failure	1903/28 798 (6·6%)	261/4642 (5·6%)	1575/10 262 (15·3%)	2/203 (1·0%)
Atrial fibrillation	7472/31 193 (24·0%)	1217/5578 (21·8%)	1444/10 262 (14·1%)	5/102 (4·9%)
Hypertension	15 154/29 287 (51·7%)	2483/4745 (52·3%)	6061/10 262 (59·1%)	137/200 (68·5%)
Peripheral vascular disease	1538/28 503 (5·4%)	189/4636 (4·1%)	920/10 262 (9·0%)	11/203 (5·4%)
Chronic kidney disease	2454/28 751 (8·5%)	364/4638 (7·8%)	523/10 262 (5·1%)	33/102 (32·4%)
Obstructive lung disease	5235/28 605 (18·3%)	719/4649 (15·5%)	899/10 262 (8·8%)	31/203 (15·3%)
Peptic ulcer disease	2381/31 193 (7·6%)	351/5578 (6·3%)	734/10 262 (7·2%)	1/102 (1·0%)
Prior ischaemic events				
Myocardial infarction	6086/29 340 (20·7%)	902/4725 (19·1%)	2222/10 262 (21·7%)	34/203 (16·7%)
Cerebrovascular ischaemia	2820/28 796 (9·8%)	364/4640 (7·8%)	1219/10 262 (11·9%)	9/203 (4·4%)
Prior coronary revascularization				
PCI	2104/28 851 (7·3%)	348/4650 (7·5%)	818/10 262 (8·0%)	40/200 (20·0%)
Coronary artery bypass grafting	2069/28 964 (7·1%)	279/4666 (6·0%)	825/10 262 (8·0%)	12/200 (6·0%)
Prior bleeding events				
Major bleed w/i six months	3372/31 193 (10·8%)	505/5578 (9·1%)	235/10 262 (2·3%)	1/102 (1·0%)
Intracranial haemorrhage	274/31 193 (0·9%)	39/5578 (0·7%)	99/10 262 (1·0%)	··

***Table 1*: Baseline characteristics of patients in the ONCO-ACS development and validation cohorts.**
Data are median (IQR), mean (SD) or n/N (%). BMI = body mass index. ECG=electrocardiogram. PCI = percutaneous coronary intervention. *Estimated according to Du Bois and Du Bois. †Defined as elevation in total cholesterol requiring dietary or drug treatment. ‡Refers to values > 99th percentile. ¶ Estimated according to Chronic Kidney Disease Epidemiology Collaboration 2021 creatinine equation.

	Development cohort (England w/o Midlands; *n* = 31 193)	Validation cohort 1 (English Midlands; *n* = 5578)	Validation cohort 2 (Sweden; *n* = 10 262)	Validation cohort 3 (Switzerland; *n* = 203)
Type of intervention				
PCI	5161/8049 (64·1%)	1074/1489 (72·1%)	4765/10 262 (46·4%)	177/199 (88·9%)
Angiography only	1181/8049 (14·7%)	183/1489 (12·3%)	2000/10 262 (19·5%)	1/199 (0·5%)
Access site				
Radial	5255/7958 (66·0%)	1375/1880 (73·1%)	3281/10 262 (32·0%)	17/56 (30·4%)
Femoral	2905/7959 (36·5%)	561/1880 (29·8%)	3283/10 262 (32·0%)	39/56 (69·6%)
Brachial	9/7958 (0·1%)	4/1880 (0·2%)	9/10 262 (0·1%)	0/56 (0·0%)
Procedural characteristics				
Multivessel disease*	5346/8167 (65·5%)	1139/1895 (70·7%)	3329/6071 (54·8%)	87/199 (43·7%)
Vein graft recanalization	68/8167 (0·8%)	14/1895 (0·7%)	128/4764 (2·7%)	5/78 (6·4%)
Drug-eluting stent	5211/7810 (66·7%)	1176/1822 (64·5%)	1915/4764 (40·2%)	150/152 (98·7%)
Stent diameter ≤ 3 mm	2924/7026 (41·6%)	799/1713 (46·6%)	3255/4764 (68·3%)	67/93 (72·0%)
Left ventricular ejection fraction (%)				
< 30%	1743/13 211 (13·2%)	259/1999 (13·0%)	502/6705 (7·5%)	17/147 (11·6%)
30%–49%	4607/13 211 (34·9%)	699/1999 (35·0%)	2613/6705 (39·0%)	49/147 (33·3%)
≥ 50%	6861/13 211 (51·9%)	1041/1999 (52·1%)	3590/6705 (53·5%)	81/147 (55·1%)
Periprocedural medication				
$P2Y_{12}$ receptor inhibitor	22 888/28 891 (79·2%)	4172/5131 (81·3%)	4489/4680 (95·9%)	162/167 (97·0%)
Unfractionated heparin	5115/26 371 (19·4%)	944/3854 (24·5%)	415/10 222 (4·1%)	184/203 (90·6%)
Low-molecular-weight heparin	14 924/26 837 (55·6%)	2459/3867 (63·6%)	3682/10 222 (36·0%)	7/203 (3·4%)
Fondaparinux	7396/22 675 (32·6%)	453/3153 (14·4%)	2931/10 222 (28·7%)	3/199 (1·5%)
Bivalirudin	290/9983 (2·9%)	61/1383 (4·4%)	1405/4243 (33·1%)	4/198 (2·0%)
β-blocker	14 266/19 174 (74·4%)	1914/2540 (75·4%)	4402/10 222 (43·1%)	30/102 (29·4%)
Diuretics	9445/26 571 (35·5%)	1332/3861 (34·5%)	2464/10 221 (24·1%)	22/101 (21·8%)
In-hospital complications				
In-hospital cardiac arrest	1812/29 947 (6·1%)	321/5549 (5·8%)	236/10 119 (2·3%)	16/102 (15·7%)
In-hospital death	3614/31 193 (11·6%)	528/5578 (9·5%)	620/10 262 (6·0%)	16/203 (7·9%)
Discharge medication				
ASS	21 198/29 311 (72·3%)	4001/5249 (76·2%)	8813/10 217 (86·3%)	181/187 (96·8%)
$P2Y_{12}$ receptor inhibitor	14 252/22 003 (64·8%)	2785/3900 (71·4%)	6582/10 233 (64·3%)	177/197 (89·8%)
Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker	17 584/28 967 (60·7%)	3326/5230 (63·6%)	6494/10 212 (63·6%)	150/187 (80·2%)
Oral anticoagulant	1663/26 384 (6·3%)	269/3857 (7·0%)	780/10 215 (7·6%)	9/152 (5·9%)
β-blocker	18 506/29 087 (63·6%)	3484/5239 (66·5%)	8534/10 213 (83·6%)	145/187 (77·5%)
Statin	20 946/29 108 (72·0%)	3962/5245 (75·5%)	7555/10 213 (74·0%)	176/186 (94·6%)
Aldosterone antagonist	1396/20 942 (6·7%)	218/3799 (5·7%)	177/2797 (6·3%)	1/57 (1·8%)
Oral glucose-lowering medication	2594/28 960 (9·0%)	435/5136 (8·5%)	1094/10 216 (10·7%)	20/201 (10·0%)
Insulin	1447/28 960 (5·0%)	304/5136 (5·9%)	1014/10 219 (9·9%)	15/186 (8·1%)

***Table 2*: Treatment characteristics of patients in the ONCO-ACS development and validation cohorts.** Data are n/N (%). ASS=acetylsalicylic acid; PCI = percutaneous coronary intervention. *Defined as stenosis in any two of the following: left main coronary artery, left anterior descending coronary artery, left circumflex coronary artery, right coronary artery.

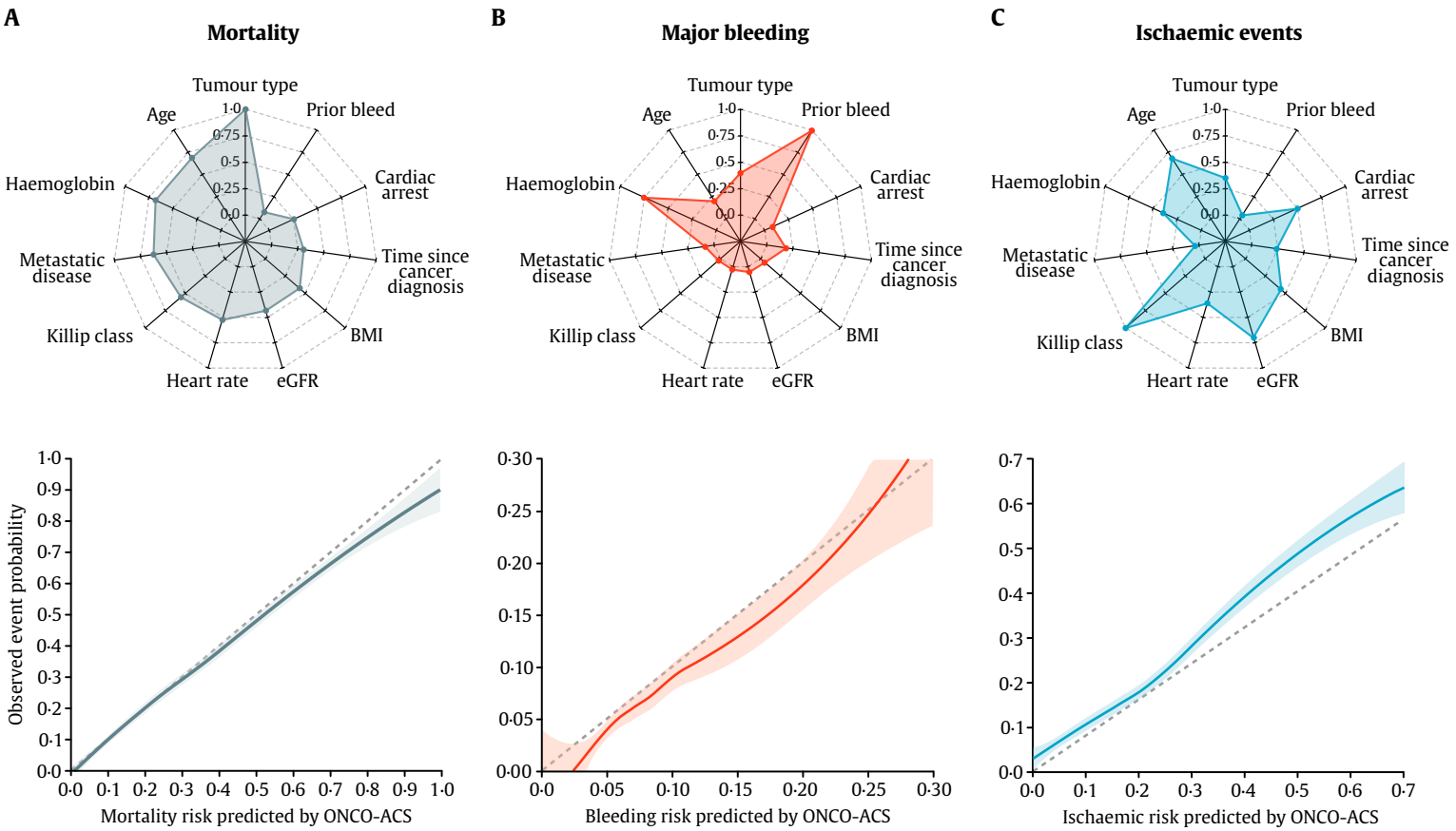
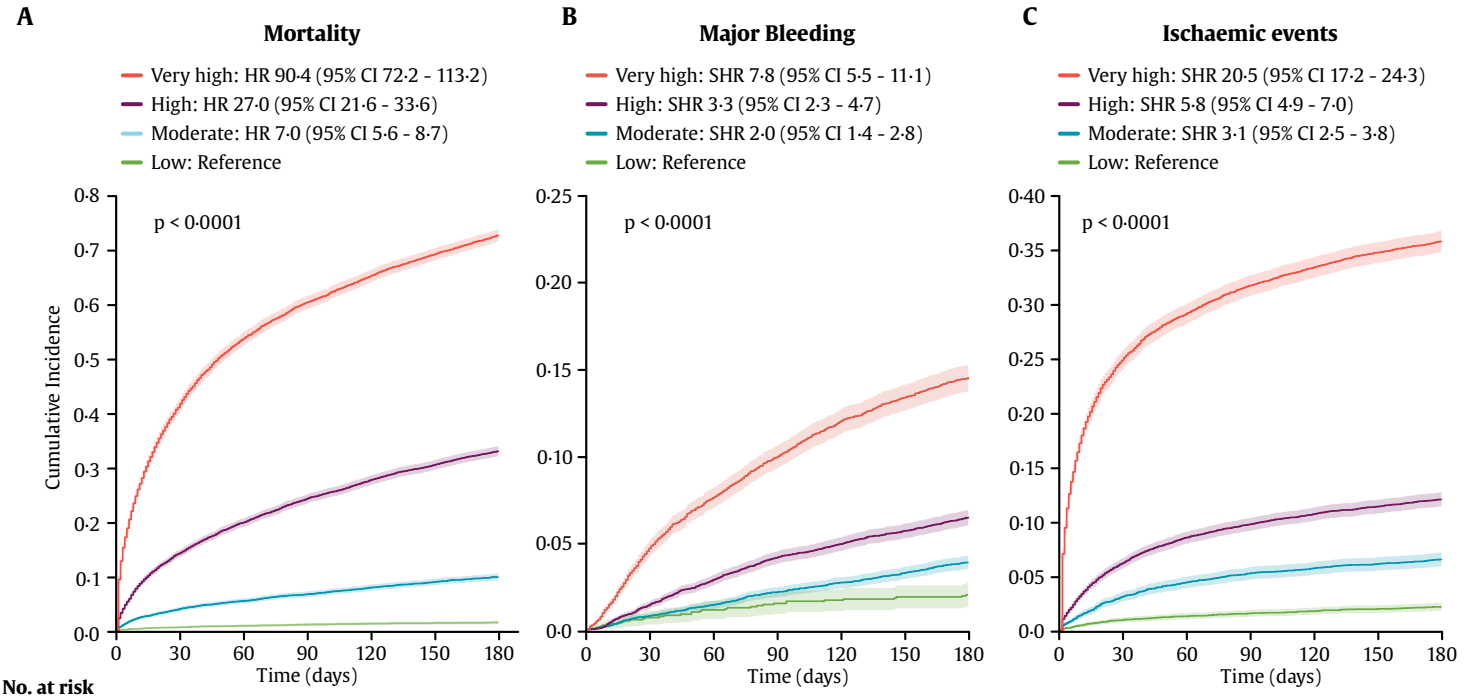

A
Mortality
Tumour type
Prior bleed
Cardiac arrest
Time since cancer diagnosis
BMI
eGFR
Heart rate
Killip class
Metastatic disease
Haemoglobin
Age
1·0
0·75
0·5
0·25
0·0
B
Major bleeding
C
Ischaemic events
Observed event probability
Mortality risk predicted by ONCO-ACS
Bleeding risk predicted by ONCO-ACS
Ischaemic risk predicted by ONCO-ACS

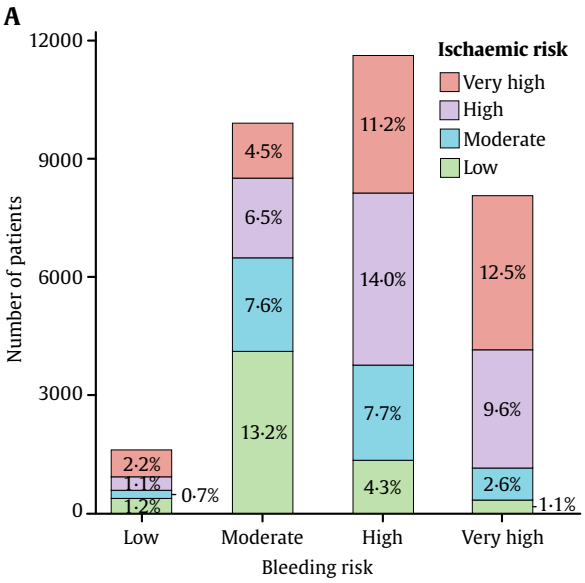
Figure 1



No. at risk (no. censored)

Low	5962 (0)	5927 (0)	5910 (0)	5897 (0)	5887 (0)	5881 (0)	5874 (0)	1607 (0)	1153 (450)	1067 (522)	1033 (551)	1007 (574)	983 (597)	963 (614)	6162 (0)	6023 (85)	5931 (151)	5853 (214)	5783 (272)	5726 (318)	5681 (351)
Moderate	8902 (0)	8558 (0)	8422 (0)	8314 (0)	8205 (0)	8114 (0)	8029 (0)	9903 (0)	9019 (824)	8715 (1052)	8495 (1200)	8495 (1332)	8160 (1429)	7994 (1531)	5811 (0)	5435 (202)	5186 (371)	5032 (483)	4919 (565)	4827 (635)	4713 (721)
High	9881 (0)	8495 (0)	7935 (0)	7510 (0)	7170 (0)	6893 (0)	6643 (0)	11 621 (0)	9937 (1540)	9271 (2032)	8812 (2342)	8475 (2586)	8174 (2793)	7893 (2991)	9738 (0)	8555 (604)	7921 (999)	7525 (1272)	7188 (1521)	6927 (1714)	6703 (1874)
Very high	6448 (0)	3818 (0)	3017 (0)	2583 (0)	2275 (0)	2018 (0)	1789 (0)	8062 (0)	6206 (1505)	5384 (2077)	4847 (2425)	4441 (2668)	4144 (2854)	3899 (3007)	9482 (0)	6295 (859)	5489 (1256)	4982 (1511)	4652 (1685)	4370 (1833)	4136 (1971)

Figure 2


A
12000
9000
6000
3000
0
Number of patients
Ischaemic risk
Very high
High
Moderate
Low
2·2%
1·1%
0·7%
1·2%
4·5%
6·5%
7·6%
13·2%
11·2%
14·0%
7·7%
4·3%
12·5%
9·6%
2·6%
1·1%
Low
Moderate
High
Very high
Bleeding risk

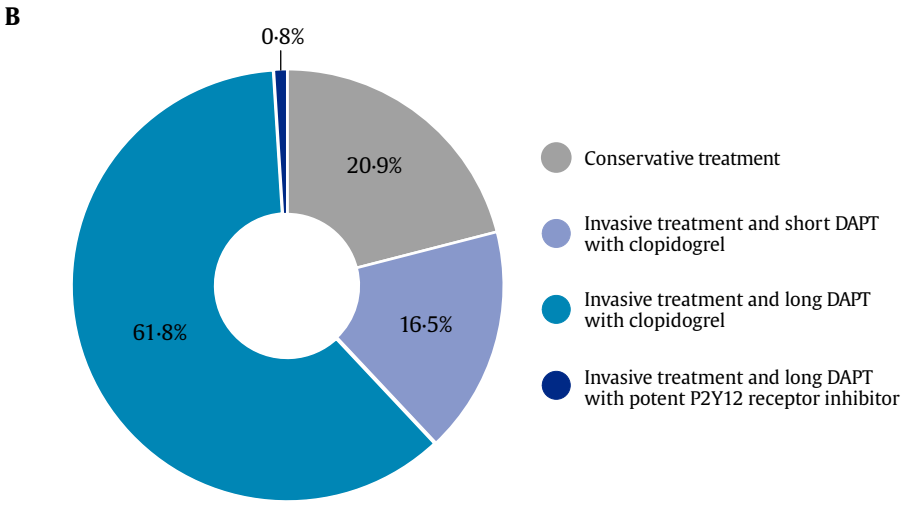

B
0·8%
20·9%
16·5%
61·8%
Conservative treatment
Invasive treatment and short DAPT with clopidogrel
Invasive treatment and long DAPT with clopidogrel
Invasive treatment and long DAPT with potent P2Y12 receptor inhibitor

Figure 3

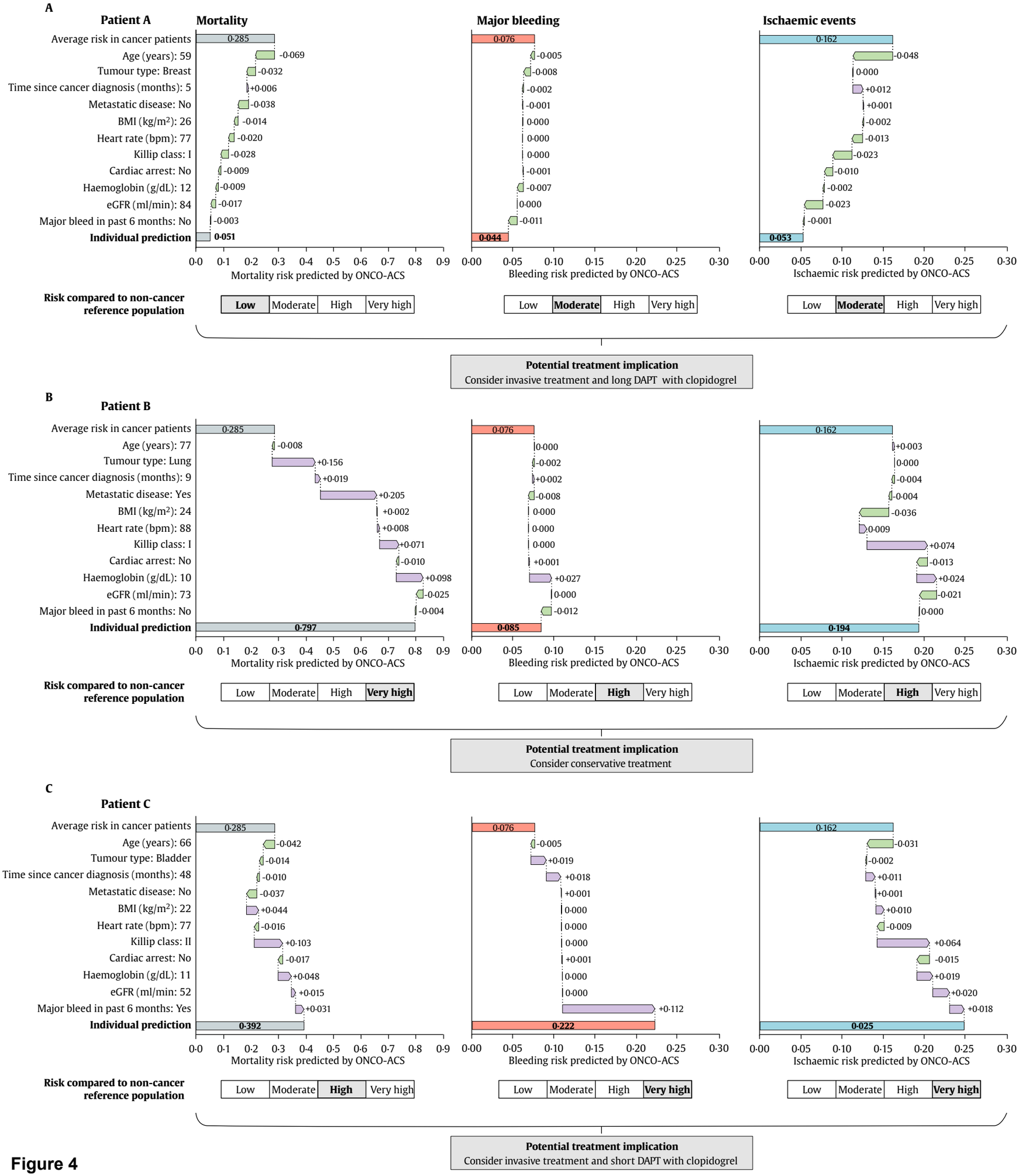

A
Patient A
Mortality
Major bleeding
Ischaemic events
Average risk in cancer patients
Age (years): 59
Tumour type: Breast
Time since cancer diagnosis (months): 5
Metastatic disease: No
BMI (kg/m²): 26
Heart rate (bpm): 77
Killip class: I
Cardiac arrest: No
Haemoglobin (g/dL): 12
eGFR (ml/min): 84
Major bleed in past 6 months: No
Individual prediction
0·285
-0·069
-0·032
+0·006
-0·038
-0·014
-0·020
-0·028
-0·009
-0·009
-0·017
-0·003
0·051
0·076
-0·005
-0·008
-0·002
-0·001
0·000
0·000
0·000
-0·001
-0·007
0·000
-0·011
0·044
0·162
-0·048
0·000
+0·012
+0·001
-0·002
-0·013
-0·023
-0·010
-0·002
-0·023
-0·001
0·053
0·0 0·1 0·2 0·3 0·4 0·5 0·6 0·7 0·8 0·9
Mortality risk predicted by ONCO-ACS
0·00 0·05 0·10 0·15 0·20 0·25 0·30
Bleeding risk predicted by ONCO-ACS
0·00 0·05 0·10 0·15 0·20 0·25 0·30
Ischaemic risk predicted by ONCO-ACS
Risk compared to non-cancer reference population
Low Moderate High Very high
Low Moderate High Very high
Low Moderate High Very high
Potential treatment implication
Consider invasive treatment and long DAPT with clopidogrel
B
Patient B
Average risk in cancer patients
Age (years): 77
Tumour type: Lung
Time since cancer diagnosis (months): 9
Metastatic disease: Yes
BMI (kg/m²): 24
Heart rate (bpm): 88
Killip class: I
Cardiac arrest: No
Haemoglobin (g/dL): 10
eGFR (ml/min): 73
Major bleed in past 6 months: No
Individual prediction
0·285
-0·008
+0·156
+0·019
+0·205
+0·002
+0·008
+0·071
-0·010
+0·098
-0·025
-0·004
0·797
0·076
0·000
-0·002
+0·002
-0·008
0·000
0·000
0·000
+0·001
+0·027
0·000
-0·012
0·085
0·162
+0·003
0·000
-0·004
-0·004
-0·036
0·009
+0·074
-0·013
+0·024
-0·021
0·000
0·194
0·0 0·1 0·2 0·3 0·4 0·5 0·6 0·7 0·8 0·9
Mortality risk predicted by ONCO-ACS
0·00 0·05 0·10 0·15 0·20 0·25 0·30
Bleeding risk predicted by ONCO-ACS
0·00 0·05 0·10 0·15 0·20 0·25 0·30
Ischaemic risk predicted by ONCO-ACS
Risk compared to non-cancer reference population
Low Moderate High Very high
Low Moderate High Very high
Low Moderate High Very high
Potential treatment implication
Consider conservative treatment
C
Patient C
Average risk in cancer patients
Age (years): 66
Tumour type: Bladder
Time since cancer diagnosis (months): 48
Metastatic disease: No
BMI (kg/m²): 22
Heart rate (bpm): 77
Killip class: II
Cardiac arrest: No
Haemoglobin (g/dL): 11
eGFR (ml/min): 52
Major bleed in past 6 months: Yes
Individual prediction
0·285
-0·042
-0·014
-0·010
-0·037
+0·044
-0·016
+0·103
-0·017
+0·048
+0·015
+0·031
0·392
0·076
-0·005
+0·019
+0·018
+0·001
0·000
0·000
0·000
+0·001
0·000
0·000
+0·112
0·222
0·162
-0·031
-0·002
+0·011
+0·001
+0·010
-0·009
+0·064
-0·015
+0·019
+0·020
+0·018
0·025
0·0 0·1 0·2 0·3 0·4 0·5 0·6 0·7 0·8 0·9
Mortality risk predicted by ONCO-ACS
0·00 0·05 0·10 0·15 0·20 0·25 0·30
Bleeding risk predicted by ONCO-ACS
0·00 0·05 0·10 0·15 0·20 0·25 0·30
Ischaemic risk predicted by ONCO-ACS
Risk compared to non-cancer reference population
Low Moderate High Very high
Low Moderate High Very high
Low Moderate High Very high
Potential treatment implication
Consider invasive treatment and short DAPT with clopidogrel

Figure 4

-- ONLINE SUPPLEMENTARY APPENDIX –

Prediction of mortality, bleeding, and ischaemic events in patients with cancer and acute coronary syndrome: a model development and validation study

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Description of the statistical analyses (detailed)

Multinational study design and datasets

In England, we used population-representative individual-level data of multiple national health datasets within the framework of the Virtual Cardio-Oncology Research Initiative (VICORI; https://vicori.le.ac.uk). VICORI constitutes the first whole-country cardio-oncology research platform[1] based on different electronic health records linking the National Cancer Registration Dataset (NCRD; https://digital.nhs.uk/data-and-information/keeping-data-safe-and-benefitting-the-public/gdpr/gdpr-register/national-cancer-registration-dataset)[2] with cardiac audits within the National Institute for Cardiovascular Outcome Research (NICOR; https://www.nicor.org.uk)[3], such as the Myocardial Ischaemia National Audit Project (MINAP; https://www.nicor.org.uk/national-cardiac-audit-programme/heart-attack-audit-minap)[4] and the British Cardiovascular Intervention Society National Adult Percutaneous Coronary Interventions (BCIS NAPCI; https://www.bcis.org.uk/current-pci-database/) dataset, with additional linkage to the Hospital Episode Statistics (HES; https://digital.nhs.uk/services/hospital-episode-statistics), Admitted Patient Care (APC; https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity), and data on mortality from the Office for National Statistics (ONS; https://www.ons.gov.uk). The NCRD is collated, maintained, and quality-assured by the National Disease Registration Service (NDRS; https://digital.nhs.uk/ndrs/). It systematically collects all data on pre-malignant and malignant neoplasms in England since 1971, including International Classification of Diseases and Related Health Problems 10th Revision (ICD-10) codes C00 to C97 (without ICD-10 C44; non-melanoma skin cancer).[2] The high quality of the NCRD is reflected by 85.3% of cancer diagnoses being microscopically verified, and <1% of registries being death-certificate-only entries (data from 2016).[2]

The HES, developed in 1987[5], provides data on patients admitted to a hospital within the National Health System (NHS), including clinical information on diagnosis and procedures, demographics, administrative data, and geographical information.[6] MINAP is a prospective nation-wide registry of patients with acute coronary syndrome (ACS) admitted to all acute care hospitals within the NHS. It is part of the National Cardiac Audit Programme, managed by the National Institute for Cardiovascular Outcomes Research (NICOR), and constitutes the largest single health-care system ACS registry worldwide, covering the entire patient pathway from symptom onset to hospital discharge.[7,8] Patient demographics, clinical parameters and investigations, medical history, drug treatment prior to admission, information on the primary reperfusion strategy, in-hospital drug treatment, and clinical complications are documented.[7] Of note, completeness for key variables age, admission blood pressure, and heart rate within the registry is over 91%.[4] A total of 815 170 patients presenting with ACS to any of 209 participating hospitals in England between Jan 1, 2005, and Mar 31, 2018 were included.[7,8] Of the 815 170 patients presenting with ACS from Jan 1, 2005 to Mar 31, 2017, 36 771 had current or previous cancer within 5 years prior to presentation (Suppl. table 10).

In Sweden, we linked individual-level data across the Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART; https://www.ucr.uu.se/swedeheart/dokument-sh/arsrapporter-sh),[9] the Swedish National Patient Registry (NPR; https://www.socialstyrelsen.se/en/statistics-and-data/registers/national-patient-register/),[10] the National Cancer Registry (NCR; https://www.socialstyrelsen.se/en/statistics-and-data/registers/national-cancer-register/), Statistics Sweden (SS; https://www.scb.se/en/), and the National Cause-of-Death Registry (NCDR; https://www.socialstyrelsen.se/en/statistics-and-data/registers/national-cause-of-death--register/).[11]

SWEDEHEART constitutes a prospective nation-wide registry of patients with ACS.[12] Over 100 patient-related variables are prospectively collected, including demographics, administrative data, risk factors, medical history, medical treatment before admission, electrocardiographic changes, biochemical markers, other clinical features and investigations, medical treatment during hospitalisation, interventions, hospital outcome, diagnosis at discharge, and medication at discharge. The NPR provides information on patients treated in Swedish hospitals. It has a low underreporting rate for inpatient data, but does not contain data on primary care or on patients treated by other health care professionals than physicians in somatic outpatient care.[10] It contains information on patient data (sex, age), geographical data (hospital/clinic, department), administrative data (for inpatients: date of admission/discharge, length of stay, unplanned/planned admission, where patient was admitted from/discharged to; for outpatients: date of admission/discharge, unplanned/planned admission), and medical data (main diagnosis, secondary diagnosis, external cause of injury/poisoning, procedures).[10] The NCR contains data on cancer diagnosis including time of diagnosis, type of cancer, staging and histopathology. It has a high coverage rate, and accurate coding based on histopathology in about 99% of entries.[13] The SS dataset provides data on place of residence, ethnic background, financial status and marital status. The NCDR documents all deaths occurring in Sweden together with the cause of death (based on ICD-10).[11] Between Jan 1, 2004 and Dec 31, 2014, 194 059 patients with ACS were admitted to one of 80 hospitals in Sweden. Of these, 10 262 had current or previous cancer within 5 years prior to presentation.

In Switzerland, data from the nation-wide Acute Myocardial Infarction in Switzerland (AMIS) Plus registry (NCT01305785; https://amis-plus.ch)[14] and the Special Programme University Medicine Acute Coronary Syndrome (SPUM-ACS) cohort (NCT01000701; https://clinicaltrials.gov/study/NCT01000701?cond=NCT01000701&rank=1)[8,15,16] were used. AMIS Plus constitutes a national registry of patients with ACS admitted to hospitals in Switzerland.[14] Data on patient demographics, risk factors, symptoms, laboratory parameters, invasive treatment strategy, complications and drug-based treatment are documented by over 100 participating hospitals across Switzerland.[14] SPUM-ACS constitutes a prospective multicentre cohort study including patients admitted to one of four major university hospitals in Switzerland with a diagnosis of ACS.[8,15,16] Between Jan 1, 2005 and Aug 8, 2023, 8530 patients with ACS were admitted to University Hospital Bern, Switzerland, and University Hospital Zurich, Switzerland. Cancer-related information was extracted by manual chart review. Of these, 203 had a history of current or previous cancer within 5 years prior to presentation. Patients enrolled in both registries were considered only once.

Outcomes and follow-up

Mortality of any cause at 6 months (180 days) after admission, major bleeding[17] at 6 months (180 days) after admission and ischaemic events[18-21], defined as a composite of cardiovascular death, non-fatal myocardial infarction and non-fatal ischaemic stroke at 6 months (180 days) after admission are the primary outcomes of the respective ONCO-ACS prediction models (Suppl. table 14). In analyses involving mortality as the outcome, follow-up time was calculated from admission to the earliest of death of any cause or censoring. In analyses involving major bleeding as the outcome, follow-up time was calculated from admission to the earliest of fatal or non-fatal major bleeding, death of other causes (ie, the competing event), or censoring. In analyses involving ischaemic events as the outcome, follow-up time was calculated from admission to the earliest occurrence of the fatal or nonfatal composite ischaemic outcome, death of other causes (ie, the competing event), or censoring. The maximum follow-up was truncated at 6 months (180 days), in line with the prediction horizon.

In England, clinical outcomes were obtained from HES and ONS data. Given limited data availability within VICORI at the time of the analyses, ischaemic events refer to a composite of cardiovascular death due to myocardial infarction or ischaemic stroke, nonfatal myocardial infarction, and nonfatal ischaemic stroke in patients without cancer in England. In Sweden, outcomes were obtained from the NCDR and the NPR. In England and Sweden, complete follow-up was available in all participants (Suppl. figure 2).[22,23] In AMIS Plus, events were ascertained through manual medical chart review using predefined variable definitions conducted by independent investigators who were not involved in data analysis. In SPUM-ACS, events were recorded by the investigators using pre-specified protocols and externally confirmed by an independent event adjudication committee.

Model training and cross-validation

We leveraged a widely used and well-established ensemble learning algorithm that has proven high accuracy in numerous applications in medicine.[24-29] XGBoost (XGB) constructs ensembles from decision tree models with trees added to the ensemble one at a time to correct the prediction errors made by prior models (ie, boosting). For the prediction of major bleeding and ischaemic events, we adapted the XGB approach to handle right-censored data in the setting of competing risks using jack-knife pseudo-observations for the Aalen-Johansen cumulative incidence function at 180 days as a continuous outcome variable,[30-32] with non-bleeding-related mortality and non-ischemia-related mortality representing competing risks, respectively.[33] These values are a marginal (pseudo) probability that permit direct modelling of an individual's event risk given a set of predictor values.[34] Given that pseudo-values are not restricted to lie between 0 and 1, we clipped the model predictions to be between 0 and 1 to represent predicted probabilities. Pseudo-values are equal to the failure indicator of an individual (ie, equal to 0) until an event occurs, and remain either at 0 or increase to 1, depending on the cause of failure. In the case of censoring, they tend to be negative at first and subsequently increase above 1 in case of failing from the cause in question. In case of failure from the other cause, they remain negative (and decrease).[35] Continuous data were left unscaled, as described previously.[30] Categorical variables were transformed into one or more numeric binary terms (dummy variables) using the one-hot encoding procedure, as described previously.[30] For comparison of variable importance between patients with and without cancer (38 variables) and for evaluating variable importance in the full, maximally complex model containing both traditional and cancer-related predictor variables (53 candidate predictors, Suppl. table 13), we used fivefold cross-validation with an 80:20 split due to the high computational burden. We used Latin hypercube sampling to tune for the number of trees, learning rate, maximum tree depth (ie, maximum number of levels that a decision tree), minimum child weight (ie, minimum number of data points in a node that is required for the node to be split further), and gamma (ie, minimum loss reduction required to make a further partition on a leaf node of the tree, Suppl. table 12).

We assessed the importance of individual model features using the Shapley additive explanations (SHAP) approach. Based on variable importance for the three score endpoints as well as clinical considerations, a single set of 11 predictor variables at admission was used for all final prediction models. This predictor selection approach benefits from starting with a full, plausible, maximally complex model, and then considers both the clinical and the statistical importance of predictors to select a parsimonious model while keeping the required number of predictor variables low to facilitate the clinical use. For final models (11 predictor variables), hyperparameters were tuned using tenfold cross-validation with an 80:20 split of the development cohort into a training cohort (n = 24 954) and an internal validation cohort (n = 6239).

Feature importance

To evaluate the importance of each feature (for all-cause mortality, major bleeding, ischaemic events) in each risk model, we used the SHAP approach.[36,37] SHAP values constitute model-agnostic representations of feature importance based on the cooperative game theory.[36-39] A SHAP value indicates how much a single feature, considering its interaction with other features, contributes to the difference between the actual and mean prediction, respectively, given the current set of feature values.[36] The sum of SHAP values for all features in a given patient plus the mean prediction is equivalent to the actual prediction in that patient.[37-39] We visualised individual SHAP values of each model feature using a 1:20 dilution. The mean absolute SHAP value for a single feature is the average of the absolute values of its SHAP values across all patients in the dataset and reflects the magnitude of a feature's impact on predictions, without regard to whether it increases or decreases the prediction. For the multi-level factor variables, such as Killip class and ethnicity, mean absolute values were aggregated across all factor levels. In addition, we used the XGB built-in "gain" metric to calculate feature importance. Gain quantifies feature importance during the construction of decision trees. It reflects the average improvement in a model's objective function (loss function) when a particular feature is used to split the data across all trees in the ensemble. Gain corresponds to the fractional contribution of a given feature to the model, with higher values indicating higher predictive importance.[40,41] Both mean absolute SHAP value and Gain were depicted in two alternative ways: i) normalised to the feature with the highest value to reflect the average effect on model output relative to the most important variable and ii) untransformed. Scaling to the maximum feature value was carried out separately for each endpoint and group. We illustrated individual patient examples by visualising the contribution of each score variable to a given prediction in waterfall plots using the SHAP approach.

External validation of model performance

External validation of model performance was examined in study centres different from those involved in the development process to evaluate model transportability. The performance of each ONCO-ACS prediction model was assessed by calculating the area under the time-dependent AUC (tAUC) at 6 months (180 days) of follow-up. The tAUC[42-45] represents the area under the time-dependent ROC curve and was calculated using inverse probability of censoring weighting, as reported previously.[46,47] Estimates of the tAUC were adjusted for competing risks when predicting major bleeding and ischaemic events, as appropriate. We modelled the censoring by using a Cox model and constructed 95% CIs from 300 bootstrap resamples.[8] Calibration was evaluated by constructing smoothed calibration curves and by calculating the calibration slope, adjusting for competing risks where appropriate.[48] To calculate the calibration slope in competing risks settings, pseudo-observations were regressed using a generalised linear model with a complementary log-log transformation of the risk estimates as an offset and the same complementary log-log transformed risk estimates as a covariate, as described previously.[49] The overall prediction error, considering both discrimination and calibration, was estimated using the Brier score and the competing risks-adjusted Brier score.[49] The Brier score is the average squared difference between the primary outcome at the end of the prediction horizon and the absolute risk estimates and ranges from 0 to 1 with lower values indicating better performance.[49] In addition, we calculated the diagnostic performance measures positive predictive value and negative predictive value. We used decision curve analyses to evaluate the clinical utility of the prediction models by quantifying the trade-off between correctly identifying true positives and incorrectly identifying false positives weighted according to the threshold probability.[50] Each model was compared to two default scenarios of treat all or treat none. To evaluate model fairness, we did several subgroup analyses with respect to different population characteristics including sex, ethnicity, age, ACS type, evidence of active cancer, and tumour type. Active cancer was defined as a cancer diagnosis (other than basal-cell or squamous-cell carcinoma of the skin) within 6 months, recurrent or metastatic disease, or treatment for cancer within 6 months (not available). To evaluate temporal transportability, we assessed model performance across different time periods and divided the population at the mid-point of cohort entry into an earlier period (Jan 1, 2005, to Aug 16, 2011) and a later period (Aug 17, 2011, to Mar 31, 2018). These analyses were done in external validation cohort 1 (Midlands) given that this cohort had the highest ethnic diversity and longest total observation period (Jan 1, 2005, to Mar, 31, 2018). We further compared the ONCO-ACS mortality model and the GRACE score (v. 2.0) for 6-month mortality[51], the ONCO-ACS major bleeding model to the PRECISE-DAPT score,[52] and the ONCO-

ACS ischaemia model to the Patterns of Non-Adherence to Anti-Platelet Regimen In Stented Patients (PARIS) score[53] for atherothrombotic events, by 1) assessing the difference in tAUC, 2) evaluating the continuous net reclassification improvement (NRI), and 3) calculating the integrated discrimination improvement (IDI).
The calculation of the GRACE score[51] is based on the following variables: age, systolic blood pressure, creatinine levels, heart rate, Killip class, cardiac arrest on admission, ST-segment deviation, and troponin elevation. The PRECISE-DAPT score[52] is calculated using haemoglobin levels, age, estimated glomerular filtration rate (eGFR), and history of prior bleed. In the absence of information on insulin dependency, diabetes was treated as a binary variable. The PARIS score[53] is calculated using the integer risk score for coronary thrombotic events, comprising diabetes, ACS, smoking history, eGFR, prior percutaneous coronary intervention (PCI), and prior coronary artery bypass grafting (CABG). We recalibrated the PRECISE-DAPT and PARIS score to a six-month prediction horizon and the non-identical outcome definition by estimating the baseline survival in terms of bleeding events and ischaemic events in the non-cancer reference population. For PRECISE-DAPT, we used coefficients based on integer score values as described in the supplement of the original publication.[52] For PARIS, we derived coefficients from the HRs reported in the original publication.[53]

Risk groups
To facilitate the contextualisation of predicted outcome risk in cancer patients with ACS, we based the formation of risk groups on the noncancer ACS patient population. First, separate models were trained on patients with and without cancer using all available patient characteristics. Next, the distribution of predicted risks was assessed in non-cancer patients and risk thresholds obtained thereof. These thresholds were then applied to the predictions of the final ONCO-ACS models. Accordingly, patients were classified according to predicted all-cause mortality risk into a low risk group (≤33rd percentile of the noncancer population; ie, ≤5%), a moderate risk group (>33rd percentile to ≤66th percentile of the noncancer populations; ie, >5% to ≤19%), a high risk group (>66th to ≤90th percentile of the noncancer population; ie, >19% to ≤50%), and a very high risk group (>90th percentile of the noncancer population; ie, >50%). The risk of major bleeding was similarly classified into low risk (≤33rd percentile of the noncancer population; ie, ≤4%), moderate risk (>33rd percentile to ≤66th percentile of the noncancer populations; ie, >4% to ≤5%), high risk (>66th to ≤90th percentile of the noncancer population; ie, >5% to ≤9%), and very high risk(>90th percentile of the noncancer population; ie, >9%) groups. Given the amended definition of the composite ischaemic endpoint in the noncancer patient population due to limited data availability (see above), ischaemic risk groups were created using predefined thresholds based on the ABC-ACS ischemia score by Batra G et al.[54]: low (≤5%), moderate (>5% to ≤10%), high (>10% to ≤20%), very high (>20%). A flexible parametric (Weibull) model and Fine-Gray subdistribution hazard regression models were used to estimate unadjusted hazard ratios (HRs) for mortality and subdistribution hazard ratios (SHRs) for bleeding and ischaemic events across risk groups, respectively. The respective low risk group served as reference. Differences between groups were compared with log-rank tests and Gray's tests.

Association of treatment variables with outcomes according to risk group
We explored a potential influence of risk group status on the observed association between treatment variables (ie, PCI and DAPT prescription at discharge) and clinical outcomes in terms of i) mortality at 6 months and ii) net adverse cardiovascular events, defined as the first occurrence of a composite of death, myocardial infarction, ischaemic stroke ore major bleeding at 6 months. The association between treatment variables and outcomes was modelled using multivariable-adjusted flexible parametric (Weibull) models. Given the large sample size and high event rate, we adjusted the analyses for a broad range of available patient, tumour, and treatment characteristics (see manuscript table 1 and table 2) including age, sex, heart rate, systolic blood pressure, ST-segment deviation, onset-to-door time, BMI, diabetes, hypercholesterolemia, smoking status, time since cancer diagnosis, tumour type (grouped into 6 categories: 5 most common tumour types and others), metastatic disease, haemoglobin levels, troponin elevation > 99th percentile, eGFR, glucose, cholesterol, atrial fibrillation, hypertension, chronic kidney disease, obstructive lung disease, peptic ulcer disease, prior myocardial infarction, prior cerebrovascular ischaemia, prior percutaneous coronary intervention, prior coronary artery bypass grafting, radial access site, multivessel disease, use of drug-eluting stent, diameter of drug-eluting stent (<3mm), left ventricular ejection fraction, procedural P2Y12 receptor inhibitor use, procedural unfractionated heparin use, procedural low-molecular heparin use, procedural fondaparinux use, procedural β-blocker use, procedural diuretics use, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker at discharge, β-blocker at discharge, statin at discharge. In addition, analyses on PCI were adjusted for DAPT-related variables (ie, acetylsalicylic acid at discharge and P2Y12 receptor inhibitor), and analyses on DAPT were adjusted for PCI status. Based on clinical considerations and guideline recommendations, we tested for an interaction of mortality risk groups with PCI, and of bleeding and ischaemic risk groups with DAPT. First, we employed a global test comparing models with and without interaction term using a likelihood ratio test and obtained significant results (each $p<0{\cdot}0001$). Next, we evaluated the coefficient of the interaction term of the multilevel risk group variable with the treatment variable

and report respective p-values in Suppl. tables 25 and 26. Finally, we estimated HRs and corresponding 95% CIs in the individual risk groups. For DAPT, we repeated this step after combining bleeding risk and ischaemic risk groups into three clinically meaningful categories.

Multiple imputation
Completeness, representation, and plausibility of the data were checked for each patient cohort, as appropriate.[55] Subsequently, analyses were carried out using multiply imputed data (10 imputations). Point estimates and standard errors were pooled across all imputed datasets using Rubin's rules.[56,57] We employed random forest models for continuous, ordinal, and binary variables to impute missing data under the missing at random assumption. The imputation models contained all predictor variables, endpoint indicators, corresponding Nelson-Aalen cumulative hazard estimates, and the date of cohort entry. We chose to use random forest imputation models due to high computational efficiency and their ability to handle complex non-linear relationships between imputed variables, as reported previously.[58] Training and cross-validation of newly developed prediction models and analyses involving patient stratification were performed on a single imputed dataset generated, as described above.[8,30,59,60] Convergence was assessed visually. Strip plots were used to visualise and compare imputed data with observed data.

Deployment of the ONCO-ACS risk score
All ONCO-ACS risk models will be available online. ONCO-ACS requires a single set of eleven variables that are commonly available in clinical and pre-clinical care settings.

Software packages
Analyses were performed in R (version 4.3 or later). The software environment in R for the performed analyses was created by the R packages *CalibrationCurves*, *DALEX*, *DataExplorer*, *Hmisc*, *PredictABEL*, *Rcpp*, *VIM*, *boot*, *caret*, *cmprsk*, *dplyr*, *eventglm*, *faux*, *flexsurv*, *geepack*, *ggplot2*, *ggsurvfit*, *ggalluvial*, *mice*, *miceadds*, *nricens*, *pec*, *pROC*, *psfmi*, *randomForest*, *readxl*, *recipes*, *riskRegression*, *rmda*, *rms*, *shapviz*, *survminer*, *survival*, *tableone*, *tabnet*, *themis*, *tidycmprsk*, *tidymodels*, *tidyverse*, *timeROC*, *vtable*, *waterfalls*, *xgboost*.

Public involvement
Following a previous publication on machine learning-based risk assessment in underrepresented patient populations (ie, female patients with non-ST-elevation ACS),[8] we fostered the public communication about the potentials of machine learning-enhanced risk stratification for individualised treatment. With the support of public relation teams from the Royal Brompton and Harefield Hospitals, UK and the University of Zurich, Switzerland, the topic was made accessible to the public via study summaries in lay terms broadcasted on BBC Radio 4, lay summary videos on social media channels, and discussed in various print media (for professionals and laymen alike). In the process of the public dialogue, it became evident that other groups of vulnerable individuals, such as cancer patients, are not adequately represented in available risk tools for patients with ACS, despite increasing numbers of patients with cancer worldwide[61]. Based on continuous discourse with healthcare professionals and the public relating to improved means for personalised risk assessment in these patients, we set out to develop a cancer-specific machine learning-based risk assessment tool model to address this unmet medical need. The study proposal was also reviewed and approved by the VICORI patient panel. Study results were discussed with the VICORI patient and public involvement group.

Ethics
Data from the MINAP were anonymised, and as such, did not require ethical approval according to NHS research governance arrangements. The National Institute of Cardiovascular Outcomes Research (NICOR) that includes the MINAP database (reference number: NIGB: ECC 1-06 (d)/2011), has support under section 251 of the NHS Act 2006 to use patient information for medical research without consent.[62,63] The VICORI programme has received favourable ethical opinion from the North East – Newcastle & North Tyneside 2 Research Ethics Committee (REC reference 18/NE/0123). The analyses involving data from the Swedish registries were approved by the Swedish Ethical Review Authority (registration number: dnr 2013/525). Ethical approval for AMIS Plus was granted by the Swiss Over-Regional Ethics Committee for Clinical Studies, the Swiss Board for Data Security, and all Cantonal Ethics Committees (reference number: 1.05.01.10–40) and for SPUM-ACS by the Cantonal Ethics Committee Zurich (reference number: EK-1688/2019-01809). The study was conducted in compliance with the declaration of Helsinki.

Supplementary table 1: Summary of participating study centres in the development cohort with geographic location in England

Development cohort (England w/o Midlands)					
Hospital name	**Hospital location**	**Hospital name**	**Hospital location**	**Hospital name**	**Hospital location**
Addenbrooke's Hospital	East of England	Hammersmith Hospital	London	Peterborough District Hospital	East of England
Airedale General Hospital	Yorkshire and the Humber	Harefield Hospital	London	Pinderfields General Hospital	Yorkshire and the Humber
Arrowe Park Hospital	North West	Harrogate District Hospital	Yorkshire and the Humber	Pontefract General Infirmary	Yorkshire and the Humber
Barnet General Hospital	London	Hexham General Hospital	North East	Poole Hospital	South West
Barnsley District General Hospital	Yorkshire and the Humber	Hillingdon Hospital	London	Princess Alexandra Hospital	East of England
Barts and The London	London	Hinchingbrooke Hospital	East of England	Princess Royal Hospital Haywards Heath	South East
Basildon Hospital	East of England	Homerton Hospital	London	Princess Royal University Hospital Bromley	London
Bassetlaw District General Hospital	Yorkshire and the Humber	Hope Hospital	North West	Queen Alexandra Hospital Portsmouth	South East
Bedford Hospital	East of England	Horton General Hospital	South East	Queen Elizabeth Hospital Gateshead	North East
Blackpool Victoria Hospital	North West	Huddersfield Royal Infirmary	Yorkshire and the Humber	Queen Elizabeth Hospital Kings Lynn	East of England
Bradford Royal Infirmary	Yorkshire and the Humber	Hull Royal Infirmary	Yorkshire and the Humber	Queen Elizabeth Hospital Woolwich	London
Bristol Royal Infirmary	South West	James Cook University Hospital	North East	Queen Elizabeth II Hospital Welwyn	East of England
Broomfield Hospital	East of England	James Paget Hospital	East of England	Queen Elizabeth the Queen Mother	South East
Calderdale Royal Hospital	Yorkshire and the Humber	John Radcliffe Hospital	South East	Queen Marys Hospital Sidcup	London
Castle Hill Hospital	Yorkshire and the Humber	Kent & Sussex Hospital	South East	Queen's Hospital Romford	London
Central Middlesex Hospital	London	Kent and Canterbury Hospital	South East	Rochdale Infirmary	North West
Charing Cross Hospital	London	King George Hospital	London	Rotherham General Hospital	Yorkshire and the Humber
Chase Farm Hospital	London	King's College Hospital	London	Royal Albert Edward Infirmary	North West
Chelsea & Westminster Hospital	London	Kingston Hospital	London	Royal Berkshire Hospital	South East
Cheltenham General Hospital	South West	Leeds General Infirmary	Yorkshire and the Humber	Royal Blackburn Hospital	North West
Chorley and South Ribble Hospital	North West	Leighton Hospital	North West	Royal Bolton Hospital	North West
Colchester General Hospital	East of England	Lister Hospital	East of England	Royal Bournemouth General Hospital	South West
Conquest Hospital	South East	Liverpool Heart and Chest Hospital	North West	Royal Brompton Hospital	London
Countess of Chester Hospital	North West	London Chest Hospital	London	Royal Cornwall Hospital	South West
Cumberland Infirmary	North West	Luton & Dunstable Hospital	East of England	Royal Devon & Exeter Hospital	South West
Darent Valley Hospital	South East	Macclesfield District General	North West	Royal Free Hospital	London
Darlington Memorial Hospital	North East	Maidstone General Hospital	South East	Royal Hallamshire Hospital	Yorkshire and the Humber
Derriford Hospital	South West	Manchester Royal Infirmary	North West	Royal Hampshire County Hospital	South East
Dewsbury and District Hospital	Yorkshire and the Humber	Mayday University Hospital	London	Royal Lancaster Infirmary	North West
Diana Princess of Wales Hospital Grimsby	Yorkshire and the Humber	Medway Maritime Hospital	South East	Royal Liverpool University Hospital	North West
Doncaster Royal Infirmary	Yorkshire and the Humber	Milton Keynes General Hospital	South East	Royal London Hospital	London
Dorset County Hospital	South West	Montagu Hospital	Yorkshire and the Humber	Royal Oldham Hospital	North West
Ealing Hospital	London	Newham General Hospital	London	Royal Preston Hospital	North West
East Surrey Hospital	South East	Norfolk and Norwich Hospital	East of England	Royal Surrey County Hospital	South East
Eastbourne District General Hospital	South East	North Devon District Hospital	South West	Royal Sussex County Hospital	South East
Epsom Hospital	South East	North Hampshire Hospital	South East	Royal United Hospital Bath	South West
Fairfield General Hospital	North West	North Manchester General Hospital	North West	Royal Victoria Infirmary	North East
Freeman Hospital	North East	North Middlesex Hospital	London	Southend Hospital	East of England
Frenchay Hospital	South West	North Tyneside General Hospital	North East	Salisbury District Hospital	South West
Friarage Hospital	Yorkshire and the Humber	Northern General Hospital	Yorkshire and the Humber	Scarborough General Hospital	Yorkshire and the Humber
Frimley Park Hospital	South East	Northumbria Specialist Emergency Care Hospital	North East	Scunthorpe General Hospital	Yorkshire and the Humber
Furness General Hospital	North West	Northwick Park Hospital	London	South Tyneside District Hospital	North East
Gloucestershire Royal Hospital	South West	Papworth Hospital	East of England	Southampton General Hospital	South East

Development cohort (England w/o Midlands) - continued

Hospital name	Hospital location	Hospital name	Hospital location	Hospital name	Hospital location
Southmead Hospital	South West	The Great Western Hospital	South West	West Cumberland Hospital	North West
Southport and Formby District General Hospital	North West	The Ipswich Hospital	East of England	West Middlesex University Hospital	London
St Bartholomews Hospital	London	Torbay Hospital	South West	West Suffolk Hospital	East of England
St George's Hospital	London	Trafford General Hospital	North West	Weston General Hospital	South West
St Helier Hospital	London	University College Hospital	London	Wexham Park Hospital	South East
St Mary's Hospital Newport	Ile of Wight	University College Hospital Gower Street	London	Whipps Cross Hospital	London
St Mary's Hospital Paddington	London	University Hospital Aintree	North West	Whiston Hospital	North West
St Peter's Hospital	South East	University Hospital Lewisham	London	Whittington Hospital	London
St Richards Hospital	South East	University Hospital of Hartlepool	North East	William Harvey Hospital	South East
St Thomas' Hospital	London	University Hospital of North Durham	North East	Worthing Hospital	South East
Stepping Hill Hospital	North West	University Hospital of North Tees	North East	Wycombe General Hospital	South East
Stoke Mandeville Hospital	South East	Wansbeck General Hospital	North East	Wythenshawe Hospital	North West
Sunderland Royal Hospital	North East	Warrington District General Hospital	North West	Yeovil District Hospital	South West
Tameside General Hospital	North West	Watford General Hospital	East of England	York District Hospital	Yorkshire and the Humber
Taunton & Somerset Hospital	South West	West Cornwall Hospital	South West		

Data retrieved from the British Cardiovascular Intervention Society (https://www.bcis.org.uk/) and the University Hospital Association (https://www.universityhospitals.org.uk/).[8]

Supplementary table 2: Summary of participating study centres in external validation cohort 1 with geographic location in England

Validation cohort 1 (Midlands)					
Hospital name	**Hospital location**	**Hospital name**	**Hospital location**	**Hospital name**	**Hospital location**
Birmingham Heartlands Hospital	West Midlands	Lincoln County Hospital	East Midlands	Russells Hall Hospital	West Midlands
Chesterfield Royal Hospital	East Midlands	Manor Hospital	West Midlands	Sandwell District Hospital	West Midlands
City Hospital Birmingham	West Midlands	New Cross Hospital	West Midlands	Selly Oak Hospital	West Midlands
County Hospital Hereford	West Midlands	Newark Hospital	East Midlands	Skegness and District General Hospital	East Midlands
County Hospital Louth	East Midlands	Northampton General Hospital	East Midlands	Solihull Hospital	West Midlands
George Elliot Hospital	West Midlands	Nottingham City Hospital	East Midlands	Staffordshire General Hospital	West Midlands
Glenfield Hospital	East Midlands	Pilgrim Hospital	East Midlands	The Alexandra Hospital Worcestshire	West Midlands
Good Hope Hospital	West Midlands	Princess Royal Hospital Telford	West Midlands	University Hospital Coventry	West Midlands
Grantham and District Hospital	East Midlands	Queen Elizabeth Hospital Birmingham	West Midlands	University Hospital of North Staffordshire	West Midlands
Kettering General Hospital	East Midlands	Queen's Hospital Burton	West Midlands	University Hospital Queen's Medical	East Midlands
Kings Mill Hospital	East Midlands	Royal Derby Hospital	East Midlands	Warwick Hospital	West Midlands
Leicester Royal Infirmary	East Midlands	Royal Shrewsbury Hospital	West Midlands	Worcestershire Royal Hospital	West Midlands

Supplementary table 3: Summary of participating study centres in external validation cohort 2 with geographic location in Sweden

Validation cohort 2 (Sweden)					
Hospital name	**Hospital location**	**Hospital name**	**Hospital location**	**Hospital name**	**Hospital location**
Alingsås Hospital	Västra Götaland County	Karolinska University Hospital, Solna	Stockholm County	Sala Hospital	Västmanland County
Ängelholm Hospital	Skåne County	Katrineholm Hospital	Södermanland County	Simrishamn Hospital	Skåne County
Arvika Hospital	Värmland County	Kiruna Hospital	Norrbotten County	Skåne University Hospital	Skåne County
Avesta Hospital	Dalarna County	Köping Hospital	Västmanland County	Skellefteå Hospital	Västerbotten County
Bollnäs Hospital	Gävleborg County	Kristianstad Hospital	Skåne County	Skene Hospital	Skene Hospital
Borås Hospital	Västra Götaland County	Kungälv Hospital	Västra Götaland County	Skövde Hospital	Västra Götaland County
Eksjö Hospital	Jönköping County	Lidköping Hospital	Västra Götaland County	Södersjukhuset	Stockholm County
Enköping Hospital	Uppsala County	Lindesberg Hospital	Örebro County	Södertälje Hospital	Stockholm County
Eskilstuna Hospital	Södermanland County	Linköping Hospital	Östergötland County	Sollefteå Hospital	Västernorrland County
Fagersta Hospital	Västmanland County	Ljungby Hospital	Kronoberg County	Stockholm Danderyd Hospital	Stockholm County
Falun Hospital	Dalarna County	Ludvika Hospital	Dalarna County	Stockholm St Göran Hospital	Stockholm County
Finspångs Lasarett	Östergötland County	Lycksele Hospital	Västerbotten County	Sunderbyn Hospital	Norrbotten County
Gällivare Hospital	Norrbotten County	Malmö Hospital	Skåne County	Sundsvall Hospital	Västernorrland County
Gävle Hospital	Gävleborg County	Mora Hospital	Dalarna County	Torsby Hospital	Värmland County
Halmstad Hospital	Halland County	Motala Hospital	Östergötland	Trelleborg Hospital	Skåne County
Härnösand Hospital	Västernorrland County	Norrköping Vrinnevi Hospital	Östergötland	Trollhättan NU-sjukvården Hospital	Västra Götaland County
Hässleholm Hospital	Skåne County	Norrtälje Hospital	Stockholm County	Uddevalla Hospital	Västra Götaland County
Helsingborg Hospital	Skåne County	Nyköping Hospital	Södermanlands	Umeå University Hospital	Västerbotten County
Hudiksvall Hospital	Gävleborg County	Örebro Hospital	Örebro County	Uppsala University Hospital	Uppsala County
Jönköping Hospital	Jönköping County	Örnsköldsvik Hospital	Västernorrland	Varberg Hospital	Halland County
Kalix Hospital	Norrbotten County	Oskarshamn Hospital	Kalmar County	Värnamo Hospital	Jönköping County
Kalmar Hospital	Jämtland County	Östersund Hospital	Jämtland County	Västerås Hospital	Västmanland County
Karlshamn Hospital	Blekinge County	Piteå Hospital	Norrbotten County	Västervik Hospital	Kalmar County
Karlskoga Hospital	Örebro County	Säffle Hospital	Värmland County	Växjö Hospital	Kronoberg County
Karlskrona Hospital	Blekinge County	Sahlgrenska University Hospital, Mölndal	Västra Götaland County	Visby Hospital	Gotland County
Karlstad Hospital	Värmland County	Sahlgrenska University Hospital, Östra	Västra Götaland County	Ystad Hospital	Skåne County
Karolinska University Hospital, Huddinge	Stockholm County	Sahlgrenska University Hospital, Sahlgrenska	Västra Götaland County		

Supplementary table 4: Summary of participating study centres in external validation cohort 3 with geographic location in Switzerland.

Validation cohort 3 (Switzerland)	
Hospital name	**Hospital location**
University Hospital Zurich	Canton of Zurich
University Hospital Bern	Canton of Bern

Supplementary table 5: Baseline characteristics of patients with and without cancer from England

	Patients with cancer (*n* = 36 771)	Patients without cancer (*n* = 778 399)	p-value
Age, years	76 (68–82)	69 (58–79)	< 0·0001
Sex			< 0·0001
Female	11 422/36 668 (31·1%)	265 406/775 864 (34·2%)	
Male	25 246/36 668 (68·9%)	510 458/775 864 (65·8%)	
Ethnicity			< 0·0001
Asia	310/36 376 (0·9%)	4008/377 701 (1·1%)	
Black	881/36 376 (2·4%)	23 804/37 7701 (6·3%)	
Mixed	71/36 376 (0·2%)	852/377 701 (0·2%)	
White	34 796/36 376 (95·7%)	34 1574/37 7701 (90·4%)	
Other	318/36 376 (0·9%)	7463/377 701 (2·0%)	
Haemodynamics			
Heart rate, beats per minute	80 (68–96)	78 (66–92)	< 0·0001
Systolic blood pressure, mm Hg	136 (29)	139 (29)	< 0·0001
Cardiac arrest	1962/36 771 (5·3%)	42 402/778 399 (5·4%)	0·36
Killip class			< 0·0001
I	11 673/15 697 (74·4%)	253 420/315 043 (80·4%)	
II	2664/15 697 (17·0%)	40 137/315 043 (12·7%)	
III	1063/15 697 (6·8%)	15 566/315 043 (4·9%)	
IV	297/15 697 (1·9%)	5920/315 043 (1·9%)	
ST-segment deviation	17 559/35 286 (49·8%)	397 272/749 540 (53·0%)	< 0·0001
Onset-to-door time, min	188 (102–496)	179 (96–481)	< 0·0001
Cardiometabolic factors			
BMI, kg/m^2	26 (23–29)	27 (24–30)	< 0·0001
Body surface area, m^2*	1·9 (0·2)	1·9 (0·2)	< 0·0001
Diabetes	7869/35 394 (22·2%)	153 058/748 618 (20·4%)	< 0·0001
Dyslipidaemia†	9489/33 106 (28·7%)	227 456/700 956 (32·4%)	< 0·0001
Smoking status			< 0·0001
Never	13 157/33 281 (39·5%)	277 351/716 978 (38·7%)	
Former	14 521/33 281 (43·6%)	236 743/716 978 (33·0%)	
Current	5603/33 281 (16·8%)	202 884/716 978 (28·3%)	
Clinical chemistry and haematology			
Haemoglobin, g/dL	12·4 (2·2)	13·5 (2·0)	< 0·0001
Troponin elevation†	33 252/34 844 (95·4%)	687 806/732 287 (93·9%)	< 0·0001
Estimated glomerular filtration rate, mL/min‡	67 (24)	74 (25)	< 0·0001
Glucose, mmol/L	7·1 (6·0–9·3)	7·0 (6·0–9·0)	< 0·0001
Total cholesterol, mmol/L	4·4 (3·6–5·4)	4·8 (4·0–5·8)	< 0·0001
Medical history			
Heart failure	2164/33 440 (6·5%)	35 851/704 434 (5·1%)	< 0·0001
Hypertension	17 637/34 032 (51·8%)	356 266/718 327 (49·6%)	< 0·0001
Peripheral vascular disease	1727/33 139 (5·2%)	29 702/698 136 (4·3%)	< 0·0001
Chronic kidney disease	2818/33 389 (8·4%)	38 148/703 490 (5·4%)	< 0·0001
Obstructive lung disease	5954/33 254 (17·9%)	104 797/699 988 (15·0%)	< 0·0001
Prior ischaemic events			
Myocardial infarction	6988/34 065 (20·5%)	124 459/718 760 (17·3%)	< 0·0001
Cerebrovascular ischaemia	3184/33 436 (9·5%)	57 388/704 745 (9·5%)	< 0·0001
Prior coronary revascularisation			
PCI	2452/33 501 (7·3%)	51 119/707 264 (7·2%)	0·54
Coronary artery bypass grafting	2348/33 630 (7·0%)	39 885/708 768 (5·6%)	< 0·0001
Prior bleeding events			
Major bleed w/i six months	3877/36 771 (10·5%)	1376/778 399 (0·2%)	< 0·0001
Medication at admission			
ASS	8422/33 938 (24·8%)	157 864/722 040 (21·9%)	< 0·0001

β-blocker	9195/30 737 (29·9%)	167 984/645153 (26·0%)	< 0·0001
Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker	11 211/30 697 (36·5%)	219 482/644 760 (34·0%)	< 0·0001
Statin	13 988/32 433 (43·1%)	267 108/681 203 (39·2%)	< 0·0001

Data are median (IQR), mean (SD) or n/N (%). ASS=acetylsalicylic acid. BMI=body mass index. ECG=electrocardiogram. PCI=percutaneous coronary intervention. †Defined as elevation in total cholesterol requiring dietary or drug treatment. ‡according to CKD-EPI 2021 equation[64] *according to BSA equation by Du Bois and Du Bois[65]

Supplementary table 6: Treatment characteristics of patients with and without cancer from England

	Patients with cancer (*n* = 36 771)	Patients without cancer (*n* = 778 399)	p-value
Type of intervention			
PCI	6235/9538 (65·4%)	169 296/226 071 (74·9%)	< 0·0001
Angiography only	1364/9538 (14·3%)	29 544/226 071 (13·1%)	0·0005
Procedural characteristics			
Multivessel disease*	6685/10 062 (66·4%)	183 897/293 689 (62·6%)	< 0·0001
Left ventricular ejection fraction (%)			< 0·0001
< 30%	2002/15 210 (13·2%)	37 421/330 518 (11·3%)	
30%–49%	5306/15 210 (34·9%)	108 846/330 518 (32·9%)	
≥ 50%	7902/15 210 (52·0%)	184 251/330 518 (55·7%)	
Periprocedural medication			
$P2Y_{12}$ receptor inhibitor	27 060/34 022 (79·5%)	589 195/717 596 (82·1%)	< 0·0001
Unfractionated heparin	6059/30 225 (20·0%)	162 522/636 114 (25·5%)	< 0·0001
Low-molecular-weight heparin	17 383/30 704 (56·6%)	359 384/647 028 (55·5%)	0·0002
Fondaparinux	7849/25 828 (30·4%)	156 053/530 053 (29·4%)	0·0011
Bivalirudin	351/11 366 (3·1%)	8688/223 043 (3·9%)	< 0·0001
β-blocker	16 180/21 714 (74·5%)	342 359/438 217 (78·1%)	< 0·0001
Diuretics	10 777/30 432 (35·4%)	181 156/637 535 (28·4%)	< 0·0001
In-hospital adverse events			
In-hospital cardiac arrest	2133/35 496 (6·0%)	38 463/748 999 (5·1%)	< 0·0001
In-hospital death	4239/36 771 (11·5%)	52 848/778 399 (6·8%)	< 0·0001
Discharge medication			
ASS	25 199/34 560 (72·9%)	575 517/729 684 (78·9%)	< 0·0001
$P2Y_{12}$ receptor inhibitor	17 037/25 903 (65·8%)	382 537/528 486 (72·4%)	< 0·0001
Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker	20 910/34 197 (61·1%)	505 611/723 146 (69·9%)	< 0·0001
Oral anticoagulant	1932/30 241 (6·4%)	33 495/635 067 (5·3%)	< 0·0001
β-blocker	21 990/34 326 (64·1%)	503 107/725 693 (69·3%)	< 0·0001
Statin	24 908/34 353 (72·5%)	573 130/726 579 (78·9%)	< 0·0001
Aldosterone antagonist	1614/24 741 (6·5%)	34 824/501 372 (6·9%)	0·0111
Oral glucose-lowering medication	3029/34 096 (8·9%)	61 497/720 546 (8·5%)	0·025
Insulin	1751/34 096 (5·1%)	36 284/720 546 (5·0%)	0·42

Data are n/N (%). ASS=acetylsalicylic acid. PCI=percutaneous coronary intervention. *Defined as stenosis in any two of the following: left main coronary artery, left anterior descending coronary artery, left circumflex coronary artery, right coronary artery.

Supplementary table 7: Outcomes at 6 months of patients with and without cancer from England

	Patients with cancer (*n* = 36 771)	Patients without cancer (*n* = 778 399)	p-value
Death	10 222/36 771 (27·8%)	96 190/778 399 (12·4%)	< 0·0001
Major bleeding	2673/36 771 (7·3%)	9982/778 399 (1·3%)	< 0·0001
Ischaemic events	5907/36 771 (16·1%)	22 330/778 399 (2·9%)	< 0·0001

Supplementary table 8: Outcomes at 6 months of patients in the ONCO-ACS development and validation cohorts

	Development cohort (England w/o Midlands; *n* = 31 193)	Validation cohort 1 (Midlands; *n* = 5578)	Validation cohort 2 (Sweden; *n* = 10 262)	Validation cohort 3 (Switzerland; *n* = 203)
Death	8881/31 193 (28·5%)	1341/5578 (24·0%)	1813/10 262 (17·7%)	32/202 (15·8%)
Major bleeding	2335/31 193 (7·5%)	338/5578 (6·1%)	637/10 262 (6·2%)	4/202 (2·0%)
Ischaemic events	5067/31 193 (16·2%)	840/5578 (15·1%)	1468/10 262 (14·3%)	25/202 (12·4%)

Supplementary table 9: Sex-specific, ethnic group-specific, age-specific, ACS type-specific, tumour type-specific, and period-specific crude cumulative incidence of mortality, major bleeding and ischaemic events in patients with cancer

		Mortality	Major bleeding	Ischaemic events
	Patients	Cumulative incidence (95% CI)	Cumulative incidence (95% CI)	Cumulative incidence (95% CI)
Overall	36 771	27·80 (27·34–28·26)	7·27 (7·00–7·53)	16·06 (15·69–16·44)
Sex				
Female	11 449	30·05 (29·20–30·88)	6·38 (5·94–6·83)	16·93 (16·24–17·61)
Male	25 322	26·78 (26·24–27·33)	7·67 (7·34–8·00)	15·67 (15·23–16·12)
Ethnicity				
White	35 186	28·05 (27·58–28·52)	7·16 (6·90–7·43)	16·16 (15·78–16·54)
Non white	1585	22·21 (20·13–24·23)	9·59 (8·14–11·04)	13·94 (12·24–15·65)
Age				
≤ 55 years	1641	13·41 (11·74–15·04)	5·12 (4·05–6·19)	6·28 (5·10–7·45)
55-70 years	9976	18·51 (17·75–19·27)	5·97 (5·51–6·44)	9·59 (9·02–10·17)
> 70 years	25 154	32·42 (31·84–33·00)	7·92 (7·59–8·26)	19·27 (18·78–19·76)
ACS type				
STEMI	11 805	29·01 (28·19–29·83)	6·66 (6·21–7·11)	19·03 (18.32–19·73)
NSTE-ACS	24 966	27·23 (26·67–27·78)	7·56 (7·23–7·89)	14·66 (14·23–15·1)
Tumour type				
Prostate	9578	19·88 (19·08–20·67)	7·40 (6·88–7·93)	15·64 (14·91–16·37)
Colorectal	5140	24·98 (23·79–26·15)	8·21 (7·46–8·96)	15·14 (14·16–16·12)
Breast	3562	21·45 (20·09–22·79)	5·45 (4·70–6·19)	16·68 (15·45–17·90)
Lung	3425	49·58 (47·87–51·22)	6·60 (5·77–7·43)	17·34 (16·08–18·61)
Bladder	2076	28·71 (26·74–30·63)	12·04 (10·64–13·44)	17·92 (16·27–19·57)
All other types	12 990	30·61 (29·81–31·40)	6·71 (6·28–7·14)	15·94 (15·31–16·57)
Evidence of active cancer				
Yes	12 699	41·00 (40·13–41·84)	7·38 (6·92–7·83)	17·64 (16·98–18·30)
No	24 072	20·84 (20·32–21·35)	7·21 (6·88–7·54)	15·23 (14·78–15·69)
Period				
Period 1 (2005–2011)	17 438	29·97 (29·29–30·65)	6·38 (6·01–6·74)	17·66 (17·09–18·22)
Period 2 (2011–2018)	19 333	25·84 (25·22–26·46)	8·07 (7·69–8·46)	14·63 (14·13–15·13)

Incidence values are percentages. Results are based on patients from the UK. ACS=acute coronary syndrome. CI=confidence interval. NSTE-ACS=non-ST elevation acute coronary syndrome. STEMI=ST-elevation myocardial infarction.

Supplementary table 10: Time since cancer diagnosis

Time since cancer diagnosis (relative to index ACS)	
Year	**Count (%)**
1	14 012/36 771 (38·1%)
2	7150/36 771 (19·4%)
3	5872/36 771 (16·0%)
4	5139/36 771 (14·0%)
5	4598/36 771 (12·5%)

Results are based on patients from the UK.

Supplementary table 11: Sample size considerations for score development

	Sample size	Shrinkage	Parameters	Cox-Snell R^2	SSP	Event rate
All-cause mortality						
Criteria 1	823	0·900	15	0·15	55	0·285
Criteria 2	375	0·806	15	0·15	25	0·285
Criteria 3	823	0·900	15	0·15	55	0·285
Minimum sample size	823	0·900	15	0·15	55	0·285
Major bleeding						
Criteria 1	823	0·900	15	0·15	55	0·075
Criteria 2	658	0·878	15	0·15	44	0·075
Criteria 3	823	0·900	15	0·15	55	0·075
Minimum sample size	823	0·900	15	0·15	55	0·075
Ischaemic events						
Criteria 1	823	0·900	15	0·15	55	0·162
Criteria 2	455	0·834	15	0·70	31	0·162
Criteria 3	823	0·900	15	0·15	55	0·162
Minimum sample size	823	0·900	15	0·15	55	0·162

This table shows the required sample size for powered model development for the prediction of time-to-event outcomes computed according to the three criteria proposed by Riley *et al.* (2020).[66,67] For time-to-event outcomes, these criteria include 1) small overfitting defined by an expected shrinkage of predictor effects by 10% or less (Criteria 1), 2) small absolute difference of 0·05 in the model's apparent and adjusted Nagelkerke's R-squared value (Criteria 2), and 3) precise estimation (within +/- 0·05) of the average outcome risk in the population for a key timepoint of interest for prediction (Criteria 3). Given an overall event rate of 0·285 for mortality, 0·075 for major bleeding, and 0·162 for ischaemic events at 6 months in the development dataset and assuming 15 model parameters and conservative 15% of the maximal Cox-Snell R^2, our calculations suggest that at least 823 observations are required to develop an accurate prediction model for each outcome. SSP=sample size per parameter.

Supplementary table 12: Hyperparameter tuning

Basic architecture	Hyperparameter	Description	Range explored	Final selected value Mortality model	Final selected value Bleeding model	Final selected value Ischaemia model
Computational engine: xgboost[68] No. of predictors: 11 No. of features after preprocessing: 43	trees (nrounds)	No. of boosting rounds	1–2000	1262	962	922
	tree_depth (max_depth)	Maximum depth of the tree (i.e. number of splits)	1–15	3	2	2
	learn_rate (eta)	Rate at which the algorithm learns from each iteration (lower value prevent overfitting, while higher values speed up learning, but may lead to overfitting)	10^{-10}–10^{-1}	$4{\cdot}8918 \times 10^{-2}$	$1{\cdot}1600 \times 10^{-2}$	$1{\cdot}2538 \times 10^{-1}$
	min_n (min_child_weight)	Minimum no. of data points in a node required for the node to be split further	2–40	26	20	25
	loss_reduction (gamma)	Minimum reduction in the loss function required to split further	10^{-10}–$31{\cdot}6228$	$1{\cdot}5256 \times 10^{-9}$	$1{\cdot}2300 \times 10^{-3}$	$4{\cdot}4160 \times 10^{-5}$
	sample_size (subsample)	Proportion of the data set used for modeling within an iteration.	All training data were used to construct each tree.			
	mtry (colsample_bytree)	No. of predictors that are randomly sampled at each split	All predictors were used to construct each tree (no feature subsampling).			
	stop_iter (early_stopping_rounds)	No. of iterations without improvement in the objective function before training is halted	We did not allow early stopping based on the number of boosting iterations.			

Models were tuned using 10-fold cross validation employing an 80:20 data split at each fold. Hyperparameter combinations were obtained using grid search with Latin hypercube sampling. For models to predict competing risks-adjusted incidence of major bleeding and of ischaemic events was the root mean squared error. For the model to predict all-cause mortality the evaluation metric was the area under the receiver operating characteristic curve. L1 regularisation (alpha) was set to default (ie, 0). L2 regularisation (lamda) was set to default (ie, 2).

Supplementary table 13: Summary of available candidate predictors at admission

Variable	Data source	Code
• Age	MINAP	1.06, 3.06
• Female sex	MINAP, NCRD if missing	1.07
• Ethnicity		
Asian	MINAP, NCRD if missing	1.13
Black		
Mixed		
White		
Other		
Haemodynamics		
• Heart rate	MINAP	2.21
• Systolic blood pressure	MINAP	2.2
• Cardiac arrest	MINAP	3.15
• Killip class		
I	MINAP	2.41
II		
III		
IV		
ECG features		
• ST-segment deviation	MINAP	2.03
• Left bundle branch block	MINAP	2.03
• Infarct location based on ECG	MINAP	2.36
• Onset-to-door time	MINAP	3.01, 3.06
Cardiometabolic risk factors		
• BMI	MINAP	2.29, 2.3
• Body surface area	MINAP	2.29, 2.3
• Dyslipidemia	MINAP	2.08
• Diabetes mellitus	MINAP	2.17
• Cigarette smoking		
Never	MINAP	2.16
Former		
Current		
• Tumour type		
Anus	NCRD (ICD-10)	C21
Bladder		C67
Brain		C71
Breast		C50
Cervix		C53
Colorectal		C18-C20
Hodgkin lymphoma		C81
Kidney		C64
Larynx		C32
Leukaemia		C91-C95
Liver		C22
Lung		C33-C34
Melanoma		C43
Mesothelioma		C45
Myeloma		C90
Non-Hodgkin lymphoma		C82-C86
Oesophagus		C15
Ovary		C56-C57.7
Pancreas		C25
Prostate		C61
Small intestine		C17
Stomach		C16
Testis		C62
Thyroid		C73
Uterus		C54-C55
Vulva		C51
Other		C00-C97 (Other cancer), excluding C44 and types above; as reported previously[69]
• Time since cancer diagnosis	MINAP and NCRD	3.06, DIAGNOSISDATE1
• Metastatic disease	NCRD	STAGE_BEST, M_BEST
Clinical chemistry and haematology		
• Troponin elevation	MINAP	2.14
• Haemoglobin	MINAP	2.35
• Estimated glomerular filtration rate	MINAP	2.34, 1.06, 3.06, 1.07
• Glucose	MINAP	2.28
• Cholesterol	MINAP	2.15
Medical history		

• Hypertension	MINAP	2.07
• Chronic bleeding diathesis	HES (ICD-10)	D66-D68
• Liver fibrosis or cirrhosis	HES (ICD-10)	K74, K70.2, K76.1, K70.3, P78.8, K71.7
• Portal hypertension	HES (ICD-10)	K76.6
• Peptic ulcer disease	HES (ICD-10)	K22.1, K25, K25.0, K25.1, K25.2, K25.3, K25.4, K25.5, K25.6, K25.7, K25.9, K26, K26.0, K26.1, K26.2, K26.3, K26.4, K26.5, K26.6, K26.7,K26.9, K27, K27.0, K27.1, K27.2, K27.3, K27.4, K27.5, K27.6, K27.7, K27.9, K28, K28.0, K28.1, K28.2, K28.3, K28.4, K28.5, K28.6, K28.7, K28.9
• Atrial fibrillation	HES (ICD-10)	I48, I48.0, I48.1, I48.2, I48.3, I48.4, I48.9
• Peripheral vascular disease	MINAP	2.09
• Heart failure	MINAP	2.13
• Chronic kidney disease	MINAP	2.12
• Obstructive lung disease	MINAP	2.11
• Cerebral arteriovenous malformation	HES (ICD-10)	Q28.2
• Major trauma or major surgery within 30 days prior to admission	HES (ICD-10)	Major trauma: S00 to T14.0, T79; as reported previously[70] Major surgery: A01-A09, A10-A12, A16-A18, A20, A22, A24-A32, A34, A36, A38-A45, A47-A49, A51, A57 B01-B02, B04, B06, B08-B10, B12, B14, B16-B18, B20, B22-B23, B25, B27-B29, B38-B39 C01, C05 D10, D19 E01, E12-E13, E19, E21, E23, E28-E31, E33, E39-E44, E46-E47, E52-E55, E57, E59, E61-E62 F22-F23, F28, F38-F39 G01-G11, G13, G21, G23-G36, G38, G40-G41, G48-G53, G57-G61, G63, G67-G74, G76, G78, G82 H01-H17, H19, H29-H30, H33-H36, H40-H41, H46-H47, H49, H62 J01-J05, J07-J08, J16, J18-J21, J23, J27-J33, J37, J52, J54-J63, J65, J68-J70, J72 K01-K15, K17-K20, K22-K34, K36-K38, K40-K48, K52-K57, K66-K67, K69, K71 L01-L10, L12-L13, L16, L18-L22, L25-L30, L33-L34, L37-L38, L41-L42, L45-L53, L56-L60, L62, L65, L67-L70, L74-L75, L77, L79-L81, L90 M01-M06, M08, M17-M18, M20-M23, M25, M34-M37, M51-M52, M61-M62, M72-M73, M75 N05-N06, N26 O05-O10, O15, O17-O27, O29 P05, P17-P18, P20, P31 Q01, Q07-Q08, Q22-Q25, Q43-Q45, Q47 S17-S20, S54-S55 T01-T03, T05, T07-T10, T14-T17, T28, T30, T33-T34, T36-T39, T41, T50-T53, T56, T76-T77, T85, T89, T94 V01, V03-V11, V13-V17, V19-V46, V48-V49, V52, V54, V56-V58, V60-V61, V66-V68 W05-W06, W08-W10, W15-W25, W27-W28, W30, W37-W49, W50-W58, W60-W65, W67, W80, W93-W98 X01-X03, X05, X07-X10, X14-X15, X17, X19-X25, X45; as reported previously[71]
Prior ischaemic events		
• Myocardial infarction	MINAP	2.05
• Angina pectoris	MINAP	2.06
• Cerebrovascular ischemia	MINAP	2.10
Prior coronary revascularisation		
• PCI	MINAP	2.19
• Coronary artery bypass grafting	MINAP	2.18
Prior bleeding events		
• Major bleed within 6 months prior to admission	HES (ICD-10)	D50.0, D50.8, D50.9, D68.3, H35.6, H43.1, H45.0, I60, I61, I62.0, I62.1, I62.9, I85.0, I98.20, I98.3, K22.10, K22.12, K22.14, K22.16, K25.0, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.2, K27.4, K27.6, K28.0, K28.2, K28.4, K28.6, K29.0, K31.80, K55.20, K62.5, K66.1, K92.0, K92.1, K92.2, M25.0, N02.0, N02.1, N02.2, N02.3, N02.4, N02.5, N02.6, N02.7, N02.8, N02.9, N93.8, N93.9, N95.0, R04.1, R04.2, R04.8, R04.9, R31, R58; as reported previously[17]
• Major bleed or transfusion within 6 months prior to admission or at any time, if recurrent	HES (ICD-10) HES (OPCS4)	Bleeding: I60, I61, I620, I621, I629, K920, K921; as reported previously[72] Transfusion: X331, X332, X333, X337, X338, X339, X341, X342, X343, X344, as reported previously[73]
• Major bleed or transfusion within 12 months prior to admission	HES (ICD-10) HES (OPCS4)	Bleeding: D50.0, D50.8, D50.9, D68.3, H35.6, H43.1, H45.0, I60, I61, I62.0, I62.1, I62.9, I85.0, I98.20, I98.3, K22.10, K22.12, K22.14, K22.16, K25.0, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.2, K27.4, K27.6, K28.0, K28.2, K28.4, K28.6, K29.0, K31.80, K55.20, K62.5, K66.1, K92.0, K92.1, K92.2, M25.0, N02.0, N02.1, N02.2, N02.3, N02.4, N02.5, N02.6, N02.7, N02.8, N02.9, N93.8, N93.9, N95.0, R04.1, R04.2, R04.8, R04.9, R31, R58; as reported previously[17] Transfusion: X331, X332, X333, X337, X338, X339, X341, X342, X343, X344, as reported previously[73]
• Any bleed or transfusion within 12 months prior to admission	HES (ICD-10) HES (OPCS4)	Bleeding: I60, I61, I620, I621, I629, K920, K921; as reported previously[72] Transfusion: X331, X332, X333, X337, X338, X339, X341, X342, X343, X344, as reported previously[73]
• Intracranial haemorrhage	HES (ICD-10)	S06.4, S06.5, I62.0, I61
• Traumatic intracranial haemorrhage within 12 months prior to admission	HES (ICD-10)	S06.4, S06.5, S06.3
Medication at presentation		
• ASS	MINAP	2.04
• Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker	MINAP	2.25
• β-blocker	MINAP	2.24
• Oral glucose-lowering medication	MINAP	2.17
• Statin	MINAP	2.26
• Thrombolysis as first reperfusion treatment	MINAP	3.36

England	
Outcome	**Data item**
Death	ONS: Death of any cause; as reported previously[8]
Major Bleeding	HES (ICD-10): D50.0, D50.8, D50.9, D68.3, H35.6, H43.1, H45.0, I60, I61, I62.0, I62.1, I62.9, I85.0, I98.20, I98.3, K22.10, K22.12, K22.14, K22.16, K25.0, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.2, K27.4, K27.6, K28.0, K28.2, K28.4, K28.6, K29.0, K31.80, K55.20, K62.5, K66.1, K92.0, K92.1, K92.2, M25.0, N02.0, N02.1, N02.2, N02.3, N02.4, N02.5, N02.6, N02.7, N02.8, N02.9, N93.8, N93.9, N95.0, R04.1, R04.2, R04.8, R04.9, R31, R58; as reported previously[17]
Composite ischaemic outcome, as reported previously[18-21]	
Cardiovascular death	ONS (ICD-10): Death due to G45, I20, I21, I22, I50, I60, I61, I62, I63, I64, I70, I71, I72, I73, I74, I77, I78, I79; as reported previously[74]
Myocardial infarction	HES (ICD-10): I21, I21.0, I21.1, I21.2, I21.3, I21.4, I21.9, I22, I22.0, I22.1, I22.8, I22.9, I23, I23.0, I23.1, I23.2, I23.3, I23.4, I23.5, I23.6, I23.8; as reported previously[75]
Ischaemic stroke	HES (ICD-10): I63; as reported previously[76-78]

Sweden	
Outcome	**Data item**
Death	NCDR: Death of any cause; as reported previously.[79]
Major Bleeding	NPR/SWEDEHEART† (ICD-10): D50.0, D62.9, I60, I61, I62, I85.0, I98.3, K22.6, K25.0, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.2, K27.4, K27.6, K28.0, K28.2, K28.4, K28.6, K29.0, K62.5, K66.1, K92.0, K92.1, K92.2, N02, N93.8, N93.9, N95.0, N50.1, R31.9, R04.1, R04.2, R04.8, R04.9, T81.0; as reported previously[80,81] OR SWEDEHEART: TIMI major bleeding during index hospitalisation; as reported previously.[82]
Composite ischaemic outcome, as reported previously[18-21]	
Cardiovascular death	NCDR (ICD-10): Death due to G45, I20, I21, I22, I50, I60, I61, I62, I63, I64, I70, I71, I72, I73, I74, I77, I78, I79; as reported previously[74]
Myocardial infarction	NPR (ICD-10): I21, I21.0, I21.1, I21.2, I21.3, I21.4, I21.9, I22, I22.0, I22.1, I22.8, I22.9, I23, I23.0, I23.1, I23.2, I23.3, I23.4, I23.5, I23.6, I23.8; as reported previously[75]
Ischaemic stroke	NPR (ICD-10): I63; as reported previously[76-78]

Switzerland	
Outcome	**Criteria**
Death	Death of any cause
Major Bleeding	BARC class 3 or 5 bleeding; as reported previously.[83-85]
Composite ischaemic outcome, as reported previously[18-21]	
Cardiovascular death	Any death due to cardiac and/or vascular causes (eg, due to myocardial infarction, stroke, or thromboembolism)
Myocardial infarction	Clinical diagnosis of myocardial infarction following the index ACS
Ischaemic stroke	Stroke due to ischaemic cause. Stroke due to non-ischaemic causes, such as intracranial haemorrhages, and transient ischaemic attacks were not considered.

ASS=acetylsalicylic acid. HES=Hospital Episode Statistics. MINAP=Myocardial Ischaemia National Audit Project. NCRD=National Cancer Registration Dataset. ONS=Office for National Statistics. Variables obtained from the HES were defined according to International Classification of Diseases and Related Health Problems 10th Revision (ICD-10) codes.

Supplementary table 14: Summary of outcome definitions

HES=Hospital Episode Statistics. ICD-10=International Classification of Diseases and Related Health Problems 10th Revision. MINAP=Myocardial Ischaemia National Audit Project. ONS=Office for National Statistics. TIMI=Thrombolysis in Myocardial Infarction. NCDR=National Cause-of-Death Registry. NPR=National Patient Registry. BARC=Bleeding Academic Research Consortium. SWEDEHEART=Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies. †SWEDEHEART documents major bleeding according to the TIMI classification and additional bleeding-related ICD codes for the index hospitalisation. Of the 203 cancer patients with ACS in Switzerland, 101 patients were included from SPUM-ACS (NCT01000701) and 102 patients were included from AMIS-Plus (NCT01305785). Outcomes in SPUM-ACS were ascertained by an independent Clinical Event Adjudication Committee comprising three certified external expert cardiologists blinded to patient's baseline characteristics using prespecified adjudication forms. Outcomes in AMIS-Plus were ascertained through manual chart review of hospital by independent investigators, who were not involved in data analyses.

Supplementary table 15: Missing data summary of cancer patients with ACS

	Development cohort (England w/o Midland; *n* = 31 193)	Validation cohort 1 (Midlands; *n* = 5578)	Validation cohort 2 (Sweden; *n* = 10 262)	Validation cohort 3 (Switzerland; *n* = 203)
Age, years	0 (0·0%)	0 (0·0%)	0 (0·0%)	0 (0·0%)
Sex	72 (0·2%)	31 (0·6%)	0 (0·0%)	0 (0·0%)
Ethnicity	359 (1·2%)	36 (0·6%)	1 (0·0%)	..
Haemodynamics				
Heart rate, beats per minute	3431 (11·0%)	854 (15·3%)	723 (7·1%)	2 (1·0%)
Systolic blood pressure, mm Hg	3413 (10·9%)	886 (15·9%)	812 (7·9%)	1 (0·5%)
Cardiac arrest	0 (0·0%)	0 (0·0%)	967 (9·4%)	0 (0·0%)
Killip class	17 611 (56·5%)	3463 (62·1%)	537 (5·2%)	4 (2·0%)
ST-segment deviation	1280 (4·1%)	205 (3·7%)	2761 (26·9%)	11 (5·4%)
Left bundle branch block	1280 (4·1%)	205 (3·7%)	10 138 (98·8%)	101 (49·8%)
Onset-to-door time, min	11 982 (38·4%)	1562 (28·0%)	1371 (13·4%)	86 (42·4%)
Cardiometabolic risk factors				
BMI, kg/m^2	18 464 (59·2%)	3269 (58·6%)	2569 (25·0%)	14 (6·9%)
Body surface area, m^2*	18 439 (59·1%)	3262 (58·5%)	2569 (25·0%)	14 (6·9%)
Diabetes	1183 (3·8%)	194 (3·5%)	0 (0·0%)	3 (1·5%)
Dyslipidaemia†	2737 (8·8%)	928 (16·6%)	86 (0·8%)	6 (3·0%)
Smoking status	3031 (9·7%)	459 (8·2%)	1041 (10·1%)	12 (5·9%)
Tumour type	0 (0·0%)		0 (0·0%)	0 (0·0%)
Time since tumour diagnosis, months	0 (0·0%)	0 (0·0%)	0 (0·0%)	0 (0·0%)
Metastatic disease	16 891 (54·1%)	3154 (56·5%)	3000 (29·2%)	0 (0·0%)
Number of tumour diagnoses	0 (0·0%)	0 (0·0%)	0 (0·0%)	0 (0·0%)
Clinical chemistry and haematology				
Haemoglobin, g/dL	7391 (23·7%)	1727 (31·0%)	2521 (24·6%)	28 (13·8%)
Troponin elevation†	1704 (5·5%)	223 (4·0%)	2 (0·0%)	38 (18·7%)
Creatinine, mg/dL	6994 (22·4%)	1310 (23·5%)	609 (5·9%)	6 (3·0%)
Estimated glomerular filtration rate, ml/min‡	7039 (22·6%)	1333 (23·9%)	609 (5·9%)	6 (3·0%)
Glucose, mg/dL	7872 (25·2%)	1156 (20·7%)	1817 (17·7%)	40 (19·7%)
Total cholesterol, mg/dL	15 503 (49·7%)	2209 (39·6%)	3788 (36·9%)	59 (29·1%)
Medical history				
Heart failure	2395 (7·7%)	936 (16·8%)	0 (0·0%)	0 (0·0%)
Atrial fibrillation	0 (0·0%)	0 (0·0%)	0 (0·0%)	101 (49·8%)
Hypertension	1906 (6·1%)		0 (0·0%)	3 (1·5%)
Peripheral vascular disease	2690 (8·6%)	942 (16·9%)	0 (0·0%)	0 (0·0%)
Chronic kidney disease	2442 (7·8%)	940 (16·9%)	0 (0·0%)	101 (49·8%)
Obstructive lung disease	2588 (8·3%)	929 (16·7%)	0 (0·0%)	0 (0·0%)
Peptic ulcer disease	0 (0·0%)	0 (0·0%)	0 (0·0%)	101 (49·8%)
Prior ischaemic events				
Myocardial infarction	1853 (5·9%)	853 (15·3%)	0 (0·0%)	0 (0·0%)
Cerebrovascular ischaemia	2397 (7·7%)	938 (16·8%)	0 (0·0%)	0 (0·0%)
Prior coronary revascularisation				
PCI	2342 (7·5%)	928 (16·6%)	0 (0·0%)	3 (1·5%)
Coronary artery bypass grafting	2229 (7·1%)	912 (16·3%)	0 (0·0%)	3 (1·5%)
Prior bleeding events				
Major bleed in past six months	0 (0·0%)	0 (0·0%)	0 (0·0%)	101 (49·8%)
Bleed requiring hospitalisation or transfusion in the past six months	0 (0·0%)	0 (0·0%)	0 (0·0%)	..
Intracranial bleed	0 (0·0%)	0 (0·0%)	0 (0·0%)	..
Medication at presentation				
ASS	2248 (7·2%)	585 (10·5%)	91 (0·9%)	24 (11·8%)
β-blocker	4607 (14·8%)	1427 (25·6%)	108 (1·1%)	23 (11·3%)
Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker	4643 (14·9%)	1431 (25·7%)	98 (1·0%)	24 (11·8%)
Statin	3456 (11·1%)	882 (15·8%)	88 (0·9%)	24 (11·8%)
Outcome				
Death at 6 months	0 (0·0%)	0 (0·0%)	0 (0·0%)	0 (0·0%)
Major bleed at 6 months	0 (0·0%)	0 (0·0%)	0 (0·0%)	0 (0·0%)
Ischaemic event at 6 months	0 (0·0%)	0 (0·0%)	0 (0·0%)	0 (0·0%)

ASS=acetylsalicylic acid. BMI=body mass index. ECG=electrocardiogram. PCI=percutaneous coronary intervention. †Defined as elevation in total cholesterol requiring dietary or drug treatment. ‡according to CKD-EPI 2021 equation[64] *according to BSA equation by Du Bois and Du Bois[65]

Supplementary table 16: Performance metrics

	Internal validation		External validation					
	Testing dataset (*n* = 6239)		Midlands (*n* = 5578)		Sweden (*n* = 10 262)		Switzerland (*n* = 203)	
	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
Mortality								
tAUC	0·84	0·83–0·85	0·84	0·82–0·85	0·80	0·79–0·82	0·83	0·76–0·91
Calibration slope	1·02	0·96–1·07	0·95	0·87–1·02	0·85	0·80–0·90	0·96	0·60–1·32
Brier Score	0·086	0·081–0·091	0·081	0·075–0·087	0·072	0·068–0·076	0·052	0·030–0·075
Major bleeding								
tAUC	0·70	0·68–0·73	0·70	0·67–0·74	0·67	0·65–0·70	0·74	0·57–0·91
Calibration slope	1·16	0·98–1·33	1·06	0·86–1·27	1·17	0·98–1·36	1·06	-0·66–2·77
Brier Score	0·059	0·054–0·065	0·051	0·046–0·056	0·055	0·050–0·059	0·018	0·001–0·034
Ischaemic events								
tAUC	0·79	0·78–0·81	0·76	0·74–0·78	0·70	0·69–0·72	0·73	0·61–0·86
Calibration slope	1·11	1·01–1·20	0·94	0·82–1·05	0·73	0·65–0·81	0·99	0·49–1·48
Brier Score	0·098	0·093–0·104	0·096	0·090–0·102	0·099	0·094–0·103	0·074	0·045–0·103

CI=confidence interval. tAUC=time-dependent area under the curve.

Supplementary table 17: Subgroup analyses of performance on external validation

	Mortality				Major bleeding				Ischaemic events			
	Patients/Events	tAUC (95% CI)	Calibration slope	Brier Score	Patients/Events	tAUC (95% CI)	Calibration slope	Brier Score	Patients/Events	tAUC (95% CI)	Calibration slope	Brier Score
Overall	5578/1341	0·84 (0·82–0·85)	0·95 (0·87–1·02)	0·081 (0·075–0·087)	5578/338	0·70 (0·67–0·74)	1·06 (0·86–1·27)	0·051 (0·046–0·056)	5578/840	0·76 (0·74–0·78)	0·94 (0·82–1·05)	0·096 (0·090–0·102)
Sex												
Female	1661/427	0·81 (0·78–0·84)	0·91 (0·78–1·05)	0·085 (0·074–0·095)	1661/76	0·70 (0·63–0·77)	0·94 (0·51–1·37)	0·040 (0·031–0·048)	1661/265	0·75 (0·71–0·79)	0·98 (0·79–1·17)	0·100 (0·087–0·110)
Male	3917/914	0·84 (0·83–0·86)	0·96 (0·88–1·05)	0·079 (0·072–0·086)	3917/262	0·71 (0·67–0·74)	1·09 (0·86–1·32)	0·056 (0·050–0·063)	3917/575	0·77 (0·74–0·79)	0·92 (0·78–1·05)	0·095 (0·087–0·102)
Ethnicity												
White	5363/1304	0·84 (0·82–0·85)	0·94 (0·87–1·01)	0·082 (0·076–0·088)	5363/325	0·70 (0·67–0·74)	1·06 (0·85–1·27)	0·051 (0·046–0·057)	5363/813	0·76 (0·74–0·78)	0·93 (0·81–1·04)	0·097 (0·090–0·103)
Non white	215/37	0·85 (0·77–0·92)	1·05 (0·69–1·42)	0·049 (0·027–0·071)	215/13	0·72 (0·59–0·86)	1·15 (0·14–2·15)	0·050 (0·024–0·076)	215/27	0·73 (0·59–0·86)	1·13 (0·02–2·26)	0·076 (0·049–0·106)
Age												
≤ 55 years	291/33	0·88 (0·79–0·94)	0·88 (0·50–1·27)	0·058 (0·035–0·082)	291/12	0·61 (0·42–0·81)	0·80 (-0·47–2·06)	0·036 (0·016–0·056)	291/19	0·80 (0·67–0·94)	0·68 (-0·01–1·38)	0·049 (0·027–0·072)
55-70 years	1624/263	0·87 (0·84–0·89)	0·97 (0·85–1·10)	0·062 (0·053–0·072)	1624/85	0·72 (0·66–0·79)	1·31 (0·89–1·73)	0·044 (0·035–0·053)	1624/145	0·73 (0·67–0·78)	0·81 (0·56–1·06)	0·067 (0·056–0·078)
> 70 years	3663/1045	0·81 (0·79–0·83)	0·94 (0·85–1·03)	0·090 (0·082–0·098)	3663/241	0·69 (0·65–0·73)	0·99 (0·75–1·24)	0·056 (0·049–0·062)	3663/676	0·74 (0·72–0·77)	0·97 (0·83–1·10)	0·112 (0·104–0·120)
ACS type												
STEMI	2082/539	0·86 (0·84–0·88)	0·99 (0·87–1·10)	0·082 (0·073–0·092)	2082/126	0·70 (0·65–0·75)	1·10 (0·77–1·43)	0·051 (0·043–0·060)	2082/366	0·80 (0·77–0·83)	0·96 (0·80–1·12)	0·104 (0·093–0·114)
NSTE-ACS	3496/802	0·82 (0·80–0·84)	0·92 (0·84–1·01)	0·080 (0·073–0·087)	3496/212	0·71 (0·67–0·75)	1·04 (0·78–1·30)	0·051 (0·044–0·058)	3496/474	0·74 (0·71–0·77)	0·86 (0·69–1·02)	0·091 (0·084–0·099)
Tumour type												
Prostate	1554/255	0·84 (0·81–0·87)	0·99 (0·84–1·15)	0·067 (0·057–0·078)	1554/80	0·67 (0·60–0·75)	1·16 (0·73–1·59)	0·043 (0·034–0·052)	1554/222	0·76 (0·72–0·81)	0·98 (0·72–1·25)	0·089 (0·077–0·100)
Colorectal	754/193	0·84 (0·79–0·87)	0·99 {0·79–1·19)	0·092 (0·076–0·109)	754/61	0·69 (0·61–0·77)	0·68 (0·24–1·12)	0·069 (0·053–0·085)	754/117	0·80 (0·74–0·86)	1·08 (0·76–1·40)	0·097 (0·081–0·114)
Breast	567/101	0·79 (0·74–0·85)	0·88 (0·63–1·13)	0·082 (0·064–0·100)	567/27	0·77 (0·65–0·89)	1·86 (1·10–2·63)	0·039 (0·025–0·053)	79/567	0·76 (0·70–0·82)	1·09 (0·72–1·46)	0·082 (0·064–0·100)
Lung	469/215	0·76 (0·73–0·82)	0·81 (0·62–1·01)	0·090 (0·073–0·107)	469/22	0·71 (0·59–0·83)	0·98 (0·06–1·91)	0·042 (0·025–0·068)	469/86	0·74 (0·67–0·81)	0·86 (0·52–1·20)	0·122 (0·099–0·145)
Bladder	308/80	0·82 (0·76–0·88)	0·92 (0·66–1·19)	0·091 (0·067–0·116)	308/46	0·70 (0·61–0·79)	0·94 (0·32–1·56)	0·119 (0·087–0·150)	308/47	0·77 (0·69–0·85)	1·26 (0·55–1·97)	0·092 (0·067–0·118)
All other types	1926/497	0·83 (0·81–0·85)	0·95 (0·83–1·07)	0·082 (0·073–0·092)	1926/102	0·68 (0·62–0·74)	0·95 (0·56–1·34)	0·046 (0·037–0·054)	1926/289	0·75 (0·72–0·78)	0·81 (0·61–1·00)	0·099 (0·089–0·110)
Evidence of active cancer												
Yes	1848/684	0·81 (0·79–0·84)	0·89 (0·79–1·00)	0·090 (0·080–0·099)	1848/120	0·68 (0·62–0·75)	1·02 (0·60–1·44)	0·057 (0·046–0·068)	1848/307	0·76 (0·72–0·79)	0·85 (0·67–1·04)	0·111 (0·010–0·123)
No	3730/657	0·82 (0·80–0·84)	0·96 (0·86-1·07)	0·076 (0·069–0·083)	3730/218	0·71 (066–0·76)	1·08 (0·82–1·33)	0·048 (0·041–0·055)	3730/533	0·76 (0·74–0·79)	0·99 (0·84–1·14)	0·088 (0·081–0·096)

Results are based on patients in validation cohort 1. ACS=acute coronary syndrome. CI=confidence interval. NSTE-ACS=non-ST elevation acute coronary syndrome. STEMI=ST-elevation myocardial infarction. tAUC=time-dependent area under the curve.

Supplementary table 18: Temporal transportability

	Mortality				Major bleeding				Ischaemic events			
	Patients/Events	tAUC (95% CI)	Calibration slope	Brier Score	Patients/Events	tAUC (95% CI)	Calibration slope	Brier Score	Patients/Events	tAUC (95% CI)	Calibration slope	Brier Score
Overall	5578/1341	0·84 (0·82–0·85)	0·95 (0·87–1·02)	0·081 (0·075–0·087)	5578/338	0·70 (0·67–0·74)	1·06 (0·86–1·27)	0·051 (0·046–0·056)	5578/840	0·76 (0·74–0·78)	0·94 (0·82–1·05)	0·096 (0·090–0·102)
Periods according to temporal split												
Period 1 (2005–2011)	2682/697	0·83 (0·81–0·85)	0·98 (0·87–1·08)	0·089 (0·080–0·98)	2682/138	0·69 (0·64–0·73)	0·98 (0·64–1·31)	0·044 (0·037–0·051)	2682/474	0·77 (0·74–0·80)	1·05 (0·85–1·24)	0·111 (0·101–0·120)
Period 2 (2011–2018)	2896/644	0·84 (0·82–0·86)	0·92 (0·83–1·01)	0·073 (0·065–0·080)	2896/200	0·72 (0·68–0·76)	1·10 (0·84–1·36)	0·058 (0·050–0·065)	2896/366	0·76 (0·73–0·78)	0·89 (0·73–1·05)	0·082 (0·074–0·089)

Results are based on patients in validation cohort 1. CI=confidence interval. tAUC=time-dependent area under the curve.

Supplementary table 19: Diagnostic measures

	Mortality							
	Internal validation		External validation					
	Testing dataset (*n* = 6239)		Midlands (*n* = 5578)		Sweden (*n* = 10 262)		Switzerland (*n* = 203)	
	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
NPV	0·91	0·90–0·92	0·92	0·91–0·93	0·93	0·92–0·94	0·90	0·85–0·94
PPV	0·50	0·48– 0·52	0·47	0·43– 0·50	0·35	0·33–0·37	0·41	0·23–0·59
	Major Bleeding							
	Internal validation		External validation					
	Testing dataset (*n* = 6239)		Midlands (*n* = 5578)		Sweden (*n* = 10 262)		Switzerland (*n* = 203)	
	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
NPV	1	1–1	1	1–1	1	1–1	1	1–1
PPV	0	0–0	0	0–0	0	0–0	0	0–0
	Ischaemic Events							
	Internal validation		External validation					
	Testing dataset (*n* = 6239)		Midlands (*n* = 5578)		Sweden (*n* = 10 262)		Switzerland (*n* = 203)	
	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
NPV	0·99	0·98–0·99	0·99	0·98–0·99	0·99	0·99–0·99	0·96	0·93–0·99
PPV	0·15	0·13– 0·17	0·10	0·07–0·13	0·04	0·03–0·06	0·23	0·05–0·40

CI=confidence interval. NA=not applicable. NPV=negative predictive value. PPV=positive predictive value. Diagnostic performance measures, such as NPV and PPV, can yield extreme values, such as 1 and 0, when calculated in a prognostic study framework due to outcome imbalance (ie, non-occurrence of the outcome is considerably more frequent than its occurrence). This was most pronounced for the major bleeding for which the upper limit of predicted risk did not exceed 0.5. Consequently, all NPV values are 1 and all PPV values 0.

Supplementary table 20: Absolute patient count per category of bleeding and ischaemic risk

	Bleeding risk (Count; %)			
Ischaemic risk (Count; %)	**Low**	**Moderate**	**High**	**Very high**
Low	375/31 193 (1·2%)	4109/31 193 (13·2%)	1344/31 193 (4·3%)	334/31 193 (1·1%)
Moderate	207/31 193 (0·7%)	2375/31 193 (7·6%)	2416/31 193 (7·7%)	813/31 193 (2·6%)
High	342/31 193 (1·1%)	2024/31 193 (6·5%)	4370/31 193 (14·0%)	3002/31 193 (9·6%)
Very high	683/31 193 (2·2%)	1395/31 193 (4·5%)	3491/31 193 (11·2%)	3913/31 193 (12·5%)

Results are based on patients in the development cohort.

Supplementary table 21: Absolute patient count of potential treatment stratification in cancer patients with ACS

Potential treatment stratification	Count (%)	
Conservative treatment	6530/31 193 (20·9%)	
Invasive treatment and short DAPT with clopidogrel	5154/31 193 (16·5%)	
Invasive treatment and long DAPT with clopidogrel	19 263/31 193 (61·8%)	
Invasive treatment and long DAPT with potent P2Y12 receptor inhibitor	246/31 193 (0·8%)	

Results are based on patients in the development cohort. DAPT=dual antiplatelet therapy.

Supplementary table 22: Comparison of ONCO-ACS models to established prediction models.

	Mortality – GRACE 2.0							
	Internal validation		External validation					
	Testing dataset (*n* = 6239)		Midlands (*n* = 5578)		Sweden (*n* = 10 262)		Switzerland (*n* = 203)	
	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
Delta tAUC†	0·10	0·09–0·12	0·10	0·08–0·11	0·04	0·03–0·05	0·19	0·10–0·28
IDI	0·17	0·16– 0·19	0·16	0·14–0·18	0·10	0·09–0·11	0·17	0·08–0·25
NRI	0·55	0·46–0·64	0·54	0·42–0·67	0·37	0·27–0·46	0·51	-0·18–1·21
	Major Bleeding – PRECISE-DAPT							
	Internal validation		External validation					
	Testing dataset (*n* = 6239)		Midlands (*n* = 5578)		Sweden (*n* = 10 262)		Switzerland (*n* = 203)	
	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
Delta tAUC†	0·04	0·01–0·06	0·03	-0·00–0·06	0·01	-0·02–0·03	0·04	-0·10–0·17
IDI	0·03	0·03–0·04	0·03	0·02–0·03	0·01	0·01–0·02	0·01	-0·01–0·03
NRI	0·00	-0·00–0·01	0·00	-0·02–0·03	0·26	0·18–0·34	0	0–0
	Ischaemic Events – PARIS							
	Internal validation		External validation					
	Testing dataset (*n* = 6239)		Midlands (*n* = 5578)		Sweden (*n* = 10 262)		Switzerland (*n* = 203)	
	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
Delta tAUC†	0·20	0·17–0·22	0·16	0·13–0·19	0·10	0·08–0·12	0·12	-0·03–0·26
IDI	0·14	0·13– 0·15	0·12	0·10–0·13	0·07	0·06–0·08	0·13	0·04–0·21
NRI	0·37	0·30–0·45	0·37	0·27–0·47	0·29	0·20–0·37	0·31	-0·38–1·00

CI=confidence interval. IDI=Integrated discrimination index. NRI=Net reclassification improvement index. tAUC=time-dependent area under the curve.

Supplementary table 23: Sex-specific, ethnic group-specific, age-specific, ACS type-specific, tumour type-specific, and period-specific crude cumulative incidence of mortality, major bleeding and ischaemic events in patients with cancer based on complete case analysis

		Mortality	Major bleeding	Ischaemic events
	Patients	Cumulative incidence (95% CI)	Cumulative incidence (95% CI)	Cumulative incidence (95% CI)
Overall	5292	20·65 (19·56–21·74)	7·92 (7·19–8·65)	11·43 (10·58–12·29)
Sex				
Female	1641	21·21 (19·20–23·16)	6·95 (5·72–8·18)	11·52 (9·97–13·06)
Male	3651	20·41 (19·09–21·70)	8·35 (7·46–9·25)	11·39 (10·36–12·42)
Ethnicity				
White	4990	20·72 (19·59–21·84)	7·72 (6·98–8·46)	11·26 (10·39–12·14)
Non white	272	18·75 (13·98–23·26)	12·13 (8·24–16·02)	13·97 (9·84–18·10)
Age				
≤ 55 years	264	10·61 (6·81–14·24)	3·79 (1·48–6·10)	6·44 (3·47–9·41)
55-70 years	1599	14·07 (12·35–15·76)	6·32 (5·12–7·51)	7·07 (5·81–8·32)
> 70 years	3429	24·50 (23·04–25·92)	8·98 (8·03–9·94)	13·85 (12·70–15·01)
ACS type				
STEMI	1910	21·94 (20·06–23·77)	7·17 (6·02–8·33)	12·83 (11·33–14·33)
NSTE-ACS	3382	19·93 (18·57–21·26)	8·34 (7·41–9·27)	10·64 (9·61–11·68)
Tumour type				
Prostate	1407	13·15 (11·36–14·90)	8·24 (6·81–9·68)	11·09 (9·45–12·73)
Colorectal	812	17·49 (14·83–20·06)	7·64 (5·81–9·46)	12·07 (9·83–14·31)
Breast	539	11·87 (9·10–14·56)	5·94 (3·94–7·93)	10·76 (8·14–13·38)
Lung	678	42·48 (38·63–46·08)	7·23 (5·28–9·18)	13·72 (11·13–16·31)
Bladder	258	21·32 (16·16–26·16)	14·73 (10·39–19·06)	12·40 (8·37–16·43)
All other types	1598	22·47 (20·39–24·49)	7·63 (6·33–8·94)	10·51 (9·01–12·02)
Evidence of active cancer				
Yes	2010	31·44 (29·38–33·44)	8·56 (7·33–9·78)	12·44 (10·99–13·88)
No	3282	14·05 (12·85–15·23)	7·53 (6·62–8·43)	10·82 (9·75–11·88)
Period				
Period 1 (2005–2011)	64	34·38 (21·64–45·04)	7·81 (1·18–14·45)	14·06 (5·47–22·66)
Period 2 (2011–2018)	5228	20·49 (19·38–21·57)	7·92 (7·19–8·65)	11·40 (10·54–12·26)

Incidence values are percentages. Results are based on patients from the UK. ACS=acute coronary syndrome. CI=confidence interval. NSTE-ACS=non-ST elevation acute coronary syndrome. STEMI=ST-elevation myocardial infarction.

Supplementary table 24: Performance metrics based on complete case analysis

	Internal validation		External validation					
	Testing dataset (*n* = 920)		Midlands (*n* = 702)		Sweden (*n* = 4511)		Switzerland (*n* = 68)	
	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
Mortality								
tAUC	0·84	0·82–0·87	0·87	0·84–0·90	0·81	0·79–0·83	0·73	0·61–0·86
Calibration slope	0·95	0·80–1·09	1·01	0·84–1·19	0·83	0·76–0·90	0·66	0·20–1·12
Brier Score	0·064	0·053–0·076	0·052	0·040–0·064	0·052	0·047–0·057	0·098	0·051–0·145
Major bleeding								
tAUC	0·78	0·71–0·84	0·76	0·70–0·82	0·69	0·65–0·72	0·82	0·71–0·93
Calibration slope	1·45	1·04–1·86	1·41	0·92–1·89	1·19	0·92–1·45	2·13	-0·21–4·48
Brier Score	0·066	0·052–0·080	0·070	0·053–0·086	0·056	0·049–0·062	0·026	0·001–0·052
Ischaemic events								
tAUC	0·75	0·70–0·80	0·75	0·69–0·81	0·68	0·65–0·71	0·62	0·43–0·80
Calibration slope	0·93	0·68–1·19	0·94	0·57–1·31	0·58	0·45–0·70	-0·02	-0·11–0·07
Brier Score	0·084	0·070–0·098	0·059	0·045–0·072	0·081	0·074–0·088	0·128	0·066–0·190

CI=confidence interval. tAUC=time-dependent area under the curve.

Supplementary table 25: Treatment with percutaneous coronary intervention and its association with clinical outcomes in cancer patients with ACS stratified according to mortality risk

	Patients treated with PCI	Number of fatal events at 6 months	Multivariable-adjusted† HR for mortality	p	Number of net adverse clinical events‡ at 6 months	Multivariable-adjusted† HR for net adverse clinical events‡	p
All patients	14 868/31 193 (47·7%)	8881/31 193 (28·5%)	0·64 (0·60–0·67)	<0·0001	11 383/31 193 (36·5%)	0·70 (0·67–0·73)	<0·0001
Subgroups based on ONCO-ACS score	**Patients treated with PCI**	**Number of fatal events at 6 months**	**Multivariable-adjusted† HR for mortality***	**p for interaction with the association of PCI with mortality**	**Number of net adverse clinical events‡ at 6 months**	**Multivariable-adjusted† HR for net adverse clinical events‡**	**p for interaction with the association of PCI with net adverse clinical events‡***
Mortality risk							
Very high (>50%)	1910/6409 (29·8%)	4532/6409 (70·7%)	0·84 (0·77–0·90)	0·012	4862/6409 (75·9%)	0·88 (0·82–0·95)	0·69
High (>19% to ≤50%)	3947/9929 (39·8%)	3289/9929 (33·1%)	0·61 (0·55–0·66)	0·51	4249/9929 (42·8%)	0·67 (0·62–0·72)	0·015
Moderate (>5% to ≤19%)	4909/8946 (54·9%)	949/8946 (10·6%)	0·44 (0·37–0·51)	0·34	1788/8946 (20·0%)	0·59 (0·53–0·66)	0·006
Low (≤5%)	4102/5909 (69·4%)	111/5909 (1·9%)	0·49 (0·31–0·77)	Ref.	484/5909 (8·2%)	0·76 (0·61–0·94)	Ref.

*A global test for interaction comparing models with and without interaction term (mortality risk group*PCI) yielded significant results (each p<0.0001). ‡Net adverse cardiovascular events were defined as the first occurrence of death, myocardial infarction, ischaemic stroke, or major bleeding. HR refers to the baseline hazard ratios. †Models were adjusted for: age, sex, heart rate, systolic blood pressure, ST-segment deviation, onset-to-door time, BMI, diabetes, hypercholesterolemia, smoking status, time since cancer diagnosis, tumour type (according grouped into 5 most common types and others), metastatic disease, haemoglobin levels, troponin elevation > 99th percentile, eGFR, glucose, cholesterol, atrial fibrillation, hypertension, chronic kidney disease, obstructive lung disease, peptic ulcer disease, prior myocardial infarction, prior cerebrovascular ischaemia, prior percutaneous coronary intervention, prior coronary artery bypass grafting, radial access site, multivessel disease, use of drug-eluting stent, diameter of drug-eluting stent (<3mm), left ventricular ejection fraction, procedural P2Y12 receptor inhibitor use, procedural unfractionated heparin use, procedural low-molecular heparin use, procedural fondaparinux use, procedural β-blocker use, procedural diuretics use, acetylsalicylic acid at discharge, P2Y12 receptor inhibitor at discharge, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker at discharge, β-blocker at discharge, statin at discharge. Results are based on imputed data from the development cohort. HR=hazard ratio. PCI=percutaneous coronary intervention.

Supplementary table 26: Treatment with dual antiplatelet therapy and its association with clinical outcomes in cancer patients with ACS stratified according to mortality risk, bleeding risk, and ischaemic risk

	Patients treated with DAPT	Number of fatal events at 6 months	Multivariable-adjusted† HR for mortality	p	Number of net adverse clinical events‡ at 6 months	Multivariable-adjusted† HR for net adverse clinical events‡	p
All patients	19 255/31 193 (61·7%)	8881/31 193 (28·5%)	0·75 (0·71–0·80)	<0·0001	11 383/31 193 (36·5%)	0·82 (0·78–0·86)	<0·0001
Subgroups based on ONCO-ACS score	**Patients treated with DAPT**	**Number of fatal events at 6 months**	**Multivariable-adjusted† HR for mortality**	**p for interaction with the association of DAPT with mortality#**	**Number of net adverse clinical events‡ at 6 months**	**Multivariable-adjusted† HR for net adverse clinical events‡**	**p for interaction with the association of DAPT with net adverse clinical events‡#**
Bleeding risk							
Very high (>9%)	4086/8092 (50·5%)	3436/8092 (42·5%)	0·76 (0·70–0·84)	<0·0001	4396/8092 (54·3%)	0·82 (0·76–0·89)	<0·0001
High (>5% to ≤9%)	7390/11 553 (64·0%)	3205/11 553 (27·7%)	0·82 (0·75–0·90)	<0·0001	4077/11 553 (35·3%)	0·88 (0·81–0·96)	<0·0001
Moderate (>4% to ≤5%)	6902/9949 (69·4%)	1618/9949 (16·3%)	0·75 (0·65–0·86)	<0·0001	2229/9949 (22·4%)	0·85 (0·76–0·95)	<0·0001
Low (≤4%)	877/1599 (54·8%)	622/1599 (38·9%)	0·43 (0·32–0·57)	Ref.	681/1599 (42·6%)	0·49 (0·38–0·63)	Ref.
Ischaemic risk							
Very high (>20%)	4311/9521 (45·3%)	4834/9521 (50·8%)	0·64 (0·59–0·70)	<0·0001	5665/9521 (59·5%)	0·72 (0·67–0·77)	<0·0001
High (>10% to ≤20%)	6140/9726 (63·1%)	2730/9726 (28·1%)	0·86 (0·78–0·95)	0·043	3619/9726 (37·2%)	0·89 (0·81–0·97)	<0·0001
Moderate (>5% to ≤10%)	4194/5888 (71·2%)	917/5888 (15·6%)	0·97 (0·82–1·15)	0·41	1352/5888 (23·0%)	0·96 (0·83–1·11)	0·0067
Low (≤5%)	4610/6058 (76·1%)	400/6058 (6·6%)	0·91 (0·69–1·21)	Ref.	747/6058 (12·3%)	0·96 (0·78–1·19)	Ref.
Risk Profiles							
High potential benefit							
Bleeding risk (≤5%) AND ischaemic risk (>20%)	2442/4485 (54·4%)	1688/4485 (37·6%)	0·58 (0·50–0·67)	<0·0001	1972/4485 (44·0%)	0·68 (0·59–0·77)	<0·0001
Moderate potential benefit							
Bleeding risk (≤5%) AND ischaemic risk (≤20%) or Bleeding risk (>5%) AND ischaemic risk (>10%)	13 346/21 825 (61·2%)	6428/21 825 (29·5%)	0·78 (0·73–0·83)	<0·0001	8250/21 825 (37·8%)	0·83 (0·79–0·88)	<0·0001
Low potential benefit							
Bleeding risk (>5%) AND ischaemic risk (≤10%)	3467/4883 (71·0%)	765/4883 (15·7%)	0·94 (0·78–1·14)	<0·0001	1161/4883 (23·8%)	0·98 (0·83–1·14)	<0·0001

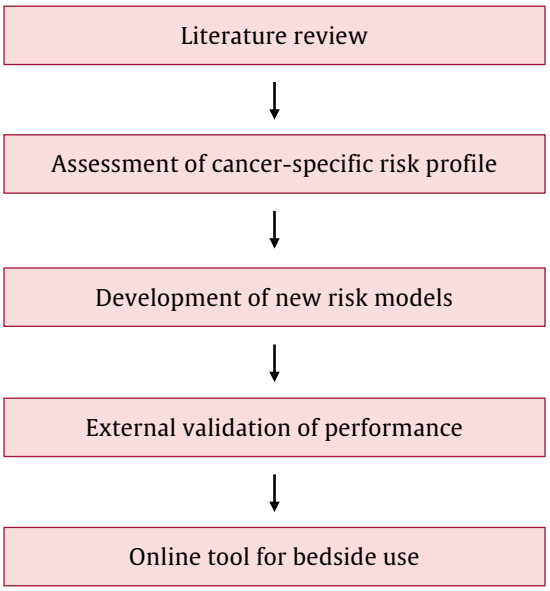
#A global test for interaction comparing models with and without interaction term (mortality risk group*DAPT at discharge) yielded significant results (each p<0.0001). ‡Net adverse cardiovascular events were defined as the first occurrence of death, myocardial infarction, ischaemic stroke, or major bleeding. HR refers to the baseline hazard ratios. †Models were adjusted for: age, sex, heart rate, systolic blood pressure, ST-segment deviation, onset-to-door time, BMI, diabetes, hypercholesterolemia, smoking status, time since cancer diagnosis, tumour type (according grouped into 5 most common types and others), metastatic disease, haemoglobin levels, troponin elevation > 99th percentile, eGFR, glucose, cholesterol, atrial fibrillation, hypertension, chronic kidney disease, obstructive lung disease, peptic ulcer disease, prior myocardial infarction, prior cerebrovascular ischaemia, prior percutaneous coronary intervention, prior coronary artery bypass grafting, radial access site, percutaneous coronary intervention, multivessel disease, use of drug-eluting stent, diameter of drug-eluting stent (<3mm), left ventricular ejection fraction, procedural P2Y12 receptor inhibitor use, procedural unfractionated heparin use, procedural low-molecular heparin use, procedural fondaparinux use, procedural β-blocker use, procedural diuretics use, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker at discharge, β-blocker at discharge, statin at discharge. Results are based on imputed data from the development cohort. DAPT=dual antiplatelet therapy. HR=hazard ratio.

Supplementary table 27: Treatment with percutaneous coronary intervention and DAPT stratified by risk group.

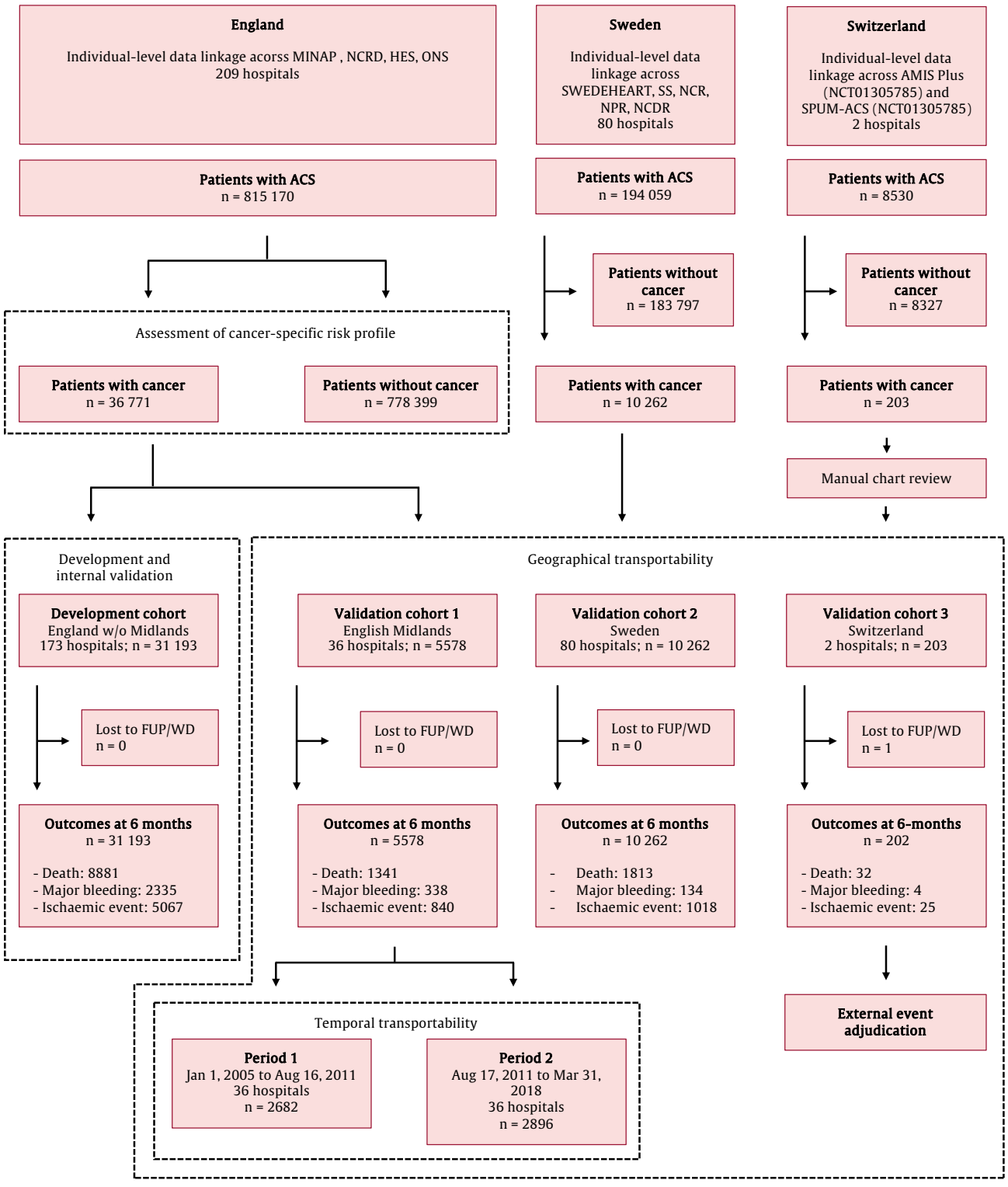
Subgroups based on ONCO-ACS score	Patients treated with PCI (count; %)	Patients treated with DAPT at discharge (count; %)
Mortality risk		
Very high (>50%)	1910/6409 (29·8%)	2423/6409 (36·2%)
High (>19% to ≤50%)	3947/9929 (39·8%)	5820/9929 (58·6%)
Moderate (>5% to ≤19%)	4909/8946 (54·9%)	6478/8946 (72·4%)
Low (≤5%)	4102/5909 (69·4%)	4534/5909 (76·7%)
Bleeding risk		
Very high (>9%)	2912/8092 (36·0%)	4086/8092 (50·5%)
High (>5% to ≤9%)	5205/11 553 (45·1%)	7390/11 553 (64·0%)
Moderate (>4% to ≤5%)	5860/9949 (58·9%)	6902/9949 (69·4%)
Low (≤4%)	891/1599 (55·7%)	877/1599 (54·8%)
Ischaemic risk		
Very high (>20%)	3228/9521 (33·9%)	4311/9521 (45·3%)
High (>10% to ≤20%)	4268/9726 (43·9%)	6140/9726 (63·1%)
Moderate (>5% to ≤10%)	3301/5888 (56·1%)	4194/5888 (71·2%)
Low (≤5%)	4071/6058 (67·2%)	4610/6058 (76·1%)

Results are based on imputed data from the development cohort. DAPT=dual antiplatelet therapy. PCI=percutaneous coronary intervention.

Supplementary figure 1: Study flow chart

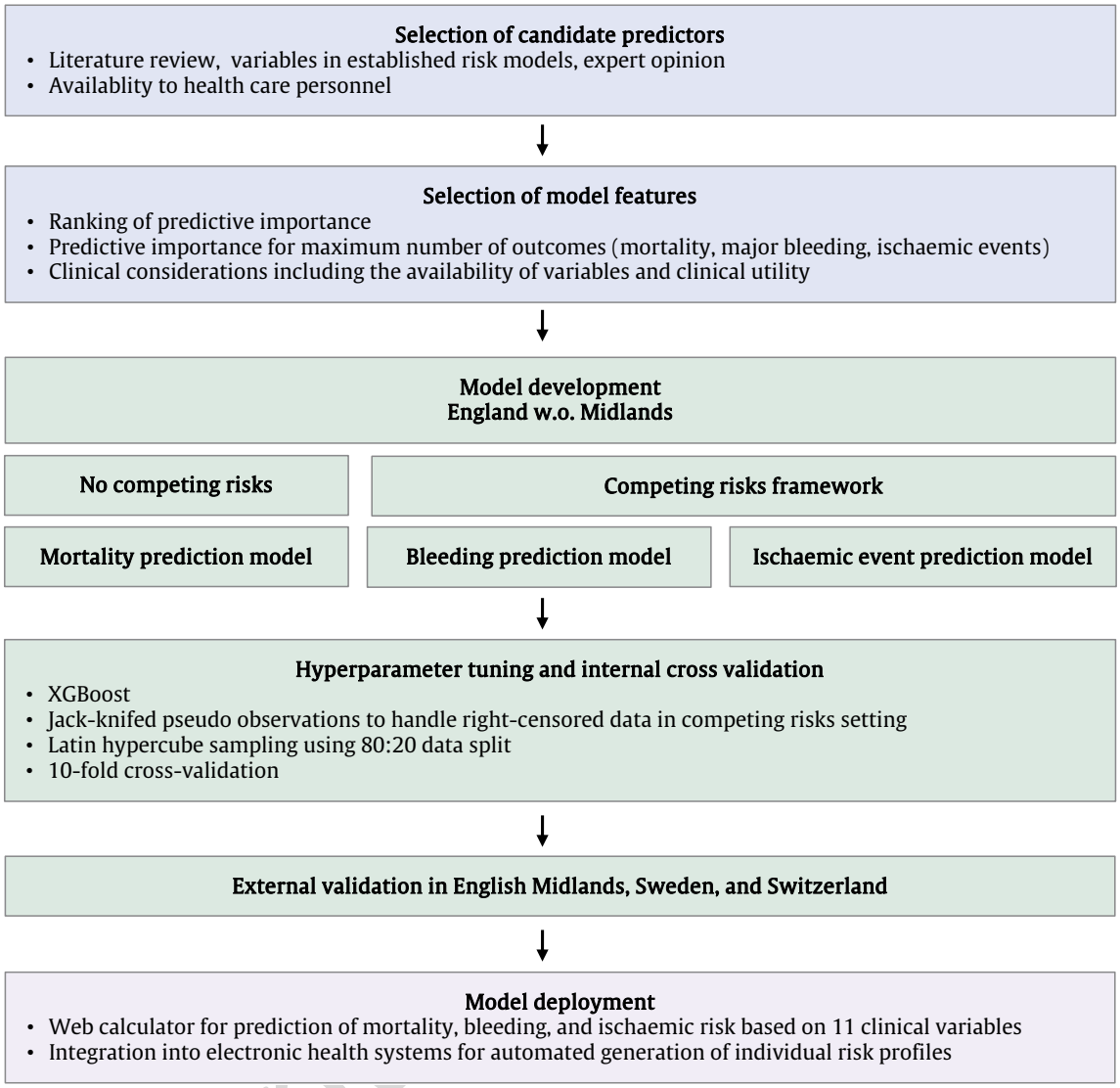


Supplementary figure 2: Patient flow chart



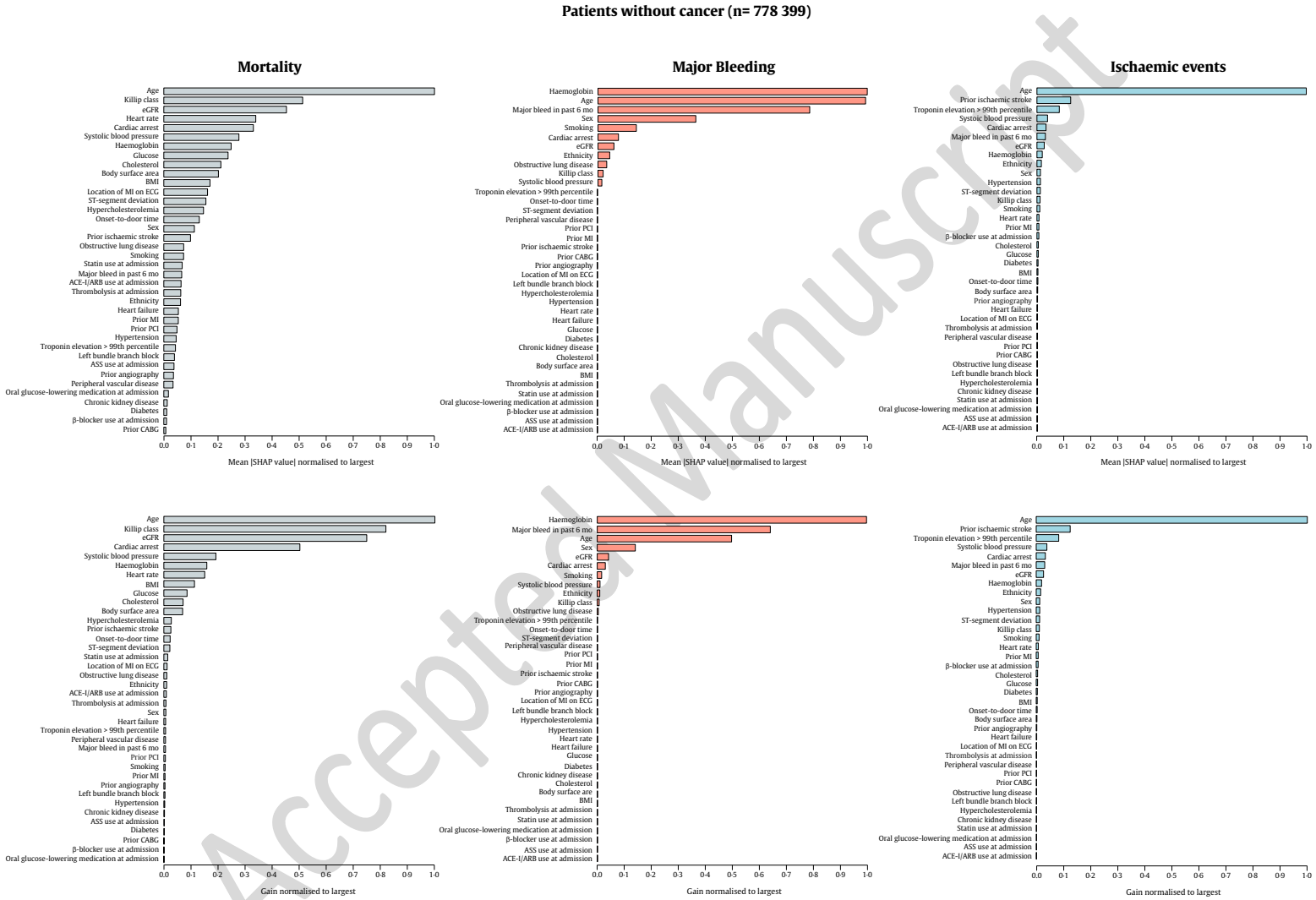
ACS=acute coronary syndrome. AMIS=Acute Myocardial Infarction in Switzerland. FUP=lost to follow-up. HES=Hospital Episode Statistics. MINAP=Myocardial Ischaemia National Audit Project. NCRD=National Cancer Registration Dataset. NCDR=National Cause-of-Death Registry. NPR=National Patient Registry. NCR=National Cancer Registry. ONS=Office for National Statistics. SPUM-ACS=Special Programme University Medicine Acute Coronary Syndrome. SS=Statistics Sweden. SWEDEHEART=Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies. WD=withdrawn. w/o=without

Supplementary figure 3: Model development, validation, and deployment



w/o=without

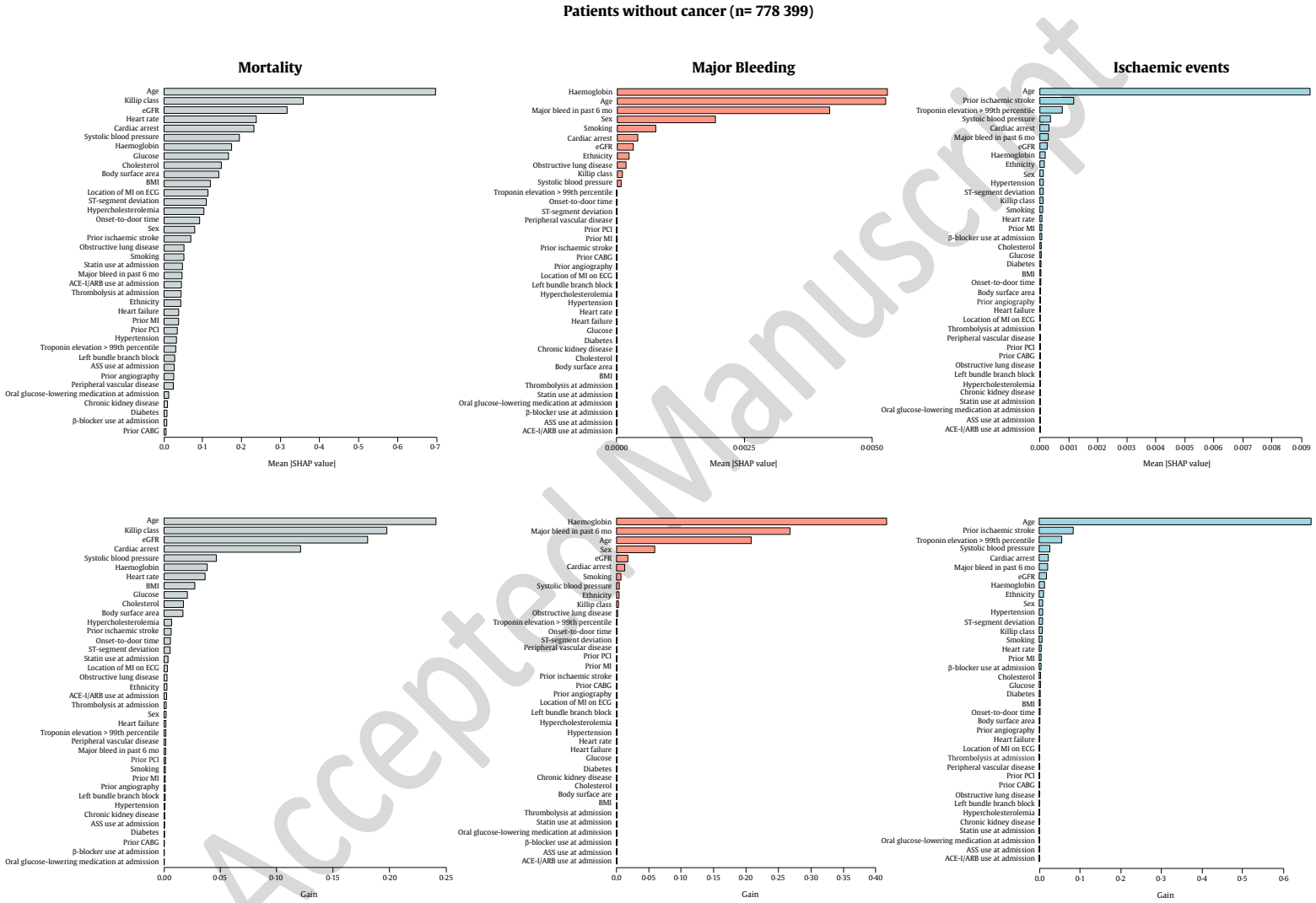
Supplementary figure 4: Predictive value of traditional risk factors in patients without cancer (normalised to largest)



The variable importance of all 38 predictor variables available in patients without cancer for the respective outcome is displayed. Bars represent mean (ie, aggregated across all patients) absolute SHAP values (top) or Gain (bottom) of the respective feature, scaled to the feature with the highest value. For multi-level factor variables such as Killip class, bars represent the sum of mean absolute SHAP values across all factor levels. Gain corresponds to the fractional contribution of a given feature to the model, with higher values indicating higher predictive

importance. SHAP and Gain normalised to largest. Results are based on patients from the UK. ACE-I=angiotensin-converting enzyme-inhibitor. ARB=angiotensin receptor blocker. ASS=acetylsalicylic acid. BMI=body mass index. ECG=electrocardiogram. eGFR=estimated glomerular filtration rate. CABG=coronary artery bypass grafting. MI=myocardial infarction. PCI=percutaneous coronary intervention. SHAP=Shapley additive explanations.

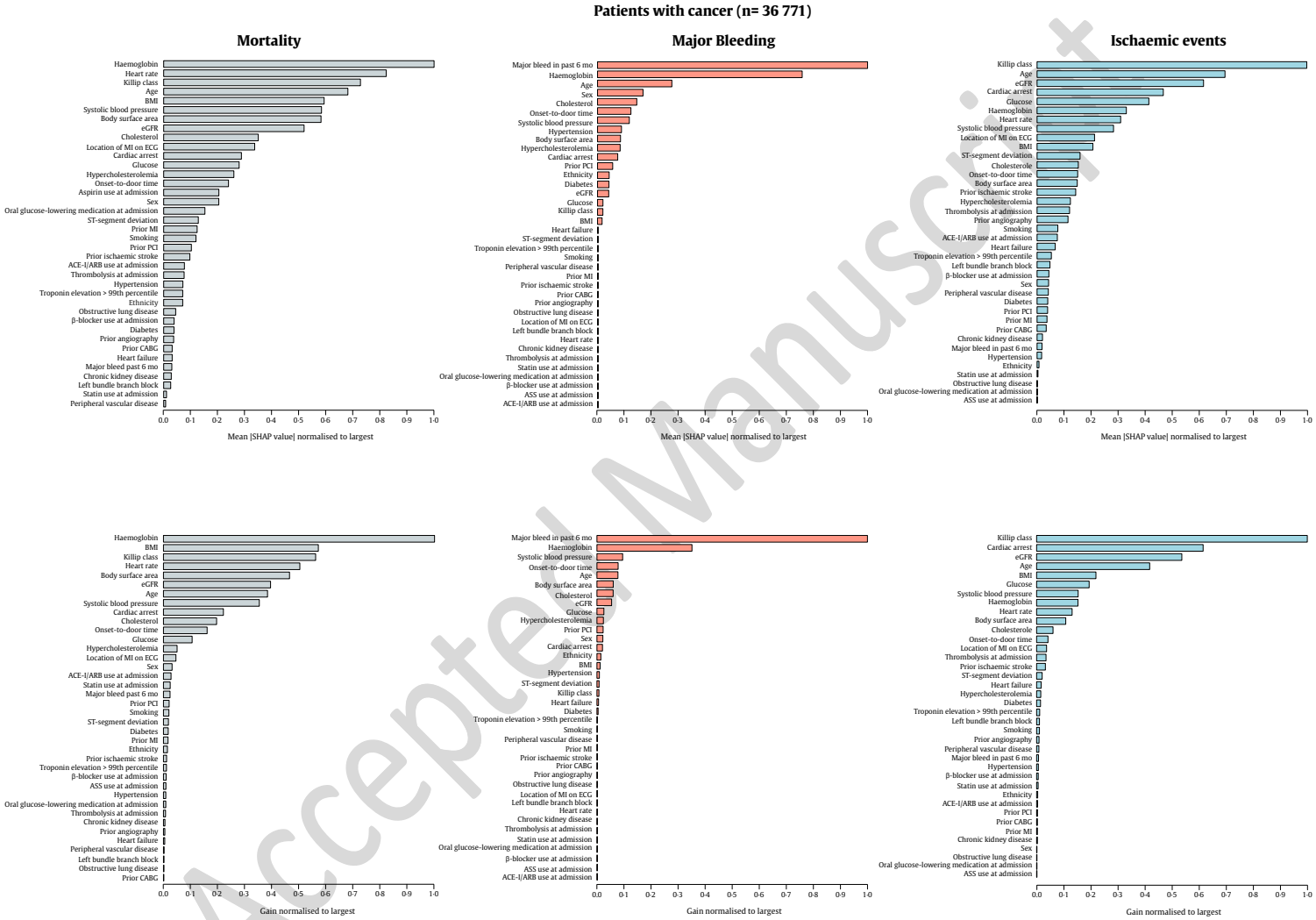
Supplementary figure 5: Predictive value of traditional risk factors in patients without cancer (untransformed)



The variable importance of all 38 predictor variables available in patients without cancer for the respective outcome is displayed. Bars represent untransformed mean (ie, aggregated across all patients) absolute SHAP values (top) or Gain (bottom) of the respective feature. For multi-level factor variables such as Killip class, bars represent the sum of mean absolute SHAP values across all factor levels. Gain corresponds to the fractional contribution of a given feature to the model, with higher values indicating higher predictive importance. Results are based on patients

from the UK. ACE-I=angiotensin-converting enzyme-inhibitor. ARB=angiotensin receptor blocker. ASS=acetylsalicylic acid. BMI=body mass index. ECG=electrocardiogram. eGFR=estimated glomerular filtration rate. CABG=coronary artery bypass grafting. MI=myocardial infarction. PCI=percutaneous coronary intervention. SHAP=Shapley additive explanations.

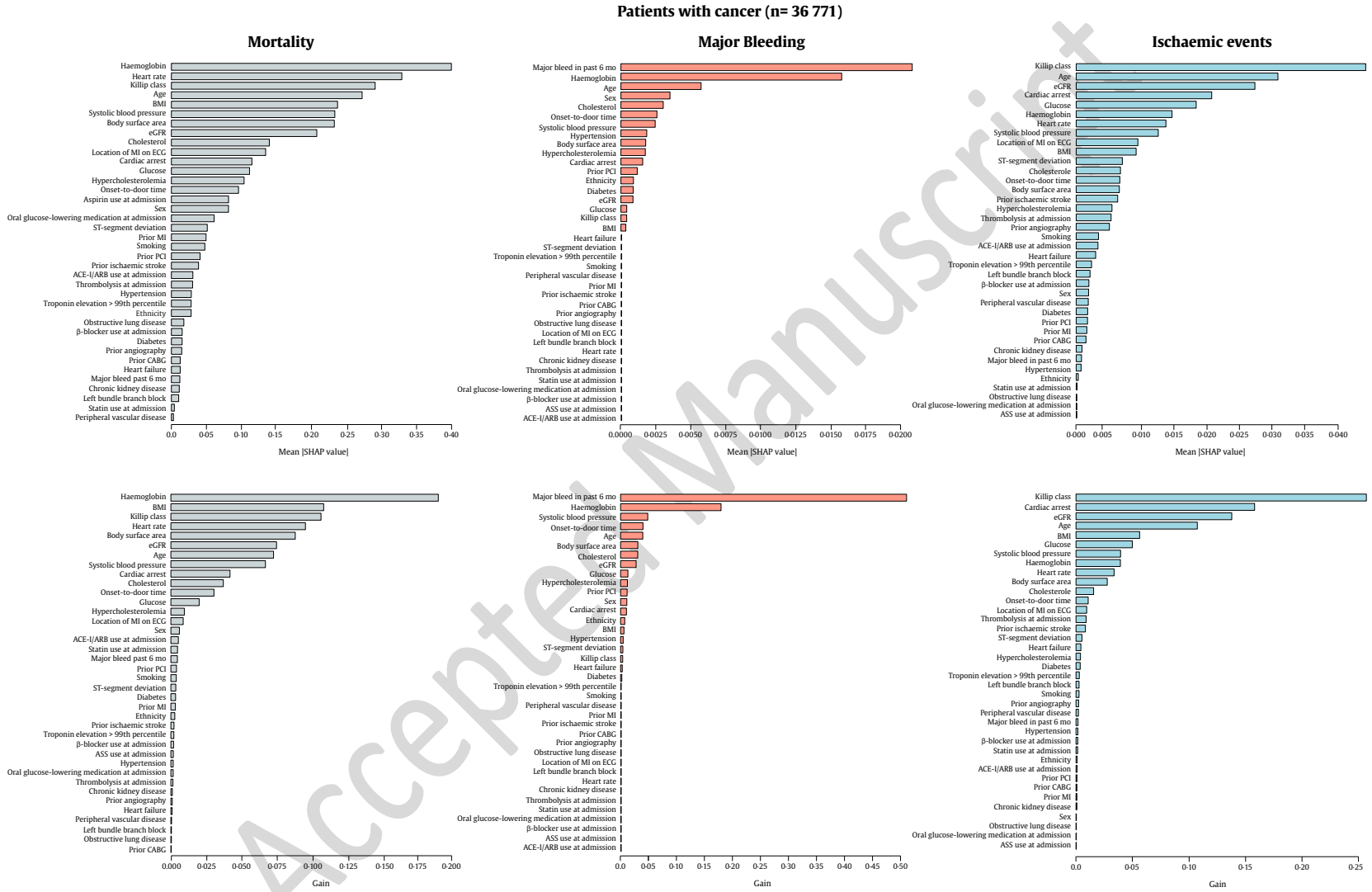
Supplementary figure 6: Predictive importance of traditional risk factors in patients with cancer (normalised to largest)



The variable importance of all 38 predictor variables available in patients with cancer for the respective outcome is displayed. Bars represent mean (ie, aggregated across all patients) absolute SHAP values (top) or Gain (bottom) of the respective feature, scaled to the feature with the highest value for each endpoint. For multi-level factor variables, such as Killip class, bars represent the sum of mean absolute SHAP values across all factor levels. Gain corresponds to the fractional contribution of a given feature to the model, with higher values indicating higher predictive importance. Results are based on patients from the UK. ACE-I=angiotensin-converting enzyme-inhibitor. ARB=angiotensin receptor blocker. ASS=acetylsalicylic acid. BMI=body mass index.

ECG=electrocardiogram. eGFR=estimated glomerular filtration rate. CABG=coronary artery bypass grafting. MI=myocardial infarction. PCI=percutaneous coronary intervention. SHAP=Shapley additive explanations.

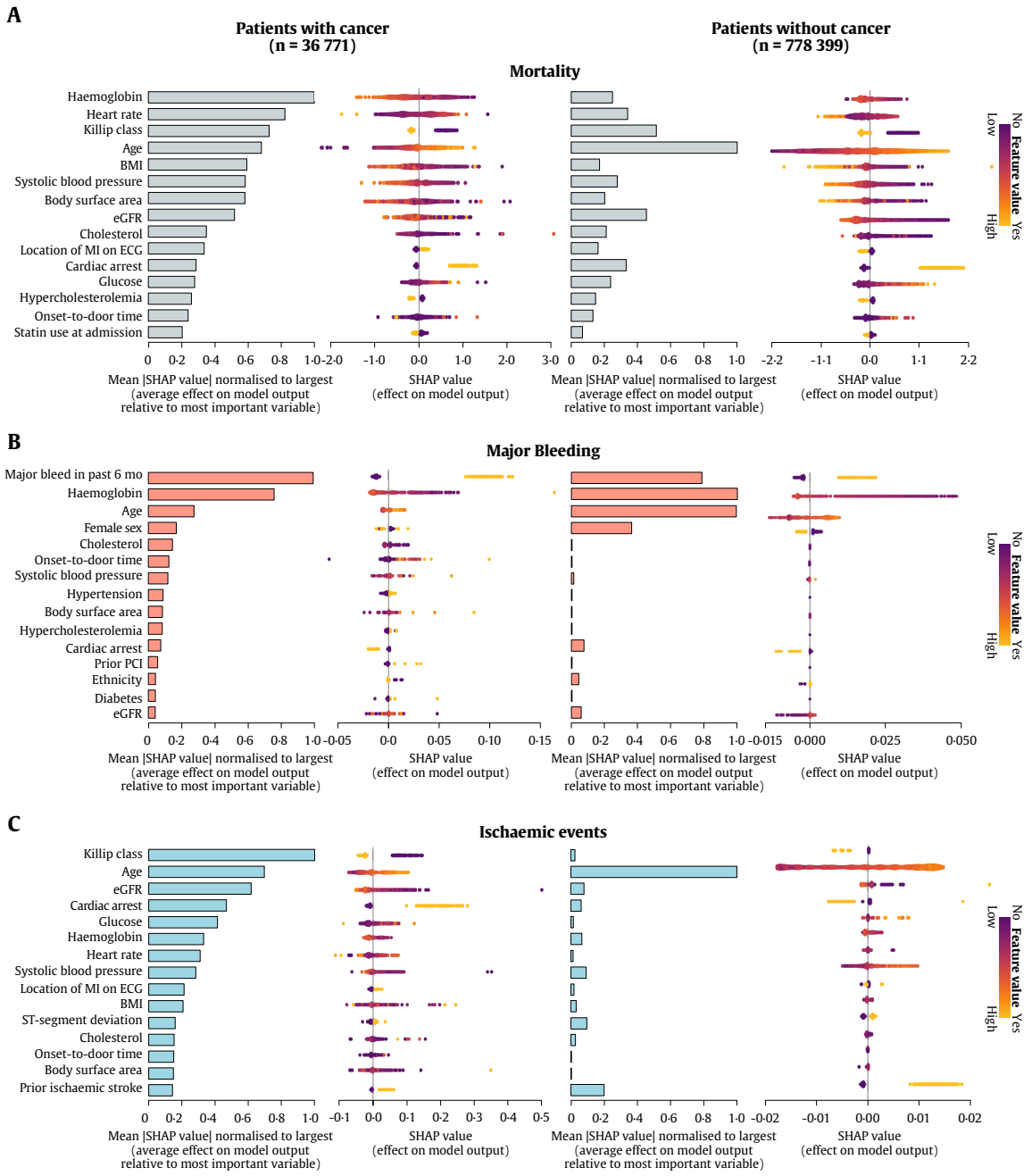
Supplementary figure 7: Predictive importance of traditional risk factors in patients with cancer (untransformed)



The variable importance of all 38 predictor variables available in patients with cancer for the respective outcome is displayed. Bars represent untransformed mean (ie, aggregated across all patients) absolute SHAP values (top) or Gain (bottom) of the respective feature. For multi -level factor variables, such as Killip class, bars represent the sum of mean absolute SHAP values across all factor levels. Gain corresponds to the fractional contribution of a given feature to the model, with higher values indicating higher predictive importance. Results are based on patients

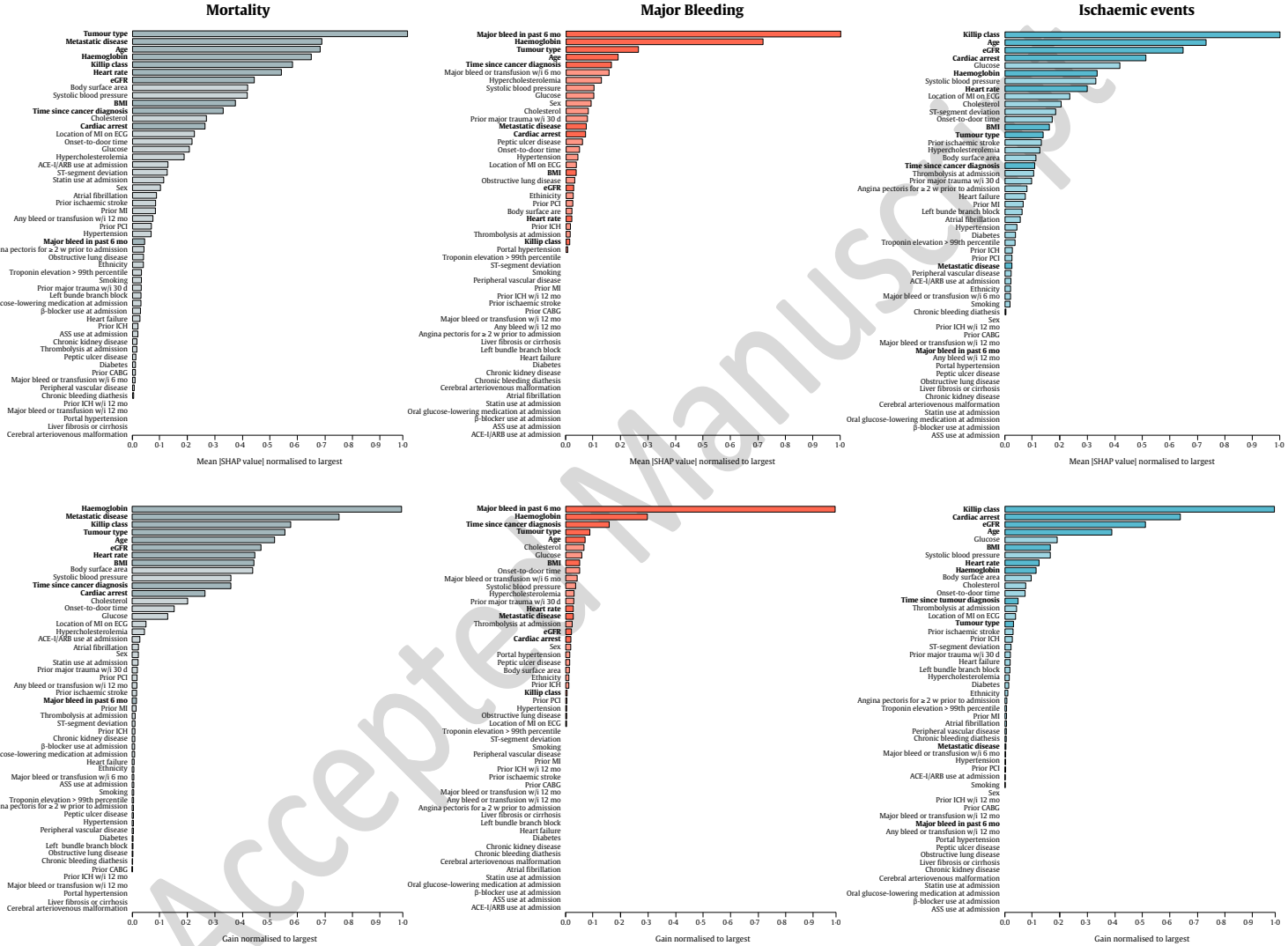
from the UK. ACE-I=angiotensin-converting enzyme-inhibitor. ARB=angiotensin receptor blocker. ASS=acetylsalicylic acid. BMI=body mass index. ECG=electrocardiogram. eGFR=estimated glomerular filtration rate. CABG=coronary artery bypass grafting. MI=myocardial infarction. PCI=percutaneous coronary intervention. SHAP=Shapley additive explanations.

Supplementary figure 8: Predictive value of top 15 baseline characteristics in patients with and without cancer



Variables ranked according to their importance for the prediction of (A) all-cause mortality at 6 months, (B) major bleeding at 6 months, and (C) ischaemic events at 6 months after admission with ACS. Six separate models for mortality, bleeding and ischaemic events in patients with (left) and without (right) cancer were developed using identical predictor variables. The 15 top-ranked variables in cancer patients are shown for each model. Each point represents a patient with its colour indicating the feature value and its position indicating the Shapley (SHAP) value. For example, the effect of the age feature on model output is strong positive when the patient is relatively old (yellow) and strong negative when a patient is relatively young (purple). Bars represent mean absolute SHAP values of a feature across all patients were scaled to the feature with the highest value for each endpoint and group. For the multi-level factor variables, such as Killip class and ethnicity, dots refer to the reference levels (ie, Killip class I and White ethnicity, respectively) and bars represent the sum of mean absolute values across all factor levels. Results are based on patients from the UK. BMI=body mass index, ECG=electrocardiography, eGFR=estimated glomerular filtration rate, MI=myocardial infarction, PCI=percutaneous coronary intervention.

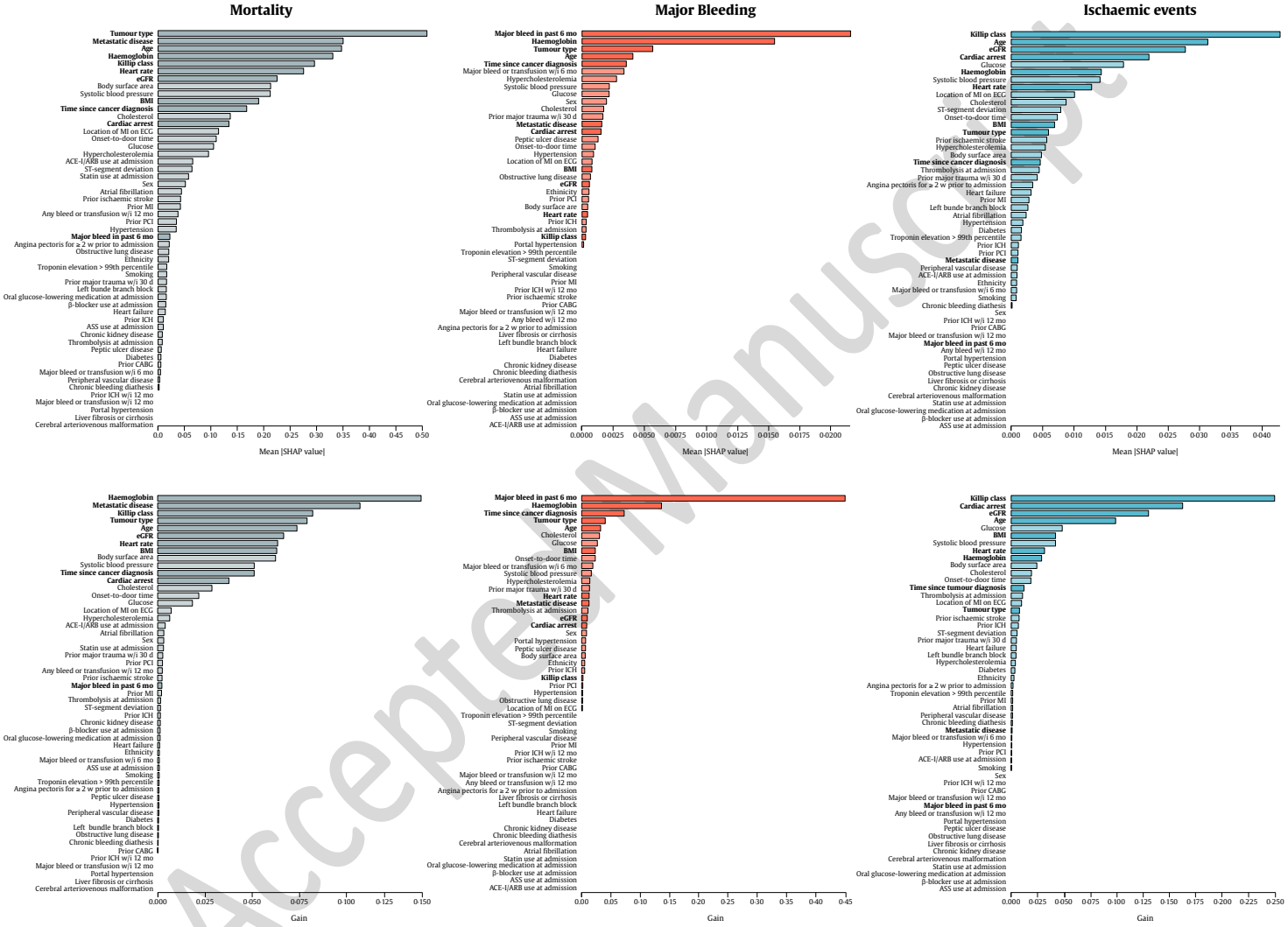
Supplementary figure 9: Predictive importance of candidate predictor variables in cancer patients with ACS (normalised to largest)



The variable importance of all 53 candidate predictor variables for the respective outcome is displayed. Bars represent mean (ie, aggregated across all patients) absolute SHAP values (top) or Gain (bottom) of the respective feature, scaled to the feature with the highest value for each endpoint. For the multi-level factor variables, such as Killip class and ethnicity, bars represent the sum of mean absolute SHAP values across all factor levels. Gain corresponds to the fractional contribution of a given feature to the model, with higher values indicating higher predictive importance. The 11 variables included in the final ONCO-ACS prediction models are highlighted in bold. Results are based on patients in the development cohort. ACE-I=angiotensin-

converting enzyme-inhibitor. ARB=angiotensin receptor blocker. BMI=body mass index. ECG=electrocardiogram. eGFR=estimated glomerular filtration rate. CABG=coronary artery bypass grafting. ICH=intracranial haemorrhage. MI=myocardial infarction. PCI=percutaneous coronary intervention. SHAP=Shapley additive explanations. w/i=within

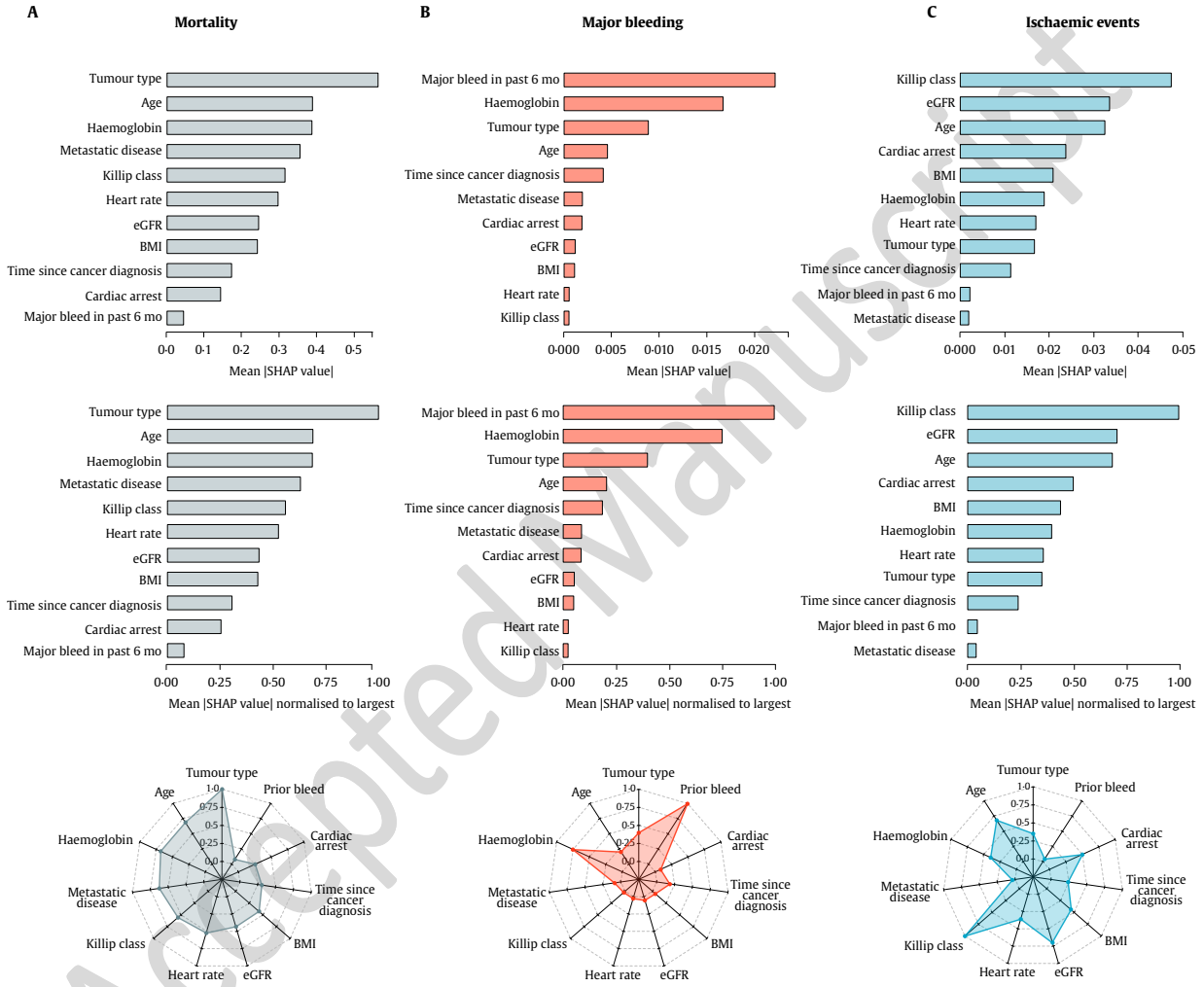
Supplementary figure 10: Predictive importance of candidate predictor variables in cancer patients with ACS (untransformed)



The variable importance of all 53 candidate predictor variables for the respective outcome is displayed. Bars represent untransformed mean (ie, aggregated across all patients) absolute SHAP values (top) or Gain (bottom) of the respective feature. For the multi-level factor variables, such as Killip class and ethnicity, bars represent the sum of mean absolute SHAP values across all factor levels. Gain corresponds to the fractional contribution of a given feature to the model, with higher values indicating higher predictive importance. The 11 variables included in the final ONCO-ACS prediction models are highlighted in bold. Results are based on patients in the development cohort. ACE-I=angiotensin-converting enzyme-inhibitor. ARB=angiotensin receptor

blocker. BMI=body mass index. ECG=electrocardiogram. eGFR=estimated glomerular filtration rate. CABG=coronary artery bypass grafting. ICH=intracranial haemorrhage. MI=myocardial infarction. PCI=percutaneous coronary intervention. SHAP=Shapley additive explanations. w/i=within

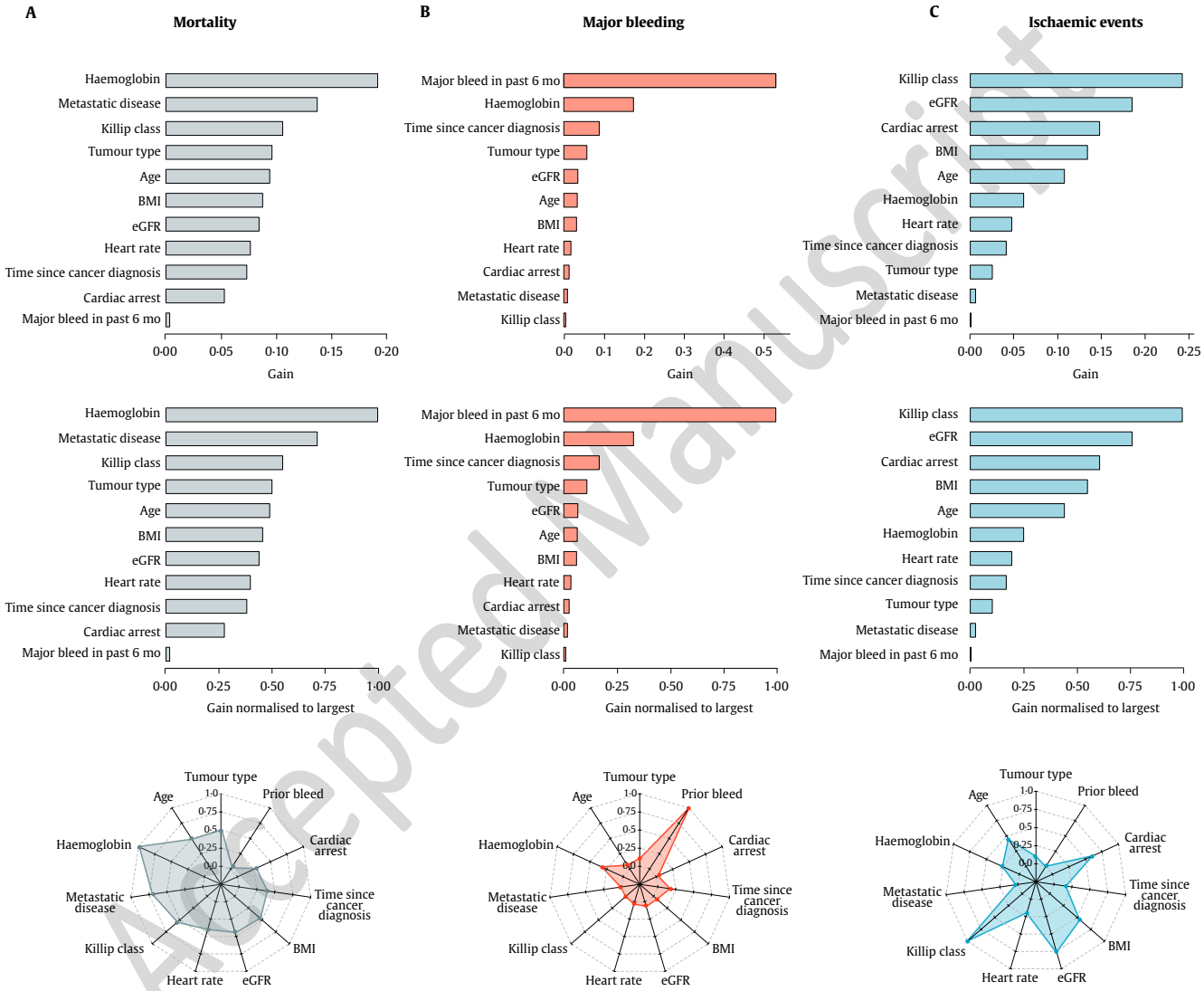
Supplementary figure 11: Variable importance in the final ONCO-ACS models according to mean absolute SHAP



The variable importance of the final 11 predictor variables in ONCO-ACS for prediction of (A) mortality, (B) major bleeding and (C) ischaemic events is displayed (top – untransformed mean absolute SHAP value; middle – mean absolute SHAP value normalised to largest) together with radar plots (bottom – mean absolute SHAP value normalised to largest). Bars represent untransformed mean (ie, aggregated across all patients) absolute SHAP values of the respective feature (top) or mean (ie, aggregated across all patients) absolute SHAP values of the respective feature scaled to the feature with the highest value for each endpoint (middle). Radar plots depict mean (ie, aggregated across all patients) absolute SHAP values of the respective feature scaled

to the feature with the highest value (bottom). Results are based on patients in the development cohort. BMI=body mass index. eGFR=estimated glomerular filtration rate. SHAP=Shapley additive explanations.

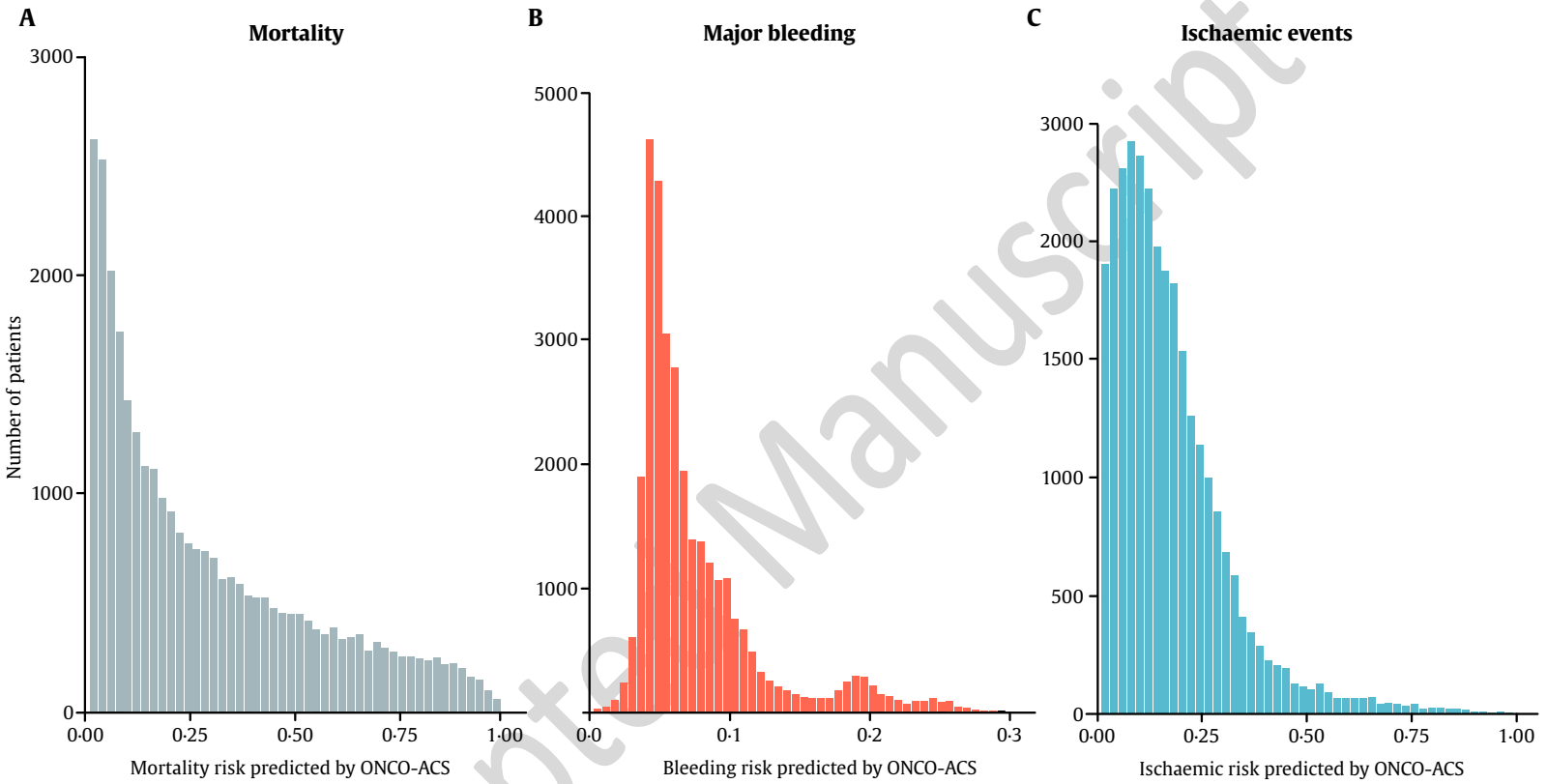
Supplementary figure 12: Variable importance in the final ONCO-ACS models according to Gain



The variable importance of the final 11 predictor variables in ONCO-ACS for prediction of (A) mortality, (B) major bleeding and (C) ischaemic events is displayed (top – untransformed Gain; middle – Gain normalised to largest) together with radar plots (bottom – Gain normalised to largest). Bars represent untransformed Gain (top), or Gain scaled to the feature with the highest

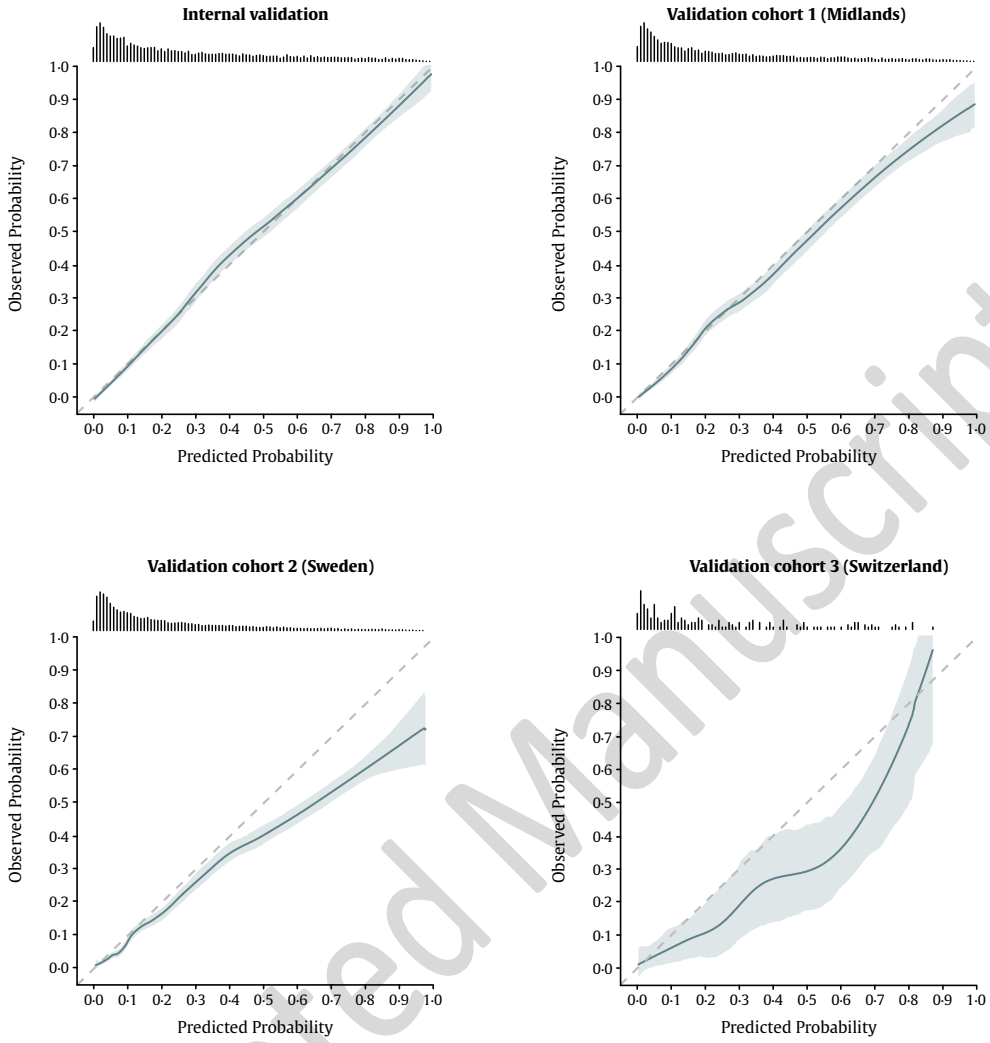
value for each endpoint (middle). Radar plots show Gain scaled to the feature with the highest importance (bottom). Gain corresponds to the fractional contribution of a given feature to the model, with higher values indicating higher predictive importance. Results are based on patients in the development cohort. BMI=body mass index. eGFR=estimated glomerular filtration rate.

Supplementary figure 13: Histogram of predicted risk



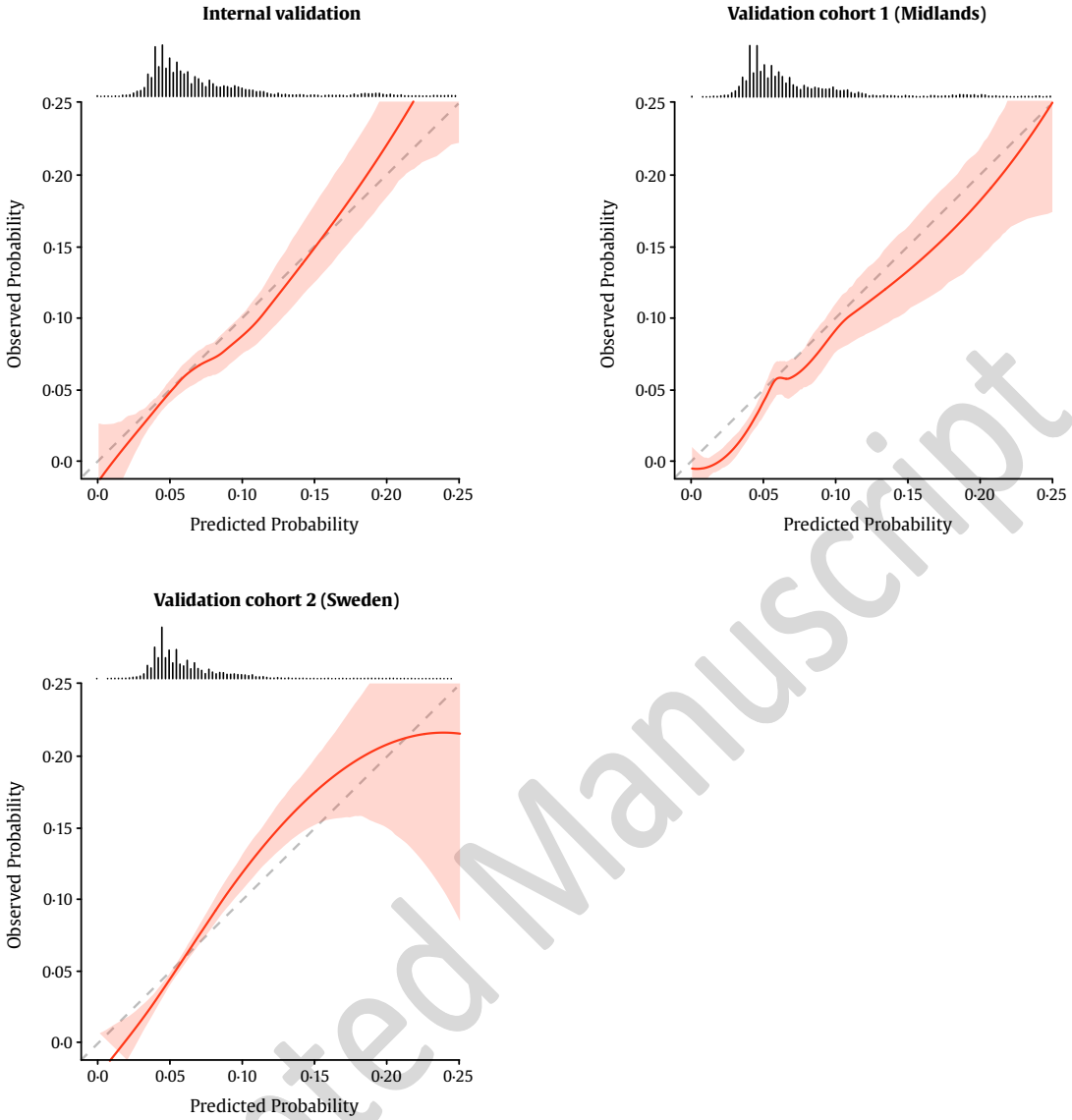
Histogram showing the risk of mortality (A), major bleeding (B), and ischaemic events (C) predicted by the ONCO-ACS score. Results are based on patients in the development cohort.

Supplementary figure 14: Calibration plots for mortality model



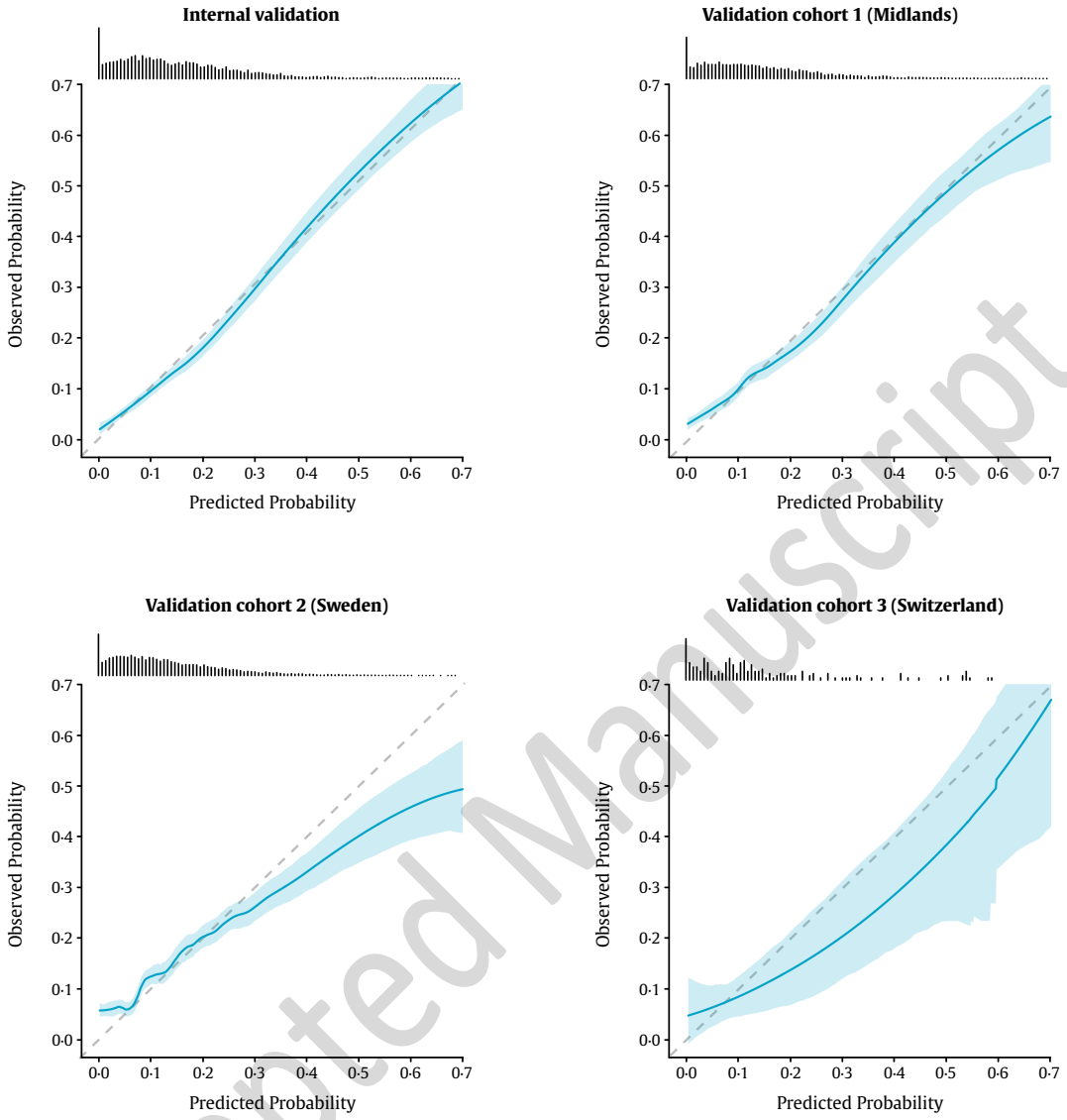
Predicted and observed risk of mortality at 6 months in internal and external validation cohorts. Colour bands signify 95% confidence intervals. The distribution of predicted risks is summarised as a histogram on top of the respective graphs.

Supplementary figure 15: Calibration plots for major bleeding model



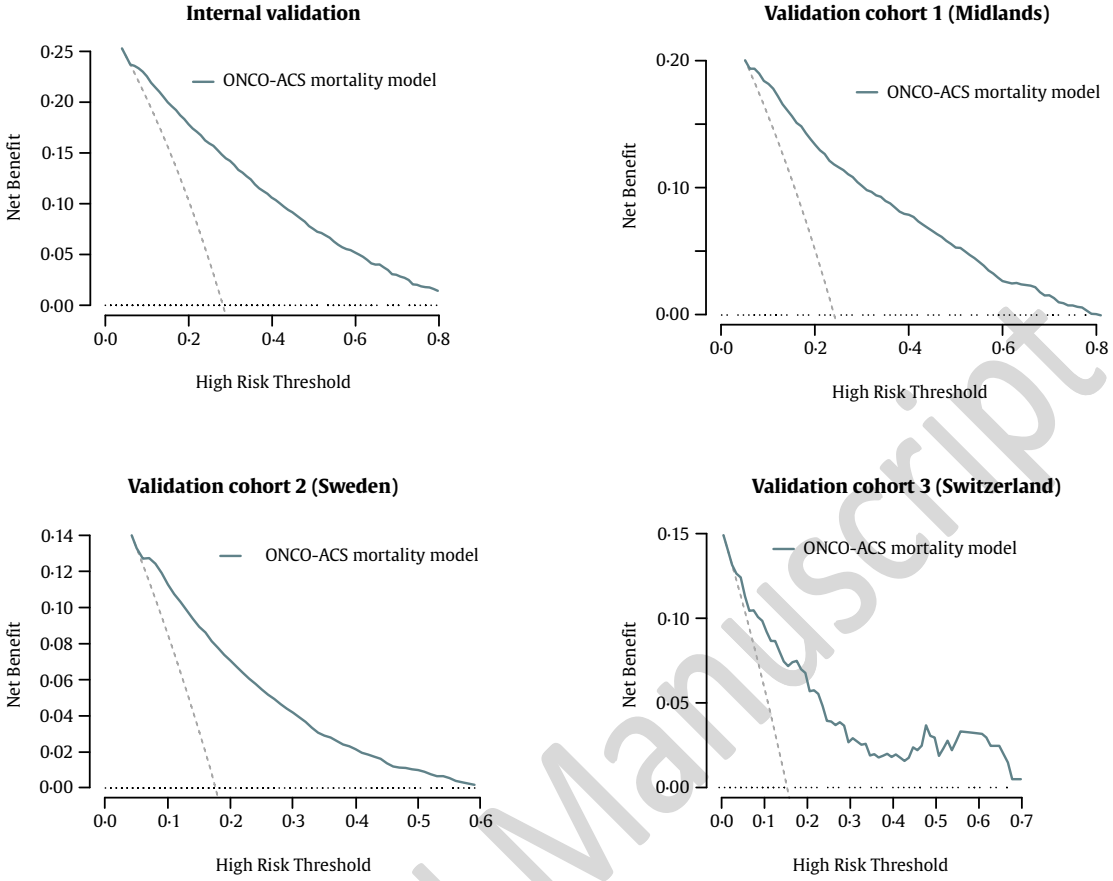
Predicted and observed risk of major bleeding at 6 months in internal and external validation cohorts. Colour bands signify 95% confidence intervals. The distribution of predicted risks is summarised as a histogram on top of the respective graphs. In Switzerland, the low event count precludes meaningful graphical presentation of the calibration.

Supplementary figure 16: Calibration plots for ischaemia model



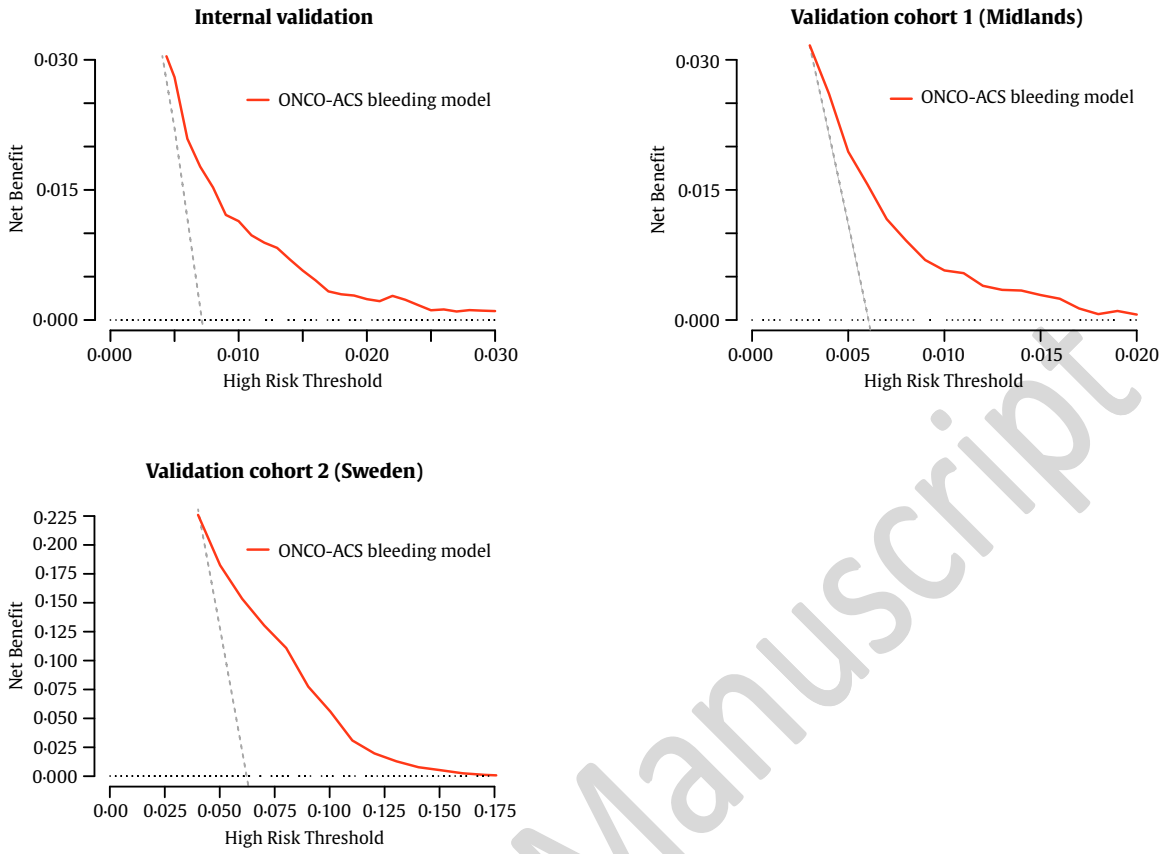
Predicted and observed risk of ischaemic events at 6 months in internal and external validation cohorts. Colour bands signify 95% confidence intervals. The distribution of predicted risks is summarised as a histogram on top of the respective graphs.

Supplementary figure 17: Decision curve analysis for mortality model



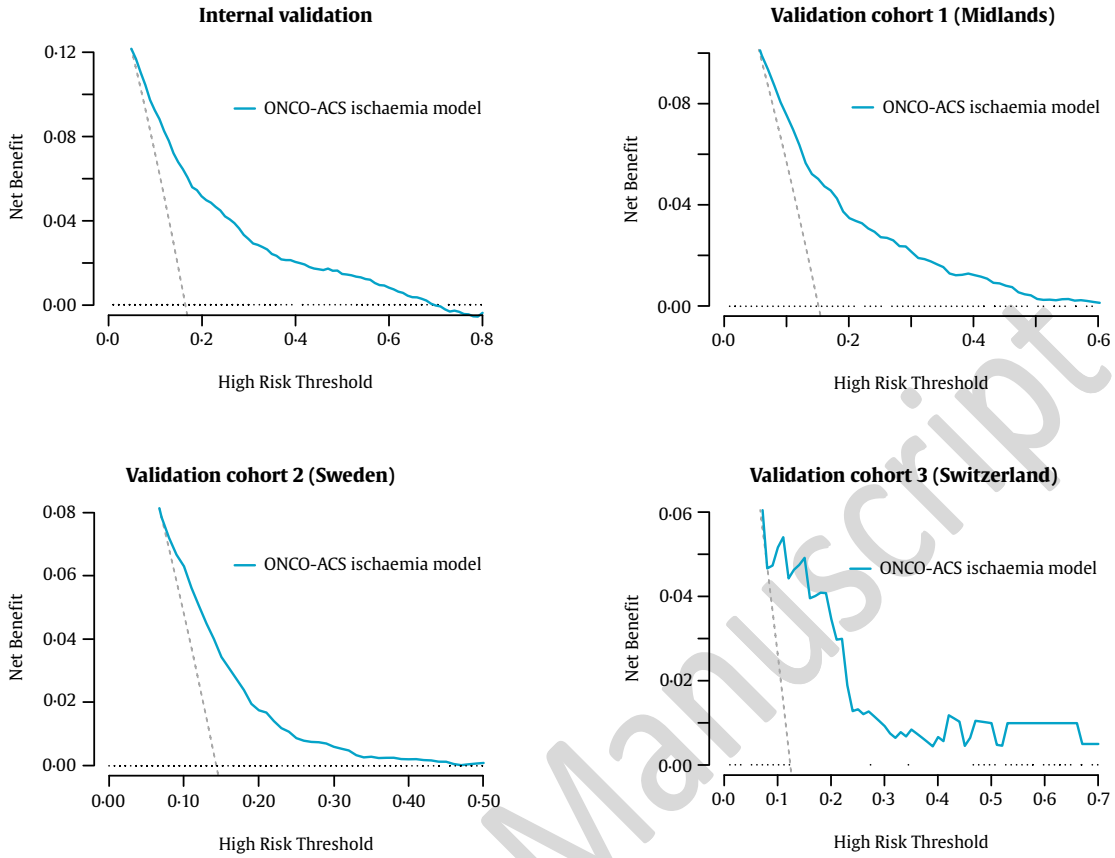
The plot displays the net benefit of the ONCO-ACS mortality model across a range of decision thresholds. Horizontal black dotted lines represent a treat-none-scenario. Oblique grey dashed lines represent a treat-all-scenario.

Supplementary figure 18: Decision curve analysis for major bleeding model



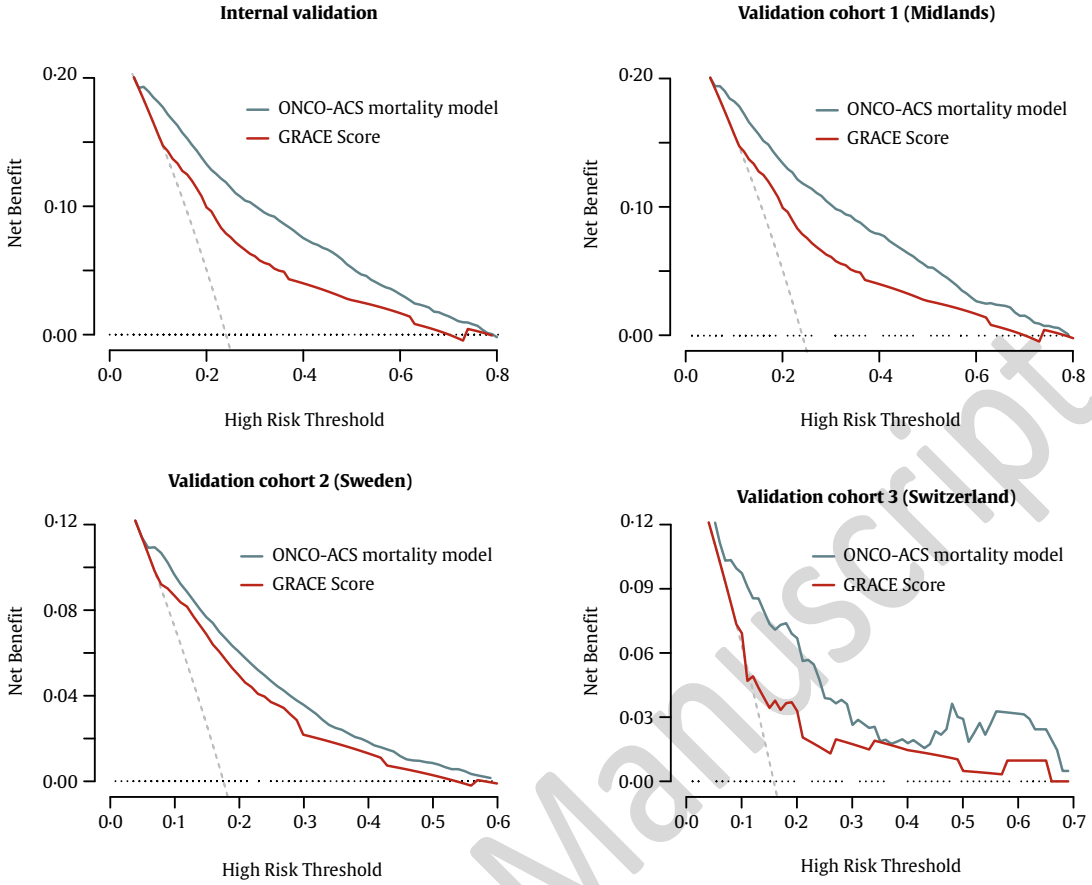
The plot displays the net benefit of the ONCO-ACS bleeding model across a range of decision thresholds. Horizontal black dotted lines represent a treat-none-scenario. Oblique grey dashed lines represent a treat-all-scenario. In Switzerland (validation cohort 3), the decision curve model did not converge due to the low event count.

Supplementary figure 19: Decision curve analysis for ischaemia model



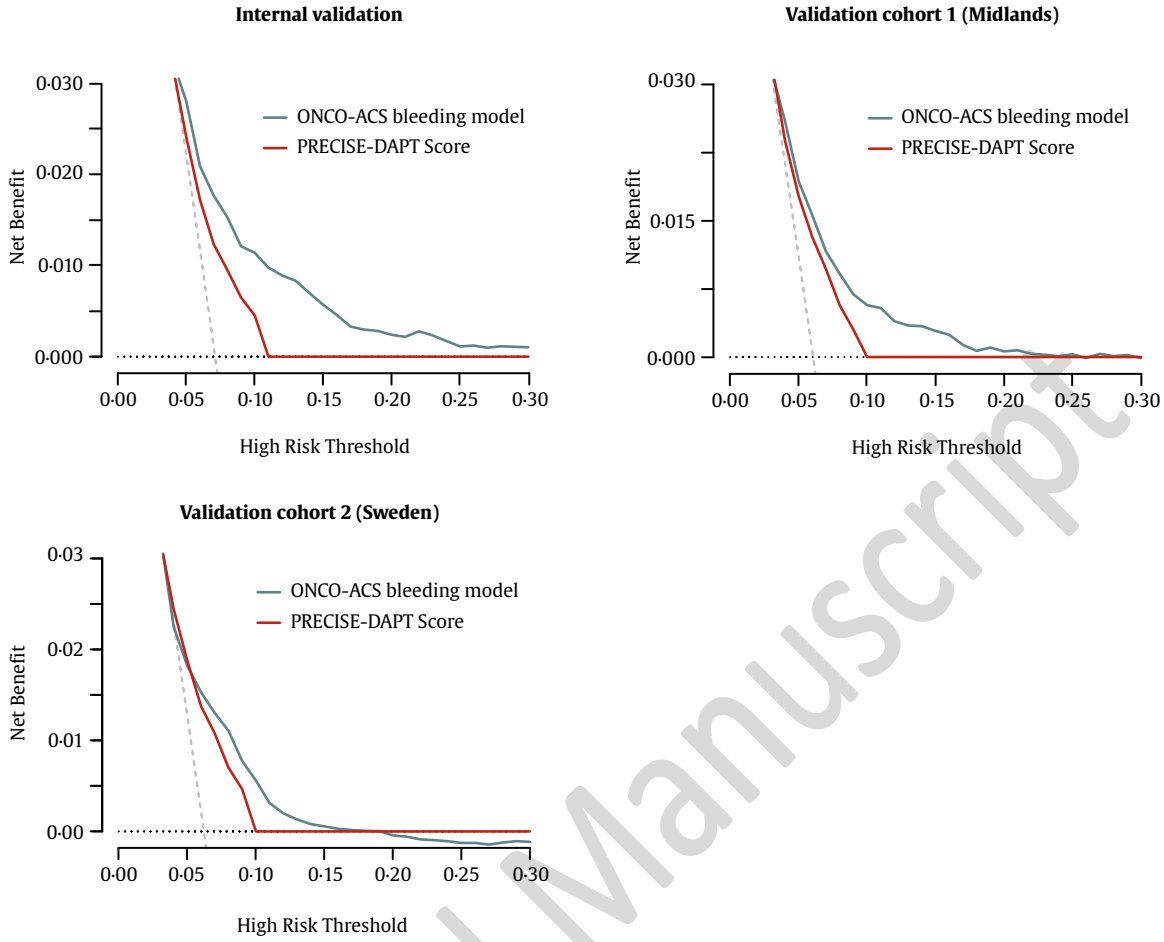
The plot displays the net benefit of the ONCO-ACS ischaemia model across a range of decision thresholds. Horizontal black dotted lines represent a treat-none-scenario. Oblique grey dashed lines represent a treat-all-scenario.

Supplementary figure 20: Decision curve analysis for mortality model compared to GRACE score



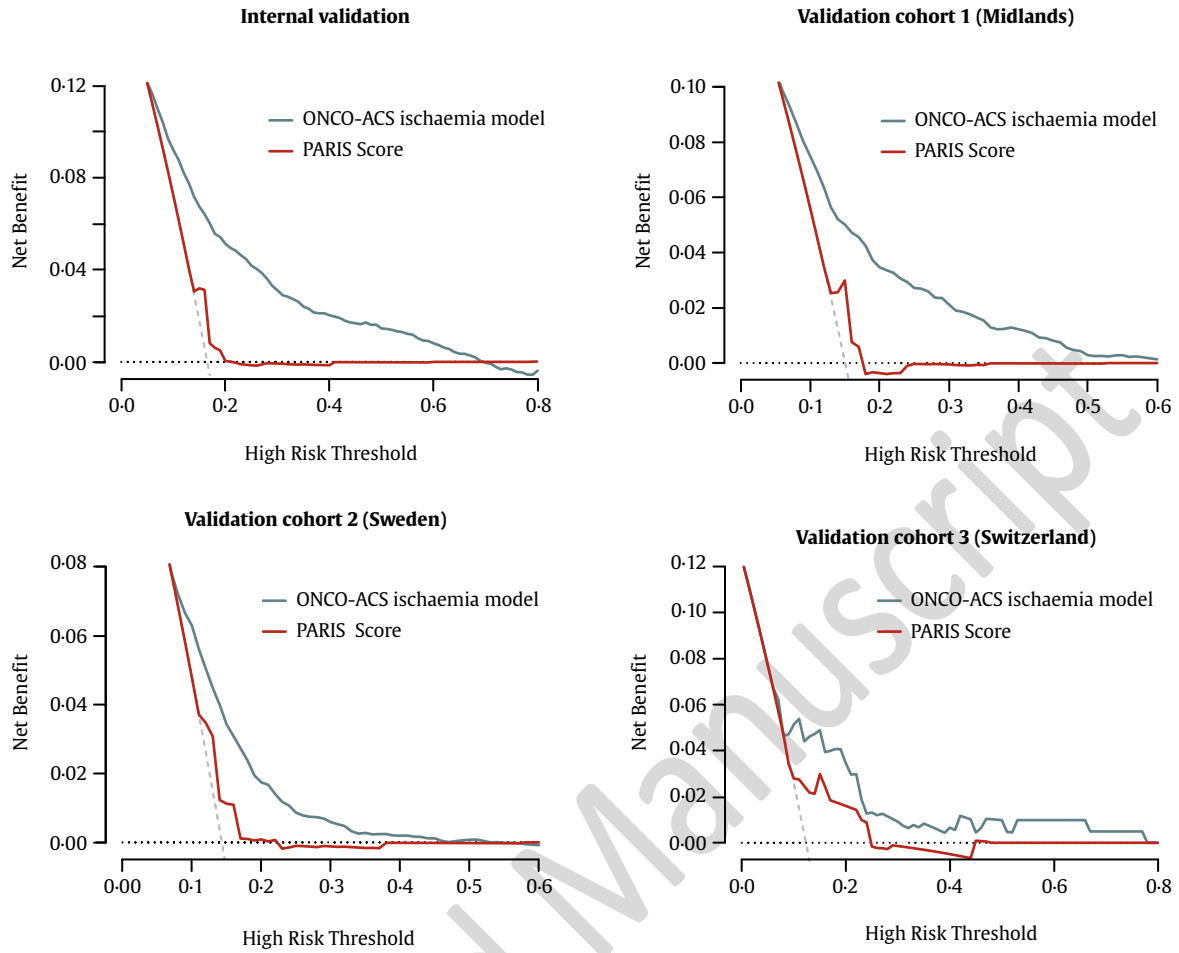
The plot displays the net benefit of the ONCO-ACS mortality model and of the GRACE Score for each decision threshold. Horizontal black dotted lines represent a treat-none-scenario. Oblique grey dashed lines represent a treat-all-scenario. Across a range of clinically relevant decision thresholds, the net benefit of the ONCO-ACS mortality model was consistently higher than that of the GRACE Score, suggesting helpful clinical utility above and beyond the GRACE Score.

Supplementary figure 21: Decision curve analysis for bleeding model compared to PRECISE-DAPT score



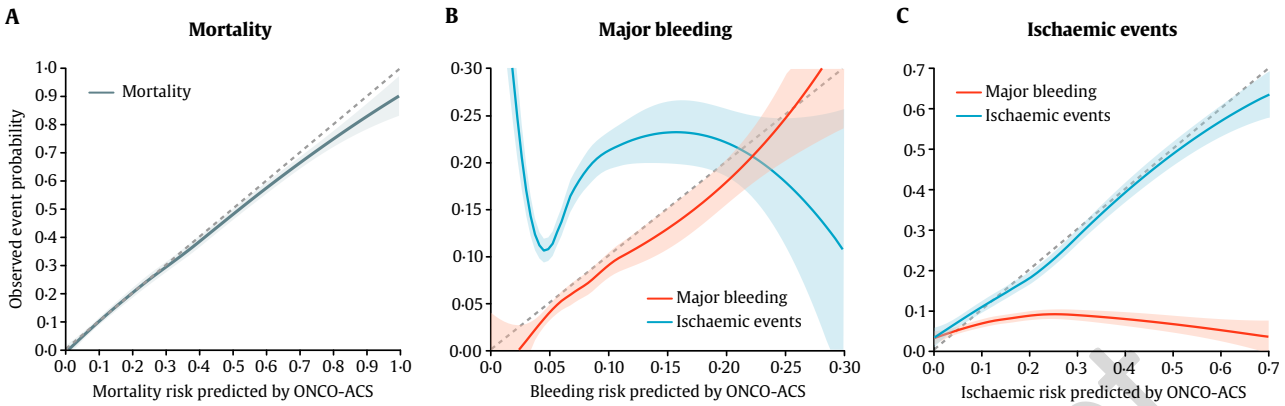
The plot displays the net benefit of the ONCO-ACS bleeding model and of the PRECISE-DAPT Score for each decision threshold. Horizontal black dotted lines represent a treat-none-scenario. Oblique grey dashed lines represent a treat-all-scenario. Across a range of clinically relevant decision thresholds, the net benefit of the ONCO-ACS bleeding model was consistently higher than that of the PRECISE-DAPT Score, suggesting helpful clinical utility above and beyond the PRECISE-DAPT Score. In Switzerland (validation cohort 3), the decision curve model did not converge due to the low event count.

Supplementary figure 22: Decision curve analysis for ischaemia model compared to PARIS score



The plot displays the net benefit of the ONCO-ACS ischaemia model and of the PARIS Score for each decision threshold. Horizontal black dotted lines represent a treat-none-scenario. Oblique grey dashed lines represent a treat-all-scenario. Across a range of clinically relevant decision thresholds, the net benefit of the ONCO-ACS ischaemia model was consistently higher than that of the PARIS Score, suggesting helpful clinical utility above and beyond the PARIS Score.

Supplementary figure 23: Outcome-specific risk prediction by the ONCO-ACS score



Predicted vs observed event probability for each score outcome (bottom) for (A) all-cause mortality, (B) major bleeding, and (C) ischaemic events at 6 months. Observed probabilities of both major bleeding and ischaemic events plotted as a function of each, predicted bleeding risk and predicted ischaemic risk. Colour bands signify 95% confidence intervals. Results are based on patients in validation cohort 1.

Supplementary figure 24: TRIPOD-AI checklist

TRIPOD+AI

Version: 11-January-2024

Section/Topic	Item	Development / evaluation[1]	Checklist item	Reported on page
TITLE				
Title	1	D;E	Identify the study as developing or evaluating the performance of a multivariable prediction model, the target population, and the outcome to be predicted	1
ABSTRACT				
Abstract	2	D;E	See TRIPOD+AI for Abstracts checklist	2-3
INTRODUCTION				
Background	3a	D;E	Explain the healthcare context (including whether diagnostic or prognostic) and rationale for developing or evaluating the prediction model, including references to existing models	5
	3b	D;E	Describe the target population and the intended purpose of the prediction model in the context of the care pathway, including its intended users (e.g., healthcare professionals, patients, public)	5
	3c	D;E	Describe any known health inequalities between sociodemographic groups	5
Objectives	4	D;E	Specify the study objectives, including whether the study describes the development or validation of a prediction model (or both)	5
METHODS				
Data	5a	D;E	Describe the sources of data separately for the development and evaluation datasets (e.g., randomised trial, cohort, routine care or registry data), the rationale for using these data, and representativeness of the data	5-7, Suppl.
	5b	D;E	Specify the dates of the collected participant data, including start and end of participant accrual; and, if applicable, end of follow-up	5-7, Suppl.
Participants	6a	D;E	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including the number and location of centres	5-7, Suppl.
	6b	D;E	Describe the eligibility criteria for study participants	5-6, Suppl.
	6c	D;E	Give details of any treatments received, and how they were handled during model development or evaluation, if relevant	5-7, Suppl.
Data preparation	7	D;E	Describe any data pre-processing and quality checking, including whether this was similar across relevant sociodemographic groups	Suppl.
Outcome	8a	D;E	Clearly define the outcome that is being predicted and the time horizon, including how and when assessed, the rationale for choosing this outcome, and whether the method of outcome assessment is consistent across sociodemographic groups	7, Suppl.
	8b	D;E	If outcome assessment requires subjective interpretation, describe the qualifications and demographic characteristics of the outcome assessors	7, Suppl.
	8c	D;E	Report any actions to blind assessment of the outcome to be predicted	Suppl.
Predictors	9a	D	Describe the choice of initial predictors (e.g., literature, previous models, all available predictors) and any pre-selection of predictors before model building	7-8, Suppl.
	9b	D;E	Clearly define all predictors, including how and when they were measured (and any actions to blind assessment of predictors for the outcome and other predictors)	7-8, Suppl.
	9c	D;E	If predictor measurement requires subjective interpretation, describe the qualifications and demographic characteristics of the predictor assessors	7-8, Suppl.
Sample size	10	D;E	Explain how the study size was arrived at (separately for development and evaluation), and justify that the study size was sufficient to answer the research question. Include details of any sample size calculation	6-8, Suppl.
Missing data	11	D;E	Describe how missing data were handled. Provide reasons for omitting any data	10, Suppl.
Analytical methods	12a	D	Describe how the data were used (e.g., for development and evaluation of model performance) in the analysis, including whether the data were partitioned, considering any sample size requirements	7-10, Suppl.
	12b	D	Depending on the type of model, describe how predictors were handled in the analyses (functional form, rescaling, transformation, or any standardisation).	7-8, Suppl.
	12c	D	Specify the type of model, rationale[2], all model-building steps, including any hyperparameter tuning, and method for internal validation	7-8, Suppl.
	12d	D;E	Describe if and how any heterogeneity in estimates of model parameter values and model performance was handled and quantified across clusters (e.g., hospitals, countries). See TRIPOD-Cluster for additional considerations[3]	Suppl.
	12e	D;E	Specify all measures and plots used (and their rationale) to evaluate model performance (e.g., discrimination, calibration, clinical utility) and, if relevant, to compare multiple models	7-9, Suppl.
	12f	E	Describe any model updating (e.g., recalibration) arising from the model evaluation, either overall or for particular sociodemographic groups or settings	Suppl.
	12g	E	For model evaluation, describe how the model predictions were calculated (e.g., formula, code, object, application programming interface)	Suppl.
Class imbalance	13	D;E	If class imbalance methods were used, state why and how this was done, and any subsequent methods to recalibrate the model or the model predictions	Suppl.
Fairness	14	D;E	Describe any approaches that were used to address model fairness and their rationale	Suppl.
Model output	15	D	Specify the output of the prediction model (e.g., probabilities, classification). Provide details and rationale for any classification and how the thresholds were identified	Suppl.

[1] D=items relevant only to the development of a prediction model; E=items relating solely to the evaluation of a prediction model; D;E=items applicable to both the development and evaluation of a prediction model

[2] Separately for all model building approaches.

[3] TRIPOD-Cluster is a checklist of reporting recommendations for studies developing or validating models that explicitly account for clustering or explore heterogeneity in model performance (eg, at different hospitals or centres). Debray et al, BMJ 2023; 380: e071018 [DOI: 10.1136/bmj-2022-071018]

TRIPOD+AI

Version: 11-January-2024

Training versus evaluation	16	D;E	Identify any differences between the development and evaluation data in healthcare setting, eligibility criteria, outcome, and predictors	Suppl.
Ethical approval	17	D;E	Name the institutional research board or ethics committee that approved the study and describe the participant-informed consent or the ethics committee waiver of informed consent	11
OPEN SCIENCE				
Funding	18a	D;E	Give the source of funding and the role of the funders for the present study	3, 11
Conflicts of interest	18b	D;E	Declare any conflicts of interest and financial disclosures for all authors	17-18
Protocol	18c	D;E	Indicate where the study protocol can be accessed or state that a protocol was not prepared	19
Registration	18d	D;E	Provide registration information for the study, including register name and registration number, or state that the study was not registered	Suppl.
Data sharing	18e	D;E	Provide details of the availability of the study data	19
Code sharing	18f	D;E	Provide details of the availability of the analytical code[4]	19
PATIENT & PUBLIC INVOLVEMENT				
Patient & Public Involvement	19	D;E	Provide details of any patient and public involvement during the design, conduct, reporting, interpretation, or dissemination of the study or state no involvement.	Suppl.
RESULTS				
Participants	20a	D;E	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	Suppl., Suppl. Figure 2
	20b	D;E	Report the characteristics overall and, where applicable, for each data source or setting, including the key dates, key predictors (including demographics), treatments received, sample size, number of outcome events, follow-up time, and amount of missing data. A table may be helpful. Report any differences across key demographic groups.	11, Suppl.
	20c	E	For model evaluation, show a comparison with the development data of the distribution of important predictors (demographics, predictors, and outcome).	Suppl.
Model development	21	D;E	Specify the number of participants and outcome events in each analysis (e.g., for model development, hyperparameter tuning, model evaluation)	11, Suppl.
Model specification	22	D	Provide details of the full prediction model (e.g., formula, code, object, application programming interface) to allow predictions in new individuals and to enable third-party evaluation and implementation, including any restrictions to access or re-use (e.g., freely available, proprietary)[5]	Suppl.
Model performance	23a	D;E	Report model performance estimates with confidence intervals, including for any key subgroups (e.g., sociodemographic). Consider plots to aid presentation.	11-13, Suppl.
	23b	D;E	If examined, report results of any heterogeneity in model performance across clusters. See TRIPOD Cluster for additional details[3].	Suppl.
Model updating	24	E	Report the results from any model updating, including the updated model and subsequent performance	N/A
DISCUSSION				
Interpretation	25	D;E	Give an overall interpretation of the main results, including issues of fairness in the context of the objectives and previous studies	13-15
Limitations	26	D;E	Discuss any limitations of the study (such as a non-representative sample, sample size, overfitting, missing data) and their effects on any biases, statistical uncertainty, and generalizability	15
Usability of the model in the context of current care	27a	D	Describe how poor quality or unavailable input data (e.g., predictor values) should be assessed and handled when implementing the prediction model	15
	27b	D	Specify whether users will be required to interact in the handling of the input data or use of the model, and what level of expertise is required of users	15
	27c	D;E	Discuss any next steps for future research, with a specific view to applicability and generalizability of the model	15

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[4] This relates to the analysis code, for example, any data cleaning, feature engineering, model building, evaluation.
[5] This relates to the code to implement the model to get estimates of risk for a new individual.

Supplementary figure 25: STROBE Statement

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1, 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-7, Suppl.
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5-7, Suppl.
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7, Suppl.
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7, Suppl.
Bias	9	Describe any efforts to address potential sources of bias	7-10, Suppl.
Study size	10	Explain how the study size was arrived at	6-7, Suppl.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-9, Suppl.
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-10, Suppl.
		(*b*) Describe any methods used to examine subgroups and interactions	9, Suppl.
		(*c*) Explain how missing data were addressed	10, Suppl.
		(*d*) If applicable, explain how loss to follow-up was addressed	Suppl.
		(*e*) Describe any sensitivity analyses	10
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	11, Suppl.
		(b) Give reasons for non-participation at each stage	Suppl.
		(c) Consider use of a flow diagram	Suppl. Figure 2
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11, Suppl.
		(b) Indicate number of participants with missing data for each variable of interest	Suppl.
		(c) Summarise follow-up time (eg, average and total amount)	Suppl.
Outcome data	15*	Report numbers of outcome events or summary measures over time	Suppl.

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-12, Suppl.
		(*b*) Report category boundaries when continuous variables were categorised	11-12, Suppl.
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Suppl.
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12-13, Suppl.
Discussion			
Key results	18	Summarise key results with reference to study objectives	13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-15
Generalisability	21	Discuss the generalisability (external validity) of the study results	15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	3, 11

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