Explicit risk in acute coronary syndrome management

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At least implicitly, most clinical decisions represent an integration of disease and treatment-based risk assessments. Often, as is the case with acute coronary syndrome (ACS), these decisions need to be made quickly at a time when data elements are limited, and published risk models are very useful in clarifying time-dependent determinants of risk. The present review emphasizes the value of explicit risk assessment and reinforces the fact that patients at highest risk are often those most likely to benefit from newer and more invasive therapies. Suggested ways to incorporate published ACS risk models into clinical practice are included. In addition, the need to adopt a longer-term view of risk in ACS patients is stressed, with particular regard to the important role of heart failure prediction and treatment.

Key Words: *Acute coronary syndrome; Risk prediction*

Effective acute coronary syndrome (ACS) management requires diagnostic accuracy, familiarity with proven-effective treatment options and a dynamic understanding of the determinants of risk. Risk is the probability balance of an adverse health status, after factoring in disease and treatment factors, and physicians are charged with understanding this complex balance (1). Unfortunately, patients who stand to benefit (perhaps more) from treatment are not being treated because there is an exaggerated fear of risks of treatment (2-4). This phenomenon, often referred to as the 'risk-treatment paradox', is particularly true for elderly patients (5).

Furthermore, the increasing trend of public reporting of outcome measures has been met with skepticism by many clinicians believing that disease complexity has not been fairly factored into these calculations (6). The result is a treatment selection bias in favour of the patients with the predicted best outcome, while avoiding those at high risk but with the greatest possible net benefit from proven interventions and therapies (7).

The present paper reviews existing approaches to estimating risk, and discusses how these can be implemented in clinical practice to improve therapeutic decision-making for ACS. The ultimate objective of our paper is to promote provider and health system action to implement systems for enhancing risk-informed care. Because an ACS event is the first exposure for many patients to the concept of living with a chronic disease, ongoing clarity as to short- and long-term risk determinants is critical to them and to their families (8).

Le risque explicite dans la prise en charge du syndrome coronarien aigu

Au moins implicitement, la plupart des décisions cliniques intègrent une évaluation de la maladie et du risque lié au traitement. Souvent, comme dans le cas du syndrome coronarien aigu (SCA), il faut prendre ces décisions rapidement à un moment où les éléments de données sont limités, et les modèles de risque publiés sont très utiles pour clarifier les déterminants temporels du risque. La présente analyse fait ressortir l'intérêt de l'évaluation explicite du risque et le fait que les patients les plus vulnérables sont souvent ceux qui profiteront probablement le plus des thérapies plus récentes et plus efficaces. On propose des moyens d'intégrer les modèles publiés de risque de SCA à la pratique clinique. De plus, on souligne la nécessité d'adopter une perspective à plus long terme du risque de SCA chez les patients, notamment le rôle important de la prévision et du traitement de l'insuffisance cardiaque.

THE ACS SPECTRUM AND RISK

ACSs are sudden and unexpected clinical events resulting from atherosclerotic plaque disruption (4,9). ACS subgroups include ST segment elevation myocardial infarction (STEMI), in which fibrin formation dominates with transient or persistent vessel occlusion, leading to myonecrosis with ST segment elevation; non-STEMI (NSTEMI), in which platelet deposition is dominant, leading to myonecrosis but without ST segment elevation; and unstable angina (UA), characterized by ischemic rest pain when intrinsic lytic mechanisms dominate, preventing myonecrosis. Recent analysis of consecutive ACS admissions to Calgary, Alberta, hospitals indicate that the relative size of the subgroups are STEMI, 27%; NSTEMI, 28%; and UA, 45% (unpublished data from the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease [APPROACH] registry). Subgroup distinction is central to risk assessment because the determinants of risk and time-to-treatment requirements vary.

The time it takes to heal or 'passivate' the active plaque defines the duration of recurrent event vulnerability during which aggressive antiplatelet therapy may be beneficial. This period varies greatly and is usually unknown in individual patients, but ranges from one month to longer than one year (4,10-12).

The importance of understanding 'risk over time' is highlighted in Figure 1. From clinical trial (Global Use of Strategies To Open occluded arteries in acute coronary syndromes [GUSTO] IIb [12]) and population-based (APPROACH) registries, observed mortality in the three ACS subgroups increases over the first year. Although the

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Figure 1 Mortality trends over one year for Global Use of Strategies To Open occluded arteries in acute coronary syndromes (GUSTO) IIb and Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) acute coronary syndrome (ACS) patients by ACS subgroup. The lines above the GUSTO bars indicate how the presence (upper dot) and absence (lower dot) of recurrent severe ischemia in that registry strikingly influenced mortality (12). NSTEMI Non-ST segment elevation myocardial infarction; STEMI ST segment elevation myocardial infarction

30-day mortality for NSTEMI and UA is less than that for STEMI, by one year the ST segment elevation ACS (NSTEACS) mortality dominates, with doubling of the 30-day mortality for both NSTEMI and UA in GUSTO IIb and more than a threefold mortality increase for NSTEMI and UA in Calgary patients over the first year. Over the past two decades, STEMI incidence and mortality has been declining, while the NSTEMI incidence has been increasing with only a slight reduction in mortality (13,14).

THE COMPONENTS OF RISK IN ACS

Risk analysis in ACS has three stages: accurate early diagnosis, very early risk assignment and dynamic risk re-evaluation. Current ACS guidelines highlight the critical importance of accurate diagnosis in risk assessment and therapy selection. Recent treatment guidelines list (in decreasing level of diagnostic certainty) the following features: classic nature of symptoms, prior documentation of coronary disease, sex, age, and the two comorbidities of diabetes and peripheral vascular disease (4). It has been estimated that between one-third to one-half of all ACS patients are misdiagnosed, or the severity of their status is misjudged or delayed, thus precluding the application of proven effective therapies (15-17).

The second stage, very early risk assessment, addresses the critical need to rapidly identify patients most likely to benefit from therapies that have a limited window of opportunity. Of necessity, this stage of risk assessment is limited to variables that are immediately available on presentation. The final stage is that of dynamic and repetitive re-evaluation of risk that informs important but less time-sensitive investigation and treatment decisions. Items included in this later evaluation include recurrent symptoms, the development of signs of heart failure or new mitral regurgitation, cardiac biomarker elevation after initially normal values, dynamic ST segment shifts, persistence of ST depression (particularly at the time of discharge), and perhaps late assessment of C-reactive protein and brain natriuretic peptide (BNP) as well (18-22). The importance of recurrent ischemia was addressed in the GUSTO IIb registry, in which recurrent severe ischemia was associated with a doubling of mortality for all ACS subgroups after 30 days, six months and one year (Figure 1) (12).

ACS RISK MODELS

STEMI models

Table 1 summarizes key STEMI risk models, one developed from the large InTIME thrombolytic trial (Thrombolysis in Myocardial Infarction [TIMI] model) (23) and three models developed from direct percutaneous coronary intervention (PCI) data (from the Primary Angioplasty in Myocardial Infarction [PAMI] and Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications [CADILLAC] clinical trials and from the Zwolle, the Netherlands, clinical centre experience). The risk models include demographic variables such as age and body weight, covariates of infarction size such as Killip class, anterior infarction location, tachycardia (more than 100 beats/min), reduced systolic blood pressure (SBP) (lower than 100 mmHg) and reduced ejection fraction and factors that increase diagnostic certainty such as prior myocardial events (23-26). The importance of diagnostic certainty on risk when combined with age was reported by the Coronary Artery Surgery Study (CASS) investigators as early as the late 1970s (27).

Clinical trial-derived STEMI risk models should be applied with caution. First, Table 1 identifies key inclusion and exclusion criteria applied during the originating clinical trials that limit wide application of the derived risk score. Furthermore, the trial-based models do not perform well when applied to patients that were under-represented, although not specifically excluded, in the clinical trials such as elderly patients (28). (This weakness led to the development and validation of a new model by the Cooperative Cardiovascular Project using a Medicare cohort, with resulting improved predictive accuracy in elderly patients [29].)

Second, trial-derived models were largely based on dichotomous variables resulting in good risk discrimination between low- and high-risk groups, although their ability to calibrate risk among individual patients is suboptimal (16). Because STEMI patients at all risk levels (with similar symptom duration) require equally rapid deployment of thrombolytic therapy or direct PCI, early risk assessment is most useful in shaping the course of subsequent treatment and investigation. A 'low-risk' designation identifies patients least likely to benefit from rescue PCI after thrombolytic therapy failure and, therefore, those who are suitable for Emergency Medical Services delivery to the closest acute care facility, whether or not interventional capabilities exist. Also, lower risk patients may be most suitable for early discharge strategies. A 'high-risk' designation, on the other hand, identifies those who may benefit from initial Emergency Medical Services delivery or early hospital transfer to centres with more resource-intensive treatments.

A simple STEMI risk model based solely upon the three continuous variables of age, heart rate (HR) and SBP has been developed for the STEMI first responder in the field and in the emergency department (30). The resulting calculation $(HR \times [age / 10]^2 / SBP)$ has significant calibration potential, allowing for separation of patients into five distinct risk categories. In STEMI patients, and to a lesser extent in NSTEMI patients, the three variables in this model show a continuous relationship with risk, particularly on one side of certain inflection points: older than 65 years of age, HR more than 100 beats/min and SBP less than 100 mmHg. These numbers are consistent with the dichotomous thresholds used in the TIMI and GUSTO I risk scores. The utility of this five-category score and how specific values translate to action require more study.

NSTEACS

Although most large NSTEACS clinical trials include a report on the multivariable predictors of adverse outcomes in their study cohorts, only four risk models are available that have gone through a convincing validation process. These models are described in Table 2. The Efficacy and Safety of Subcutaneous Enoxaparin in unstable and non-Q wave Coronary Events (ESSENCE) (31,32), Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor suppression Using Integrilin Therapy (PURSUIT) (1,33) and TIMI (34) models were based on

TABLE 1

Four risk models for ST elevation myocardial infarction (STEMI), one in a lytic population (TIMI) and three in direct STEMI percutaneous coronary intervention (PCI) population (Zwolle, PAMI and CADILLAC)

	PAMI (56)	Zwolle, the Netherlands (57)	TIMI (23)	CADILLAC (58)
Type	Trial	Centre registry	Trial	Trial
Sponsorship	Industry	—	Industry	Industry
Era	1990 to 1998	1994 to 2001	1997 to 1998	1997 to 1999
Test cohort	n=3252 (C=0.78)	n=1791 (C=0.91)	InTIME II: n=15,078	CADILLAC (59) n=2082
Validation – initial	Air PAMI	n=747 from 2001 to 2003	TIMI 9 and GUSTO I	Stent PAMI: n=900
Model use/later validation work	Analysis of risk determinants in elderly subjects (>75 years)		NRMI-3 validation: 84,029 patients, 1998 to 2000 (60)	
End point(s)	Death	Death	Death	Death
Follow-up	6 months	30 days	30 days (also to 1 year)	1 year
Inclusion	Pain <12 h; STEMI PCI only	STEMI <6 h or 6–24 h with ongoing symptoms; STEMI PCI only	STEMI <6 h; thrombolysis cohort	STEMI <12 h; culprit diameter 2.5 mm to 4.0 mm
Exclusion	Lytics; cardiogenic shock; stroke <1 month; ESRD; severe PVD		Stroke; high BP; cardiogenic shock; bleeding risk	Lytics; bleeding risks; stroke within 2 years; ESRD; severe liver disease
Model*	Total score 15 (Low risk ≤4; high risk ≥9)	Total score 16 (Low risk ≤4; high risk ≥8)	Total score 14 (Low risk ≤3; high risk >6)	Total score 18 (Low risk ≤2; high risk >6)
Age	>75 years (7); 65–75 years (3)	<60 years (0); >60 years (2)	65–75 years (1); >75 years (2)	>65 years (2)
↓Systolic BP	—	—	<100 mmHg (2)	—
↑Heart rate	>100 beats/min (2)	—	>100 beats/min (2)	—
Ischemic time	—	<4 hrs (0); >4 hrs (1)	>4 hrs (1)	—
CHF	Killip >1 (2)	Killip 1 (0), 2 (4) or 3–4 (9)	Killip 2–4 (2)	Killip 2–3 (3); EF <40% (4)
Location	Anterior/LBBB (2)	Anterior – No (0), Yes (1)	Anterior/LBBB (1)	—
Risk factors			1 of hypertension, diabetes mellitus or angina history (1)	
• Hypertension	—	—	+	—
• Smoking	—	Univariate only	—	—
• Diabetes	Yes (2)	—	+	—
Arrhythmia	+ in elderly study	—	—	—
EF	+ in elderly study	—	—	—
Sex	—	Univariate only	—	—
TIMI pre-PCI	—	Univariate only	—	—
TIMI post-PCI	—	3 (0), 2 (1) or 0–1 (2)	—	TIMI 0–2 (2)
3-vessel disease	—	No (0), Yes (1)	—	(2)
↑Creatinine	—	—	—	(3)
IABP use	+ in elderly study only	—	—	—
Weight	—	—	<67 kg (1)	—
Anemia	—	—	—	(2)
Limitations	Applies to STEMI PCI and IABP candidates only			

*Model: Scores attributed to risk factors are in parentheses. Total – Highest possible score. BP Blood pressure; CADILLAC Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications; CHF Congestive heart failure; EF Ejection fraction; ESRD End-stage renal disease; GUSTO Global Use of Strategies To Open occluded arteries in acute coronary syndromes; IABP Intra-aortic balloon pump; LBBB Left bundle branch block; NRMI National Registry of Myocardial Infarction; PAMI Primary Angioplasty in Myocardial Infarction; PVD Peripheral vascular disease; TIMI Thrombolysis in Myocardial Infarction

clinical trial data from the mid-1990s, while the community-based Global Registry of Acute Coronary Events (GRACE) registry (35,36) was initiated in 1999 and recruitment is still ongoing. The end points in all registries were death and myocardial infarction, and the length of follow-up was short (in-hospital to 30 days), although six month follow-up predictors have been since explored by the GRACE registry.

Trial-based registries are attractive in that their data are prospectively collected with rigorous data definitions, there are very little missing data and there is uniformly excellent characterization of the patients' underlying cardiovascular status. On the other hand, there is reason to question the generalizability of their findings to the 'real world' patient. As with the STEMI models, clinical trialists were reluctant to include high-risk patients with significant comorbidity

that might have confounded treatment-effect analyses. There is also a tendency to avoid highest risk patients due to reluctance on the part of physicians and patients to include patients in research projects when the stakes are high. Importantly, elderly patients are frequently under-represented, particularly in antithrombotic and antiplatelet trials, due to increased bleeding risk, frailty and follow-up concerns (37).

All registries required prolonged rest pain for enrolment, and the trial-based registries tended to exclude UA (without evidence of myocardial necrosis) unless there was clear documentation of prior coronary artery disease (CAD). Although the GRACE community-based cohort includes a broader range of ACS patients, recruitment in this registry is not continuous because recruitment is limited to 600 patients per year per region. The table itemizes the important registry inclusion and exclusion criteria that lead to gaps in their risk model; in

TABLE 2
Four risk models for non-ST elevation myocardial infarction and unstable angina

	ESSENCE (31,32)	PURSUIT (1,33)	TIMI (34)	GRACE (35,36)
Type	Trial	Trial	Trial	Community
Sponsorship	Industry	Industry	Industry	Industry
Era	1994 to 1996	1995 to 1997	1996 to 1998	1999 to 2002
Test cohort	n=3171	n=9461 (C=0.81)	n=1957 (C=0.65)	n=15,007
Validation – initial	Internal (probability deciles versus outcome), C=0.71	Internal (bootstrapping)	Later TIMI cohort (n=1953) and ESSENCE cohort (n=3171)	Later GRACE cohort (n=7638) and GUSTO IIb cohort (n=12,142) (36)
Model use/later validation work		CCU cohort in Portugal (revasc benefit) (61); C=0.630 Canadian ACS Registry (64), (n=4627); C=0.84 Prediction of mortality over time in GUSTO IIb (19) (n=7294) C=0.87	PRISM-PLUS (n=1915) (62) identified those with greatest GP IIb/IIIa benefit (C=0.64) CCU cohort in Portugal (revasc benefit) (61); C=0.59 Revasc benefit prediction in STEACS patients (65)	Validation or death at 6 mos in EFFECT study (63) (n=11,510) AMI cohort (C=0.81) Canadian ACS Registry (64) (n=4627); C=0.83 CCU cohort in Portugal (revasc benefit) (61); C=0.715
End point(s)	Death + MI	Death + MI	Death + MI + severe ischemia	Death + MI
Follow-up	14 + 30 days	30 days	14 days	In-hospital + 6 mos
Inclusion	Rest pain >10 min within 24 h; one of ST Δ , Past MI/revasc or test confirming ischemia	Rest pain >10 min within 24 h; one of ST Δ <12 h or marker positive	Rest pain within 24 h. One of ST Δ , Hx CAD or positive markers	n=600. Per regional 'cluster' per year with ACS; all ACS
Exclusion	LBBB/pacer; ST $\uparrow$; bleeding risk; CrCl <30 mL/min	ST $\uparrow$; Bleeding risk; Stroke; high BP; Renal disease; Recent lytic or GP IIb/IIIa	Planned revasc; Bleeding risks; CHF; $\uparrow$ Creatinine	ACS onset in hospital; Prior MI or ASA use; marker –ve and no confirmed CAD
Model	5-factor	Total 20 points	Total 7 points	Bedside calculator
Age	Dichotomous (75 years)	4 categories	> or <65 years (1)	Continuous
$\downarrow$ SBP	–	2 categories	–	Continuous
$\uparrow$ HR	–	3 categories	–	Continuous
ST Shift	Dichotomous	Dichotomous	Dichotomous (1)	+
CHF	S3 +/-	Rales +/-	–	+
Marker +ve	Dichotomous	–	1	+
Risk factors			(Maximum 1 point)	
• Hypertension	–	–	+	–
• Smoking	–	–	+	–
• Diabetes	–	–	+	–
• Lipid disorder	–	–	+	–
• Family history	–	–	+	–
Angina <24 h	–	–	1	–
Angina history	+	–	–	–
ASA use <7 days	–	–	1	–
Lesion >50%	–	–	1	–
$\uparrow$ Creatinine	–	–	–	+
Arrest on admission	–	–	–	+
Limitations	High-risk exclusion bias; only dichotomous variables; modest discrimination ability	See exclusions: high-risk exclusion bias; over-estimates risk	Modest discrimination ability; poor calibration; only dichotomous variables	'Cold' and 'warm' recruiting; no anatomic detail; see exclusions

Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor suppression Using Integrelin Therapy (PURSUIT) points-to-risk conversion formula is published (Boersma et al [1]) and Global Registry of Acute Coronary Events (GRACE) calculation tool is available online at <<http://www.outcomes-umassmed.org/grace/>>. Thrombolysis in Myocardial Infarction (TIMI) score is as shown (low-risk <2; high-risk 5–7). ACS Acute coronary syndrome; ASA Acetylsalicylic acid; BP Blood pressure; CAD Coronary artery disease; CCU Coronary care unit; CHF Congestive heart failure; ESSENCE Efficacy and Safety of Subcutaneous Enoxaparin in unstable and non-Q wave Coronary Events Study; GP Glycoprotein; GUSTO Global Use of Strategies To Open occluded arteries in acute coronary syndromes; HR Heart rate; Hx History; MI Myocardial infarction; mos Months; LBBB Left bundle branch block; PRISM-PLUS Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms; Revasc Revascularization; SBP Systolic BP; ST Δ ST segment change on electrocardiogram; STEACS ST segment elevation acute coronary syndrome

particular, patients with potential bleeding risk, history of stroke, renal disease and poorly controlled blood pressure are usually excluded. Although the GRACE registry is much more inclusive in this regard, patients who develop ACS in the hospital, patients with prior myocardial infarction or prior acetylsalicylic acid use, patients who lack prior confirmation of CAD and those without cardiac marker evidence of myonecrosis are excluded, all factors that limit model generalizability.

The community-based GRACE registry has been validated in a number of settings, and both discrimination and calibration abilities are highly rated. Age, HR and SBP are included as continuous variables, and dichotomous risk items include ST segment shift, evidence of heart failure, positive cardiac markers, elevated creatinine and documentation of cardiac arrest on presentation. The formula converting these variables to a calculated risk is complex, but it is accessible

on-line, making it somewhat 'bedside friendly'. There are a number of important exclusions in this registry, listed in Table 2, that influence generalizability. Furthermore, the 'warm' and 'cold' recruitment strategy of GRACE has been criticized. Under this strategy, patient data can be entered prospectively at the time of admission or by the less satisfactory approach of significantly delayed administrative database profiling (6,38).

The ESSENCE model (31,32) was based on five dichotomous factors of equal weighting: age older than 75 years, documented ST segment shift, signs of heart failure, positive cardiac markers and a history of past angina. Although elevated cardiac markers were an inclusion criterion or a risk determinant in all of the models, the actual level of the cardiac enzyme rise has never been shown to influence prognosis (39). As was the case with the STEMI models, the dependence of the ESSENCE and TIMI models on dichotomous variables allows modest ability to discriminate between those at highest and lowest risk, but calibration – the ability to quantify risk within patient groups – is poor.

The PURSUIT model (1,33) is based on a 20-point system that has some continuous aspects increasing its calibration potential. The presence of ST segment shift and evidence of heart failure are included in the model as dichotomous variables, but age, HR and SBP are divided into a number of categories, creating some continuous elements in the model. There were a number of high-risk exclusion items in this model; hence, absolute risk tends to be overestimated. Bedside risk calculation with the PURSUIT model requires a memory aid (1), and the clinical relevance of the calculated risk level, as in all models, is more useful in relative than in absolute terms.

The TIMI model is still widely used as a risk discriminator and several large validation studies have been performed. Risk determinants include age older than 65 years, the presence of ST segment shift, positive cardiac markers, prior documentation of a coronary lesion larger than 50%, recent acetylsalicylic acid use and at least one risk factor. A score of two points or less is regarded as 'low risk' and five to seven points is classified as 'high risk'. Calibration with this model is poor and its discriminating ability is only modest despite its wide use and inclusion in guideline documents (4).

HEALTH STATUS MEASURES AND RISK

Health status measures quantify patients' perceptions of how their disease affects their function, symptoms and quality of life. While these measures are increasingly being used as end points for clinical trials, they can also be used in identifying patients at high risk for mortality and/or morbidity (40). Using the self-administered Seattle Angina Questionnaire (SAQ), the most commonly used health status measure for patients with CAD (41), scores were demonstrated to be independently associated with one-year mortality and hospitalization from ACS among outpatients with CAD. Furthermore, it was identified that the SAQ significantly increased the validity of risk-adjustment models of mortality.

In an effort to determine the generalizability of using the SAQ in the risk-adjusted models of mortality, a cohort of in- and outpatients catheterized for CAD in Alberta was studied using the APPROACH registry (42). Unadjusted Kaplan-Meier curves are presented in Figure 2. Using a Cox model, results of the study indicated that the physical limitation scale remained independently predictive of survival with patients reporting severe physical limitations (hazard ratio [HR] 1.90; 95% CI 1.4 to 2.6), moderate physical limitation (HR 1.67; 95% CI 1.4 to 2.0) and mild physical limitation (HR 1.57; 95% CI 1.4 to 1.8) compared with patients reporting minimal or no physical limitations. Furthermore, patients reporting angina that occurred several times per day also were significantly less likely to survive (HR 1.30; 95% CI 1.0 to 1.7) than patients reporting angina less than once per week. Inclusion of the SAQ domains increased the mortality models c-statistic (0.76 to 0.79), confirming the significant prognostic impact of adding the SAQ variables to a risk-adjusted model. While the independent prognostic ability of health status may be obvious on clinical

Figure 2) Chart reflects the association of minimal, mild, moderate and severe physical limitation (Seattle Angina Questionnaire) with survival over time after diagnostic catheterization in consecutive consenting patients in the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) registry (unpublished data)

grounds (it is obvious to a clinician that a physically active patient with infrequent angina will survive longer) (40), such clinical judgment may not be reproducible whereas self-administered measures like the SAQ capture data in a reproducibly valid manner (43). While health status measures continue to be used as end points for clinical trials, it is apparent that these measures contribute significantly to risk models, and may prove useful in identifying high-risk patients who may warrant more aggressive interventions.

HEART FAILURE: A 'COMMON FINAL PATHWAY' FOR ACS PATIENTS

The ACS risk models included in the present report all focus on informing important short-term treatment opportunities, and factors that predict later postdischarge events have been poorly characterized. The Predicting Risk of Death In Cardiac disease Tool (PREDICT) project of the Minnesota Heart Survey (44) recognized the need for a longer range prediction tool and identified factors available through abstraction of ACS hospital admission records that predict cardiac events up to six years after discharge. Included in the PREDICT model were shock, heart failure, electrocardiogram features, cardiac disease history, renal disease and age. PREDICT, however, has received limited validation and does not factor in variables that become evident well after admission or after discharge. There is a clear need for a dynamic prediction tool that addresses the important late events in this chronic disease. Of the variables that should figure prominently in this model, one is heart failure.

Although heart failure mortality rates have been on the decline for men and women over the past 25 years, the number of patients living with heart failure and its attendant risk has been steadily on the rise, primarily due to population aging patterns (45). Heart failure figures prominently in most ACS risk models. It is a variable that is more predictive of mortality and recurrent infarction than electrocardiogram changes or serum evidence of myonecrosis (46). The impact of heart failure in ACS is particularly dramatic in patients younger than 55 years of age and in patients with renal insufficiency (47,48). Heart failure plays an ongoing role in the natural history of patients with ACS, because a large majority of ACS patients eventually develop heart failure and 84% of all deaths after myocardial infarction are preceded by a heart failure diagnosis (49).

Of acute MI (AMI) patients who develop heart failure, 25% have a prior history of congestive heart failure, 50% show the first evidence of failure during their hospitalization and 25% develop heart failure after discharge. By five years postinfarction, 63% to 76% of all

surviving AMI patients carry a heart failure diagnosis (49,50). The subgroup that develops heart failure during their index AMI hospital admission carries the highest mortality rate (47,50).

Predictors of death at 30 days and one year in patients with heart failure have been partially characterized by the Enhanced Feedback for Effective Cardiac Treatment (EFFECT) study, with advanced age, hemoglobin level and blood urea nitrogen test results being prominent determinants (51). Also the Acute Decompensated HEart failure (ADHERE) national registry confirmed the predictive power of elevated blood urea nitrogen, and identified an SBP of less than 115 mmHg and high HR as additional physiological predictors of mortality in the heart failure population (52).

Less well-characterized, however, is the additional role of heart failure as a modifiable end point in ACS patients. What are the determinants of delayed heart failure development in each ACS subgroup and can they be modified? GUSTO IIb and APPROACH data (Figure 1) confirm an accelerating mortality for all ACS subgroups over the first year, with a particularly large mortality rise in the NSTEMI group – patients that have proportionately more diffuse disease. Is it possible that heart failure development can be modulated by NSTEMI medical and interventional decisions during initial ACS admission and after discharge? Markers of neurohumeral activation in ACS correlate with mortality, but it is unclear exactly how BNP or N terminal-proBNP values, if routinely measured, can inform therapy (18,53).

At the very least, the critical long-term importance of heart failure in the natural history of ACS patients indicates that there should be a renewed attempt to document known historical and physical examination features of heart failure during hospitalization, to track adherence to heart failure treatment guidelines and to document the systolic function findings of multimodality imaging techniques used.

FROM RISK ASSESSMENT TO ACTION

Whether performed very deliberately using a pocket risk calculator at the bedside or less consciously through an integration of clinical experience, awareness of a patient's history, examination and laboratory data, as well as the opinions of colleagues, clinical decision-making is usually all about assessing risk. The risk determinants and models discussed herein were designed to bring clarity at key early time-sensitive ACS decision points. However, other important factors are at play, acutely and over time, that are more difficult to model. For example, patient realities such as depression and reduced functional capacity also have been shown to be at least part of the explanation for the 'risk-treatment paradox' previously mentioned (54).

Despite their limitations, the models discussed have value in clinical practice. The ACS risk scores do not chart a clinical course, but they are useful in reinforcing or encouraging reassessment of initial clinical impressions as to risk. In addition, the RR scores may prompt the physician to act responsibly and consider less resource-intensive therapies in patients with clear low-risk features. Equally, appropriate risk assessment tempers the risk-adverse tendencies of physicians who gravitate toward treatments and interventions with the best-expected outcomes. There is a need for a calculation or risk assessment process to remind clinicians that a 78-year-old diabetic patient with renal insufficiency, heart failure and ST depression has much to gain by appropriate aggressive interventions and therapies. Finally, patients should be introduced to the process of risk assessment so that they can confirm their treatment expectations, as well as better understand their chronic disease and the risks and benefits of recommended treatment options (8,55).

How can the insights from the literature be transformed into a credible plan for ongoing real-time risk assessment and for guiding clinical decision-making? We submit that the solution requires more than a pocket computer, and three system components are needed:

- **Immediate access to key data elements:** All historical, physical examination, laboratory and imaging data elements that help to define risk should be immediately accessible from a single reliable source. Ideally, this should be the electronic health record system

charged with data quality and completeness in each cardiac centre. If an adequate electronic health record system is not yet available, a more focused cardiovascular database should be maintained as a resource to inform clinical decision-makers.

- **An effective and immediate 'presentation vector':** Based on a computerized presentation layer that compiles and appropriately weights the variables in the database-derived risk scores, clinicians can be notified immediately of the determinants of risk in their patient at the time when key decisions are required. But equally importantly, features unique to a specific patient that were excluded or under-represented in risk model development can be identified, allowing more room for clinician discretion.
- **Evidence and treatment guidelines prompt:** After presenting and quantifying risk determinants at key decision points, there is also an important opportunity to provide on-line reminders to physicians on current practice guidelines that apply and specific treatment benefits expected to be achieved based upon clinical trials.

These features should be helpful to all stakeholders, but they will be most useful in providing explicit reinforcement to physicians who must make important judgments implicitly when they have a limited depth of experience with certain complex cases. At a patient level, these explicit risk data also can be transformed into effective individualized consent documents and educational materials (41).

At a program level, risk models have a role in informing policy and auditing on many levels. ACS risk assessments are useful in defining the appropriateness of patient transport at various stages in their ACS hospitalization and patient designation for early discharge. They can also be useful in selecting advanced imaging alternatives and in identifying patients at high late risk that would benefit from closer follow-up after discharge by cardiac rehabilitation programs and arrhythmia or heart function clinics. In addition, quality-conscious organizations with outcome and data collection capabilities can apply risk models to confirm that patients at high risk are being given an opportunity to benefit from the best therapies, that those at low risk are not receiving an inappropriately large share of limited resources, and that institutional ACS quality indicators are in line with published and regional expectations.

Centres that engage in clinical research will benefit from established programs of patient risk assessment and outcome monitoring. The risk models will permit identification of patients most likely to benefit from new therapies with useful insight into sample size calculations and study feasibility.

There is always a price to pay for exposing patients to treatment-related risk and unrealistic treatment expectations, and for expending limited health care resources when the opportunity for clinical benefit is marginal. Understanding the short- and long-term risk models and the ability to use them wisely is key to effective investigation and treatment decision-making. ACS events are defining moments in the patient's journey with CAD, but there are other important stages that require greater insight – in particular, the key role of heart failure and our ability to predict its development and guide its treatment.

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