REGIONE DEL VENETO

PROGETTO REGIONALE SU MALATTIA CARDIACA E NEOPLASIA

Progetto triennale

Giugno 2015-Maggio 2018

Alla Presidenza della Regione Veneto

Dr. Luca Zaia

Venezia

Al Dr. Domenico Mantoan
Direzione Generale Sanita' e Sociale
Venezia

Alla Dr.ssa Francesca Russo
Dirigente Settore Promozione e Sviluppo Igiene e Sanita' Pubblica
Venezia

Al Direttore Generale ULSS 7 Treviso
Dr. Francesco Benazzi
Pieve di Soligo (TV)

Al Direttore Generale ULSS 3
Dr. Giorgio Roberti
Bassano del Grappa (VI)

Al Direttore Generale ULSS 19
Dr. Antonio Fernando Compostella
Adria (RO)

Al Direttore UOC Affari Generali ULSS 7
Dr. Filippo Spampinato
Pieve di Soligo (TV)

Studio prospettico su Neoplasia Maligna dopo Sindrome Coronarica Acuta:

The ABC - 4 Study on Acute Coronary Syndrome (Adria, Bassano, Conegliano, Padova)*

ABC Study on Heart Disease Association
www.abcheartdiseasestudy.org

The ABC Study on Heart Disease

Responsabile clinico-scientifico del Progetto:

Giuseppe Berton MD, FESC
U.O.C. Cardiologia – Ospedale di Conegliano (TV)

Co-Autori del Progetto Regionale:
Rocco Cordiano, MD
U.O.C. Cardiologia – Ospedale di Adria (RO)

Fiorella Cavuto, MD
Cardiologia – Bassano del Grappa (VI)

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Beatrice Segafredo, MD
Cardiologia – Bassano del Grappa (VI)

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Capitolo 1

Presentazione del Progetto Regionale

SCOPO DEL PROGETTO REGIONALE

Il presente Progetto Regionale e' realizzato dall'ABC Study Association. E' interesse precipuo dell'associazione lo svolgimento di attivita' di ricerca scientifica e, in particolare:

a) promuovere e sostenere il progetto clinico-scientifico "The ABC Study on Heart Desease"

b) promuovere e sostenere il progetto della Regione Veneto "The ABC – 4 Study on Heart Desease", di cui alla deliberazione n. 748 del 14 maggio 2015

c) promuovere, sostenere e mantenere il website www.abcheartdeseasestudy.org che e' l'espressione dell'ABC Study on Heart Desease

d) supportare studi clinico-scientifici, specialmente sulla malattia cardiaca;

e) promuovere la metodica di follow up a lungo termine del paziente come metodo clinico per la conoscenza e la cura della malattia;

f) sostenere la produzione scientifica, specialmente, ma non limitatamente, riguardo all'ABC Study on Heart Desease.

g) sulla base di tutti i precedenti punti:
- favorire la prevenzione della malattia cardiaca e neoplastica
- promuovere attivita' formativa ed educativa per operatori sanitari e cittadinanza.

Bur n. 54 del 01/06/2015

(Codice interno: 298792)

DELIBERAZIONE DELLA GIUNTA REGIONALE n. 748 del 14 maggio 2015

Approvazione dello Studio prospettico su Neoplasia maligna dopo sindrome coronarica acuta. The ABC - 4 study on acute coronary syndrome.

[Sanità e igiene pubblica]

Note per la trasparenza:
Con il presente provvedimento si approva lo studio sulle neoplasie dopo una sindrome coronarica acuta. Il presente provvedimento non comporta spesa per il bilancio regionale.

L'Assessore Luca Coletto riferisce quanto segue.

Il programma "Guadagnare Salute - rendere facili le scelte salutari", approvato con D.P.C.M. del 4 maggio 2007, prevede il potenziamento a livello regionale di politiche e strategie a sostegno della promozione della salute, secondo i principi e l'implementazione delle azioni di competenza regionale previsti dal Programma nazionale "Guadagnare Salute - rendere facili le scelte salutari".

Secondo i dati dell'Organizzazione Mondiale della Sanità (OMS) l'86% dei decessi e il 75% delle spese sanitarie in Europa ed in Italia sono causate da alcune patologie (malattie cardiovascolari, tumori, diabete mellito, malattie respiratorie croniche ed altre) che hanno in comune fattori di rischio modificabili, quali il fumo, l'obesità e sovrappeso, l'abuso di alcol, la sedentarietà, l'eccesso di grassi nel sangue e l'ipertensione arteriosa, è evidente che la mancata azione su di essi comporta un aumento di morti premature e di malattie evitabili.

Con Deliberazione della Giunta Regionale n. 1565 del 26 agosto 2014 la Regione ha previsto che in ogni Azienda Ulss il programma ministeriale "Guadagnare Salute - rendere facili le scelte salutari" venisse sviluppato mediante la costituzione di Gruppi Aziendali Guadagnare Salute, formalizzati con delibere dei Direttori Generali delle Aziende Ulss. Questo consente di sviluppare nel territorio di competenza le azioni per il contrasto dei principali fattori di rischio (abitudine al fumo, sedentarietà, alcol, alimentazione scorretta), in accordo con le linee strategiche regionali. Pertanto a livello aziendale, nell'ottica dell'intersettorialità e multifattorialità, è stata disposta la costituzione e/o lo sviluppo di tavoli di lavoro intersettoriali, l'attivazione di accordi formali intersettoriali, l'avvio e lo sviluppo di azioni intersettoriali di promozione della salute.

La Sindrome coronarica acuta o *SCA* è una definizione che riunisce le diverse manifestazioni cliniche della cardiopatia ischemica è curabile se diagnosticata in fretta, i trattamenti variano a seconda dei segni, sintomi e condizioni di salute generale. Pochi sono gli studi che si occupano, però, delle incidenze della malattia nel lungo termine e che rapporto ci sia tra la SCA e le diverse neoplasie.

Nelle Aziende Ulss n. 3 di Bassano del Grappa, n. 7 di Conegliano, n. 19 di Adria e presso l'Azienda Ospedaliera di Padova si sta portando avanti uno studio clinico-scientifico complesso ed articolato sulla Neoplasia maligna dopo la sindrome coronarica acuta.

In quest'ambito è stato realizzato un primo studio che ha investigato i fattori associati a 10 anni di sopravvivenza libera da eventi gravi dopo la sindrome coronarica acuta (Predictors of ten-year event-free survival in patients with acute myocardial infarction /The Adria, Bassano, Conegliano, and Padova Hospitals [ABC] study on myocardial infarction- 2012) ed un secondo studio che ha investigato i fattori associati alla mortalità ed alle cause di decesso in un follow up di 12 anni dopo la SCA(Prospective history of long-term mortality and modes of death in patients discharged after acute coronary syndrome: the ABC-2 * study on acute coronary syndrome- 2014).

Rappresenta un'ulteriore ed importante fase la realizzazione dello studio di cui all'Allegato "A" al presente provvedimento, che ne costituisce parte integrante, il cui obiettivo è quello di valutare l'incidenza delle neoplasie maligne in soggetti che hanno avuto la sindrome coronarica acuta (SCA) seguendoli per 15 anni mediante un follow-up clinico periodico.

Vista l'importanza che lo studio ha sull'ampliamento delle conoscenze utili per l'individuazione potenziali fattori di rischio riguardo alle neoplasie maligne post SCA, al fine di sostenere la fattibilità dello studio si ritiene di determinare in euro

30.000,00 l'importo massimo delle obbligazioni di spesa alla cui assunzione provvederà, in favore dell'Azienda Ulss n.7, con proprio atto il Dirigente del Settore Promozione e Sviluppo Igiene e Sanità Pubblica disponendo la copertura finanziaria sul capitolo n.102324 " *Spesa sanitaria corrente per il finanziamento dei LEA- Gestione sanitaria Accentrata presso la Regione - Trasferimenti correnti*". Lo studio sarà rifinanziabile sulla base della valutazione dei risultati per i successivi due anni, onde consentire di completare il ciclo di analisi.

Alla luce di queste considerazioni si ritiene di approvare lo "Studio prospettico su Neoplasia maligna dopo sindrome coronarica acuta. The ABC - 4 study on acute coronary syndrome" di cui all'Allegato "A" al presente provvedimento che ne costituisce parte integrante.

Il relatore conclude la propria relazione e propone all'approvazione della Giunta Regionale il seguente provvedimento.

LA GIUNTA REGIONALE

Udito il relatore, il quale dà atto che la struttura proponente ha attestato l'avvenuta regolare istruttoria della pratica anche in ordine alla compatibilità con la vigente legislazione statale e regionale;

Visto il D.P.C.M. del 4 maggio 2007;

Visto l'articolo 4 della L.R. 1/1997, successivamente integrato e modificato dalla L.R. 54/2012;

Visto l'art. 2, comma 2, lett. o) della Legge Regionale n. 54 del 31 dicembre 2012;

Vista la Deliberazione della Giunta Regionale n. 1565 del 26 agosto 2014.

delibera

1) di prendere atto di quanto espresso in premessa, che costituisce parte integrante e sostanziale del presente provvedimento;

2) di approvare lo "Studio prospettico su Neoplasia maligna dopo sindrome coronarica acuta. The ABC - 4 study on acute coronary syndrome" di cui all'Allegato "A" al presente provvedimento che ne costituisce parte integrante;

3) di determinare, al fine di sostenere la fattibilità dello studio di cui al punto 2), in euro 30.000,00 l'importo massimo delle obbligazioni di spesa alla cui assunzione provvederà, in favore dell'Azienda Ulss n.7, con proprio atto il Dirigente del Settore Promozione e Sviluppo Igiene e Sanità Pubblica disponendo la copertura finanziaria sul capitolo n.102324 " *Spesa sanitaria corrente per il finanziamento dei LEA- Gestione sanitaria Accentrata presso la Regione - Trasferimenti correnti*";

4) di dare atto che lo studio di cui al punto 2) sarà rifinanziabile per i successivi due anni sulla base della valutazione dei risultati;

5) di incaricare la Sezione Attuazione Programmazione Sanitaria all'esecuzione del presente atto;

6) di pubblicare il presente provvedimento sul Bollettino Ufficiale della Regione Veneto.

ALLEGATOA alla Dgr n. 748 del 14 maggio 2015

Studio prospettico su Neoplasia Maligna
dopo Sindrome Coronarica Acuta:
The ABC* - 4 Study on Acute Coronary Syndrome
* (Adria, Bassano, Conegliano, Padova)

INTRODUZIONE

I 2 lavori scientifici più recenti già realizzati nell'ambito dell'ABC Study on **Acute Coronary Syndrome** (ACS), sono stati entrambi pubblicati negli Stati Uniti (*American Journal Of Cardiology* 2012 e *International journal of Cardiovascular Research* 2014).

Un primo studio ha investigato i fattori associati a 10 anni di sopravvivenza libera da eventi gravi dopo la sindrome coronarica acuta (Predictors of ten-year event-free survival in patients with acute myocardial infarction /The Adria, Bassano, Conegliano, and Padova Hospitals [ABC] study on myocardial infarction- 2012) ed un secondo studio che ha investigato i fattori associati alla mortalità ed alle cause di decesso in un follow up di 12 anni dopo la SCA(Prospective history of long-term mortality and modes of death in patients discharged after acute coronary syndrome: the ABC-2 * study on acute coronary syndrome- 2014).

Sebbene siano ampiamente studiate le cause di mortalità a breve termine dopo la Sindrome Coronarica Acuta (SCA)[1], ad oggi sono pochissimi gli studi nel lungo termine. Alcuni hanno posto in evidenza come, avanzando nel follow-up dei pazienti con storia di SCA, le cause di mortalità extracardiache, tra le quali spiccano le neoplasie maligne, prendono il sopravvento sulle cause di mortalità cardiache.[2],[3]

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[1] - Trends in cause of death after percutaneous coronary intervention.
Spoon DB, Psaltis PJ, Singh M, Holmes DR Jr, Gersh BJ, Rihal CS, Lennon RJ, Moussa ID, Simari RD, Gulati R. Circulation. 2014 Mar 25;129(12):1286-94. doi: 10.1161/CIRCULATIONAHA.113.006518. Epub 2014 Feb 10.

[2] Short- and Long-TermCause of Death in Patients Treated With Primary PCI for STEMI.
Pedersen F, Butrymovich V, Kelbæk H, Wachtell K, Helqvist S, Kastrup J, Holmvang L, Clemmensen P, Engstrøm T, Grande P, Saunamäki K, Jørgensen E.
J Am CollCardiol. 2014 Nov 18;64(20):2101-8. doi: 10.1016/j.jacc.2014.08.037. Epub 2014 Nov 10.

[3] - Long-term outcomes and causes of death after acute coronary syndrome in patients in the bologna, Italy, area.
Vagnarelli F, Tagliseri N, Ortolani P, Norscini G, Cinti L, Bacchi Reggiani ML, Marino M, Lorenzini M,

Qualche autore ha osservato aspetti di parallelismo tra il processo arteriosclerotico, infiammatorio, e neoplastico.[4] Mancano tuttavia studi prospettici che ricerchino potenziali fattori di rischio per neoplasia post SCA.

SCOPO DEL LAVORO

Obiettivo del nostro lavoro è **studiare l'incidenza di neoplasie maligne nei pazienti con SCA**, arruolati nell'ABC Study* (Adria, Bassano, Conegliano, Padova Holspitals), seguiti in modo prospettico per lunghissimo tempo (15 anni). Inoltre, individuare tra le caratteristiche cliniche ed i trattamenti terapeutici, incluse le procedure di rivascolarizzazione, **eventuali fattori di rischio o associazioni per l'insorgenza di neoplasia.**

MATERIALI E METODI

599 pazienti affetti da SCA, arruolati nell'ABC Study, con assenza (per protocollo) di malattia neoplastica all'arruolamento, sono stati seguiti prospetticamente per 15 anni mediante follow-up clinico periodico. Di ciascuno di essi sono registrate:

1) comparsa di neoplasia maligna
2) sede della malattia
3) data di diagnosi e durata della patologia
4) data di decesso per eteroplasia.

Abbiamo inoltre registrato, in accordo col protocollo di studio, i dati demografici, clinico-cardiaci, eventuali procedure e terapie assunte.

RISULTATI

Ci prefiggiamo di completare la raccolta e l'analisi dei dati statistico/scientifiche entro il termine del 2015.

I risultati così ottenuti saranno presentati presso:

- ULSS 7

Bugani G, Corsini A, Semprini F, Nanni S, Tricoci P, De Palma R, Rapezzi C, Melandri G.
Am J Cardiol. 2015 Jan 15;115(2):171-7. doi: 10.1016/j.amjcard.2014.10.019. Epub 2014 Oct 29.

- Regione Veneto
- ev. pubblicazioni scientifiche nazionali e internazionali (in base all'importanza dei risultati)

Unità Operativa di Riferimento del progetto:
Cardiologia, O.C. Conegliano, ULSS 7, Veneto

Responsabile clinico - scientifico del progetto:
Dott. Giuseppe Berton,MD, FESC,

Collaboratori principali del progetto:
Cardiologia, O.C. Conegliano, ULSS 7, Veneto
Dott. Francesco Bagato,MD

Cardiologia, O.C. Adria, ULSS19, Veneto
Dott. Rocco Cordiano,MD

Cardiologia, ULSS 3, Bassano del Grappa, Veneto
Dott.ssa Fiorella Cavuto,MD

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* Atherosclerosis, Cancer, Wound Healing, and Inflammation – Shared or Paired Evolution.
Lucas A. /Int J Cardiovasc Res 2012, 1:1

REGIONE DEL VENETO

giunta regionale

DECRETO N. 017 DEL 13 GEN. 2015

OGGETTO: "Studio prospettico su Neoplasia maligna dopo sindrome coronarica acuta. The ABC – 4 study on acute coronary syndrome". Impegno di spesa e liquidazione.

NOTE PER LA TRASPARENZA:
con il presente provvedimento si impegna per il 2015 la somma complessiva di euro 30.000,00, a favore dell'Azienda Ulss n. 7 di Pieve di Soligo, al fine di assicurare le attività dello "Studio prospettico su Neoplasia maligna dopo sindrome coronarica acuta. The ABC – 4 study on acute coronary syndrome". La spesa sarà da imputarsi al capitolo 102324 del bilancio regionale di esercizio 2015.

IL DIRIGENTE
SETTORE PROMOZIONE E SVILUPPO IGIENE E SANITA' PUBBLICA

Considerato che la Sindrome coronarica acuta o *SCA* è una definizione che riunisce le diverse manifestazioni cliniche della cardiopatia ischemica è curabile se diagnosticata in fretta, i trattamenti variano a seconda dei segni, dei sintomi e delle condizioni di salute generali. Pochi sono gli studi che si occupano, però, dell'incidenza della malattia nel lungo termine e che rapporto c'è tra la SCA e le diverse neoplasie.

Dato atto che con provvedimento di Giunta Regionale n. 748 del 14.05.2015 è stato approvato lo Studio prospettico su Neoplasia maligna dopo sindrome coronarica acuta. The ABC – 4 study on acute coronary syndrome il cui obiettivo è quello di valutare l'incidenza delle neoplasie maligne in soggetti che hanno avuto la sindrome coronarica acuta (SCA) seguendoli per 15 anni mediante un follow-up clinico periodico.

Vista l'importanza che lo studio ha sull'ampliamento delle conoscenze utili per l'individuazione dei potenziali fattori di rischio riguardo alle neoplasie maligne post SCA, si ritiene di sostenerlo impegnando la somma di euro 30.000,00, sul capitolo di spesa 102324 (*Spesa Sanitaria Corrente per il finanziamento dei LEA – Gestione Sanitaria Accentrata presso la Regione – trasferimenti correnti L.R. 14/09/1994, n. 55 -Art. 20, C. 1, punto B, lett.. A D.Lgs 23.06.2011, n. 118 – art. 22. L.R. 02.04.20145, n. 11*) del bilancio regionale di esercizio 2015 che presenta la necessaria disponibilità, a favore dell'Azienda Ulss n. 7 di Pieve di Soligo.

Dato atto che tale finanziamento dovrà essere utilizzato per la creazione, il mantenimento e l'aggiornamento del database sul trattamento farmacologico, sul trattamento riperfusivo coronarico meccanico non primario e su lo stroke reinfarto miocardico così come indicato nel piano finanziario, predisposto dal referente scientifico del progetto, contenuto nell'**Allegato "A"** al presente provvedimento e di cui costituisce parte integrante.

Dato atto che l'importo di euro 30.000,00 è finanziato con una quota parte del Fondo sanitario regionale 2014 incassato mensilmente in gestione sanitaria in relazione a quanto stabilito dall'art. 77 quater del D.L. 112/2008 e destinata alla gestione sanitaria accentrata regionale e il relativo capitolo di uscita rientra tra quelli individuati nell'Allegato A1 della D.G.R. n. 1102 del 12.06.2012 e successive modifiche ed integrazioni, e soggetti a specifica perimetrazione nell'ambito delle uscite di parte corrente della gestione accentrata regionale.

Vista la D.G.R. n. 2727 del 24.12.2012 ad oggetto "D.G.R. n. 1102/2012 integrazioni alle linee guida regionali attuative del titolo II del Decreto Legislativo n. 118/2011" trattandosi di finanziamento regionale a

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gestione sanitaria, in applicazione dell'art. 21 del D.Lgs. n. 118/2011 il suddetto importo è da imputarsi nel conto di Tesoreria unica intestata a "Regione Veneto Sanità" n. 306697 acceso presso la Tesoreria Provinciale Sezione di Venezia – Banca d'Italia e che l'intero importo verrà liquidato in un'unica soluzione all'approvazione del presente provvedimento. L'Azienda Ulss 7 dovrà presentare entro il 30.05.2016, al Settore Promozione e Sviluppo Igiene e Sanità Pubblica, una relazione scientifica che illustri i risultati raggiunti e una rendicontazione economica con il dettaglio delle spese sostenute al 31.12.2015.

Richiamato il decreto del Direttore Sezione Attuazione Programmazione Sanitaria n. 64 del 29.04.2014 ad oggetto "Regolamento regionale 3 dicembre 2013, n. 4, art. 6 individuazione degli atti e provvedimenti amministrativi dei responsabili dei settori afferenti alla Sezione Attuazione Programmazione Sanitaria", con il quale è stato riconosciuto il potere di sottoscrizione di atti e provvedimenti amministrativi di rispettiva competenza dei responsabili di Settore afferenti la Sezione Attuazione Programmazione Sanitaria in particolare per le materie in oggetto al Settore Promozione e Sviluppo Igiene e Sanità Pubblica.

Vista la legge n. 39 del 29.11.2001;
Viste le D.G.R. n. 1140 del 05/07/2013 Decreto legislativo n. 118/2011 - Titolo II: linee guida regionali per la gestione sanitaria accentrata (GSA) e la D.G.R. n. 829 del 29.06.2015 che approva le direttive per la gestione del Bilancio di previsione 2015.

DECRETA

1. di prendere atto di quanto espresso in premessa, che costituisce parte integrante e sostanziale del presente provvedimento;

2. di assegnare per le motivazioni indicate nelle premesse, un finanziamento di euro 30.000,00 all'Azienda Ulss n. 7 di Pieve di Soligo (Codice Bilancio 1 05 03 codice gestionale 1538- Codifica Piano dei Conti fino al V livello U 1 04 01 02 011);

3. di impegnare la somma di euro 30.000,00 sul capitolo di spesa n. 102324 (*Spesa Sanitaria Corrente per il finanziamento dei LEA – Gestione Sanitaria Accentrata presso la Regione – trasferimenti correnti L.R. 14/09/1994, n. 55 -Art. 20, C. 1, punto B, lett. A D.Lgs 23.06.2011, n. 118 – art. 22. L.R. 02.04.20145, n. 11*) del bilancio di previsione per l'esercizio finanziario 2015 che presenta sufficiente disponibilità;

4. di liquidare a favore dell'Azienda Ulss n. 7 la somma indicata al punto 3) in un'unica soluzione all'adozione del presente provvedimento, a valere sul conto di Tesoreria Provinciale n. 306697 della gestione sanitaria;

5. di dare atto che la spesa di cui si dispone l'impegno con il presente atto non rientra nelle tipologie soggette a limitazioni ai sensi della L.R. n. 1/2011;

6. di dare atto che la presente obbligazione non ha natura di debito commerciale;

7. di stabilire che entro il 30.05.2016 l'Azienda Ulss n. 7 dovrà presentare, al Settore Promozione e Sviluppo Igiene e Sanità Pubblica, una relazione scientifica, che illustri i risultati raggiunti, e una rendicontazione economica con il dettaglio delle spese sostenute al 31.12.2015;

8. di trasmettere il presente decreto per il visto di monitoraggio al Responsabile GSA per la successiva trasmissione alla Sezione Ragioneria per quanto di competenza;

9. di pubblicare il presente provvedimento sul Bollettino Ufficiale Regionale.

- F.to Dr.ssa - Francesca Russo -

SEZIONE RAGIONERIA

Ai sensi dell'art. 43 della L.R. 29 novembre 2001, n. 39 si appone il visto e si registra in contabilità l'impegno di spesa

n. _____ cap. _____ del bilancio _____ di €. _____

Venezia, _____

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REGIONE DEL VENETO
giunta regionale

Allegato A al Decreto n. 017 **del** 13 AGO. 2015

Piano Finanziario 2015 per "the ABC Study on Heart disease"

Organizzazione eventi (formazione, seminari)	€ 3000,00
Materiale divulgativo e informativo	€ 500,00
Missioni e congressi scientifici	€ 5000,00
Personale (inclusa borsa di studio)	€ 9000,00
Lavoro per preparazione ed up-grade data sets in STATA ed analisi statistica (incluso software STATA 14)	€ 3000,00
WEB-site per "the ABC Study on Heart disease" :	
Preparazione WEB-site	€ 2000,00
Mantenimento, aggiornamento WEB-site, annuale	€ 2000,00
Spese generali	€ 5500,00
TOTALE	€ 30000,00

The ABC Study on Heart Disease

The Association Act (statuto associazione)

STATUTO dell' "ABC Study on Heart Disease Association (A Veneto Region Project)"

Articolo 1 - Tra gli aderenti al presente statuto si costituisce una Associazione denominata "ABC Study on Heart Disease Association" (A Veneto Region Project)".
L'Associazione è ordinata ed amministrata ai sensi degli articoli 36 e seguenti del Codice Civile, dal presente Statuto e dalle deliberazioni degli organi sociali.
La sede sociale è in Conegliano (TV) via Colombo n.74. L'Associazione con delibera del consiglio direttivo ha facoltà di variare sede sociale, di istituire sedi secondarie e di svolgere le proprie attività anche al di fuori della propria sede sociale. L'Associazione può aderire ed affiliarsi ad altre organizzazioni, enti ed associazioni operanti in Italia e all'estero.
L'Associazione non ha scopi di lucro ed è aperta a tutti indipendentemente dalle opinioni politiche, confessionali ed ideologiche e dall'appartenenza a categorie, enti e razze diverse.

Articolo 2 - L'Associazione intende perseguire esclusivamente finalità di solidarietà sociale, ad eccezione di quelle ad esse direttamente connesse ovvero accessorie. Scopo dell'Associazione è lo svolgimento di attività di ricerca scientifica di particolare interesse sociale. In particolare l'Associazione intende:
a) promuovere e sostenere il progetto clinico-scientifico "the ABC Study on Heart Disease", già operativo dal 1992.
b) promuovere e sostenere il progetto della Regione Veneto "the ABC-4 Study on Heart Disease", DGR del Veneto n°748 del 14 maggio 2015.
c) promuovere, sostenere e mantenere il website: www.abcheartdiseasestudy.org, che è espressione dell'ABC Study on Heart Disease.
d) supportare studi clinico-scientifici, specialmente sulla malattia cardiaca;
e) promuovere la metodica di follow up a lungo termine del paziente come metodo clinico per la conoscenza e la cura della malattia
f) sostenere la produzione scientifica specialmente, ma non limitatamente, in riguardo all'ABC Study on Heart Disease.
L'associazione inoltre potrà svolgere attività direttamente connesse a quelle istituzionali, destinate al reperimento di fondi, ovvero accessorie in quanto integrative delle stesse, nei limiti consentiti dal D.Lgs. del 4 dicembre 1997 n. 460 e successive modifiche ed integrazioni.

REGIONE DEL VENETO

IL PRESIDENTE

Venezia, 3 marzo 2016

Preg.mo dr. Berton,

La ringrazio per avermi informato sui nuovi sviluppi dell'importante progetto regionale "The ABC Study on Acute Coronary Syndrome", che la Regione del Veneto ha voluto sostenere all'interno del più ampio programma nazionale "Guadagnare salute – rendere facili le scelte naturali".

La Regione crede fortemente nella ricerca, come in quella portata avanti dalla Sua équipe. Sarebbe, davvero, auspicabile che questo studio prospettico diventasse un piccolo caso Framingham. I presupposti ci sono: un'indagine epidemiologica sviluppata sul lungo periodo e sulla raccolta di dati statistici – scientifici, relativi ai pazienti monitorati.

Riconosco che si tratta di un lavoro prezioso svolto da persone competenti e motivate a migliorare la salute dei nostri cittadini, in sintonia con le azioni poste in campo dalla Regione in ambito sanitario.

In attesa di essere aggiornato sui futuri sviluppi dello studio, auguro buon lavoro a Lei e ai suoi colleghi degli Ospedali di Adria, Bassano del Grappa, Conegliano e Padova coinvolti nel progetto.

Cordialmente,

Luca Zaia

Preg.mo Signor
Dr. Giuseppe Berton
Responsabile Clinico – Scientifico del Progetto
regionale "The ABC Study on Acute
Coronary Syndrome"

The ABC Study on Heart Disease

"ABC Study on Heart Disease Association"
website: www.abcheartdiseasestudy.org

Conegliano, 31maggio2016

Al Sig. Presidente della Regione Veneto
Dott. Luca Zaia
Venezia

Oggetto: Rendiconto del primo anno del Progetto Regionale triennale *The ABC Study on Acute Coronary Syndrome**
*(*ABC is acronym for Adria, Bassano, Conegliano, and Padova Hospitals)*

Gentile Presidente Zaia,

La presente lettera, che accompagna il rendiconto del primo anno del Progetto Regionale triennale in oggetto, è per ringraziarLa dell'opportunità che la Regione Veneto ci ha dato di lavorare e studiare sulla malattia di cuore e neoplasie. E per il sostegno concreto che la Regione ci ha dato.

Il presente rendiconto riporta brevemente: 1) lo sviluppo del Progetto e dell'Associazione ABC Study, 2) i risultati osservazionali di base, 3) l'attività formativa professionale e 4) l'attività divulgativa ed informativa associata alla ricerca. 5) Include anche i risultati scientifici principali riportati nella letteratura internazionale.

Principalmente il primo anno e' stato dedicato all'esame del follow up di 17 anni dei pazienti con valutazione di:
•mortalità globale,
•cause di decesso
•eventi cardiovascolari non fatali
•neoplasie (esordio, durata, sede)
•terapia farmacologica durante l'intero follow up
•procedure di rivascolarizzazione meccanica di angioplastica percutanea non primaria durante l'intero follow up
•procedure di rivascolarizzazione meccanica con by pass aorto coronarico durante l'intero follow up.

Il secondo anno sarà dedicato alla continuazione del follow up clinico e all'analisi della sopravvivenza riferita agli eventi fatali e non fatali.

Il terzo, alla continuazione del follow up clinico, alla costruzione di modelli di rischio e ricerca di possibili associazioni cliniche.

Vorremmo inoltre, mentre lavoriamo sulla relazione nel lungo termine tra queste due malattie, focalizzare la nostra attenzione anche sulla prevenzione e su aspetti formativi per operatori sanitari e cittadinanza. Per favorire questi obiettivi abbiamo istituito anche un apposito website (www.abcheartdiseasestudy.org).

Sarà per noi un onore, oltre che un dovere, tenerLa informata sullo sviluppo ed i risultati del Progetto.
Desidero infine ringraziare le numerose persone, della Regione Veneto, Venezia, delle ULSS coinvolte e dell'Associazione ABC Study, coinvolte nel Progetto per il lavoro ed il sostegno.

Con gratitudine, il più cordiale saluto,
a nome dell'Associazione per lo studio e la prevenzione della malattia del cuore.

Giuseppe Berton
Cardiologia, Conegliano

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ospedale 0438663613
personale 3496078176

LINEA GENERALE DELLO SVILUPPO TRIENNALE DEL PROGETTO REGIONALE

PRIMO ANNO 1 giugno 2015-31 maggio 2016

- **Follow up clinico dei pazienti dopo sindrome coronarica acuta. Valutazione di mortalita' globale, cause di decesso, hard end point, trattamento farmacologico. Trattamento con rivascolarizzazione coronarica (angioplastica o bypass aorto-coronarico).**
- **Incidenza di neoplasia**

Arruolamento pazienti con Sindrome Coronarica Acuta

Incidenza neoplasia

Durata neoplasia

SECONDO ANNO 1 giugno 2016-31 maggio 2017

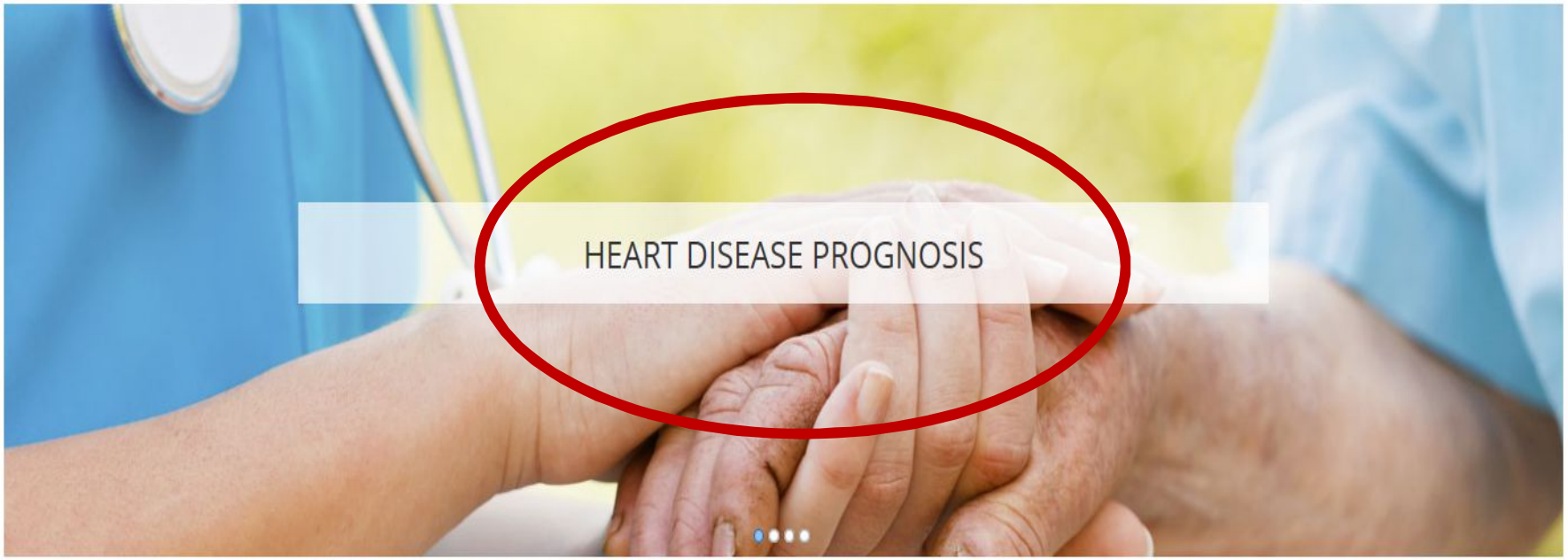
- **Follow up clinico dei pazienti dopo sindrome coronarica acuta. Valutazione di mortalita', cause di decesso, hard end point e trattamento terapeutico.**
- **Analisi di sopravvivenza riferita agli eventi fatali e non fatali; analisi della sopravvivenza per mortalita' globale e mortalita' da neoplasie.**
- **Tipo di neoplasia e tempi di neoplasia.**

TERZO ANNO 1 giugno 2017-31 maggio 2018

- **Continuazione del follow up clinico dei pazienti dopo sindrome coronarica acuta, analisi della sopravvivenza per mortalita' globale e mortalita' da neoplasie.**
- **Costruzione di modelli di rischio e ricerca di possibili associazioni cliniche tra esposizione a rischio ed eventi avversi.**

Capitolo 2

The ABC Study on Heart Disease


The ABC Study on Heart Disease
Search ...
About
The Association
Our investigators
Bibliography
Veneto Region Project
For Researchers
A patient's story
New meetings
Contact us
HEART DISEASE PROGNOSIS

Partecipating Institutions

Adria Hospital

Bassano Hospital

Conegliano Hospital

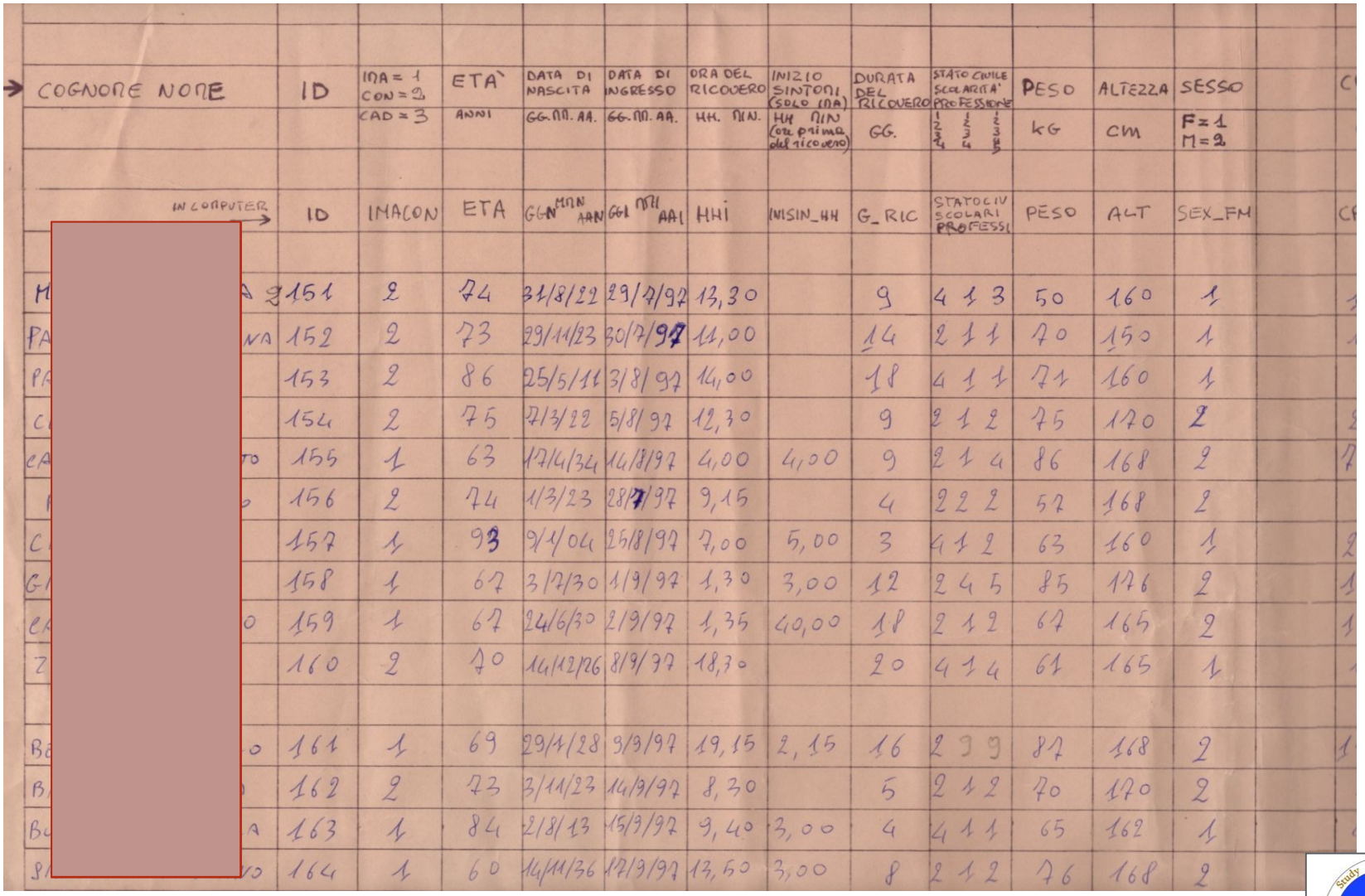
Padova Hospital

In 1992, a little group of medical researchers and other participants embarked on an project to investigate new clinical factors for heart disease, studying patients with acute coronary syndrome and following them for many years. Today, the observations on the long-term survival after acute coronary syndrome are internationally acknowledged. Main results appears on the most important cardiovascular texts across the world. The study is called "**the ABC heart disease study**".

A Timeline of Clinical Research Milestones

1992	Start of the ABC Study on Heart Disease
1997	Albumin excretion rate (marker of endothelial dysfunction) found to increase during acute myocardial infarction and to predict early mortality (in-hospital).
2003	C-reactive protein (inflammation) in acute myocardial infarction found to be association with heart failure and mortality.
2008	Albumin excretion in acute myocardial infarction found associated to long-term mortality (seven years)
2009	Atrial fibrillation during acute myocardial infarction found associated to sudden death after 7-year of follow-up.
2009	Low-dose digitalis during acute myocardial infarction found to be protective for long-term sudden death (seven years).
2012	The four factors of the ABC model (estimated glomerular filtration rate, albumin/creatinine excretion ratio, history of angina, and previous myocardial infarction) improved the predictive power of other traditional models for long-term event-free survival.
2014	The ABC-2 study identified clinical predictors of long-term mortality (twelve years) after ACS that might help prognostication, patient education, and risk modification. It showed that the analysis of the modes of death might improve the risk assessment.

The beginning, 1992...



COGNOME NOME	ID	IMA = 1 CON = 2 CAD = 3	ETA' ANNI	DATA DI NASCITA GG.MM.AA.	DATA DI INGRESSO GG.MM.AA.	ORA DEL RICOVERO HH. MIN.	INIZIO SINTOMI (SOLO IMA) HH MIN (ore prima del ricovero)	DURATA DEL RICOVERO GG.	STATO CIVILE SCOLARITA' PROFESSIONE 1 2 3 4 / 1 2 3 4 / 1 2 3 VR	PESO kG	ALTEZZA cm	SESSO F=1 M=2
IN COMPUTER →	ID	IMACON	ETA	GG MM AA	GG MM AA	HH	INISIN_HH	G_RIC	STATOCIV SCOLARI PROFESSI	PESO	ALT	SEX_FM
M	151	2	74	31/8/22	29/7/97	13,30		9	4 1 3	50	160	1
PA	152	2	73	29/11/23	30/7/97	11,00		14	2 1 1	70	150	1
PA	153	2	86	25/5/11	3/8/97	14,00		18	4 1 1	71	160	1
C	154	2	75	7/3/22	5/8/97	12,30		9	2 1 2	75	170	2
CA	155	1	63	17/4/34	14/8/97	4,00	4,00	9	2 1 4	86	168	2
	156	2	74	1/3/23	28/7/97	9,15		4	2 2 2	57	168	2
C	157	1	93	9/1/04	25/8/97	7,00	5,00	3	4 1 2	63	160	1
G	158	1	67	3/7/30	1/9/97	1,30	3,00	12	2 4 5	85	176	2
CA	159	1	67	24/6/30	2/9/97	1,35	40,00	18	2 1 2	67	165	2
Z	160	2	70	14/12/26	8/9/97	18,30		20	4 1 4	61	165	1
Ba	161	1	69	29/1/28	3/9/97	19,15	2,15	16	2 3 9	87	168	2
B	162	2	73	3/11/23	14/9/97	8,30		5	2 1 2	70	170	2
Bu	163	1	84	2/8/13	15/9/97	9,40	3,00	4	4 1 1	65	162	1
SI	164	1	60	14/11/36	12/9/97	13,50	3,00	8	2 1 2	76	168	2

This study would never be done without the help of many people who shared with us their knowledge and experience and passion.

To all of them goes our deep gratitude !

Forse tutte queste persone in tutti questi anni hanno contribuito a costruire alcuni pensieri nuovi sulla Medicina.

The ABC Study on Heart Disease

Primary Investigators

ABC Heart Disease Study Primary Investigators

Giuseppe Berton, MD, FESC
Consultant Cardiologist
Conegliano General Hospital, Italy

Rocco Cordiano, MD
Consultant Cardiologist
Adria General Hospital, Italy

Rosa Palmieri, MD
Consultant Cardiologist
Adria General Hospital, Italy

Fiorella Cavuto, MD
Consultant Cardiologist
Bassano del Grappa General Hospital, Italy

Paolo Palatini, MD
Professor of Medicine
University of Padova, Italy

Acknowledgments

... We are deeply grateful to Dr. **Paolo Mormino** for his assistence in statistical analysis since the beginning of this study...

Collaborators

This study would never be done without the help of many people who shared with us their knowledge and experience and passion.
To all of them goes our deep gratitude!

ABC Heart Disease Study Collaborators

Accorsi Franco, Cardiology, Conegliano; **Bagato Francesco**, Cardiology, Adria, **Berton Giuseppe**, Cardiology, Conegliano; **Buttazzi Patrizio**, Cardiology, Conegliano; **Cavuto Fiorella**, Cardiology, Bassano; **Citro Tiziana**, Internal Medicine, Conegliano; **Civiero Jessica**, Cardiology, Bassano; **Cordiano Rocco**, Cardiology, Adria; **Cucchini Francesco**, Cardiology, Bassano; **Delise Pietro**, Cardiology, Conegliano; **De Longhi Chiara**, Cardiology, Conegliano; **De Toni Renzo**, Medical Clinic IV, Padova; **Giacomini Giulia**, Cardiology, Conegliano; **Guarnieri Gianluigi**, Internal Medicine, Conegliano; **Katz Ethan**, Quantitative Health Sciences, Cleveland, USA; **Maccioni Antonio**, Internal Medicine, Conegliano; **Mastrosimone Stefania**, Nephrology, Treviso; **Mazzuco Stefano**, Statistic Dptm, Venezia; **Mbaso Sebastian**, Cardiology, Bassano; **Michelazzo Paola**, Cardiology, Bassano; **Mormino Paolo**, Medical Clinic IV, Padova; **Oliana Federica**, Cardiology, Conegliano; **Palatini Paolo**, Medical Clinic IV, Padova; **Pagliara Valeria**, Internal Medicine, Treviso; **Palmieri Rosa**, Cardiology, Adria; **Pellegrinet Marco**, Cardiology, Conegliano; **Petucco Stefania**, Cardiology, Bassano; **Pianca Sigismondo**, Internal Medicine, Vittorio Veneto; **Querzoli V**, Analysis Lab, Adria; **Sessa L**, Analysis Lab, Conegliano; **Sponton GL**, Analysis Lab, Adria; **Stefani Maria**, Cardiology, Bassano; **Zampieri P**, Cardiology, Rovigo.

The Nurses of the Cardiology Departments of Conegliano, Adria, and Bassano General Hospitals for patient care.

Acknowledgments

We would like to thank on behalf of all the nurses, (simply for being the very first two involved in the study ...a long time ago!):

Paola Michelazzo,RN, and **Jessica Civiero**,RN, (Bassano del Grappa)

Chief department - Acknowledgments

Veneto Region referee
Dr. **Francesca Russo**

Conegliano Hospital
Dr. **F. Accorsi**
Dr. **P. Delise**

Adria Hospital
Dr. **A.Caruso**
Dr. **M.Licitra**

Bassano del Grappa Hospital
Prof. **F. Cucchini**

Medical Clinic IV, University of Padova
Prof. **C. Dal Palù**
Prof. **P. Palatini**
Dott. **R.De Toni**

Thanks to the Medical Researchers

Dott. **Rocco Cordiano**, O.C. Adria
Dott.ssa **Rosa Palmieri**, O.C. Adria
Dott. **Sebastan Mbaso**, O.C.Bassano
Dott.ssa **Maria Stefani**, O.C. Dolo
Dott.ssa **Stefania Petucco**, O.C. Bassano
Dott.ssa **Fiorella Cavuto**, O.C. Bassano
Dott. **GianLuigi Guarnieri**, O.C. Conegliano
Dott. **Giuseppe Berton**, O.C. Conegliano
for thefollow-up of patientsover the years!

Thanks to the Doctors:

Marco Pellegrinet, MD,
Francesco Bagato, MD,

for working onour research !

Scholarship 2016 for the Regional Project:

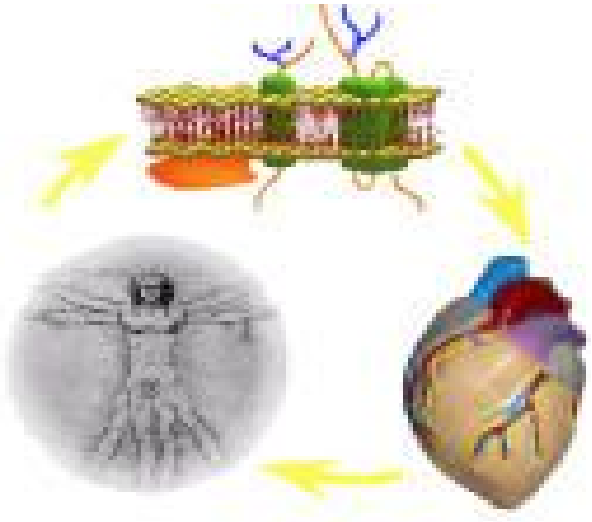
Dott.ssa **Beatrice Segafredo**, MD

Thanks to

Rosanna Cedran, RN, for the translation of the ABC study in Italian, **Gilberto Paro**, RN, for having had the idea of translating the work into italian, and **Lidia Mandaio**, RN, for a meeting coordination.

La questione fondamentale e':

"Cosa accade dopo l'infarto di cuore?"



"Di tutto...!"

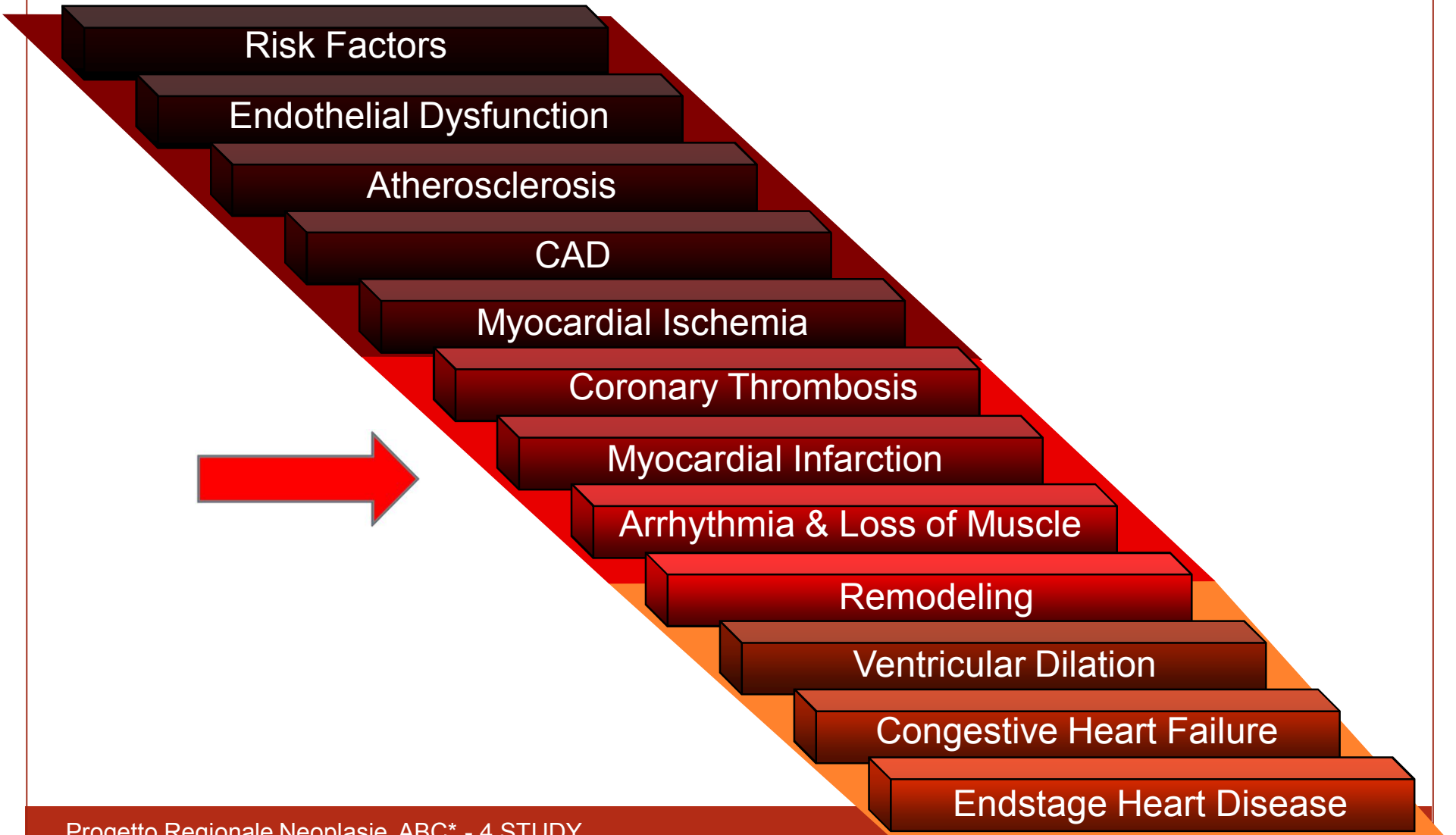
Prognosis...

"In acute diseases it is not quite safe to prognosticate either death or recovery."

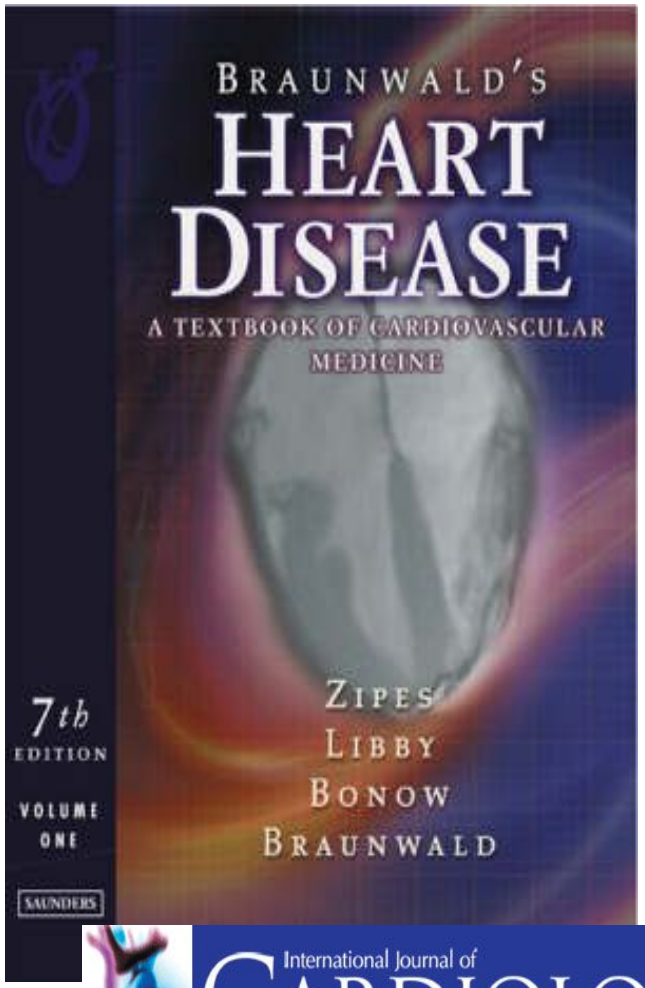
460 b.c. Aphorisms, II, 19

Ippocrate

The Progressive Development of Cardiovascular Disease



Progetto Regionale Neoplasie, ABC* - 4 STUDY



Albumin Excretion Rate Increases During Acute Myocardial Infarction and Strongly Predicts Early Mortality

Giuseppe Berton, MD; Tiziana Citro, MD; Rosa Palmieri, MD; Stefania Petucco, MD; Renzo De Toni, DBSc; Paolo Palatini, MD

Background This study was undertaken to assess whether albumin excretion rate (AER) increases during acute myocardial infarction (AMI) and whether it predicts in-hospital mortality.

Methods and Results The study was carried out in 496 subjects admitted to hospital for suspected AMI. Of these, 360

in hospital according to whether they had normal AER, microalbuminuria, or overt albuminuria, mortality rate progressively increased with increasing levels of AER ($P<.0001$). In a Cox's proportional hazards model, AER was a better predictor of in-hospital mortality than Killip class or echocardiographic left ventricular ejection fraction. A cutoff value of 50 mg/24 h for first-day AER and 30 mg/24 h for third-day AER yielded a sensitivity of 92.3% and of 88.5% and a specificity of 72.4% and of 79.3%, respectively, for mortality. Adjusted relative risks for the two cutoff values were 17.3 (confidence limits, 4.6 to 112.7) and 8.4 (confidence limits, 2.4 to 39.3), respectively.

Conclusions These data show that AER increases during AMI and that it yields prognostic information additional to that provided by clinical or echocardiographic evaluation of left ventricular performance. **(*Circulation*. 1997;96:3338-3345.)**

Key Words • myocardial infarction • heart failure • mortality • microalbuminuria

American Heart Association.
Learn and Live.

Circulation

JOURNAL OF THE AMERICAN HEART ASSOCIATION

International Journal of CARDIOLOGY

EUROPEAN SOCIETY OF CARDIOLOGY®

JAMES T. WILLERSON
JAY N. COHN
HEIN J.J. WELLENS
DAVID R. HOLMES, JR.
EDITORS

Cardiovascular Medicine

THIRD EDITION

Il nostro lavoro è osservato con attenzione dalla Comunità Scientifica Internazionale ed è ormai entrato nella Letteratura Scientifica specifica.

Capitolo 3

Risultati preliminari ABC Study

American Journal of Cardiology
April 1, 2012

Predictors of Ten-Year Event-Free Survival in Patients With Acute Myocardial Infarction (from the ABC Study on Myocardial Infarction)*

(*ABC is acronym for Adria, Bassano, Conegliano, and Padova Hospitals)

Order of Authors: Giuseppe Berton, MD; Rocco Cordiano,MD; Fiorella Cavuto,MD; Giulia Giacomini, PhD; Renzo de Toni,PhD; Paolo Palatini,MD.

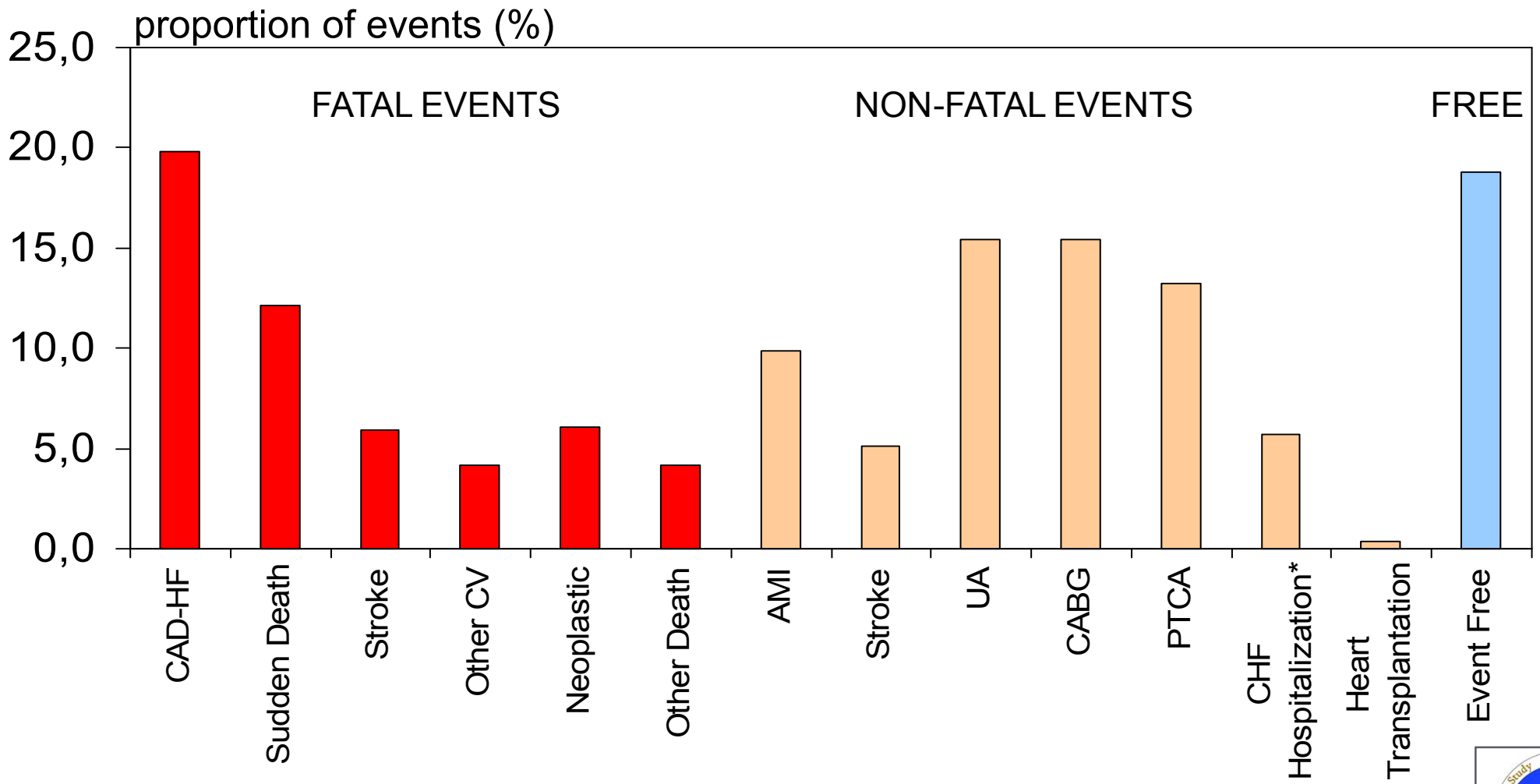
Sebbene siano ampiamente studiate le cause di mortalità a breve termine dopo Sindrome Coronarica Acuta (SCA), ad oggi sono pochissimi gli studi nel lungo termine.

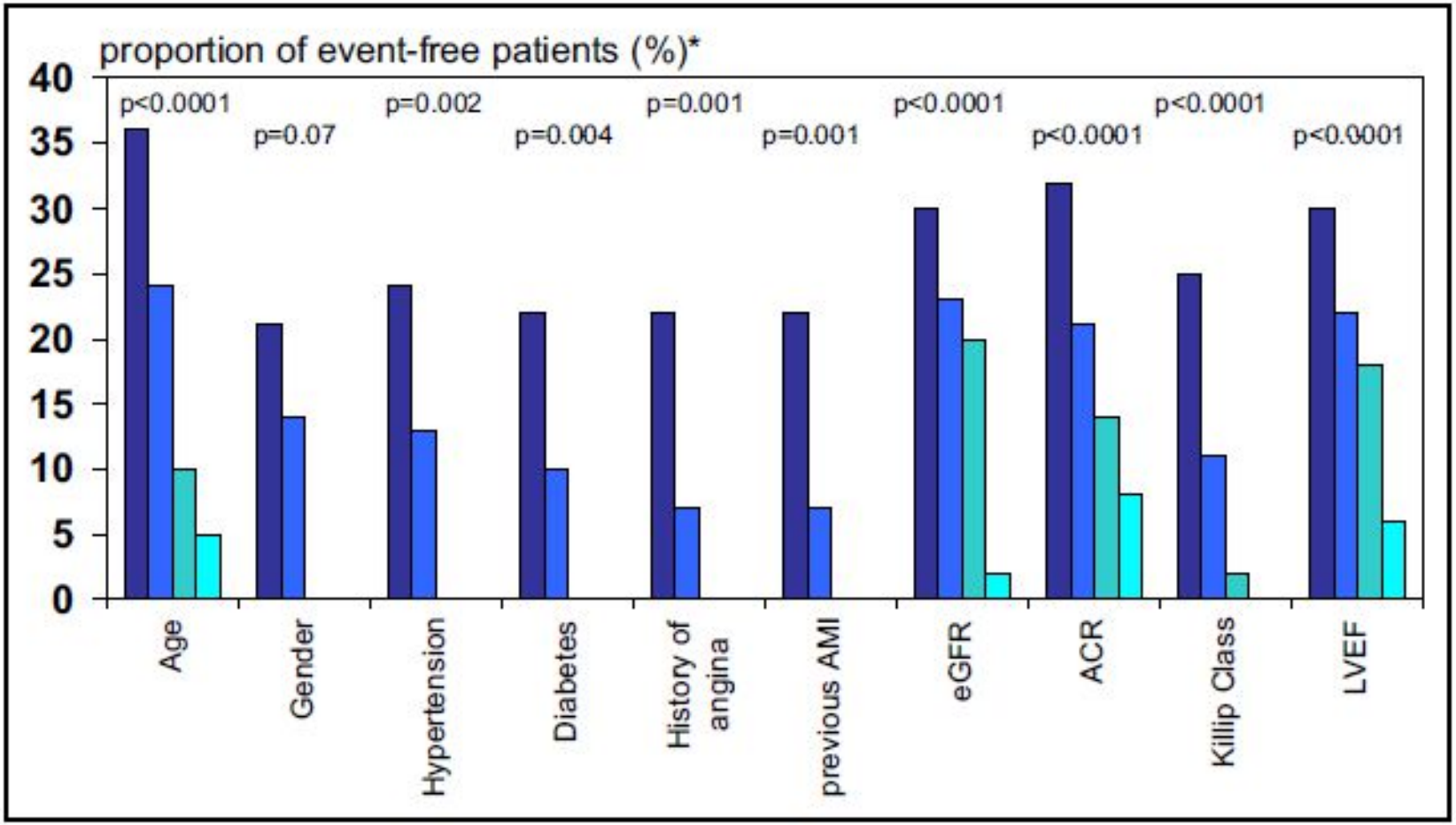
In questo studio del 2012 sono stati arruolati e seguiti con un lungo follow up (tuttora in corso) 504 pazienti con SCA.

uninvestigated. We analyzed noninvasive clinical variables in association with long-term EFS after AMI. The present prospective study included 504 consecutive patients with AMI at 3 hospitals from 1995 to 1998 (Adria, Bassano, Conegliano, and Padova Hospitals [ABC] study). Thirty-seven variables were examined, including demographics, cardiovascular risk

567 eligible patients
(on admission to intensive care units)
62 patients excluded:
-Lack of consent n=6
-Concomitant disease n=33
-Death within 72 hours n=7
-Insufficient data n=12
-Inclusion in randomised trial n=4
505 patients enrolled
40 in-hospital deaths
465 patients alive at discharge
1 drop-out
464 patients at follow-up end
95 EFS patients
409 patients with events
(597 cumulative events)
145 patients alive with CV events
264 all-cause deaths

Adverse events in 504 AMI pts through 10 year follow-up at Adria, Bassano and Conegliano Hospitals (1998-2008)




proportion of event-free patients (%)*
40
35
30
25
20
15
10
5
0
p<0.0001
p=0.07
p=0.002
p=0.004
p=0.001
p=0.001
p<0.0001
p<0.0001
p<0.0001
p<0.0001
Age
Gender
Hypertension
Diabetes
History of angina
previous AMI
eGFR
ACR
Killip Class
LVEF

Predictors of Ten-Year Event-Free Survival in Patients With Acute Myocardial Infarction (from the Adria, Bassano, Conegliano, and Padova Hospitals [ABC] Study on Myocardial Infarction)

acute heart damage. In conclusion, 10-year EFS was strongly associated with 4 factors (ABC model) typically neglected in studies of AMI survival, including estimated glomerular filtration rate, albumin/creatinine excretion ratio, a history of angina, and previous myocardial infarction. This model had greater predictive power and improved the power of 2 other models using

Lo studio dei dati raccolti dopo 10 anni dall'evento ha confermato il ruolo di alcuni fattori sulla sopravvivenza dopo infarto, dai quali è nato l'"ABC model". Tale modello di rischio si basa sullo studio dei soggetti "event-free".

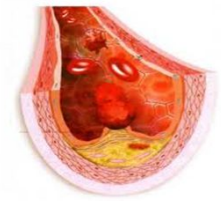
E' nostra intenzione produrre un calcolatore per stimare il rischio nella popolazione affetta da Sindrome Coronarica Acuta

L'ABC model si fonda su 3 punti:

Storia di danno cardiaco
precedente infarto miocardico o angina pectoris

Disfunzione renale
Filtrato gomerulare renale

Disfunzione endoteliale generale acuta
Rapporto albumina/creatinina



Berton et al., Int J Cardiovasc Res 2014, 3:2
http://dx.doi.org/10.4172/2324-8602.1000160

International Journal of Cardiovascular Research

Research Article A SCITECHNOL JOURNAL

Prospective History of Long-Term Mortality and Modes of Death in Patients Discharged After Acute Coronary Syndrome: The ABC-2* Study on Acute Coronary Syndrome

Giuseppe Berton[1*], Rocco Cordiano[2], Rosa Palmieri[2], Fiorella Cavuto[3], Marco Pellegrinet[4] and Paolo Palatini[5]

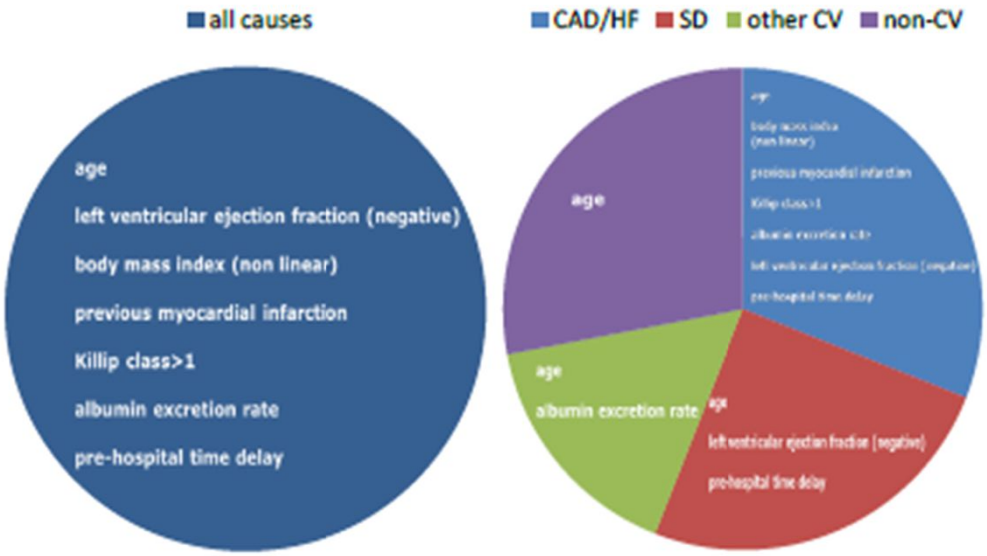
Lo scopo del presente lavoro del 2014 era quello di esaminare il valore prognostico di molteplici caratteristiche cliniche sulla mortalità a lungo termine e le cause di decesso dopo Sindrome Coronarica Acuta con un follow up di 12 anni.

Conclusion

The ABC-2 study identified clinical predictors of long-term mortality after ACS that might help prognostication, patient education, and risk modification. Furthermore, the present study showed that the analysis of the modes of death might improve the risk assessment.

Panel a

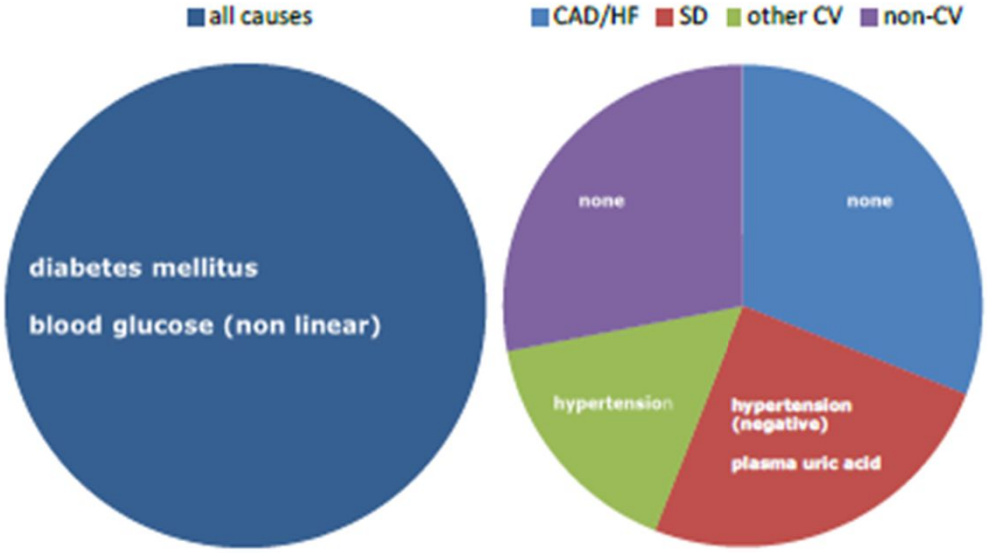
association with all-causes mortality and single causes of death



Panel b

association with all-causes mortality and no single cause of death

association with a single cause of death, and no association with all-causes mortality



Capitolo 4

Come e' nato

The ABC* - 4 STUDY on HEART DISEASE
Progetto NEOPLASIA

Avanzando nel follow-up dei pazienti con storia di Sindrome Coronarica Acuta (SCA), le cause di mortalita' extracardiache, tra le quali spiccano le neoplasie maligne, incrementano marcatamente rispetto alle cause di mortalita' cardiaca...

REGIONE DEL VENETO
giunta regionale – 9^ legislatura

ALLEGATOA alla Dgr n. 748 del 14 maggio 2015

Studio prospettico su Neoplasia Maligna dopo Sindrome Coronarica Acuta: The ABC* - 4 Study on Acute Coronary Syndrome
* (Adria, Bassano, Conegliano, Padova)

SCOPO DEL LAVORO

Obiettivo del nostro lavoro è **studiare l'incidenza di neoplasie maligne nei pazienti con SCA**, arruolati nell'ABC Study* (Adria, Bassano, Conegliano, Padova Holspitals), seguiti in modo prospettico per lunghissimo tempo (15 anni). Inoltre, individuare tra le caratteristiche cliniche ed i trattamenti terapeutici, incluse le procedure di rivascolarizzazione, **eventuali fattori di rischio o associazioni per l'insorgenza di neoplasia.**

Bur n. 54 del 01/06/2015

(Codice interno: 298792)

DELIBERAZIONE DELLA GIUNTA REGIONALE n. 748 del 14 maggio 2015

Approvazione dello Studio prospettico su Neoplasia maligna dopo sindrome coronarica acuta. The ABC - 4 study on acute coronary syndrome.

[Sanità e igiene pubblica]

Lo studio interessa tre diverse aree geografiche corrispondenti al territorio di tre diverse ULSS Venete, la cui popolazione afferisce ai tre ospedali coinvolti dallo studio originario (*ABC Adria Bassano Conegliano Hospital).

The ABC* - 4 STUDY
on HEART DISEASE
ACS patients by ULSS by City

AZIENDA SANITARIA ULSS 7

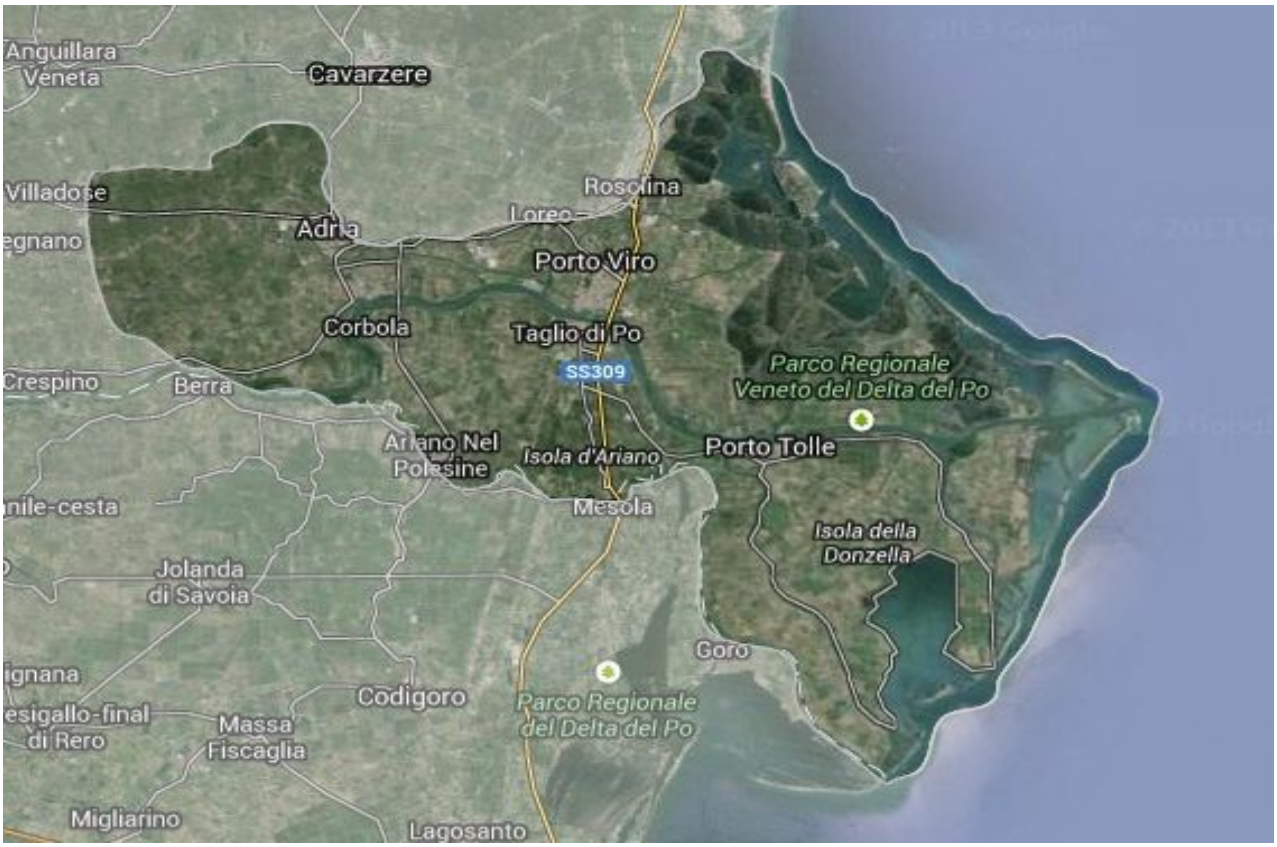
Bassano del Grappa	**32,1%**
Romano d'Ezzelino	**12,6%**
Cassola	**5,0%**
Nove	**5,0%**
Rosà	**3,8%**
Valstagna	**3,8%**
Asiago	**1,3%**
Enego	**0,6%**
Gallio	**0,6%**

The ABC* - 4 STUDY
on HEART DISEASE
ACS patients by ULSS by City

Conegliano	**20,7%**
Vittorio Veneto	**19,2%**
Susegana	**6,9%**
Pieve di Soligo	**5,3%**
Vazzola	**5,3%**
Farra di Soligo	**4,3%**
San Vendemiano	**4,3%**
Colle Umberto	**2,7%**
Mareno di Piave	**2,7%**
Sernaglia	**2,7%**
San Pietro di Feletto	**2,7%**

The ABC* - 4 STUDY
on HEART DISEASE
ACS patients by ULSS by City

Adria	**37,7%**
Cavarzere	**13,5%**
Taglio di Po	**7,9%**
Ariano	**6,7%**
Porto Tolle	**4,8%**
Loreo	**3,6%**
Corbola	**3,2%**
Rosolina	**2,8%**
Codigoro	**2,4%**
Contarin	**2,4%**
Portoviro	**2,0%**



Progetto Regionale Neoplasie, ABC* - 4 STUDY

I dati osservati

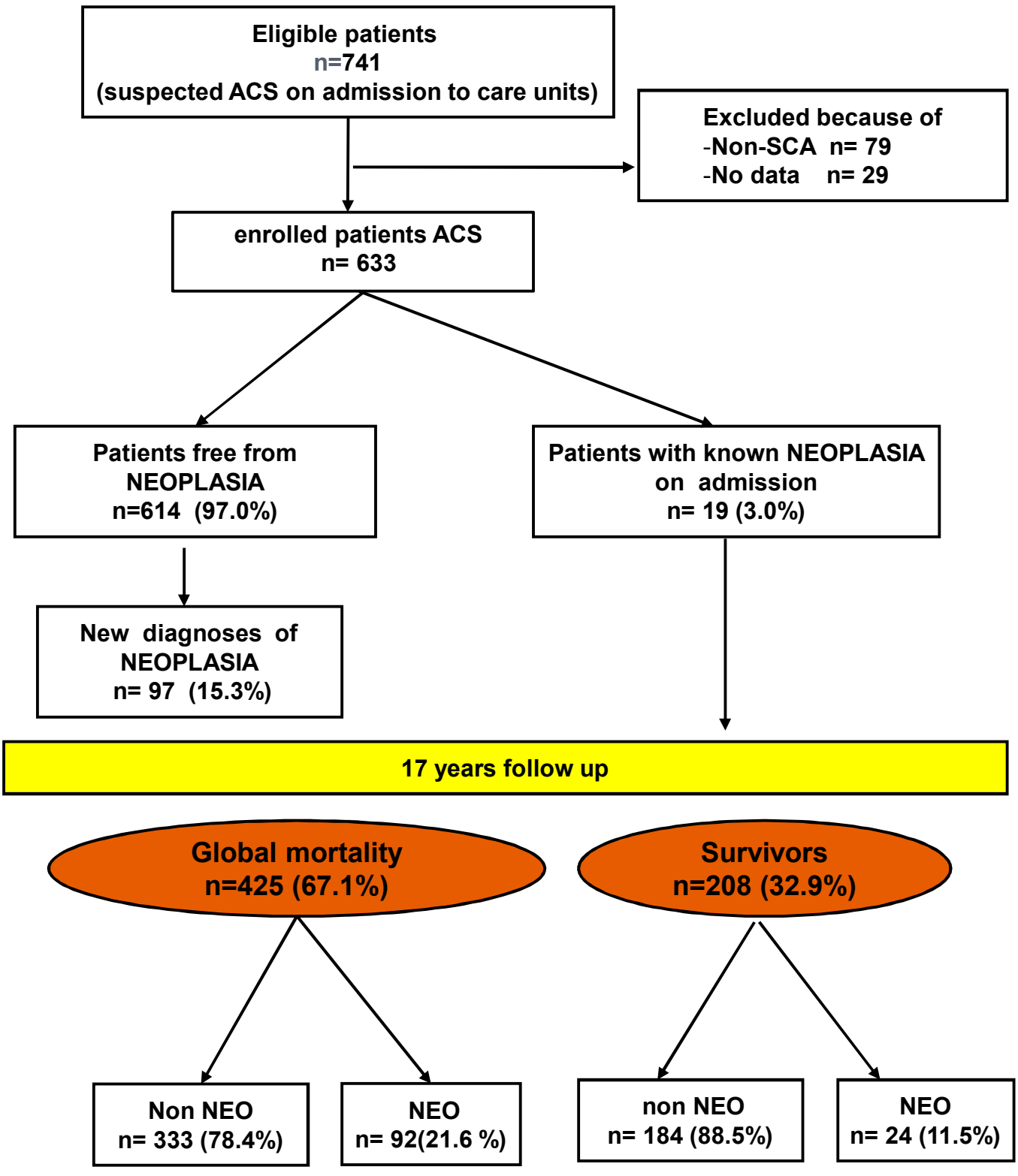
Dati generali e di sopravvivenza con curve di Kaplan.-Meier e stima del rischio istantaneo nel tempo dell'intera popolazione in studio e per ospedali.

Patients Characteristics

	Total	No NEOPLASIA	NEOPLASIA	TEST	p
N=	633	517	116		
Age	66.5±12.0 67 (59-75)	66.5 ± 12.5 67 (58-76)	66.8 ± 9.6 67 (61-74)	t=-0.24	0.81
Female gender	192 (30%)	169 (33%)	23 (20%)	chi2=7.4	0.006
ST elevation miocardial infarction	399 (63%)	335 (65%)	64 (55%)	chi2=3.8	0.05
Hypertension	308 (49%)	258 (50%)	50 (43%)	chi2=1.7	0.18
Diabetes	149 (23%)	134 (26%)	15 (13%)	chi2=8.9	0.003
Smoking habit	420 (66%)	329 (64%)	91 (78%)	chi2=9.3	0.002
Alchool habit	473 (75%)	384 (74%)	89 (77%)	chi2=0.3	0.58
Sistolic blood pressure	123±18 120(110-130)	123±18 120(110-130)	124±17 120(110-130)	t=-0.21	0.83
Diastolic blood pressure	76±11 79 (70-80)	76±11 75 (70-80)	77±11 80 (70-83)	t=-1.27	0.20
Heart rate	74±16 72(61-82)	75±16 72(63-83)	72±15 71(60-80)	t=-1.31	0.19
Cholesterol	210± 50 207 (176-243)	212 ± 51 210(178-244)	202 ± 43 200(171-236)	t=2.06	0.03

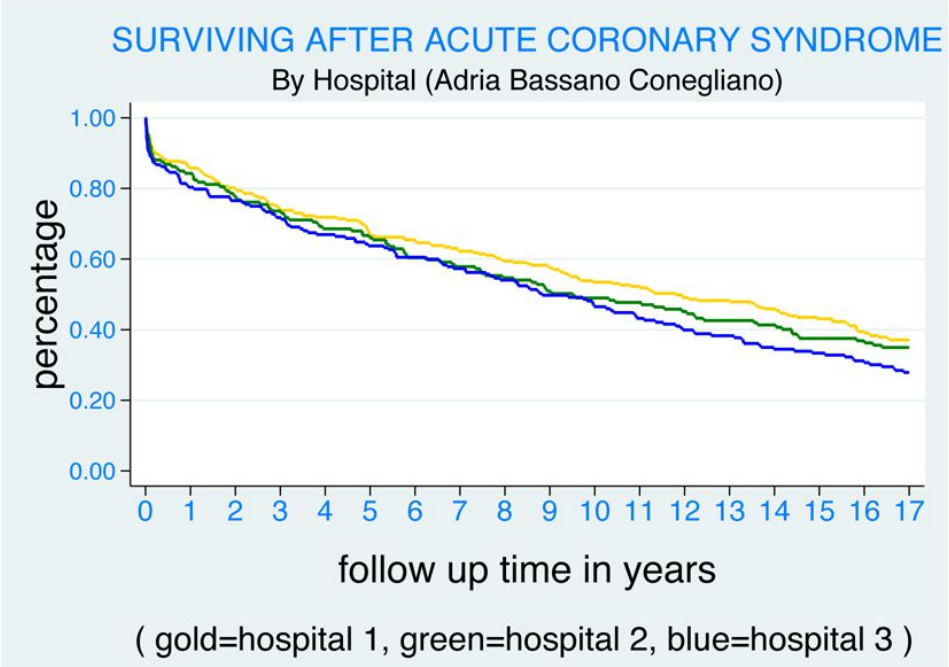
Values are expressed as means ± SD and median (IQ) or proportions

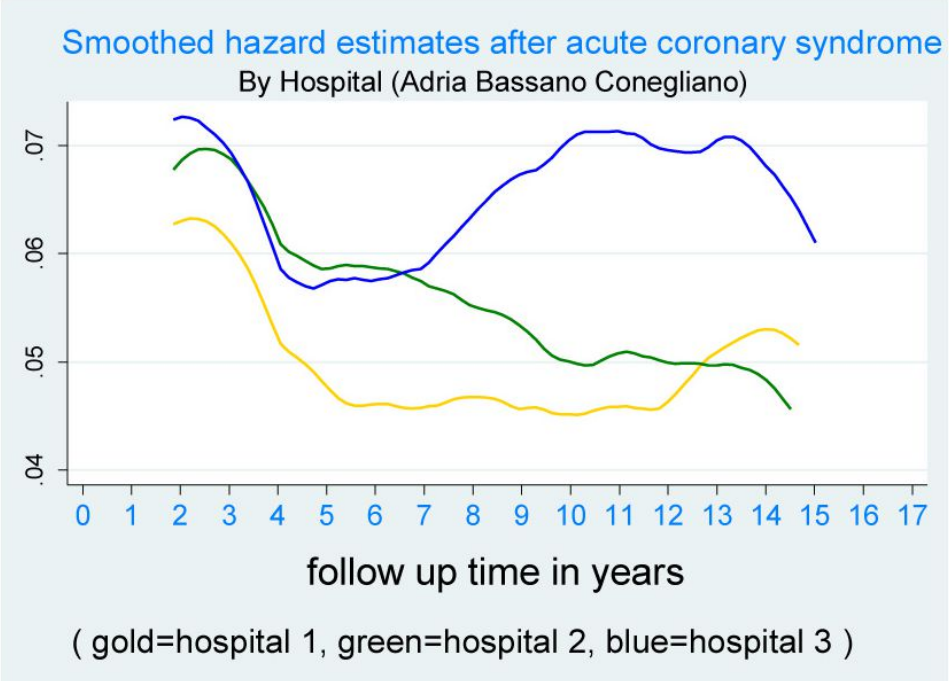
FLOW CHART OF STUDY DEVELOPMENT



Progetto Regionale Neoplasie, ABC* - 4 STUDY

All cause global mortality in the whole sample of 633 patients with Acute Coronary Syndrome enrolled in 3 Veneto Region Hospitals and followed up through 17 years.





Type of Neoplasia and Incidence Rate

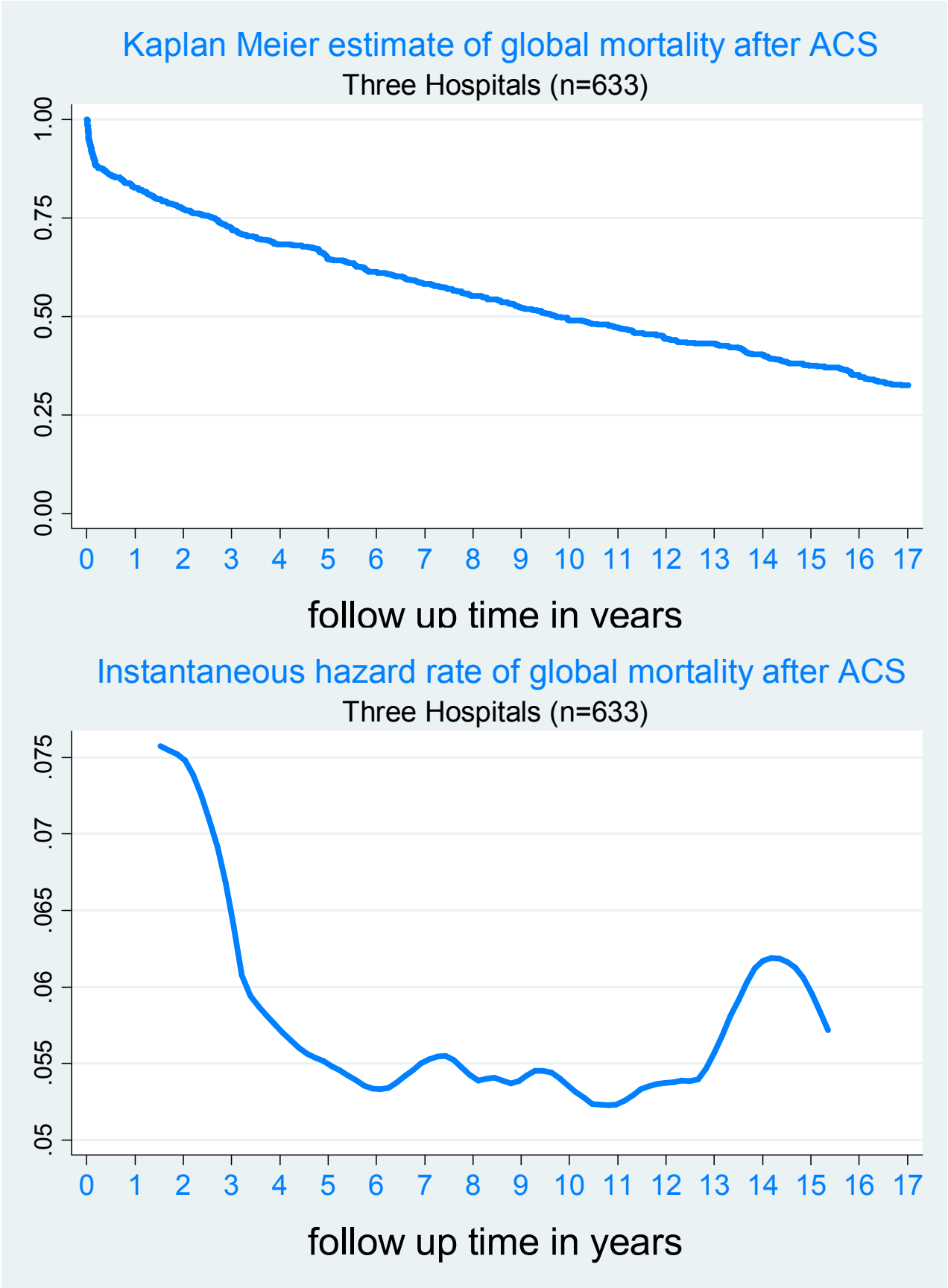
		Men		Women		Tot (n)	
Total patients with NEO		N=93	%	N=23		**116**	%
Type	**Bladder**	8	7.7%	0	0.0%	**8**	6.1%
	Blood	8	7.7%	1	3.8%	**9**	6.9%
	Brain	1	0.9%	1	3.8%	**2**	1.5%
	Breast	0	0.0%	9	34.6%	**9**	6.9%
	Colorectal	16	15.4%	5	19.2%	**21**	16.1%
	Kidney	7	6.7%	2	7.7%	**9**	6.9%
	Liver	5	4.8%	1	3.8%	**6**	4.6%
	Pancreas	6	5.8%	1	3.8%	**7**	5.4%
	Prostatic	19	18.3%	0	0.0%	**19**	14.6%
	Respiratory	29	27.9%	4	15.4%	**33**	25.4%
	Skin	2	1.9%	0	0.0%	**2**	1.5%
	Tyroid	0	0.0%	1	3.8%	**1**	0.8%
	Upper enteric	3	2.9%	1	3.8%	**4**	3.1%
Total NEO		**104**	100%	**26**	100%	**130**	100%

Progetto Regionale Neoplasie, ABC* - 4 STUDY

Surviving Model 1

Global Mortality

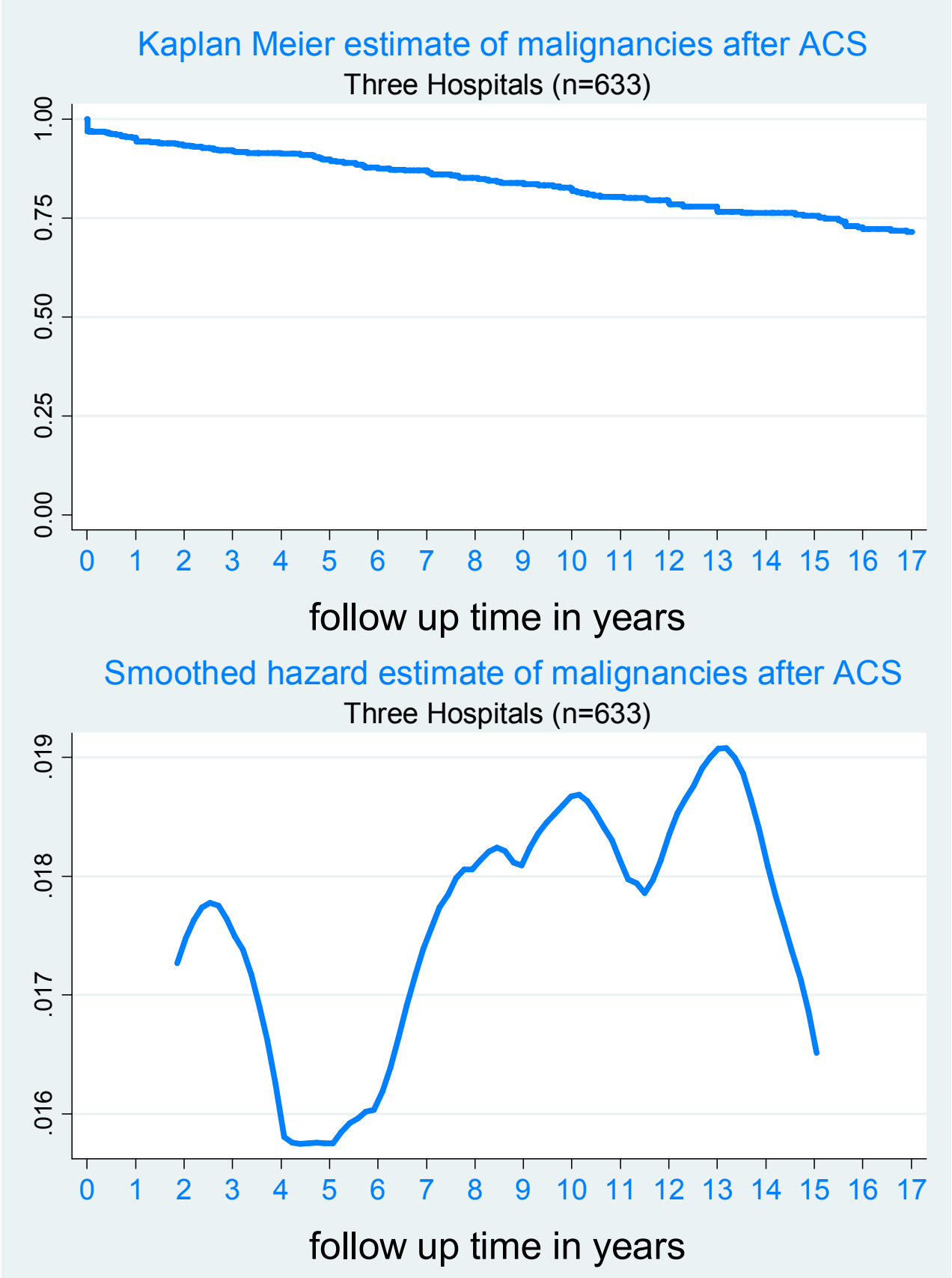
Patients n= 633	Events (Deaths) n= 425
Person years follow up	5997.2 years
Median time to the event	9.6 years
Mortality incidence Rate	**7%**


Kaplan Meier estimate of global mortality after ACS
Three Hospitals (n=633)
0.00
0.25
0.50
0.75
1.00
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17
follow up time in years
Instantaneous hazard rate of global mortality after ACS
Three Hospitals (n=633)
.05
.055
.06
.065
.07
.075
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17
follow up time in years

Surviving Model 2

patient time to neoplasia (fatal and non fatal)

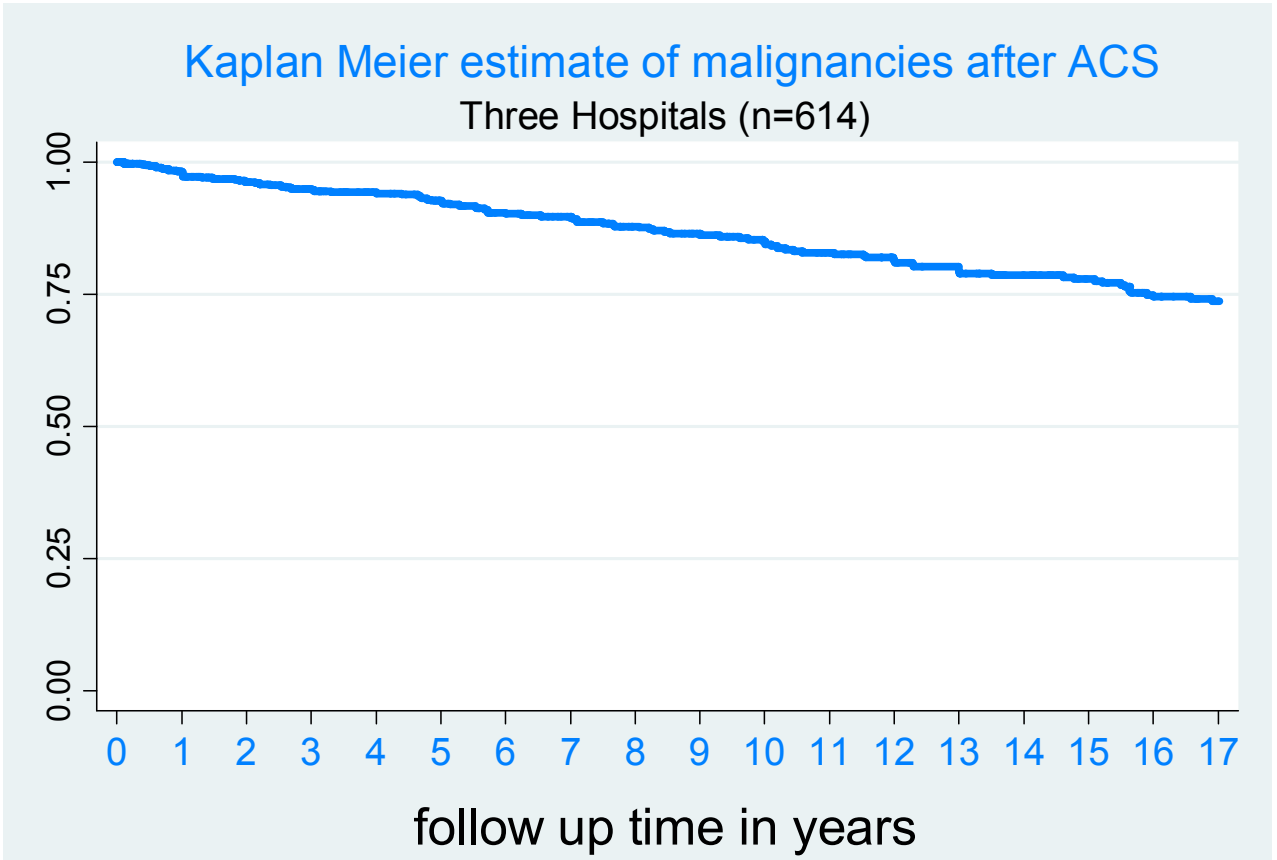
Patients n= 633	Patients with neoplasia n= 116
Person years follow up	5543.3 years
Median time to neoplasia	8.3 years
Incidence Rate	**2%**

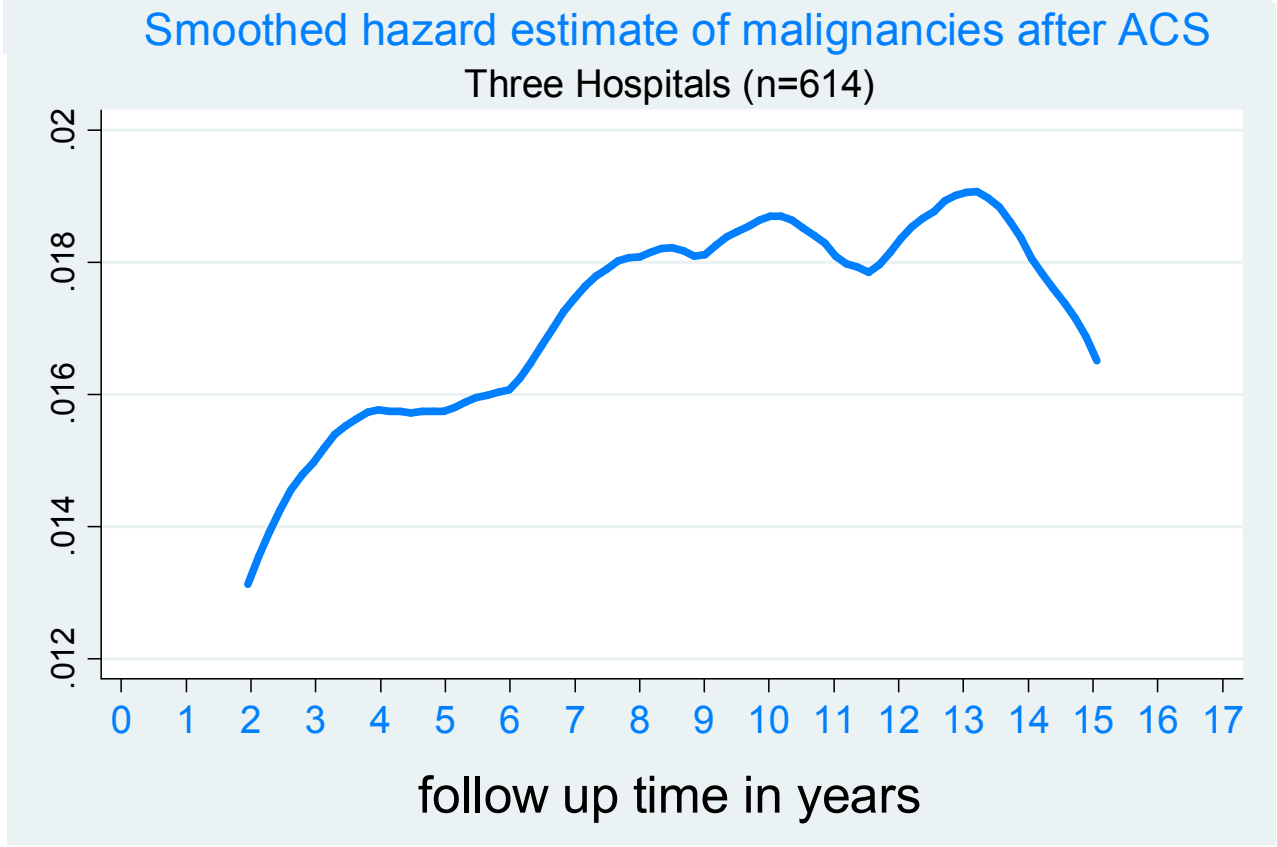

Kaplan Meier estimate of malignancies after ACS
Three Hospitals (n=633)
0.00
0.25
0.50
0.75
1.00
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17
follow up time in years
Smoothed hazard estimate of malignancies after ACS
Three Hospitals (n=633)
.016
.017
.018
.019
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17
follow up time in years

Surviving Model 3

Neoplasia-free enrolled patient time to neoplasia (fatal and non fatal)

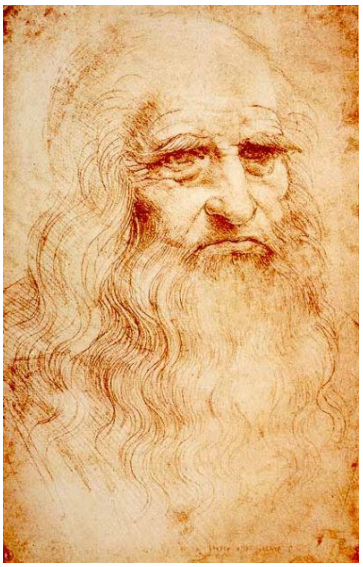
Patients n= 614	New neoplasia n= 97
Person years follow up	5543.3 years
Median time	8.7 years
Incidence Rate	**1.7%**


Kaplan Meier estimate of malignancies after ACS
Three Hospitals (n=614)
0.00
0.25
0.50
0.75
1.00
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17
follow up time in years


Smoothed hazard estimate of malignancies after ACS
Three Hospitals (n=614)
.012
.014
.016
.018
.02
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17
follow up time in years

Capitolo 5

"Guadagnare salute"
Attivita' formativa e di prevenzione promossa dalla nostra Associazione



"Those who are enamoured of practice without science are like a pilot who come into a ship without rudder or compass and never has any certainty where he is going".

"Quelli che s'innamorano di pratica senza scienza son come il nocchiere, che entra in naviglio senza timone o bussola, che mai ha certezza dove si vada".

Leonardo da Vinci

REGIONE DEL VENETO - AZIENDA U.L.S.S. n. 7 - PRESIDIO OSPEDALIERO DI CONEGLIANO
U.O.C. di CARDIOLOGIA - Direttore Dr. P. Delise

LA SOPRAVVIVENZA DOPO INFARTO MIOCARDICO

L'ESPERIENZA DI 10 ANNI NEL VENETO

The Adria, Bassano, Conegliano and Padova Hospitals (ABC) study on myocardial infarction

MEETING CLINICO

Martedì 22 maggio 2012

dalle ore 14.15 alle ore 18.45

Aula Mons. Dal Col · Viale L. Spellanzon (nei pressi dell'Ospedale)

CONEGLIANO (TV)

Direttore del meeting: *Dr. Pietro Delise* · Segreteria scientifica: *Dr. Giuseppe Berton*

IL MEETING È RIVOLTO A MEDICI E INFERMIERI

Iscrizioni Online dal 28 Marzo 2012 (fino al raggiungimento di 70 partecipanti)
Sito Web: www.ulss7.it · Sezione Convegni e Corsi di Formazione

Assistenza organizzativa e informazioni sul meeting: *sig.ra Bernardetta Dal Cin · Dr. Mauro Toaldo*
Telefono 0438.663613 · email: segreteria.cardiologia@ulss7.it

Accreditamento ECM richiesto

Progetto Regionale Neoplasie, ABC* - 4 STUDY

AZIENDA SANITARIA ULSS BASSANO DEL GRAPPA – REGIONE VENETO

REGIONE DEL VENETO
U.L.S.S. 3 BASSANO DEL GRAPPA
ABC STUDY ON HEART DISEASE ASSOCIATION

LA SOPRAVVIVENZA DOPO INFARTO MIOCARDICO NELLA DONNA E NELL'UOMO

ABC STUDY ON HEART DISEASE – A VENETO REGION PROJECT

MEETING CLINICO – MERCOLEDI' 25 NOVEMBRE 2015 – DALLE ORE 14.00 ALLE ORE 19.00

SALA CONVEGNI DEL P.O. DI RETE BASSANO – BASSANO DEL GRAPPA (VI)

RESPONSABILE DEL PROGETTO REGIONALE "THE ABC STUDY ON HEART DISEASE": DR. GIUSEPPE BERTON

SEGRETERIA SCIENTIFICA: DR.SSA FIORELLA CAVUTO

Il meeting è rivolto a Medici, Infermieri, Personale Sanitario, Studenti
ISCRIZIONE GRATUITA - ACCREDITATO CON 6 CREDITI ECM
Segreteria Organizzativa: Dr.ssa Sonia Ceccato – tel 0424/885381 – email: sonia.ceccato@aslbassano.it
website: www.abcheartdiseasestudy.org

In 1992, a little group of medical researchers and other participants embarked on an project to investigate new clinical factors for heart disease, studying patients with acute coronary syndrome and following them for many years. Today, the observations on the long-term survival after acute coronary syndrome are internationally acknowledged. Main results appears on the most important cardiovascular texts across the world. The study is called "the ABC heart disease study".

PROGRAMMA

Ore 14.00 Apertura del meeting e accoglienza/registrazione dei partecipanti
Ore 14.20 Saluto del Direttore Generale Dr. Fernando Antonio Compostella
Ore 14.30 Presentazione del Corso da parte del Direttore Sanitario Dr. Enzo Apolloni

Sessione 1

Moderatori: Dr.ssa Rosa Falmieri, Dr. Enzo Apolloni
Ore 14.40 La sopravvivenza dopo infarto miocardico (risultati ABC STUDY ON HEART DISEASE) e piccole note di analisi statistica della sopravvivenza
Dr. Giuseppe Berton
Ore 15.10 La sopravvivenza dopo infarto miocardico nella donna (risultati ABC STUDY ON HEART DISEASE)
Dr.ssa Fiorella Cavuto
Ore 15.30 Ruolo dell'ecocardiografo nella valutazione prognostica dopo sindrome coronarica acuta
Dr. Roberto Zappellini
Ore 16.00 Caso clinico e confronto con la platea
Dr. Giuseppe Berton
Ore 16.30 Coffe Break

Sessione 2

Moderatori: Dr.ssa Fiorella Cavuto, Dr. Enzo Apolloni
Ore 16.50 La rivascolarizzazione percutanea nella sindrome coronarica acuta: indicazioni attuali, limiti e prospettive
Dr. Angelo Bruno Ranzenigo
Ore 17.20 Marcatori di necrosi miocardica acuta e troponina ad alta sensibilità: importanza prognostica e differenze di genere
Dr. Giorgia De Alti
Ore 17.40 Come è nato il "progetto neoplasie"
Dr.ssa Fiorella Cavuto
Ore 18.00 Progetto regionale neoplasie – Presentazione sito web e Associazione ABC Study
Dr. Giuseppe Berton
Ore 18.30 Caso clinico e confronto con la platea
Dr. Giuseppe Berton
Ore 19.00 Compilazione questionari ECM, valutazione di gradimento e termine dell'incontro

Con il patrocinio di:

Si ringrazia per il sostegno:
BANCA DI ROMANO E S.CATERINA
Il coffee break del meeting è gentilmente offerto dal Ristorante "Al Pioppato"

Progetto Regionale Neoplasie, ABC* - 4 STUDY

CITTÀ DI CONEGLIANO

REGIONE DEL VENETO

REGIONE DEL VENETO - CITTA' DI CONEGLIANO
AVIS DI CONEGLIANO E MARENO DI PIAVE - U.L.S.S. 7PIEVE DI SOLIGO
ABC STUDY ON HEART DISEASE ASSOCIATION

LA SOPRAVVIVENZA DOPO MALATTIA DI CUORE NELLA DONNA E NELL'UOMO

ABC STUDY ON HEART DISEASE – A VENETO REGION PROJECT

INCONTRO CON LA CITTADINANZA ED OPERATORI SANITARI
GIOVEDI 26 NOVEMBRE 2015 ORE 20.30
AUDITORIUM DINA ORSI - PARE' - CONEGLIANO - TV
INFO: www.abcheartdiseasestudy.org

In 1992, a little group of medical researchers and other participants embarked on an project to investigate new clinical factors for heart disease, studying patients with acute coronary syndrome and following them for many years. Today, the observations on the long-term survival after acute coronary syndrome are internationally acknowledged. Main results appears on the most important cardiovascular tests across the world. The study is called "the ABC heart disease study".

PROGRAMMA

Ore 20.15 Accoglienza dei partecipanti
Ore 20.30 Saluto del Sindaco della Città Dr. Floriano Zambon

Presentazione della serata e moderatori:
Dott.ssa Fiorella Cavuto (Bassano del Grappa), Dott. Flaviano Giorgiano (Treviso) RN Rosanna Cedran (Conegliano)

La sopravvivenza dopo infarto miocardico (THE ABC STUDY ON HEART DISEASE, a Veneto Region Project)
Dr. Giuseppe Berton (Conegliano)

L'alimentazione nella malattia di cuore e nella prevenzione delle neoplasie
Dr. Filippo Brocadello (Padova)

Come è nato il "progetto neoplasie"
Dr.ssa Fiorella Cavuto (Bassano del Grappa)

Attività fisica e sport nella malattia cardiaca. Si può fare? È utile?
Dr. Patrizio Sarto (Treviso) Dr. Flaviano Giorgiano (Treviso)

Progetto regionale neoplasie – Presentazione sito web e Associazione ABC Study
Dr. Giuseppe Berton (Conegliano)

INFORMAZIONI ORGANIZZATIVE

RESPONSABILE DEL PROGETTO REGIONALE
"THE ABC STUDY ON HEART DISEASE":
Dr. Giuseppe Berton – U.O.C. di Cardiologia
Presidio Ospedaliero di Conegliano – ULSS 7
Tel. 0438.663.613 – e-mail giube.s@alice.it

Segreteria organizzativa:
Giancarlo Battistella - cellulare: 3396383290
e-mail: avismareno@virgilio.it

Progetto Regionale "Guadagnare Salute"
Bur n. 54 del 01/06/2015

Con il patrocinio di:

Si ringrazia per il sostegno:

Banca della Marca

AVIS

Progetto Regionale Neoplasie, ABC* - 4 STUDY

REGIONE DEL VENETO - COMUNE DI BASSANO DEL GRAPPA
U.L.S.S. 3 BASSNO DEL GRAPPA - ABC STUDY ON HEART DISEASE ASSOCIATION

LA MALATTIA DI CUORE NELLA DONNE E NELL'UOMO: SOPRAVVIVENZA E PREVENZIONE

ABC STUDY ON HEART DISEASE – A VENETO REGION PROJECT

INCONTRO CON LA CITTADINANZA ED OPERATORI SANITARI
VENERDI 20 MAGGIO 2016 ORE 20.30 - SALA CHILESOTTI - MUSEO CIVICO
Piazza Garibaldi, 34 - Bassano del Grappa (VI) - INFO: www.abcheartdiseasestudy.org

In 1990, a little group of medical researchers and other participants embarked on an project to investigate new clinical factors for heart disease, studying patients with acute coronary syndrome and following them for many years. Today, the observations on the long-term survival after acute coronary syndrome are internationally acknowledged. Main results appears on the most important cardiovascular texts across the world. The study is called "the ABC heart disease study".

PROGRAMMA

Ore 20.30 Saluto delle Autorità
Sindaco di Bassano del Grappa - Direttore Azienda ULSS 3

Presentazione della serata:
Dott.ssa Fiorella Cavuto (Bassano del Grappa) Dott. Giuseppe Berton (Conegliano)

La sopravvivenza dopo infarto miocardico (THE ABC STUDY ON HEART DISEASE - a Veneto Region Project)
Dr. Giuseppe Berton (Conegliano)

La sopravvivenza dopo infarto miocardico nella donna (THE ABC STUDY ON HEART DISEASE - a Veneto Region Project)
Dr.ssa Fiorella Cavuto (Bassano del Grappa)

Attività fisica e sport nella malattia cardiaca. Si può fare? E' utile?
Dr. Patrizio Sarto (Treviso)

La salute in tavola: migliorare la salute attraverso le scelte alimentari
Dr. ssa Chiara Vassalli (Bassano del Grappa)

Come è nato il "progetto neoplasie"
Dr.ssa Fiorella Cavuto (Bassano del Grappa)

Progetto regionale neoplasie – sito web e Associazione ABC Study
Dr. Giuseppe Berton (Conegliano)

A fine serata consegna del PREMIO "ABC STUDY ON HEART DISEASE" a persona che sia distinta per il sostegno al progetto dell'Associazione sullo Studio e Prevenzione della Malattia di Cuore.
Info: www.abcheartdiseasestudy.org

INFORMAZIONI ORGANIZZATIVE

RESPONSABILE DEL PROGETTO REGIONALE
"THE ABC STUDY ON HEART DISEASE":
Dr. Giuseppe Berton – U.O.C. di Cardiologia
Presidio Ospedaliero di Conegliano – ULSS 7
Tel. 0438.663.611 – e-mail globe.u@alice.it

SEGRETERIA ORGANIZZATIVA
(THE ABC STUDY ON HEART DISEASE ASSOCIATION):
Dr.ssa Fiorella Cavuto – Ambulatorio di Cardiologia – Distretto 1
ULSS 3 Bassano del Grappa - Tel. 0424 885348
email fiorella.cavuto@aslbassano.it - fiorellacavuto@me.com

Altre informazioni:
http://www.abcheartdiseasestudy.org/en/contact
Progetto Regionale "Guadagnare Salute"
Rer n. 34 del 03/05/2015

Con il patrocinio di:

Si ringrazia:

Progetto Regionale Neoplasie, ABC* - 4 STUDY

REGIONE DEL VENETO

ULSS 7, Ospedale di Conegliano
ABC Study on Heart Disease Association
website: www.abcheartdiseasestudy.org

Bridging the sciences
BIOSTATISTICS

L'ULSS 7incollaborazione con "The ABC Study on Heart Disease Association"
organizza:

CORSO DI STATISTICA MEDICADI BASE PERMEDICI ED OPERATORI SANITARI

COURSE OF BASIC MEDICAL STATISTICS FOR DOCTORS AND HEALTH PROFESSIONALS

Responsabile Scientifico del Corso Dr. Giuseppe Berton, MD, FESC

Obiettivo del corso:

1) fornire conoscenze biostatistiche di base, teoriche e pratiche, per la Medicina;
2) cenni di base dell'analisi della sopravvivenza (curve di Kaplan-Meier);
3) introduzione all'analisi e alla comprensione di un lavoro clinico-scientifico.

Destinatari: Medici, Operatori Sanitari e Studenti.

Per partecipare al corso non è richiesta conoscenza statistica di base.

Responsabile Scientifico del Corso:

Dott.GiuseppeBerton, Cardiologia Conegliano.
Revisore Scientifico dell'American Heart Association

Coordinamento del corso:

Dott.Giuseppe Berton
Dott.ssa Sabina Bolzan

Benvenuto ed introduzione al Corso:

Dott. Francesco Benazzi, Direttore Generale ULSS7 (ULSS Treviso)

Docenti:

Dott. Michelangelo Salemi - Direzione Medica - ULSS7
Dott.ssa Sabina Bolzan - Dipartimento di Prevenzione - ULSS 7
Dott. GiuseppeBerton - Cardiologia - ULSS7

Date e sede del corso:

mercoledì 6, mercoledì13, giovedì28 aprile 2016,
ore 9.15-13.15
presso sala 1 – Ospedale di Conegliano (TV)-31015 – via Brigata Bisagno
Il corso è interattivo, si svolge in tre mattine di 4 ore ciascuna (totale 12 ore).

Il corso è accreditato con 14 ECM.

Programma

6aprile 2016 ore 9.15-13.15

-accoglimento delle persone partecipanti 10min
-benvenuto 10min
-prognosis in the patient with heart disease: "that's the question!"
(WilliamShakespeare&GiuseppeBerton...una sera, mentre riflettevano insieme!) 20min
-indicatori di performance in Medicina 20min
-introduzione alla Statistica Medica, uso di un foglio elettronico per raccolta dati clinici e scientifici 40min
-coffe break 20min
-descrizione dei dati, la distribuzione normale, indici di distribuzione dei dati 40min
-conoscere ed usare il t di Student per dati appaiati e non appaiati, 40min
-come leggere un lavoro scientifico pubblicato: introduzione 40min

13aprile 2016 ore 9.15-13.15

-prevalenza, incidenza, tassi di eventi 50min
-conoscere ed usare il X^2 di Pearson, 40
-valutazione di sensibilità, specificità, accuratezza di un test diagnostico, 50
-coffe break 20min
-introduzione all'analisi della sopravvivenza: curve di sopravvivenza di Kaplan-Meier 40
-come leggere un lavoro scientifico pubblicato: metodo 40

28aprile 2016 ore 9.15-13.15

-numerosità campionaria, potenza di un test 50
-t di Student per dati appaiati e non appaiati, X^2 di Pearson(ripasso e pratica) 40
-indicatori di performance in Medicina, considerazioni cliniche 40
-coffe break 20min
-come leggere un lavoro scientifico pubblicato: risultati 40
Discussione 20
Test di valutazione (prova pratica su un calcolo di sensibilità, t student e X^2 di Pearson) 30
Conclusione del corso

Iscrizioni:
Il corso è a numero chiuso; per favorire l'interattività, sono ammessi un massimo di 15 partecipanti, in base
all'ordine di arrivo delle domande.

Preiscrizioni sul sito ULSS 7 – sezione corsi e convegni a partire dal 19/02/2016.
https://www.ulss7.it/web/guest/corsi-convegni
Le conferme di partecipazione verranno inviate via mail
E' preferibile, non obbligatorio, avere durante il corso un proprio computer portatile (nel corso si userà il software STATA 13)

Le pre-iscrizioni in essere saranno considerate per eventuali ulteriori edizioni.

La quota di iscrizione è di euro 100,00 + iva (22% se dovuta). La quota è gratuita per i dipendenti convenzionati dell'Azienda Ulss 7 e Abc Study.

Segreteria organizzativa:
U.o.c. Pianificazione, qualità, etica e formazione
Sezione Formazione
Via Lubin, 16 – 31053 Pieve di Soligo (TV)
Tel. 0438/664337-4508 Fax 0438/664514
Mail: qualita.formazione@ulss7.it

Ulteriori info: http://www.abcheartdiseasestudy.org/en/contact

CORSO DI STATISTICA MEDICADI BASE

L'ULSS 7 della Regione Veneto in collaborazione con "The ABC Study on Heart Disease Association"

organizza: **CORSO DI STATISTICA MEDICA DI BASE PER MEDICI ED OPERATORI SANITARI**

Per seguire il presente corso non sono richieste specifiche conoscenze di statistica iniziali.

L'ABC Study Association ha programmato altre 3 edizioni del corso, per soddisfare le richieste di iscrizione:

1a ed: 6-13-28 aprile 2016: posti esauriti

2a ed: 5-12-19 ottobre 2016: posti esauriti

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Capitolo 6

Riferimenti bibliografici

Predictors of Ten-Year Event-Free Survival in Patients With Acute Myocardial Infarction (from the Adria, Bassano, Conegliano, and Padova Hospitals [ABC] Study on Myocardial Infarction)

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The long-term event-free survival (EFS) after acute myocardial infarction (AMI) is largely uninvestigated. We analyzed noninvasive clinical variables in association with long-term EFS after AMI. The present prospective study included 504 consecutive patients with AMI at 3 hospitals from 1995 to 1998 (Adria, Bassano, Conegliano, and Padova Hospitals [ABC] study). Thirty-seven variables were examined, including demographics, cardiovascular risk factors, in-hospital characteristics, and blood components. The end point was 10-year EFS. Logistic and Cox regression models were used to identify the predictive factors. We compared 3 predictive models according to the goodness of fit and C-statistic analyses. At enrollment, the median age was 67 years (interquartile range 58 to 75), 29% were women, 38% had Killip class >1, and the median left ventricular ejection fraction was 51% (interquartile range 43% to 60%). The 10-year EFS rate was 19%. Both logistic and Cox analyses identified independent predictors, including young age (hazard ratio 1.2, 95% confidence interval 1.1 to 1.3, p = 0.0006), no history of angina (hazard ratio 1.4, 95% confidence interval 1.1 to 1.8, p = 0.009), no previous myocardial infarction (hazard ratio 1.4, 95% confidence interval 1.1 to 1.7, p = 0.01), high estimated glomerular filtration rate (hazard ratio 0.8, 95% confidence interval 0.7 to 0.9, p = 0.001), low albumin/creatinine excretion ratio (hazard ratio 1.2, 95% confidence interval 1.1 to 1.3, p <0.0001), and high left ventricular ejection fraction (hazard ratio 0.8, 95% confidence interval 0.7 to 0.9, p = 0.006). These variables had greater predictive power and improved the predictive power of 2 other models, including Framingham cardiovascular risk factors and the recognized predictors of acute heart damage. In conclusion, 10-year EFS was strongly associated with 4 factors (ABC model) typically neglected in studies of AMI survival, including estimated glomerular filtration rate, albumin/creatinine excretion ratio, a history of angina, and previous myocardial infarction. This model had greater predictive power and improved the power of 2 other models using traditional cardiovascular risk factors and indicators of heart damage during AMI. **(Am J Cardiol 2012;109:966–975)**

Fatal and nonfatal adverse events are common in the short and long term after acute myocardial infarction (AMI). It is currently considered that much of the increased cardiovascular (CV) risk remains unexplained.[1–5] To improve the development of new therapies, we require a better understanding of the natural history of coronary artery disease.[1] Many studies have investigated the prognosis after AMI, but few have focused on the factors associated with event-free survival (EFS), particularly in the long term.[6–8] Furthermore, EFS can be considered the clinical equivalent to no progression of coronary artery disease.[2] The aim of the present study was to investigate and compare how the major CV risk factors and a number of noninvasive clinical variables are associated with EFS in a 10-year follow-up study after AMI.

Methods

The Adria, Bassano, Conegliano, and Padova Hospital Study (ABC Study) is an ongoing, prospective investigation designed to reflect, as closely as possible, an unbiased population of patients with AMI. It included 567 consecutive, white patients admitted with definite AMI to the intensive care units of the Adria, Bassano, and Conegliano Hospitals (in northeast Italy) from June 21, 1995 to January 19, 1998. The original aim of the ABC study was to follow the natural long-term history of a sample of unselected patients with AMI and to evaluate the prognostic value of a number of baseline clinical variables. The criteria used for AMI diagnosis have been previously reported.[9] The patients were excluded when they displayed chronic renal failure, defined as a documented history of an estimated glomerular

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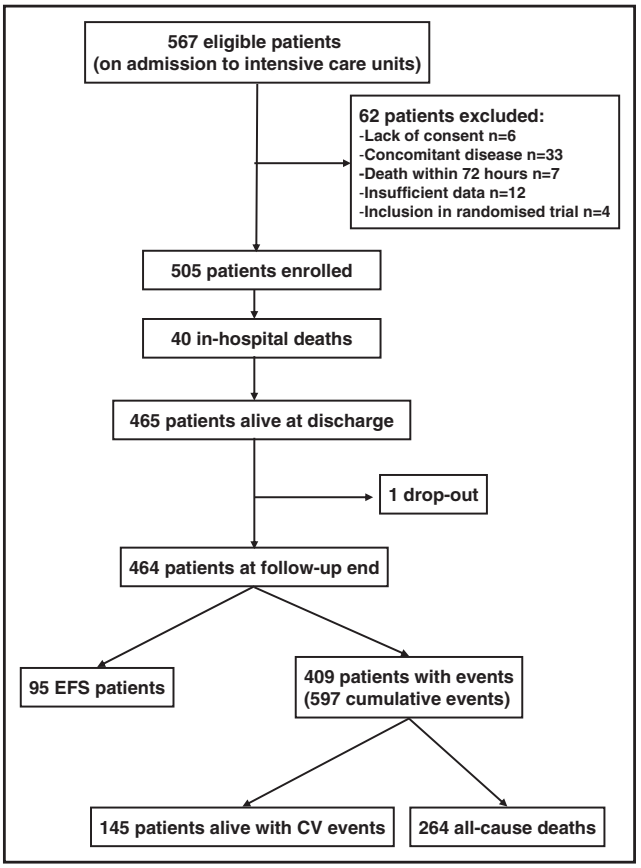

Figure 1. Flow diagram of subject progress during follow-up.

filtration rate (eGFR) <1.0 mL/s/1.73 m^2 (conventional units <60 mL/min/1.73 m^2) for 3 months, with or without kidney damage (n = 3). They were also excluded for nephrotic proteinuria (n = 2), dialysis treatment (n = 1), concomitant acute infection (n = 15), myocardial reinfarction within 3 days of admission (n = 3), surgical treatment of bone fractures (n = 2), recent surgery (n = 2), menstrual flow (n = 1), neoplastic disease (n = 4), death within 3 days of admission (n = 7), or insufficient data (n = 12). These conditions could potentially affect the variables investigated in the present study. Ten additional patients were excluded because of a lack of consent or because they were involved in a randomized treatment trial. Thus, the follow-up included 505 patients (Figure 1). All enrolled patients provided written informed consent, and the hospital ethics committees approved the study.

At enrollment, we collected a thorough patient history from the medical records and patient interviews. Unless otherwise indicated, all baseline clinical and laboratory data reported in the present study were obtained during the first 3 days of hospitalization in the intensive coronary care unit. On admission and every 4 hours thereafter, the serum enzyme levels and 12-lead electrocardiograms were obtained. Venous blood was drawn for biochemical determinations. The blood pressure and heart rate were measured between 7 and 8 A.M., and the mean of 3 recordings was used in the analyses. The presence and degree of heart failure, assessed according to the Killip classification, the presence of atrial fibrillation/flutter, ventricular tachy- and bradyarrhythmias were recorded during the first week after enrollment. The left ventricular ejection fraction (LVEF) was assessed using 2-dimensional echocardiography according to Simpson's method.[10] The LVEF was missing for 103 patients who underwent echocardiography after discharge from the intensive care unit or had technically inadequate echocardiographic images. The records were examined by 2 physicians with no knowledge of patient clinical data. The eGFR at baseline was calculated using the modified Modification of Diet in Renal Disease equation.[11] Albumin excretion was measured with 24-hour urine collection samples by radioimmunoassay and expressed as the albumin/creatinine ratio.[12] Standard urinalysis was performed at urinary sample collection.

At 1, 3, 5, 7, and 10 years after recruitment, each patient was telephoned for a clinical checkup. The prespecified primary end point of the present study was 10 years free from death and major coronary events or stroke. An event was defined as any of the following: death from any cause, nonfatal reinfarction or stroke, angina at rest with electrocardiographic changes and/or congestive heart failure requiring hospitalization, revascularization (coronary artery bypass grafting or nonprimary percutaneous coronary angioplasty), and heart transplantation. When revascularization procedures occurred during AMI or unstable angina, it was recorded as a single event (e.g., AMI treated with primary percutaneous coronary angioplasty was recorded as AMI). The absence of any of these features was considered EFS. The 2 prespecified secondary end points were EFS after discharge (i.e., excluding in-hospital mortality) and a subanalysis of only CV events (i.e., excluding non-CV death, when it was the first event). All data regarding the events were obtained from the scheduled checkup records, public administration and hospital records, family doctors, and death certificates. In keeping with the procedure used in the Global Registry of Acute Coronary Events (GRACE) study, events occurring before enrollment were entered into the Cox regression models as explanatory variables.[6] The reports were also obtained regarding changes in the major CV risk factors (i.e., smoking, hypertension, hypercholesterolemia, diabetes mellitus, and physical activity) and medications during follow-up. The prehospital time delay was defined as the interval from the onset of symptoms to arrival at the coronary care unit. Hypertension was defined as a documented history of hypertension by administration of antihypertensive therapy or a doctor's report of blood pressure ≥140/90 mm Hg. Hypercholesterolemia was defined as having a total cholesterol level of ≥6.2 mmol/L and/or treatment with lipid-lowering medication. Physical activity was considered ≥3 sessions of isotonic activities weekly that lasted ≥40 minutes.

The measured variables were analyzed as both continuous and quartiles of increasing value. Log transformations were used to correct for positive-skewed distributions, as appropriate. The unpaired Student *t* test and the Pearson chi-square test was used for the measured and categorical variables, respectively. Both logistic and Cox proportional hazard regression models were used to describe the influence of variables on EFS during follow-up.[13] Logistic regression analyses were fit to the presence/absence of events. Cox regression models were fit to the intervals elapsed

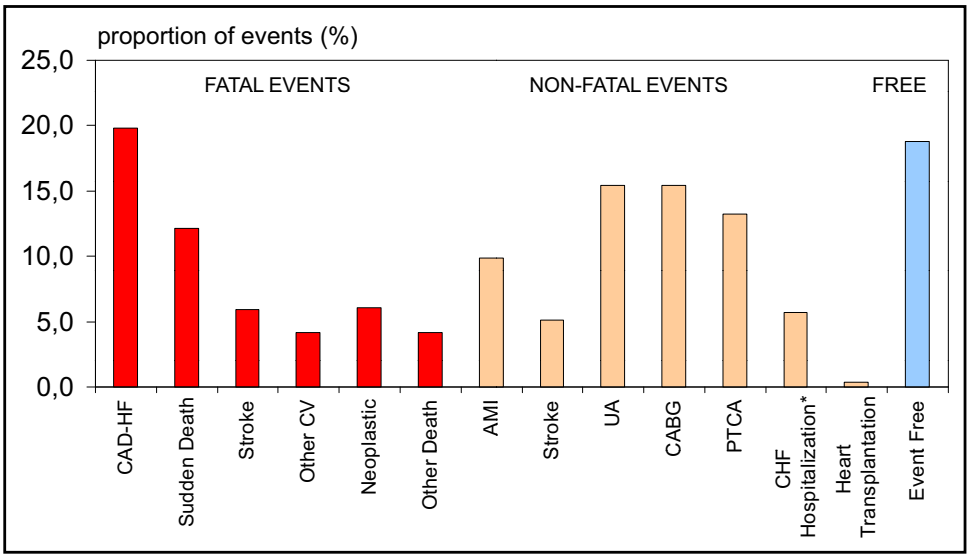

Figure 2. Adverse events occurred in 504 patients during 10 years of follow-up after AMI. *In absence of other CV events. ACR = albumin/creatinine ratio; AMI = acute myocardial infarction; CABG = coronary artery bypass grafting; CAD-HF = coronary artery disease–heart failure; CHF = congestive heart failure; PTCA = percutaneous transluminal coronary angioplasty; UA = unstable angina.

before an event. Scaled Schoenfeld residuals were used to test the proportionality assumption. The proportional hazards assumption of the Cox model was violated for several variables ($p < 0.05$) because of early events. The typical effect of this violation was that statistical comparisons were more conservative, and the 95% confidence limits were wider for the hazard ratios.[14] After censoring in-hospital mortality cases, the proportional hazards assumption was verified for all variables ($p > 0.30$). The variables were first tested at the univariate level and after age and gender adjustment. All multivariate analyses used logistic and Cox regression models with backward elimination. To avoid exclusion of potentially significant predictors, once the final model was obtained, each of the excluded variables was retested in the model.[15] Estimated coefficients and standard errors are reported for both logistic and Cox regression models. The risk estimate was quantified as the odds ratio for logistic regression analysis and as the hazard ratio for the Cox regression analyses, with 95% confidence intervals. The interval ranged from the first day of hospital admission to the first nonfatal or fatal event or to the censored time.

Only variables that were significant on both logistic and Cox multivariate analyses were included in the ABC model. The ABC model's predictive power was compared with 2 other prespecified models: (1) Framingham CV risk factors (i.e., current smoking, physical activity, hypertension, hypercholesterolemia, and diabetes mellitus), termed the "CV risk factor model"; and (2) well-recognized clinical variables associated with acute heart damage (i.e., prehospital time delay, creatine kinase-MB peak, Killip class, Q-/non–Q-wave AMI, and atrial fibrillation), termed the "acute-heart model." The improvement in predictive power was tested with the goodness-of-fit test according to the likelihood ratio chi-square analysis.[16] Model discrimination was measured using the area under the receiver operating characteristic curve, also called the C-statistic.[16] The Hosmer-Lemeshow test was used to measure model calibration.[17]

The baseline characteristics were summarized as the median and interquartile range for the continuous variables and numbers and percentages for categorical variables. The variables were tested for collinearity before evaluation in the regression models. When 2 variables (e.g., creatine kinase peak and creatine kinase-MB peak) were highly correlated ($r \geq 0.7$), we eliminated the less significant variable or the variable believed to be less clinically important.[15] To detect whether an association between a variable and outcome produced a J or U shape, all variables were checked for conformity to increasing (or decreasing) gradients. The variables significantly associated with the outcomes in the multivariate models were tested for interactions. Unless otherwise indicated, 2-tailed p values < 0.05 were deemed significant. Statistical analyses were performed using SYSTAT, version 13 (Systat Software, Chicago, Illinois) and JMP, version 4.0, for Windows 2000 (SAS Institute, Cary, North Carolina).

Results

During follow-up, 1 patient withdrew consent, and the data were censored at that time. Thus, 504 patients had 10-year follow-up data or had died and that data were used in the logistic and Cox analyses. This represented a total of 3,271.3 person-years of follow-up. At the end of the follow-up period, 409 patients had had 1 to 5 events, for a total of 597 cumulative events. Of the 504 patients, 95 had achieved EFS (Figure 1). The event rate was 18.25 events/year of follow-up for each 100 patients. The median interval to the first event was 22.5 months (interquartile range 4.0 to 94.0). Figure 2 lists the main causes of events. The differences between the patients with and without events after AMI are listed in Table 1.

At the univariate level, young age was strongly associated, and gender was not associated, with EFS (Table 2). Of the 37 baseline variables tested, 17 were associated with

Table 1
Baseline characteristics

Variable	Overall Population (n = 504)	Patients Free of Events (n = 95)	Patients With events (n = 409)	p Value
Age (years)	67 (58–75)	59 (53–66)	70 (62–77)	<0.0001
Women	29%	20%	31%	0.04
Education (high school or more)	25%	30%	24%	0.18
Current smoker	38%	55%	34%	<0.0001
Physical activity	6%	8%	5%	0.25
Hypertension	47%	33%	50%	0.002
Hypercholesterolemia	24%	24%	24%	0.96
Diabetes mellitus	24%	13%	27%	0.004
Body mass index (kg/m^2)	26 (24–28)	26 (24–28)	26 (24–28)	0.98
Alcohol use	74%	76%	74%	0.66
Coffee use	87%	93%	86%	0.07
Family coronary heart disease	24%	23%	24%	0.79
Angina pectoris	20%	6%	23%	<0.0001
Previous myocardial infarction	21%	7%	25%	<0.0001
In-hospital characteristics				
Prehospital time delay (min)*	185 (120–535)	175 (125–292)	235 (115–590)	0.002
Systolic blood pressure (mm Hg)	119 (107–130)	116 (105–128)	122 (112–132)	0.08
Diastolic blood pressure (mm Hg)	76 (69–82)	74 (68–79)	77 (71–82)	0.43
Heart rate (beats/min)	70 (63–80)	68 (61–75)	71 (64–82)	0.001
Anterior myocardial infarction	33%	37%	32%	0.39
Q-wave myocardial infarction	74%	84%	72%	0.01
Creatine kinase peak (U/L)*	1,077 (587–1,959)	1,286 (694–2,296)	1,067 (554–1,866)	0.03
Creatine kinase-MB peak (U/L)*	126 (69–236)	162 (75–274)	118 (66–229)	0.13
Killip class >1[†]	38%	19%	43%	<0.0001
Tachyarrhythmias[†‡]	24%	24%	23%	0.87
Bradyarrhythmias[†‡]	8%	7%	9%	0.70
Atrial fibrillation/flutter[†]	13%	3%	15%	0.002
Left ventricular ejection fraction (%) (n = 401)	51 (43–60)	58 (50–64)	50 (42–60)	<0.0001
Blood components				
Hemoglobin (g/L)	137 (126–147)	139 (132–148)	136 (125–147)	0.98
Blood glucose (mmol/L)	6.9 (5.8–9.5)	6.6 (5.7–8.4)	7.0 (5.8–9.9)	0.02
Total cholesterol (mmol/L)	5.4 (4.6–6.2)	5.4 (4.7–6.2)	5.3 (4.5–6.3)	0.15
High-density lipoprotein cholesterol (mmol/L)	1.1 (0.9–1.3)	1.1 (0.9–1.3)	1.1 (0.9–1.3)	0.47
Triglycerides (mmol/L)	1.4 (1.0–2.0)	1.4 (1.1–2.0)	1.4 (1.0–2.0)	0.85
Potassium (mmol/L)	4.1 (3.8–4.4)	4.1 (3.8–4.4)	4.1 (3.8–4.4)	0.11
Uric acid (μmol/L)	339 (273–404)	309 (243–374)	339 (279–410)	0.13
Kidney and endothelial function				
Plasma creatinine (μmol/L)	88 (80–106)	80 (71–88)	88 (80–106)	<0.0001
Estimated glomerular filtration rate (mL/s $\times$1.73 m^2)*	1.2 (0.9–1.4)	1.3 (1.2–1.6)	1.1 (0.9–1.4)	<0.0001
Albumin/creatinine excretion ratio (mg/mmol)*	0.8 (0.3–2.6)	0.3 (0.2–0.9)	1.0 (0.4–3.6)	<0.0001
In-hospital and follow-up medications				
Thrombolysis	40%	57%	36%	<0.0001
Adrenergic agent	10%	2%	11%	0.005
β-Receptor blocker	43%	59%	40%	<0.0001
Calcium channel blocker	44%	49%	43%	0.32
Nitrate	76%	69%	78%	0.06
Angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker	64%	57%	65%	0.14
Diuretics	51%	31%	55%	<0.0001
Antiplatelets	82%	95%	80%	<0.0001
Anticoagulants	17%	6%	19%	0.002
Digitalis	22%	5%	26%	<0.0001
Antiarrhythmics	13%	9%	14%	0.23
Lipid-lowering drug	34%	45%	31%	0.01
Cardiovascular risk factor modification during follow-up				
Current smoker	12%	9%	24%	<0.0001
Physical activity	23%	43%	18%	<0.0001
Hypertension	58%	49%	60%	0.07
Hypercholesterolemia	40%	52%	37%	0.01
Diabetes mellitus	29%	18%	31%	0.008

Data are presented as median (interquartile range) or percentages.
* p Values were calculated using Log-transformed data.
[†] During first 7 days of hospital stay.
[‡] Tachyarrhythmia and bradyarrhythmia, excluding perithrombolytic period.

Table 2
Univariate age- and gender-adjusted logistic and Cox regression for patients free from events versus patients with events

Variable	Univariate Logistic Regression			Age- and Gender-Adjusted Logistic Regression			Age- and Gender-Adjusted Cox Regression		
	$\beta \pm$ SE	OR (95% CI)	p Value	$\beta \pm$ SE	OR (95% CI)	p Value	$\beta \pm$ SE	HR (95% CI)	p Value
Young age	0.83 ± 0.12	2.3 (1.8–2.9)	<0.0001	—			0.35 ± 0.05	1.4 (1.3–1.5)	<0.0001*
Male gender	0.51 ± 0.27	1.7 (1.1–2.8)	0.06	−0.23 ± 0.31	0.8 (0.4–1.4)	0.45†	0.07 ± 0.11	1.1 (0.8–1.3)	0.55†
Low school education	−0.38 ± 0.25	0.7 (0.4–1.1)	0.13	0.06 ± 0.23	1.1 (0.6–1.8)	0.82	0.01 ± 0.12	1.0 (0.8–1.3)	0.92
No/current smoking	−0.86 ± 0.23	0.4 (0.3–0.7)	<0.0001	−0.24 ± 0.26	0.8 (0.5–1.3)	0.34	−0.17 ± 0.11	0.8 (0.7–1.0)	0.13
No hypercholesterolemia	−0.11 ± 0.25	0.9 (0.5–1.5)	0.66	0.22 ± 0.29	1.2 (0.7–2.2)	0.44	0.12 ± 0.12	1.1 (0.9–1.4)	0.30
Low body mass index	0.01 ± 0.10	1.0 (0.8–1.2)	0.91	0.18 ± 0.11	1.2 (0.9–1.5)	0.10	0.05 ± 0.05	1.0 (0.9–1.1)	0.28
No hypertension	0.68 ± 0.24	2.0 (1.2–3.2)	0.004	0.45 ± 0.26	1.6 (0.9–2.6)	0.08	0.15 ± 0.10	1.2 (0.9–1.4)	0.14
No diabetes mellitus	0.94 ± 0.33	2.5 (1.3–4.9)	0.004	0.70 ± 0.34	2.0 (0.9–4.0)	0.04	0.40 ± 0.11	1.5 (1.2–1.9)	0.0006
No physical activity	−0.47 ± 0.43	0.6 (0.3–1.4)	0.27	−0.05 ± 0.46	0.9 (0.4–2.3)	0.91	−0.07 ± 0.22	0.9 (0.6–1.4)	0.73
No alcohol use	−0.13 ± 0.26	0.9 (0.5–1.5)	0.61	−0.32 ± 0.29	0.7 (0.4–1.3)	0.28	0.04 ± 0.12	1.0 (0.8–1.3)	0.72
No coffee use	−0.74 ± 0.42	0.5 (0.2–1.1)	0.07	−0.35 ± 0.44	0.7 (0.3–1.7)	0.42	−0.15 ± 0.15	0.9 (0.6–1.2)	0.32
No family coronary heart disease	0.02 ± 0.27	1.0 (0.6–1.7)	0.95	0.30 ± 0.28	1.4 (0.8–2.4)	0.28	0.11 ± 0.12	1.1 (0.9–1.4)	0.33
No angina (before enrollment)	1.52 ± 0.44	4.5 (1.9–10.7)	0.001	1.21 ± 0.45	3.3 (1.4–8.1)	0.007	0.40 ± 0.12	1.5 (1.2–1.9)	0.001
No myocardial infarction (before enrollment)	1.43 ± 0.41	4.2 (1.9–9.3)	<0.0001	1.35 ± 0.42	3.8 (1.7–8.8)	0.002	0.41 ± 0.12	1.5 (1.2–1.9)	0.0007
Short prehospital time delay	0.27 ± 0.10	1.3 (1.1–1.6)	0.01	0.11 ± 0.11	1.1 (0.9–1.4)	0.32	0.05 ± 0.04	1.0 (0.9–1.1)	0.25
Low systolic blood pressure	0.18 ± 0.10	1.2 (1.0–1.5)	0.07	0.02 ± 0.11	1.0 (0.8–1.3)	0.87	−0.01 ± 0.05	0.9 (0.8–1.1)	0.76
Low diastolic blood pressure	0.02 ± 0.10	1.0 (0.8–1.2)	0.85	−0.06 ± 0.11	0.9 (0.8–1.2)	0.58	−0.04 ± 0.04	0.9 (0.8–1.0)	0.34
Low heart rate	0.24 ± 0.10	1.3 (1.0–1.6)	0.01	0.15 ± 0.11	1.2 (0.9–1.4)	0.16	0.10 ± 0.05	1.2 (1.1–1.3)	0.03
Nonanterior myocardial infarction	−0.24 ± 0.24	0.8 (0.5–1.2)	0.31	−0.21 ± 0.25	0.8 (0.5–1.3)	0.40	−0.03 ± 0.11	0.9 (0.8–1.2)	0.78
Non–Q-wave myocardial infarction	−0.74 ± 0.30	0.5 (0.3–0.9)	0.01	−0.55 ± 0.32	0.6 (0.3–1.1)	0.08	−0.16 ± 0.11	0.8 (0.7–1.1)	0.15
Low creatine kinase peak	−0.18 ± 0.10	0.8 (0.7–1.0)	0.07	−0.13 ± 0.11	0.9 (0.7–1.1)	0.22	−0.01 ± 0.05	0.9 (0.8–1.1)	0.78
Low creatine kinase-MB peak	−0.18 ± 0.10	0.8 (0.7–1.0)	0.08	−0.13 ± 0.11	0.9 (0.7–1.1)	0.23	−0.01 ± 0.04	0.9 (0.8–1.1)	0.96
Low Killip class	0.99 ± 0.24	2.7 (1.7–4.3)	<0.0001	0.60 ± 0.25	1.8 (1.1–3.0)	0.01	0.41 ± 0.08	1.5 (1.3–1.8)	<0.0001
No tachyarrhythmias	−0.02 ± 0.27	1.0 (0.6–1.6)	0.92	−0.20 ± 0.28	0.8 (0.5–1.4)	0.46	−0.05 ± 0.12	0.9 (0.7–1.2)	0.64
No bradyarrhythmias	0.18 ± 0.43	1.2 (0.5–2.8)	0.68	0.16 ± 0.45	1.2 (0.5–2.8)	0.72	0.31 ± 0.18	1.4 (0.9–1.9)	0.09
No atrial fibrillation/flutter	1.70 ± 0.60	5.4 (1.7–17.8)	0.005	1.30 ± 0.62	3.6 (1.1–12.3)	0.03	0.34 ± 0.14	1.4 (1.1–1.8)	0.01
Low left ventricular ejection fraction	−0.46 ± 0.12	0.6 (0.5–0.8)	<0.0001	−0.38 ± 0.13	0.7 (0.5–0.9)	0.002	−0.21 ± 0.05	0.8 (0.7–0.9)	<0.0001
Low hemoglobin	−0.18 ± 0.10	0.8 (0.7–1.0)	0.08	−0.05 ± 0.12	0.9 (0.8–1.2)	0.68	−0.04 ± 0.05	1.0 (0.9–1.0)	0.35
Low blood glucose	0.25 ± 0.10	1.3 (1.1–1.6)	0.01	0.19 ± 0.11	1.2 (1.0–1.5)	0.09	0.12 ± 0.04	1.1 (1.0–1.2)	0.005
Low total cholesterol	−0.06 ± 0.10	0.9 (0.8–1.1)	0.53	0.05 ± 0.11	1.1 (0.8–1.3)	0.62	0.02 ± 0.05	1.0 (0.9–1.1)	0.70
Low high-density lipoprotein cholesterol	−0.02 ± 0.10	1.0 (0.8–1.2)	0.87	−0.07 ± 0.11	0.9 (0.7–1.1)	0.48	−0.06 ± 0.04	0.9 (0.9–1.0)	0.19
Low triglycerides	−0.05 ± 0.10	0.9 (0.8–1.2)	0.61	0.13 ± 0.11	1.1 (0.9–1.4)	0.23	0.10 ± 0.05	1.2 (1.1–1.3)	0.03
Low potassium	0.07 ± 0.10	1.1 (0.9–1.3)	0.51	−0.02 ± 0.11	0.9 (0.8–1.2)	0.82	0.02 ± 0.04	1.0 (0.9–1.1)	0.59
Low uric acid	0.21 ± 0.10	1.2 (1.1–1.5)	0.03	0.15 ± 0.11	1.2 (0.9–1.4)	0.18	0.15 ± 0.04	1.2 (1.1–1.3)	0.001
Low estimated glomerular filtration rate	−0.64 ± 0.11	0.5 (0.4–0.7)	<0.0001	−0.40 ± 0.13	0.7 (0.5–0.9)	0.002	−0.19 ± 0.05	0.8 (0.7–0.9)	0.0002
Low albumin/creatinine excretion ratio	0.54 ± 0.11	1.7 (1.4–2.1)	<0.0001	0.35 ± 0.12	1.4 (1.1–1.8)	0.004	0.25 ± 0.05	1.3 (1.2–1.4)	<0.0001
Variable modification during follow-up									
No current smoking	−0.71 ± 0.23	0.5 (0.3–0.8)	0.002	−0.18 ± 0.26	0.8 (0.5–1.4)	0.48	−0.17 ± 0.11	0.8 (0.7–1.0)	0.12
No hypercholesterolemia	−0.54 ± 0.23	0.6 (0.4–0.9)	0.01	−0.11 ± 0.25	0.9 (0.5–1.5)	0.65	0.03 ± 0.11	1.0 (0.8–1.3)	0.77
No hypertension	0.46 ± 0.23	1.6 (1.1–2.5)	0.04	0.20 ± 0.25	1.0 (0.7–2.0)	0.81	0.01 ± 0.10	1.0 (0.8–1.2)	0.93
No diabetes mellitus	0.75 ± 0.29	2.1 (1.2–3.7)	0.009	0.66 ± 0.30	1.9 (1.1–3.5)	0.02	0.33 ± 0.11	1.4 (1.1–1.7)	0.002
No physical activity	−1.09 ± 0.24	0.3 (0.2–0.5)	<0.0001	−0.46 ± 0.27	0.6 (0.4–1.1)	0.08	−0.21 ± 0.13	0.8 (0.6–1.0)	0.10

* Unadjusted.
† Age adjusted.
CI = confidence interval; HR = hazard ratio; OR = odds ratio.

Table 3
Multivariate logistic and Cox regression models for patients free from events versus patients with events

Variable	$\beta \pm$ SE	OR (95% CI)	p Value	$\beta \pm$ SE	HR (95% CI)	p Value
Model 1	All patients (n = 504)					
Age	0.57 ± 0.14	1.8 (1.4–2.4)	<0.0001	0.19 ± 0.05	1.2 (1.1–1.3)	0.0006
Women	−0.37 ± 0.33	0.7 (0.4–1.3)	0.25	0.09 ± 0.12	1.1 (0.8–1.4)	0.47
Angina pectoris	0.98 ± 0.48	2.6 (1.1–6.8)	0.03	0.35 ± 0.13	1.4 (1.1–1.8)	0.009
Estimated glomerular filtration rate	−0.35 ± 0.13	0.7 (0.5–0.9)	0.009	−0.16 ± 0.05	0.8 (0.7–0.9)	0.001
Albumin/creatinine ratio	0.36 ± 0.13	1.4 (1.1–1.8)	0.005	0.20 ± 0.05	1.2 (1.1–1.3)	<0.0001
Previous myocardial infarction	0.99 ± 0.45	2.7 (1.1–6.5)	0.02	0.31 ± 0.12	1.4 (1.1–1.7)	0.01
Highest Killip class				0.25 ± 0.09	1.3 (1.1–1.5)	0.004
Diabetes mellitus				0.24 ± 0.12	1.3 (1.1–1.6)	0.04
Model 2	Patients with LVEF (n = 401)					
Age	0.53 ± 0.16	1.7 (1.2–2.3)	0.001	0.21 ± 0.06	1.2 (1.1–1.4)	0.001
Women	−0.55 ± 0.35	0.6 (0.3–1.1)	0.11	−0.11 ± 0.13	0.9 (0.7–1.2)	0.38
Estimated glomerular filtration rate	−0.36 ± 0.15	0.7 (0.5–0.9)	0.01	−0.16 ± 0.06	0.8 (0.7–0.9)	0.004
Albumin/creatinine ratio	0.37 ± 0.14	1.4 (1.1–1.9)	0.01	0.21 ± 0.06	1.2 (1.1–1.4)	0.0002
Angina pectoris	1.18 ± 0.51	3.3 (1.2–8.8)	0.02			
Left ventricular ejection fraction	−0.29 ± 0.13	0.7 (0.6–0.9)	0.03	−0.14 ± 0.05	0.8 (0.7–0.9)	0.006
Interactions						
Age*albumin/creatinine ratio	0.33 ± 0.12	1.4 (1.1–1.8)	0.009	0.11 ± 0.04	1.2 (1.1–1.3)	0.008
Age*left ventricular ejection fraction	−0.29 ± 0.14	0.7 (0.6–0.9)	0.03			
Killip class*estimated glomerular filtration rate	−0.69 ± 0.28	0.5 (0.3–0.9)	0.01			
Killip class*albumin/creatinine ratio				0.17 ± 0.07	1.2 (1.1–1.4)	0.02
Diabetes mellitus*angina pectoris				0.54 ± 0.26	1.7 (1.1–2.9)	0.03
Model 3	Patients alive at hospital discharge (n = 464)					
Age	0.54 ± 0.14	1.7 (1.3–2.3)	<0.0001	0.18 ± 0.06	1.2 (1.1–1.3)	0.001
Women	−0.01 ± 0.34	1.0 (0.5–1.9)	0.95	0.11 ± 0.13	1.1 (0.9–1.4)	0.38
Angina pectoris	1.00 ± 0.47	2.7 (1.1–6.9)	0.03	0.41 ± 0.14	1.5 (1.1–2.0)	0.004
Previous myocardial infarction	0.99 ± 0.45	2.7 (1.1–6.9)	0.02	0.31 ± 0.13	1.4 (1.0–1.8)	0.02
Estimated glomerular filtration rate	−0.33 ± 0.13	0.7 (0.6–0.9)	0.01	−0.14 ± 0.05	0.8 (0.7–0.9)	0.005
Albumin/creatinine ratio	0.34 ± 0.13	1.4 (1.1–1.8)	0.009	0.16 ± 0.05	1.2 (1.1–1.3)	0.001
Diabetes mellitus				0.27 ± 0.12	1.3 (1.1–1.7)	0.03
Model 4	Only CV events (n = 504)					
Age	0.29 ± 0.11	1.3 (1.1–1.7)	0.01	0.14 ± 0.06	1.2 (1.1–1.3)	0.01
Women	0.02 ± 0.28	1.0 (0.6–1.8)	0.93	0.09 ± 0.13	1.1 (0.8–1.4)	0.48
Angina pectoris	0.71 ± 0.32	2.0 (1.1–3.8)	0.02	0.36 ± 0.14	1.4 (1.1–1.9)	0.01
Previous myocardial infarction	0.66 ± 0.31	1.9 (1.1–3.5)	0.03	0.28 ± 0.12	1.3 (1.1–1.7)	0.02
Albumin/creatinine ratio	0.25 ± 0.11	1.3 (1.1–1.6)	0.02	0.19 ± 0.05	1.2 (1.1–1.3)	0.0002
Estimated glomerular filtration rate	−0.23 ± 0.10	0.8 (0.6–0.9)	0.02	−0.15 ± 0.05	0.8 (0.7–0.9)	0.005
Diabetes mellitus	0.75 ± 0.30	2.1 (1.2–3.8)	0.01	0.29 ± 0.12	1.3 (1.1–1.7)	0.01
Highest Killip class	0.65 ± 0.23	1.9 (1.2–3.0)	0.004	0.30 ± 0.09	1.3 (1.1–1.6)	0.0008
Hypertension	0.46 ± 0.23	1.6 (1.1–2.5)	0.04			
Left ventricular ejection fraction				−0.11 ± 0.05	0.9 (0.8–1.1)	0.04
Model 5	Inclusion of in-hospital medications (n = 504)					
Age	0.50 ± 0.16	1.6 (1.2–2.3)	0.002	0.18 ± 0.06	1.2 (1.1–1.3)	0.002
Women	−0.15 ± 0.36	0.9 (0.4–1.7)	0.67	0.06 ± 0.13	1.1 (0.8–1.4)	0.65
Angina pectoris	0.96 ± 0.47	2.6 (1.1–6.5)	0.04	0.47 ± 0.13	1.6 (1.2–2.0)	0.0003
Diabetes mellitus				0.33 ± 0.16	1.4 (1.1–1.9)	0.03
Previous myocardial infarction	0.92 ± 0.47	2.5 (1.1–6.3)	0.04			
Estimated glomerular filtration rate	−0.42 ± 0.14	0.7 (0.5–0.9)	0.003	−0.18 ± 0.05	0.8 (0.7–0.9)	0.0005
Albumin/creatinine ratio	0.37 ± 0.14	1.4 (1.1–1.9)	0.007	0.19 ± 0.05	1.2 (1.1–1.3)	0.0001
Left ventricular ejection fraction	−0.33 ± 0.15	0.7 (0.5–0.9)	0.02	−0.12 ± 0.06	0.8 (0.7–0.9)	0.03
Model 6	Inclusion of medications during follow-up (n = 464)					
Age	0.42 ± 0.16	1.5 (1.1–2.1)	0.008	0.13 ± 0.06	1.2 (1.1–1.3)	0.04
Women	−0.28 ± 0.36	0.8 (0.4–1.5)	0.43	0.08 ± 0.13	1.1 (0.8–1.4)	0.55
Angina pectoris	1.07 ± 0.45	2.9 (1.2–7.1)	0.01	0.41 ± 0.14	1.5 (1.1–2.0)	0.004
Previous myocardial infarction				0.26 ± 0.14	1.3 (1.0–1.7)	0.06
Estimated glomerular filtration rate	−0.34 ± 0.13	0.7 (0.5–0.9)	0.01	−0.15 ± 0.05	0.8 (0.7–0.9)	0.004
Albumin/creatinine ratio	0.28 ± 0.13	1.3 (1.1–1.7)	0.03	0.14 ± 0.05	1.2 (1.1–1.3)	0.006

Table 3
Continued

Variable	β ± SE	OR (95% CI)	p Value	β ± SE	HR (95% CI)	p Value
Model 7	Inclusion of CV risk factor modification during follow-up (n = 504)					
Age	0.52 ± 0.15	1.7 (1.2–2.3)	0.001	0.18 ± 0.06	1.2 (1.1–1.4)	0.004
Women	−0.03 ± 0.35	1.0 (0.5–1.9)	0.92	0.12 ± 0.14	1.1 (0.9–1.5)	0.39
Angina pectoris	1.04 ± 0.44	2.8 (1.2–6.7)	0.01	0.40 ± 0.14	1.5 (1.1–1.9)	0.005
Previous myocardial infarction	1.03 ± 0.41	2.8 (1.2–6.3)	0.01	0.34 ± 0.14	1.4 (1.1–1.8)	0.01
Estimated glomerular filtration rate	−0.34 ± 0.13	0.7 (0.5–0.9)	0.01	−0.15 ± 0.05	0.8 (0.7–0.9)	0.003
Albumin/creatinine ratio	0.30 ± 0.13	1.3 (1.1–1.7)	0.02	0.17 ± 0.05	1.2 (1.1–1.3)	0.0009

Abbreviations as in Table 2.

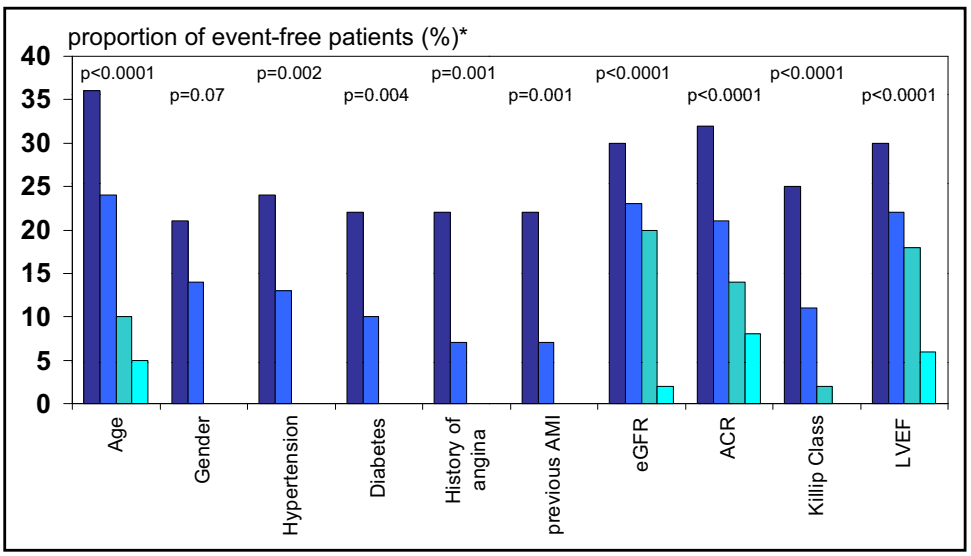

Figure 3. Proportion of patients with EFS, according to clinical variables significant on multivariate analysis. ∗By quartiles of continuous variables and classes of categorical variables. Abbreviations as in Figure 2.

EFS at the univariate level. Both the logistic and Cox analyses showed that the following were associated with EFS, independent of age and gender: no diabetes mellitus, no history of angina and/or myocardial infarction, low Killip class, high LVEF, no atrial fibrillation/flutter, high eGFR, and low albumin/creatinine ratio (Table 2). Only the Cox regression analysis showed associations between EFS and heart rate, blood glucose, triglycerides, and uric acid (Table 2). Among the CV risk factors that had changed during follow-up, the absence of diabetes mellitus and physical activity tended to be associated with EFS (Table 2).

At the multivariate level, both the logistic and the Cox regression models showed independent associations between EFS and age, no history of angina and/or myocardial infarction, high eGFR, and low albumin/creatinine ratio (Table 3, model 1). Only the Cox model showed significant associations between EFS and the absence of diabetes mellitus and low Killip class. All other variables, except for LVEF, showed a weak or no association with EFS, including the major CV risk factors (Table 3, model 2). Figure 3 shows the proportion of patients with EFS according to quartiles or classes of variables found significant in the predictive models. Independent significant interactions were found between age and the albumin/creatinine ratio, age and LVEF, Killip class and eGFR, Killip class and albumin/creatinine ratio, and diabetes mellitus and history of angina (Table 3, interaction section).

The group of patients that initially survived AMI (i.e., were discharged alive; Table 3, model 3) showed the same significant variables and similar strengths of association with EFS as those mentioned in the previous paragraph. However, the Cox analysis indicated that diabetes mellitus was also a significant factor in this group. The group of patients with events also included 33 patients with no CV events, but who had died from non-CV causes. By censoring these patients, diabetes mellitus, hypertension, Killip class, and LVEF were also associated with EFS (Table 3, model 4). No changes were observed in these associations when the in-hospital or follow-up drug treatments were included in these models (Table 3, models 5 and 6). Furthermore, no significant changes in the associations were observed between the groups of patients who did/did not receive thrombolytic therapy on admission or those with/without Q-wave AMI. No other variables were included in the final models (data not shown). Finally, the strengths of the these associations were unchanged by including major CV risk factor modification during follow-up, except for diabetes mellitus (e.g., new-onset diabetes mellitus), which tended to be negatively associated with EFS (p = 0.06; Table 3, model 7).

Table 4
Predictive models for 10-year event free survival, tested with the C-statistic analysis and the likelihood-ratio chi square test

Predictive models	C Statistic	Likelihood Ratio Chi-Square	Model Improvement Chi-Square	p Value
Model 1: cardiovascular risk factors (current smoking, physical activity, hyperlipidemia, hypertension, diabetes mellitus)	0.66	23.6		<0.0001*
Model 2: acute heart variables (prehospital time delay, Q-wave myocardial infarction, creatine kinase-MB peak, Killip class, atrial fibrillation)	0.69	40.3		<0.0001*
Model 3: ABC model (previous myocardial infarction and/or angina pectoris, estimated glomerular filtration rate, albumin/creatinine ratio)	0.75	69.2		<0.0001*
Model improvement				
Acute heart model added to cardiovascular risk factor model	0.72	53.2	29.6	<0.0001†
ABC model added to cardiovascular risk factor model	0.77	74.3	50.7	<0.0001†
ABC model added to acute heart model	0.78	83.0	42.7	<0.0001†
ABC model added to cardiovascular risk factor model and acute heart model	0.78	86.7	33.5	<0.0001†
Cardiovascular model added to acute heart model and ABC model	0.78	86.7	3.7	0.59†
Heart model added to cardiovascular model and ABC model	0.78	86.7	12.4	0.02†

* Model fitting.
† Model improvement.

The "ABC model" refers to the 4 significant variables determined with both the logistic and Cox multivariate models (apart from age and LVEF, which are well-known, strong predictors in all models). We compared the prognostic power of the ABC model with that of the "CV risk factor model," and the "acute heart model" (described in the "Methods" section). All 3 models were well-calibrated (CV risk model, $p = 0.34$; acute heart model, $p = 0.32$; ABC model, $p = 0.86$), and all 3 showed significant fits with the data (Table 4). Both the C-statistic analysis and the likelihood ratio analysis indicated that the acute heart model had better prognostic power than the CV risk factor model (Table 4). However, the ABC model had the best prognostic power. Furthermore, including the factors of the ABC model improved the predictive power of both the CV risk factor model and the acute heart model (Table 4). The inclusion of age and LVEF in each of the 3 models did not modify the results.

Discussion

The ABC study was the first prospective investigation of 10-year EFS after AMI in an unselected sample of patients without substantial withdrawals. The present study showed that 10-year EFS was strongly associated with no history of angina and/or myocardial infarction, low albuminuria, and elevated eGFR, that we termed the ABC model. According to most studies, young age and high LVEF were also strongly associated with EFS.[2] These findings remained unaltered after including the administration of the main classes of medications. Because the long-term risk assessment might have been influenced by the high rate of events that occurred during the index hospitalization, we performed the same analysis starting at the index hospital discharge. That analysis produced very similar associations and confirmed the strength of the results obtained during the whole study period.

The present study suggested that the prediction of a long-term "good prognosis" could chiefly be with factors other than traditional CV risk factors and indicators of acute heart damage. The ABC model, improved the prediction power of the other models that included the CV risk factors and in-hospital clinical variables. Furthermore, the ABC model showed strong association with EFS in both logistic (determined by the absence/presence of the event) and time to event analyses. This supported the hypothesis that this model could predict clinical nonprogression of coronary artery disease. The predictive power of the ABC model was not significantly influenced by the inclusion of age and LVEF, which are strong predictors of CV events in virtually all good predictive models of patients with coronary artery disease.[1–3]

Although EFS is a basic, well-defined concept, it becomes more complex when the length of EFS time is considered. Shortly after AMI, EFS is strongly influenced by the initial acute event and its possible complications. In contrast, at long time after AMI, EFS tends to be related more to coronary artery disease progression than to the initial acute event.[2] Consistent with other reports, including the recent GRACE United Kingdom–Belgium study, our study showed that patients with myocardial infarctions had very poor prognosis in the short and long term.[2–4] Although this is the era of thrombolytic and mechanical reperfusion and effective guideline-driven drug treatment, the event rate after AMI remains high, and late morbidity and mortality are substantially underrecognized.[3] The scenario of "real world" events might be underrepresented owing to the scarcity of long-term studies, investigations of subpopulations of patients with AMI and/or selected outcomes, or the high proportion of patients lost to follow-up.[18,19] One of the main findings of the present study was that major CV risk factors had a lower influence than the ABC model on EFS during a 10-year period. A recent report of young patients with a first myocardial infarction showed that the Framingham risk score was inadequate for predicting cardiac risk.[4,18] The indicators of infarct size, such as peak creatine kinase and creatine kinase-MB concentrations, were not associated with EFS. A reasonable explanation is that a reduction of myocardial necrosis by early reperfusion benefits left ventricular function and patient survival but that viable myocardium in the territory supplied by an open infarct-related

coronary artery is more prone to recurrent ischemia.[20] Although the presence of heart failure was associated with EFS independent of age and gender, it tended to decrease the predictive power in the multivariate models. In contrast, the LVEF maintained a strong, independent association with EFS.[21]

The Thrombolysis In Myocardial Infarction study showed that a history of angina and myocardial infarction was associated with adverse events in the short term.[22] Our data showed that this factor remained independent and highly influential for 10 years after AMI. It could be that this association was related to the older age of the patients with a history of cardiac events; however, our data indicated that the association was independent of age and gender. The association between EFS and eGFR or albumin/creatinine ratio has been largely uninvestigated. The present study showed that eGFR and albumin/creatinine ratio were independent factors that were strongly associated with EFS. Previous studies showed that the albumin/creatinine ratio had independent prognostic value for mortality after AMI.[9,23–25] Other research groups have postulated that microalbuminuria represents an index of general endothelium dysfunction.[26,27] Renal function was shown to be an independent predictor of mortality in patients with AMI, and even mild renal failure has been shown to be a major risk factor for CV complications and mortality after AMI.[28,29] Thus, it is reasonable that the combination of these 4 factors in the ABC model showed greater predictive power than the models that included only the CV risk factors or in-hospital indicators of acute heart damage.

A major limitation of the ABC study was that at patient enrollment, percutaneous coronary angioplasty was not currently in use for reopening coronary arteries in patients with ST-segment elevation AMI. Thus, it remains uncertain whether early mechanical reperfusion might have modified the above-reported predictive models. However, we observed that the predictive model results were similar for patients with/without Q-wave AMI and those with/without thrombolytic treatment. Because the present study included only white patients, we cannot generalize these findings to other populations and ethnic groups. In future studies, our findings could be corroborated by model validation in an external test set over a long period.

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Prospective History of Long-Term Mortality and Modes of Death in Patients Discharged After Acute Coronary Syndrome: The ABC-2* Study on Acute Coronary Syndrome

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Abstract

Background: The aim of this study was to examine the prognostic value of several clinical characteristics on long-term mortality and causes of death after acute coronary syndrome.

Methods: The ABC-2 study is a prospective investigation comprising 557 patients with acute coronary syndrome. During hospitalization, 33 clinical variables, including demographics, cardiovascular risk factors, in-hospital characteristics, and blood components, were examined. "Acute models" were survival models containing the variables accrued within 72 h from admission, and "sub-acute models" contained data accrued over a 7-day period. Cox regression models were used for the survival analysis.

Results: The 12-year follow-up study revealed that 51.2% of the patients died (15.8% of the patients died from coronary artery disease and/or heart failure, 12.6% of the patients experienced sudden death, 8.3% of the patients died from other-cardiovascular diseases, and 14.5% of the patients died from non-cardiovascular causes. The following factors were independently associated with all-cause mortality in both the acute and sub-acute models: age, left ventricular ejection fraction (negative), body mass index (non-linear), previous myocardial infarction, diabetes mellitus, blood glucose (non-linear), Killip class>1, albumin/creatinine ratio, and pre-hospital time delay. The variables associated with coronary artery disease and/or heart failure included age, left ventricular ejection fraction (negative), body mass index (non-linear), previous myocardial infarction, Killip class>1, albumin/creatinine ratio, and pre-hospital time delay, while the variables associated with sudden death included age, hypertension (negative), uric acid, left ventricular ejection fraction (negative), and pre-hospital time delay, and those associated with other- cardiovascular causes included age, hypertension, and albumin/creatinine ratio. The only variable associated with non- cardiovascular mortality was age. The C-statistic of the predictive models was 0.86 for all-cause mortality, whereas the C-statistic ranged from 0.74 to 0.80 for cardiovascular causes.

Conclusions: The ABC-2 study revealed clinical predictors of long-term mortality after acute coronary syndrome that might help prognostication, patient education, and risk modification. Furthermore, the results showed that the modes of death are independently associated with different baseline clinical features.

Keywords

Acute coronary syndrome; Mortality; Risk prediction; Survival analysis (*ABC is acronym for Adria, Bassano, Conegliano, and Padova Hospitals)

Introduction

Although the treatments used in the last decades have improved the prognosis of patients with acute coronary syndrome (ACS), major adverse events, and death have been observed in many of these patients [1-4]. Furthermore, much of the increased cardiovascular (CV) risk associated with ACS remains unexplained [2,5]. Several studies have contributed to our understanding of the characteristics that predict death. However, most of them focused on predictors of death during index hospitalization or the first year after ACS, and few ones have examined long-term mortality [6-8]. Furthermore, most of these studies assessed only a few clinical factors simultaneously [7]. To achieve broad applicability and avoid emphasis on individual risk factors rather than the overall risk, the risk assessment should consider a reasonable number of potentially relevant prognostic indicators derived from unselected samples of patients [9]. Indeed, the examination of the causes of death could be useful for risk stratification and pathophysiological inferences [10,11]. To our knowledge, there have been no other studies concerning the long-term causes of death in patients after ACS.

The aim of the present study was to examine the prognostic value of baseline clinical characteristics associated with long-term mortality and causes of death in an unselected sample of ACS patients discharged alive after index hospitalization.

Methods

Patients

The Adria, Bassano, Conegliano, and Padova Hospital Study on Acute Coronary Syndrome (the ABC-2 Study on ACS) is an ongoing an ongoing, prospective investigation reflecting an unbiased population of ACS patients. The sample includes Caucasian patients with definite ACS (ST elevation myocardial infarction [STEMI], non-ST elevation myocardial infarction [NSTEMI], and unstable angina [UA], admitted to the intensive care units at Adria, Bassano, and Conegliano Hospitals between June 21, 1995 and January 19, 1998. The original aim of the ABC study was to examine the natural history of a sample of unselected, consecutive ACS patients and evaluate the prognostic value of a number of baseline clinical features. The criteria for the diagnosis of ACS included the clinical presentation, electrocardiogram (ECG) findings, and the identification of serum biochemical necrosis markers. Specifically, acute myocardial infarction is defined as the typical rise and gradual decline of creatine kinase MB expression, accompanied by at least one of the following conditions: ischemic symptoms, development of pathologic ECG Q waves, and ECG changes indicative of ischemia (i.e., ST segment

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elevation or depression). UA is considered as the occurrence of one or more episodes of angina at rest during the preceding 48 h, corresponding to Braunwald class III, with ECG changes indicative of ischemia [2]. The ACS type was examined as a dichotomic variable, based on absence/presence of ST elevation ACS. A total of 778 eligible patients were considered upon admission (Figure 1). Among these, 47 patients had diseases other than coronary artery disease (CAD), and 53 patients had CAD, but not ACS; these patients were excluded from the study. Forty-five patients were excluded from the study for concomitant conditions potentially affecting the investigated variables (Figure 1). Thirty-four additional patients were excluded for other reasons, as shown in Figure 1. Forty-two of the enrolled patients died during index hospitalization and were excluded from the present analysis. Hence, the post-discharge follow-up study included 557 patients (Figure 1). Each patient received an anonymous code, and no personal data or identifiers were included in the baseline or follow-up database. Written informed consent was obtained from all enrolled patients, and the study was approved through the hospital ethics committee.

Measurements

Upon enrollment, a thorough patient history was obtained from medical records and patient interviews. All baseline clinical and laboratory data reported in the present study were obtained during

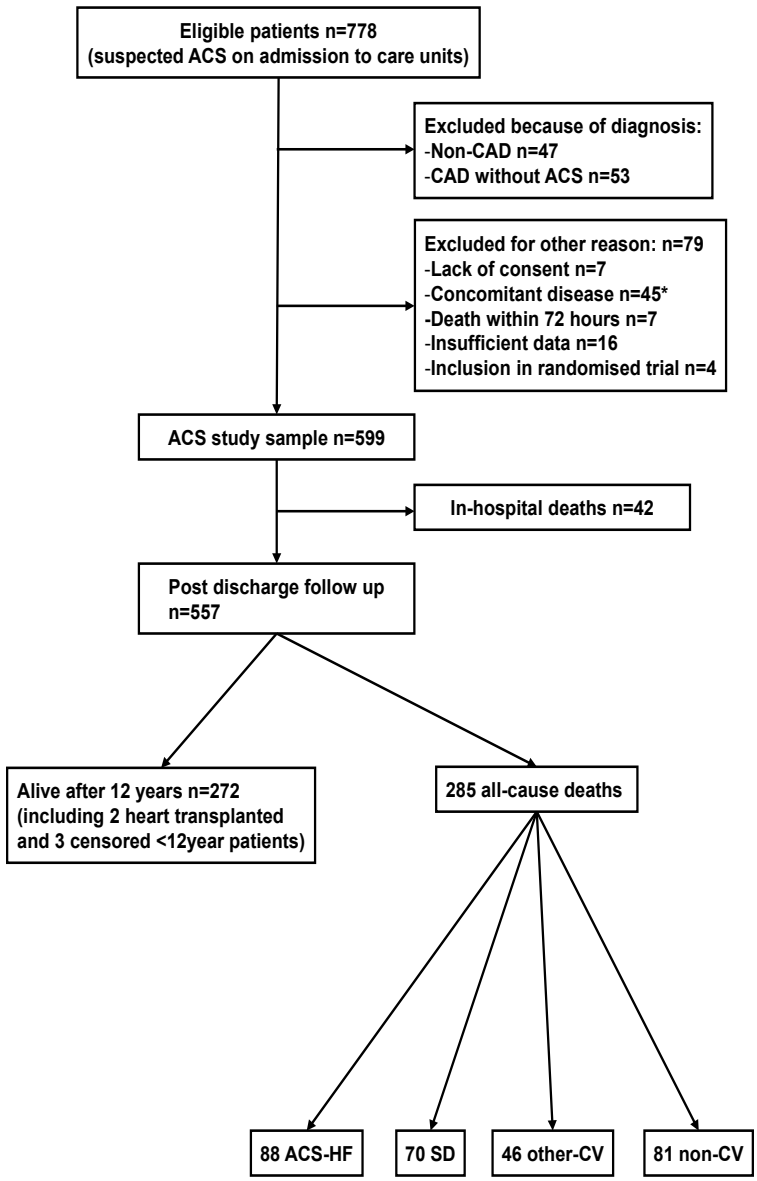

Figure 1: Flow diagram of subject progress during follow-up. ACS indicates Acute Coronary Syndrome, CAD indicates Coronary Artery Disease, CV, cardiovascular, HF indicates Heart Failure, and SD indicates Sudden Death.
*The exclusion criteria included chronic renal failure, with a documented history of estimated glomerular filtration rate (eGFR) <1.0 mL/s/1.73 m² for 3 months, with or without kidney damage, or dialysis treatment (n=7); nephrotic proteinuria (n=2); concomitant acute infection (n=19); myocardial re-infarction within 3 days of admission (n=5); surgical treatment for bone fractures (n=3); recent surgery (n=2); systemic lupus erythematosus (n=1); menstrual flow (n=1); neoplastic disease (n=5); death within 3 days of admission (n=7); or insufficient data (n=16).

the first 7 days of hospitalization in the Intensive Coronary Care Unit. Hypertension was defined as a systolic blood pressure of 140 mm Hg or higher diastolic blood pressure of 90 mm Hg or higher the use of at least one class of anti-hypertensive agents. Diabetes mellitus was defined as a fasting blood glucose level of 126 mg/dL or higher the use of insulin or at least one oral hypoglycemic agent. Patients with cholesterol levels of 240 mg/dL or higher those taking lipid-lowering agents were classified as hyperlipidemic. The body mass index was calculated as kg body weight/m^2 body height. Upon admission, and every 4 h thereafter, the serum enzyme levels were recorded, and a 12-lead ECG test was performed. The venous blood was drawn for biochemical determinations. The blood pressure and heart rate were measured between 7 and 8 a.m., and the mean value of three recordings was used in the analyses. The presence and degree of heart failure were assessed according to the Killip classification [12]. The presence of atrial fibrillation/flutter, ventricular tachy- and brady-arrhythmias was recorded during the first week of hospitalization. Left ventricular ejection fraction (LVEF) was assessed using two-dimensional echocardiography according to Simpson's method [13]. The LVEF was not obtained for 81 patients who underwent echocardiography after discharge from the intensive care units or possessed technically inadequate echocardiographic images. Two physicians, with no knowledge of the patient clinical data, examined the records. The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) equation [14]. The albumin excretion was measured in 24-h urine samples using a radioimmunoassay, and the data were expressed as the ratio of albumin to creatinine (ACR) [15].

Follow-up and outcomes

At one, three, five, seven, ten, and twelve years after recruitment, each patient underwent a clinical check-up. At each recruitment hospital, 2 cardiologists carefully performed a 12-year follow-up on the surviving cohort. The primary aim of this study was to determine the 12-year all-causes mortality and modes of death associated with ACS. Two researchers, with no knowledge of baseline patient data, examined the modes of death, which were classified into the following categories:

1) CAD and/or heart failure progression (CAD-HF).

2) Sudden death (SD) defined as witnessed, out-of-hospital death within 1 h after the onset of acute symptoms or unwitnessed, unexpected death (e.g., during sleep) in patients within the 24 h prior to the onset of symptoms [16].

3) Other cardiovascular (CV) causes and

4) non-CV causes. All data were obtained from scheduled examinations, public administrations, hospital records, family doctors, postmortem examinations, and death certificates. The medications administered during index hospitalization and follow-up treatments were also recorded. If a patient underwent heart transplantation, he/she was excluded from the primary survival analysis. He/she was only included in a secondary sub-analysis to verify the general results.

Statistical analysis

The measured variables were analyzed as both continuous variables in table and increasing quartile values (in other analyses) (Table 1). Log transformations were used to correct for positive-skewed distributions, as appropriate. Unpaired Student's t-test and Pearson's chi-square (χ^2) test were used to analyze measured and categorical variables, respectively. The Cox proportional hazard regression analysis was used to describe the influence of the variables on mortality during follow-up. If a patient dropped out before completing 12 years of follow up, her/his data were censored at that time. Scaled Schoenfeld residuals were used to test the proportionality assumption. The proportional-hazards assumption was verified for all variables ($p>0.30$). To avoid the exclusion of potentially significant predictors, the excluded variables were retested in the final model. Because ACS is a pathophysiologically dynamic process operating over time, the surviving models including variables accrued within 72 h after admission, were referred to as "acute models", and those including variables accrued at 7 days after admission were called "sub-acute models". The variables were tested for co linearity. All variables were assessed for conformity to increasing (or decreasing) gradients to determine whether the association between a variable and an outcome produced a non-linear, J/U-shaped trend. If a variable showed a J/U shape, the non-linear hazard was estimated by adding to the Cox model the quadratic term of the variable, beside the untransformed variable [11]. The discriminative power of the final parsimonious models was determined as the area under the receiver operating characteristic curve, also called the C-statistic, which evaluates the ability of a model to accurately classify events. The Hosmer-Leme show test was used to assess model calibration. The baseline characteristics were summarized using median values and interquartile ranges for continuous variables and numbers and percentages for categorical variables. The International System of Units was used throughout the text. Unless otherwise indicated, two-tailed p values <0.05 were considered significant. The statistical analyses were performed using STATA 12 (College Station, Texas, USA) and JMP 8.0 (SAS Institute, Cary, NC, USA).

Results

Death rate

The 557 patients included in this study underwent a 12-year follow up, unless preempted by death, and three patients were excluded (two patients withdrew consent and one patient moved overseas). Among these, two patients underwent heart transplantation. After 12 years, 285 patients died (51.2%), and the entire sample represented 4587.2 person-years of follow-up. Among the deceased patients, 88 (15.8%) patients died from CAD-HF (reinfarction, n=31, heart failure, n=29, acute pulmonary edema, n=13, cardiogenic shock, n=5; in-hospital arrhythmic death, n=6; other cardiac cause, n=4). Seventy (12.6%) patients died from SD. Forty-six (8.3%) patients died from other CV causes (stroke, n=28; pulmonary embolism, n=5; fatal complication of coronary bypass surgery, n=3; other causes, n=10), and 81 (14.5%) patients died from non-CV causes (neoplastic disease, n=46; respiratory infection, n=7; non-neoplastic cachexia, n=5, other non CV causes, n=23).

The median (IQ) time to death was 4.2 (1.4-7.8) years for all-cause mortality, 3.1 (0.9-7.8) years for CAD-HF, 2.9 (0.8-5.1) years for SD, 3.3 (2.3-6.3) years for the other CV mortality, and 6.3 (3.1-9.5) years for non-CV mortality. Table 1 shows the clinical features of the patients, their primary treatments and the differences between deceased and surviving patients. Death was more frequently observed in older female patients. Most of the clinical characteristics were significantly different in dead patients compared with the survivors (Table 1).

Potential predictors of mortality, causes of death and influence of age and gender

Among the 33 clinical variables tested (Table 1), 26 variables were associated with all-cause mortality at univariable level. After adjusting for age and gender, only the following 10 variables were associated with all-cause mortality in both acute and sub-acute

Table 1: Baseline characteristics of the patients with acute coronary syndrome

Variable name	Overall Population (N=557)	Survivors (N=272)	Dead patients (N=285)	P value
Demographics				
Age (years)	67(58-74)	60(52-67)	72(66-78)	<0.0001
Gender (female)	29	20	37	<0.0001
Education (high school or above)	26	33	19	<0.0001
Coexisting conditions				
Current smoking	38	47	28	<0.0001
Physical activity	7	11	4	0.002
Hypertension	46	38	54	<0.0001
Hypercholesterolemia	27	29	25	0.19
Diabetes mellitus	21	14	29	<0.0001
Body mass index (Kg/m²)	26(24-28)	26(24-28)	25(23-28)	0.003
Alcohol use	74	77	72	0.12
Coffee use	88	91	84	0.008
Medical history				
Family coronary heart disease	26	30	23	0.03
History of angina	25	18	32	<0.0001
Previous myocardial infarction	24	16	32	<0.0001
In-hospital characteristics				
Pre-hospital time delay* (min) (n=465)	185(120-517)	175(110-311)	235(120-660)	<0.0001
Systolic blood pressure (mmHg)	117(106-127)	115(107-128)	122 (112-139)	0.002
Diastolic blood pressure (mmHg)	78(70-84)	80(71-83)	74(68-80)	0.43
Heart rate (beats/min)	70(60-78)	67(58-75)	72(64-83)	<0.0001
ST-elevation myocardial infarction	61	66	57	0.05
CK MB-peak (U/L)*	103(43-207)	106(40-228)	99(44-193)	0.86
Killip class > 1	32	18	46	<0.0001
Tachy-arrhythmias † ‡	20	17	22	0.15
Brady-arrhythmias † ‡	7	8	6	0.18
Atrial fibrillation/flutter †	10	5	15	<0.0001
LVEF (%) (n=476)	52(45-60)	59(50-64)	39(49-57)	<0.0001
Thrombolysis	35	47	25	<0.0001
Blood components				
Hemoglobin (g/L)	137(126-147)	138(129-148)	135(124-146)	0.01
Blood glucose (mmol/L)	6.6(5.5-8.8)	6.5(5.5-8.1)	6.9(5.7-10.2)	<0.0001
Total cholesterol (mmol/L)	5.4(4.6-6.3)	5.5(4.8-6.4)	5.3(4.4-6.1)	<0.0001
Uric acid (µmol/L)	327(274-393)	315(256-369)	345(285-416)	<0.0001
Potassium (mEq/L)	4.1(3.8-4.4)	4.1(3.8-4.4)	4.1(3.8-4.4)	0.009
Sodium (mEq/L)	140(138-142)	140(138-142)	140(138-142)	0.78
Kidney and endothelial function				
eGFR (mL/s x 1.73 m²) *	1.2(1.0-1.4)	1.3(1.2-1.5)	1.1(0.9-1.3)	<0.0001
ACR (mg/mmol) *	0.6(0.3-1.7)	0.4(0.2-0.9)	1.1(0.4-2.9)	<0.0001
Follow-up treatments				
ß-receptor blocker	49	66	34	<0.0001
Calcium channel-blocker	54	61	48	0.002
Long-acting nitrate	82	76	88	<0.0001
ACE-inhibitor/Angiotensin II receptor blocker	71	74	68	0.09
Diuretic	58	45	70	<0.0001
Antiplatelet	90	96	83	<0.0001
Anticoagulant	20	16	23	0.04
Digitalis	25	11	38	<0.0001
Antiarrhythmic	16	13	18	0.13
Lipid-lowering drug	41	63	19	<0.0001
Coronary artery bypass graft surgery	19	27	11	<0.0001
Percutaneous coronary angioplasty	19	31	7	<0.0001

The values are presented as medians and interquartile ranges or percentages. Pre-hospital time delay indicates the time from the onset of symptoms to the arrival at the coronary care unit for patients with definite myocardial infarction; CK-MB, creatine kinase-MB isoenzyme; LVEF, left ventricular ejection fraction; eGFR, estimated glomerular filtration rate by MDRD; ACR, albumin to creatinine excretion ratio; CV, cardiovascular. *P values were calculated for log-transformed data. † During the first 7 days of hospital stay. ‡ Tachy-arrhythmia and brady-arrhythmia, excluding the perithrombolytic period..

models: diabetes mellitus, previous myocardial infarction, pre-hospital time delay, ST-elevation myocardial infarction, atrial fibrillation/flutter, LVEF (negative), Killip class>1, heart rate, blood glucose (non-linear association), and ACR. Diabetes mellitus, previous myocardial infarction, pre-hospital time delay, atrial fibrillation/flutter, LVEF (negative), Killip class>1, heart rate, blood glucose (non-linear association), ACR, uric acid, sodium (negative), eGFR (negative), plasma albumin (negative), alcohol use (negative), and blood hemoglobin (negative), were associated with one or more causes of death. History of hypertension and/or systolic and diastolic blood pressures were negatively associated with sudden death and positively associated with other CV causes (data not shown).

Predictive models for all-cause mortality

The variables independently associated with all-cause mortality are reported in Table 2. When LVEF was included in the analysis, the following factors remained significantly associated with all-cause mortality in both acute and sub-acute models: age, LVEF (negative), body mass index (non-linear), previous myocardial infarction, diabetes mellitus, blood glucose (non-linear), Killip class>1, ACR, and pre-hospital time delay (Table 2 and Figure 2). Notably, body mass index and blood glucose level in the acute model showed a non-linear association with outcome (J or U curve association), and mortality was associated with the first and 4th quartiles (external quartiles) (Table 2). Heart rate, uric acid, and

Table 2: Multivariable Cox regression models for all cause mortality versus 12-year survivors.

	Acute model			Sub-acute model		
Variable	**β ± SE**	**Hazard ratio (95% CI)**	**P value**	**β ± SE**	**Hazard ratio (95% CI)**	**P value**
All Patients	**(n=557, deaths n=287)**			**(n=499, deaths n=255)**		
Age	0.69 ± 0.07	8.0(5.3-12.0)	<0.0001	0.73 ± 0.07	8.9(5.8-13.7)	<0.0001
Gender (female)	-0.17 ± 0.14	0.8(0.6-1.1)	0.21	-0.29 ± 0.14	0.7(0.6-0.9)	0.04
Body mass index	0.13 ± 0.06	1.3(1.1-1.6)	0.03*	0.16 ± 0.06	1.4(1.1-1.8)	0.01*
Previous myocardial infarction	0.77 ± 0.14	2.2(1.6-2.8)	<0.0001	0.89 ± 0.15	2.4(1.8-3.3)	<0.0001
Diabetes mellitus †	0.55 ± 0.14	1.7(1.3-2.3)	0.0002	0.77 ± 0.15	2.2(1.6-2.9)	<0.0001
Blood glucose †	0.18 ± 0.06	1.4(1.1-1.8)	0.002*	0.32 ± 0.06	2.6(1.8-3.7)	<0.0001
Heart rate	0.18 ± 0.06	1.7(1.2-2.4)	0.003	0.16 ± 0.06	1.6(1.1-2.4)	0.01
Killip class>1	0.37 ± 0.15	1.4(1.1-1.9)	0.01	0.43 ± 0.20	1.5(1.1-2.7)	0.03
ACR	0.26 ± 0.06	2.1(1.5-3.1)	<0.0001	0.23 ± 0.06	2.0(1.4-2.8)	<0.0001
Diastolic blood pressure	-0.18 ± 0.09	0.6(0.3-0.9)	0.04			
Uric acid	0.16 ± 0.06	1.6(1.1-2.2)	0.005			
Potassium	0.12 ± 0.05	1.4(1.1-2.0)	0.02			
Sodium				-0.18 ± 0.06	0.6(0.4-0.8)	0.001
Atrial fibrillation/flutter				0.43 ± 0.20	1.5(1.1-2.2)	0.03
Pre-hospital time delay	0.16 ± 0.06	1.6(1.1-2.3)	0.007	0.14 ± 0.06	1.6(1.1-2.4)	0.02
Patients with LVEF	**(n=476, deaths n=229)**			**(n=424, deaths n=201)**		
Age	0.64 ± 0.08	6.8(4.3-10.9)	<0.0001	0.73 ± 0.08	9.0(5.6-14.7)	<0.0001
Gender (female)	0.01 ± 0.15	1.0(0.7-1.4)	0.69	-0.13 ± 0.17	0.9(0.6-1.2)	0.44
LVEF	-0.21 ± 0.07	0.5(0.3-0.8)	0.002	-0.24 ± 0.07	0.5(0.3-0.7)	0.0005
Body mass index	0.14 ± 0.07	1.3(1.1-1.7)	0.04*	0.18 ± 0.07	1.4(1.1-1.9)	0.01*
Previous myocardial infarction	0.62 ± 0.16	1.9(1.4-2.5)	<0.0001	0.79 ± 0.17	2.2(1.6-3.1)	<0.0001
Blood glucose †	0.16 ± 0.07	1.4(1.1-1.8)	0.02*	0.31 ± 0.07	2.6(1.7-3.9)	<0.0001
Diabetes mellitus †	0.66 ± 0.16	1.9(1.4-2.6)	<0.0001	0.76 ± 0.16	2.1(1.3-2.9)	<0.0001
Killip class>1	0.41 ± 0.17	1.5(1.1-2.1)	0.01	0.57 ± 0.23	1.8(1.1-2.7)	0.01
ACR	0.25 ± 0.07	2.1(1.4-3.2)	0.0004	0.20 ± 0.07	1.8(1.2-2.8)	0.003
Diastolic blood pressure	-0.21 ± 0.10	0.5(0.3-0.9)	0.03			
Uric acid	0.15 ± 0.06	1.6(1.1-2.3)	0.01			
Heart rate				0.18 ± 0.07	1.7(1.1-2.6)	0.01
Sodium				-0.19 ± 0.06	0.6(0.4-0.8)	0.003
Pre-hospital time delay	0.16 ± 0.06	1.6(1.1-2.3)	0.01			
Patients with LVEF, models including reperfusion treatments and medications through follow-up time as confounders						
Age	0.64 ± 0.08	6.8(4.3-10.9)	<0.0001	0.73 ± 0.08	9.0(5.6-14.7)	<0.0001
Gender (female)	0.01 ± 0.15	1.0(0.7-1.4)	0.69	-0.13 ± 0.17	0.9(0.6-1.2)	0.44
LVEF	-0.21 ± 0.07	0.5(0.3-0.8)	0.002	-0.24 ± 0.07	0.5(0.3-0.7)	0.0005
Previous myocardial infarction	0.62 ± 0.16	1.9(1.4-2.5)	<0.0001	0.79 ± 0.17	2.2(1.6-3.1)	<0.0001
Diabetes mellitus †	0.66 ± 0.16	1.9(1.4-2.6)	<0.0001	0.76 ± 0.16	2.1(1.3-2.9)	<0.0001
ACR	0.25 ± 0.07	2.1(1.4-3.2)	0.0004	0.20 ± 0.07	1.8(1.2-2.8)	0.003
Uric acid	0.15 ± 0.06	1.6(1.1-2.3)	0.01			
Blood glucose				0.31 ± 0.07	2.6(1.7-3.9)	<0.0001
Sodium				-0.19 ± 0.06	0.6(0.4-0.8)	0.003

*Non-linear association (U/J-shaped relationship); † Excluding reciprocally blood glucose and diabetes mellitus from the model;
Abbreviations as shown in Table 1

plasma sodium (negative) were independently associated in acute or sub-acute models. When medications (β-blocker, ACE-inhibitor/anti angiotensin II receptor blocker, and lipid lowering treatment) and reperfusion treatments (thrombolysis, percutaneous coronary angioplasty, and coronary artery by-pass surgery) were included in the final models as confounders, the variables body mass index, Killip class>1, and pre-hospital time delay were most affected, and the association of these variables was no longer significant (Table 2 and Figure 2). The figure summarizes the variables (including age, gender and LVEF) independently associated with all-cause and/or cause of death in both acute and sub-acute models (Figure 2).

Predictive models based on cause of death

The variables independently associated with CAD-HF are shown in Table 3. When LVEF was included in the model, the following variables remained significantly associated in both acute and sub-acute models: age, LVEF (negative), body mass index (non-linear), previous myocardial infarction, Killip class>1, ACR, and pre-hospital

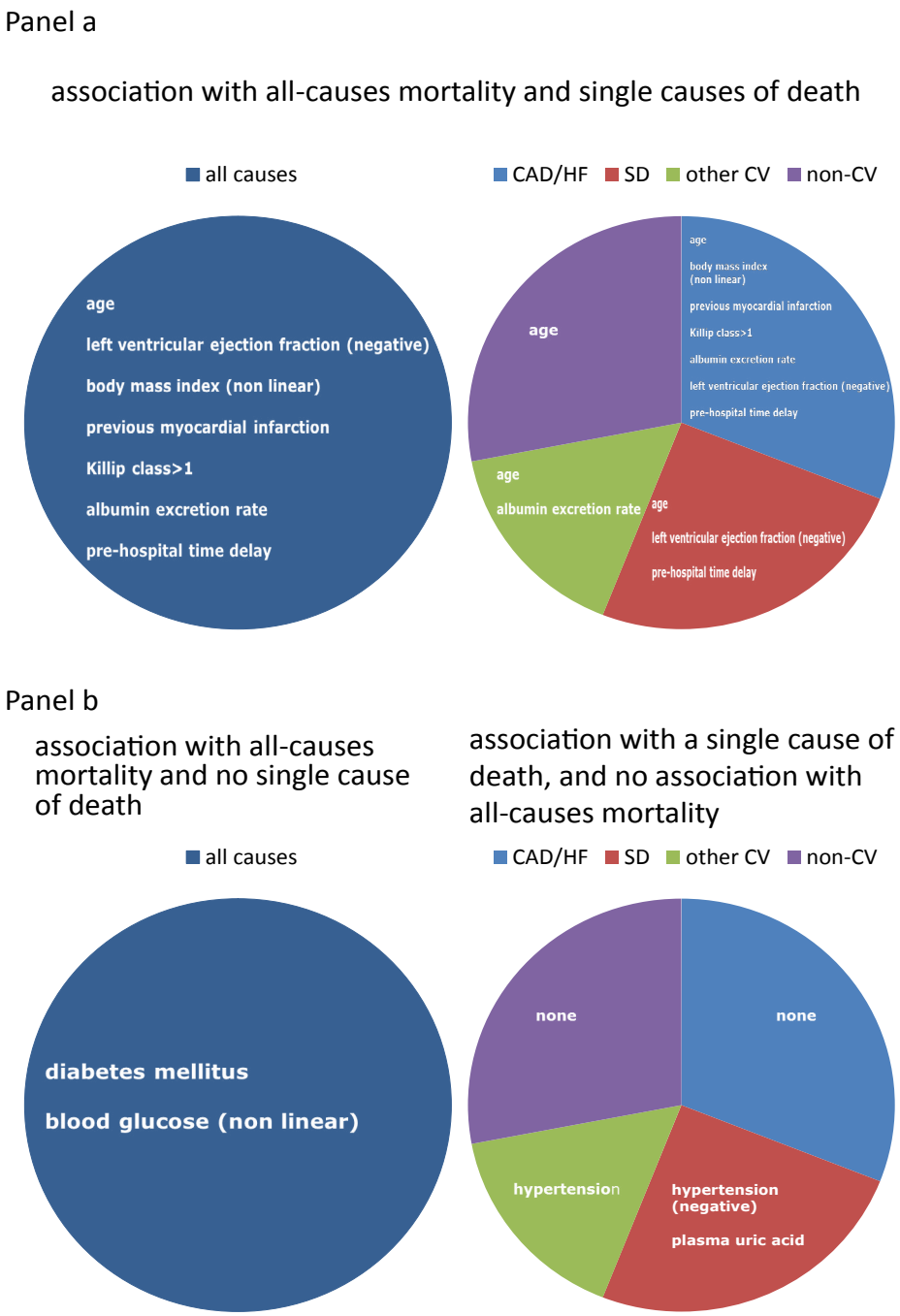

Figure 2: Summary of the independent predictors of 12-year mortality and modes of death after ACS in both acute and sub-acute models.

time delay (Table 3 and Figure 2). SD was associated with age, hypertension (negative), uric acid, LVEF (negative), and pre-hospital time delay (Table 3 and Figure 2). Other CV mortality was associated with age, hypertension, and ACR. LVEF was not independently associated with other CV mortality (Table 3 and Figure 2). Non-CV causes of death were primarily associated with age, and the association with LVEF (negative) was only slightly significant (Table 3 and Figure 2).

Predictive accuracy of the parsimonious models

The multivariable models of Table 2 were well calibrated for all-cause mortality in acute and sub-acute models, with and without

Table 3: Multivariable Cox regression models for mortality by modes of death versus 12-year survivors.

	Acute model			Sub-acute model		
Mode of death: coronary artery disease–heart failure progression						
All Patients (n=557)	**(n=557, deaths n=90)**			**(n=499, deaths n=80)**		
Age	0.64 ± 0.12	6.8(3.3-14.1)	<0.0001	0.70 ± 0.13	8.3(3.8-18.3)	<0.0001
Gender (female)	-0.02 ± 0.24	1.0(0.6-1.6)	0.93	-0.30 ± 0.26	0.7(0.4-1.2)	0.24
Body mass index	0.24 ± 0.11	1.6(1.1-2.5)	0.02*	0.32 ± 0.12	1.9(1.2-3.0)	0.006*
Previous myocardial infarction	1.29 ± 0.23	3.6(2.3-5.7)	<0.0001	1.31 ± 0.26	3.7(2.2-6.1)	<0.0001
Blood glucose †	0.21 ± 0.11	1.5(1.1-2.4)	0.04*	0.43 ± 0.11	3.6(1.9-7.1)	<0.0001
Diabetes mellitus †	0.74 ± 0.24	2.1(1.3-3.3)	0.002	0.92 ± 0.25	2.5(1.5-4.1)	0.0005#
ACR	0.38 ± 0.11	3.1(1.6-6.0)	0.0005	0.48 ± 0.12	4.2(2.2-8.5)	<0.0001
Killip class>1	0.80 ± 0.24	2.2(1.4-3.5)	0.001	0.76 ± 0.35	2.1(1.1-4.1)	0.04T
Heart rate				0.40 ± 0.12	3.3(1.7-6.7)	0.0005
Pre-hospital time delay	0.25 ± 0.10	2.1(1.1-3.9)	0.01	0.23 ± 0.10	2.0(1.1-3.8)	0.02
Patients with LVEF	**(n=476, deaths n=74)**			**(n=424, deaths n=65)**		
Age	0.64 ± 0.13	6.7(3.1-15.1)	<0.0001	0.61 ± 0.15	6.2(2.7-15.0)	<0.0001
Gender (female)	0.06 ± 0.26	1.1(0.6-1.8)	0.81	-0.25 ± 0.30	0.8(0.4-1.4)	0.39
LVEF	-0.24 ± 0.12	0.5(0.2-0.9)	0.03	-0.18 ± 0.13	0.6(0.3-1.2)	0.14
Body mass index	0.28 ± 0.12	1.8(1.1-2.9)	0.01*	0.30 ± 0.13	1.8(1.1-3.1)	0.02*
Previous myocardial infarction	0.96 ± 0.26	2.6(1.6-4.3)	0.0003	1.05 ± 0.30	2.9(1.6-5.1)	0.0007
ACR	0.35 ± 0.12	2.8(1.4-6.0)	0.003	0.48 ± 0.13	4.3(2.0-9.7)	0.0001
Diabetes mellitus †	0.88 ± 0.26	2.4(1.4-4.0)	0.001			
Killip class>1	0.67 ± 0.28	1.9(1.1-3.3)	0.01	0.59 ± 0.26	1.8(1.1-3.0)	0.02
Blood glucose †				0.38 ± 0.12	3.2(1.6-6.6)	0.001
Heart rate				0.35 ± 0.13	2.8(1.3-6.1)	0.007
Pre-hospital time delay	0.25 ± 0.12	2.1(1.1-4.3)	0.02	0.25 ± 0.12	2.1(1.1-4.3)	0.03
Mode of death: sudden death						
All Patients	**(n=557, deaths n=70)**			**(n=499, deaths n=65)**		
Age	0.51 ± 0.13	4.7(2.2-10.0)	<0.0001	0.61 ± 0.14	6.2(2.8-13.9)	<0.0001
Gender (female)	-0.21 ± 0.29	0.8(0.4-1.4)	0.45	-0.56 ± 0.32	0.6(0.3-1.1)	0.07
Previous myocardial infarction	0.64 ± 0.27	1.9(1.1-3.2)	0.02	1.14 ± 0.27	3.1(1.8-5.3)	<0.0001
Diastolic blood pressure §	-0.31 ± 0.11	0.4(0.2-0.8)	0.006	-0.23 ± 0.11	0.5(0.3-0.9)	0.04
Hypertension §	-0.64 ± 0.26	0.5(0.3-0.9)	0.01	-0.79 ± 0.27#	0.4(0.3-0.8)	0.003
Uric acid	0.28 ± 0.12	2.3(1.2-4.8)	0.01	0.26 ± 0.12	2.2(1.1-4.4)	0.02
Killip class>1	0.73 ± 0.29	2.1(1.2-3.6)	0.01			
Heart rate	0.36 ± 0.12	2.9(1.4-6.1)	0.002			
Blood glucose †				0.50 ± 0.12	4.4(2.2-9.2)	<0.0001
Diabetes mellitus †				0.71 ± 0.29	2.0(1.1-3.5)	0.02
Hemoglobin				-0.32 ± 0.13	0.4(0.2-0.8)	0.01
Sodium				-0.30 ± 0.11	0.4(0.2-0.8)	0.006
Atrial fibrillation/flutter				0.98 ± 0.33	2.7(1.3-5.0)	0.006
Pre-hospital time delay	0.38 ± 0.12	3.2(1.5-6.7)	0.001	0.39 ± 0.12	3.2(1.5-6.8)	0.001
Patients with LVEF	**(n=476, deaths n=54)**			**(n=424, deaths n=50)**		
Age	0.43 ± 0.15	3.6(1.5-8.7)	0.003	0.47 ± 0.16	4.1(1.6-10.5)	0.02
Gender (female)	0.05 ± 0.32	1.0(0.5-2.0)	0.86	0.31 ± 0.35	1.4(0.7-2.7)	0.38
LVEF	-0.61 ± 0.15	0.2(0.1-0.4)	<0.0001	-0.63 ± 0.16	0.2(0.1-0.4)	<0.0001
Hypertension §	-0.81 ± 0.31	0.4(0.2-0.8)	0.006	-0.92 ± 0.33	0.4(0.2-0.7)	0.003
Uric acid	0.42 ± 0.13	3.5(1.6-8.1)	0.001	0.31 ± 0.14	2.5(1.1-5.7)	0.02
Killip class>1	0.65 ± 0.32	1.9(1.1-3.6)	0.04			
Diastolic blood pressure §	-0.51 ± 0.22	0.2(0.1-0.8)	0.02			
Heart rate	0.26 ± 0.13	2.2(1.1-4.8)	0.04			
Blood glucose				0.55 ± 0.14	5.1(2.3-12.4)	<0.0001
Previous myocardial infarction				0.66 ± 0.32	1.9(1.1-3.6)	0.04

Pre-hospital time delay	0.30 ± 0.14	2.4(1.1-5.6)	0.02	0.29 ± 0.14	2.4(1.1-5.5)	0.03
Mode of death: other CV causes						
All Patients (n=557)	**(n=557, deaths n=46)**			**(n=499, deaths n=41)**		
Age	0.77 ± 0.19	10.2(3.5-32.9)	<0.0001	0.82 ± 0.19	11.8(3.9-38.5)	<0.0001
Gender (female)	0.19 ± 0.31	1.2(0.6-2.2)	0.54	-0.17 ± 0.34	0.8(0.4-1.7)	0.62
Hypertension	0.73 ± 0.35	2.1(1.1-4.3)	0.02	0.74 ± 0.36	2.1(1.1-4.5)	0.03
Blood glucose	0.31 ± 0.16	1.9(1.1-2.5)	0.04*	0.52 ± 0.18	2.8(1.4-5.9)	0.002*
ACR	0.67 ± 0.17	7.4(2.8-21.7)	<0.0001	0.46 ± 0.16	4.0(1.6-10.5)	0.002
eGFR (MDRD)	-0.36 ± 0.16	0.3(0.1-0.8)	0.01			
Killip class>1				0.91 ± 0.41	2.5(1.1-5.4)	0.04
Patients with LVEF	**(n=476, deaths n=37)**			**(n=424, deaths n=33)**		
Age	0.84 ± 0.20	12.5(4.0-42.9)	<0.0001	0.88 ± 0.21	14.1(4.2-51.2)	<0.0001
Gender (female)	0.04 ± 0.35	1.0(0.5-2.1)	0.91	-0.15 ± 0.38	0.9(0.4-1.8)	0.69
LVEF	-0.06 ± 0.15	0.8(0.3-2.0)	0.68	0.06 ± 0.17	1.2(0.4-3.4)	0.70
Hypertension	0.80 ± 0.37	2.2(1.1-4.8)	0.02	0.76 ± 0.39	2.1(1.1-4.8)	0.04
ACR	0.71 ± 0.19	8.4(2.9-27.5)	<0.0001	0.42 ± 0.18	3.6(1.3-10.7)	0.01
Blood glucose				0.44 ± 0.19	2.4(1.2-5.3)	0.01*
Mode of death: non-CV causes						
All Patients	**(n=557, deaths n=81)**			**(n=424, deaths n=65)**		
Age	0.86 ± 0.12	13.3(6.5-28.4)	<0.0001	0.82 ± 0.13	11.8(5.5-25.9)	<0.0001
Gender (female)	-0.24 ± 0.25	0.8(0.5-1.3)	0.33	-0.27 ± 0.28	0.8(0.4-1.3)	0.32
Family coronary heart disease				-0.75 ± 0.36	0.5(0.2-0.9)	0.02
School Education				-0.69 ± 0.35	0.5(0.2-0.9)	0.03
Total cholesterol				-0.23 ± 0.12	0.5(0.2-0.9)	0.04
Patients with LVEF	**(n=476, deaths n=64)**			**(n=424, deaths n=53)**		
Age	0.90 ± 0.14	14.9(6.6-35.1)	<0.0001	0.84 ± 0.15	12.6(5.3-31.3)	<0.0001
Gender (female)	-0.08 ± 0.28	0.5(0.5-1.6)	0.76	-0.07 ± 0.31	0.9(0.5-1.7)	0.82
LVEF	-0.23 ± 0.12	0.5(0.2-0.9)	0.04	-0.25 ± 0.13	0.5(0.2-1.0)	0.05
Family coronary heart disease				-0.72 ± 0.39	0.5(0.2-0.9)	0.04
School Education				-0.85 ± 0.41	0.4(0.2-0.9)	0.02
Total cholesterol	-0.22 ± 0.11	0.5(0.3-0.9)	0.04			

*Non-linear association (U/J-shaped relationship); † Excluding reciprocally blood glucose and diabetes mellitus from the model; § Excluding reciprocally hypertension and blood pressure from the models.
Abbreviations as shown in Table 1

LVEF (Hosmer-Lemeshow test p=0.87, p=0.57, p=0.56, and p=0.34, respectively). The models for all-cause and causes of death showed significant fits to the data (p<0.0001 for all models). The models for all-cause mortality showed elevated discriminant power, and the C-statistic was 0.86 in for acute and sub-acute measurements with or without the inclusion of LVEF (Table 4). The highest C-statistic values were observed for other-CV causes, while the lowest values were observed for non-CV causes, and the C-statistic values were similar for CAD-HF causes and SD (Table 4).

Discussion

The major findings of this prospective long-term study indicate that:

1) Long-term mortality after ACS is independently associated with a number of clinical features, beyond traditional CV risk factors;

2) Different modes of death are associated with different clinical features; and

3) Some predictors are not linearly associated with the outcomes. Adjustment for medications and coronary mechanical reperfusion during the follow up study did not substantially affect the results obtained herein.

According with other analysis, even carried out in patients treated with primary angioplasty, we found that patients with ST-elevation myocardial infarction tend to have worse long-term prognosis, even if in the final parsimonial models this feature resulted no longer significant [17]. In the present study, age was the only clinical variable independently associated with 12-year overall mortality and all single-cause mortality, even when LVEF was included in the models. These results suggest that age, *per se*, might influence patient outcomes after ACS, regardless of the mode of death [18]. BMI showed an independent, non-linear (U-shaped) association with the overall mortality. Previous studies have shown that BMI is non-linearly associated with outcomes in patients with first myocardial infarction; however, this study provides the first information for the association of BMI with increased CAD-HF mortality [19]. The presence of diabetes mellitus and blood glucose levels were independently associated with all-cause-mortality. While the presence of diabetes mellitus was more strongly associated with CAD-HF mortality than other causes of death, the blood glucose levels were associated with all CV causes of mortality. Notably, the blood glucose levels showed an independent non-linear (J/U-shaped) association in acute models and a linear relationship in sub-acute models. Several studies have shown that hyperglycemia during ACS is associated with poor patient outcomes, but much less is known about the influence of low glucose levels [20]. Indeed, the present study suggests that in ACS patients, therapeutic efforts should be aimed at both lowering and maintaining glycemic levels in a range approximating central quartiles [21]. In

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Table 4: Predictive models for 12-year all-cause mortality and causes of death determined using the C-statistic analysis.

	Acute model	Sub-acute model
	C-statistic value	C-statistic value
Predictive model for:		
ALL-CAUSE MORTALITY		
All Patients	0.86	0.86
Patients with LVEF	0.86	0.86
CORONARY ARTERY DISEASE–HEART FAILURE PROGRESSION		
All Patients	0.75	0.78
Patients with LVEF	0.76	0.78
SUDDEN DEATH		
All patients	0.75	0.74
Patients with LVEF	0.78	0.78
OTHER CV CAUSES		
All patients	0.80	0.80
Patients with LVEF	0.80	0.79
NON-CV CAUSES		
All patients	0.69	0.73
Patients with LVEF	0.71	0.72

Abbreviations as shown in Table 1

the present study, history of hypertension and actual blood pressure values were not associated with all-cause mortality. Moreover, the present results suggest a positive association of these variables with other-CV causes and a negative association with SD. A blood pressure "paradox" in early outcome was observed in non-ST elevation ACS, thus lower blood pressure was associated with an increased risk of in-hospital CV events [22]. Indeed, the Thrombolysis in Myocardial Infarction (TIMI)-22 trials showed a J/U-shaped association between blood pressure and the risk of CV events after ACS [23]. It has been suggested that subjects with severe stenosis of the coronary arteries have a poor coronary flow reserve, making the myocardium vulnerable to low coronary perfusion pressures tolerated in patients without ischemia [24]. It has been recently shown that the elevated levels of uric acid are an independent predictor of 1-year mortality across the entire spectrum of ACS patients treated with percutaneous coronary intervention [25]. The results of the present study showed that plasma uric acid levels are associated with long-term mortality, and the predicted increased mortality primarily reflected SD. Even if uric acid causes endothelial dysfunction, leading to reduced nitric oxide levels, the mechanism of association between uric acid levels and SD remains unknown [25].

The TIMI study showed that history of angina and/or myocardial infarction is associated with short-term adverse events [26]. However, the present study showed that history of angina did not significantly influence mortality, while previous myocardial infarction highly influenced 12-year mortality after ACS. The presence of heart failure and LVEF has been strongly associated with all-cause mortality [27]. Indeed, although LVEF has been associated with both CAD-HF mortality and SD, the presence of heart failure has primarily been associated with CAD-HF mortality, suggesting that long-term SD was more affected by structural ventricular modifications than hemodynamic changes during ACS [18,19]. The present study showed that albumin excretion is one of the strongest factors associated with all-cause mortality after ACS. Indeed, albumin excretion has been primarily associated with an excess of CAD-HF and other-CV mortality, while no association with SD and non-CV mortality was observed. As albumin excretion is typically considered a marker of acute endothelial dysfunction during ACS, the degree of endothelial dysfunction might dictate different modes of death [28]. This observation might have implications for either prognostic purposes or pathophysiological interpretations of the vascular changes occurring during ACS [29,30]. Renal function has been implicated as an independent predictor of mortality in patients with ACS, and we recently showed a strong association between eGFR and 10-year event-free survival [3,31]. This evidence suggests that in the long term, variables other than eGFR might be more informative on mortality risk. The delay between the onset of symptoms and admission to the coronary care unit is important for the outcome of patients with acute myocardial infarction [32]. The results of the present study confirmed that time delay was strongly associated with all-cause mortality, and the predicted risk primarily affects CAD-HF and SD.

Limitations of the study

A major limitation of the ABC study on ACS was that, at the time of patient enrollment, percutaneous coronary angioplasty was not currently in use for reopening coronary arteries in patients with STEMI. Thus, it remains uncertain whether early mechanical reperfusion modified the predictive models. However, we observed that the results of the predictive model were similar for patients with STEMI and NTEMI. Furthermore, the data adjustment for thrombolytic treatment, percutaneous coronary angioplasty and coronary artery bypass graft surgery did not modify the results of the study. Furthermore, the design and analysis of the present study did not consider the extent and severity of coronary disease, as the anatomic burden is an important determinant of prognosis. Because this study was conducted in Caucasian patients, we cannot generalize these findings to other populations and ethnic groups.

Conclusion

The ABC-2 study identified clinical predictors of long-term mortality after ACS that might help prognostication, patient education, and risk modification. Furthermore, the present study showed that the analysis of the modes of death might improve the risk assessment.

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Contributors

Dr. Berton and Dr. Palatini designed the study. Dr. Cordiano and Dr. Palmieri contributed to the original data collection. Dr. Cavuto and Dr. Cordiano contributed to data handling and patient follow-up. Dr. Cordiano and Dr. Pellegrinet contributed to the creation of the dataset and preparation of the tables and figures. Dr. Berton contributed to the analysis and interpretation of the data and the preparation of the manuscript. All authors contributed to the accuracy of the data analysis.

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Editorial

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Atherosclerosis, Cancer, Wound Healing, and Inflammation - Shared or Parallel Evolution

Alexandra Lucas[1*]

Wound healing is a complex process involving inflammatory cell activation and invasion as well as scar tissue deposition (in the form of fibrotic tissue and collagen matrix). With tissue repair there is active cell proliferation designed to heal the damaged tissues. Recent work has suggested that cancer is a form of dysregulated wound healing where inflammatory responses and cellular proliferation goes awry. Additionally other diseases such as the highly prevalent atherosclerotic coronary plaque are hypothesized to be a form of unregulated wound healing. The 'Response to Injury' hypothesis was first presented by Russell Ross as an explanation for atherosclerosis. The basic premise for this theory on the etiology of atherosclerotic arterial disease is that all forms of damage to the arterial wall, whether hypertension, hyperlipidemia, angioplasty injury or transplantation, cause an accelerated injury response with aggressive inflammatory cell responses and cell proliferation, in short an unchecked form of wound healing. Prior to Dr Ross' theory, Earl Benditt postulated that human atheromata were benign intimal tumors. He demonstrated that many atherosclerotic plaques were derived from individual smooth muscle cells using X chromosome inactivation patterns with results that were highly suggestive of a proliferating monoclonal tumour cell. More recent work has now linked excess inflammation with growth and instability of atherosclerotic plaque and with progression of invasive cancers. There are thus now many parallels in developing cancer and atherosclerosis and many close associations between cancer, atheroma and wound healing. These findings raise one basic question – Are carcinogenesis and atherogenesis manifestations of the same initiating disease generating events or simply parallel manifestations of similar pathogenic disease mechanisms, e.g. are these shared or parallel evolutions.

The history of our understanding of the pathogenesis of wound healing and inflammation helps in understanding these disorders and the underlying mechanisms of disease. Ilya Ilyich Mechnikov (1845-1916), a Russian biologist and zoologist who moved to work at the Institute Pasteur in Paris, was the first to discover the existence of innate immunity, also termed inflammation. Although the innate immune system is now known to cure the majority of infections and drives wound healing after injury long before the adaptive immune response becomes active, Mechnikov's initial discovery of this more ancient defense system was viewed with some suspicion and he shared the Nobel Prize for his work in 1908 with Paul Ehrlich. He discovered the inflammatory / innate immune response system by examining wound healing using basic scientific bench work, not translational nor applied research designed to examine a specific disease. In these experiments, he inserted splinters into transparent star fish and noted an immediate rapid massing of inflammatory cells around the splinter. Subsequently similar early cell responses were seen in water fleas infected with microbes. Within minutes he saw a rapid response to these injuries and infections with a swarming of inflammatory mononuclear cells around the offending agents. Another early pioneer was Rudolf Virchow who is attributed with first describing the close association between vascular cell injury, clot formation and inflammation, Virchow's triad of arterial or endothelial injury, stasis of blood flow, and hypercoagulability / thrombosis. Virchow was a remarkable German physician and scientist (1821-1902) who worked as a true Renaissance man, an anthropologist and biologist who improved public health in addition to his work in pathology and science. These two remarkable scientists thus developed the basis for our current understanding of innate immunity and wound healing which are only in recent years becoming recognized as pivotal driving events in progression of wound healing, atheroma, and cancer and no doubt many other disorders.

The parallels in these diseases become more evident with each new study into the mechanisms underlying the development of cancer and atherosclerosis. Certainly with atherosclerosis, the original theories suggested either a pure smooth muscle cell proliferative etiology or insudation of lipids, the lipid hypothesis with fat filled foam cells initiating plaque growth. And as mentioned there were early proposals of benign monoclonal tumor cell growth in the intimal layer initiating plaque growth. Current work has however changed these original ideas and the central roles of inflammatory macrophage (foam cells) and T cells in driving cell proliferation, tissue breakdown, and even plaque instability and rupture are now recognized. When plaque is unstable inflammatory macrophage can release metabolizing proteases that disrupt the overlying fibrous cap exposing the inner thrombotic plaque. The inner plaque 'gruel', which is the meaning of the Greek term 'athero', is composed of collagen and fat in addition to invading cells. This gruel is highly thrombotic and exposure to circulating blood leads to sudden thrombotic occlusions, the cause for heart attacks, strokes and peripheral gangrene. These same events also drive progressive dilatation and rupture of the arterial wall, e.g. aneurysm formation which in cases of sudden rupture has very high associated mortality.

In atherosclerotic plaque progression and rupture or in aneurysmal dilatation one sees a veritable army of inflammatory macrophage and T cells, adipocytes, smooth muscle cells as well as fibroblasts interacting to either cause arterial damage, plaque rupture or accelerated plaque growth. The damaged endothelium lining the arterial wall and smooth muscle cells also contribute to increased inflammatory responses and atheroma progression. Cell invasion and proliferation is driven by inflammatory cytokines, chemokines and growth factors. The serine proteases in the thrombotic and

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thrombolytic cascades also interact with inflammatory mediators both causing plaque rupture or hemorrhage or sudden thrombotic arterial occlusions. The coagulation proteases also activate inflammatory cells and mediators in a reciprocal fashion such that inflammation begets clot and clot begets inflammation, much as Virchow predicted.

Now current researchers are finding that cancers are also driven by injury and inflammation with similar activations of inflammatory mediators, growth factors and indeed the serine proteases in the coagulation cascades. In fact a tripartite interaction between chronic infections, recurrent inflammation and damage to the colon epithelium is believed to drive cancer progression. Excess inflammation as in inflammatory bowel disease, Crohn's disease and ulcerative colitis, are associated with increased risk of colon cancer. Selected chronic bacterial infections also increase risk of developing tumours in the gastrointestinal tract. Obesity is associated with elevated inflammation and increased risk for early cardiovascular diseases. More recent work has begun to uncover an association between obesity and risk for some cancers, similar to the risk of cardiovascular disease and diabetes in obesity. Cancers throughout the mammalian body are now reported to arise and progress both at sites of injury and scar and in areas with recurrent inflammation and irritation. The same inflammatory responses cells, e.g. Neutrophils, macrophage and T cells are activated and in some cancers appear to drive tumour progression. The close associations of tumor associate macrophage (TAM) and tumor associate neutrophils (TAN) can both initiate cancer cell growth and progression. The recurrent inflammation seen in inflammatory bowel disease is closely associated with increased risk of cancer development and many of the same inflammatory mediators are reported as associated with or driving cancer growth. The cytokine interleukin 6 via STAT signaling, the chemokines that attract cells to sit of injury, caspase associated inflammasome, the thrombotic and thrombolytic serine proteases are present both as markers for tumors as well as potentially driving cancer growth and spread. Many newer therapeutic approaches to cancer have been based upon targeting inflammatory mediator such as chemokies and cytokines and growth factors. The thrombolytic protease, urokinase and tissue type plasminogen activator (tPA and uPA) can activate matrix degrading enzymes (matrix metalloproteinases or MMPs) that in turn can allow cell invasion and increased tumor angiogenesis. The prostaglandins also are active in cancer as well as in atherosclerosis and treatment with aspirin and NSAIDs are associated with altered risk of cancer or plaque rupture and thrombotis. Many of these parallels in cancer and atherosclerosis are also seen in wound healing. These parallels in disease progression in cancer, atherosclerosis, and wound healing were beautifully described in a recent talk by Dr Pual Martin at the Keystone meeting on Carcinogenesis and Inflammation.

However, although there are many similar or parallel events driving both diseases, cancers and atheromata, these are not absolute matches for these often similar events. While many of the same pathways and inflammatory responses are seen in atheroma, cancer and wound healing each tumor and each individual has unique modifying events. We have not yet proven whether these are simply similar parallel evolutions of common similar defense responses or whether these diseases represent a shared origin in pathogenic mechanisms or whether these diseases have evolved from a similar set of stimulating events but differing initiators. Thus these observations form a foundation upon which to pursue further studies to examine the origins of these diseases and shared events driven by inflammatory events in wound healing. Further work on these shared events may indeed lead to discovery of newer therapeutic targets shared by many diseases with associated inflammation driven pathogenesis.

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