



REGIONE DEL VENETO

PROGETTO REGIONALE SU MALATTIA CARDIACA E NEOPLASIA

Progetto triennale - Giugno 2015-Maggio 2018
Presentazione del II Anno di Lavoro
Revisione attuale: 30 giugno 2017

*Alla Presidenza della Regione Veneto
Dr. Luca Zaia*

Venezia



The ABC Study on Heart Disease

The longest running follow up on coronary artery disease

"Nel cercare qualcosa contano un'enorme curiosità, la tenacia ed il persistere, nonostante le amarezze e le delusioni: per ogni vittoria ti aspettano cento fallimenti".

Albert Bruce Sabin

"Il sapere, dunque, trascende i singoli e viene a porsi oltre i singoli, e si pone, di fronte all'uomo quale è di fatto, come liberazione dalla passività, in un giusto rapporto sociale."

Platone, Repubblica

**Questo libro è dedicato alle mille persone che hanno lavorato con noi,
con impegno e buona volontà.
E a tutte quelle che ci hanno sostenuto, anche solo col pensiero.**

*Responsabile del Progetto
Giuseppe Berton, MD, FESC
Cardiologia, Conegliano*



The ABC Study on Heart Disease

*Motto dell'Associazione:
Seguire il Paziente nel lungo tempo*

*Motto of our Association
Follow the Patient over time*





The ABC Study on Heart Disease

Oggetto: Rendiconto del secondo anno del Progetto Regionale triennale

*The ABC Study on Acute Coronary Syndrome)**

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

Conegliano, 31 gennaio 2017

Gentile Presidente Luca Zaia,

Accludo a questa lettera il rendiconto del secondo anno del Progetto Regionale in oggetto, per ringraziarla dell'opportunità che la Regione Veneto ci ha dato di lavorare sulla malattia di cuore e neoplasie. E per il sostegno concreto ad un progetto clinico-scientifico che dura da molti anni.

Ora questo progetto ha acquisito caratteristiche, a cominciare dalla lunghezza del follow up (completati 17 anni), che lo rendono unico a livello internazionale.

Vorremmo anche proporre 2 nuovi progetti da affiancare a quello in atto, se la nostra Regione li considererà di interesse.

Inoltre portiamo avanti il corso di Statistica Medica, il primo a livello ospedaliero in Veneto, che ha avuto insperato successo, con partecipanti da ogni parte della Regione.

La Regione ci stimola anche a fare "prevenzione della malattia cardiaca" e cerchiamo di impegnarci per quello che possiamo.

Tutto questo senza nominare del progetto neoplasie nella malattia di cuore, una materia che credo possa essere considerata "un dramma nel dramma" soprattutto per i pazienti. Su questo spero pianteremo un progetto scientifico "strong".

Tengo però a dire che la base di tutto questo è strettamente clinico-pratica, e si fonda sul modo che usiamo di seguire il paziente.

Sarei contento se, pian piano, anche in Veneto e in Italia, si affermasse l'idea che seguire il paziente nel lungo tempo, è cruciale...per mille cose, ma qualche segnale c'è.

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

Giuseppe Berton
Cardiologia, Conegliano

giube.s@alice.it

ospedale 0438663613

personale 3496078176

Al Dr. Luca Coletto
Assessore alla Sanita'
Regione Veneto, Venezia

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

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

Al Dr. Tiziano Martello
Dirigente Assistenza Ospedaliera
Regione Veneto, Venezia

Al Direttore Generale ULSS 2 Marca Trevigiana
Dr. Francesco Benazzi
Treviso

Al Direttore Generale ULSS 7 Pedemontana
Dr. Giorgio Roberti
Bassano del Grappa (VI)

Al Direttore Generale ULSS 5 Polesana
Dr. Antonio Fernando Compostella
Rovigo

Al Direttore UOC Affari Generali ULSS 2
Dr. Livio Dal Cin
Pieve di Soligo (TV)

Al Direttore UOC Cardiologia ULSS 2 Marca Trevigiana
Dr. Roberto Mantovan
Conegliano (TV)

REGIONE DEL VENETO



ULSS2
MARCA TREVIGIANA

REGIONE DEL VENETO



ULSS5
POLESANA

REGIONE DEL VENETO

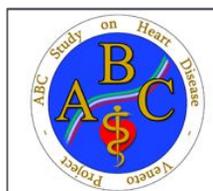


ULSS7
PEDEMONTANA

*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)

Francesco Bagato, MD
U.O.C. Cardiologia – Ospedale di Adria (RO)

Editing del Rendiconto del Progetto Regionale
Beatrice Segafredo, MD
Cardiologia – Bassano del Grappa (VI)



The ABC Study on Heart Disease

ABC Study on Heart Disease Association (A veneto Region Project)

Coordinatori Scientifici del Progetto Regionale :

Dr. Giuseppe Berton, MD, FESC
Presidente, Responsabile clinico-scientifico
giube.s@alice.it

Dr. Rocco Cordiano, MD
Vice-Presidente
rocco.cordiano@gmail.com

Dr.ssa Fiorella Cavuto, MD
Segretario
fiorellacavuto@me.com

Website: www.abcheartdiseasestudy.org

E-mail : info@abcheartdiseasestudy.org

Cod. Fisc.: 91041990267

Campi di interesse

1. Sindrome coronarica acuta:

- A) Disfunzione endoteliale acuta
- B) Processo infiammatorio acuto
- C) Scompenso di cuore

2. Follow-up a lungo termine nella sindrome coronarica acuta:

- A) Studio delle cause di decesso nel lungo termine
- B) Analisi della sopravvivenza nel lungo termine
- C) Ricerca di marcatori di sopravvivenza

3. Relazione tra sindrome coronarica acuta e neoplasia maligna:

- A) Tipi di neoplasia.
- B) Tempo alla neoplasia, durata della neoplasia, sopravvivenza
- C) Ricerca di associazioni tra malattia di cuore e neoplasia

INDICE

1. Presentazione del Progetto Regionale
 - Documenti
 - Sviluppo
2. The ABC Study Association
3. Risultati preliminari ABC Study
4. ABC-4 Study on Heart Disease - Progetto Neoplasia
5. RISULTATI I ANNO
6. RISULTATI II ANNO
7. “Guadagnare Salute”: Attività Formativa e prevenzione
8. Bibliografia

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 Disease"
- b) promuovere e sostenere il progetto della Regione Veneto "The ABC – 4 Study on Heart Disease", di cui alla deliberazione n. 748 del 14 maggio 2015
- c) promuovere, sostenere e mantenere il website "www.abcheartdeseasestudy.org, che è l'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.
- g) sulla base ti tutti i precedenti punti:
 - favorire la prevenzione della malattia cardiaca e neoplastica
 - promuovere attivita' formativa ed educativa per operatori sanitari e cittadinanza.



Capitolo 1

Presentazione del Progetto Regionale

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



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.

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 Diretori 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, Tavolo 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 del segno, 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 que st'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 del 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 del 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.



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,

Accludo questa lettera al rendiconto del primo anno del Progetto Regionale in oggetto, per ringraziarla dell'opportunità che la Regione Veneto ci ha dato di lavorare sulla malattia di cuore e neoplasie. E per il sostegno concreto che la Regione ci da, ad un progetto clinico-scientifico che dura da molti anni.

Il presente rendiconto riporta: 1) lo sviluppo del progetto, 2) i risultati osservazionali di base, 3) l'attività formativa professionale e 4) divulgativa associata all'intera 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 rivascularizzazione meccanica di angioplastica percutanea non primaria durante l'intero follow up
- procedure di rivascularizzazione 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, puntare la nostra attenzione anche sulla prevenzione e su aspetti formativi per operatori sanitari e cittadinanza.

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

giube.s@alice.it
ospedale 0438663613
personale 3496078176

Capitolo 2



The ABC Study on Heart Disease



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:

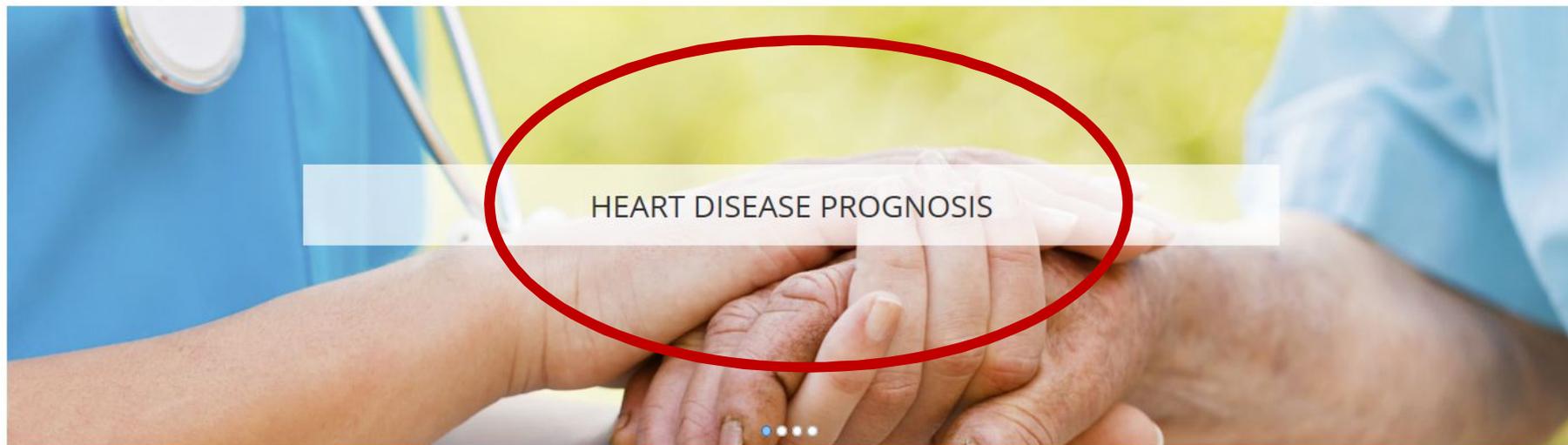
- a) promuovere e sostenere il progetto clinico-scientifico "the ABC Study on Heart Disease", già operativo dal 1992.
- b) promuovere e sostenere il progetto della Regione Veneto "the ABC-4 Study on Heart Disease", DGR del Veneto n°748 del 14 maggio 2015.
- c) promuovere, sostenere e mantenere il website: 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.

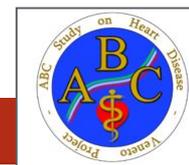


The ABC Study on Heart Disease

- [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”**.

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. MM.	INIZIO SINTOMI (SOLO IMA) HH MM (ore prima del ricovero)	DURATA DEL RICOVERO GG.	STATO CIVILE SECONDA PROFESSIONE 1 2 3 4 1 2 3 4 PREVISTO	PESO KG	ALTEZZA CM	SESSO F=1 M=2	C
	ID	IMA CON	ETA	GG MM AN	GG MM AA	HH	MM	G_RIC	STATO CIV SCOLARI PROFESSI	PESO	ALT	SEX_FM	C
M	151	2	74	31/8/22	29/7/92	13,30		9	4 1 3	50	160	1	
PA	152	2	73	29/11/23	30/7/92	11,00		14	2 1 1	70	150	1	
PA	153	2	86	25/5/11	3/8/92	14,00		18	4 1 1	71	160	1	
CA	154	2	75	7/3/22	5/8/92	12,30		9	2 1 2	75	170	2	
CA	155	1	63	17/4/34	16/8/92	4,00	4,00	9	2 1 4	86	168	2	
	156	2	74	1/3/23	28/7/92	9,15		4	2 2 2	52	168	2	
CA	157	1	93	9/1/04	26/8/92	7,00	5,00	3	4 1 2	63	160	1	
GA	158	1	67	3/2/30	1/9/92	1,30	3,00	12	2 4 5	85	176	2	
CA	159	1	67	24/6/30	2/9/92	1,35	40,00	18	2 1 2	67	165	2	
Z	160	2	70	16/12/26	8/9/92	18,30		20	4 1 4	61	165	1	
BA	161	1	69	29/1/28	9/9/92	19,15	2,15	16	2 3 9	82	168	2	
B	162	2	73	3/11/23	14/9/92	8,30		5	2 1 2	70	170	2	
BA	163	1	84	2/8/13	15/9/92	9,40	3,00	4	4 1 1	65	162	1	
SA	164	1	60	16/11/36	12/9/92	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

Rosa Palmieri, MD

Consultant Cardiologist

Adria General Hospital, Italy

Paolo Palatini, MD

Professor of Medicine

University of Padova, Italy

Rocco Cordiano, MD

Consultant Cardiologist

Adria General Hospital, Italy

Fiorella Cavuto, MD

Consultant Cardiologist

Bassano del Grappa General Hospital, Italy

Acknowledgments

... We are deeply grateful to Dr. **Paolo Mormino** for his assistance 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. **Sebastian 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 the follow-up of patients over the years!

Thanks to the Doctors:

Marco Pellegrinet, MD,

Francesco Bagato, MD,

for working on our research !

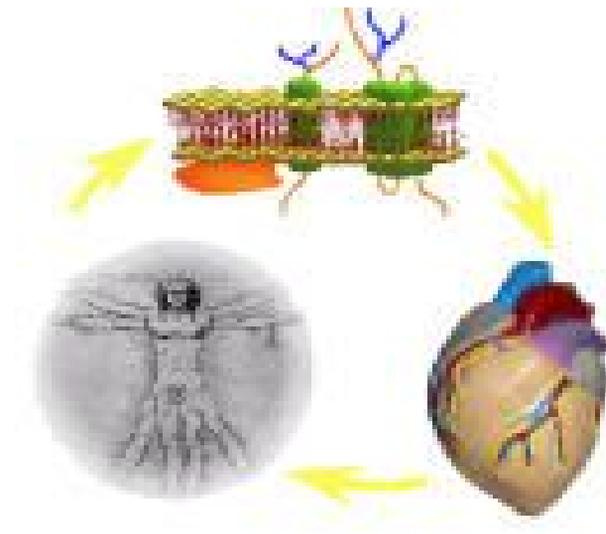
Scholarship 2016 for the Regional Project:

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?"

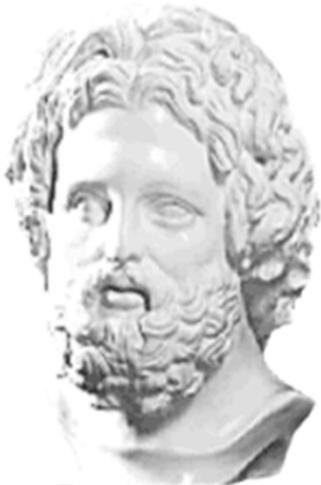


"Di tutto...!"

Prognosis...

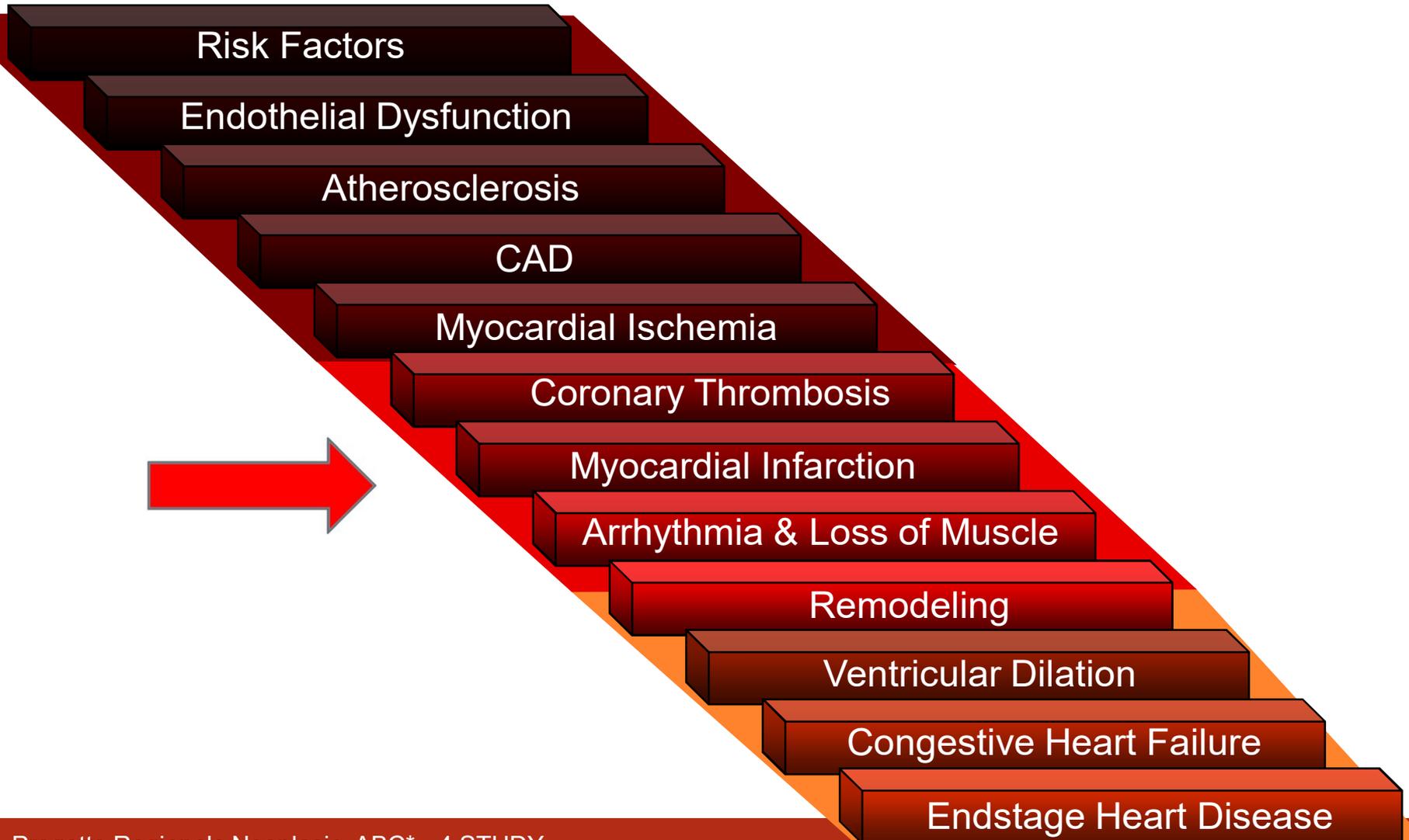
“In acute diseases it is not quite safe to prognosticate either death or recovery.”

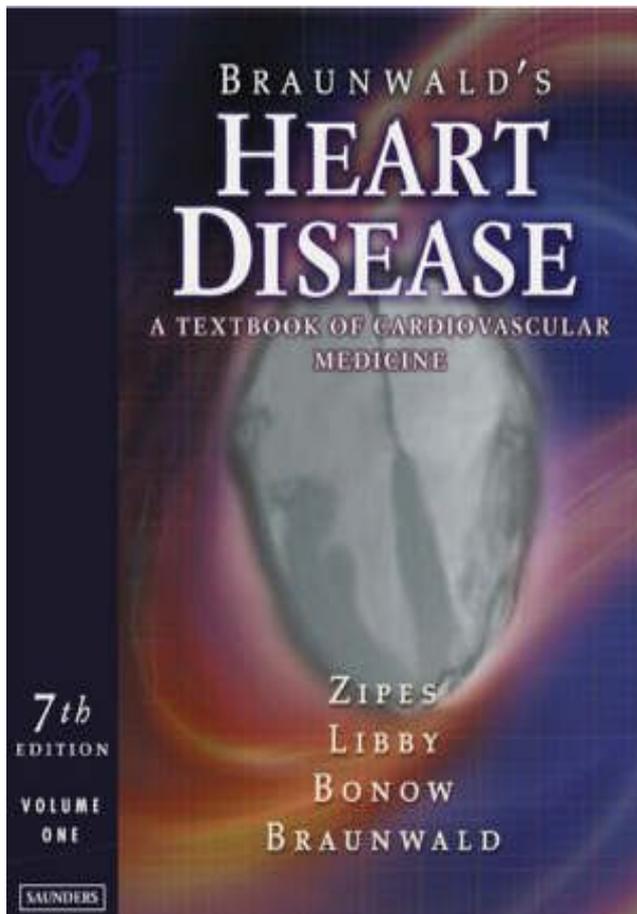
460 b.c. Aphorisms, II, 19



Ippocrate

The Progressive Development of Cardiovascular Disease





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

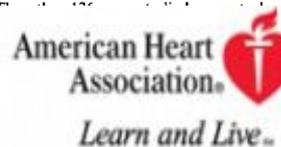
Background This study was undertaken to assess whether albumin excretion rate (AER) increases during acute myocardial infarction (AMI) and whether it predicts in-hospital mortality.

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



Circulation

JOURNAL OF THE AMERICAN HEART ASSOCIATION



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

The
American Journal
of
Cardiology

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)

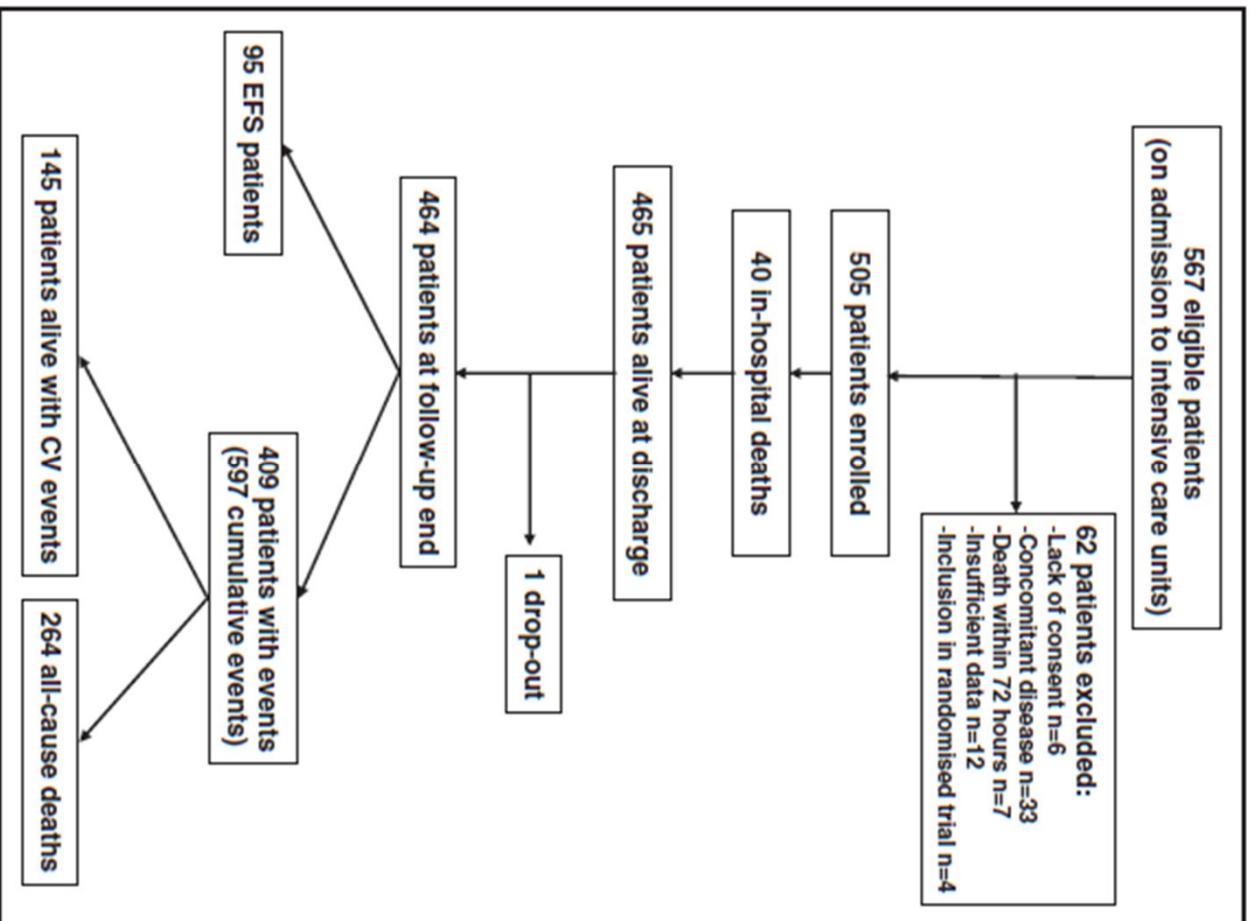
Order of Authors: Giuseppe Berton, MD; Rocco Cordiano, MD;
Fiorella Cavuto, MD; Giulia Giacomini, PhD; Renzo de Toni, PhD;
Paolo Palatini, MD.



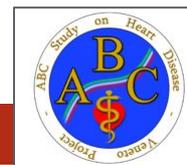
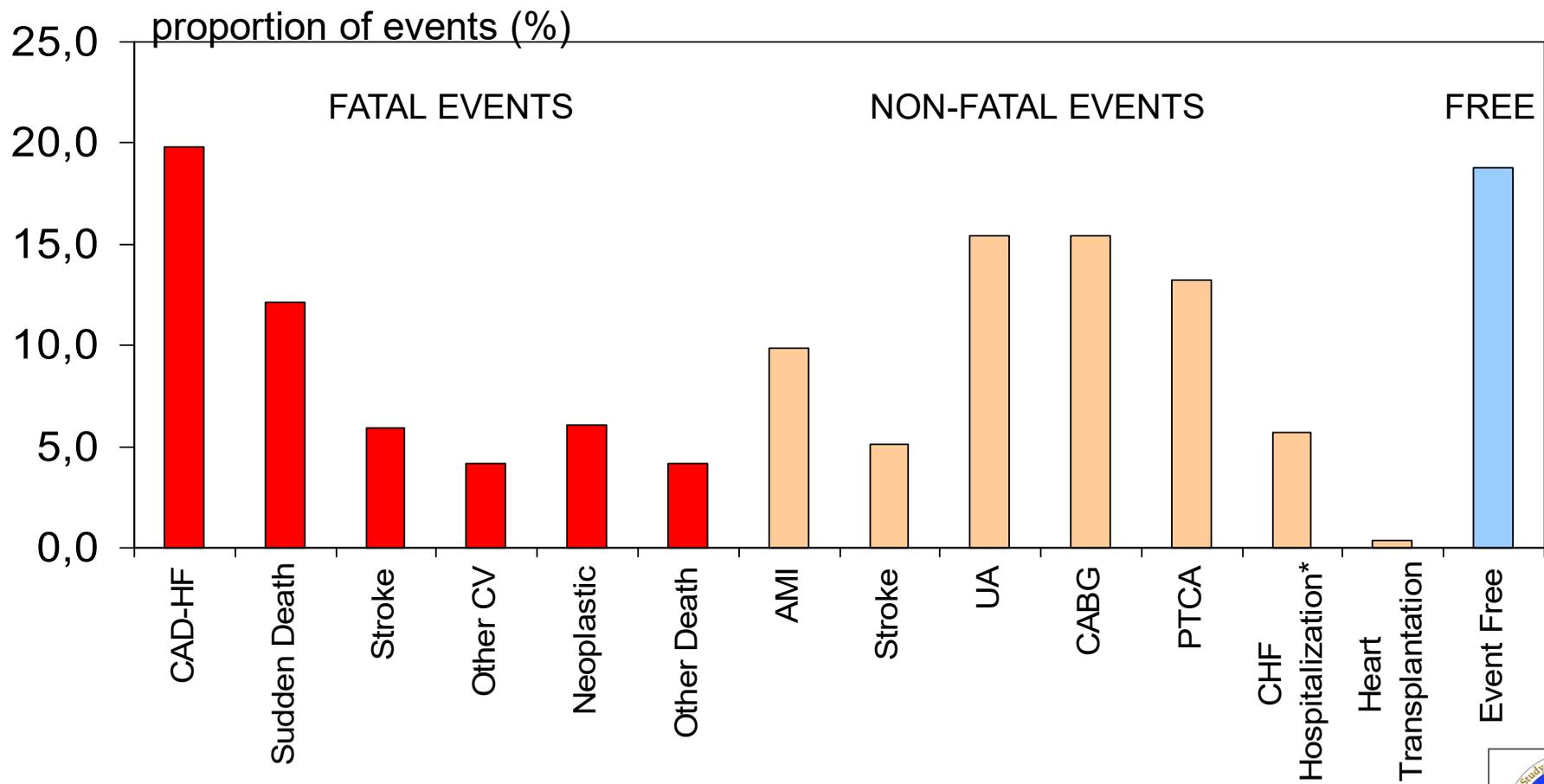
Sebbene siano ampiamente studiate le cause di mortalità a breve termine dopo Sindrome Coronarica Acuta (SCA), ad oggi sono pochissimi gli studi nel lungo termine.

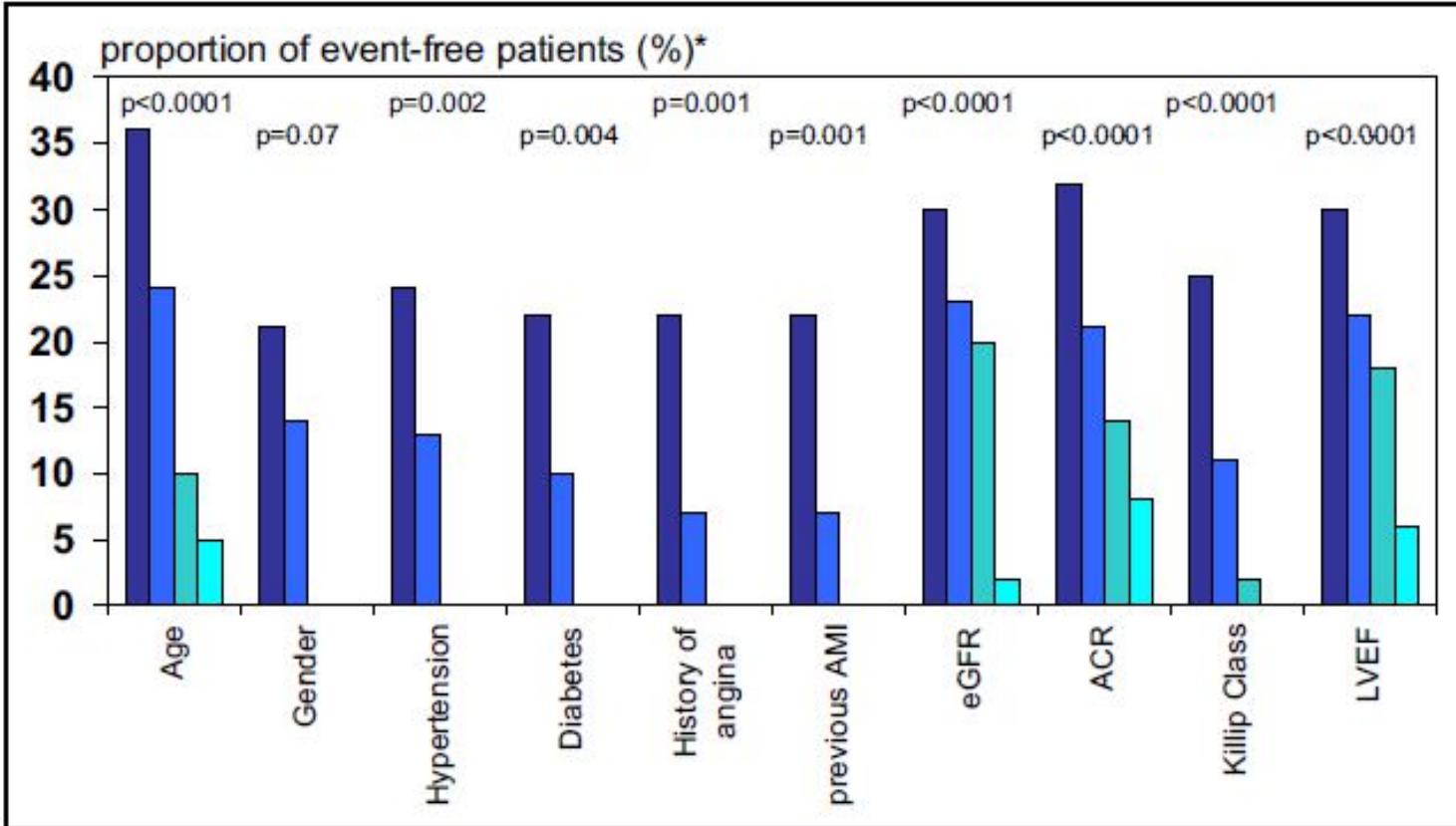
In questo studio del 2012 sono stati arruolati e seguiti con un lungo follow up (tuttora in corso) **504** pazienti con SCA.

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



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





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 dalla sindrome coronarica acuta ha evidenziato 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”.

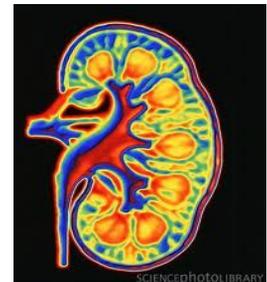
E' nostra intenzione produrre un calcolatore per stimare il rischio nella popolazione affetta da Sindrome Coronarica Acuta

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 urinaria





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 Cordiano², Rosa Palmieri², Fiorella Cavuto³, Marco Pellegrinet⁴ and Paolo Palatini⁵

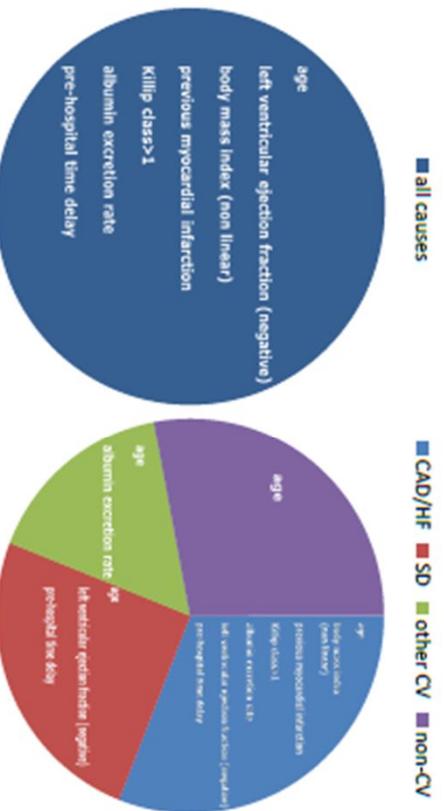
Lo scopo del presente lavoro del 2014 era quello di esaminare il valore prognostico di molteplici caratteristiche cliniche sulla mortalità a lungo termine e le cause di decesso dopo Sindrome Coronarica Acuta con un follow up di 12 anni.

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

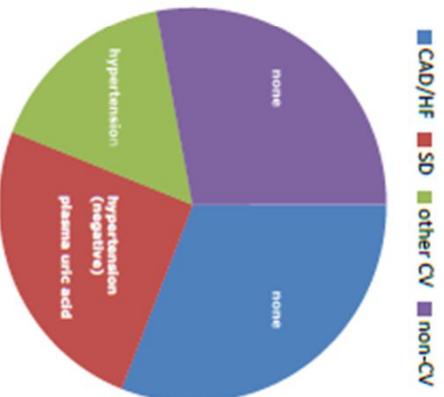


Panel b

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

The ABC*-4 STUDY on HEART
DISEASE
Progetto NEOPLASIA

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



REGIONE DEL VENETO

giunta regionale – 9^a legislatura

ALLEGATO A 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.**

**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}

¹ - Trends in cause of death after percutaneous coronary intervention.

Spoon DB, Psaltis PJ, Singh M, Holmes DR Jr, Gerth 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-Term Cause of Death in Patients Treated With Primary PCI for STEMI.

Pedersen F, Butrymovich V, Kelbæk H, Wachtell K, Holqvist S, Kastrup J, Holmvang L, Clemmensen P, Engstrom T, Grande P, Saunamäki K, Jørgensen E.

J Am Coll Cardiol. 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, Tagliari N, Ortolani P, Norcini 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 Hospitals), 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, Senzprini F, Nanni S, Tricoci P, De Palma R, Raponzi 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

⁴ Atherosclerosis, Cancer, Wound Healing, and Inflammation – Shared or Parallel Evolution.

Lucas A. /Int J Cardiovasc Res 2012, 1:1

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

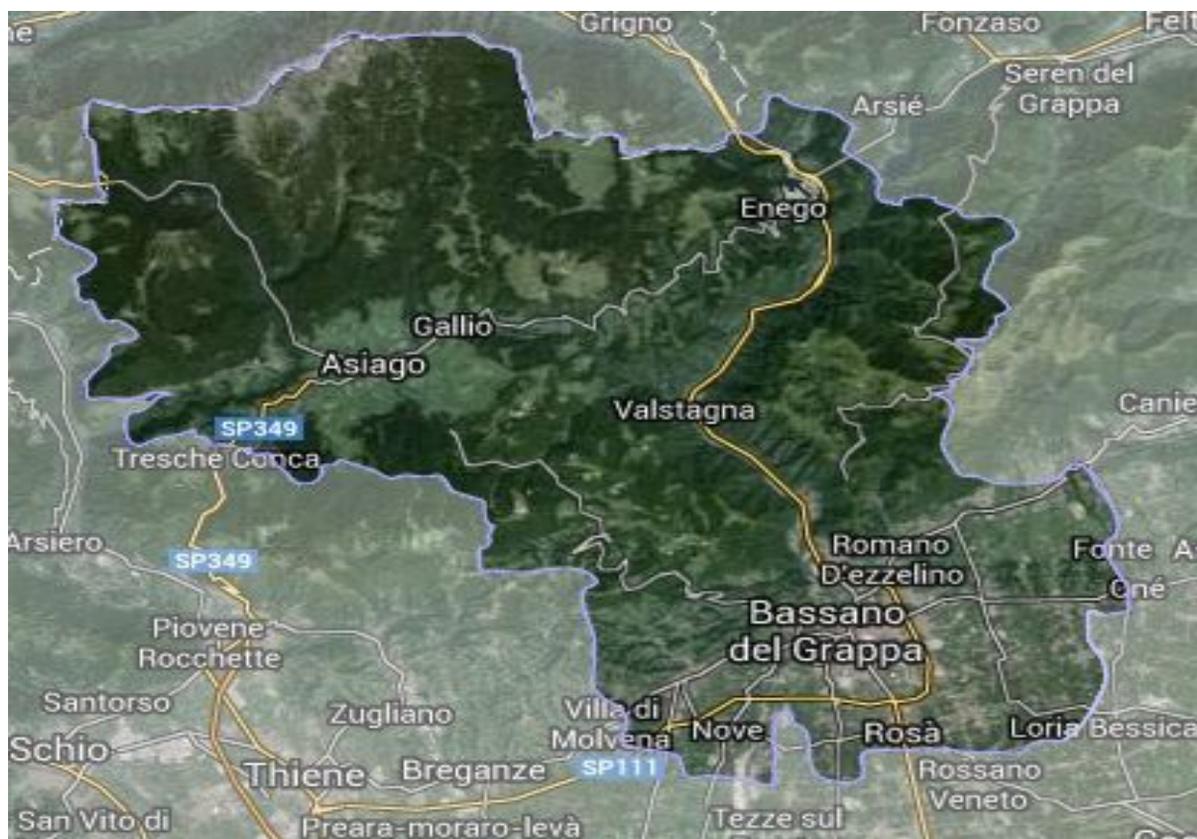
Bassano del Grappa	32,1%
Romano d'Ezzelino	12,6%

REGIONE DEL VENETO



ULSS7
PEDEMONTANA

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%

REGIONE DEL VENETO



ULSS2
MARCA TREVIGIANA



The ABC* - 4 STUDY on HEART DISEASE

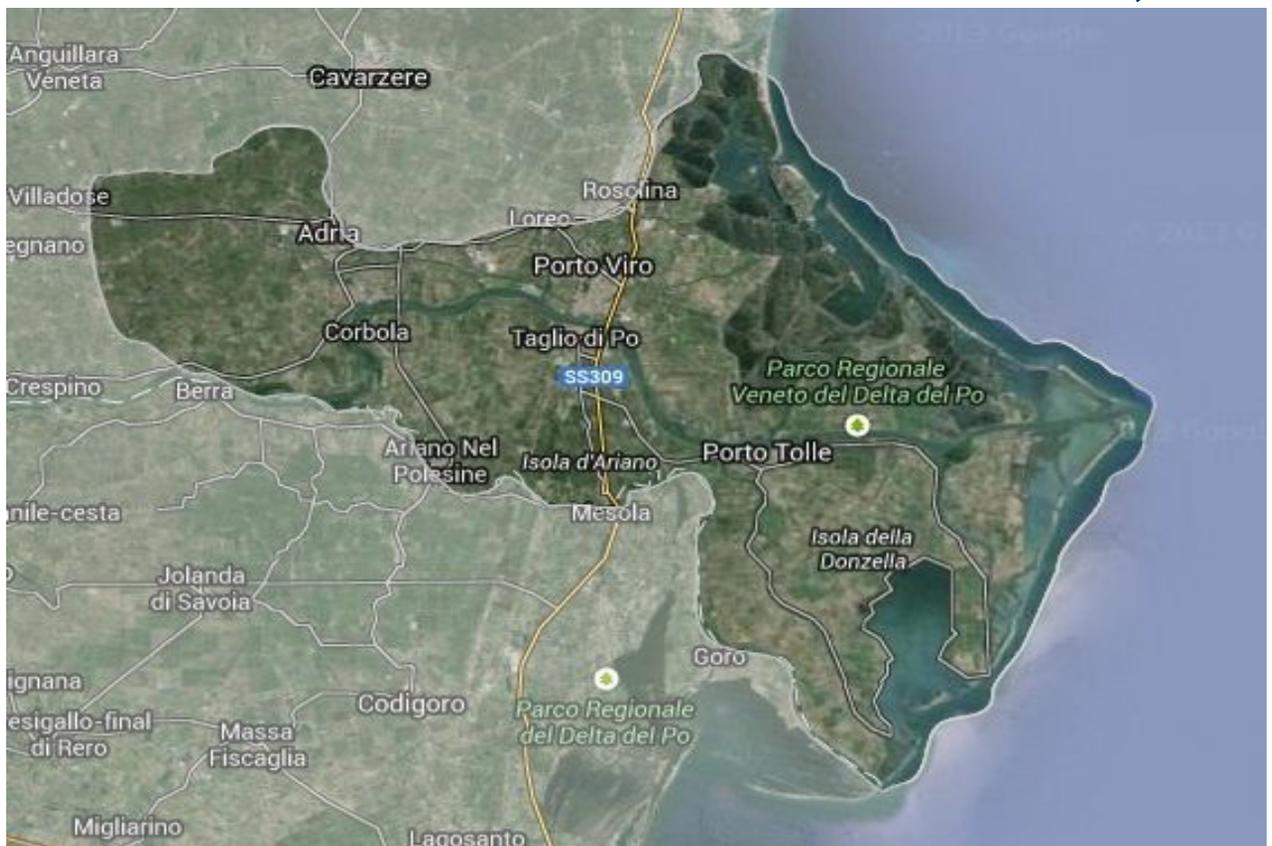
ACS patients by ULSS by City

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%

REGIONE DEL VENETO



ULSS5
POLESANA





Capitolo 5

Risultati Primo Anno del Progetto Regionale



REGIONE DEL VENETO

giunta regionale

DECRETO N. **017** DEL **13.06.2015**

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 del 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.Lg. 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 ripercussivo 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

Mod. B - copia

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;

Mod. B – copia

Ddr n.

017

del

13 AGO. 2015

pag. 2 di 3

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, _____

Mod. B - copia Ddr n. **017** del 13/06/2015 pag. 3 di 3

**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

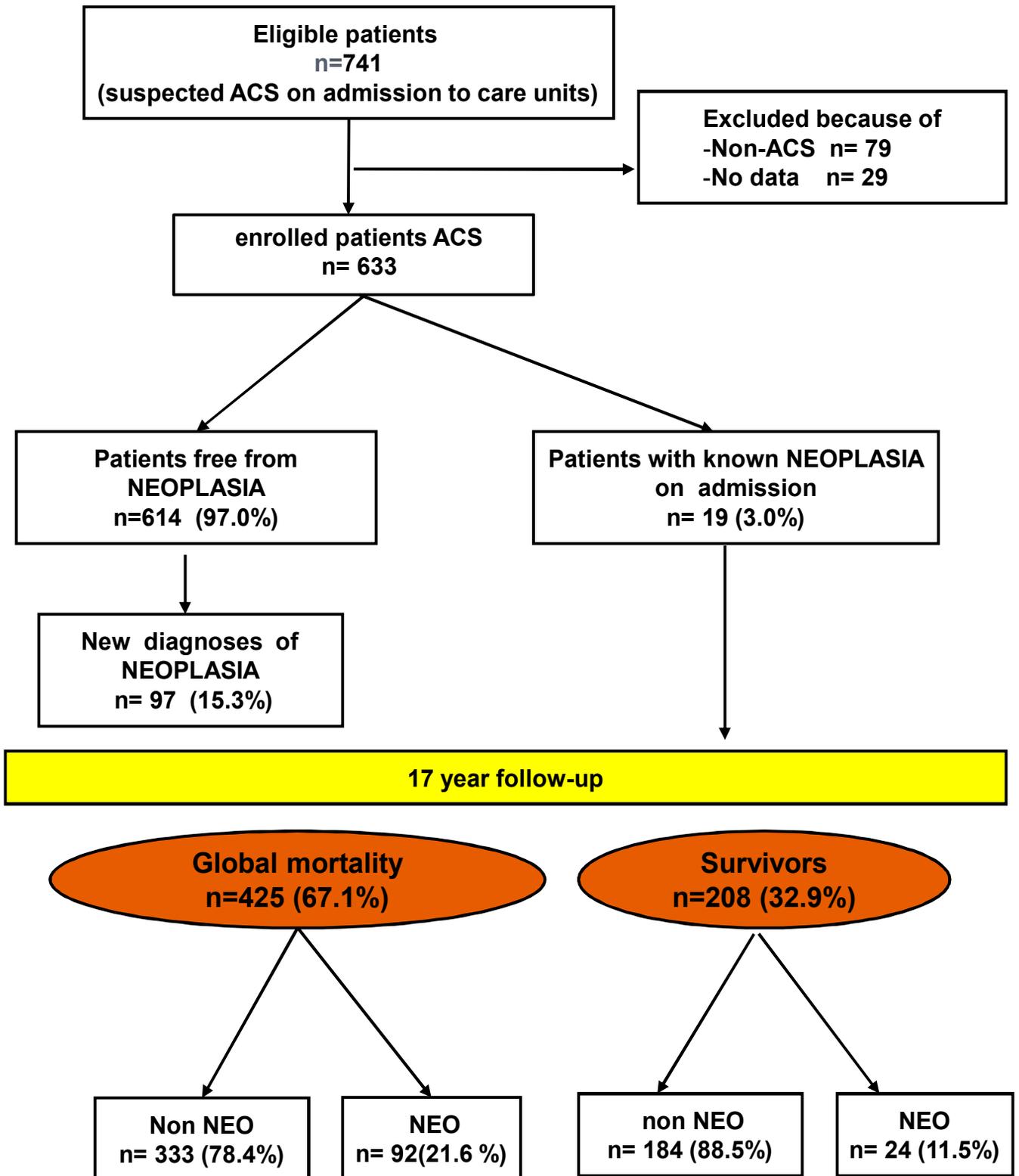
I dati osservati

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.

Table 1: Patients CharacteristicsValues are expressed as mean \pm SD and median (IQ)

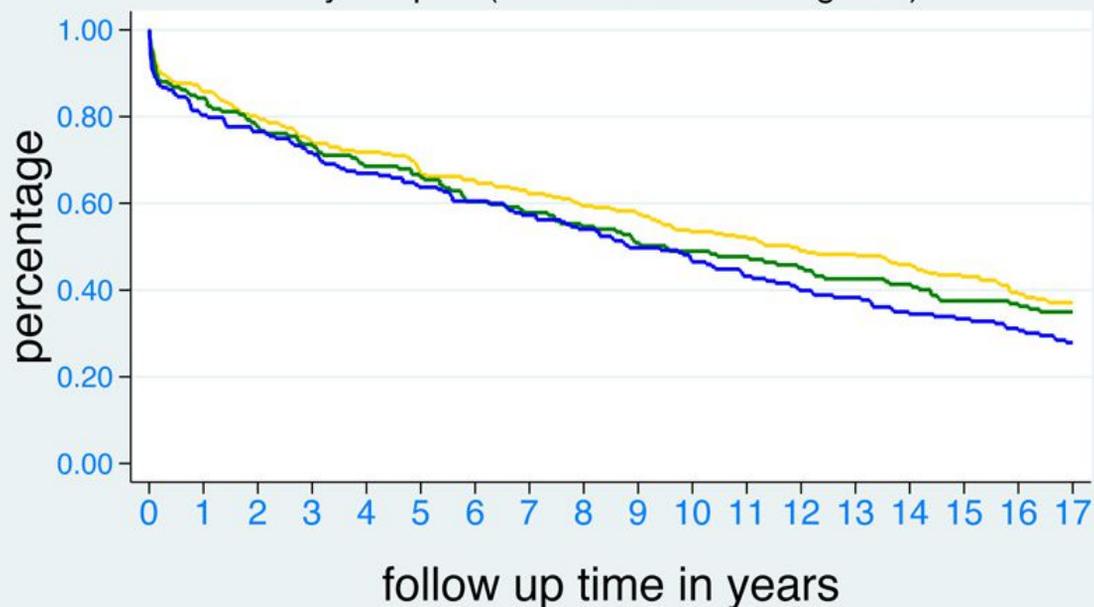
	Total	No NEOPLASIA	NEOPLASIA	TEST	p
N=	633	517	116		
Age	66.5 \pm 12.0 67 (59-75)	66.5 \pm 12.5 67 (58-76)	66.8 \pm 9.6 67 (61-74)	t=-0.24	0.81
Female gender	192 (30%)	169 (33%)	23 (20%)	chi2=7.4	0.006
ST elevation myocardial infarction	399 (63%)	335 (65%)	64 (55%)	chi2=3.8	0.05
Hypertension	308 (49%)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

FLOW CHART OF STUDY DEVELOPMENT



SURVIVING AFTER ACUTE CORONARY SYNDROME

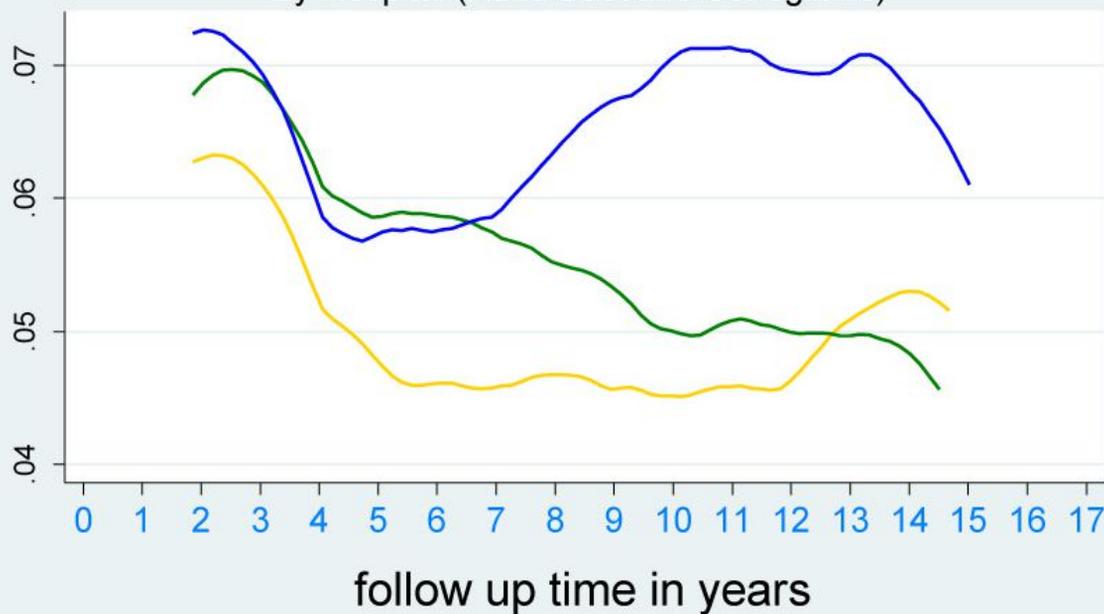
By Hospital (Adria Bassano Conegliano)



(gold=hospital 1, green=hospital 2, blue=hospital 3)

Smoothed hazard estimates after acute coronary syndrome

By Hospital (Adria Bassano Conegliano)



(gold=hospital 1, green=hospital 2, blue=hospital 3)

Table 2: Type of Neoplasia and Incidence Rate

		M		F		Tot (n)		P
Total patients with NEO		N=		N=		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%	

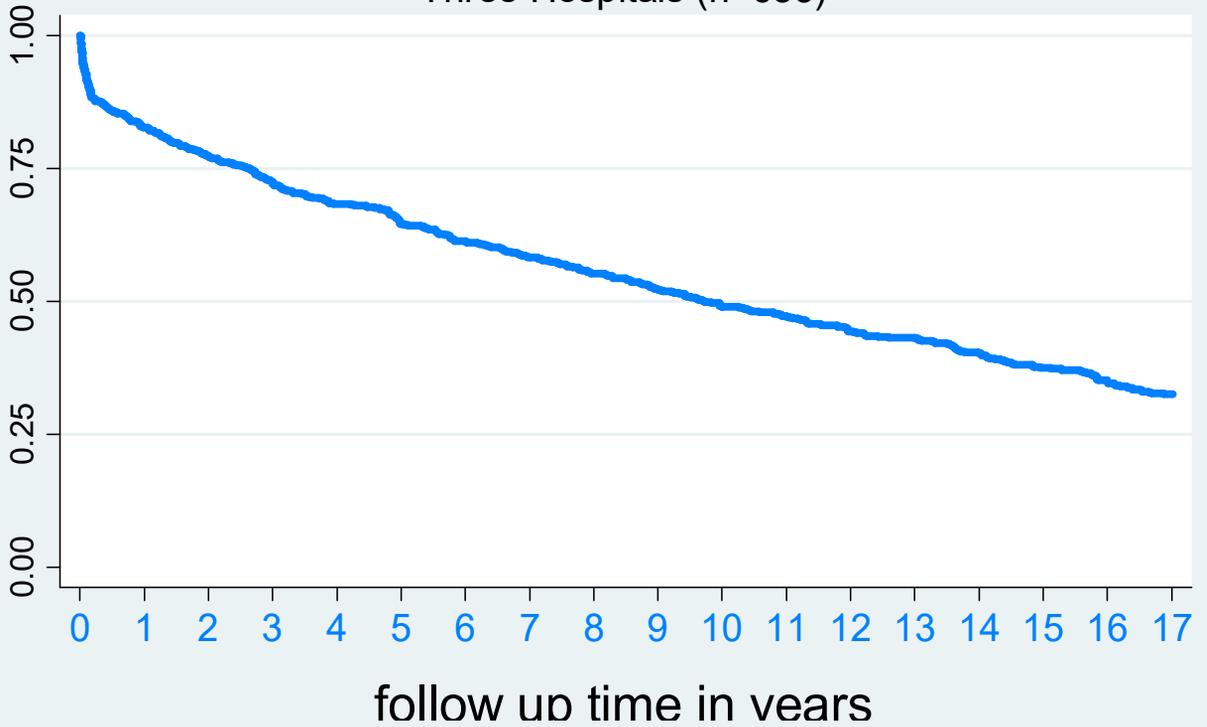
Survival Model 1

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%

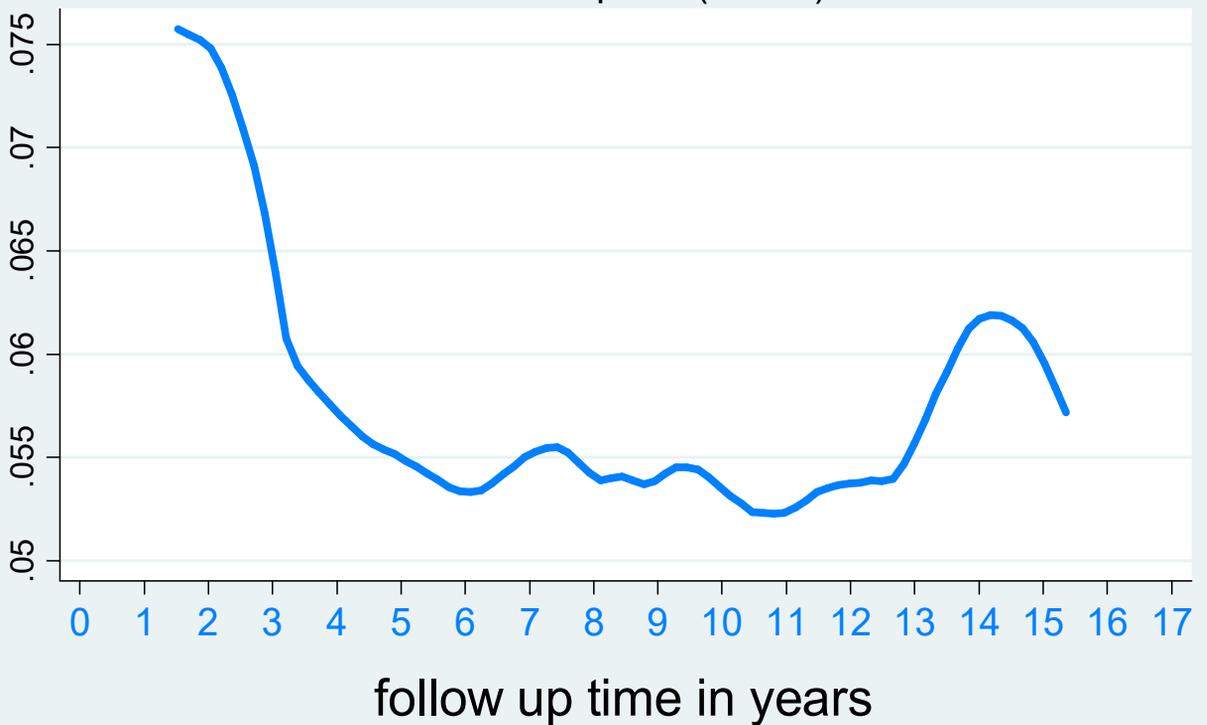
Kaplan Meier estimate of global mortality after ACS

Three Hospitals (n=633)



Instantaneous hazard rate of global mortality after ACS

Three Hospitals (n=633)



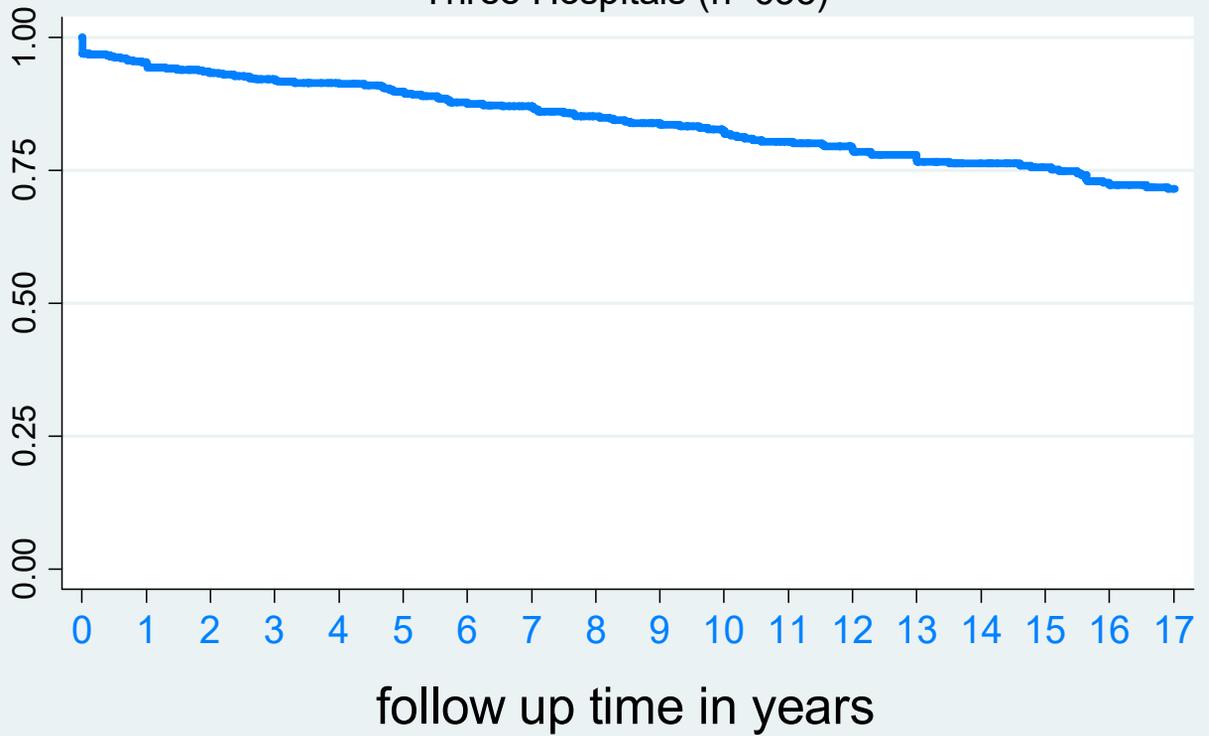
Survival Model 2

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%

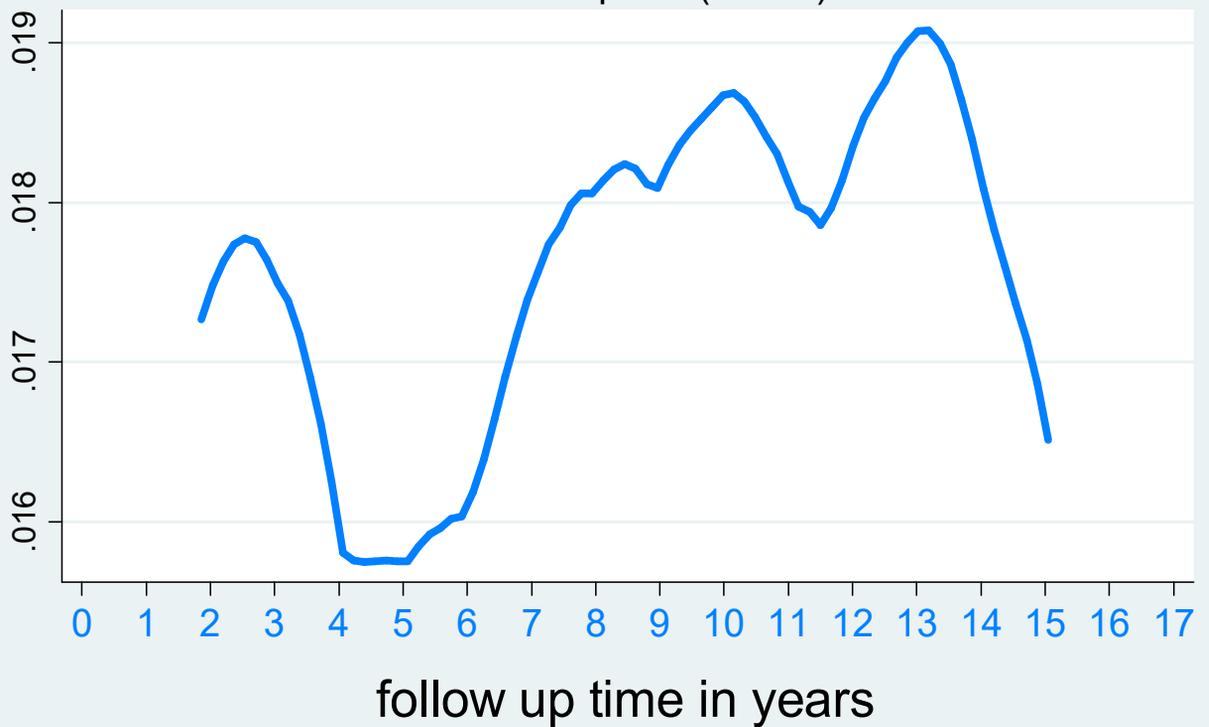
Kaplan Meier estimate of malignancies after ACS

Three Hospitals (n=633)



Smoothed hazard estimate of malignancies after ACS

Three Hospitals (n=633)



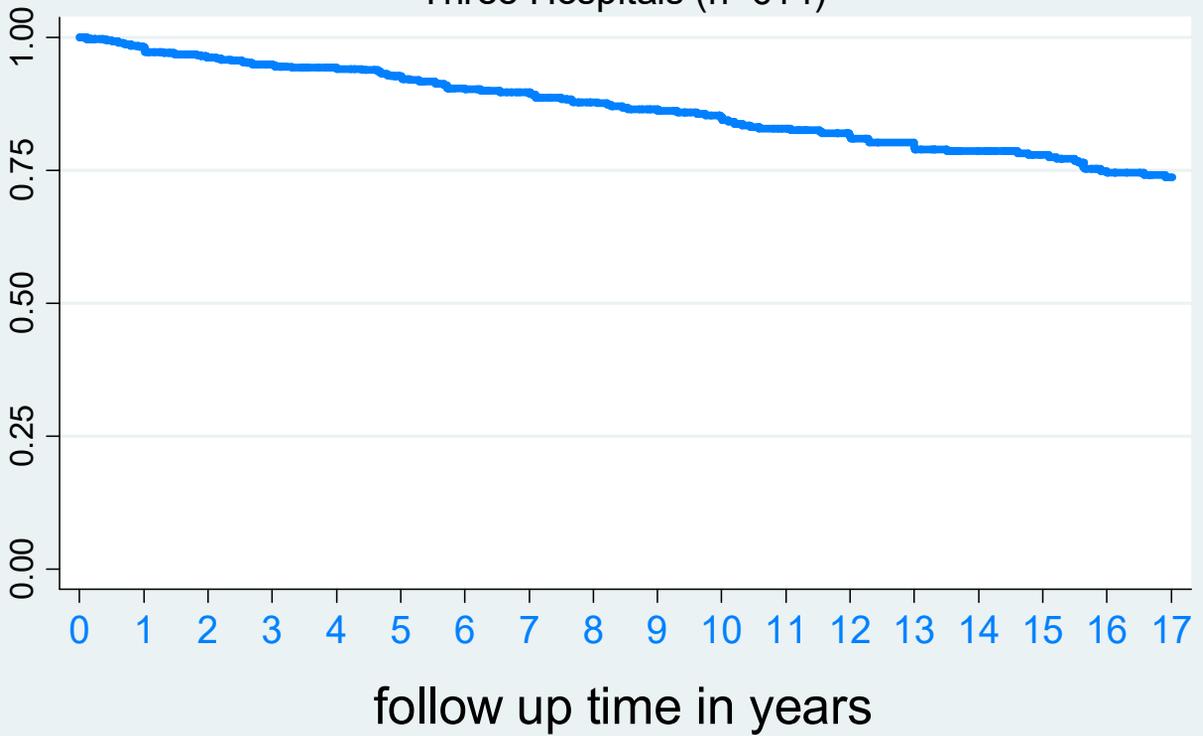
Survival Model 3

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%

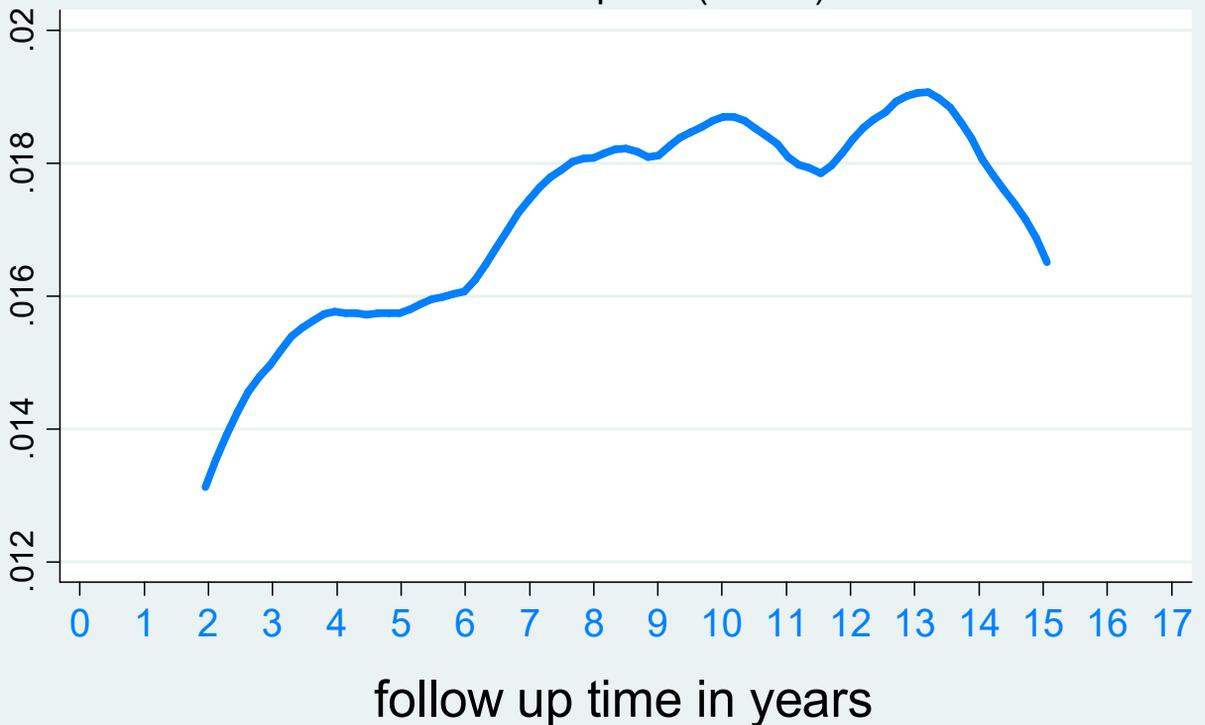
Kaplan Meier estimate of malignancies after ACS

Three Hospitals (n=614)



Smoothed hazard estimate of malignancies after ACS

Three Hospitals (n=614)



Capitolo 6

Risultati **Secondo Anno**
del Progetto Regionale



160482

**REGIONE DEL VENETO**

giunta regionale

DECRETON. 13 DEL 14.06.2016.

OGGETTO: "Studio prospettico su Neoplasia maligna dopo sindrome coronarica acuta. The ABC - 4 study on acute coronary syndrome". Impegno di spesa e liquidazione, anno 2016.

NOTE PER LA TRASPARENZA:

con il presente provvedimento si impegna per il 2016 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".

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 è ritenuto di sostenerlo impegnando per l'anno 2015 con DDR n. 17 del 13.05.2015, la somma di euro 30.000,00, 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.

Considerato che si vuole assicurare il proseguo di tali attività anche per l'anno 2016 si ritiene di impegnare la somma di euro 30.000,00, a favore dell'Azienda Ulss n. 7 di Pieve di Soligo, 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.

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 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 31.01.2017, 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 31.12.2016.

Mod. A - originale



160482

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. n. 522 del 26.04.2016 che approva le direttive per la gestione del Bilancio di previsione 2016-2018.

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. Articolo 002 trasferimenti correnti a Amministrazioni locali*), art. 002, del bilancio di previsione per l'esercizio finanziario 2016 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 31.01.2017 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 31.12.2016;
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;



180482

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

- Dr.ssa - *Francesca Russo* -

VISTO:
il Responsabile della Gestione
Sanitaria Accentrata
IL DIRETTORE
Dott. Mauro Bonfin

MB

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, _____

Mod. A - originale

Ddr n. _____

del _____

pag. 3 di 3



"ABC Study on Heart Disease Association"

website: www.abcheartdiseasestudy.org

Adria, Bassano, Conegliano, 6gennaio2017

Alle persone dell'Associazione,

Ai partecipanti al Corso di Statistica Medica,

e alle persone che sostengono le idee del nostro progetto, anche solo col pensiero!

Con gli auguri di Buon Natale e Felice Anno Nuovo a tutti voi unisco un piccolo riepilogo dell'attività svolta dalla nostra Associazione in questo anno 2016:

- 1) prima di tutto abbiamo continuato il follow-up dei pazienti con malattia di cuore. Questo viene detto per primo, anche se non lo è in ordine temporale, perché rappresenta comunque e sempre la base del nostro lavoro e del nostro studio.
- 2) da marzo a maggio 2016 abbiamo consegnato una borsa di studio (per la collaborazione al lavoro del Progetto Regionale, sezione malattia di cuore)
- 3) il 20 maggio 2016 è stato organizzato un Convegno informativo e sulla prevenzione cardiovascolare destinato alla popolazione a Bassano del Grappa (VI)
- 4) il 23 maggio 2016 è stato presentato un Poster al III World HeartFailure (European Society of Cardiology) a Firenze
- 6) da giugno a dicembre 2016 abbiamo consegnato una borsa di studio (per la collaborazione al lavoro del Progetto Regionale, sezione neoplasie)

7) dal 2 al 4 giugno 2016 sono state presentate 3 Comunicazioni orali al Congresso Nazionale ANMCO a Rimini

8) il 24-25 giugno siamo stati invitati a presentare una relazione ed un poster al I International Meeting On HeartDisease a Tolosa

9) il 15 novembre 2016 è stato presentato un Poster all' American HeartAssociation Society a New Orleans

10) nel corso del 2016 abbiamo organizzato e realizzato un corso di Statistica Medica di Base per Operatori Sanitari. Sono state fatte 3 edizioni, a marzo, ottobre, novembre, 2016, presso l'Ospedale di Conegliano.

11) il 2 dicembre 2016 è stato organizzato un Convegno informativo su cuore e sport destinato alla popolazione a Conegliano (TV)

12) ma soprattutto stiamo continuando il follow up dei pazienti.

Se desiderate potete seguirci sul WEBSITE dell'Associazione.

**Con tanti cari Auguri di serenità e buone cose,
La Segreteria dell'Associazione "ABC Study onHeartDisease"
Fiorella Cavuto**

FLOW CHART OF STUDY DEVELOPMENT

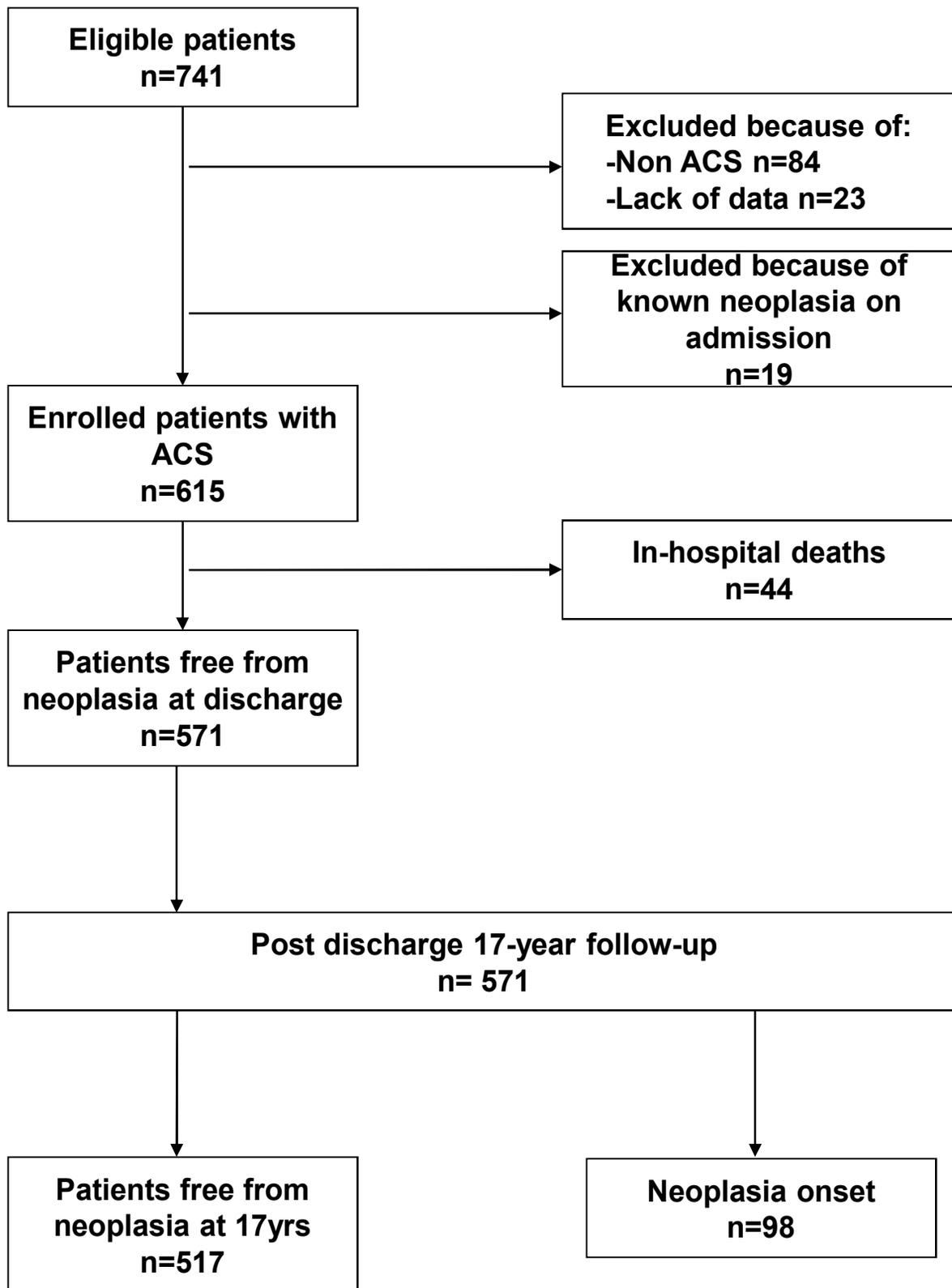


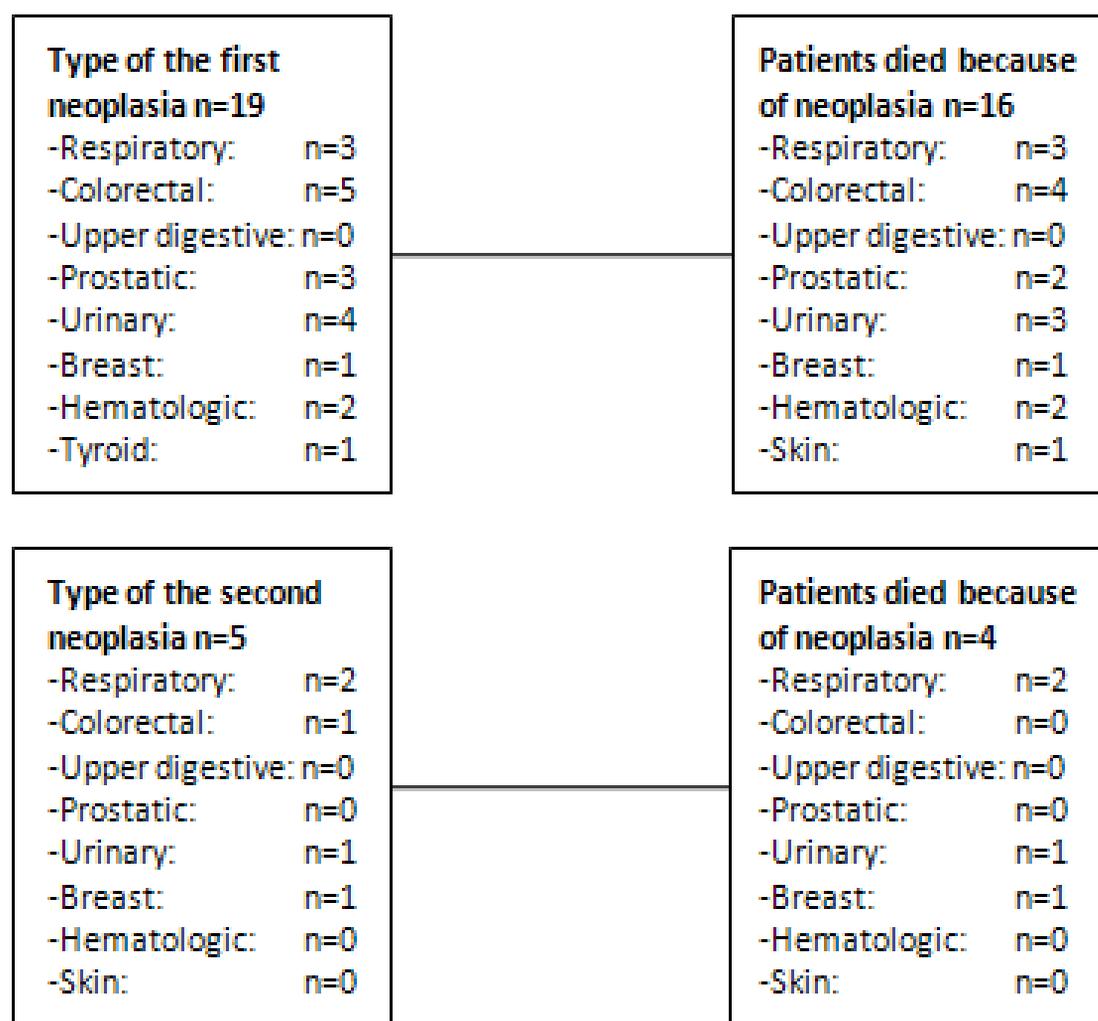
Figure 1:

Flow diagram of subject progress during follow-up. ACS indicates Acute Coronary Syndrome.

*The exclusion criteria included patients without acute coronary syndrome (n=84); presence of malignant neoplasia at enrollment (n=19); insufficient data (n=23).

FLOW CHART OF STUDY DEVELOPMENT – TYPE OF NEOPLASIA

Patients excluded because of known neoplasia on admission n=19



FLOW CHART OF STUDY DEVELOPMENT – TYPE OF NEOPLASIA

Post discharge 17-year follow-up n= 571
Neoplasia onset n=98

Type of the first neoplasia n=98

- Respiratory: n=25
- Colorectal: n=15
- Upper digestive: n=15
- Prostatic: n=15
- Urinary: n=11
- Breast: n=7
- Hematologic: n=6
- Other: n=4

Patients died because of neoplasia n=76

- Respiratory: n=21
- Colorectal: n=15
- Upper digestive: n=14
- Prostatic: n=6
- Urinary: n=7
- Breast: n=4
- Hematologic: n=6
- Other: n=3

Type of the second neoplasia n=8

- Respiratory: n=2
- Colorectal: n=0
- Upper digestive: n=2
- Prostatic: n=2
- Urinary: n=1
- Breast: n=0
- Hematologic: n=1
- Other: n=0

Patients died because of neoplasia n=4

- Respiratory: n=2
- Colorectal: n=0
- Upper digestive: n=1
- Prostatic: n=1
- Urinary: n=0
- Breast: n=0
- Hematologic: n=0
- Skin: n=0

I dati preliminari qui presentati sono la base su cui tenteremo di costruire una rigorosa e stringente analisi statistica e scientifica

**NEOPLASTIC DISEASE AFTER ACS: FEATURES AND
INCIDENCE (THE ABC-4* STUDY ON HEART DISEASE)
(*ADRIA, BASSANO, CONEGLIANO, AND PADOVA
HOSPITALS)**

Brief Title: Neoplastic disease after ACS

Table 1: Baseline characteristics of the patients with acute coronary syndrome by incidence of neoplastic disease.

Variable name	Overall sample (n=615)	Non neoplastic (n=517)	Neoplastic (n=98) ¹	P value
Demographics				
Age (years)	67(59-75)	67(58-76)	67(61-72)	0.84
Gender (female)	31	33	20	0.01
Education (high school or above)	13	14	10	0.34
Coexisting conditions				
Body mass index (kg/m ²)	26 (24-28)	26(24-28)	25(24-28)	0.74
Curent smoking	66	64	81	0.001
Coffee use	88	87	90	0.45
Alcohol use	74	74	74	0.96
Hypertension	49	50	44	0.26
Diabetes mellitus	24	26	13	0.006
Medical history				
History of angina	25	24	29	0.36
Previous myocardial infarction	23	24	21	0.61
Atrial fibrillation	11	12	8	0.25

In-hospital characteristics				
Hospital				0.44
Adria	41	43	36	
Bassano	27	26	28	
Conegliano	32	31	36	
Pre-hospital time delay (min)* (n=514)	210(120-570)	240(120-600)	180(120-360)	0.02
Systolic blood pressure(mmHg)	120(110-130)	120(110-130)	120(115-130)	0.57
Diastolic blood pressure(mmHg)	80(70-80)	75(70-80)	80(70-85)	0.06
Heart rate (beats/min)	72(60-82)	72(63-83)	70(60-80)	0.09
LVEF (%) (n=514)	52(45-60)	51(44-60)	56(47-63)	0.02
Killip class >1	37	40	22	0.001

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;

CK-MB, creatine kinase-MB isoenzyme; CPK, creatine phosphokinase; LDH, lactate dehydrogenase-1 isoenzyme; LVEF, left ventricular ejection fraction; Hgb, haemoglobin; eGFR, estimated glomerular filtration rate by MDRD; ACR, albumin to creatinine excretion ratio.

*Pvalues were calculated on log-transformed data.

¹patients who developed at least a malignant neoplasm after they were discharged from the hospital.

Blood components				
Blood cholesterol level (mg/dL) (n=589)	208(176-243)	210(178-244)	201(170-238)	0.05
HDL (mg/dL) - 1 st day (n=614)	44(37-51)	43(37-51)	44(38-51)	0.82
Blood glucose level (mg/dL)	122(102-164)	124(103-173)	112.5(98.0-139.0)	0.03
Total serum protein level (g/dL) (n=614)	6.7(6.4-7.1)	6.8(6.4-7.2)	6.6(6.4-7.0)	0.08
Hgb (g/dL)	13.6(12.4-14.6)	13.6(12.4-14.6)	13.8(12.4-14.7)	0.55
CK-MB peak (U/L)*	104(44-209)	106.0(46.0-212.2)	77.5(34.0-186.0)	0.07
LDH peak (U/L)*	881(535-1454)	915(557-1524)	701.5(454.0-1200.0)	0.002
[K ⁺] (mEq/L)	4.1(3.8-4.4)	4.1(3.8-4.4)	4.0(3.7-4.3)	0.08
[Na ⁺] (mEq/L)	140(138-142)	140(138-142)	140(138-142)	0.99
Uric acid level (mg/dL)	5.7(4.7-6.9)	5.8(4.8-6.9)	5.3(4.1-6.7)	0.01
Serum creatinine level (mg/dL)	1.0(0.9-1.1)	1.0(0.9-1.1)	0.9(0.8-1.1)	0.05

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;

CK-MB, creatine kinase-MB isoenzyme; CPK, creatine phosphokinase; LDH, lactate dehydrogenase-1 isoenzyme; LVEF, left ventricular ejection fraction; Hgb, haemoglobin; eGFR, estimated glomerular filtration rate by MDRD; ACR, albumin to creatinine excretion ratio.

*Pvalues were calculated on log-transformed data.

¹patients who developed at least a malignant neoplasm after they were discharged from the hospital.

TYPE OF NEO - 1st NEOPLASIA ONSET

Table 2: time to neoplasia onset and duration of the neoplastic disease in patients who developed at least a neoplasia during a 17-year follow-up.

Type of first neoplasia	n	Time to first neoplasia onset				Duration of the first neoplasia	
		Min	Max	Mean±sd	Median (I.Q.)	Mean±sd	Median (I.Q.)
Pre admission	19	-23.0	-0.1	-4.2±6.5	-1.1(-5.0- -0.9)	11.9±8.4	10.0(5.9-17.1)
Pre admission alive at17yrs	3	-2.0	-0.1	-0.8±1.0	-0.3(-2.0- -0.1)	17.8±1.0	17.3(17.1-19.0)
Pre admission dead at17yrs	16	-23.0	-0.1	-4.9±6.9	-1.4(-6.0- -1.0)	10.7±8.8	8.7(5.6-12.8)
Post discharge	98	0.1	16.9	7.4±5.0	7.1(2.7-11.5)	3.2±4.0	1.4(0.6-4.3)
Post discharge alive at17yrs	22	0.6	16.9	9.2±5.1	9.1(5.5±12.3)	7.8±5.1	7.9(4.7-11.5)
Post discharge dead at17yrs	76	0.1	15.9	6.9±4.8	6.1(2.6-10.4)	1.9±2.4	1.0(0.6-2.1)
Respiratory	25	0.1	16.6	5.6±4.7	5.0(1.5-7.5)	2.8±4.4	0.9(0.5-2.5)
Colorectal	15	0.5	15.9	7.3±5.6	8.3(2.1-13.0)	2.3±1.9	2.2(0.6-3.6)
Upper digestive	15	0.7	15.2	9.2±5.0	10.6(5.0-13.0)	1.2±1.3	1.0(0.5-1.3)
Prostatic	15	1.9	15.1	8.0±3.9	8.1(4.9-11.1)	6.7±4.8	6.2(1.8-10.0)
Urinary	11	0.9	16.9	9.6±6.0	10.0(4.4-15.6)	2.6±3.4	1.3(0.3-1.9)
Breast	7	0.6	12.0	6.5±3.7	5.7(4.7-9.7)	7.3±5.0	5.0(4.3-11.5)
Hematologic	6	2.0	13.0	6.4±4.4	5.6(3.0-9.0)	1.7±2.4	0.8(0.5-1.3)
Other	4	0.4	15.6	7.7±6.2	7.4(3.7-11.6)	1.1±0.5	1.2(0.7-1.4)

SINGLE NEOPLASIA	n	Time to neoplasia onset				Duration of neoplastic disease	
		Min	Max	Mean±sd	Median (I.Q.)	Mean±sd	Median (I.Q.)
Pre admission	14	-23.0	-0.01	-4.6±7.4	-1.1(-5.0- -1.0)	11.9±9.6	9.3(5.2-17.1)
Post discharge	90	0.1	16.9	7.6±5.1	7.3(2.6-12.0)	2.8±3.7	1.2(0.6-3.3)

DOUBLE NEOPLASIA	n	Time to neoplasia onset				Duration of neoplastic disease	
		Min	Max	Mean±sd	Median (I.Q.)	Mean±sd	Median (I.Q.)
Pre admission	5	-8.3	-0.3	3.2±3.3	-1.7(-4.6- -0.9)	11.6±4.3	10.0(9.6-14.7)
Post discharge	8	2.4	10.4	5.8±2.5	5.2(4.5-7.0)	8.0±4.6	7.6(4.0-11.8)

Type of second neoplasia	n	Time to second neoplasia onset				Duration of neoplastic disease	
		Min	Max	Mean±sd	Median (I.Q.)	Mean±sd	Median (I.Q.)
Pre admission	5	3.4	8.6	6.0±2.2	6.0(4.4-7.8)	11.9±8.4	10.0(5.9-17.1)
Post discharge	8	6.6	16.4	11.8±3.3	12.1(9.4-14.3)	3.2±4.0	1.4(0.6-4.3)

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 **ABC-1 Study on Heart Disease.** 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 **ABC-2 Study on Heart Disease.** It 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.
- 2016 **ABC-3 Study on Heart Disease.** It indicates that women and men with acute coronary syndrome have different long-term cardiovascular mortality risk across increasing degrees of heart failure. Gender is an independent effect modifier of heart failure for cardiovascular mortality.





Heart failure in women and men during acute coronary syndrome and long-term cardiovascular mortality (the ABC-3* Study on Heart Disease) (*Adria, Bassano, Conegliano, and Padova Hospitals)

Giuseppe Berton^{a,*}, Rocco Cordiano^b, Fiorella Cavuto^c, Francesco Bagato^b, Marco Pellegrinet^d, Arianna Cati^a

^a Department of Cardiology, Conegliano General Hospital, Conegliano, Italy

^b Department of Internal Medicine and Cardiology, Adria General Hospital, Adria, Italy

^c Department of Cardiology, Bassano del Grappa General Hospital, Bassano del Grappa, Italy

^d Department of Internal Medicine and Cardiology, Udine University Hospital, Udine, Italy

ARTICLE INFO

Article history:

Received: 14 April 2016

Received in revised form: 7 June 2016

Accepted: 21 June 2016

Available online: 23 June 2016

Key words:

Gender

Heart failure

Killip class

LVEF

Acute coronary syndrome

Cardiovascular mortality

Survival analysis

ABSTRACT

Aims: We investigated the gender-based differences in the association between heart failure (HF) during acute coronary syndrome (ACS) and post-discharge, long-term cardiovascular (CV) mortality.

Methods and results: The present study included 557 patients enrolled in three intensive coronary care units and discharged alive. HF during ACS was evaluated by Killip class and left ventricular ejection fraction (LVEF). Interaction between gender and HF after 15 years of follow up was studied using Cox models including a formal interaction term. Median age was 67 (interquartile range [IQR], 59–75) years, 29% were females, 37% had non-ST elevation myocardial infarction and 32% Killip class > 1, and median LVEF was 53% (IQR 46–61). All but five patients were followed up to 15 years, representing 5332 person-years. Of these, 40.2% died of CV-related causes. Crude CV mortality rate was higher among women (52.2%) than men (35.3%; $P < 0.0001$). At a univariable level, a negative interaction between female gender and Killip class for CV mortality was found [hazard ratio (HR) = 0.51 (0.34–0.77), $P = 0.002$]. In five multivariable models after controlling for age, main CV risk factors, clinical features, post-discharge medical treatment, and mechanical coronary reperfusion, the interaction was significant across all models [HR = 0.63 (0.42–0.95), $P = 0.02$ in the fully adjusted model]. LVEF showed no significant hazard associated with female gender on univariable analysis [HR = 1.4 (0.9–0.2.0), $P = 0.11$] but did so in all adjusted models [HR = 1.7 (1.2–2.5), $P = 0.005$ in the fully adjusted model].

Conclusion: Gender is a consistent, independent effect modifier in the association between HF and long-term CV mortality after ACS.

© 2016 Elsevier Ireland Ltd. All rights reserved.

1. Introduction

Natural history studies have suggested differences in survival between men and women in a broad spectrum of heart failure (HF) severity [1–4]. The Framingham Heart Study found that the prognosis for women was better than for men after the onset of signs of HF [1,2]. In patients with acute coronary syndrome (ACS), women have a worse prognosis than men, but the adverse course was attributed to their baseline characteristics and not to gender per se [5,6]. Indeed, it is well established that the presence of HF during ACS is one of the most important clinical manifestations leading to adverse outcomes [6,7]. Nonetheless, the relationship between gender and HF for adverse prognosis after ACS has not been thoroughly examined, especially in the long

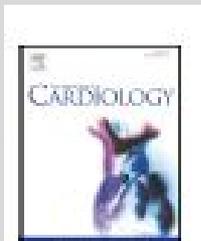
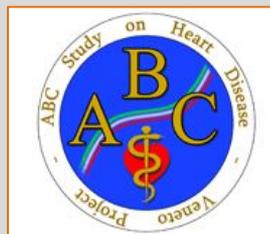
term. Studies have focused on gender differences for adverse outcomes associated with age, type of ACS, or treatment [8–11]. Furthermore, a recent overview of the current understanding of possible gender differences in cardiovascular (CV) risk factors, therapy, and prognosis of ACS reported no data on the relationship between gender and HF [12]. Our aim was to investigate prospectively the gender-based differences in the association between HF during ACS and post-discharge, long-term CV mortality.

2. Methods

2.1. Patients

The Adria, Bassano, Conegliano, and Padova Hospital Study on Heart Disease (the ABC Study on ACS) is an ongoing, prospective investigation designed to reflect, as closely as possible, an unbiased population of patients with ACS. The sample includes Caucasian patients with definite

* Corresponding author at: Cardiology Department, Conegliano General Hospital, Via Biagia Biagino, 31015 Conegliano (TV), Italy.
E-mail address: giuseppe@libero.it (G. Berton).



(the ABC-3* Study on Heart Disease) (*Adria, Bassano, Conegliano, and Padova Hospitals)

Heart Failure in Women and Men During Acute Coronary Syndrome and Long-term Cardiovascular Mortality

**Giuseppe Berton ^a, Rocco Cordiano^b, Fiorella Cavuto ^c,
Francesco Bagato ^b, Marco Pellegrinet ^d, Arianna Cati ^a**

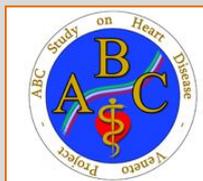
^aDep. of Cardiology, Conegliano General Hospital

^b Dep. of Internal Medicine and Cardiology, Adria General Hospital

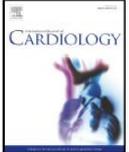
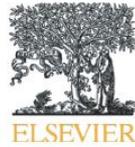
^c Dep. of Cardiology, Bassano del Grappa General Hospital

^d Dep. of Internal Medicine and Cardiology, Udine University Hospital

Heart Failure in Women and Men During Acute Coronary Syndrome and Long-term CV Mortality



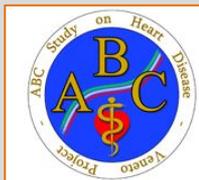
Summary



We investigated the **gender-based differences** in the association between heart failure (HF) during acute coronary syndromes (ACS) and post discharge, long term cardiovascular (CV) mortality.

The present study included **557 patients with ACS** enrolled in three intensive coronary care units and discharged alive. HF during ACS was evaluated by Killip class and left ventricular ejection fraction (LVEF). We used Cox model to study the interaction between gender and HF after **15 year** follow-up.

Our results demonstrated that gender is a consistent, independent effect modifier in the association between HF and long term CV mortality after ACS.



Why is your research important?

**BECAUSE IT SHOWED THAT WOMEN AND MEN WITH ACS
HAVE DIFFERENT LONG-TERM CV MORTALITY RISK
ACROSS INCREASING DEGREES OF HF,
EVEN AFTER CONTROLLING THE SURVIVAL MODELS FOR AGE,
MAIN CLINICAL FEATURES, AND MAIN TREATMENTS.**

**Thus, gender is an independent effect modifier
of HF for CV mortality**



Background

Natural history studies suggested differences in survival between men and women in a broad spectrum of heart failure (HF) severity.

In patients with acute coronary syndrome (ACS), women have a worse prognosis than men, but the adverse course was attributed to their baseline characteristics and not to gender per se. Indeed it is well established that the presence of HF during ACS is one of the most important clinical manifestations leading to adverse outcomes. The relationship between gender and HF for adverse prognosis after ACS has not been thoroughly examined, especially in the long term



Our aim was to investigate prospectively the gender-based differences in the association between HF during ACS and post-discharge long-term CV mortality.

Methods

A total of 778 eligible patients were considered upon admission; the post-discharge follow-up study included **557 patients with ACS (STEMI-NSTEMI-Unstable Angina UA)**

The variables analyzed were LVEF in tertiles and Killip class

At 1, 3, 5, 7, 10, 12, and **15 years** after recruitment, each patient underwent a clinical check-up. The entire sample represented **5332 person-years of follow-up**

Unpaired Student's t-test and Pearson chi-square (χ^2) test were used for measured and categorical variables respectively.

Cox survival regressions, including a *formal interaction term* between gender and HF and adjusting for main clinical variables and main treatments.

The *risk estimate* was quantified as the hazard ratio (HR). To show graphically gender HR ratios for CV mortality across increasing degrees of Killip class and tertiles of LVEF, *marginal analysis* was used.

Results

224 patients (40.2%) died of a CV-related cause.

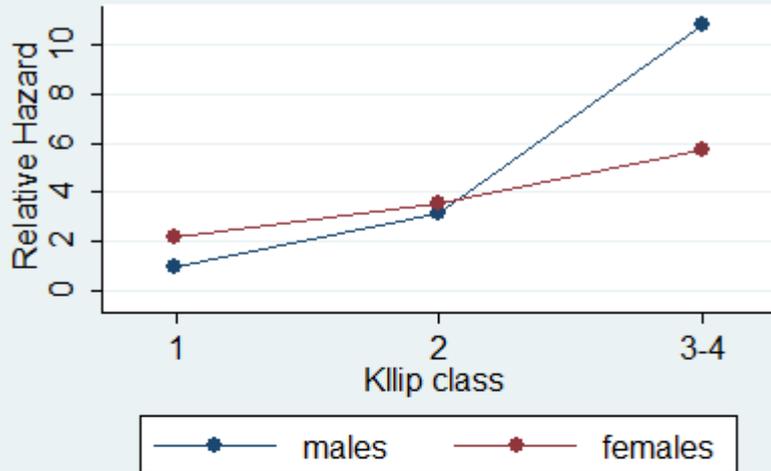
Crude mortality rate was higher among women (52.2%) than among men (35.3%; $P < 0.0001$).

Interaction between gender and HF for the risk of 15-year CV mortality as assessed by Mantel-Haenszel test of homogeneity.

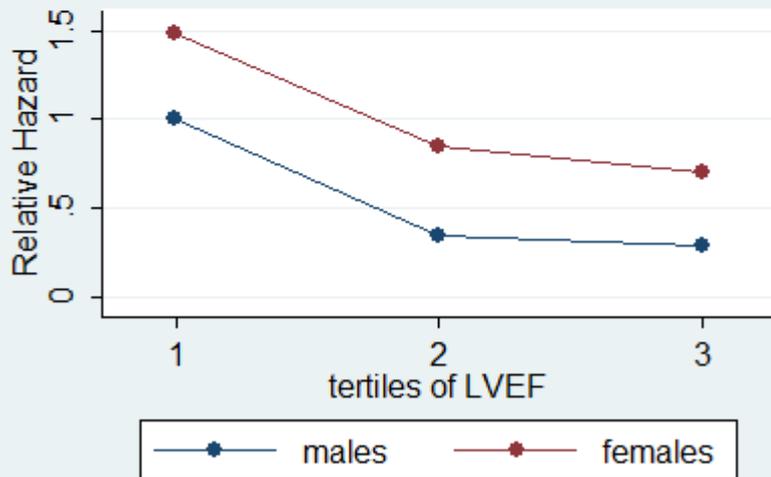
Mantel-Haenszel test of homogeneity by gender	Relative risks (95%CI) across Killip classes	P value
Men	2.4 (1.9–3.1)	0.001
Women	1.3 (0.9–1.7)	
Overall	2.0 (1.6–2.4)	
Test of homogeneity		0.001
Mantel-Haenszel test of homogeneity by gender	Relative risks (95%CI) across left ventricular ejection fraction tertiles	P value
Men	0.44 (0.33–0.59)	0.03
Women	0.70 (0.51–0.97)	
Overall	0.53 (0.43–0.66)	
Test of homogeneity		0.03

Women were older and were more liable to show hypertension, diabetes mellitus, history of angina, higher systolic BP values and total plasma cholesterol values at enrollment, lower BMI, less likely smoke. They had more frequent and more severe signs of HF and a lower heart rate, estimated GFR, and CK-MB peak. LVEF was similar between men and women. Main treatments differed by gender, including thrombolytic treatment at enrollment and mechanical revascularization during follow-up, which were all less frequently used for women

Univariate analysis



unadjusted



unadjusted

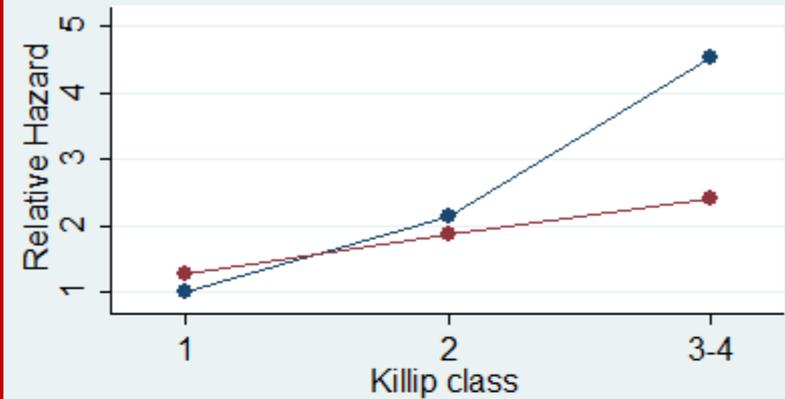
We observed a negative interaction between female gender and Killip class for CV mortality: women with a lower degree of Killip class had higher risk than men while with increasing Killip class, they had lower risk than men

The same univariate analysis using increasing tertiles of LVEF did not show such an interaction with gender.

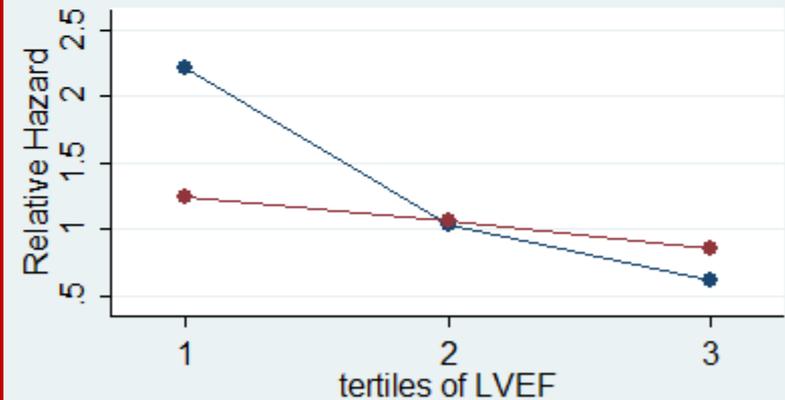
Multivariate analysis

In the multivariable analysis we obtained two coherent and identical risk model, which confirmed the same **prognostic inversion** for Killip Class and for LVEF too.

The higher the degree of Killip class, the lower the mortality risk for women compared to men.



full adjusted



full adjusted

Conclusions



The main result of the ABC-3 Study on ACS is that women and men with ACS have different long-term CV mortality risk across increasing degrees of HF, even after controlling the survival models for age, main clinical features, and main treatments.

Gender is an independent effect modifier of HF for CV mortality.

Next steps

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



1. A key question is why women have different outcomes in relation to HF. *There is a lack of studies comparing biological mechanisms of disease between men and women to better define vascular and pathophysiological processes which could lead to this emerging evidence.*
2. Percutaneous coronary angioplasty was not currently in use for reopening coronary arteries in patients with STEMI. Thus, it remains uncertain whether early mechanical reperfusion might have modified the predictive models. *However, we observed that the results of the predictive model were similar for patients with and without Q-wave myocardial infarction and those with and without thrombolytic treatment*

A patient's story

Introduction to the ABC study site

The ABC heart disease study site is about medicine and clinical research. tell us what you suggest to manage and treat this patient, through the steps



● A PATIENT'S STORY - 1ST PART

The ABC on heart disease study website deal with medicine and clinical research. At first we would like to introduce you to the site with a patient's clinical story. This is an interactive presentation and you can tell us your suggestions to manage and treat this patient, through the steps that follow.

The story of the cyclist-painter with heart failure and arrhythmias including atrial fibrillation –

Part one

A man, not a patient , that regularly goes cycling, until a windy day in winter...

The case moves from the beginning (palpitations during sport) to a major clinical event – a SYNCOPÉ –

You can learn more about this case on our website:

*ABC Study on Heart Disease Association
www.abcheartdiseasestudy.org*

A patient's story



2nd PART

The story of the cyclist-painter with heart failure and arrhythmias including atrial fibrillation –

Part two

Now for our *patient* there is a long way, with many hospitalizations and examinations, drugs and invasive treatments.

And, most of all, sport restriction.

But this “aggressive” clinical care doesn’t always mean health or healing...

You can learn more about this case on our website:

*ABC Study on Heart Disease Association
www.abcheartdiseasestudy.org*

A patient's story



3rd PART

The story of the cyclist-painter with heart failure and arrhythmias including atrial fibrillation –

Part three

Despite all problems and complications, he's now feeling better: maybe a less invasive and aggressive approach gave him more results, both on subjective symptoms and on physical performances (he doesn't give up on cyclism and work outs!)

You can learn more about this case on our website:

*ABC Study on Heart Disease Association
www.abcheartdiseasestudy.org*

The story of the cyclist-painter with heart failure and arrhythmias (including atrial fibrillation).

Case report of the *ABC study on heart disease Association* (*ABC is acronym for Adria, Bassano, Conegliano, and Padova Hospitals)

B. Segafredo¹, F. Cavuto¹, M. Pellegrinet², S. Mastrosimone³, S. Cuckon⁴, G. Berton⁴ -
(1) Bassano General Hospital, Bassano, Italy (2) Internal Medicine Clinic, Udine, Italy
(3) Treviso General Hospital, Treviso, Italy. (4) Conegliano General Hospital, Conegliano, Italy

key words: atrial fibrillation, AF ablation, sport

Our patient is -nowadays- a 63yo man, normotensive, ex mild-smoker, hypercholesterolemic, with family history of atrial fibrillation. He is affected by mild mitral valve prolapse and he is a cyclist at a competitive level, with regular sport idoneity from 37 up to 55 years. Some more relevant anamnestic notes are reumatic fever with pancarditis at the age of 16, and left hip replacement at 51.

His story begins with palpitation during intense sport activity at the age of 43. After several sport eligibility examinations ventricular isolated ectopic beats were recognized, both at rest and on maximal effort, non inducible at electrophysiologic study. Against medical advice to reduce sport activity, he continued high level cycling and regularly gets his fitness sport certificate for cycling competition up to 55yr. At this time AF was first documented. He started oral anticoagulant treatment with warfarine but no antiarrhythmic medication cause of constitutional bradycardia, and he was suggested to undergo AF ablation.

He had a syncope after exercise with severe politrauma. The ECG on admission in emergency department showed AF and the **Echocardiogram** revealed a sport-induced remodeling with normokinetic LV, mild dilatation of aorta and mild mitral regurgitation. After long rehabilitation and virtually no sport activity, he finally underwent **PV Crioablation**. Because of evidence of sinus rhythm on ECG, anticoagulation was then interrupted. Regular rhythm monitoring (24 hours ECG, loop recorder, event-recorder), both with and without antiarrhythmic drugs (Flecainide) demonstrating paroxistical AF, followed.

At that time, he felt anxious and stressed (mother health's problems, job and family problems). However he started cycling again, on mountain and plane, with competitions without symptoms on effort.

At 58 years one more major clinical event, with hospitalization for diplopia in relapse of persistent AF, occurred. Admission **Echocardiogram** revealed a severe reduction in LVEF (32%). He underwent **coronary angiography** that did not show critical coronary lesions with a short intramiocardial bridge on medium LAD. After one month of anticoagulation electrical rhythm cardioversion (ongoing Amiodarone treatment) was performed effectively followed by early relapse of AF and spontaneous restoration of SR two months later.

Under clinical suspicion of myocarditis he underwent **cardiac MRI** that confirmed dilated-ipokinetic cardiomyopathy (LVEF 40%) without myocardial fibrosis (LGE), possible apical non compaction.

After a period of sport restriction, our patient started cycling again on a regular base, only on plan, without symptoms. Few weeks later he felt palpitations at rest chiefly after lunch and Atrial Flutter was detected. He was suggested to undergo one more time electrical CV, but he firmly disagreed.

At this point the patient and his clinical cardiologist agreed for an alternative strategy, based on rhythm control using Amiodarone and low dose digoxin. Some week later, "spontaneous" restoration of sinus rhythm was observed. Amiodarone treatment was reduced and digoxin stopped; several ECG demonstrated SR maintenance for a long period. **Echocardiogram** showed an improvement of left ventricular function (almost normalization of LVEF, close to 50%). The patient referred well-being except symptoms of chronic gastropathy, sometimes dizziness, but no syncope, and he felt even better in cycling performance.

At 63 years old Amiodarone was stopped cause of extreme bradycardia, and few weeks later was recorded relapse of atrial fibrillation. The patient accepted electrical cardioversion, that was effective, but after a family dinner and heated discussion, he clearly felt arrhythmia (AF) with rapid ventricular response. Amiodarone was introduced again with reduction in mean heart rate.

Now the patient is asymptomatic with a good rate control in persistent AF, increased his cycling activity, Warfarin is well tolerated, and he feels comfortable in his usual life activities. This long and varied clinical case reminds us that often in medicine, major treatments and aggressive medical cares do not mean major patient's benefit.



Capitolo 7

**“Guadagnare salute”
Attività 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. Spellanzone (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



Amministrazione
Comunale di
Mareno di Piave

24^a Edizione "Incontri di Educazione Sanitaria"
**LA MALATTIA DI CUORE NELLA
DONNA E NELL'UOMO:**
UN NUOVO MODO DI STUDIARE LA SOPRAVVIVENZA
DOPO L'INFARTO
(The ABC-3 Study on Acute Coronary Syndrome)

CENTRO CULTURALE (piazza municipio) Mareno di Piave

Giovedì 21 Maggio 2015 - ore 20.30

SOPRAVVIVENZA DOPO L'INFARTO: "Differenze di Genere"

* Dott. Nadir Sitta • *Cardiologia Conegliano • Ulss7*

COME LO STILE DI VITA INFLUENZA LA MALATTIA CARDIACA

* Dott. Filippo Brocadello • *Specialista Scienze dell'Alimentazione • Padova*

**COME OSSERVARE LE DIFFERENZE FRA DONNA E UOMO
CON SCOMPENSO CARDIACO**

* Dott. Giuseppe Berton • *Cardiologia Conegliano • Ulss7*

INFARTO MIocardico E SCOMPENSO DI CUORE NELLA DONNA

* Dott.ssa Monica Centa • *Cardiologia Conegliano • Ulss7*

**INTERAZIONE FRA SCOMPENSO CARDIACO E GENERE:
"come modifica la sopravvivenza"**

* Dott. Giuseppe Berton • *Cardiologia Conegliano • Ulss7*

PRESENTA E MODERA

* Dott. Giovanni Turiano • *Cardiologia Conegliano • Ulss7*

(agli operatori sanitari si rilascia attestato di partecipazione)

Segreteria organizzativa inf. Battistella Giancarlo (339.6383290 AVIS MARENO

e-mail: avismareno@virgilio.it - tel.0438-309215

U.O.C di Cardiologia ulss7, tel 0438.663613



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@asilbassano.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 Saluta del Direttore Generale Dr. Francesco Antonio Tomperella
 Ore 14.30 Presentazione del Corso da parte del Direttore Sanitario Dr. Enzo Apolloni

Sessione 1

Moderatori: Dr.ssa Rosa Palmeri, 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 Bertoni
 Ore 15.00 La sopravvivenza dopo infarto miocardico nella donna (risultati ABC STUDY ON HEART DISEASE)
 Dr.ssa Fiorella Cavuto
 Ore 15.30 Ruolo del Paccardiofilo nella valutazione prognostica dopo sindrome coronarica acuta
 Dr. Roberto Zappellin
 Ore 16.00 Case cliniche correlate con la platea
 Dr. Giuseppe Bertoni
 Ore 16.30 Carlo Deadi

Sessione 2

Moderatori: Dr.ssa Fiorella Cavuto, Dr. Enzo Apolloni
 Ore 16.40 La rivascolarizzazione percutanea nella sindrome coronarica acuta: indicazioni attuali, limiti e prospettive
 Dr. Angelo Bruno Ranzani
 Ore 17.00 Mancatori di nuovi marcatori acuti e troponina ad alta sensibilità: importanza prognostica e differenza di genere
 Dr. Giorgio Biagini
 Ore 17.30 Case a solo il "prezetto respirato"
 Dr.ssa Fiorella Cavuto
 Ore 18.00 Progetto regionale ospedaliero – Presentazione sito web e Associazione ABC Study
 Dr. Giuseppe Bertoni
 Ore 18.30 Case clinico e confronto con la platea
 Dr. Giuseppe Bertoni
 Ore 19.00 Complimentare-sindromi/TCM, valutazione di gradimento e terorie dell'incidento

Con il patrocinio di:



Si ringrazia per il sostegno:





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
GIOVEDÌ 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 a 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 20.15 Accoglienza dei partecipanti

Ore 20.30 Saluto del Sindaco della Città Dr. Fioriano Zambon

Presentazione della serata e moderatori:

Dott.ssa Fiorella Cavuto (Bassano del Grappa), Dott. Flaviano Giorgiano (Treviso) RN Rossana 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 Brocadedello (Padova)

Come è nato il "progetto neoplasie"

Dott.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 gjube.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:



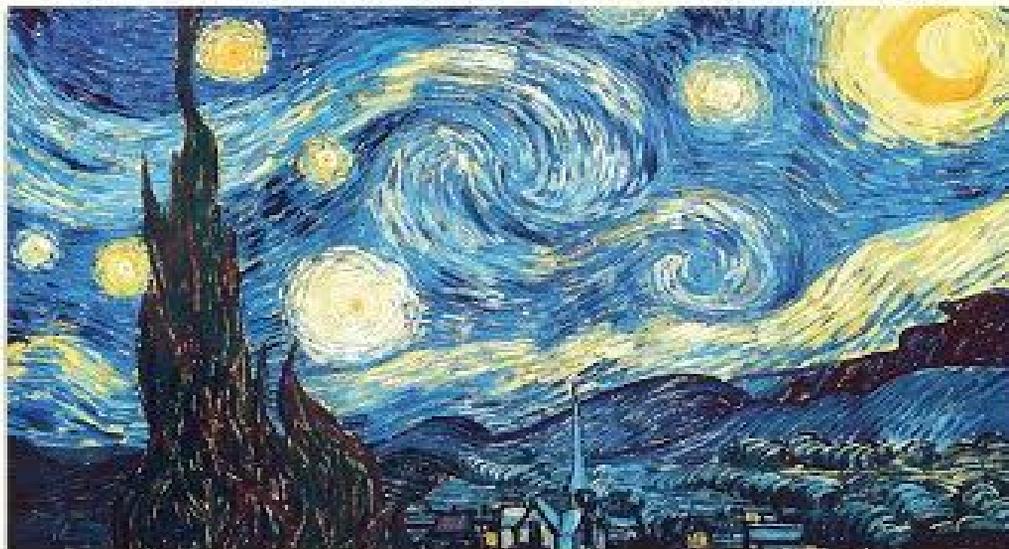
Si ringrazia per il sostegno:



REGIONE DEL VENETO - COMUNE DI BASSANO DEL GRAPPA
U.L.S.S. 3 BASSANO 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 1992, a little group of medical researchers and other participants embarked on a 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 20.00 Italiano delle Autorità
Sindaco di Bassano del Grappa - Direttore Azienda ULSS 3

Presentazione della serata:
Dott.ssa Fiorella Cavato (Bassano del Grappa) / Dott. Giuseppe Bertoni (Conegliano)

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

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

Attività fisica e sport nella malattia cardiaca. Si può fare? E come?
Dr. Patrizio Sarno (Treviso)

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

Come è nata il "progetto neoplasie"
Dott.ssa Fiorella Cavato (Bassano del Grappa)

Progetto regionale neoplasie - sito web e associazione ABC Study
Dr. Giuseppe Bertoni (Conegliano)

A fine serata: consegna del PROFILO "ABC STUDY ON HEART DISEASE" a persona che si è iscritta 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 Bertoni - U.O.C. di Cardiologia
Presidio Ospedaliero di Conegliano - ULSS 7
Tel. 0422.663.811 - e-mail: gj@bc.uspallioce.it

SEGRETARIA ORGANIZZATIVA
(THE ABC STUDY ON HEART DISEASE ASSOCIATION):
Dott.ssa Fiorella Cavato - Ambulatorio di Cardiologia - Distretto 1
ULSS 3 Bassano del Grappa - Tel. 0424.885148
email: fiorella.cavato@asl3bassano.it - fiorellacavato@me.com

Altre informazioni:
<http://www.abcheartdiseasestudy.org/en/contact>
Progetto Regionale "Guardare Salute"
Ber n. 34 del 03/05/2015

Con il patrocinio di:



Si ringrazia:





REGIONE DEL VENETO



REGIONE DEL VENETO - CITTA' DI CONEGLIANO

ABC STUDY ON HEART DISEASE ASSOCIATION "A VENETO REGION PROJECT"

US-ACLI VENETO - U.L.S.S. 7 - ULSS 3 - ULSS19

CUORE PREVENZIONE SPORT

CONEGLIANO (SALA TONIOLO) - VENERDI 2 DICEMBRE 2016 ORE 20.30



**2° EDIZIONE DELL'INCONTRO
CON LA CITTADINANZA ED OPERATORI SANITARI**

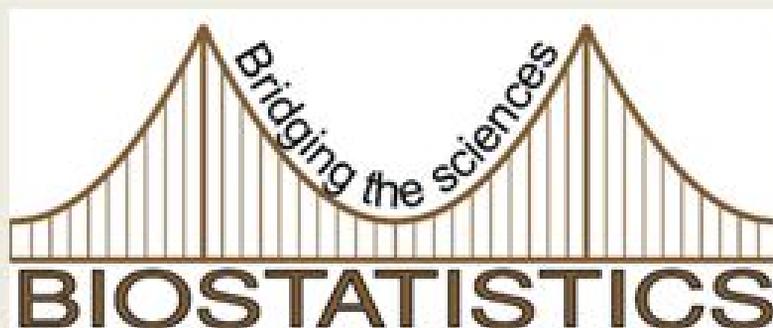
INFO: www.abcheartdiseasestudy.org

Segreteria organizzativa: Rosanna Sodran e-mail rosanna.sodran@libera.it 347-3598030



REGIONE DEL VENETO

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



L'ULSS in collaborazione con "The ABC Study on Heart Disease Association"
organizza:

**CORSO DI STATISTICA MEDICADI BASE
PER MEDICI 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. Giuseppe Berton, 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. Giuseppe Berton - Cardiologia - ULSS7

Date e sede del corso:

mercoledì 6, mercoledì 13, giovedì 28 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

6 aprile 2016 ore 9.15-13.15

- accogliimento 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
- caffè 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

13 aprile 2016 ore 9.15-13.15

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

28 aprile 2016 ore 9.15-13.15

- numerosità campionaria, potenza di un test 50
- t di Student per dati appaiati e non appaiati, χ^2 di Pearson(ripasso e pratica) 40
- indicatori di performance in Medicina, considerazioni cliniche 40
- caffè 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 χ^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.p.c.](#) Pianificazione, qualità, etica e formazione

Sezione Formazione

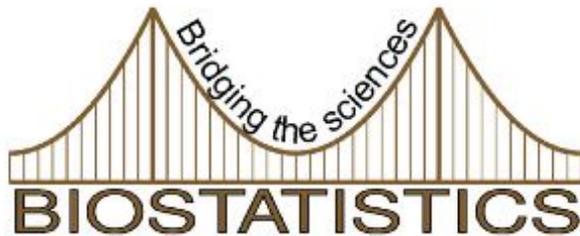
Via Lubin, 16 – 31053 Pieve di Soligo (TV)

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**

3a ed: 2-9-24 novembre 2016: **posti esauriti**

4a ed: 1-8-15 febbraio 2017: **posti disponibili**

Le iscrizioni terminano venerdì 18 marzo 2016

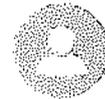


Capitolo 8

Principali Riferimenti Bibliografici

(http://www.escardio.org) Our mission: to reduce the burden of cardiovascular disease

Doctor Giuseppe Berton
ESC ID: 82212



Log out

View my profile

Home (https://escardio--community.force.com/ESCDashboard?site=a3457000000XtS) / MyESC (/MyESC/default.aspx)

Home (https://escardio--community.force.com/ESCDashboard?site=a3457000000XtS)

Products and Services (https://escardio--community.force.com/CPBase__store?site=a3457000000XtS)

My Membership (https://escardio--community.force.com/ESCMembership?site=a3457000000XtS)

Grants (https://escardio--community.force.com/ESCGrants?site=a3457000000XtS)

Congresses (/MyESC/modules/congress/default.aspx)

My Journals (/MyESC/modules/journal/default.aspx)

My Directory (https://escardio--community.force.com/ESCMGroups?site=a3457000000XtS)

My Expense Claims (http://escol.escardio.org/ExpenseClaim/default.aspx)

Abstract 60900

Abstract Preview

HEART FAILURE 2016	
Doctor: Giuseppe Berton (EUD ID: 82212) Via Colombo, 74 31015 - Conegliano Italy Phone: +39 043 865 8287 - Fax: +39 043 865 8380 Email: giub@s@alice.it	
Title:	Heart failure in women and men during acute coronary syndrome: interaction for long-term cardiovascular mortality (The ABC-4 Study on Heart Disease)
Topic:	01 01 - Acute heart failure (diagnosis, pathophysiology)
Acronym:	Adna Bassano Conegliano Study on Heart Disease
Category:	Clinical
Option:	Presented Abstract
On Behalf:	ABC Study on Heart Disease
G. Berton ¹ , R. Cordiano ² , F. Cavuto ³ , F. Bagato ¹ , S. Mastrsimone ¹ - (1) Conegliano General Hospital, Conegliano, Italy (2) Adna General Hospital, Adria, Italy (3) Bassano General Hospital, Bassano, Italy	
Background Natural history studies have suggested important differences in survival between men and women in a broad spectrum of heart failure (HF) severity. Nonetheless, the relationship between gender and HF for adverse prognosis after acute coronary syndrome (ACS) has not been thoroughly examined, especially in the long term. We investigated the gender-based differences in the association between HF during ACS and post-discharge, long-term cardiovascular (CV) mortality.	
Methods The present study included 557 patients enrolled in three intensive coronary care units and discharged alive. HF during ACS was evaluated by Killip class and left ventricular ejection fraction (LVEF). Interaction between gender and HF after 15 years of follow up was studied using Cox models including a formal interaction term.	
Results Median age was 67 (interquartile range [IQR], 59–75) years, 29% were females, 37% had non-ST elevation myocardial infarction and 32% Killip class>1, and median LVEF was 53% (IQR 46–61). All but five patients were followed up to 15 years, representing 5332 person-years. Of these, 40.2% died of CV-related causes. Crude CV mortality rate was higher among women (52.2%) than men (35.3%, P<0.0001). At a univariable level, a negative interaction between female gender and Killip class for CV mortality was found [hazard ratio (HR)=0.51 (0.34–0.77), P=0.002]. In five multivariable models after controlling for age, main CV risk factors, clinical features, post-discharge medical treatment, and mechanical coronary reperfusion, the interaction was significant across all models [HR=0.63 (0.42–0.95), P=0.02 in the fully adjusted model]. LVEF showed no significant hazard associated with female gender on univariable analysis [HR=1.4 (0.9–2.0), P=0.11] but did so in all adjusted models [HR=1.7 (1.2–2.5), P=0.005 in the fully adjusted model].	
Conclusions Gender is a consistent, independent effect modifier in the association between HF and long-term CV mortality after ACS.	

QUIT

- ESC Website (http://www.escardio.org)
- Contact us (http://www.escardio.org/Contact?service=Escol)



T4056 — 2016

AHA

Heart Failure in Women and Men During Acute Coronary Syndrome: interaction for Long-term Cardiovascular Mortality (The ABC-3 Study on Heart Disease)

[View ePoster](#)

Heart Failure and Cardiomyopathies

HF.APS.P210 | *Differences and Disparities in Heart Failure*

11.51 Heart Failure: Disease Management, Quality of Care, and Clinical Outcomes

Presented on Tuesday, November 15, 2016 10:45 AM

Author(s): Fiorella Cavuto, ULSS 3, Bassano General Hosp, Bassano del Grappa, Italy; Giuseppe Berton, ULSS 7, Conegliano General Hosp, Conegliano, Italy; Francesco Bagato, ULSS 19, Adria General Hosp, Adria, Italy; Paola Michelazzo, Jessica Civiero, ULSS 3, Bassano General Hosp, Bassano del Grappa, Italy; Rocco Cordiano, ULSS 19, Adria General Hosp, Adria, Italy; Beatrice Segafredo, ULSS 3, Bassano General Hosp, Bassano del Grappa, Italy; Gerlando Alessio Maria Preti, Arianna Cati, ULSS 7, Conegliano General Hosp, Conegliano, Italy; Francesca Russo, Veneto Region, Venezia, Italy

Introduction: Natural history studies have suggested important differences in survival between men and women in a broad spectrum of heart failure (HF) severity. Nonetheless, the relationship between gender and HF for adverse prognosis after acute coronary syndrome (ACS) has not been thoroughly examined, especially in the long term. We investigated the gender-based differences in the association between HF during ACS and post-discharge, long-term cardiovascular (CV) mortality.

Methods: The present study included 557 patients enrolled in three intensive coronary care units and discharged alive. HF during ACS was evaluated by Killip class and left ventricular ejection fraction (LVEF). Interaction between gender and HF after 15 years of follow up was studied using Cox models including a formal interaction term.

Results: Median age was 67 (interquartile range [IQR], (59-75) years, 29% were females, 37% had non-ST elevation myocardial infarction and 32% Killip class>1, and median LVEF was 53% (IQR 46-61). All but five patients were followed up to 15 years, representing 5332 person-years. Of these, 40.2% died of CV-related causes. Crude CV mortality rate was higher among women (52.2%) than men (35.3%; $P<0.0001$). At a univariable level, a negative interaction between female gender and Killip class for CV mortality was found [hazard ratio (HR)=0.51 (0.34-0.77), $P=0.002$]. In five multivariable models after controlling for age, main CV risk factors, clinical features, post-discharge medical treatment, and mechanical coronary reperfusion, the interaction was significant across all models [HR=0.63 (0.42-0.95), $P=0.02$ in the fully adjusted model]. LVEF showed no significant hazard associated with female gender on univariable analysis [HR=1.4 (0.9-2.0), $P=0.11$] but did so in all adjusted models [HR=1.7 (1.2-2.5), $P=0.005$ in the fully adjusted model].

Conclusions: Gender is a consistent, independent effect modifier in the association between HF and long-term CV mortality after ACS

Disclosure: F. Cavuto: None. G. Berton: None. F. Bagato: None. P. Michelazzo: None. J. Civiero: None. R. Cordiano: None. B. Segafredo: None. G.A. Preti: None. A. Cati: None. F. Russo: None.

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)

Giuseppe Berton, MD^{a,*}, Rocco Cordiano, MD^b, Fiorella Cavuto, MD^c, Giulia Giacomini, PhD^a, Renzo De Toni, PhD^d, and Paolo Palatini, MD^d

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. © 2012 Elsevier Inc. All rights reserved. (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} Further-

more, 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

^aDepartment of Cardiology, Conegliano General Hospital, Conegliano, Italy; ^bDepartment of Internal Medicine and Cardiology, Adria General Hospital, Adria, Italy; ^cDepartment of Cardiology, Bassano del Grappa General Hospital, Bassano del Grappa, Italy; ^dDepartment of Clinical and Experimental Medicine, University of Padova, Padua, Italy. Manuscript received October 12, 2011; revised manuscript received and accepted November 9, 2011.

This work was supported by grants from the University of Padova, Padua, Italy, for the collection, management, and analysis of the data.

*Corresponding author: Tel: (+39) 04-3866-3613; fax: (+39) 04-3866-3360.

E-mail address: giube.s@alice.it (G. Berton).

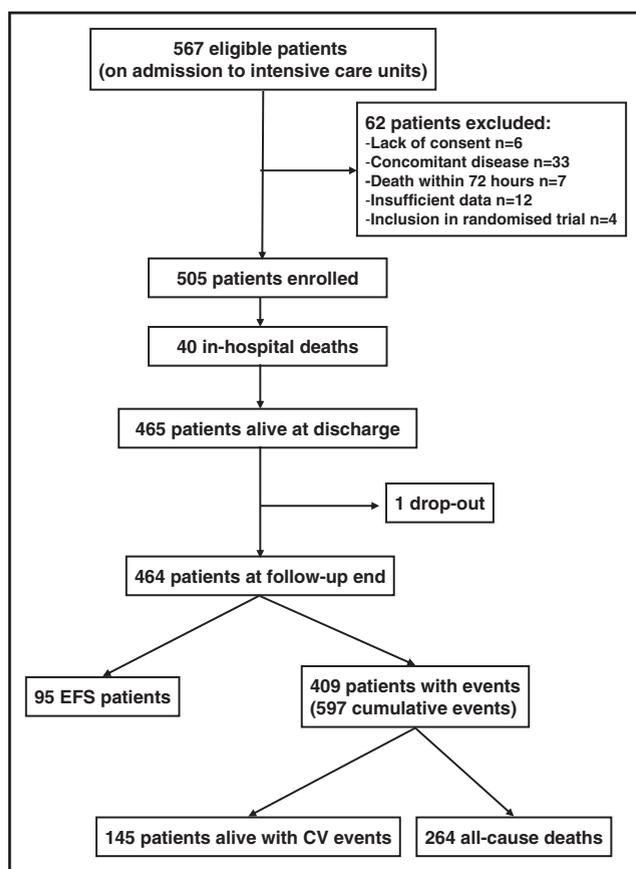


Figure 1. Flow diagram of subject progress during follow-up.

filtration rate (eGFR) $<1.0 \text{ mL/s/1.73 m}^2$ (conventional units $<60 \text{ mL/min/1.73 m}^2$) 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 $\geq 140/90 \text{ mm Hg}$. Hypercholesterolemia was defined as having a total cholesterol level of $\geq 6.2 \text{ mmol/L}$ 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

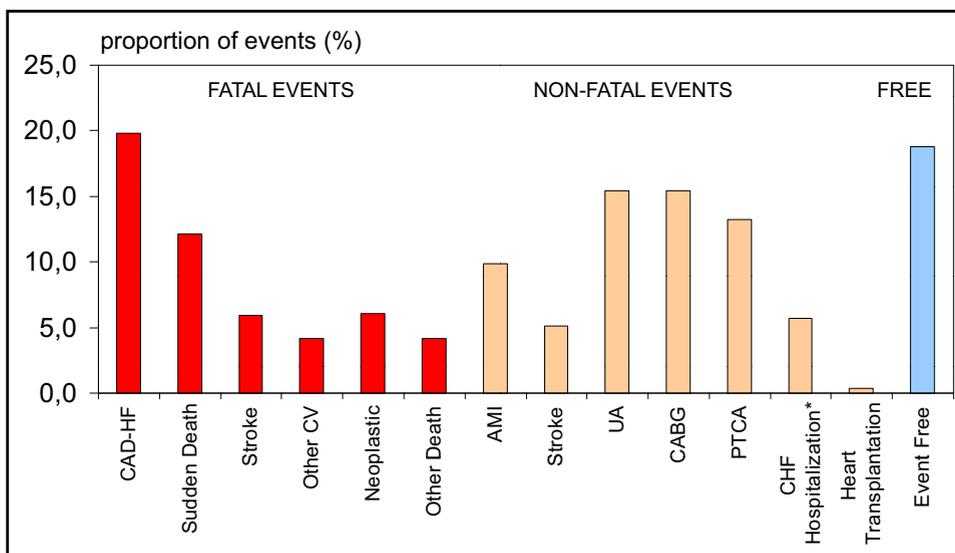


Figure 2. Adverse events occurred in 504 patients during 10 years of follow-up after AMI. *In absence of other CV events. ACR = albumin/creatinine ratio; AMI = acute myocardial infarction; CABG = coronary artery bypass grafting; CAD-HF = coronary artery disease–heart failure; CHF = congestive heart failure; 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 × 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 \pm 0.12	2.3 (1.8–2.9)	<0.0001	—			0.35 \pm 0.05	1.4 (1.3–1.5)	<0.0001*
Male gender	0.51 \pm 0.27	1.7 (1.1–2.8)	0.06	–0.23 \pm 0.31	0.8 (0.4–1.4)	0.45 [†]	0.07 \pm 0.11	1.1 (0.8–1.3)	0.55 [†]
Low school education	–0.38 \pm 0.25	0.7 (0.4–1.1)	0.13	0.06 \pm 0.23	1.1 (0.6–1.8)	0.82	0.01 \pm 0.12	1.0 (0.8–1.3)	0.92
No/current smoking	–0.86 \pm 0.23	0.4 (0.3–0.7)	<0.0001	–0.24 \pm 0.26	0.8 (0.5–1.3)	0.34	–0.17 \pm 0.11	0.8 (0.7–1.0)	0.13
No hypercholesterolemia	–0.11 \pm 0.25	0.9 (0.5–1.5)	0.66	0.22 \pm 0.29	1.2 (0.7–2.2)	0.44	0.12 \pm 0.12	1.1 (0.9–1.4)	0.30
Low body mass index	0.01 \pm 0.10	1.0 (0.8–1.2)	0.91	0.18 \pm 0.11	1.2 (0.9–1.5)	0.10	0.05 \pm 0.05	1.0 (0.9–1.1)	0.28
No hypertension	0.68 \pm 0.24	2.0 (1.2–3.2)	0.004	0.45 \pm 0.26	1.6 (0.9–2.6)	0.08	0.15 \pm 0.10	1.2 (0.9–1.4)	0.14
No diabetes mellitus	0.94 \pm 0.33	2.5 (1.3–4.9)	0.004	0.70 \pm 0.34	2.0 (0.9–4.0)	0.04	0.40 \pm 0.11	1.5 (1.2–1.9)	0.0006
No physical activity	–0.47 \pm 0.43	0.6 (0.3–1.4)	0.27	–0.05 \pm 0.46	0.9 (0.4–2.3)	0.91	–0.07 \pm 0.22	0.9 (0.6–1.4)	0.73
No alcohol use	–0.13 \pm 0.26	0.9 (0.5–1.5)	0.61	–0.32 \pm 0.29	0.7 (0.4–1.3)	0.28	0.04 \pm 0.12	1.0 (0.8–1.3)	0.72
No coffee use	–0.74 \pm 0.42	0.5 (0.2–1.1)	0.07	–0.35 \pm 0.44	0.7 (0.3–1.7)	0.42	–0.15 \pm 0.15	0.9 (0.6–1.2)	0.32
No family coronary heart disease	0.02 \pm 0.27	1.0 (0.6–1.7)	0.95	0.30 \pm 0.28	1.4 (0.8–2.4)	0.28	0.11 \pm 0.12	1.1 (0.9–1.4)	0.33
No angina (before enrollment)	1.52 \pm 0.44	4.5 (1.9–10.7)	0.001	1.21 \pm 0.45	3.3 (1.4–8.1)	0.007	0.40 \pm 0.12	1.5 (1.2–1.9)	0.001
No myocardial infarction (before enrollment)	1.43 \pm 0.41	4.2 (1.9–9.3)	<0.0001	1.35 \pm 0.42	3.8 (1.7–8.8)	0.002	0.41 \pm 0.12	1.5 (1.2–1.9)	0.0007
Short prehospital time delay	0.27 \pm 0.10	1.3 (1.1–1.6)	0.01	0.11 \pm 0.11	1.1 (0.9–1.4)	0.32	0.05 \pm 0.04	1.0 (0.9–1.1)	0.25
Low systolic blood pressure	0.18 \pm 0.10	1.2 (1.0–1.5)	0.07	0.02 \pm 0.11	1.0 (0.8–1.3)	0.87	–0.01 \pm 0.05	0.9 (0.8–1.1)	0.76
Low diastolic blood pressure	0.02 \pm 0.10	1.0 (0.8–1.2)	0.85	–0.06 \pm 0.11	0.9 (0.8–1.2)	0.58	–0.04 \pm 0.04	0.9 (0.8–1.0)	0.34
Low heart rate	0.24 \pm 0.10	1.3 (1.0–1.6)	0.01	0.15 \pm 0.11	1.2 (0.9–1.4)	0.16	0.10 \pm 0.05	1.2 (1.1–1.3)	0.03
Nonanterior myocardial infarction	–0.24 \pm 0.24	0.8 (0.5–1.2)	0.31	–0.21 \pm 0.25	0.8 (0.5–1.3)	0.40	–0.03 \pm 0.11	0.9 (0.8–1.2)	0.78
Non-Q-wave myocardial infarction	–0.74 \pm 0.30	0.5 (0.3–0.9)	0.01	–0.55 \pm 0.32	0.6 (0.3–1.1)	0.08	–0.16 \pm 0.11	0.8 (0.7–1.1)	0.15
Low creatine kinase peak	–0.18 \pm 0.10	0.8 (0.7–1.0)	0.07	–0.13 \pm 0.11	0.9 (0.7–1.1)	0.22	–0.01 \pm 0.05	0.9 (0.8–1.1)	0.78
Low creatine kinase-MB peak	–0.18 \pm 0.10	0.8 (0.7–1.0)	0.08	–0.13 \pm 0.11	0.9 (0.7–1.1)	0.23	–0.01 \pm 0.04	0.9 (0.8–1.1)	0.96
Low Killip class	0.99 \pm 0.24	2.7 (1.7–4.3)	<0.0001	0.60 \pm 0.25	1.8 (1.1–3.0)	0.01	0.41 \pm 0.08	1.5 (1.3–1.8)	<0.0001
No tachyarrhythmias	–0.02 \pm 0.27	1.0 (0.6–1.6)	0.92	–0.20 \pm 0.28	0.8 (0.5–1.4)	0.46	–0.05 \pm 0.12	0.9 (0.7–1.2)	0.64
No bradyarrhythmias	0.18 \pm 0.43	1.2 (0.5–2.8)	0.68	0.16 \pm 0.45	1.2 (0.5–2.8)	0.72	0.31 \pm 0.18	1.4 (0.9–1.9)	0.09
No atrial fibrillation/flutter	1.70 \pm 0.60	5.4 (1.7–17.8)	0.005	1.30 \pm 0.62	3.6 (1.1–12.3)	0.03	0.34 \pm 0.14	1.4 (1.1–1.8)	0.01
Low left ventricular ejection fraction	–0.46 \pm 0.12	0.6 (0.5–0.8)	<0.0001	–0.38 \pm 0.13	0.7 (0.5–0.9)	0.002	–0.21 \pm 0.05	0.8 (0.7–0.9)	<0.0001
Low hemoglobin	–0.18 \pm 0.10	0.8 (0.7–1.0)	0.08	–0.05 \pm 0.12	0.9 (0.8–1.2)	0.68	–0.04 \pm 0.05	1.0 (0.9–1.0)	0.35
Low blood glucose	0.25 \pm 0.10	1.3 (1.1–1.6)	0.01	0.19 \pm 0.11	1.2 (1.0–1.5)	0.09	0.12 \pm 0.04	1.1 (1.0–1.2)	0.005
Low total cholesterol	–0.06 \pm 0.10	0.9 (0.8–1.1)	0.53	0.05 \pm 0.11	1.1 (0.8–1.3)	0.62	0.02 \pm 0.05	1.0 (0.9–1.1)	0.70
Low high-density lipoprotein cholesterol	–0.02 \pm 0.10	1.0 (0.8–1.2)	0.87	–0.07 \pm 0.11	0.9 (0.7–1.1)	0.48	–0.06 \pm 0.04	0.9 (0.9–1.0)	0.19
Low triglycerides	–0.05 \pm 0.10	0.9 (0.8–1.2)	0.61	0.13 \pm 0.11	1.1 (0.9–1.4)	0.23	0.10 \pm 0.05	1.2 (1.1–1.3)	0.03
Low potassium	0.07 \pm 0.10	1.1 (0.9–1.3)	0.51	–0.02 \pm 0.11	0.9 (0.8–1.2)	0.82	0.02 \pm 0.04	1.0 (0.9–1.1)	0.59
Low uric acid	0.21 \pm 0.10	1.2 (1.1–1.5)	0.03	0.15 \pm 0.11	1.2 (0.9–1.4)	0.18	0.15 \pm 0.04	1.2 (1.1–1.3)	0.001
Low estimated glomerular filtration rate	–0.64 \pm 0.11	0.5 (0.4–0.7)	<0.0001	–0.40 \pm 0.13	0.7 (0.5–0.9)	0.002	–0.19 \pm 0.05	0.8 (0.7–0.9)	0.0002
Low albumin/creatinine excretion ratio	0.54 \pm 0.11	1.7 (1.4–2.1)	<0.0001	0.35 \pm 0.12	1.4 (1.1–1.8)	0.004	0.25 \pm 0.05	1.3 (1.2–1.4)	<0.0001
Variable modification during follow-up									
No current smoking	–0.71 \pm 0.23	0.5 (0.3–0.8)	0.002	–0.18 \pm 0.26	0.8 (0.5–1.4)	0.48	–0.17 \pm 0.11	0.8 (0.7–1.0)	0.12
No hypercholesterolemia	–0.54 \pm 0.23	0.6 (0.4–0.9)	0.01	–0.11 \pm 0.25	0.9 (0.5–1.5)	0.65	0.03 \pm 0.11	1.0 (0.8–1.3)	0.77
No hypertension	0.46 \pm 0.23	1.6 (1.1–2.5)	0.04	0.20 \pm 0.25	1.0 (0.7–2.0)	0.81	0.01 \pm 0.10	1.0 (0.8–1.2)	0.93
No diabetes mellitus	0.75 \pm 0.29	2.1 (1.2–3.7)	0.009	0.66 \pm 0.30	1.9 (1.1–3.5)	0.02	0.33 \pm 0.11	1.4 (1.1–1.7)	0.002
No physical activity	–1.09 \pm 0.24	0.3 (0.2–0.5)	<0.0001	–0.46 \pm 0.27	0.6 (0.4–1.1)	0.08	–0.21 \pm 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	$\beta \pm SE$	OR (95% CI)	p Value	$\beta \pm SE$	HR (95% CI)	p Value
Model 7 Inclusion of CV risk factor modification during follow-up (n = 504)						
Age	0.52 \pm 0.15	1.7 (1.2–2.3)	0.001	0.18 \pm 0.06	1.2 (1.1–1.4)	0.004
Women	–0.03 \pm 0.35	1.0 (0.5–1.9)	0.92	0.12 \pm 0.14	1.1 (0.9–1.5)	0.39
Angina pectoris	1.04 \pm 0.44	2.8 (1.2–6.7)	0.01	0.40 \pm 0.14	1.5 (1.1–1.9)	0.005
Previous myocardial infarction	1.03 \pm 0.41	2.8 (1.2–6.3)	0.01	0.34 \pm 0.14	1.4 (1.1–1.8)	0.01
Estimated glomerular filtration rate	–0.34 \pm 0.13	0.7 (0.5–0.9)	0.01	–0.15 \pm 0.05	0.8 (0.7–0.9)	0.003
Albumin/creatinine ratio	0.30 \pm 0.13	1.3 (1.1–1.7)	0.02	0.17 \pm 0.05	1.2 (1.1–1.3)	0.0009

Abbreviations as in Table 2.

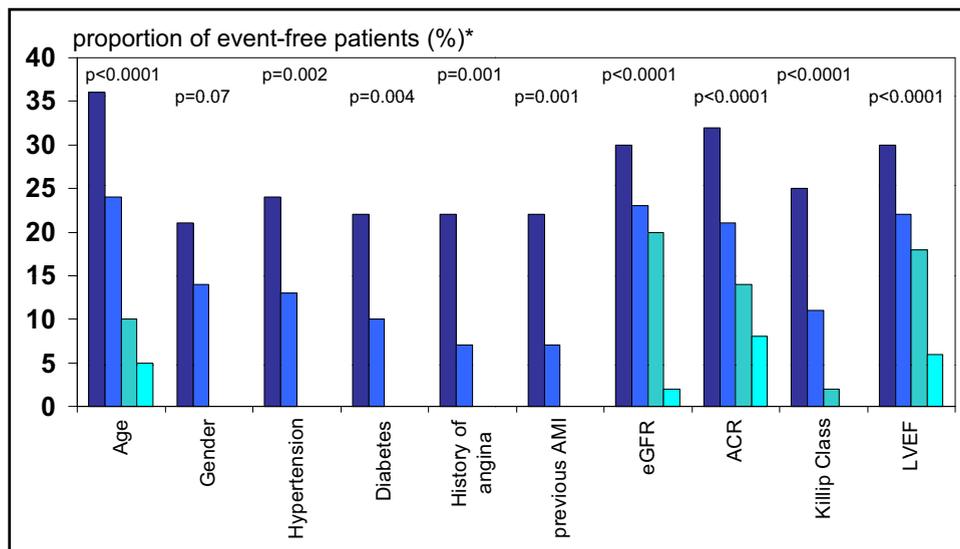


Figure 3. Proportion of patients with EFS, according to clinical variables significant on multivariate analysis. *By quartiles of continuous variables and classes of categorical variables. Abbreviations as in Figure 2.

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 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.

Acknowledgment: We would like to thank Paola Michelazzo, RN, Jessica Civiero, RN, Chiara DeLonghi, RN, Gianfranco Baro, RN, Daniela Donadel, RN, Raffaella Frare, RN, and Rosa Palmieri, MD, for their assistance with data handling. We are deeply grateful to Paolo Mormino, MD, for his assistance in statistical analysis since the beginning of the present study. We also thank the nurses of the emergency care units for patient management. Finally, we thank the general laboratory personnel of the Conegliano, Adria, and Bassano General Hospitals.

1. Bueno H, Armstrong PW, Buxton MJ, Danchin N, Lubsen J, Roland E, Verheugt FW, Zalewski A, Jackson N, Komajda M, Steg PG; Cardiovascular Round Table Clinical Trials ThinkTank Participants.

The future of clinical trials in secondary prevention after acute coronary syndromes. *Eur Heart J* 2011;32:1583–1589.

2. Fox KA, Carruthers KF, Dunbar DR, Graham C, Manning JR, De Raedt H, Buyschaert I, Lambrechts D, Van de Werf F. Underestimated and under-recognized: the late consequences of acute coronary syndrome (GRACE UK-Belgian study). *Eur Heart J* 2010;31:2755–2764.
3. Nikus KC, Eskola MJ, Virtanen VK, Harju J, Huhtala H, Mikkelsson J, Karhunen PJ, Niemelä KO. Mortality of patients with acute coronary syndromes still remains high: a follow-up study of 1188 consecutive patients admitted to a university hospital. *Ann Med* 2007;39:63–71.
4. Halon DA, Rennert HS, Flugelman MY, Jaffe R, Lewis BS. Burden of late repeat hospitalization in patients undergoing angioplasty or bypass surgery: a long-term (13 years) report from the Lady Davis Carmel Medical Center registry. *Cardiology* 2002;98:67–74.
5. Nordestgaard BG. Does elevated C-reactive protein cause human atherothrombosis? Novel insights from genetics, intervention trials, and elsewhere. *Curr Opin Lipidol* 2009;20:393–401.
6. Brieger D, Fox KA, Fitzgerald G, Eagle KA, Budaj A, Avezum A, Granger CB, Costa B, Anderson FA Jr, Steg PG; Global Registry of Acute Coronary Events Investigators. Predicting freedom from clinical events in non-ST-elevation acute coronary syndromes: the Global Registry of Acute Coronary Events. *Heart* 2009;95:888–894.
7. Brzostek T, Van de Werf F, Scheys I, Lesaffre E, Dubiel J, De Geest H. Prediction of event-free survival after hospital discharge in acute myocardial infarction treated with tissue-plasminogen activator. *Acta Cardiol* 1994;49:9–24.
8. Halon DA, Merdler A, Flugelman MY, Shifroni G, Khader N, Shiran A, Shahla J, Lewis BS. Importance of diabetes mellitus and systemic hypertension rather than completeness of revascularization in determining long-term outcome after coronary balloon angioplasty (the LDCMC registry). Lady Davis Carmel Medical Center. *Am J Cardiol* 1998;82:547–553.
9. Berton G, Citro T, Palmieri R, Petucco S, De Toni R, Palatini P. Albumin excretion rate increases during acute myocardial infarction and strongly predicts early mortality. *Circulation* 1997;96:3338–3345.
10. Erbel R, Krebs W, Henn G, Schweizer P, Richter HA, Meyer J, Effert S. Comparison of single-plane and biplane volume determination by two-dimensional echocardiography: 1. Asymmetric model hearts. *Eur Heart J* 1982;3:469–474.
11. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 1999;130:461–470.
12. Jensen JS, Clausen P, Borch-Johnsen K, Jensen G, Feldt-Rasmussen B. Detecting microalbuminuria by urinary albumin/creatinine concentration ratio. *Nephrol Dial Transplant* 1997;12S2:6–9.
13. Annesi I, Moreau T, Lellouch J. Efficiency of the logistic regression and Cox proportional hazards models in longitudinal studies. *Stat Med* 1989;8:1515–1521.
14. Mark DB, Nelson CL, Califf RM, Harrell FE, Lee KL, Jones RH, Fortin DF, Stack RS, Glower DD, Smith LR, DeLong ER, Smith PK, Reves JG, Jollis JG, Tcheng JE, Muhlbaier LH, Lowe JE, Phillips HR, Pryor DB. Continuing evolution of therapy for coronary artery disease. Initial results from the era of coronary angioplasty. *Circulation* 1994;89:2015–2025.
15. Moss M, Wellman DA, Cotsonis GA. An appraisal of multivariable logistic models in the pulmonary and critical care literature. *Chest* 2003;123:923–928.
16. Grunkemeier GL, Jin R. Receiver operating characteristic curve analysis of clinical risk models. *J Thorac Surg* 2001;72:323–326.
17. Hosmer DW, Lemeshow S. A goodness-of-fit test for the multiple logistic regression model. *Stat* 1980;10:1043–1069.
18. Lee GK, Lee LC, Liu CW, Lim SL, Shi LM, Ong HY, Lim YT, Yeo TC. Framingham risk score inadequately predicts cardiac risk in young patients presenting with a first myocardial infarction. *Ann Acad Med Singapore* 2010;39:163–167.
19. Ruygrok PN, de Jaegere PT, van Domburg RT, van den Brand MJ, Serruys PW, de Feyter PJ. Clinical outcome 10 years after attempted percutaneous transluminal coronary angioplasty in 856 patients. *J Am Coll Cardiol* 1996;27:1669–1677.

20. Brown KA, Weiss RM, Clements JP, Wackers FJ. Usefulness of residual ischemic myocardium within prior infarct zone for identifying patients at high risk late after acute myocardial infarction. *Am J Cardiol* 1987;60:15–19.
21. Berning J, Steensgaard-Hansen FV, Appleyard M. prognostication in acute myocardial infarction by early echocardiographic estimation of left ventricular ejection fraction: multivariate statistical comparison with a clinical prognostic index and its components. *Dan Med Bull* 1992;39:177–181.
22. Mueller HS, Forman SA, Menegus MA, Cohen LS, Knatterud GL, Braunwald E; The TIMI Investigators. Prognostic significance of non-fatal reinfarction during 3-year follow-up: results of the Thrombolysis In Myocardial Infarction (TIMI) phase II clinical trial. *J Am Coll Cardiol* 1995;26:900–907.
23. Schiele F, Meneveau N, Chopard R, Descotes-Genon V, Oettinger J, Seronde MF, Briand F, Bernard Y, Ecarnot F, Bassand JP, de Cardiologie de Franche Comte R. Prognostic value of albuminuria on 1-month mortality in acute myocardial infarction. *Am Heart J* 2009; 157:327–333.
24. Koulouris S, Lekatsas I, Karabinos I, Ioannidis G, Katostaras T, Kranidis A, Triantafyllou K, Thalassinou N, Anthopoulos L. Microalbuminuria: a strong predictor of 3-year adverse prognosis in nondiabetic patients with acute myocardial infarction. *Am Heart J* 2005;149:840–845.
25. Berton G, Cordiano R, Mazzucco S, Katz E, De Toni R, Palatini P. albumin excretion in acute myocardial infarction: a guide for long-term prognosis. *Am Heart J* 2008;156:760–768.
26. Stehouwer CD, Nauta JJ, Zeldenrust GC, Hackeng WH, Donker AJ, den Ottolander GJ. Urinary albumin excretion, cardiovascular disease, and endothelial dysfunction in non-insulin-dependent diabetes mellitus. *Lancet* 1992;340:319–323.
27. Naidoo DP. The link between microalbuminuria, endothelial dysfunction and cardiovascular disease in diabetes. *Cardiovasc J S Afr* 2002; 13:194–199.
28. Gibson CM, Pinto DS, Murphy SA, Morrow DA, Hobbach HP, Wiviott SD, Giugliano RP, Cannon CP, Antman EM, Braunwald E; TIMI Study Group. Association of creatinine and creatinine clearance on presentation in acute myocardial infarction with subsequent mortality. *J Am Coll Cardiol* 2003;42:1535–1543.
29. Palmer SC, Yandle TG, Frampton CM, Troughton RW, Nicholls MG, Richards AM. Renal and cardiac function for long-term (10 year) risk stratification after myocardial infarction. *Eur Heart J* 2009;12:1486–1494.



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 Cordiano², Rosa Palmieri², Fiorella Cavuto³, Marco Pellegrinet⁴ and Paolo Palatini⁵

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, 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

*Corresponding author: Dr. Giuseppe Berton, Cardiology Department, Conegliano General Hospital Via Brigata Bisagno, 31015 Conegliano (TV), Italy, Tel: +390438663613; Fax: +390438663360; E-mail: giube.s@alice.it

Received: March 04, 2014 Accepted: April 16, 2014 Published: April 24, 2014

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

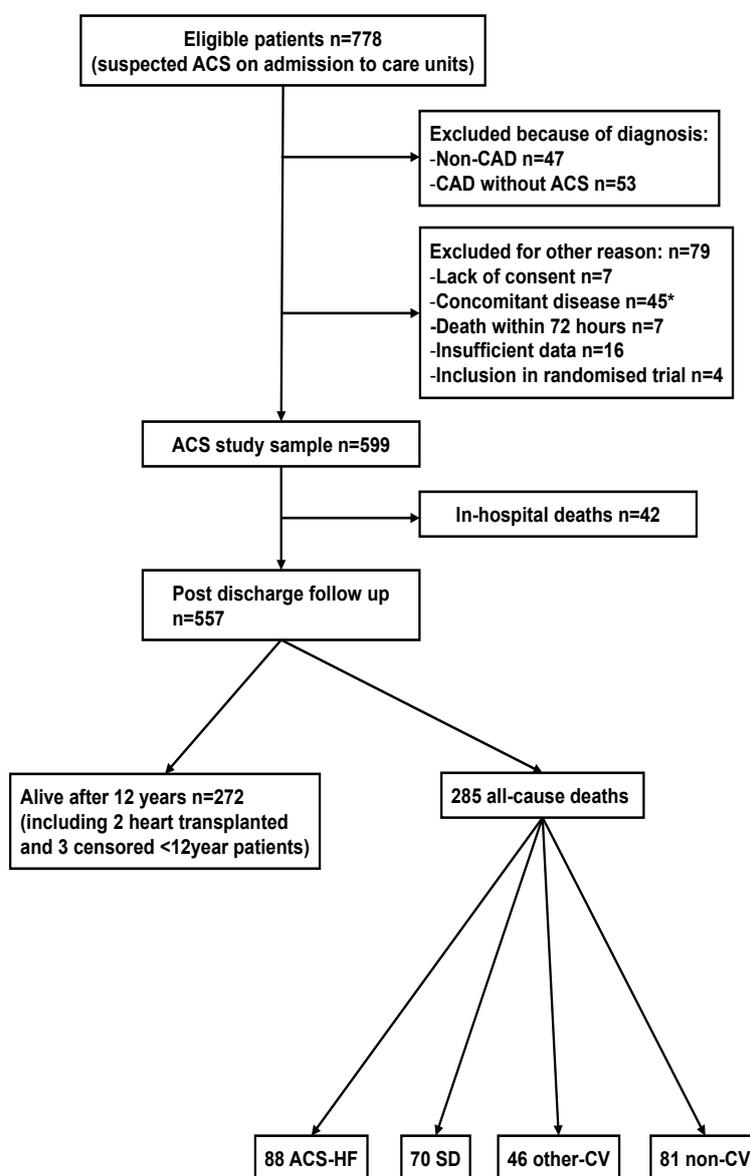


Figure 1: Flow diagram of subject progress during follow-up. ACS indicates Acute Coronary Syndrome, CAD indicates Coronary Artery Disease, CV, cardiovascular, HF indicates Heart Failure, and SD indicates Sudden Death.

*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/m² 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 bradyarrhythmias 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-Lemeshow 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/m ²)	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 m ²) *	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				
β-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.

Variable	Acute model			Sub-acute model		
	$\beta \pm SE$	Hazard ratio (95% CI)	P value	$\beta \pm SE$	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

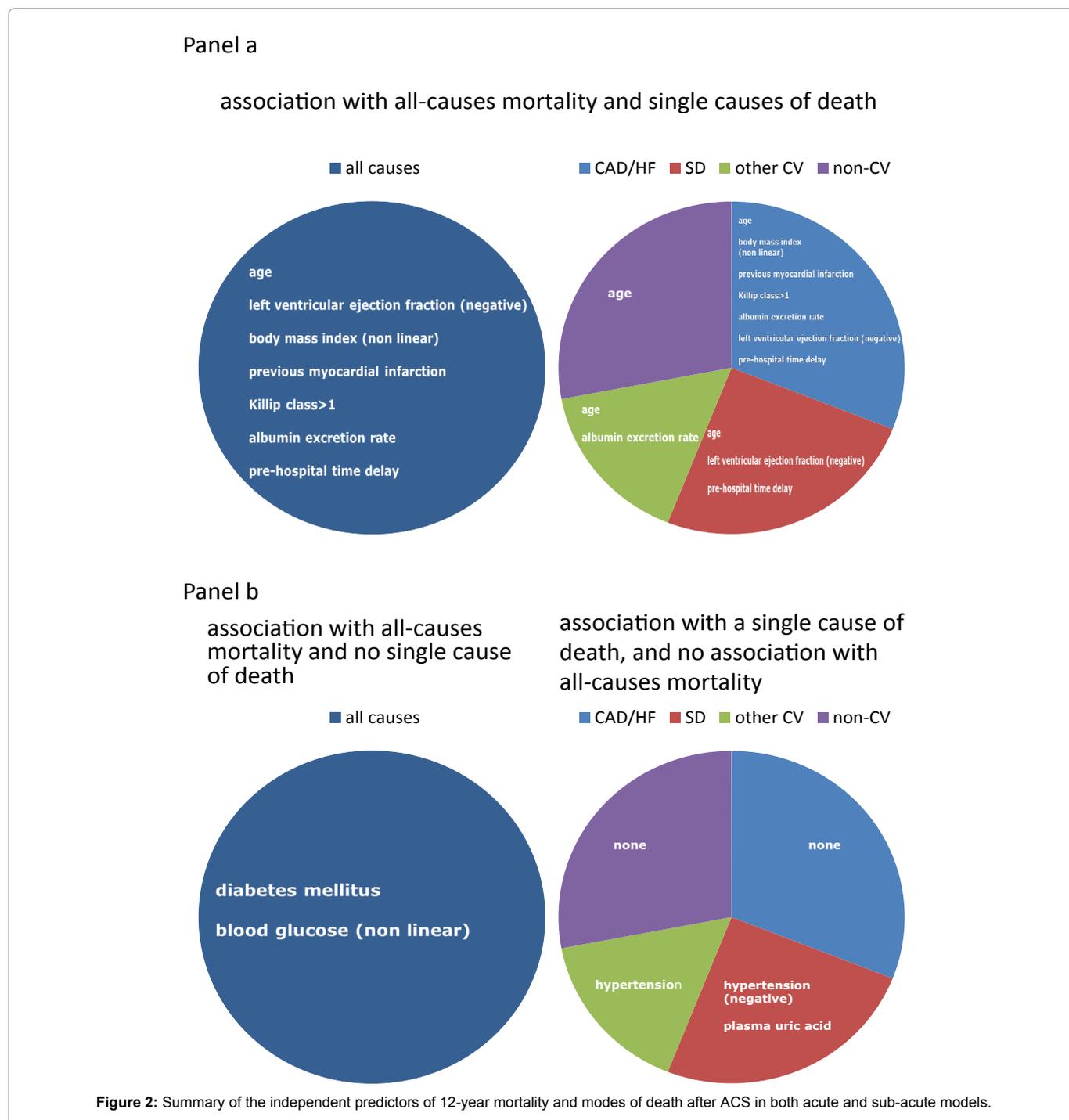
*Non-linear association (U/J-shaped relationship); † Excluding reciprocally blood glucose and diabetes mellitus from the model; Abbreviations as shown in Table 1

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



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

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

	Acute model C-statistic value	Sub-acute model 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 NSTEMI. 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.

Acknowledgments

The authors would like to thank Paola Michelazzo, RN, Jessica Civiero, RN, and Laura Trevisan, RN for assistance in patient management. The authors would also like to thank Rosa Palmieri, MD, Daniela Donadel, RN, and Raffaella Frare,

RN for their assistance with data handling, and the nurses of the emergency care units for patient management. Moreover, the authors would also like to thank Paolo Mormino, MD for assistance with the statistical analysis. Moreover, the authors would like to thank Renzo De Toni, PhD, Patrizio Buttazzi, PhD, and the general laboratory personnel of the Conegliano, Adria, and Bassano General Hospitals for assistance with laboratory data collection.

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.

Funding Sources

This work was supported through grants from the University of Padova, Padova, Italy for the collection, management, and analysis of the data.

References

- Nabel EG, Braunwald E (2012) A tale of coronary artery disease and myocardial infarction. *N Engl J Med* 366: 54-63.
- Fox KA, Carruthers KF, Dunbar DR, Graham C, Manning JR, et al. (2010) Underestimated and under-recognized: the late consequences of acute coronary syndrome (GRACE UK-Belgian Study). *Eur Heart J* 31: 2755-2764.
- Berton G, Cordiano R, Cavuto F, Giacomini G, De Toni R, et al. (2012) 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). *Am J Cardiol* 109: 966-975.
- Nikus KC, Eskola MJ, Virtanen VK, Harju J, Huhtala H, et al. (2007) Mortality of patients with acute coronary syndromes still remains high: a follow-up study of 1188 consecutive patients admitted to a university hospital. *Ann Med* 39: 63-71.
- Bueno H, Armstrong PW, Buxton MJ, Danchin N, Lubsen J, et al. (2011) The future of clinical trials in secondary prevention after acute coronary syndromes. *Eur Heart J* 32: 1583-1589.
- Allen LA, O'Donnell CJ, Camargo CA Jr, Giugliano RP, Lloyd-Jones DM (2006) Comparison of long-term mortality across the spectrum of acute coronary syndromes. *Am Heart J* 151: 1065-1071.
- Agarwal SK, Singla I, Hreybe H, Saba S (2009) Clinical predictors of late death in survivors of acute myocardial infarction. *Tex Heart Inst J* 36: 24-30.
- Eggers KM, Kempf T, Venge P, Wallentin L, Wollert KC, et al. (2010) Improving long-term risk prediction in patients with acute chest pain: the Global Registry of Acute Coronary Events (GRACE) risk score is enhanced by selected nonnecrosis biomarkers. *Am Heart J* 160: 88-94.
- Marchioli R, Avanzini F, Barzi F, Chieffo C, Di Castelnuovo A, et al. GISSI-Prevenzione Investigators (2001) Assessment of absolute risk of death after myocardial infarction by use of multiple-risk-factor assessment equations: GISSI-Prevenzione mortality risk chart. *Eur Heart J* 22: 2085-2103.
- Qian RL, Feng JG (1991) Causes of death and long-term prognosis after myocardial infarction in patients with diabetes mellitus. *Chin Med J (Engl)* 104: 18-21.
- Bangalore S, Qin J, Sloan S, Murphy SA, Cannon CP; PROVE IT-TIMI 22 Trial Investigators (2010) What is the optimal blood pressure in patients after acute coronary syndromes?: Relationship of blood pressure and cardiovascular events in the Pravastatin OR atorVastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction (PROVE IT-TIMI) 22 trial. *Circulation* 122: 2142-2151.
- Killip T III, Kimball JT (1967) Treatment of myocardial infarction in a coronary care unit: A two year experience with 250 patients. *Am J Cardiol* 20: 457-464.
- Erbel R (1982) Comparison of single-plane and biplane volume determination by two-dimensional echocardiography: 1. Asymmetric model hearts. *Eur Heart J* 3: 469-474.
- Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, et al. (1999) A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 130: 461-470.
- Jensen JS, Clausen P, Borch-Johnsen K, Jensen G, Feldt-Rasmussen B (1997) Detecting microalbuminuria by urinary albumin/creatinine concentration ratio. *Nephrol Dial Transplant* 12S2: 6-9.
- Kim SG, Fogoros RN, Furman S, Connolly SJ, Kuck KH, et al. (1993) Standardized reporting of ICD patient outcome: the report of a North American Society of Pacing and Electrophysiology Policy Conference. *Pacing Clin Electrophysiol* 16: 1358-1362.
- Cox DA, Stone GW, Grines CL, Stuckey T, Zimetbaum PJ, et al. (2006) Comparative early and late outcomes after primary percutaneous coronary intervention in ST-segment elevation and non-ST-segment elevation acute myocardial infarction (from the CADILLAC trial). *Am J Cardiol* 98: 331-337.
- Rich MW, Bosner MS, Chung MK, Shen J, McKenzie JP (1992) Is age an independent predictor of early and late mortality in patients with acute myocardial infarction? *Am J Med* 92: 7-13.
- Kaplan RC, Heckbert SR, Furberg CD, Psaty BM (2002) Predictors of subsequent coronary events, stroke, and death among survivors of first hospitalized myocardial infarction. *J Clin Epidemiol* 55: 654-664.
- Cid-Alvarez B, Gude F, Cadarso-Suarez C, Gonzalez-Babarro E, Rodriguez-Alvarez MX, et al. (2009) Admission and fasting plasma glucose for estimating risk of death of diabetic and nondiabetic patients with acute coronary syndrome: nonlinearity of hazard ratios and time-dependent comparison. *Am Heart J* 158: 989-997.
- Gerstein HC, Miller ME, Genuth S, Ismail-Beigi F, Buse JB, et al. (2011) Long-term effects of intensive glucose lowering on cardiovascular outcomes. *N Engl J Med* 364: 818-828.
- Bangalore S, Messerli FH, Ou FS, Tamis-Holland J, Palazzo A, et al. (2009) Blood pressure paradox in patients with non-ST-segment elevation acute coronary syndromes: results from 139,194 patients in the Can Rapid risk stratification of unstable angina patients Suppress Adverse outcomes with early implementation of the American College of Cardiology/American Heart Association Guidelines (CRUSADE) quality improvement initiative. *Am Heart J* 157: 525-531.
- Bangalore S, Qin J, Sloan S, Murphy SA, Cannon CP, et al. (2010) What is the optimal blood pressure in patients after acute coronary syndromes?: Relationship of blood pressure and cardiovascular events in the Pravastatin OR atorVastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction (PROVE IT-TIMI) 22 trial. *Circulation* 122: 2142-2151.
- Cruickshank JM (1988) Coronary flow reserve and the J curve relation between diastolic blood pressure and myocardial infarction. *BMJ* 297: 1227-1230.
- Ndrepepa G, Braun S, Haase HU, Schulz S, Ranftl S, et al. (2012) Prognostic value of uric acid in patients with acute coronary syndromes. *Am J Cardiol* 109:1260-1265.
- Mueller HS, Forman SA, Menegus MA, Cohen LS, Knatterud GL, et al. (1995) Prognostic significance of nonfatal reinfarction during 3-year follow-up: results of the Thrombolysis in Myocardial Infarction (TIMI) phase II clinical trial. *The TIMI Investigators. J Am Coll Cardiol* 26: 900-907.
- Jedrzikiewicz S, Goodman SG, Yan RT, Grondin FR, Gallo R (2010) Evaluation of left ventricular ejection fraction in non-ST-segment elevation acute coronary syndromes and its relationship to treatment. *Am Heart J* 159: 605-611.
- Gerstein HC, Mann JF, Yi Q, Zinman B, Dinneen SF, et al. (2001) Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and non diabetic individuals. *JAMA* 286: 421-426.
- Gosling P, Hughes EA, Reynolds JP, Fox JP, et al. (1991) Microalbuminuria is an early response following acute myocardial infarction. *Eur Heart J* 12: 508-513.
- Berton G, Citro T, Palmieri R, Petucco S, De Toni R, et al. (1997) Albumin excretion rate increases during acute myocardial infarction and strongly predicts early mortality. *Circulation* 96: 3338-3345.
- Gibson CM, Pinto DS, Murphy SA, Morrow DA, Hobbach HP, et al. (2003) Association of creatinine and creatinine clearance on presentation in acute myocardial infarction with subsequent mortality. *J Am Coll Cardiol* 42: 1535-1543.
- Berger AK, Radford MJ, Krumholz HM (2000) Factors associated with delay in reperfusion therapy in elderly patients with acute myocardial infarction: analysis of the cooperative cardiovascular project. *Am Heart J* 139: 985-992.

Author Affiliations

Top

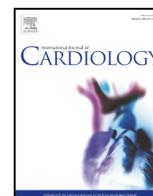
¹Department of Cardiology, Conegliano General Hospital, Conegliano, Italy

²Departments of Internal Medicine and Cardiology, Adria General Hospital, Adria, Italy

³Department of Cardiology, Bassano del Grappa General Hospital, Bassano del Grappa, Italy

⁴Department of Internal Medicine and Cardiology, Udine University Hospital, Udine, Italy

⁵Department of Clinical and Experimental Medicine, University of Padova, Padova, Italy



Heart failure in women and men during acute coronary syndrome and long-term cardiovascular mortality (the ABC-3* Study on Heart Disease) (*Adria, Bassano, Conegliano, and Padova Hospitals)



Giuseppe Berton ^{a,*}, Rocco Cordiano ^b, Fiorella Cavuto ^c, Francesco Bagato ^b, Marco Pellegrinet ^d, Arianna Cati ^a

^a Department of Cardiology, Conegliano General Hospital, Conegliano, Italy

^b Department of Internal Medicine and Cardiology, Adria General Hospital, Adria, Italy

^c Department of Cardiology, Bassano del Grappa General Hospital, Bassano del Grappa, Italy

^d Department of Internal Medicine and Cardiology, Udine University Hospital, Udine, Italy

ARTICLE INFO

Article history:

Received 14 April 2016

Received in revised form 7 June 2016

Accepted 21 June 2016

Available online 23 June 2016

Key words:

Gender

Heart failure

Killip class

LVEF

Acute coronary syndrome

Cardiovascular mortality

Surviving analysis

ABSTRACT

Aims: We investigated the gender-based differences in the association between heart failure (HF) during acute coronary syndrome (ACS) and post-discharge, long-term cardiovascular (CV) mortality.

Methods and results: The present study included 557 patients enrolled in three intensive coronary care units and discharged alive. HF during ACS was evaluated by Killip class and left ventricular ejection fraction (LVEF). Interaction between gender and HF after 15 years of follow up was studied using Cox models including a formal interaction term. Median age was 67 (interquartile range [IQR], 59–75) years, 29% were females, 37% had non-ST elevation myocardial infarction and 32% Killip class > 1, and median LVEF was 53% (IQR 46–61). All but five patients were followed up to 15 years, representing 5332 person-years. Of these, 40.2% died of CV-related causes. Crude CV mortality rate was higher among women (52.2%) than men (35.3%; $P < 0.0001$). At a univariable level, a negative interaction between female gender and Killip class for CV mortality was found [hazard ratio (HR) = 0.51 (0.34–0.77), $P = 0.002$]. In five multivariable models after controlling for age, main CV risk factors, clinical features, post-discharge medical treatment, and mechanical coronary reperfusion, the interaction was significant across all models [HR = 0.63 (0.42–0.95), $P = 0.02$ in the fully adjusted model]. LVEF showed no significant hazard associated with female gender on univariable analysis [HR = 1.4 (0.9–2.0), $P = 0.11$] but did so in all adjusted models [HR = 1.7 (1.2–2.5), $P = 0.005$ in the fully adjusted model].

Conclusion: Gender is a consistent, independent effect modifier in the association between HF and long-term CV mortality after ACS.

© 2016 Elsevier Ireland Ltd. All rights reserved.

1. Introduction

Natural history studies have suggested differences in survival between men and women in a broad spectrum of heart failure (HF) severity [1–4]. The Framingham Heart Study found that the prognosis for women was better than for men after the onset of signs of HF [1,2]. In patients with acute coronary syndrome (ACS), women have a worse prognosis than men, but the adverse course was attributed to their baseline characteristics and not to gender per se [5,6]. Indeed, it is well established that the presence of HF during ACS is one of the most important clinical manifestations leading to adverse outcomes [6,7]. Nonetheless, the relationship between gender and HF for adverse prognosis after ACS has not been thoroughly examined, especially in the long

term. Studies have focused on gender differences for adverse outcomes associated with age, type of ACS, or treatment [8–11]. Furthermore, a recent overview of the current understanding of possible gender differences in cardiovascular (CV) risk factors, therapy, and prognosis of ACS reported no data on the relationship between gender and HF [12]. Our aim was to investigate prospectively the gender-based differences in the association between HF during ACS and post-discharge, long-term CV mortality.

2. Methods

2.1. Patients

The Adria, Bassano, Conegliano, and Padova Hospital Study on Heart Disease (the ABC Study on ACS) is an ongoing, prospective investigation designed to reflect, as closely as possible, an unbiased population of patients with ACS. The sample includes Caucasian patients with definite

* Corresponding author at: Cardiology Department, Conegliano General Hospital, Via Brigata Bisagno, 31015 Conegliano, (TV), Italy.
E-mail address: giube.s@alice.it (G. Berton).

ACS (ST elevation myocardial infarction [STEMI], non-ST elevation myocardial infarction [NSTEMI], and unstable angina [UA]), admitted to the intensive care units of Adria, Bassano, and Conegliano hospitals between June 21, 1995, and January 19, 1998. The original aim of the ABC study was to follow the natural, long-term history of the patients and to evaluate the prognostic value of a number of clinical variables. The criteria for the diagnosis of ACS included the clinical presentation, electrocardiogram (ECG) findings, and the identification of serum biochemical markers of necrosis. Specifically, acute myocardial infarction was 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 elevation or depression). Myocardial infarction was also classified as type 1 and type 2, according to the third universal definition of myocardial infarction [13]. UA is described as the occurrence of one or more episodes of angina at rest within the preceding 48 h, corresponding to class III of the Braunwald classification, with ECG changes indicative of ischemia [14].

A total of 778 eligible patients were considered upon admission. Of 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. Seventy-nine patients were excluded from the study for concomitant conditions potentially affecting the investigated variables, as detailed elsewhere [7]. Forty-two of the enrolled patients died during the index hospitalization and were excluded from the present analysis. Hence, the post-discharge follow-up study included 557 patients. 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.

2.2. Measurements

At enrollment, a thorough patient history from medical records and patient interviews was collected. All baseline clinical and laboratory data reported in the present study were obtained during the first 7 days of hospitalization in the intensive coronary care unit. Details of variables accrued have been published elsewhere [7,15]. We investigated the presence and degree of HF during ACS by means of Killip class and left ventricular ejection fraction (LVEF) [16,17]. Killip classification was recorded as follows: class 1, no signs of HF; class 2, pulmonary rales; and class 3, pulmonary edema or cardiogenic shock (Killip classes 3 and 4) [15]. The highest class observed during the first 7 days of the hospital stay was used in the present analysis. LVEF was assessed using two-dimensional echocardiography according to Simpson's method [17]. The LVEF was missing for 81 patients who underwent echocardiography after discharge from the intensive care units or who had technically inadequate echocardiographic images. Two physicians, with no knowledge of the patient clinical data, examined the records.

2.3. Follow-up and outcomes

At 1, 3, 5, 7, 10, 12, and 15 years after recruitment, each patient underwent a clinical check-up. At each recruitment hospital, two cardiologists took care to follow the surviving cohort through the 15 years of follow-up. The pre-specified primary endpoint of the present study was to determine the 15-year CV mortality. Two researchers, unaware of baseline patient data, examined the modes of death. CV mortality included: CAD and/or HF progression; sudden death, 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; and other CV causes [7,18]. All data regarding the events were obtained from a scheduled check-up, public administration and hospital records, family doctors, postmortem examinations, and death certificates. Reports were also obtained regarding the medications administered during

the index hospitalization and follow-up treatments. If a patient underwent heart transplantation, that patient was censored at the time of transplantation.

2.4. Statistical analysis

Unpaired Student's t-test and Pearson chi-square (χ^2) test were used for measured and categorical variables, respectively. Log transformations were used to correct for positive-skewed distributions, as appropriate. In survival analysis, LVEF was analyzed as tertiles of increasing values. Cox proportional hazard regression analysis was used to describe the influence of the variables on mortality during follow-up [19]. If a patient dropped out before completing 15 years of follow up, that patient's data were censored at that time. Scaled Schoenfeld residuals were used to test the proportionality assumption with a 95% confidence interval (CI) [20]. The interaction between gender and HF was studied first by means of odds ratios (ORs) and the Mantel–Haenszel test of homogeneity (with $P < 0.05$ indicating dis-homogeneity of the OR). Then, Cox survival regressions, including a formal interaction term between gender and HF and adjusting for main clinical variables and main treatments, were used. The risk estimate was quantified as the hazard ratio (HR). To show graphically gender HR ratios for CV mortality across increasing degrees of Killip class and tertiles of LVEF, marginal analysis was used.

The baseline characteristics were summarized using medians and interquartile ranges for continuous variables and numbers and percentages for categorical variables. Unless otherwise indicated, two-tailed P values < 0.05 were deemed significant. The statistical analyses were performed using STATA 13.

3. Results

3.1. Baseline characteristics

A total of 28.9% of the 557 patients in the sample were women. Table 1 summarizes the main clinical characteristics by gender. Overall, women were older than men and more likely to have hypertension and diabetes mellitus and a history of angina and higher systolic blood pressure values and total cholesterol at enrollment (Table 1). They had lower body mass index and were less likely ever to have smoked. Women had more frequent and more severe signs of HF and a lower heart rate, estimated glomerular filtration rate, and CK-MB peak than men while LVEF was similar between men and women (Table 1). Main treatments differed by gender, including thrombolytic treatment at enrollment and mechanical revascularization during follow-up, which were all less frequently used for women except for angiotensin-converting enzyme inhibitor/angiotensin II receptor blockers, which were used more in women.

3.2. Death rate by gender and OR by Killip class and LVEF

All patients included in this study underwent 15-year observation or time to death, except for five who dropped out (two patients withdrew consent and one patient moved overseas) and two who underwent heart transplantation. The entire sample represented 5332 person-years of follow-up, and 224 patients (40.2%) died of a CV-related cause. Crude mortality rate was higher among women (52.2%) than among men (35.3%; $P < 0.0001$). Overall, at the univariable level, both Killip class and LVEF (increasing and decreasing risk respectively) ORs were associated with outcome (Table 2). Indeed, among male patients, OR was much higher than among females, and the Mantel–Haenszel test of homogeneity showed significant differences. This result indicates a negative interaction between gender and degree of Killip class for CV mortality, i.e., the higher the degree of Killip class, the lower the mortality risk for the women compared to the men. The same univariable

Table 1
Baseline characteristics of the patients by gender.

Variable name	Overall sample (N = 557)	Male (N = 396)	Female (N = 161)	P value
Age (years)	67 (58–74)	64 (55–71)	73 (67–79)	<0.0001
Current smoking	38	46	17	<0.0001
Hypertension	46	39	65	<0.0001
Diabetes mellitus	21	18	31	<0.0001
Body mass index (kg/m ²)	26 (24–28)	26 (24–28)	25 (22–27)	<0.0001
History of angina	25	22	32	0.02
Previous myocardial infarction	24	24	24	0.82
Pre-hospital time delay (n = 465)	180 (120–510)	180 (120–480)	240 (120–660)	0.07 ^a
ST elevation ACS	61	64	55	0.06
Type 2 myocardial infarction	8.6	7.1	12.4	0.04
Total cholesterol (mmol/L)	208 (179–243)	205 (177–238)	220 (188–247)	0.04
Systolic blood pressure (mm Hg)	121 (108–133)	119 (108–131)	124 (111–137)	0.004
Diastolic blood pressure (mm Hg)	77 (69–83)	77 (68–83)	77 (69–83)	0.82
Heart rate (beats/min)	70 (60–78)	68 (60–75)	75 (66–84)	<0.0001
CK MB peak (U/L) ^a	103 (43–207)	107 (47–221)	74 (35–175)	0.009 ^a
Killip class ^b				<0.0001
1 (no heart failure)	68	73	53	
2 (heart failure)	28	23	38	
3 (pulmonary edema/cardiogenic shock)	5	3	8	
LVEF (%) (n = 476)	53 (46–61)	53 (46–60)	52 (46–62)	0.87
eGFR (mL/s × 1.73 m ²) ^a	73 (61–87)	76 (64–88)	65 (56–81)	<0.0001 ^a
Main treatment				
Thrombolysis (at enrollment)	35	38	28	0.02
β-receptor blocker	51	55	39	0.001
ACE-inhibitor/angiotensin II receptor blocker	73	71	78	0.05
Antiplatelet	90	91	85	0.02
Lipid-lowering drug	32	36	22	0.001
PTCA (during follow-up)	19	21	13	0.03
CABG (during follow-up)	19	22	12	0.006

Values are medians and interquartile ranges or percentages. Pre-hospital time delay indicates time from onset of symptoms to arrival at coronary care unit; AMI, acute myocardial infarction; CK-MB, creatine kinase-MB isoenzyme; LVEF, left ventricular ejection fraction; eGFR, estimated glomerular filtration rate by MDRD; PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass graft.

^a P values were calculated on log-transformed data.

^b During the first 7 days of hospital stay. To convert total cholesterol to conventional units (mg/dL) divide by 0.0259; eGFR (mL/min) by 0.0167.

analysis using increasing tertiles of LVEF showed a weaker interaction with gender than did Killip class (Table 2).

3.3. Survival and interaction analysis

The proportional-hazards assumption was verified for all variables used in the present surviving models ($P > 0.30$ for each variable). On univariable Cox regression analysis, female gender appeared to be associated with a higher CV risk than being male (Table 3). As expected, also Killip class (positively) and LVEF (negatively) were associated with higher mortality. After modeling the survival time controlling for age, mortality risk was no longer associated with female gender while it remained strongly associated with Killip class and LVEF (Table 3). Hence, a formal interaction term between gender and Killip class and LVEF was introduced into the survival models. This term revealed a

negative interaction between female gender and Killip class for CV mortality (Table 3). The interaction was tested in five subsequent multivariable models after controlling for age, main CV risk factors, clinical features, post-discharge medical treatment, and mechanical coronary reperfusion. A significant negative interaction between female gender and increasing Killip class was found across all models (Table 3). The same steps were made using LVEF. At the univariable level, LVEF did not show a significant variation in hazard for female gender as compared to male gender. When the interaction was evaluated with controlling for age, the gender interaction became apparent. The adjustment for clinical and treatment variables of the subsequent models revealed a consistent significant positive interaction between female gender and increasing LVEF (Table 3). In Fig. 1, the graphical representation of interaction analysis shows the HR for CV mortality of men and women across Killip classes and LVEF. On univariable analysis, women with a lower degree of Killip class had higher risk than men while with increasing Killip class, they had lower risk than men (Fig. 1). After full adjustment of the model (using the same variables of the model in Table 3), the risk ratio maintained the same trend. LVEF at the univariable level did not show an interaction with gender, but after controlling for the abovementioned confounders, the interaction became clear (representation of full adjusted analysis is reported in Fig. 1).

4. Discussion

The main result of the ABC-3 Study on ACS is that women and men with ACS have different long-term CV mortality risk across increasing degrees of HF, even after controlling the survival models for age, main clinical features, and main treatments. Thus, gender is an independent effect modifier of HF for CV mortality.

Table 2
Interaction between gender and HF for the risk of 15-year CV mortality as assessed by Mantel–Haenszel test of homogeneity.

Mantel–Haenszel test of homogeneity by gender	Relative risks (95%CI) across Killip classes	P value
Men	2.4 (1.9–3.1)	
Women	1.3 (0.9–1.7)	
Overall	2.0 (1.6–2.4)	
Test of homogeneity		0.001
Mantel–Haenszel test of homogeneity by gender	Relative risks (95%CI) across left ventricular ejection fraction tertiles	P value
Men	0.44 (0.33–0.59)	
Women	0.70 (0.51–0.97)	
Overall	0.53 (0.43–0.66)	
Test of homogeneity		0.03

Table 3

Survival analysis and variation in the effect of sex on the risk of 15-year CV mortality by Killip class and LVEF, and the effect of adding covariables.

Variable	Hazard ratio (95%CI)	P value
Female gender	1.8 (1.4–2.4)	<0.0001
Age-adjusted female gender	1.1 (0.8–1.5)	0.48
Killip class (3 classes)	2.6 (2.1–3.1)	<0.0001
Age-adjusted Killip class	1.9 (1.5–2.3)	<0.0001
LVEF (by tertiles)	0.57 (0.48–0.69)	<0.0001
Age-adjusted LVEF	0.62 (0.52–0.75)	<0.0001
Analysis of interaction between female gender and Killip class		
	Variation in hazard of death by gender (and 95%CI)	P value for gender – Killip class interaction
Unadjusted	0.51 (0.34–0.77)	0.002
Adjusted for age	0.62 (0.41–0.95)	0.03
Adjusted for the above and hypertension, diabetes, cholesterol	0.63 (0.42–0.96)	0.03
Adjusted for the above and heart rate, MDRD	0.64 (0.42–0.96)	0.03
Adjusted for the above and treatment with β -blocker, ACEI/ATII inhibitor, statin, during follow-up	0.53 (0.33–0.85)	0.009
Adjusted for the above and thrombolysis on admission, PCI and CABG during follow-up	0.63 (0.42–0.95)	0.02
Analysis of interaction between female gender and LVEF		
		P value for gender – LVEF interaction
Unadjusted	1.4 (0.9–2.0)	0.11
Adjusted for age	1.5 (1.1–2.2)	0.04
Adjusted for the above and hypertension, diabetes, cholesterol	1.6 (1.1–2.3)	0.01
Adjusted for the above and heart rate, MDRD	1.7 (1.2–2.4)	0.006
Adjusted for the above and treatment with β -blocker, ACEI/ATII inhibitor, statin, during follow-up	1.7 (1.2–2.5)	0.004
Adjusted for the above and thrombolysis (on admission), PCI and CABG during follow-up	1.7 (1.2–2.5)	0.005

LVEF indicates left ventricular ejection fraction; eGFR, estimated glomerular filtration rate by MDRD; CV, cardiovascular; CABG, coronary artery bypass graft; PTCA, percutaneous transluminal coronary angioplasty.

According to most of the studies in coronary disease, mortality rate after ACS is higher among women than men [5]. Age has emerged as an important confounding factor in the estimation of gender risk, but after controlling for age and other clinical variables, this difference tended to disappear [5,6]. Other studies, however, found that differences in short-term outcome between men and women could not be entirely accounted for by differences in baseline characteristics and could reflect pathophysiologic and anatomical differences between genders [9]. In patients with congestive HF, women have better survival than men, and that difference is stronger among patients with a non-ischemic etiology of HF [4]. In agreement, a recent meta-analysis showed that women with HF have a lower risk of death over a 3-year follow-up when compared with men with HF, in both preserved and reduced LVEF, chiefly in non-ischemic patients [11].

A key question is why women have different outcomes in relation to HF. There is a lack of studies comparing biological mechanisms of disease between men and women to better define vascular and pathophysiological processes that are unique to women [4,21–23]. Recent reports have highlighted important sex differences in the pathophysiology, presentation, and treatment of ischemic heart disease and have shown pervasive sex-related disparities in referral and treatment [9,10]. However, few studies have investigated sex-based differences in heart disease and ACS, and most of them dealt with short-term outcomes [21]. Age is an effect modifier in patients with myocardial infarction, and young and middle-aged women have worse outcome than men [8]. Even if younger women have a higher rate of risk factors, including history of HF, this higher rate does not entirely explain sex differences in outcome [22,24]. In the present study, the sequence of adjusted survival models, including progressively the main CV risk factors, clinical variables, and treatments, showed consistently that gender is an effect modifier in the association of HF degree during ACS and outcome. Even the type of myocardial infarction did not modify the interaction between gender and HF. Such an observation is in keeping with other reports showing that myocardial infarction type does not influence long term mortality [25]. Furthermore, it is of clinical relevance that the effect modification of sex is associated with a very long follow-up time, as the ABC-3 study lasted 15 years after the ACS event.

In the present study, women were less likely to receive thrombolytic therapy, PTCA, or CABG, compared with men. According to other

reports, this observation can be due to their higher age and the higher rate of renal insufficiency [26]. However adjustment in surviving regressions by these treatments did not modify the interaction between gender and HF.

The two indicators of HF used in the present study, Killip class and LVEF, did not show a parallel association between gender and prognosis. Killip class degree appeared to modify the association of gender with CV risk, while LVEF measurement did not appear to interact with gender at univariable level. Only after controlling for age and a number of clinical variables the positive interaction with gender became clear. Accordingly, similar findings were found in patients hospitalized with HF, in whom long-term follow-up revealed a significant gender–LVEF interaction [27].

5. Limitations of the study

A major limitation of the ABC Study on Heart Disease is 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 might have modified the predictive models. However, we observed that the results of the predictive model were similar for patients with and without Q-wave myocardial infarction and those with and without thrombolytic treatment. Furthermore, adjustment of the survival models for medical and mechanical reperfusion treatment did not affect the results for gender interaction either with Killip class or LVEF.

Another limitation of the study is that diagnosis of myocardial infarction did not account for troponin measurement, as it was not in use at that time, while we used biochemical markers of necrosis the rise and gradual decline of creatine kinase and creatine kinase-MB. Nevertheless these markers of necrosis are still recommended in absence of troponin measurement [13].

Because this study was conducted in Caucasian patients, we cannot generalize these findings to other populations and ethnic groups.

6. Conclusion

Our findings support the hypothesis that gender modifies the impact of HF on prognosis long after ACS. Women with lower Killip class, or

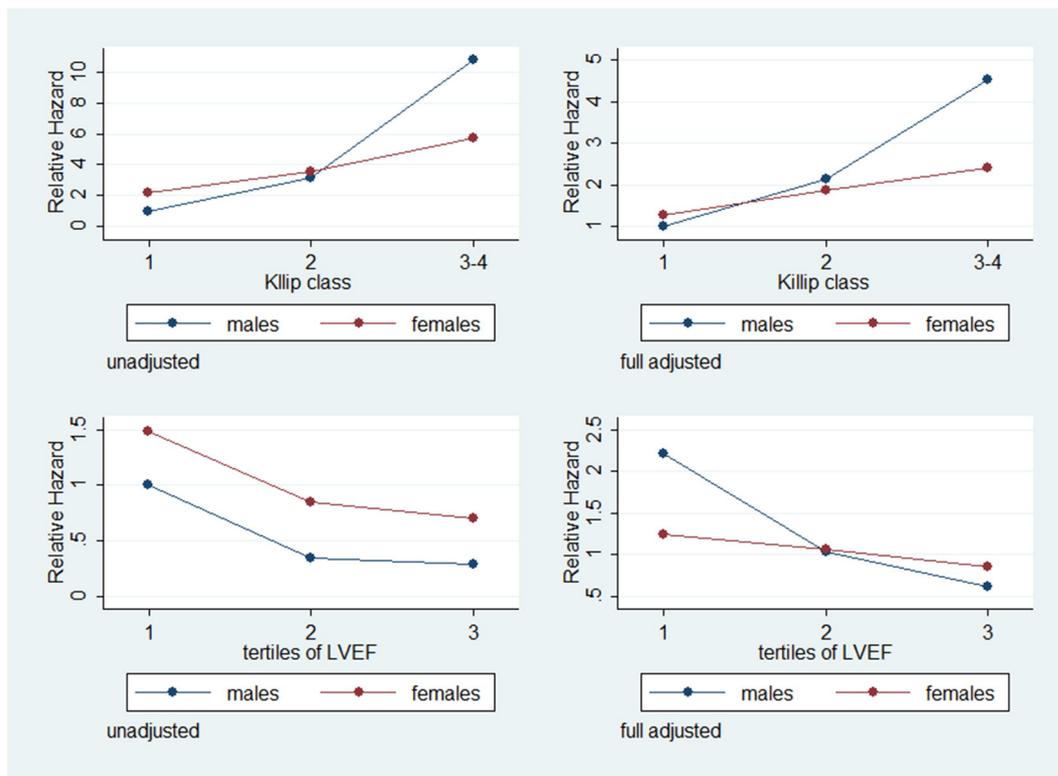


Fig. 1. Graphical representation of the interaction analysis showing the HRs for CV mortality of men and women across Killip classes and LVEF tertiles in patients followed 15 years after ACS. Left, unadjusted models; right, fully adjusted models.

higher LVEF, had higher CV mortality risk than men, and women with higher Killip class, or lower LVEF, had lower risk compared to men.

Author contributions

Dr. Berton designed the study. Dr. Cordiano and Dr. Palmieri contributed to the original data collection. Dr. Cavuto, Dr. Cordiano, and Dr. Cati 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 figure. Dr. Berton contributed to the analysis and interpretation of the data and the preparation of this manuscript. All authors contributed to the accuracy of the data analysis.

Funding

This work was supported by grant of Veneto Region, Italy (Veneto Region Act n. 748, Venice, May 14th 2015, grant number 298792). And from University of Padova (Padova, Italy) for the collection, management, and analysis of the data.

Disclosures

None.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

Acknowledgments

The authors would like to thank Paola Michelazzo, RN, Jessica Civiero, RN, and Laura Trevisan, RN, for assistance in patient management. The authors would also like to thank Rosa Palmieri, MD, and

Raffaella Frare, RN, for their assistance with data handling, and the nurses of the emergency care units for patient management. Moreover, the authors also thank Paolo Mormino, MD, for his assistance with statistical analysis from the beginning of the ABC study. Finally, the authors thank Renzo De Toni, PhD, Patrizio Buttazzi, PhD, and the general laboratory personnel of the Conegliano, Adria, and Bassano general hospitals for assistance collecting laboratory data.

References

- [1] P.A. McKee, W.P. Castelli, P.M. McNamara, et al., The natural history of congestive heart failure: the Framingham study, *N. Engl. J. Med.* 285 (1971) 1441–1446.
- [2] K.K. Ho, K.M. Anderson, W.B. Kannel, W. Grossman, et al., Survival after the onset of congestive heart failure in Framingham Heart Study subjects, *Circulation* 88 (1993) 107–115.
- [3] C.D. Kimmelstiel, M.A. Konstam, Heart failure in women, *Cardiology* 86 (1995) 304–309 (Review).
- [4] K.F. Adams Jr., C.A. Sueta, M. Gheorghade, et al., Gender differences in survival in advanced heart failure. Insights from the FIRST study, *Circulation* 99 (1999) 1816–1821.
- [5] J.L. Cabrerizo-García, J.I. Pérez-Calvo, B. Zalba-Etayo, Influence of gender on prognosis of acute coronary syndromes, *Rev. Port. Cardiol.* 34 (2015) 43–50.
- [6] K. Kanamasa, K. Ishikawa, T. Hayashi, et al., Increased cardiac mortality in women compared with men in patients with acute myocardial infarction, *Intern. Med.* 43 (2004) 911–918.
- [7] G. Berton, R. Cordiano, R. Palmieri, et al., Prospective history of long-term mortality and modes of death in patients discharged after acute coronary syndrome: the ABC-2^o study on acute coronary syndrome, *Int. J. Cardiovasc. Res.* 3 (2014) 1–10.
- [8] V. Vaccarino, L. Parsons, N.R. Every, et al., Sex-based differences in early mortality after myocardial infarction, *N. Engl. J. Med.* 341 (1999) 217–225.
- [9] J.S. Hochman, J.E. Tamis, T.D. Thompson, et al., Sex, clinical presentation, and outcome in patients with acute coronary syndromes. Global use of strategies to open occluded coronary arteries in acute coronary syndromes IIb investigators, *N. Engl. J. Med.* 341 (1999) 226–232.
- [10] K.P. Champney, P.D. Frederick, H. Bueno, et al., The joint contribution of sex, age and type of myocardial infarction on hospital mortality following acute myocardial infarction, *Heart* 95 (2009) 895–899.
- [11] M. Martínez-Sellés, R.N. Doughty, K. Poppe, et al., Gender and survival in patients with heart failure: interactions with diabetes and aetiology. Results from the MAGGIC individual patient meta-analysis, *Eur. J. Heart Fail.* 14 (2012) 473–479.

- [12] M. Claassen, K.C. Sybrandy, Y.E. Appelman, et al., Gender gap in acute coronary heart disease: myth or reality? *World J. Cardiol.* 4 (2012) 36–47.
- [13] K. Thygesen, J.S. Alpert, A.S. Jaffe, et al., Writing group on the joint ESC/ACCF/AHA/WHF task force for the universal definition of myocardial infarction. Third universal definition of myocardial infarction, *Eur. Heart J.* 33 (2012) 2551–2567.
- [14] K.A. Fox, K.F. Carruthers, D.R. Dunbar, et al., Underestimated and under-recognized: the late consequences of acute coronary syndrome (GRACE UK-Belgian Study), *Eur. Heart J.* 31 (2010) 2755–2764.
- [15] G. Berton, R. Cordiano, F. Cavuto, et al., 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), *Am. J. Cardiol.* 109 (2012) 966–975.
- [16] T. Killip III, J.T. Kimball, Treatment of myocardial infarction in a coronary care unit. A two year experience with 250 patients, *Am. J. Cardiol.* 20 (1967) 457–464.
- [17] R. Erbel, Comparison of single-plane and biplane volume determination by two-dimensional echocardiography: 1. Asymmetric model hearts, *Eur. Heart J.* 3 (1982) 469–474.
- [18] S.G. Kim, R.N. Fogoros, S. Furman, et al., Standardized reporting of ICD patient outcome: the report of a North American Society of Pacing and Electrophysiology Policy Conference, *PACE* 16 (1993) 1358–1362.
- [19] I. Annesi, T. Moreau, J. Lellouch, Efficiency of the logistic regression and Cox proportional hazards models in longitudinal studies, *Stat. Med.* 8 (1989) 1515–1521.
- [20] K.R. Hess, Graphical methods for assessing violations of the proportional hazards assumption in Cox regression, *Stat. Med.* 14 (1995) 1707–1723.
- [21] V. Vaccarino, Ischemic heart disease in women: many questions, few facts, *Circ. Cardiovasc. Qual. Outcomes* 3 (2010) 111–115.
- [22] J.S. Berger, L. Elliott, D. Gallup, et al., Sex differences in mortality following acute coronary syndromes, *JAMA* 302 (2009) 874–882.
- [23] I. Kardys, R. Vliegenthart, M. Oudkerk, et al., The female advantage in cardiovascular disease: do vascular beds contribute equally? *Am. J. Epidemiol.* 166 (2007) 403–412.
- [24] T. Simon, M. Mary-Krause, C. Funck-Brentano, et al., Sex differences in the prognosis of congestive heart failure: results from the Cardiac Insufficiency Bisoprolol Study (CIBIS II), *Circulation* 103 (2001) 375–380.
- [25] T. Baron, K. Hambraeus, J. Sundström, et al., TOTAL-AMI study group. Type 2 myocardial infarction in clinical practice, *Heart* 101 (2015) 101–106.
- [26] B. Vogel, S. Farhan, S. Hahne, et al., Sex-related differences in baseline characteristics, management and outcome in patients with acute coronary syndrome without ST-segment elevation, *Eur. Heart J. Acute Cardiovasc. Care* 7 (2015 May).
- [27] M. Martínez-Sellés, M. Domínguez, E. Martínez, et al., Women with left ventricular ejection fraction \leq 20% have better prognosis than men, *Int. J. Cardiol.* 120 (2007) 276–278.



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

*Corresponding author: Alexandra Lucas, Division of Cardiovascular Medicine and Rheumatology, University of Florida, USA, E-mail: alexandra.lucas@medicine.ufl.edu

Received: May 22, 2012 Accepted: May 25, 2012 Published: May 28, 2012

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 chemokines 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 thrombotic. 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.

Author Affiliation

[Top](#)

¹Division of Cardiovascular Medicine and Rheumatology, University of Florida, USA

Submit your next manuscript and get advantages of SciTechnol submissions

- ❖ 50 Journals
- ❖ 21 Day rapid review process
- ❖ 1000 Editorial team
- ❖ 2 Million readers
- ❖ More than 5000 
- ❖ Publication immediately after acceptance
- ❖ Quality and quick editorial, review processing

Submit your next manuscript at • www.scitechnol.com/submission