

VIII Convegno Nazionale Fondazione AMD



PALERMO, 17-19 NOVEMBRE 2016

NOVITA' IN TEMA DI CURA E GESTIONE DELLE COMPLICANZE DEL DIABETE

La cardiopatia ischemica alla luce delle nuove terapie

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Palermo*

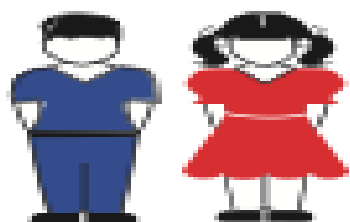
AGENDA

- Numeri... e considerazioni generali
- Diabete e cardiopatia ischemica acuta
- Diabete e cardiopatia ischemica cronica
- Considerazioni conclusive

Numeri e considerazioni generali

- Prevalenza del diabete nella popolazione generale in aumento:

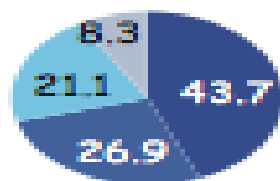
dati Istat 2001 → 2010 prevalenza da 3.9 a 4.5%



misconosciuto

DIABETES, treatment condition, %

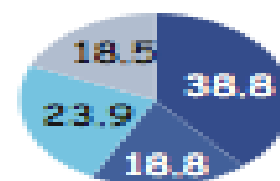
1998-02



Diabetic MEN

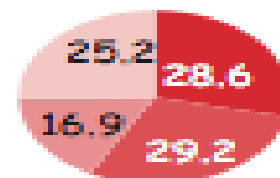
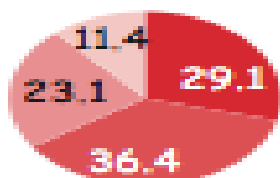
- Not Aware
- Aware, Not Treated
- Aware, Not Well Treated
- Aware, Well Treated

2008-12



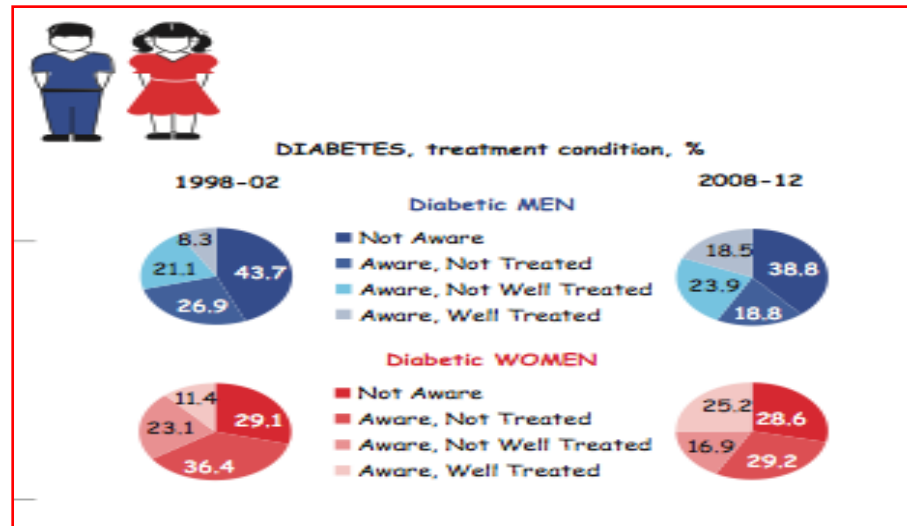
Diabetic WOMEN

- Not Aware
- Aware, Not Treated
- Aware, Not Well Treated
- Aware, Well Treated



Numeri e considerazioni generali

- Prevalenza del diabete nella popolazione generale in aumento:
dati Istat 2001 → 2010 prevalenza da 3.9 a 4.5%



- Il 60% dei diabetici sviluppa patologia CV
- Nella metà circa dei casi la mortalità dei paz diabetici è legata a cause CV

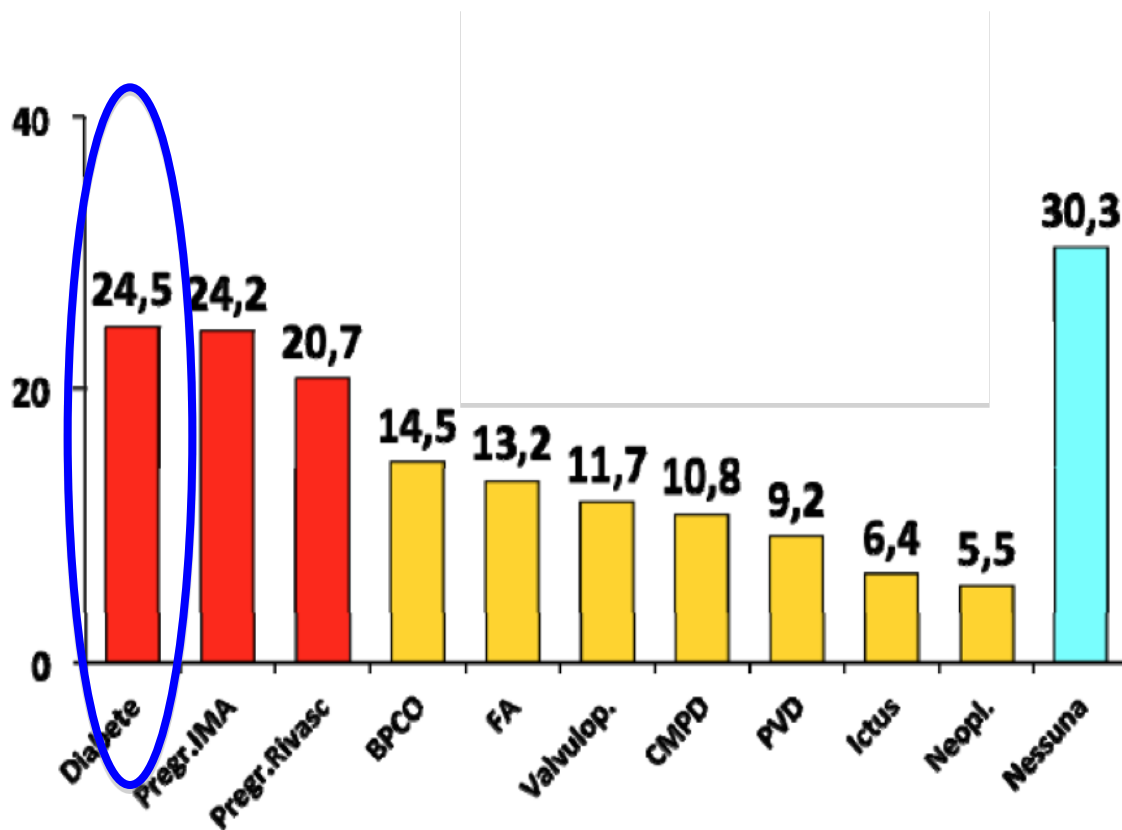
Diabete e cardiopatia ischemica acuta

Circa il 30% dei paz con SCA ha il diabete (noto)

Ricoveri in UTIC italiane 2008

Registro Blitz-3

Caratteristiche basali



Prevalence of main comorbidity

Ricoveri in UTIC italiane 2010

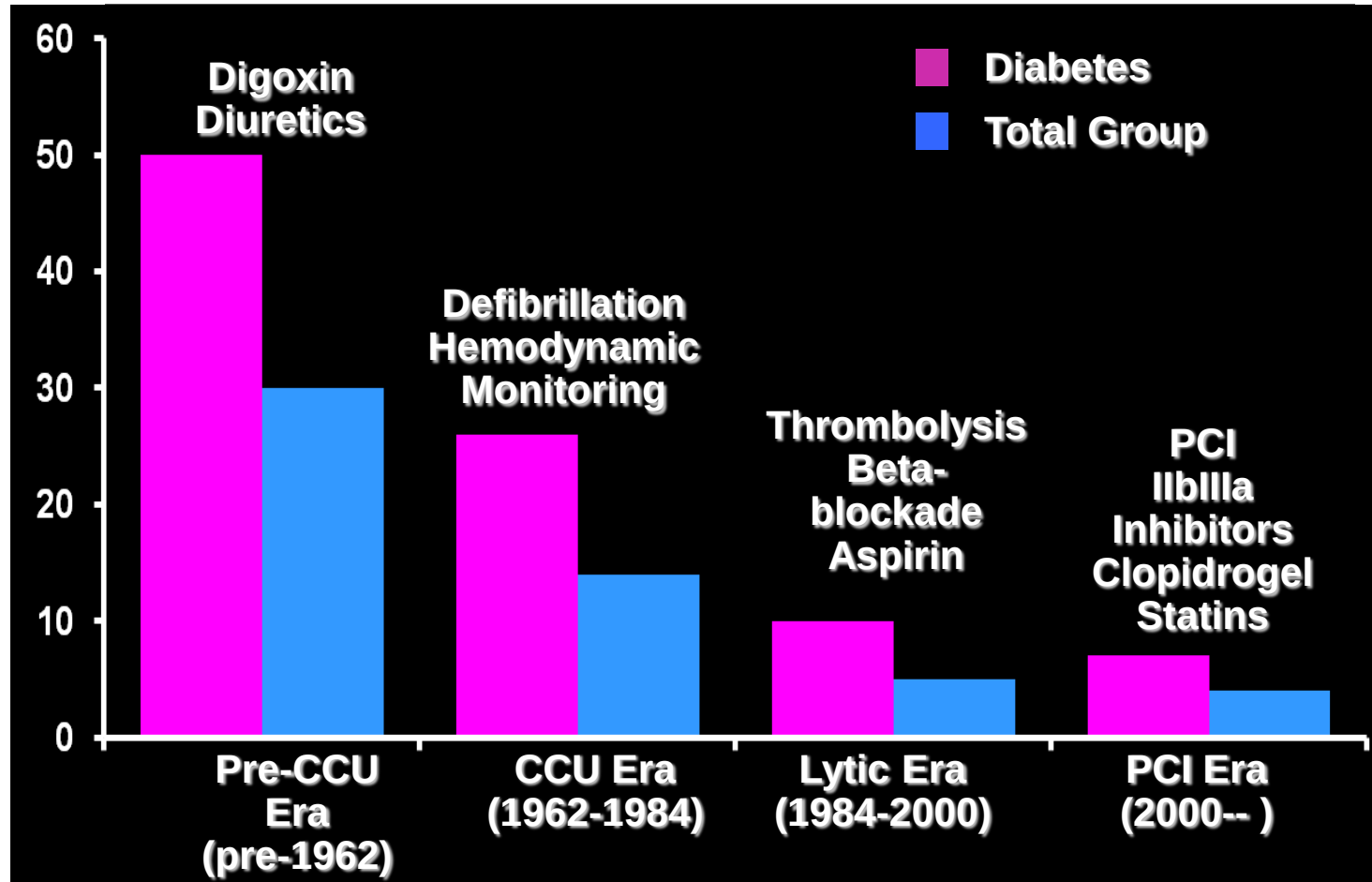
	BLITZ-4 NSTEMI	BLITZ-4 STEMI
PVD	11,4%	6%
CHF	4,9%	1,3%
Anemia	5,3%	1,9%
COPD	8,6%	5,3%
Stroke	6%	4,4%
Diabetes	30,1%	20,5%
CKD	12.2%	5,3%
Dialysis	1,3%	0,8%
Neoplastic diseases	2,9%	3%

Sindromi Coronariche Acute (SCA) nel paziente diabetico

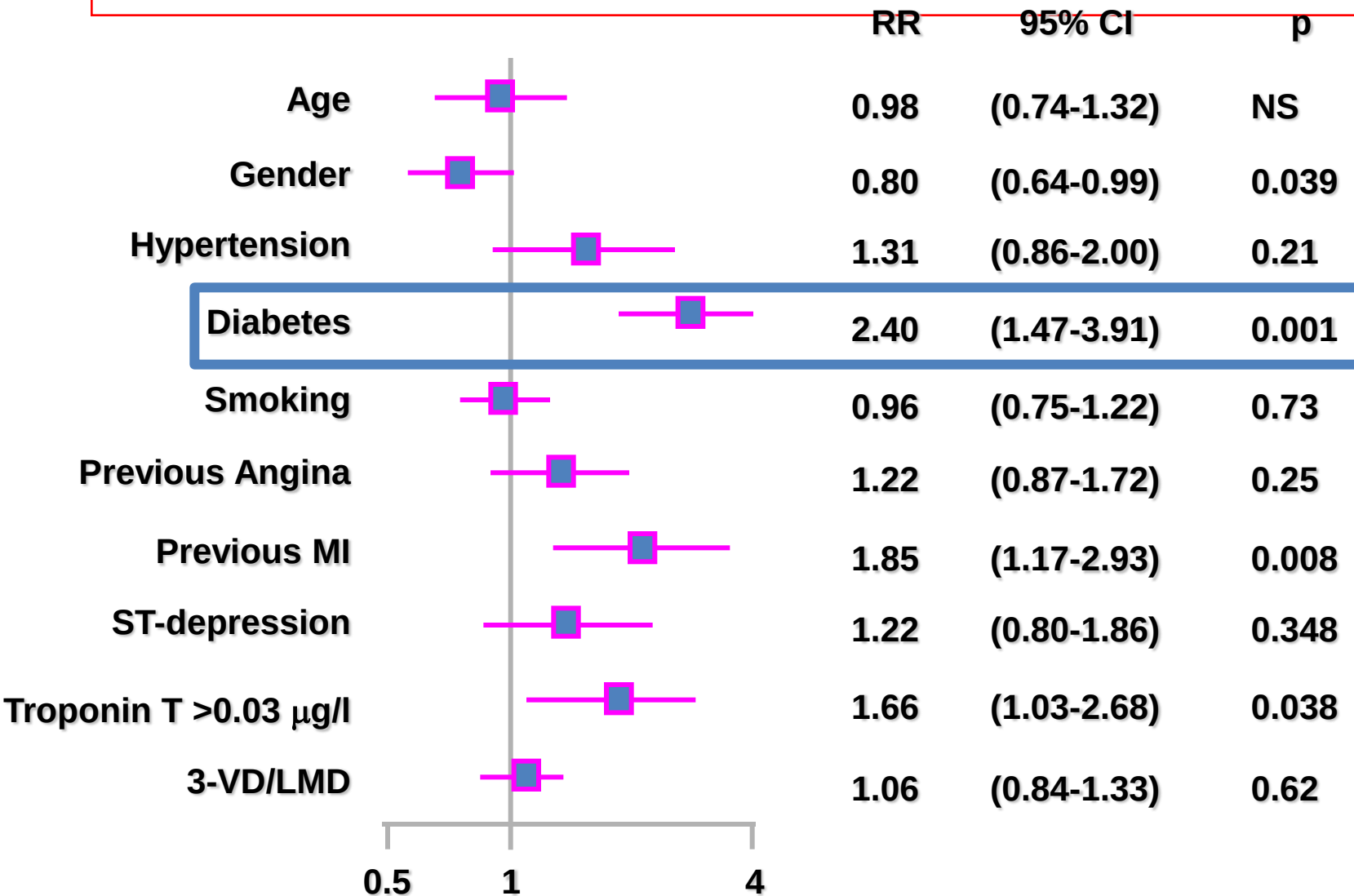
- Peggior prognosi
 - Aumentato rischio trombotico (↑rottura di placca, disfunzione piastrinica)
 - Maggiore estensione / severità della CAD
 - Più frequente disfunzione di pompa
- Minor uso dei trattamenti di provata efficacia
- Peggiori risultati della rivascolarizzazione

Diabete conferisce un rischio doppio di mortalità precoce nell'IMA nonostante i progressi nella gestione cardiologica

Early Mortality
from Acute MI



FRISC II: Diabete (e non estensione della coronaropatia) principale predittore indipendente di mortalità ed infarto



Maggior mortalità nei diabetici con SCA

(>10.000 paz da sottogruppi degli studi TIMI)

- **STEMI**

30 g.	D 8.5%	ND 5.4%	p<0.001
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1 y.	D 13.2%	ND 8.1%	p<0.001
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- **NSTEMI**

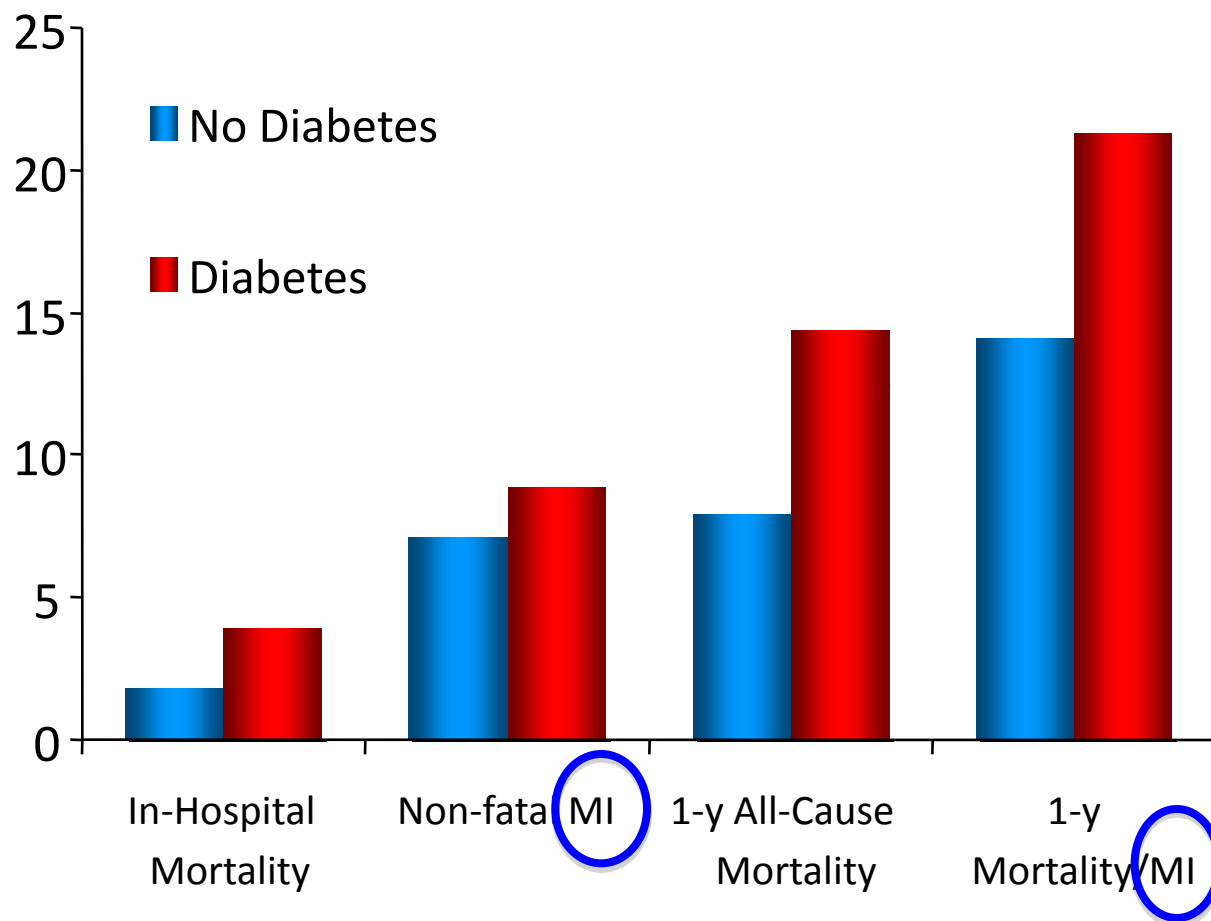
30 g.	D 2.1%	ND 1.1%	p<0.001
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1 y.	D 7.2%	ND 3.1%	p<0.001
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ACS and Diabetes

Clinical Outcomes Up to 1 Year

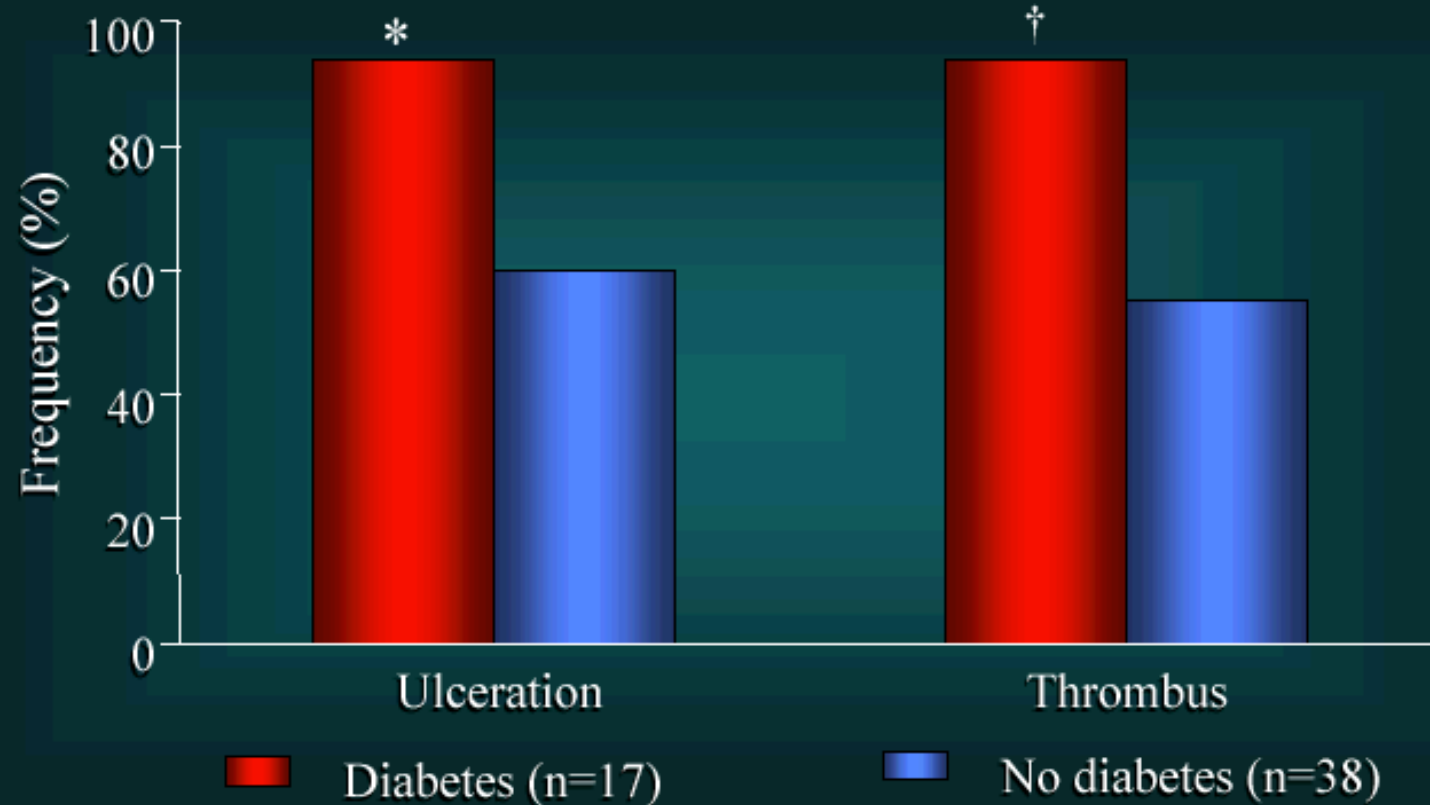
(dati di registro, Canada)



Sindromi Coronariche Acute (SCA) nel paziente diabetico

- Peggior prognosi
 - Aumentato rischio trombotico (↑rottura di placca, disfunzione piastrinica)

Diabete – rischio di rottura di placca e trombosi



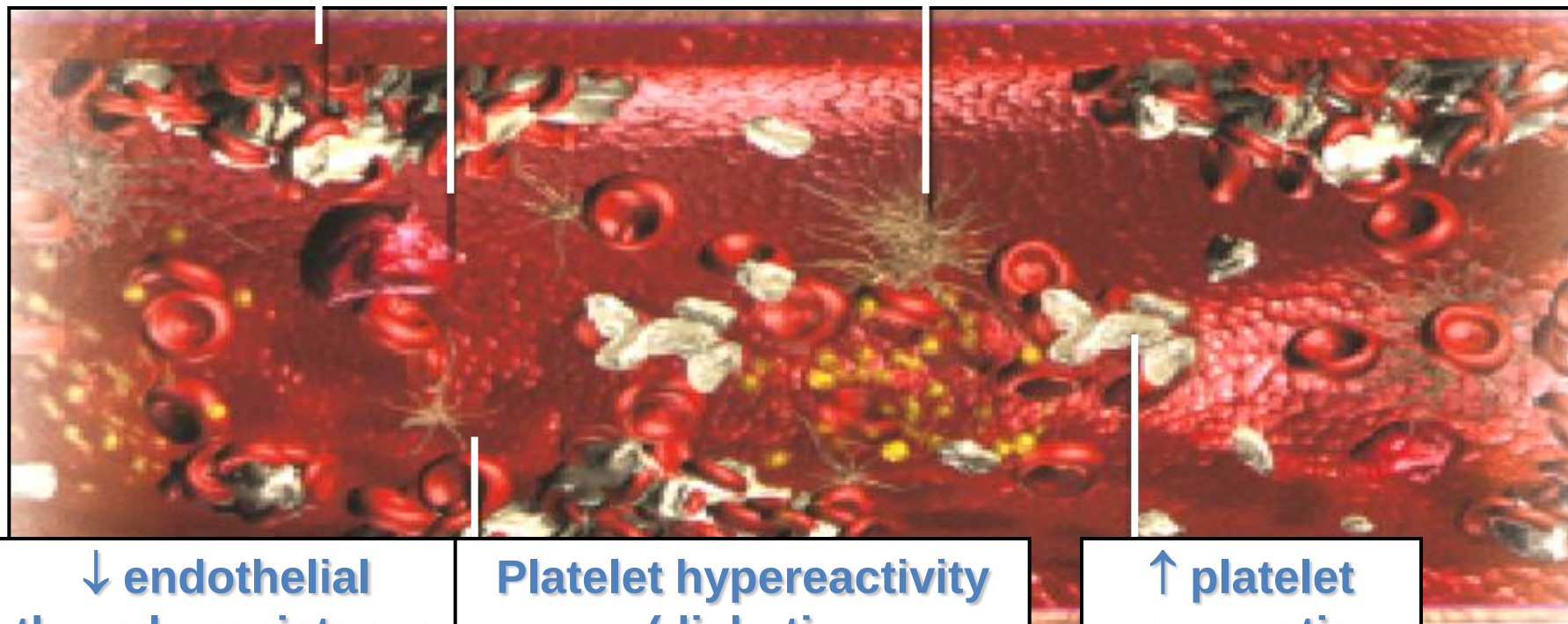
* $P=,01$; † $P=,004$.

Diabetic Vascular Pathology

**↑ plasma
coagulation**

**Altered response
to arterial injury**

**Diminished
fibrinolysis**



**↓ endothelial
thromboresistance**

**Platelet hyperactivity
(diabetic
thrombocytopathology)**

**↑ platelet
aggregation
and adhesion**

DISFUNZIONE PIASTRINICA

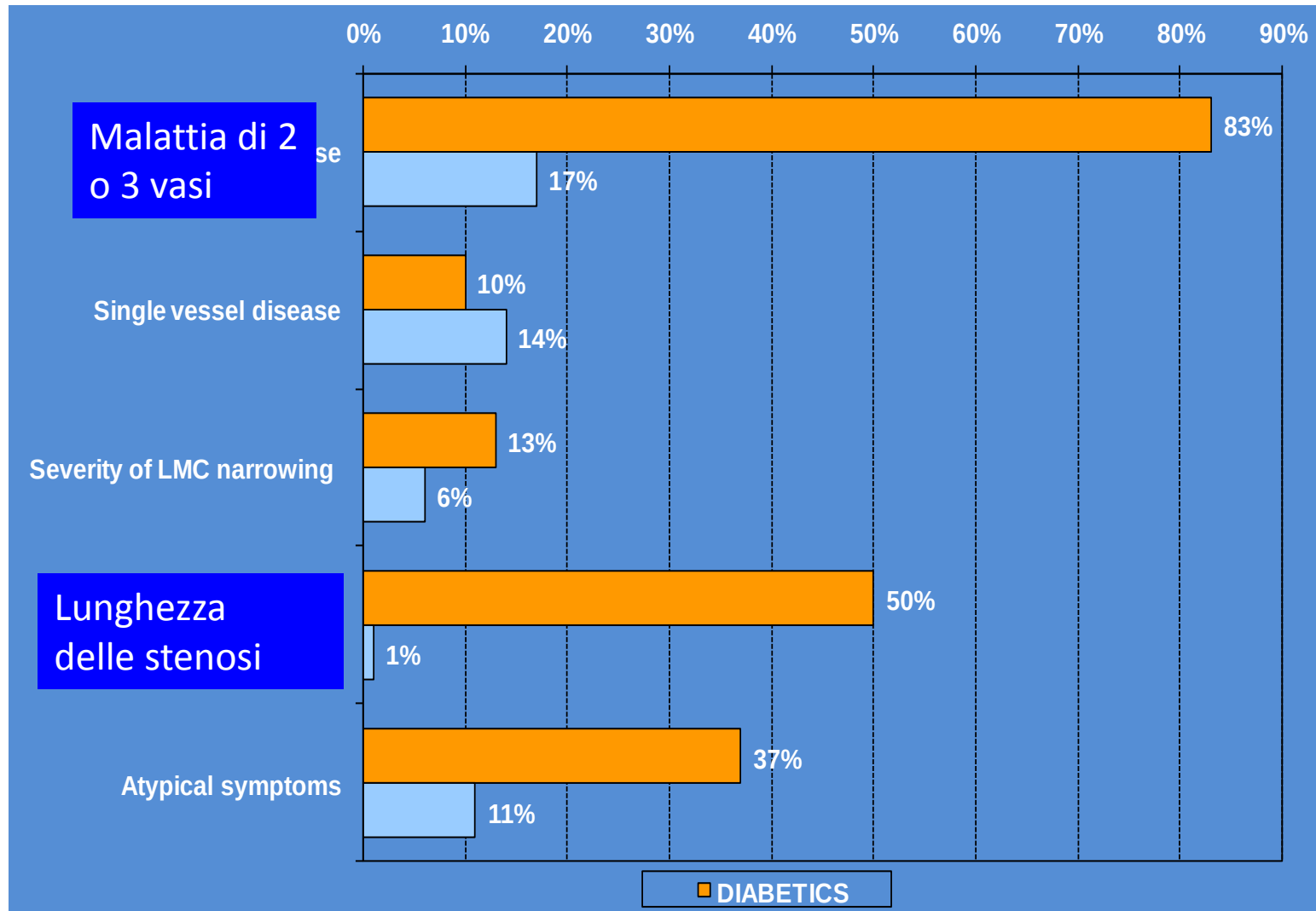
Sindromi Coronariche Acute (SCA) nel paziente diabetico

- Peggior prognosi
 - Aumentato rischio trombotico (↑rottura di placca, disfunzione piastrinica) →
↑ Reinfarto e trombosi di stent

Sindromi Coronariche Acute (SCA) nel paziente diabetico

- Peggior prognosi
 - Aumentato rischio trombotico (↑rottura di placca, disfunzione piastrinica) →
↑ Reinfarto e trombosi di stent
 - **Maggiore estensione / severità della CAD**

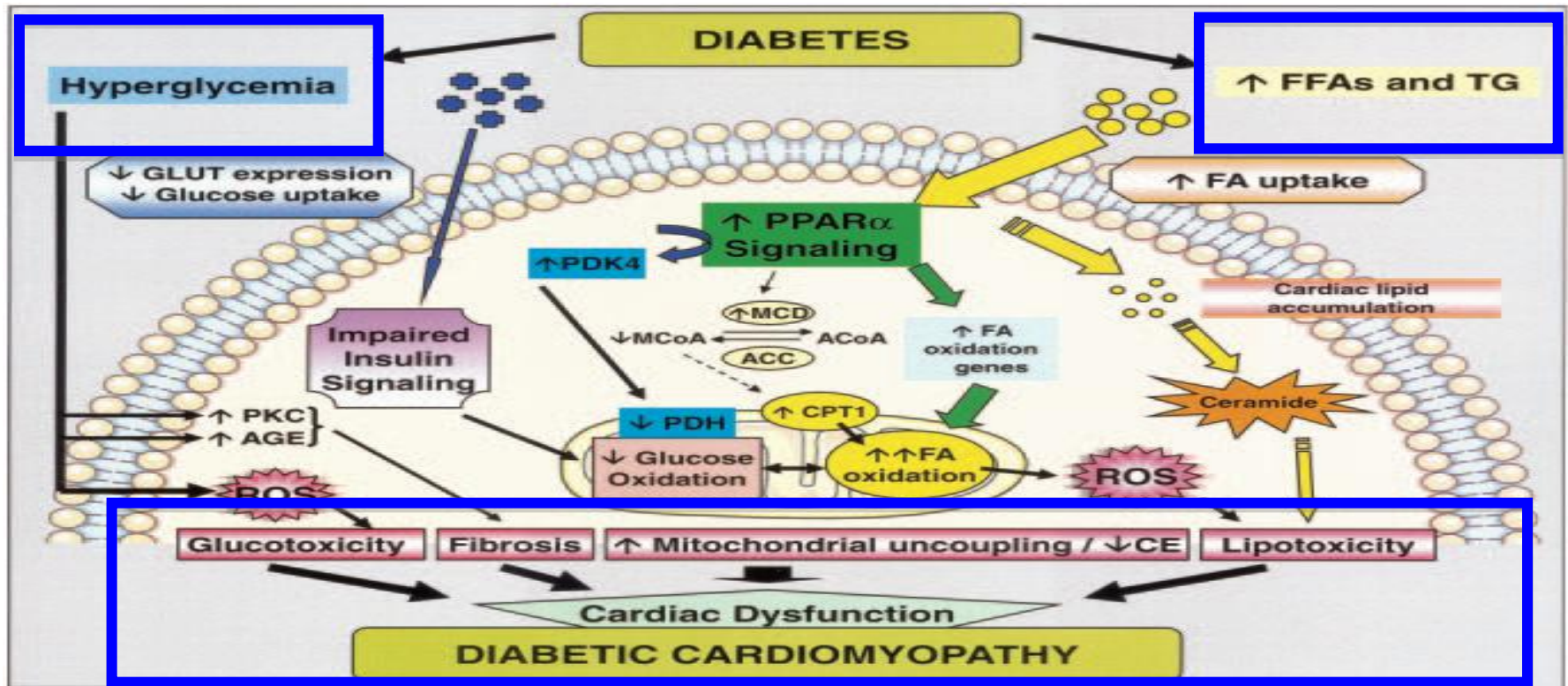
Estensione della coronaropatia nel paziente diabetico



Sindromi Coronariche Acute (SCA) nel paziente diabetico

- Peggior prognosi
 - Aumentato rischio trombotico (↑rottura di placca, disfunzione piastrinica)
 - Maggiore estensione / severità della CAD
 - **Più frequente disfunzione di pompa**

- maggior vulnerabilità del miocardio non infartuato, per cause
 - metaboliche : glicotossicità, lipotossicità



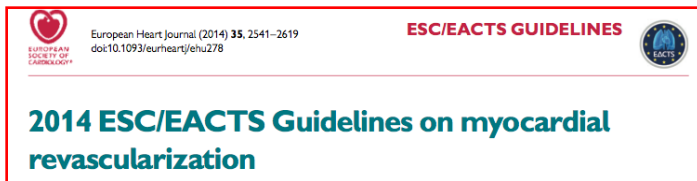
- microvascolari: patologia del microcircolo coronarico

Sindromi Coronariche Acute (SCA) nel paziente diabetico

- Peggior prognosi
 - Aumentato rischio trombotico (↑rottura di placca, disfunzione piastrinica)
 - Maggiore estensione / severità della CAD
 - Più frequente disfunzione di pompa
- **Minor uso dei trattamenti di provata efficacia**

Terapie di rivascularizzazione

- STEMI: è confermata la maggior efficacia di pPCI vs fibrinolisi



In patients presenting with STEMI, primary PCI is recommended over fibrinolysis if it can be performed within recommended time limits.	I	A	363
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Eppure spesso i paz diabetici giungono in ritardo alla riperfusione (sintomi atipici), con peggiori risultati e più frequenti complicanze emodinamiche

Terapie di rivascularizzazione

- NSTEMI: è dimostrata l'efficacia di una strategia invasiva precoce (coro e PCI; trial FRISC-II, TACTIS TIMI 18, metanalisi >9000pts

2012)

 European Heart Journal (2014) 35, 2541–2600
doi:10.1093/eurheartj/ehu278
2014 ESC/EACTS Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation

Intermediate-risk criteria	
• Diabetes mellitus	
• Renal insufficiency (eGFR <60 mL/min/1.73 m ²)	

E-ACS, an y is non-	I	A	180,338, 364–366
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 European Heart Journal (2016) 37, 267–315
doi:10.1093/eurheartj/ehv320
2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation

ESC GUIDELINES

An invasive strategy is recommended over non-invasive management.	I	A	352, 441, 442
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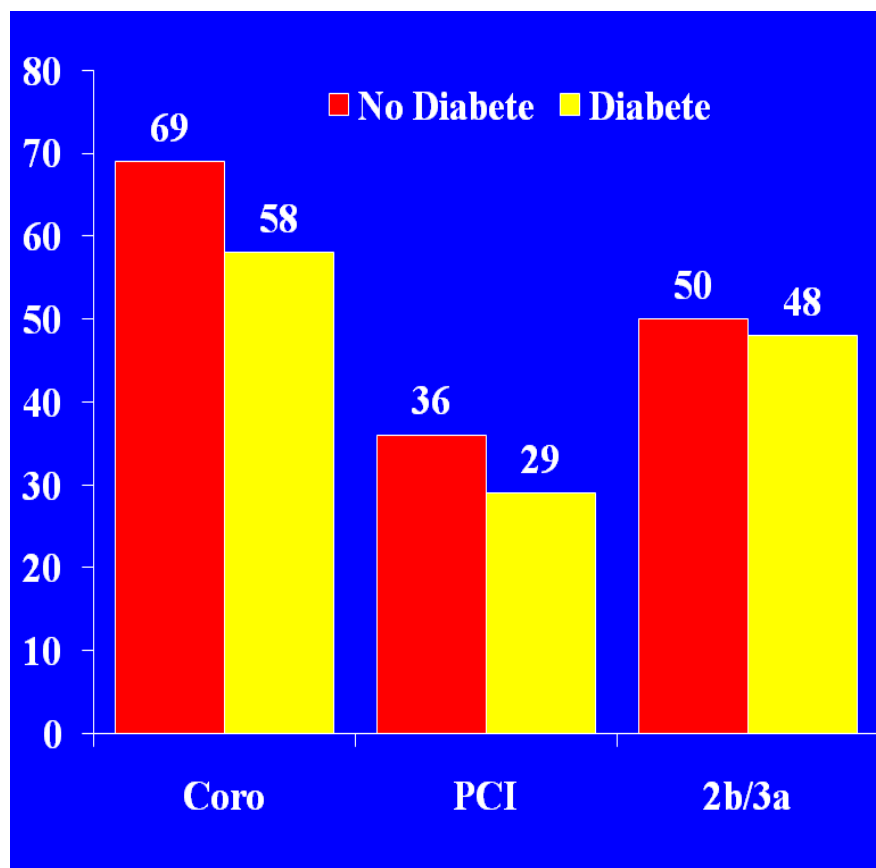
• Prior CABG	
• GRACE risk score >109 and <140	

NSTE-MI ACS

I Diabetici in Italia

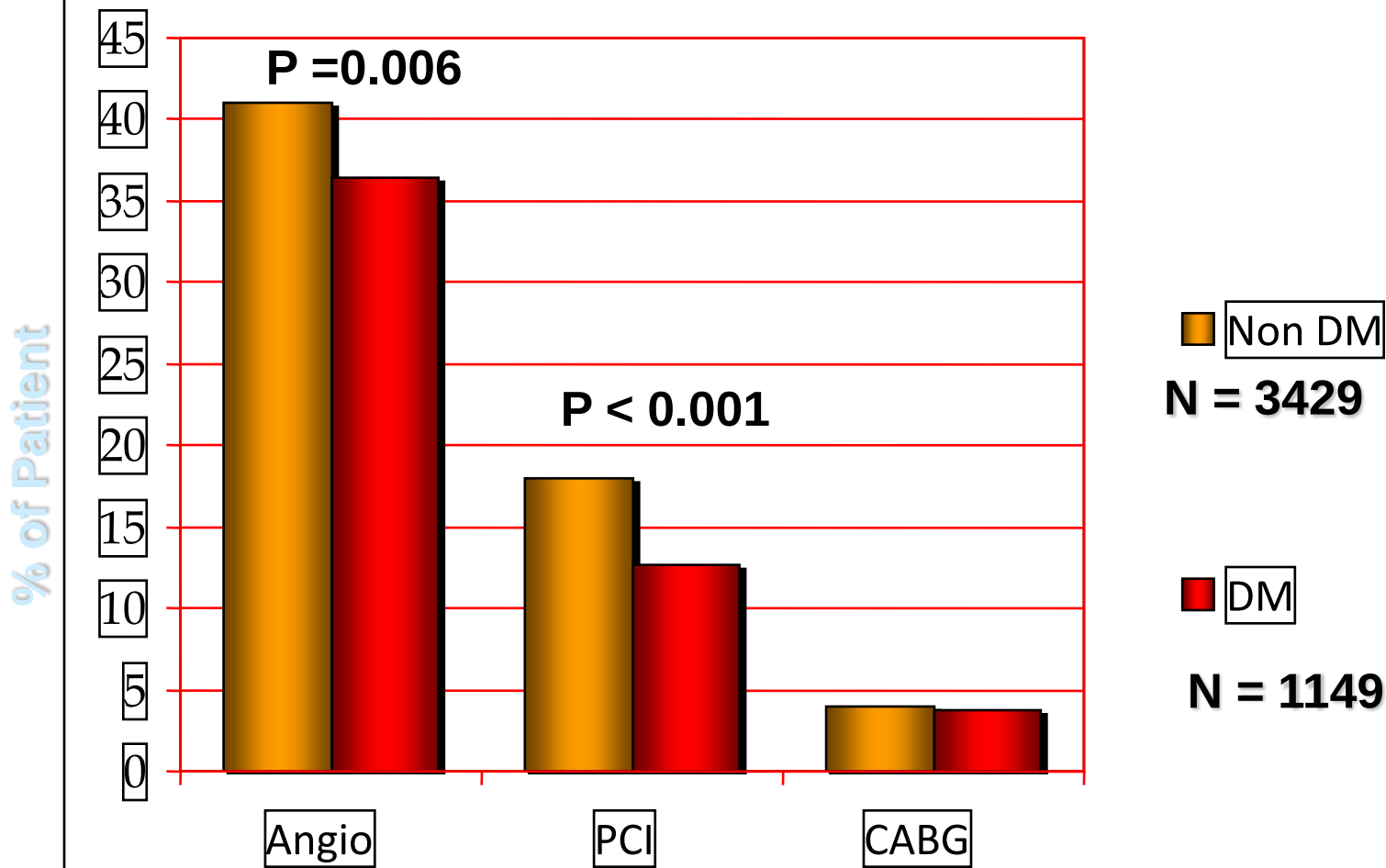


Sotto-Trattamento nei diabetici

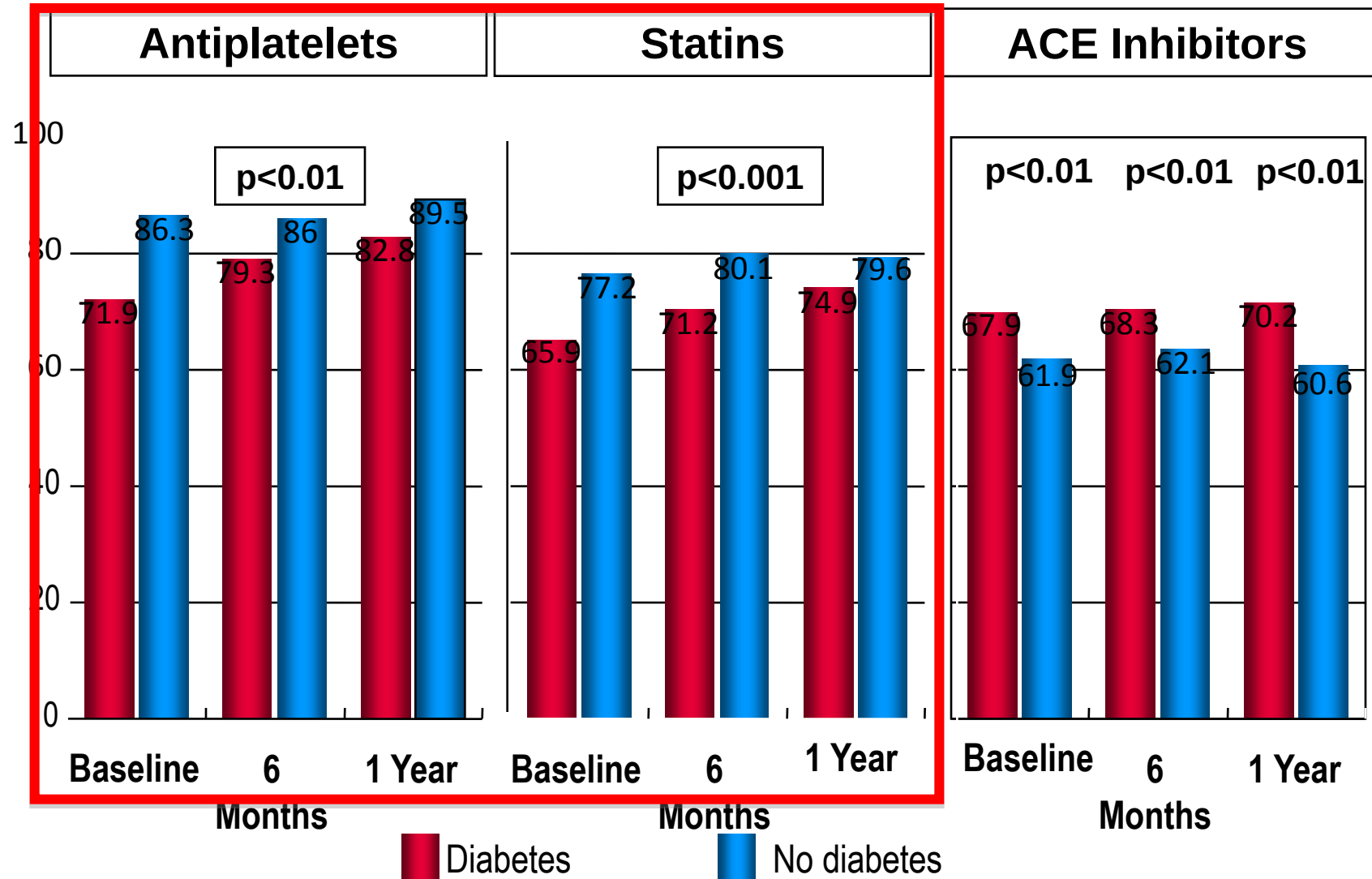


ACS and Diabetes

In-hospital Cath / Revasc



Terapie farmacologiche: sottotrattamento nei diabetici Canadian Registry: DM vs Non DM

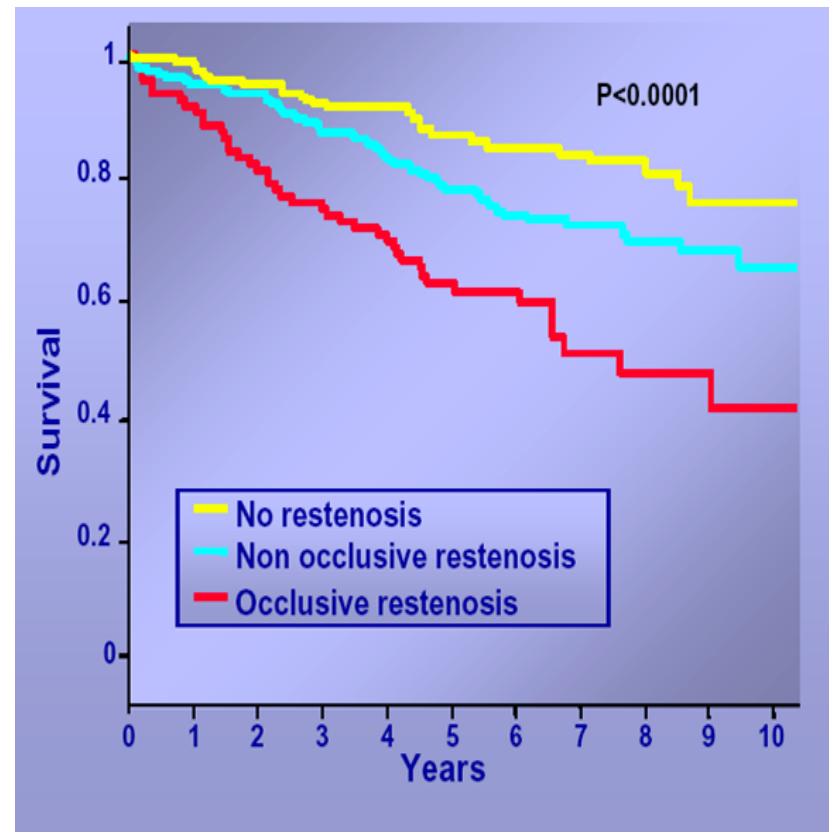
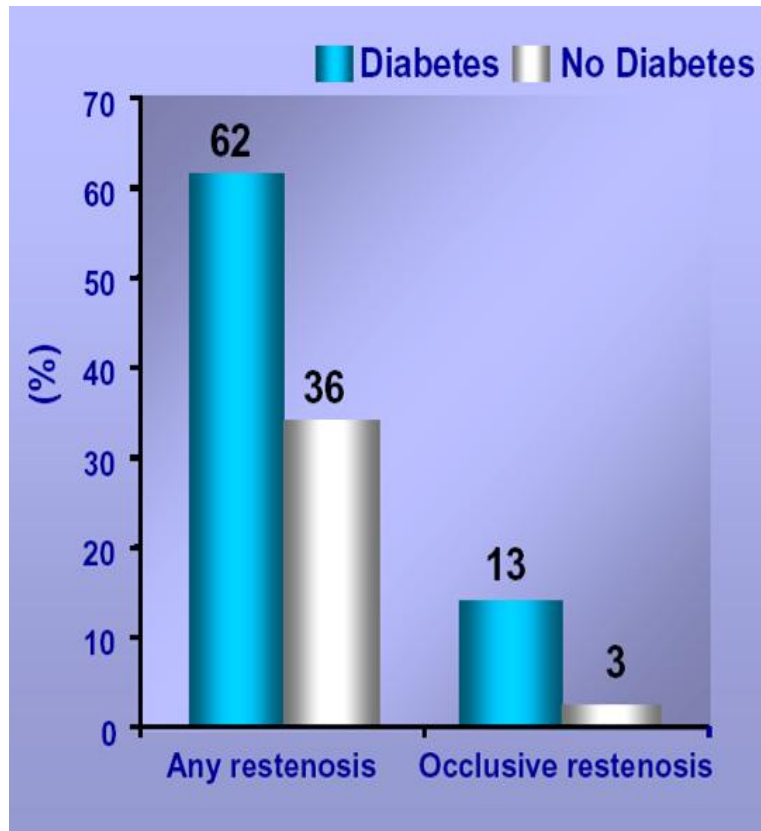


Data on file at Canadian Heart Research Centre

Sindromi Coronariche Acute (SCA) nel paziente diabetico

- Peggior prognosi
 - Aumentato rischio trombotico (↑rottura di placca, disfunzione piastrinica)
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- Minor uso dei trattamenti di provata efficacia
- **Peggiori risultati della rivascolarizzazione**

PCI in Diabetics: *Impact of Restenosis on Survival*

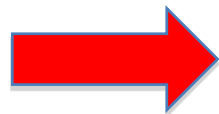


Van Belle et al, *Circulation* 2001;103:1218-24

Recommendations for the management of diabetic patients with non-ST-elevation acute coronary syndromes

Antithrombotic treatment and invasive strategy			
It is recommended to administer the same antithrombotic treatment in diabetic and non-diabetic patients.	I	C	
An invasive strategy is recommended over non-invasive management.	I	A	352, 441, 442
It is recommended to administer aspirin, a P2Y ₁₂ inhibitor, and low-molecular-weight heparin or fondaparinux in diabetic patients with normal renal function undergoing percutaneous coronary intervention (PCI). In patients with baseline renal dysfunction, aspirin, a P2Y ₁₂ inhibitor, and unfractionated heparin are recommended. In patients with baseline renal dysfunction, aspirin, a P2Y ₁₂ inhibitor, and unfractionated heparin are recommended. In patients with baseline renal dysfunction, aspirin, a P2Y ₁₂ inhibitor, and unfractionated heparin are recommended. In patients with baseline renal dysfunction, aspirin, a P2Y ₁₂ inhibitor, and unfractionated heparin are recommended.			
In patients undergoing PCI, new-generation DESs are recommended over BMSs.	I	A	240, 241, 443
In patients with stabilised multivessel CAD and an acceptable surgical risk, CABG is recommended over PCI.	I	A	379, 436, 444
In patients with stabilised multivessel CAD and a SYNTAX score ≤ 22 , PCI should be considered as an alternative to CABG.	IIa	B	435, 445

Caveat: nei diabetici più frequente la trombosi di stent



Ruolo fondamentale della terapia antiaggregante, anche nel paziente diabetico

2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation

Recommendations for the management of diabetic patients with non-ST-elevation acute coronary syndromes



Antithrombotic treatment and invasive strategy			
It is recommended to administer the same antithrombotic treatment in diabetic and non-diabetic patients.	I	C	
An invasive strategy is recommended over non-invasive management.	I	A	352, 441, 442
It is recommended to monitor renal function for 2–3 days after coronary angiography or PCI in patients with baseline renal impairment or on metformin.	I	C	
In patients undergoing PCI, new-generation DESs are recommended over BMSs.	I	A	240, 241, 443
In patients with stabilised multivessel CAD and an acceptable surgical risk, CABG is recommended over PCI.	I	A	379, 436, 444
In patients with stabilised multivessel CAD and a SYNTAX score ≤ 22 , PCI should be considered as an alternative to CABG.	IIa	B	435, 445

ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD

Antiplatelet therapy in patients with diabetes			
Recommendations	Class ^a	Level ^b	Ref. ^c
Antiplatelet therapy with aspirin in DM-patients at low CVD risk is not recommended.	III	A	272–274
Antiplatelet therapy for primary prevention may be considered in high risk patients with DM on an individual basis.	IIb	C	-
Aspirin at a dose of 75–160 mg/day is recommended as secondary prevention in DM.	I	A	270
A P2Y ₁₂ receptor blocker is recommended in patients with DM and ACS for 1 year and in those subjected to PCI (duration depending on stent type). In patients with PCI for ACS preferably prasugrel or ticagrelor should be given.	I	A	276, 277, 280, 282, 284
Clopidogrel is recommended as an alternative antiplatelet therapy in case of aspirin intolerance.	I	B	280, 285



2014 ESC/EACTS Guidelines on myocardial revascularization

10.5 Antithrombotic pharmacotherapy

There is no indication that antithrombotic pharmacotherapy should differ between diabetic and non-diabetic patients undergoing revascularization.

Standard italiani per la cura del diabete mellito 2016

6. FARMACI ANTIAGGREGANTI PIASTRINICI

RACCOMANDAZIONI

La terapia antiaggregante con acido acetilsalicilico (75-160 mg/die) è indicata nei diabetici con pregresso evento cardiovascolare, cerebrovascolare o con arteriopatia obliterante periferica.

(Livello della prova I, Forza della raccomandazione A)

Un inibitore del recettore di P2Y₁₂ (clopidogrel o prasugrel o ticagrelor) è indicato in pazienti con diabete e SCA e in coloro che sono andati incontro a procedure di rivascolarizzazione trans vascolare per almeno 1 anno dopo l'evento.

(Livello della prova I, Forza della raccomandazione A)

La terapia antiaggregante non è raccomandata nei diabetici a rischio cardiovascolare basso/moderato.

(Livello della prova III, Forza della raccomandazione A)

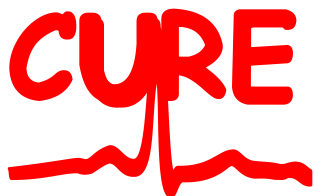
- Use aspirin therapy (75–162 mg/day) as a secondary prevention strategy in those with diabetes and a history of atherosclerotic cardiovascular disease. **A**
- For patients with atherosclerotic cardiovascular disease and documented aspirin allergy, clopidogrel (75 mg/day) should be used. **B**
- Dual antiplatelet therapy is reasonable for up to a year after an acute coronary syndrome. **B**

AMERICAN DIABETES ASSOCIATION

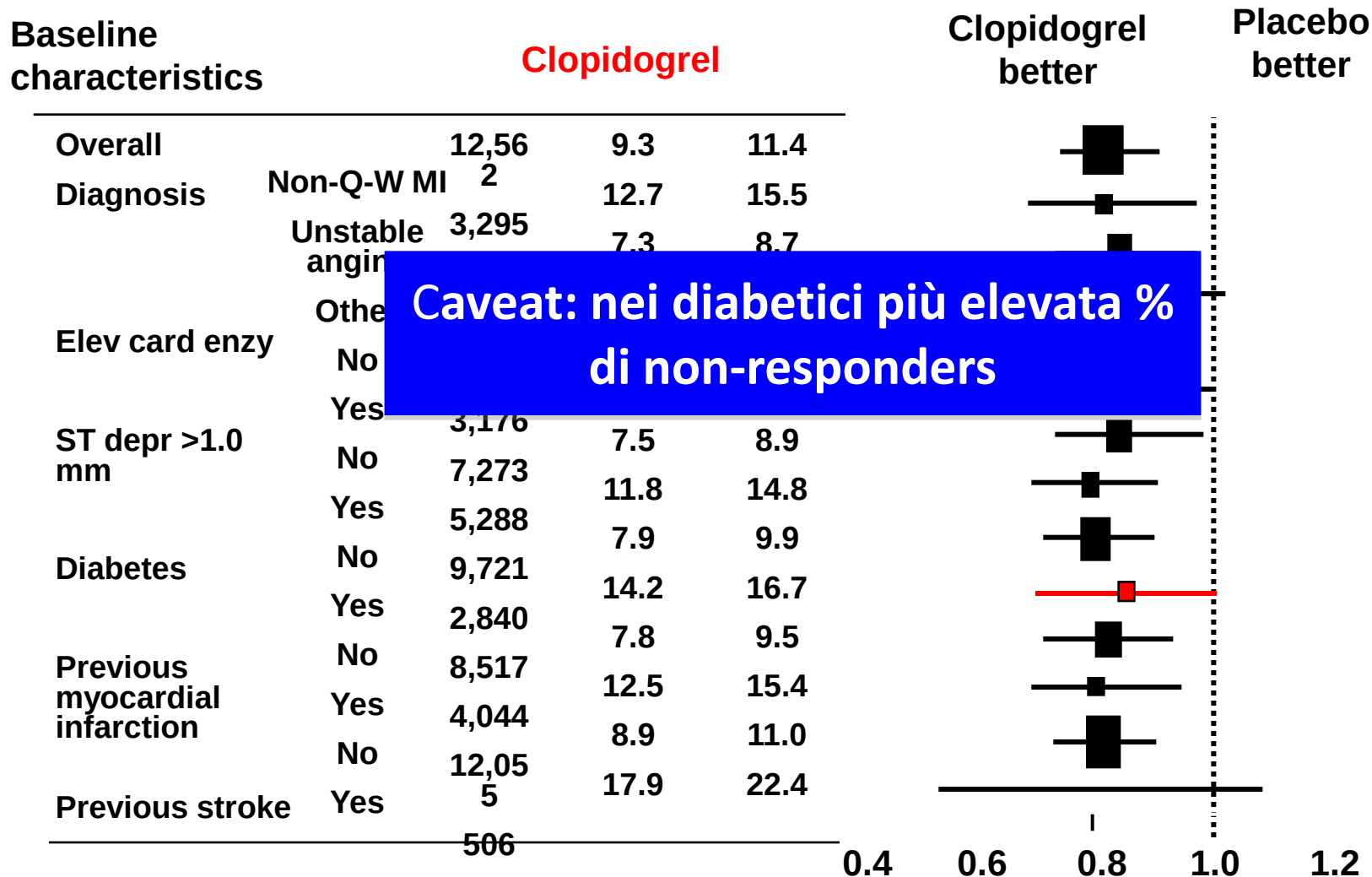
STANDARDS OF MEDICAL CARE IN DIABETES—2016

Doppia terapia antiplastrinica

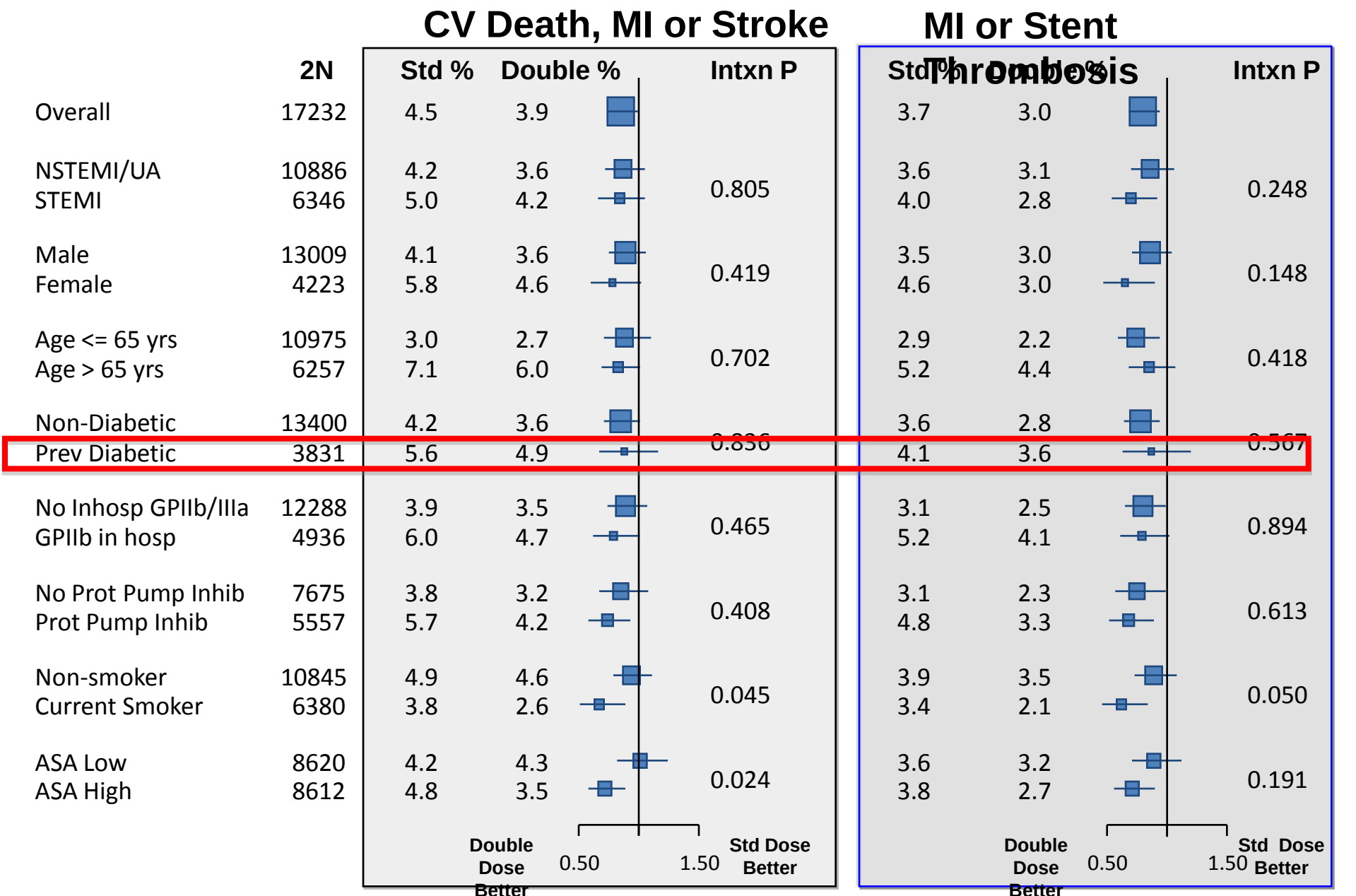
- Clopidogrel ... “il capostipite”
- I “nuovi inibitori P2Y₁₂”:
 - Prasugrel
 - Ticagrelor



Doppia antiaggregazione nelle SCA Efficacia nei diversi sottogruppi

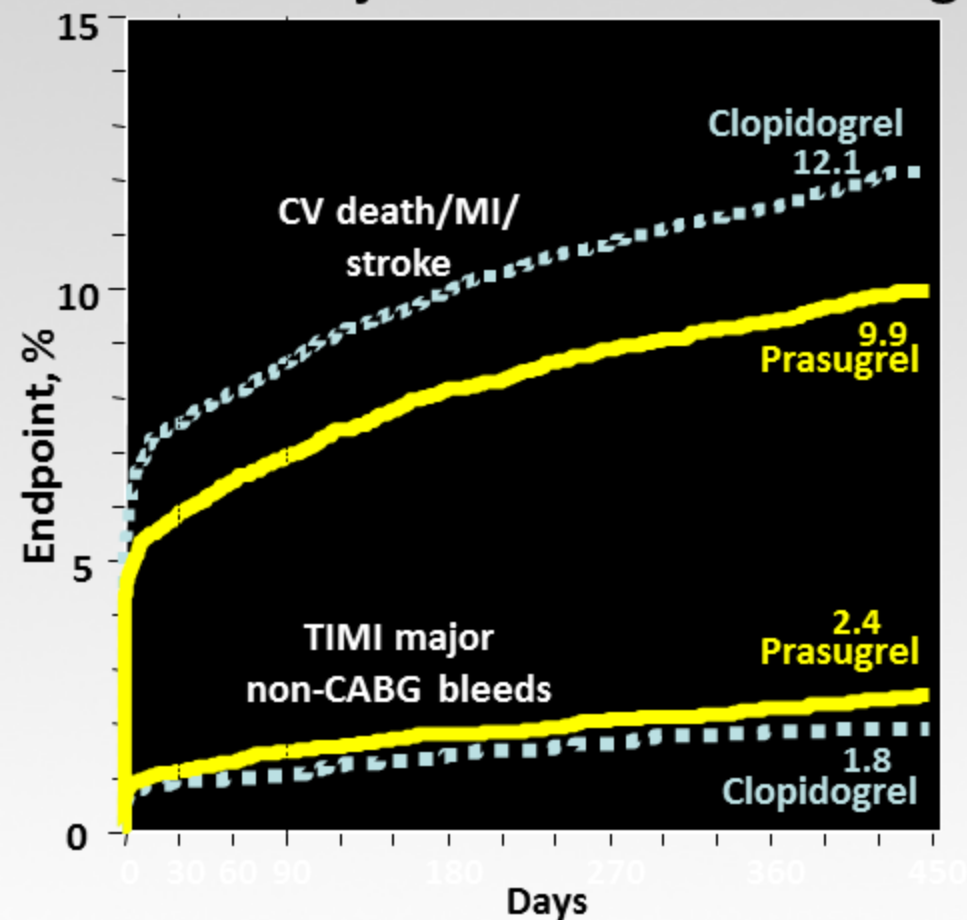


Clopidogrel: Double vs Standard Dose. PCI Cohort Subgroups

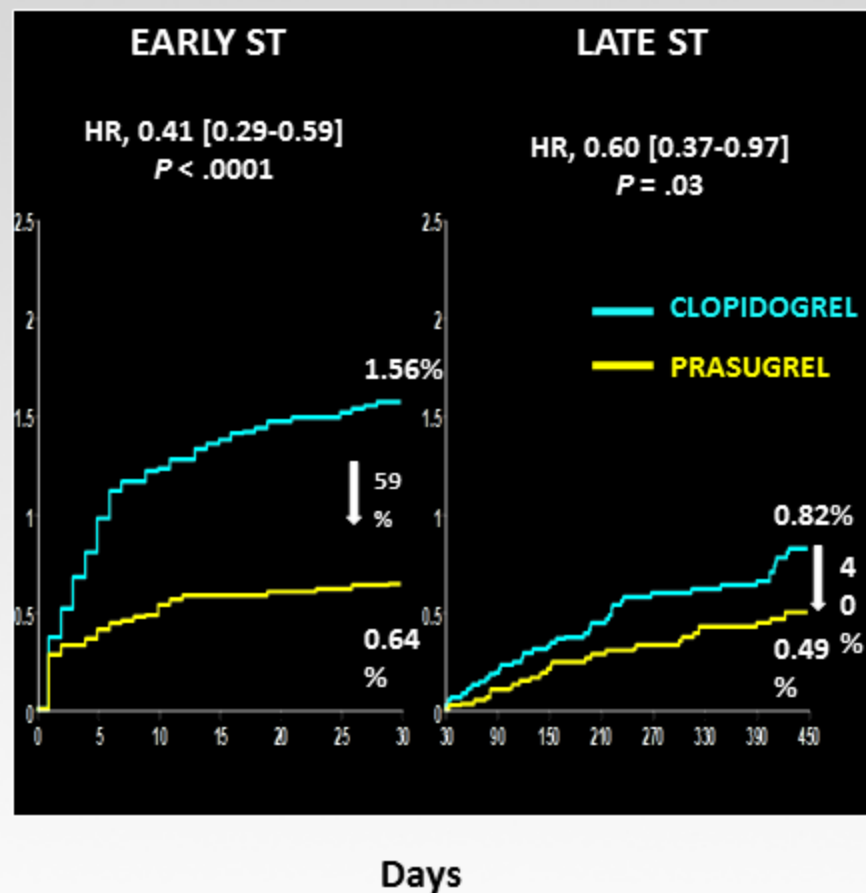


TRITON-TIMI 38

CV death, MI, stroke,
and major non-CABG bleeding



Early and late stent thrombosis

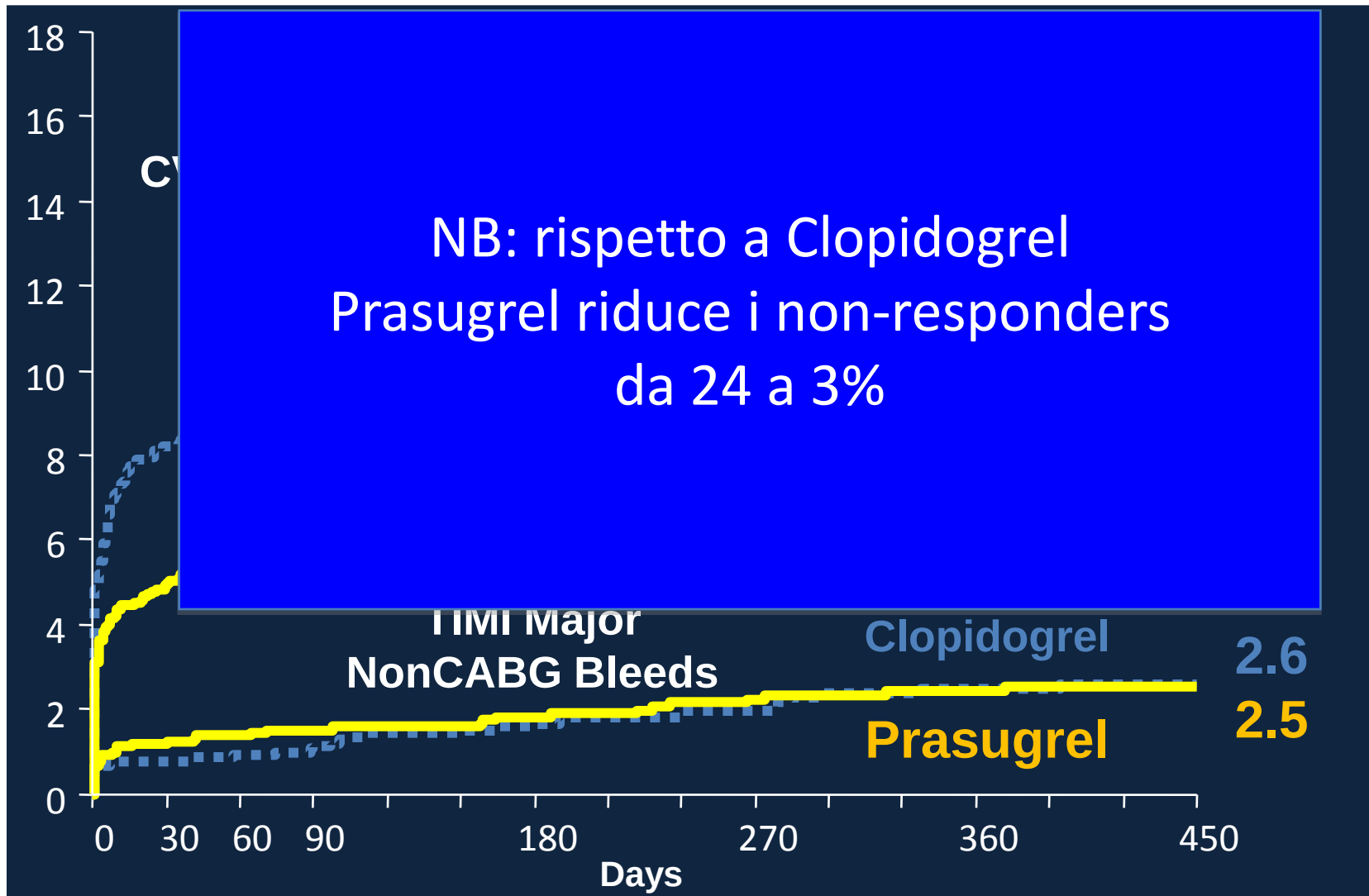


CABG = coronary artery bypass graft; CV = cardiovascular; HR = hazard ratio; MI = myocardial infarction

TRITON TIMI-38

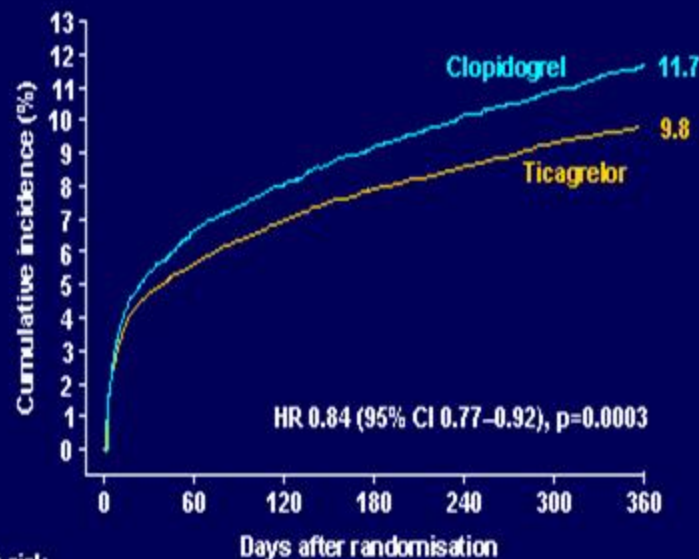
Sottogruppo diabetici

maggior beneficio netto rispetto ai paz non diabetici



Primary Outcomes of the Main PLATO Trial

K-M estimate of time to first primary efficacy event (composite of CV death, MI or stroke)



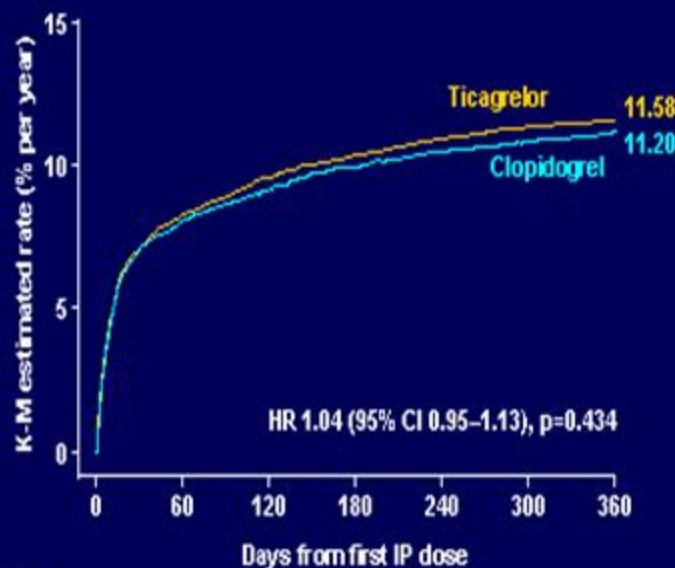
K-M = Kaplan-Meier; HR = hazard ratio; CI = confidence interval

UCR
UPPSALA CLINICAL
RESEARCH INSTITUTE

Ticagrelor vs clopidogrel

- Fewer CV deaths, MI, strokes
- Less stent thrombosis

Time to major bleeding – primary safety event



No. at risk

Ticagrelor	9,235	7,246	6,826	6,545	5,129	3,783	3,433
Clopidogrel	9,186	7,305	6,930	6,670	5,209	3,841	3,479

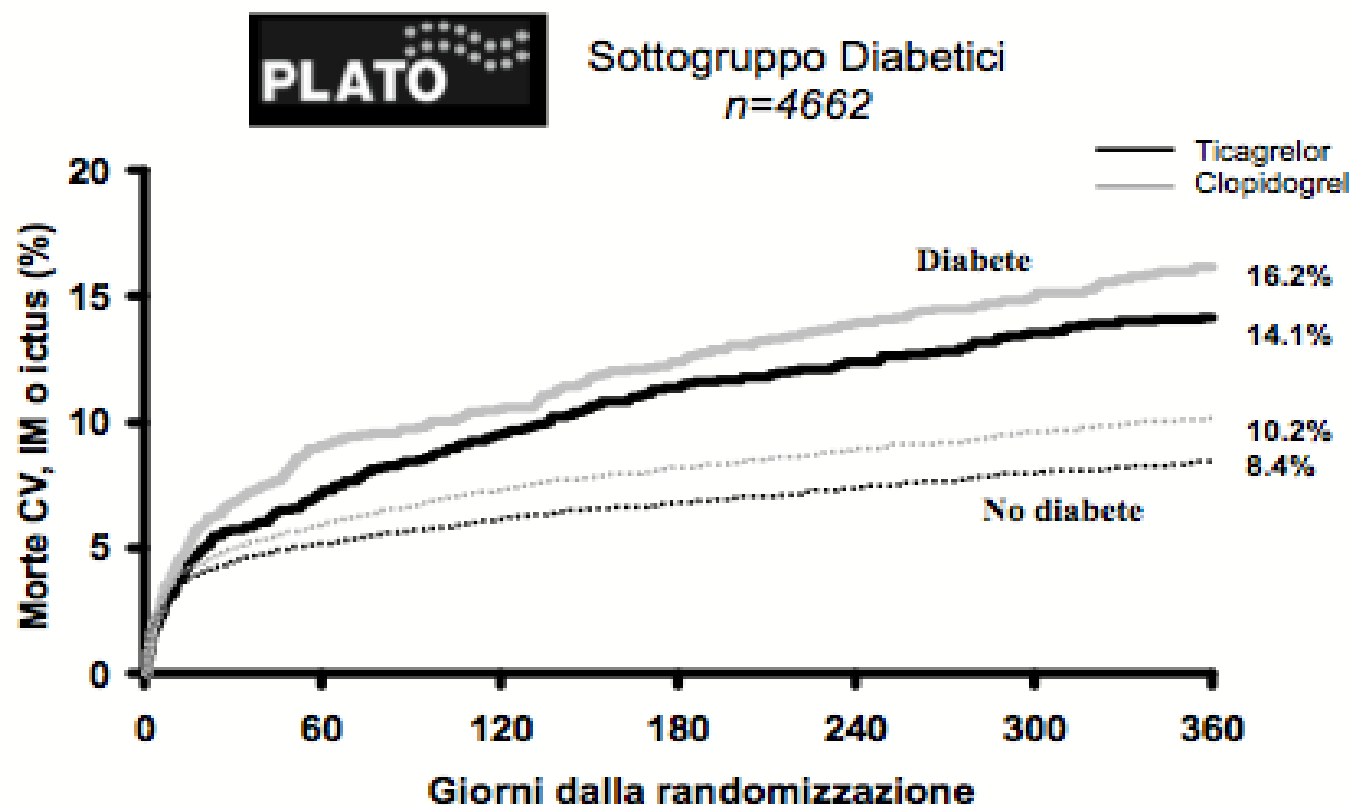
Duke Clinical Research Institute

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Ticagrelor vs clopidogrel

- Similar total major bleeding
- More non-CABG-related bleeding

Beneficio mantenuto e sovrapponibile a quello nei paz non diabetici



Numero pazienti								
Diabete								
—	Ticagrelor	2326	2113	2045	1959	1593	1199	953
—	Clopidogrel	2336	2084	2041	1968	1604	1225	975
No diabete								
.....	Ticagrelor	6999	6507	6407	6252	5143	3955	3191
.....	Clopidogrel	6952	6434	6318	6153	5044	3869	3097

Recommendations for antithrombotic treatment in patients with STEMI undergoing primary PCI

Recommendations	Class ^a	Level ^b	Ref ^c
Antiplatelet therapy			
ASA is recommended for all patients without contraindications at an initial oral loading dose of 150–300 mg (or 80–150 mg i.v.), and at a maintenance dose of 75–100 mg daily long-term regardless of treatment strategy.	I	A	774,776,794
A P2Y ₁₂ inhibitor is recommended in addition to ASA, and maintained over 12 months unless there are contraindications such as excessive risk of bleeding. Options are:	I	A	337,341,825
• Prasugrel (60 mg loading dose, 10 mg daily dose) in patients in whom coronary anatomy is known and who are proceeding to PCI if no contraindication	I	B	337
• Ticagrelor (180 mg loading dose, 90 mg twice daily) for patients at moderate-to-high risk of ischaemic events, regardless of initial treatment strategy including those pre-treated with clopidogrel if no contraindication	I	B	341
• Clopidogrel (600 mg loading dose, 75 mg daily dose), only when prasugrel or ticagrelor are not available or are contraindicated	I	B	812,825
GP IIb/IIIa antagonists should be considered for bail-out situation or thrombotic complications.	IIa	C	
Pre-treatment with prasugrel in patients in whom coronary anatomy is not known, is not recommended.	III	B	826
Pre-treatment with GP IIb/IIIa antagonists in patients in whom coronary anatomy is not known, is not recommended.	III	A	357,815

Clopidogrel solo quando prasugrel o ticagrelor non sono disponibili o sono controindicati

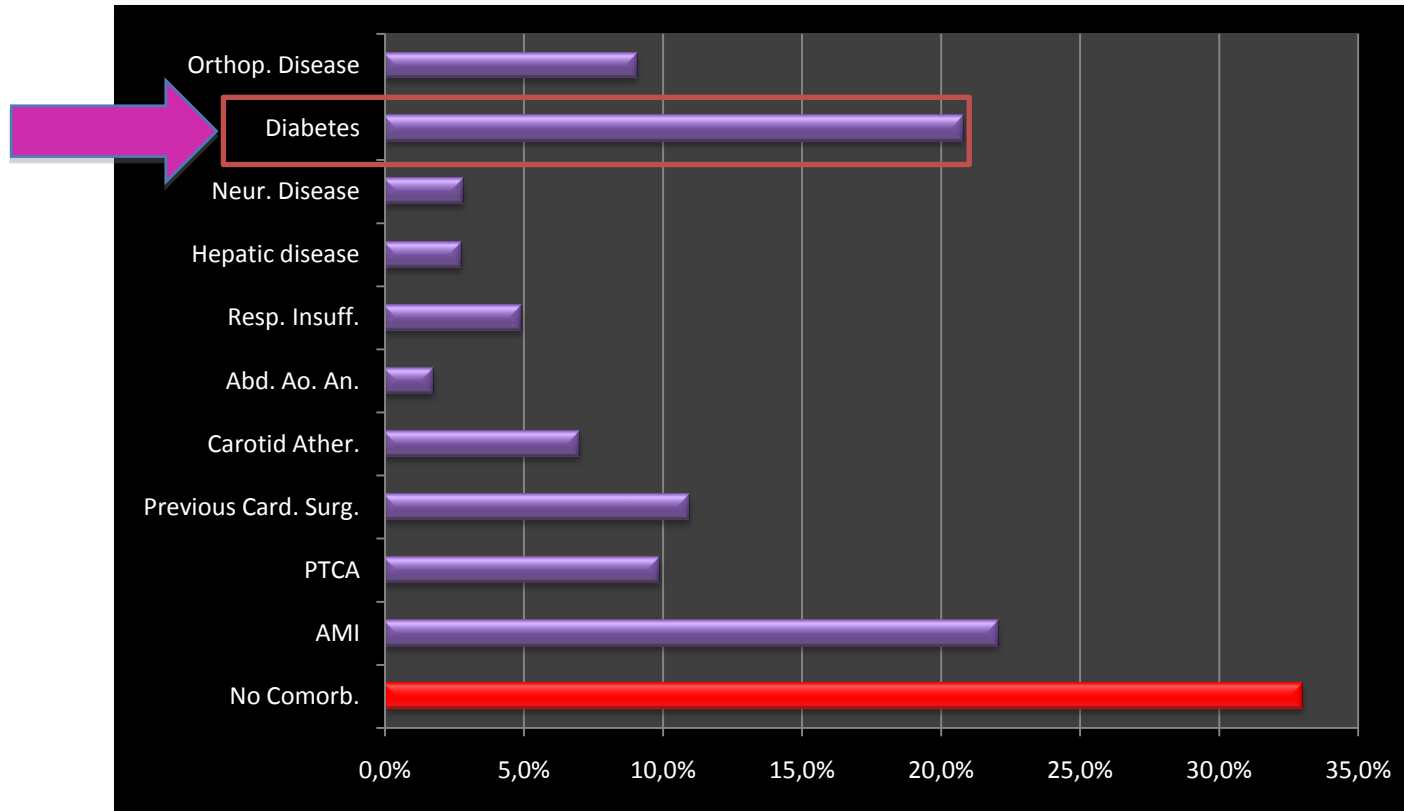
Recommendations for antithrombotic treatment in patients with NSTEMI-ACS undergoing PCI

Recommendations	Class ^a	Level ^b	Ref ^c
Antiplatelet therapy			
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Diabete e cardiopatia ischemica cronica

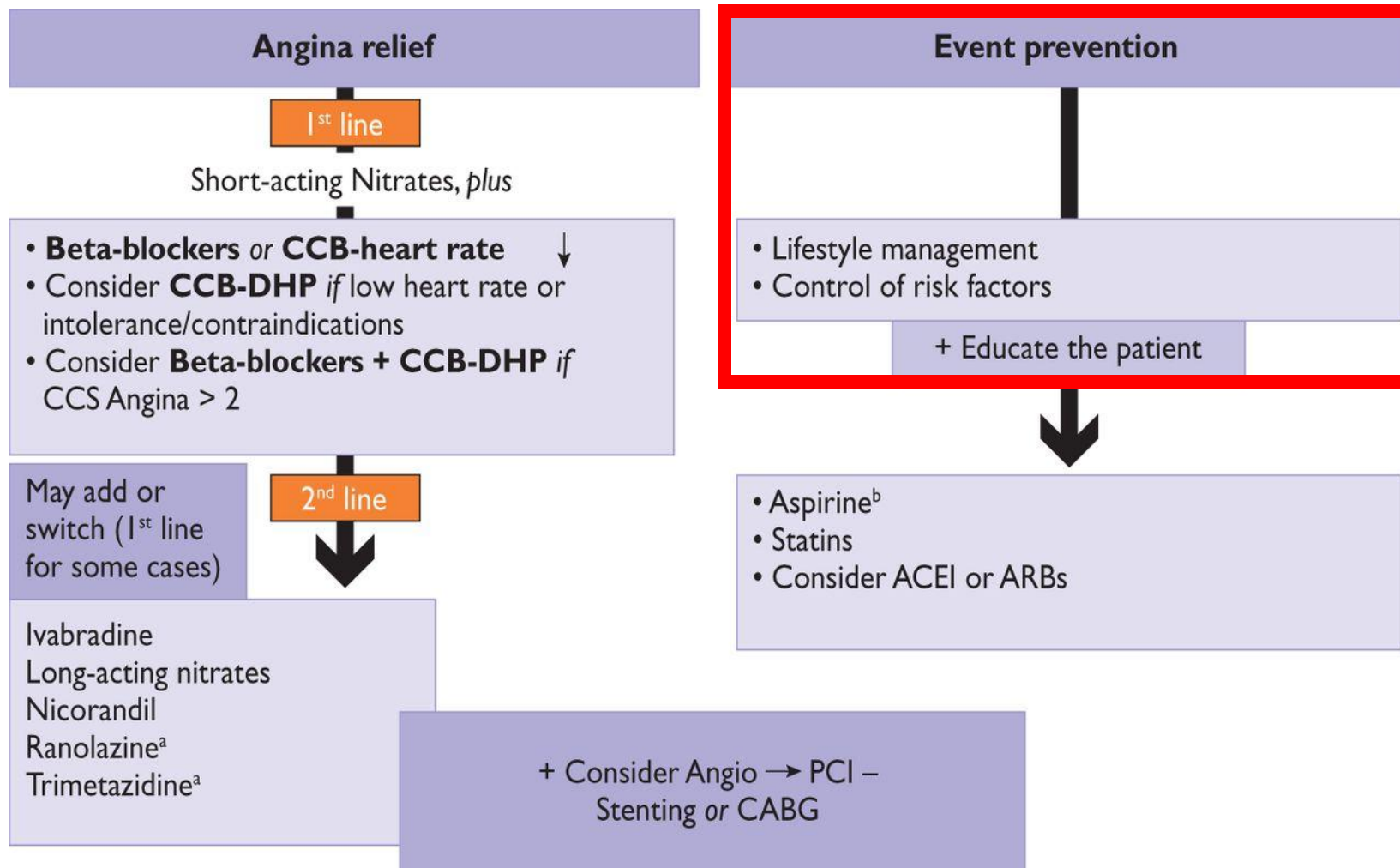
COMORBILITIES IN 2281 CR PATIENTS

N. 165 CR Units

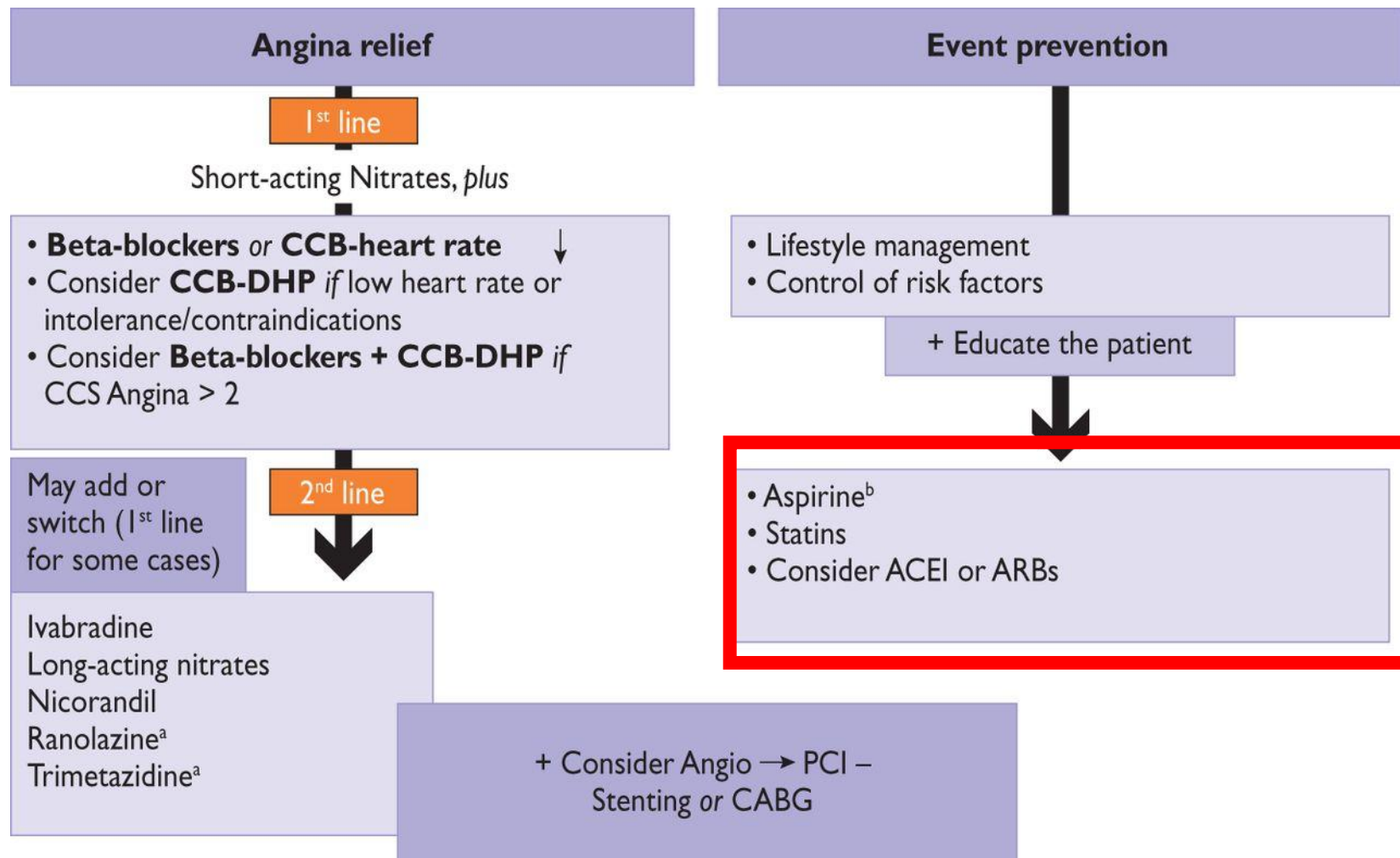


Mortalità dovuta a MCV x 2 negli uomini diabetici, x 3-5 nelle donne
Maggiore estensione della coronaropatia
Maggior carico anginoso nella patologia cronica

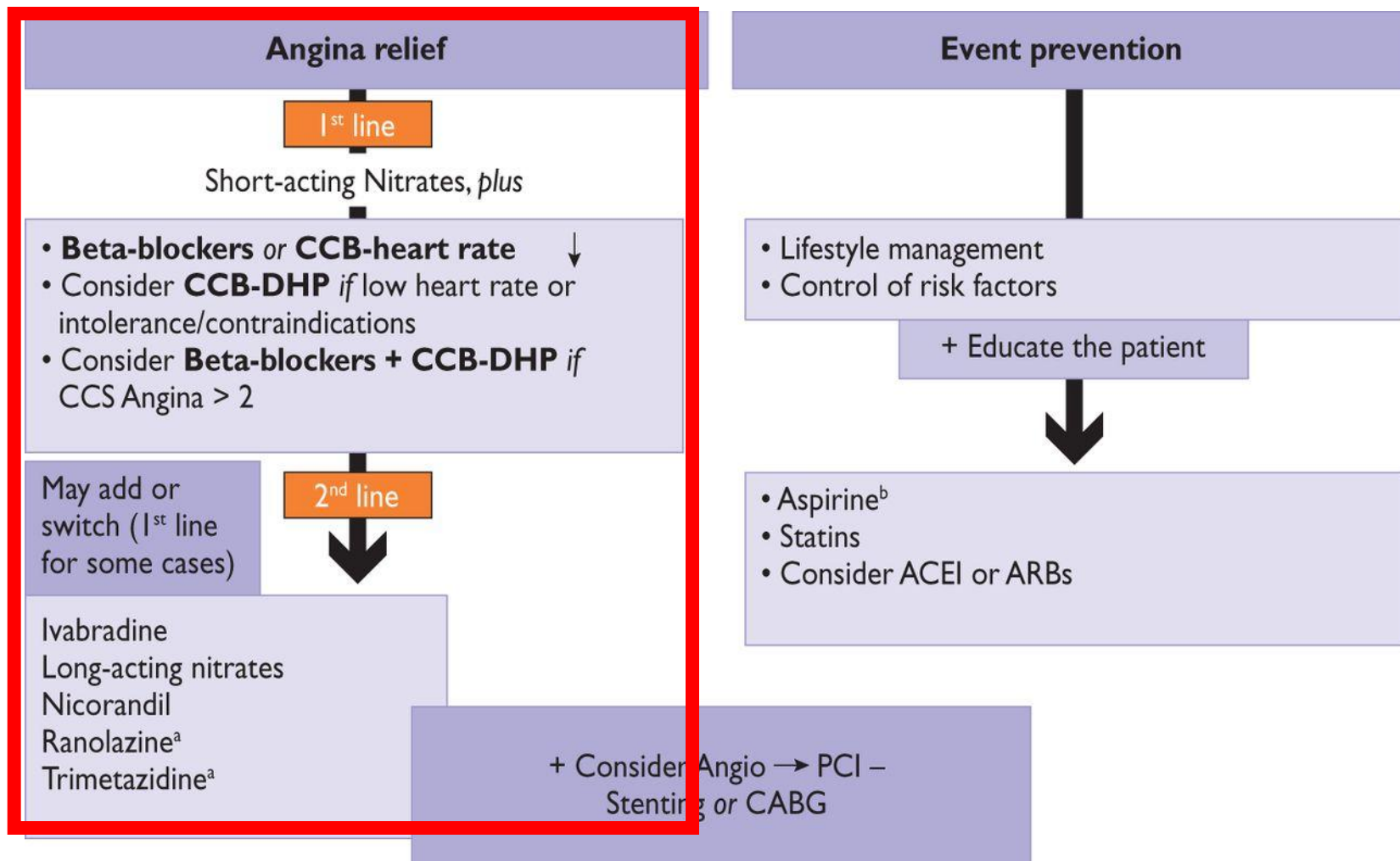
Medical management of patients with stable coronary artery disease.



Medical management of patients with stable coronary artery disease.



Medical management of patients with stable coronary artery disease.



Medical management of patient with stable CAD

Angina relief

1st line

Short-acting Nitrates, *plus*

- **Beta-blockers** or **CCB-he**
- Consider **CCB-DHP** if low intolerance/contraindication
- Consider **Beta-blockers** + CCS Angina > 2

May add or switch (1st line for some cases)

2nd line

Ivabradine
Long-acting nitrates
Nicorandil
Ranolazine^a
Trimetazidine^a

Ivabradine

Long-acting nitrates

Nicorandil

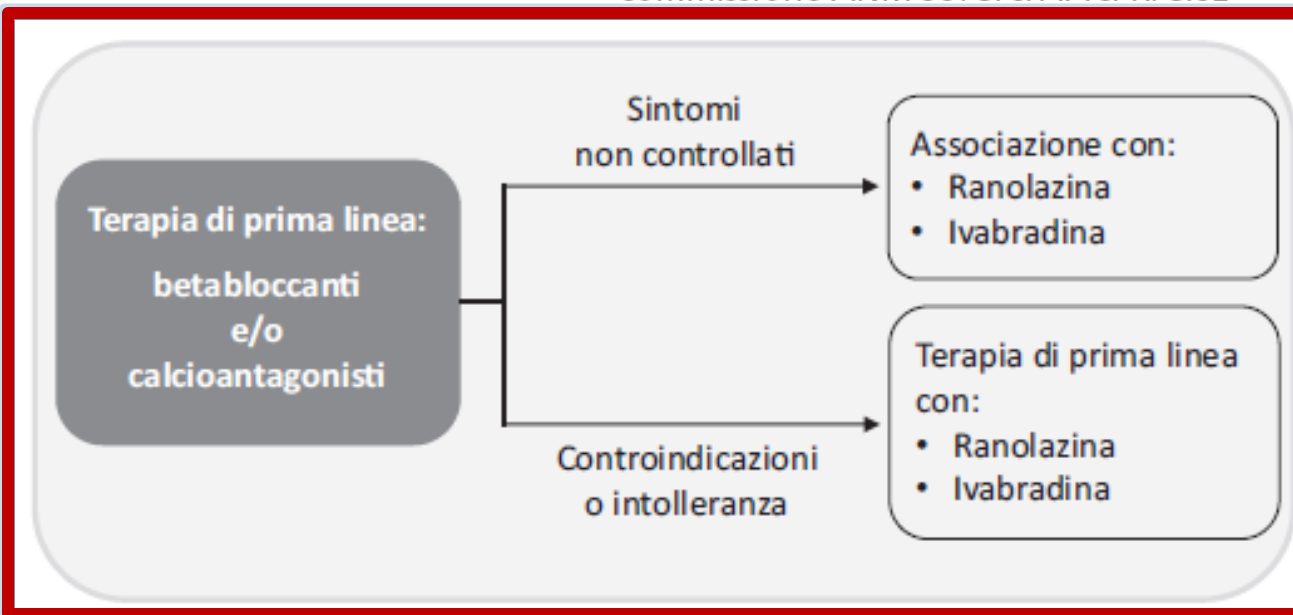
Ranolazine^a

Trimetazidine^a

Documento ANMCO/GICR-IACPR/GISE

L'organizzazione dell'assistenza nella fase post-acuta delle sindromi coronariche

Commissione ANMCO/GICR-IACPR/GISE



(ANMCO)
(GICR-IACPR)

, Francesco Bedogni,
no, Francesco Fattirolli,
e Musumeci, Zoran Olivari,
elli

iali)

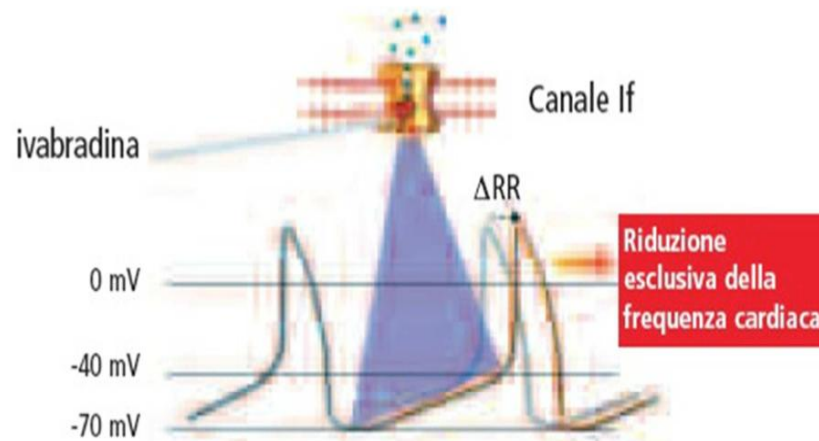
Fulvia Seccareccia e Stefano Rosato

Centro Nazionale di Epidemiologia, Sorveglianza e Promozione della Salute, Istituto Superiore di Sanità, Roma

Volume 15 — Suppl. 1 al n. 1
Gennaio 2014
www.giornaledicardiologia.it

Ivabradina Meccanismo d'azione

Inibitore selettivo e specifico della corrente If



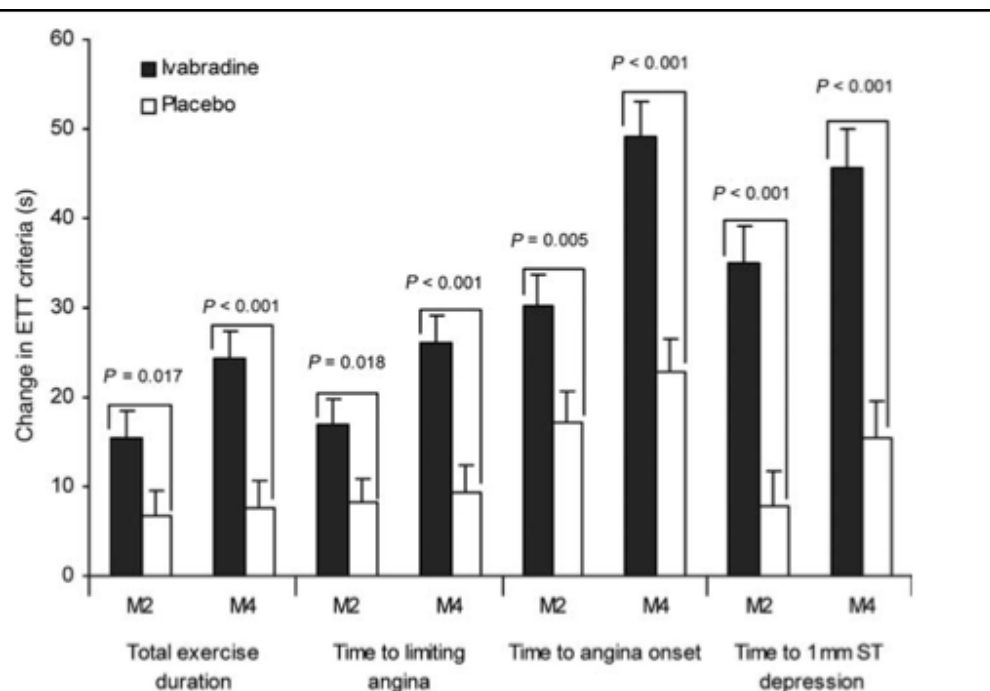
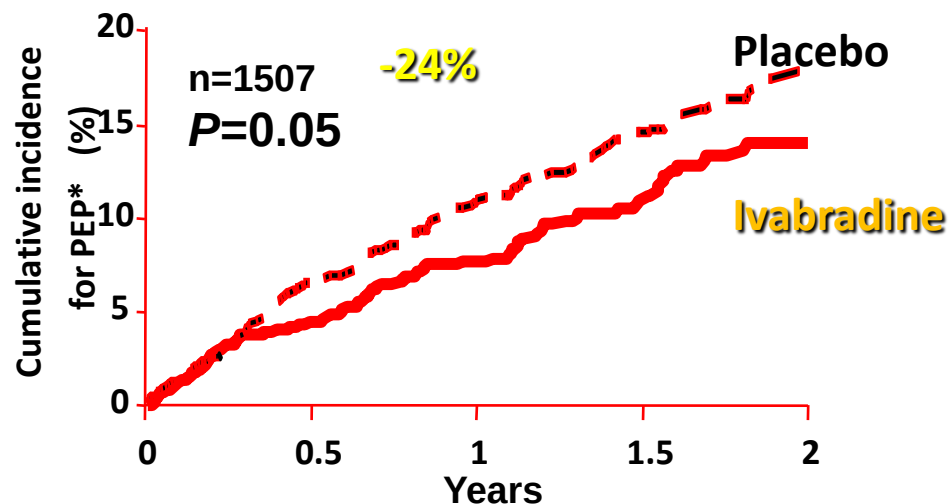
Di Francesco D, Camm AJ. Drugs. 2004;64:1757-1765.

Blocca il flusso di ioni Na e K all'interno delle cellule (nodo senoatriale) e quindi rallenta la velocità di depolarizzazione diastolica. Di fatto riduce selettivamente la frequenza cardiaca allungando la diastole.

BEAUTIFUL Ivabradine reduces primary end point in angina patients subgroup >70 bpm

Primary end point (PEP) : CV death + hospitalization for HF or MI

Non disponibili dati specifici per i diabetici



ASSOCIATE TRIAL

Ivabradina + atenololo
guadagno su tempo di
esercizio e insorgenza
di angina

RANOLAZINA

più potente inibitore dei canali lenti del Na

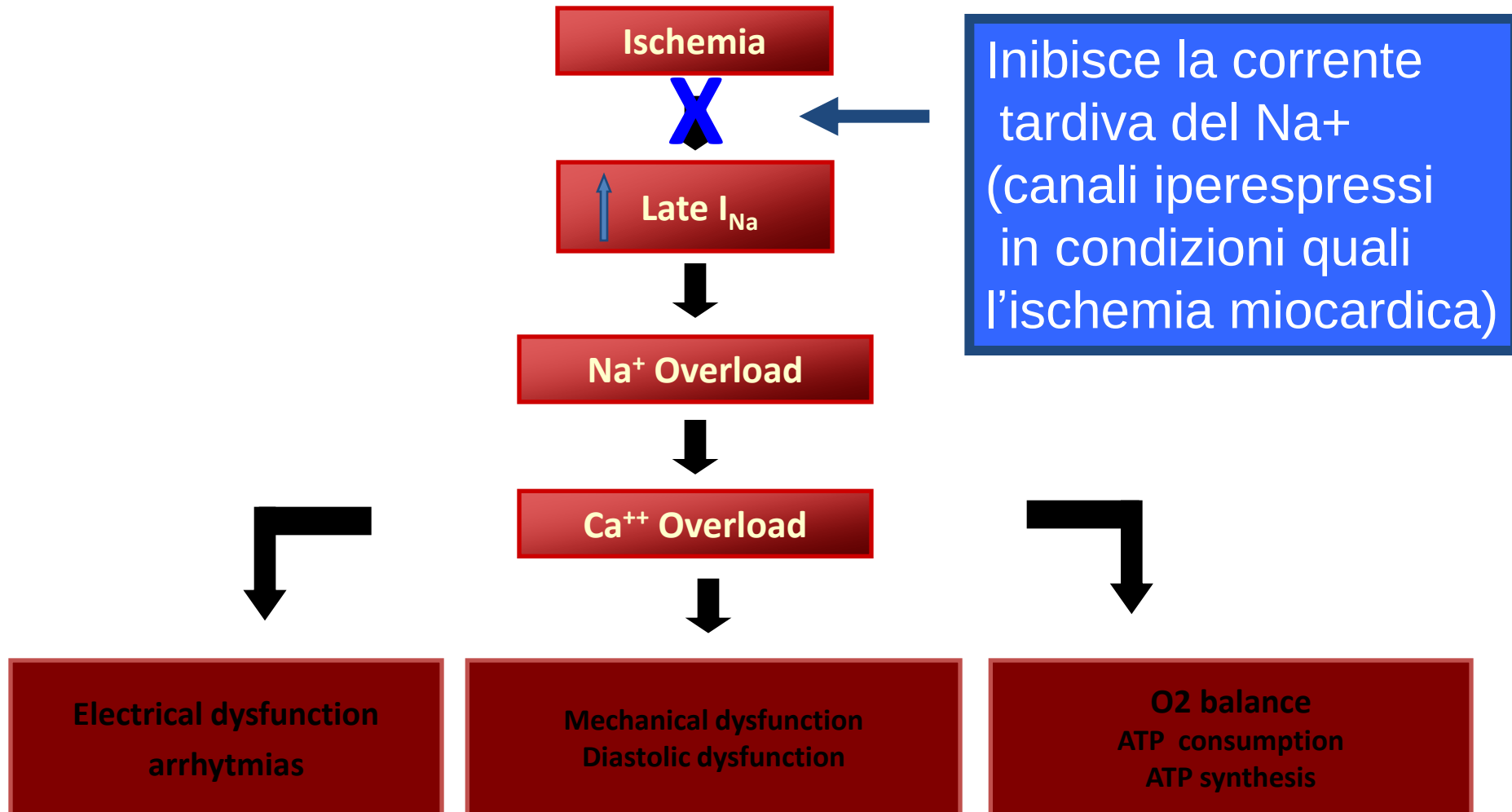
**Inibizione
Selettiva della
Corrente T Na**

```
graph TD; A["Inibizione Selettiva della Corrente T Na"] --> B["Effetto antiischemico"]; A --> C["Effetto antianginoso"];
```

***Effetto
antiischemico***

***Effetto
antianginoso***

Ranolazina: Meccanismo di azione



RANOLAZINA: Studi Clinici Principali

MARISA

N=191

**Angina
cronica**

Ranolazina
monoterapia
vs placebo

CARISA

N=823

**Angina
cronica**

Ranolazina
vs placebo
in aggiunta
alla terapia standard

ERICA

N=565

Angina
cronica

Ranolazina vs
placebo
in aggiunta ad
amlodipina 10 mg

MERLIN-

TIMI 36

N=6.560

Sindromi
Coronariche Acute
Non-STE

Ranolazina vs placebo
in aggiunta alla
terapia standard

Chaitman JAMA 2004; 291:303-316

Chaitman JACC 2004; 43:1375-82

Stone, JACC 2006; 48:566-75

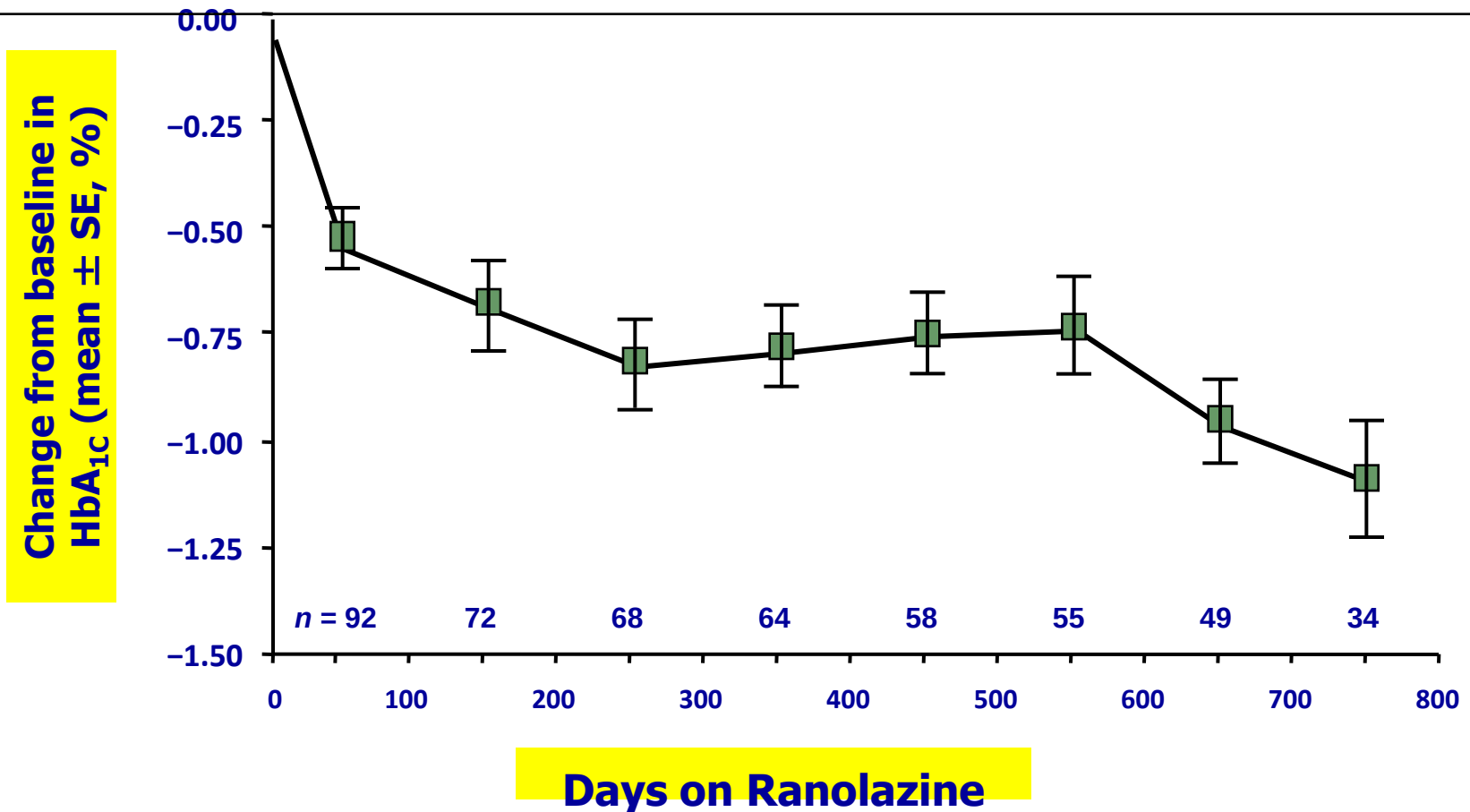
Morrow JAMA, 2007; 297:1775-1783

Nel complesso:

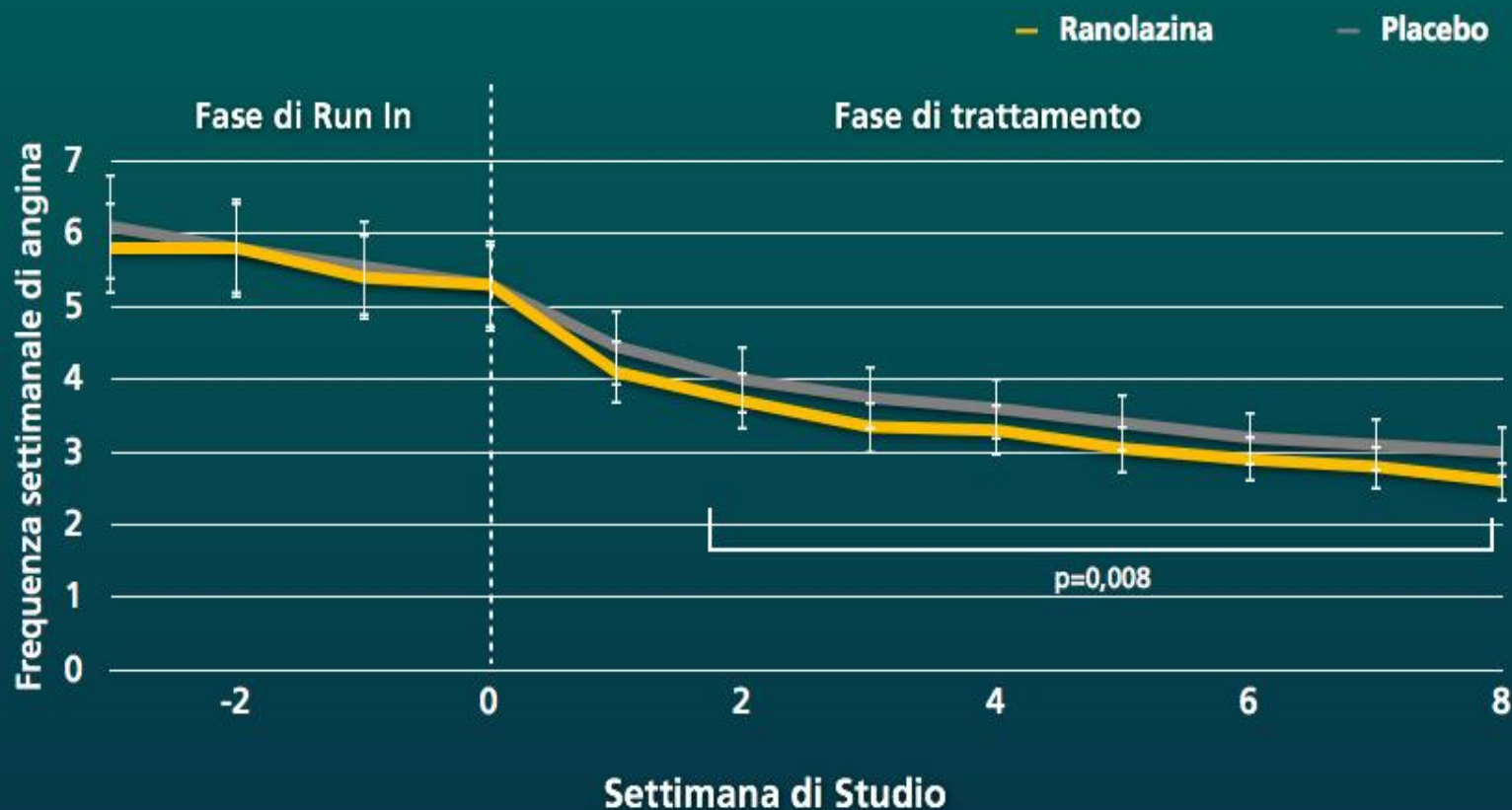
- ridotta la frequenza di episodi di angina
- ridotto l'uso di antianginosi "al bisogno"
- prolungata la durata di esercizio fisico
- prolungato il tempo di insorgenza di angina da sforzo
- Ridotta la % di ischemia ricorrente dopo SCA (-22%)
- NO problemi di sicurezza (allungamento QT)

Evidenza di riduzione della Hb glicata in analisi post-hoc

Effetti di Ranolazina sulla HbA1c in pazienti con diabete



Studio TERISA: frequenza settimanale di angina nei pz con diabete mellito in trattamento con altri antianginosi

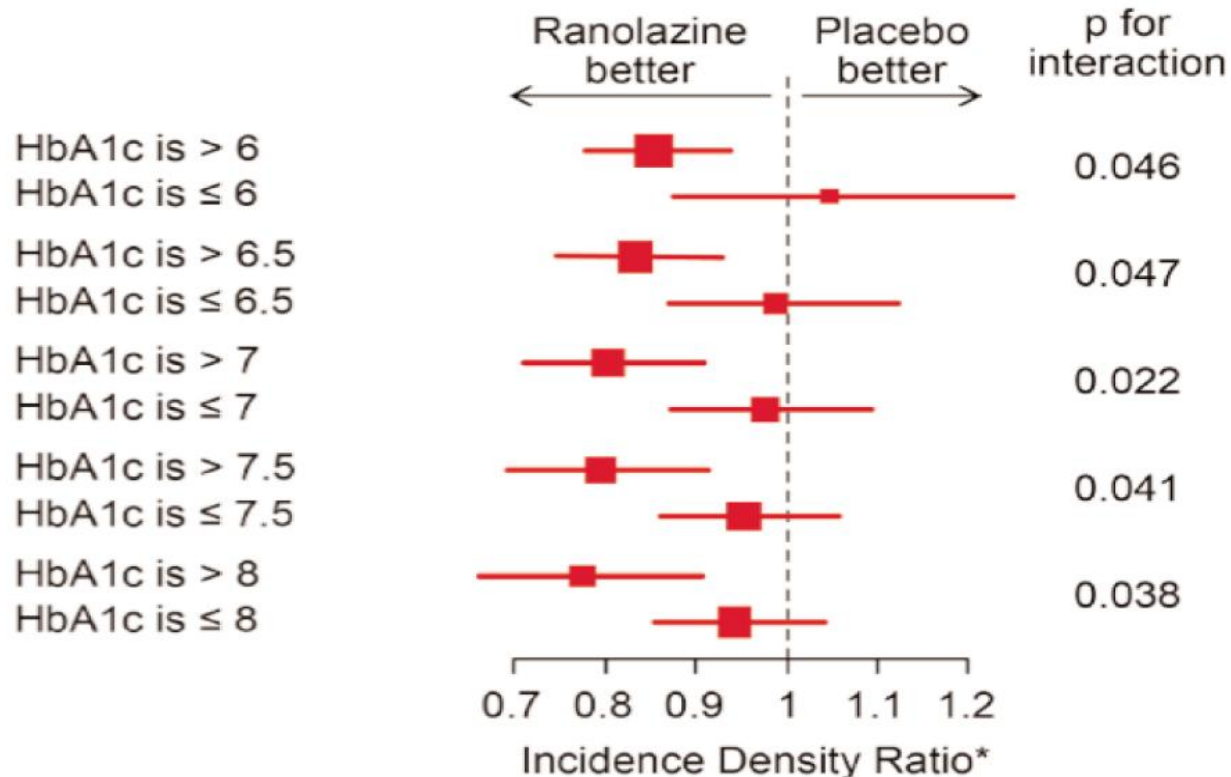




Evaluation of Ranolazine in Patients with Type 2 Diabetes Mellitus and Chronic Stable Angina. Results from the TERISA randomized clinical trial

Kosiborod MJ Am Coll Cardiol 2013

Riduzione episodi di angina e uso di antianginosi confermata nei diabetici, e più evidente in paz con Hb glicata più elevata



2013 ESC guidelines on the management of stable coronary artery disease

Ranolazine

These results suggest that this drug can be added to other well-established anti-anginal drugs, in particular in patients with higher HbA_{1c} levels, who may also more often rely on medical management.

Conclusioni

- I pazienti con cardiopatia ischemica, sia acuta che cronica, sono anche diabetici in circa un terzo dei casi.
- La presenza di diabete è un fattore prognostico negativo indipendente in questo gruppo di pazienti, che pertanto va considerato ad alto rischio.
- Ciononostante spesso questi pazienti sono sottotrattati sia riguardo al ricorso a procedure di rivascolarizzazione che riguardo alla terapia farmacologica.

Conclusioni

- Lo sforzo comune per chi di questi pazienti si occupa (cardiologi, diabetologi, medici di medicina generale) dovrebbe quindi essere quello di ottimizzare le strategie terapeutiche utilizzando tutto l'armamentario disponibile, oggi arricchitosi di nuove molecole di provata efficacia.

grazie

