SALA CONCORDIA B

URGENZE CARDIOVASCOLARI

Moderatori: **Francesco Rocco Pugliese, Furio Colivicchi** (ANMCO)

Maria Lorenza Muiesan

Le patologie associate alla sindrome coronarica acuta: quale approccio clinico?

XII congresso nazionale
simeu
RICCIONE 13-15 MAGGIO 2022

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XII congresso nazionale
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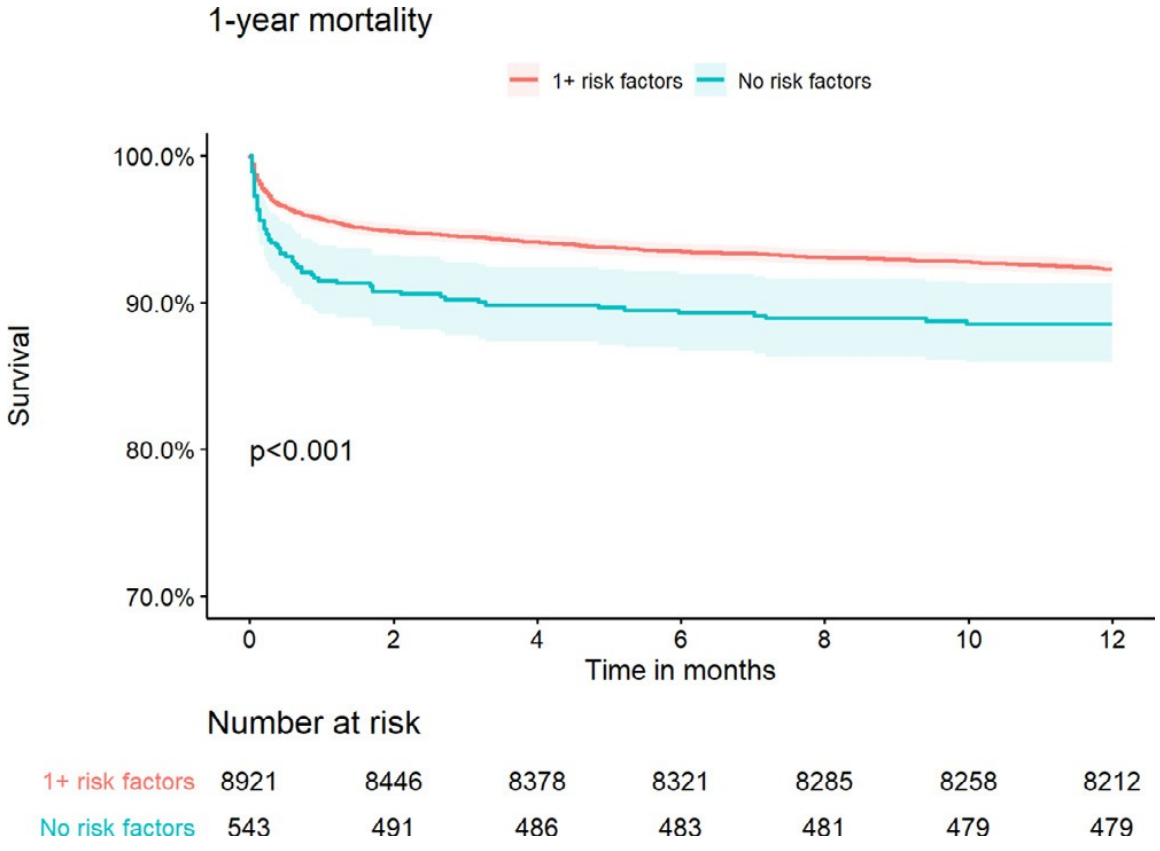
RICCIONE 13-15 MAGGIO 2022

Worse outcomes of ACS patients without versus with traditional cardiovascular risk factors

Journal of Cardiology 79 (2022) 515–521



No Risk Factors patients

less likely to receive interventional therapy during hospital stay or guideline-recommended medical therapy

25 year trends in first time hospitalisation for acute myocardial infarction, subsequent short and long term mortality, and the prognostic impact of sex and comorbidity: a Danish nationwide cohort study

BMJ 2012;344:e356 doi: 10.1136/bmj.e356

	Calendar periods of diagnosis					
	1984–8 (n=56 454)	1989–93 (n=50 249)	1994–8 (n=42 261)	1999–2003 (n=44 365)	2004–8 (n=41 002)	Total (n=234 331)
Sex:						
Female	20 201 (35.8)	18 691 (37.2)	16 238 (38.4)	17 652 (39.8)	15 926 (38.8)	88 708 (37.9)
Male	36 253 (64.2)	31 558 (62.8)	26 023 (61.6)	26 713 (60.2)	25 076 (61.2)	145 623 (62.1)
Age (years):						
15–34	206 (0.4)	196 (0.4)	223 (0.5)	228 (0.5)	224 (0.5)	1 077 (0.5)
35–49	3 845 (6.8)	3 521 (7.0)	2 974 (7.0)	3 172 (7.1)	3 185 (7.8)	16 697 (7.1)
50–59	8 334 (14.8)	7 241 (14.4)	6 176 (14.6)	6 859 (15.5)	6 296 (15.4)	34 906 (14.9)
60–69	15 610 (27.7)	12 978 (25.8)	10 020 (23.7)	9 604 (21.6)	9 227 (22.5)	57 439 (24.5)
70–79	18 465 (32.7)	16 080 (32.0)	13 309 (31.5)	12 617 (28.4)	10 526 (25.7)	70 997 (30.3)
≥80	9 994 (17.7)	10 233 (20.4)	9 559 (22.6)	11 885 (26.8)	11 544 (28.2)	53 215 (22.7)
Comorbidity category*:						
Normal	42 645 (75.5)	37 771 (75.2)	30 041 (71.1)	28 323 (63.8)	26 157 (63.8)	164 937 (70.4)
Moderate	7 455 (13.2)	6 845 (13.6)	6 409 (15.2)	7 599 (17.1)	6 633 (16.2)	34 941 (14.9)
Severe	4 168 (7.4)	3 701 (7.4)	3 571 (8.4)	4 592 (10.4)	4 295 (10.5)	20 327 (8.7)
Very severe	2 186 (3.9)	1 932 (3.8)	2 240 (5.3)	3 851 (8.7)	3 917 (9.6)	14 126 (6.0)

*Categories of comorbidity were based on Charlson comorbidity index scores of 0 (normal), 1 (moderate), 2 (severe), and ≥3 (very severe).

	Adjusted mortality rate ratio (95% CI)*	
	30 day	31-365 days
No comorbid diseases	1 (reference)	1 (reference)
Congestive heart failure	1.30 (1.20 to 1.41)	1.62 (1.48 to 1.78)
Peripheral vascular disease	1.23 (1.13 to 1.34)	1.47 (1.33 to 1.62)
Cerebrovascular disease	1.21 (1.12 to 1.30)	1.52 (1.39 to 1.65)
Dementia	1.81 (1.60 to 2.05)	1.52 (1.28 to 1.81)
Chronic pulmonary disease	1.21 (1.12 to 1.31)	1.54 (1.41 to 1.68)
Connective tissue disease	0.95 (0.82 to 1.09)	1.05 (0.89 to 1.23)
Ulcer disease	1.24 (1.10 to 1.39)	1.50 (1.31 to 1.72)
Mild liver disease	2.00 (1.48 to 2.71)	1.80 (1.22 to 2.67)
Diabetes without end organ damage	0.99 (0.89 to 1.09)	1.19 (1.05 to 1.34)
Diabetes with end organ damage	1.30 (1.16 to 1.46)	1.25 (1.09 to 1.44)
Hemiplegia	1.32 (0.79 to 2.19)	1.68 (0.97 to 2.89)
Moderate to severe renal disease	1.26 (1.11 to 1.42)	2.08 (1.83 to 2.36)
Non-metastatic solid tumour	1.22 (1.12 to 1.34)	1.69 (1.53 to 1.87)
Leukaemia	1.85 (1.32 to 2.59)	1.89 (1.21 to 2.95)
Lymphoma	1.40 (1.07 to 1.83)	1.60 (1.15 to 2.22)
Moderate to severe liver disease	2.21 (1.34 to 3.64)	1.97 (0.94 to 4.10)
Metastatic cancer	1.58 (1.25 to 2.01)	2.91 (2.33 to 3.63)

AIDS was omitted from the table because of its low prevalence (<0.1%).
*Adjusted for the other comorbidities, age, and sex.

Acute coronary syndromes in cancer patients

Irma Bisceglia[a], Maria Laura Canale[b], Chiara Lestuzzi[c], Iris Parrini[d], Giulia Russo[e], Furio Colivicchi[f], Domenico Gabrielli[g], Michele Massimo Gulizia[h], Cezar A. Iliescu[i], on the behalf of ANMCO Cardio-Oncology Task Force

- Most often NSTEMI, (dyspnea, atypical chest pain and hypotension)
- *The main precipitating factor are anemia* and hypotension related to fluid depletion
- Patients with acute MI asymptomatic (mostly patients on analgesic therapy or with chemotherapy or radiotherapy-induced neuropathy)

J Cardiovasc Med 2020, 21:944–952

ANEMIA E ACS

Prevalence of anemia on admission in the setting of ACS: **varying 10%-43%**

Table 3 Outcome related to baseline anemia in ACS studies

Authors, year	N	Population	Outcome	Investigation time	Risk (95% CI)
Meneveau et al.[3] 2009	1410	ACS	Mortality	In-hospital	HR 2.1
				30 days	HR 2.3
Tsujita et al.[4] 2010	3153	STEACS	All-cause mortality	1 year	HR 1.98 (1.05–3.73)
			Major bleeding	1 year	HR 2.15 (1.43–3.24)
Sulaiman et al.[5] 2011	7922	ACS	Mortality	In-hospital	OR 1.71 (1.34–2.17)
				30 days	OR 1.34 (1.06–1.71)
				1-year	OR 1.22 (1.01–1.49)
Kunadian et al.[6] 2014	13,032	NSTEACS	Composite ischemic event	In-hospital	RR 1.39 (1.17–1.67)
				30 days	RR 1.40 (1.20–1.62)
				1 year	RR 1.48 (1.33–1.64)
					HR 1.23 (1.05–1.44)
			Mortality	In-hospital	RR 2.07 (1.31–3.26)
				30 days	RR 2.23 (1.64–3.02)
				1 year	RR 2.35 (1.94–2.84)
					HR 1.77 (1.29–2.44)
			Major bleeding	In-hospital	RR 2.20 (1.84–2.64)
				30 days	RR 2.30 (1.94–2.73)
Morici et al.[18] 2014	637	NSTEACS, ≥75 years old	Mortality	1 year	HR 1.72 (1.14–2.60) for Hb 10–13 g/dL HR 2.50 (1.35–4.57) for Hb < 10 g/dL
Yazji et al.[8] 2017	1731	ACS	Mortality	1 year	OR 2.42 (1.40–4.16)
Lawler et al.[9] 2013	233,144	ACS	Mortality	In-hospital	RR 2.76 (1.94–3.92)
				30 days	RR 2.81 (1.91–4.14) HR 1.75 (1.02–3.01)
				1 year	RR 1.69 (1.17–2.43)
				Maximum (mean 18 months)	HR 1.63 (1.10–2.40)
					RR 2.08 (1.70–2.55) HR 1.49 (1.23–1.81)
			Re-infarction	Maximum (mean 18 months)	RR 1.25 (0.78–2.02)

Abbreviations: ACS, acute coronary syndrome; HR, hazard ratio; N, number of in-study patients; NSTEACS, non-ST-elevation acute coronary syndrome; OR, odds ratio; RR, relative risk; STEACS, ST-elevation acute coronary syndrome.

8.4 Anaemia

Anaemia is common in patients with NSTE-ACS.[451] Persistent or worsening anaemia in patients with NSTE-ACS is associated with increased mortality, recurrent MI, and major bleeding.[452] However, it is uncertain whether anaemia itself is the determinant for poorer outcome or rather a marker of comorbidity.

Given that the treatment of NSTE-ACS includes antithrombotic therapy (which may exacerbate bleeding), it is important to identify the cause of anaemia and, in particular, occult bleeds in patients presenting with NSTE-ACS. The indication for ICA, access site choice (radial approach favoured), and the need for revascularization should be carefully considered to avoid further blood loss.[453,454] Equally, the choice of antithrombotic agent requires evaluation of ischaemic and bleeding risks, favouring the use of shorter half-life or reversible agents. In the setting of anaemia related to an unknown/untreatable source, the use of DES should be limited to the new-generation devices with proven safety profiles on short-term DAPT.[455] Blood transfusion is discussed in *section 5.4.9*.

2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation

Impact of Baseline Anemia in Patients With Acute Coronary Syndromes Undergoing Percutaneous Coronary Intervention: A Prespecified Analysis From the VALIDATE-SWEDEHEART Trial

Axel Wester, MD; Rubina Attar, BMSc; Moman Aladdin Mohammad, MD; Pontus Andell, MD, PhD; Robin Hofmann, MD, PhD; Jens Jensen, MD, PhD; Karolina Szummer, MD, PhD; David Erlinge, MD, PhD; Sasha Koul, MD, PhD

J Am Heart Assoc. 2019

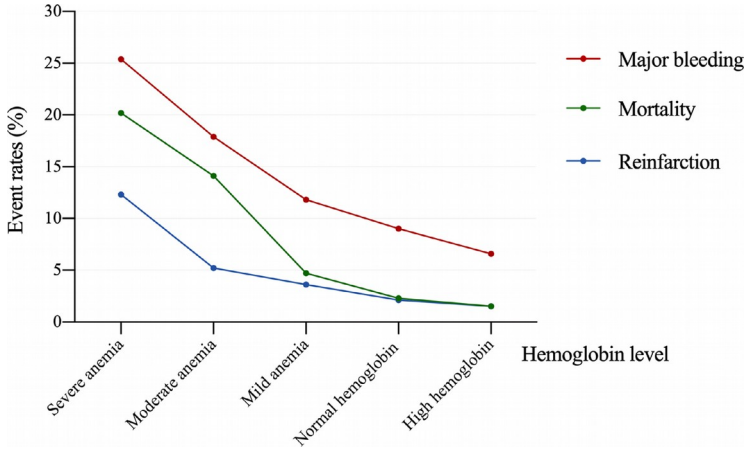
More often **ACS patients with anemia**:

- are **older, women, lower BMI**
- **comorbidities**: previous CV disease, CKD, hyperlipidemia, hypertension, DM, smoking, CAD, previous stroke, HF, malignacy, history of major bleeding
- More frequent **presentation with STEMI/Killip 3-4**
- No difference in time from symptoms onset to PCI
- **Higher** median peak **value of high sensitivity cardiac troponin T**
- **Lower LV EF**

high risk of bleeding and **high risk for ischemic events**

Patients with severe anemia (Hb <10 g/dL) had a

- **10 times higher mortality rate,**
- **6 times higher rate of myocardial reinfarction,**
- **3 times higher rate of major bleeding at 180 days**



ANEMIA E SCA

WHY A WORSE OUTCOME?

Anemia is a Marker of a preexisting, systemic underlying disease state defining a “more fragile” patient.

Systemic inflammatory response syndrome reduces the capacity for vascular healing → decreased levels of peripheral circulating endothelial progenitor cells in ACS patients affected by anemia on admission compared to non-anemic subjects.

The systemic effects of the inflammatory response induced by myocardial necrosis are not just limited to blunted erythroid function but also involve the ability to produce or mobilize endothelial progenitor cells by the bone marrow. This, in turn, may compromise the vascular healing capacity and contribute to poor prognosis of patients with ACS and anemia.

Anemia may impact on the outcome because anemic patients **may not receive guideline-recommended treatment for ACS**.

Stucchi et al Vascular Health and Risk Management 2018:14

Anemia and ACS: to treat or not to treat?

Transfusion practice and outcomes in non–ST-segment elevation acute coronary syndromes

American Heart Journal
Volume 155, Issue 6, June 2008, Pages 1047-1053

Karen P. Alexander MD [a], Anita Y. Chen MS [a], Tracy Y. Wang MD [a], Sunil V. Rao MD [a], L. Kristin Newby MD,

Conclusion

Anemia and transfusion are common in the care of NSTE ACS. The observed association between transfusion and adverse outcomes is neutral in the nadir HCT range where transfusions are most often given and trends strongly to benefit when nadir HCT is ≤24%. Although reassuring, randomized trials are needed to confirm the safety of transfusion in NSTE ACS. In the meantime, avoiding the need for transfusion is the best approach.

Blood transfusion and ischaemic outcomes according to anemia and bleeding in patients with non-ST-segment elevation acute coronary syndromes: Insights from the TAO randomized clinical trial

P. Deharo [a,b,c], G. Ducrocq [d,o], C. Bode [e], M. Cohen [f,q], T. Cuisset [a], S.R. Mehta [g], C.V. Pollack [h]

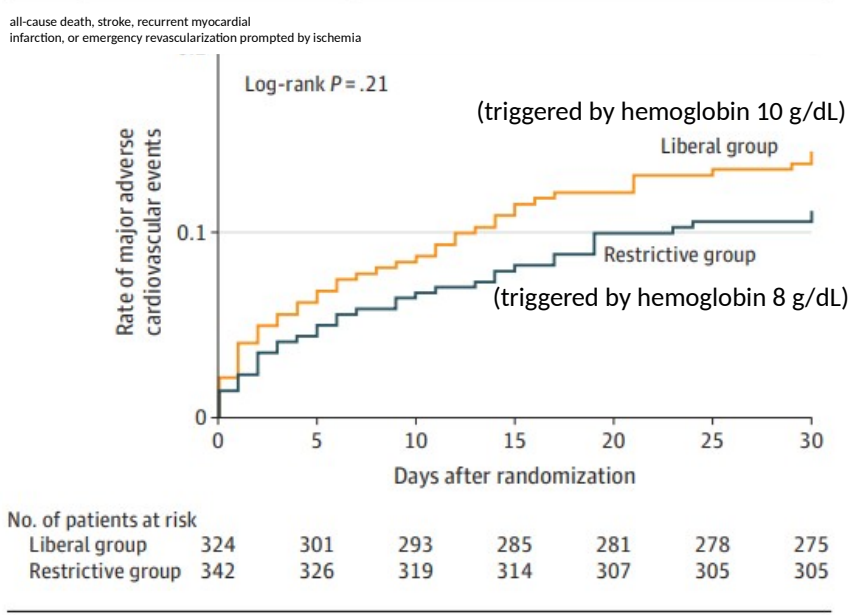
International Journal of Cardiology 318 (2020) 7–13

In patients with NSTEMI, RBC transfusion was associated with an increase of risk of death or MI at 180 days. This worse outcome appeared more pronounced in case of transfusion without overt bleeding and for hemoglobin level > 9.0 g/dl. This suggests that it may be prudent to refrain from RBC transfusion in those patients who do not have overt bleeding and have preserved hemoglobin levels. Randomized trials are required to better define patients who will benefit from RBC transfusion after a NSTEMI.

JAMA February 9, 2021 Volume 325, Number 6

Effect of a Restrictive vs Liberal Blood Transfusion Strategy on Major Cardiovascular Events Among Patients With Acute Myocardial Infarction and Anemia
The REALITY Randomized Clinical Trial

Gregory Ducrocq, MD, PhD; Jose R. Gonzalez-Juanatey, MD; Etienne Puymirat, MD; Gilles Lemesle, MD, PhD; Marine Cachanado



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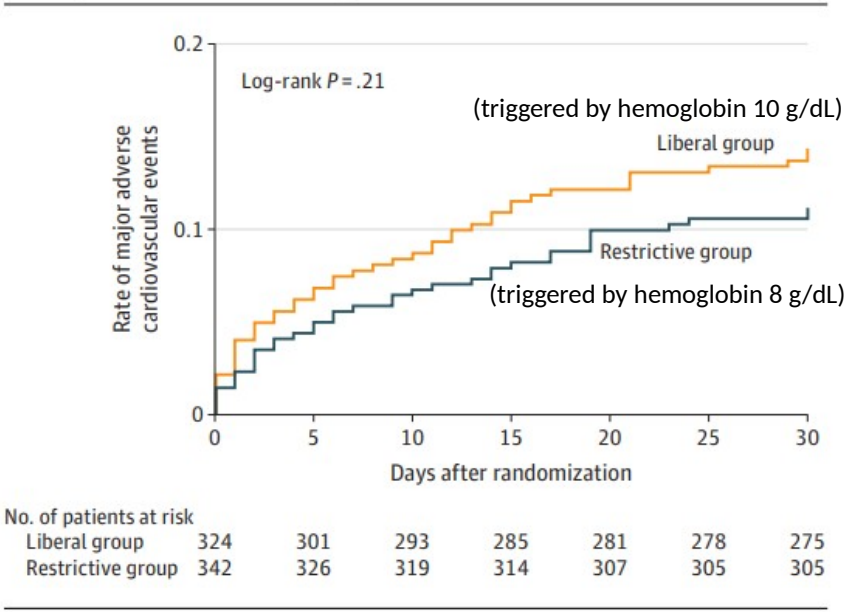
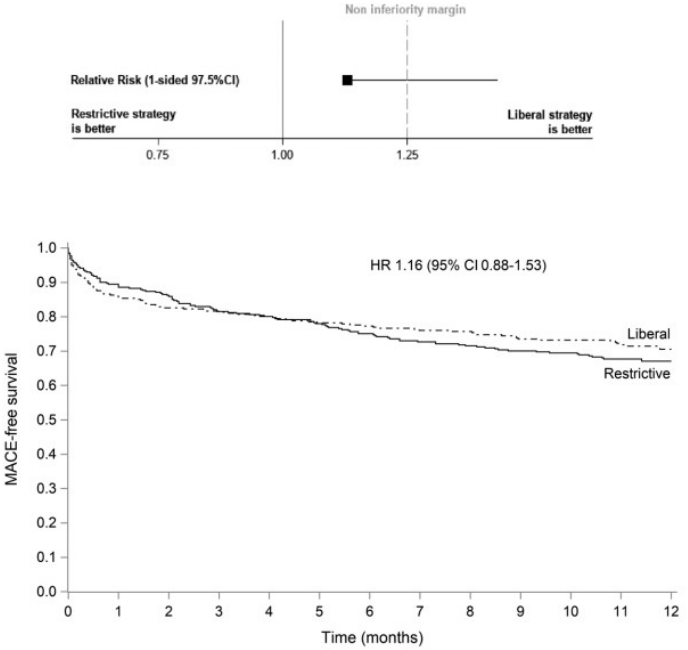


(triggered by hemoglobin 10 g/dL)

(triggered by hemoglobin 8 g/dL)

One-Year Major Cardiovascular Events After Restrictive Versus Liberal Blood Transfusion Strategy in Patients With Acute Myocardial Infarction and Anemia: The REALITY Randomized Trial

Circulation . 2022 Feb 8;145(6):486-488.



2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation

ANEMIA
Treatment

The **adequate transfusion threshold** is still being debated, although **current guidelines recommend correction of anemia <8 g/dL,** except for *hemodynamically unstable ACS patients who could benefit from Hb levels between 8 and 10 g/dL*.
No evidence supports the use of iron supplements and erythropoiesis-stimulating agents in the setting of ACS

Recommendations for bleeding management and blood transfusion in non-ST-segment elevation acute coronary syndromes for anticoagulated patients

Recommendations	Class[a]	Level[b]
In patients with dabigatran-associated ongoing life-threatening bleeding, the administration of the specific antidote for dabigatran — idarucizumab — should be considered.[264]	IIa	B
In patients with VKA-associated life-threatening bleeding events, rapid reversal of anticoagulation with four-factor prothrombin complex concentrate rather than with fresh frozen plasma or recombinant activated factor VII should be considered. In addition, repetitive 10 mg i.v. doses of vitamin K should be administered by slow injection.	IIa	C
In patients with NOAC-associated ongoing life-threatening bleeding, the administration of prothrombin complex concentrates or activated prothrombin complex concentrates should be considered when the specific antidote is unavailable.	IIa	C
In patients with rivaroxaban-, apixaban-, or edoxaban-associated ongoing life-threatening bleeding, the administration of the specific antidote — andexanet-alpha — may be considered.[265]	IIb	B
In patients with anaemia and no evidence of active bleeding, blood transfusion may be considered in case of compromised haemodynamic status, haematocrit <25%, or haemoglobin level <8 g/dL.	IIb	C

Coronary Interventions

Blood Transfusion and the Risk of Acute Kidney Injury Among Patients With Acute Coronary Syndrome Undergoing Percutaneous Coronary Intervention

Wassef Karrowni, MD; Amit Navin Vora, MD; David Dai, PhD; Daniel Wojdyla, MSc; Habib Dakik, MD; Sunil V. Rao, MD

9% of ACS patients undergoing PCI **developed AKI**
Blood transfusion was utilized in 2.2% of patients

AKI developed in 35.1% of patients who received transfusion versus 8.4% of patients without transfusion (adjusted odds ratio, 4.87 [4.71–5.04])

Risk factors to develop AKI: age, women, comorbidities (diabetes mellitus, hypertension, CKD).

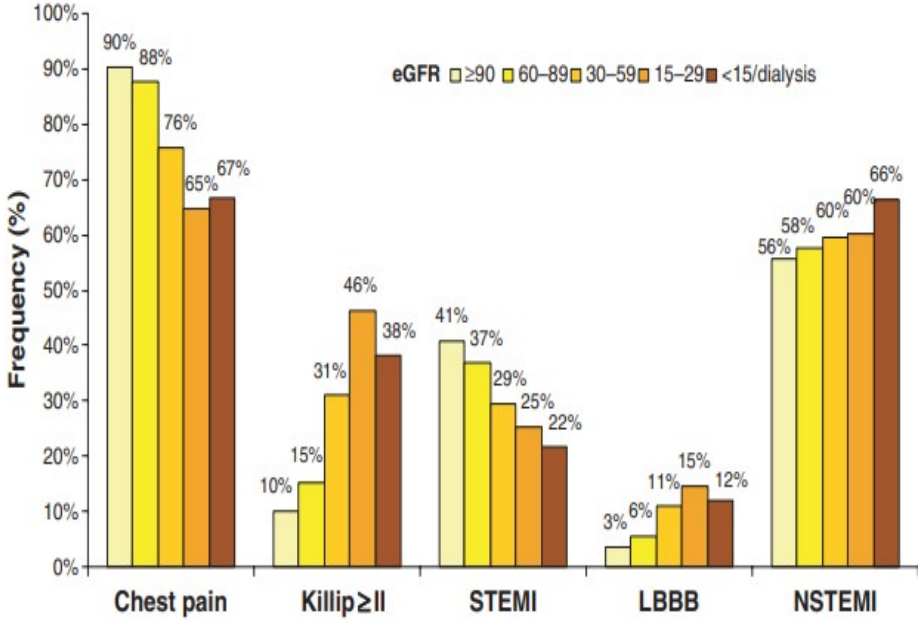
→ **independent association between blood transfusion and AKI in ACS patients undergoing PCI**. This association was significant even among patients with anemia at baseline and who did subsequently sustain a bleeding event, suggesting that a restrictive blood transfusion policy needs to be further investigated for its potential to improve the safety of PCI.

[*Circ Cardiovasc Interv*. 2016:9:e003279

CKD

- 13% general population →20-25% ACS patients
- CKD affect every stage of diagnostic and therapeutic pathway of ACS, with an important prognostic relevance
- In all patients with NSTE-ACS, assessment of kidney function by eGFR is recommended for prognostic reasons and to identify patients at risk of contrast-induced nephropathy (Liv I C)
- Hs-cTn assays maintain high diagnostic and prognostic accuracy and, therefore, clinical utility in patients with renal dysfunction.
- A threshold of <5 ng/L may rule out myocardial injury in this population

Renal function and in-hospital events in ACS



J InternMed 2010;268: 40–49

Kidney Disease and Clinical Presentation of CHD

Characteristic	Acute Myocardial Infarction (n = 803)	Stable Exertional Angina (n = 419)	p Value
Prior eGFR (ml/min/1.73 m^2)			
Mean ± SD	78.2 ± 18.7	81.2 ± 17.9	0.006
Median (interquartile range)	78.0 (66.0–90.0)	80.0 (70.0–92.0)	0.006
Category of prior eGFR (ml/min/1.73 m^2)			0.07
90–130	26.5%	31.7%	
60–89	59.5%	57.0%	
45–59	9.8%	9.3%	
<45	4.1%	1.9%	
Age (yrs)	62.5 ± 8.4	62.1 ± 8.4	0.35
Women	23.8%	33.7%	<0.001

J Am Coll Cardiol 2011;58:1600–7

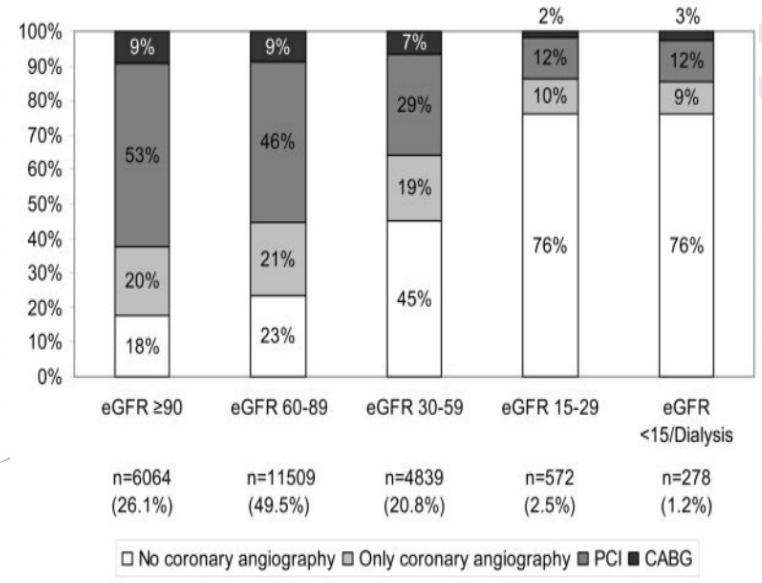
Circulation
Volume 120, Issue 10, 8 September 2009; Pages 851-858
https://doi.org/10.1161/CIRCULATIONAHA.108.838169

CORONARY HEART DISEASE

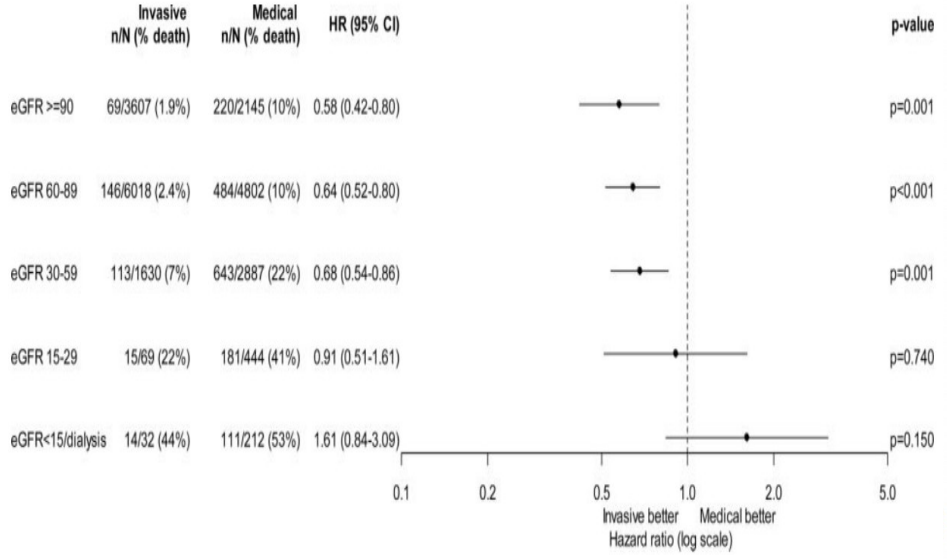
Influence of Renal Function on the Effects of Early Revascularization in Non-ST-Elevation Myocardial Infarction

Data From the Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART)

23 262 consecutive non–ST-elevation myocardial infarction patients < 80 years old were included in a nationwide coronary care unit register between 2003 and 2006.



Estimated hazard ratio for mortality at 1 year



REVASCULARIZATION and CKD

Myocardial revascularization in patients with CKD		
Use of low- or iso-osmolar contrast media (at lowest possible volume) are recommended in invasive strategies.[205,441,442,445,446]	I	A
Pre- and post-hydration with isotonic saline should be considered if the expected contrast volume is >100 mL in invasive strategies.	IIa	C
As an alternative to the pre- and post-hydration regimen, tailored hydration regimens may be considered.[441,448]	IIb	B
CABG should be considered over PCI in patients with multivessel CAD whose surgical risk profile is acceptable and life expectancy is >1 year.[449,450]	IIa	B

CABG = coronary artery bypass graft(ing); CAD = coronary artery disease; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; PCI = percutaneous coronary intervention.

[a]Class of recommendation.

[b]Level of evidence.

MEDICAL THERAPY:

2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation

The choice and dose of antithrombotic drugs should be carefully considered in patients with CKD, as these patients have an increased risk of bleeding

for patients with stage 5 CKD (eGFR <15 mL/min/1.73 m2), there are insufficient safety and efficacy data for the use of P2Y12 receptor inhibitors

ESC Guidelines

12 Key messages

- **Pre-treatment with $P2Y_{12}$ receptor inhibitors.** Routine pre-treatment with a $P2Y_{12}$ receptor inhibitor in NSTE-ACS patients in whom coronary anatomy is not known and an early invasive management is planned is not recommended given the lack of established benefit. However, it may be considered in selected cases and according to the bleeding risk of the patient.

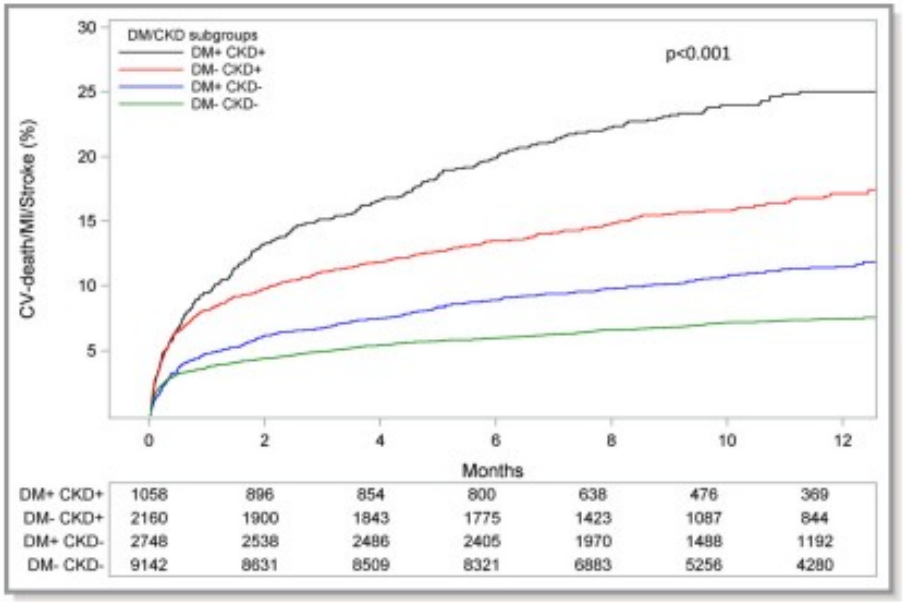
Impact of Diabetes Mellitus and Chronic Kidney Disease on Cardiovascular Outcomes and Platelet $P2Y_{12}$ Receptor Antagonist Effects in Patients With Acute Coronary Syndromes: Insights From the PLATO Trial

Group of Characteristics	Characteristic (at Baseline)	DM+/CKD+ (n=1058)	DM+/CKD− (n=2748)	DM−/CKD+ (n=2160)	DM−/CKD− (n=9142)	*P* Value
	Low-molecular-weight heparin	590 (55.8)	1460 (53.1)	1199 (55.5)	4734 (51.8)	0.003
	Fondaparinux	34 (3.2)	74 (2.7)	74 (3.4)	249 (2.7)	0.3
	Bivalirudin	25 (2.4)	90 (3.3)	34 (1.6)	158 (1.7)	<0.0001
Intended approach	Invasive	603 (57.0%)	1912 (69.6%)	1311 (60.7%)	6915 (75.6%)	<0.0001
	Noninvasive	455 (43.0%)	836 (30.4%)	849 (39.3%)	2227 (24.4%)	
Final ACS diagnosis	ST-elevation MI	244 (23.1%)	863 (31.4%)	638 (29.6%)	3980 (43.6%)	<0.0001
	Non-ST-elevation MI	559 (52.9%)	1259 (45.8%)	1038 (48.2%)	3622 (39.6%)	
	Unstable angina	224 (21.2%)	566 (20.6%)	427 (19.8%)	1336 (14.6%)	
	Other	29 (2.7%)	60 (2.2%)	50 (2.3%)	199 (2.2%)	
Randomized treatment	Delay from start of pain (h), median (Q1–Q3)	14.2 (6.8–21.2)	12.7 (5.7–20.4)	14.0 (5.8–21.1)	10.2 (4.3–19.0)	<0.0001
	Treatment duration (d), median (Q1–Q3)	258 (55–361)	276 (179–365)	265 (73–363)	284 (184–366)	<0.0001
Biomarkers	Creatinine (μmol/L), median (Q1–Q3)	115.0 (106.0–141.0)	80.0 (70.7–88.0)	106.0 (97.0–124.0)	80.0 (71.0–88.0)	<0.0001
	Glucose (mmol/L), median (Q1–Q3)	9.9 (7.2–13.5)	9.7 (7.2–13.2)	6.5 (5.6–7.9)	6.4 (5.6–7.7)	<0.0001
	HbA1c (mmol/mol), median (Q1–Q3)	7.5 (6.6–8.7)	7.6 (6.7–9.1)	5.9 (5.6–6.2)	5.8 (5.6–6.1)	<0.0001
	Hemoglobin (mmol/mol), median (Q1–Q3)	128.0 (116.0–140.0)	139.0 (128.0–149.0)	134.0 (123.0–145.0)	142.0 (132.0–151.0)	<0.0001
	NT-proBNP (pmol/L), median (Q1–Q3)	1734 (610.0–4071)	395.0 (146.0–953.0)	1002 (320.0–2544)	277.0 (99.0–721.0)	<0.0001
	Troponin I μg/L, median (Q1–Q3)	1.10 (0.12–6.00)	0.95 (0.11–4.30)	1.00 (0.11–5.70)	0.90 (0.12–4.70)	0.01
	Creatinine (mg/dL), median (Q1–Q3)	1.3 (1.2–1.6)	0.9 (0.8–1.0)	1.2 (1.1–1.4)	0.9 (0.8–1.0)	<0.0001
	CrCl (mL/min), median (Q1–Q3)	48.4 (38.9–55.1)	86.7 (73.2–104.5)	50.3 (42.7–55.9)	87.7 (74.5–104.0)	<0.0001

(J Am Heart Assoc. 2019;8: e011139. DOI: 10.1161/JAHA.118.011139.)

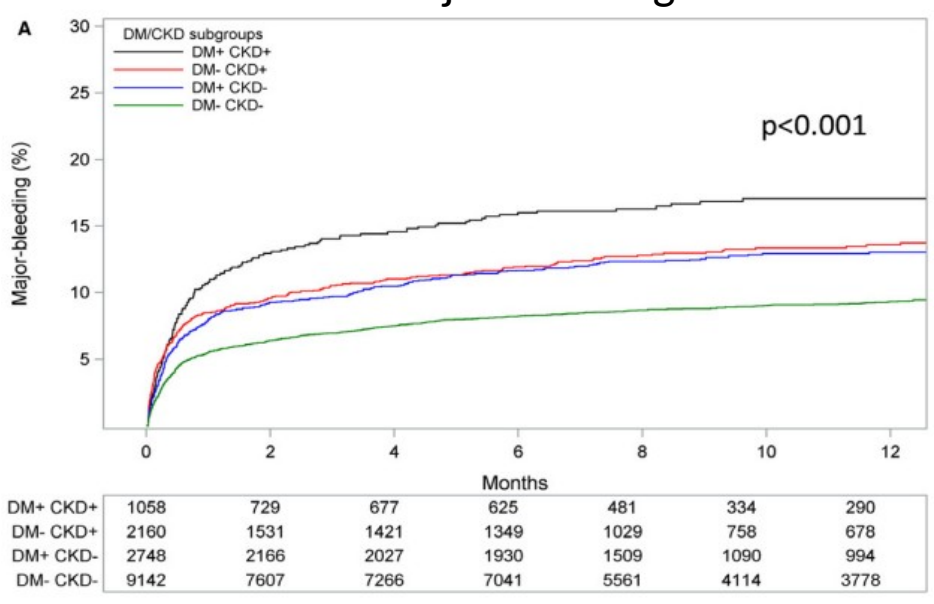
Impact of Diabetes Mellitus and Chronic Kidney Disease on Cardiovascular Outcomes and Platelet $P2Y_{12}$ Receptor Antagonist Effects in Patients With Acute Coronary Syndromes: Insights From the PLATO Trial

CV death/MI/Stroke



DM+ CKD+	1058	896	854	800	638	476	369
DM- CKD+	2160	1900	1843	1775	1423	1087	844
DM+ CKD-	2748	2538	2486	2405	1970	1488	1192
DM- CKD-	9142	8631	8509	8321	6883	5256	4280

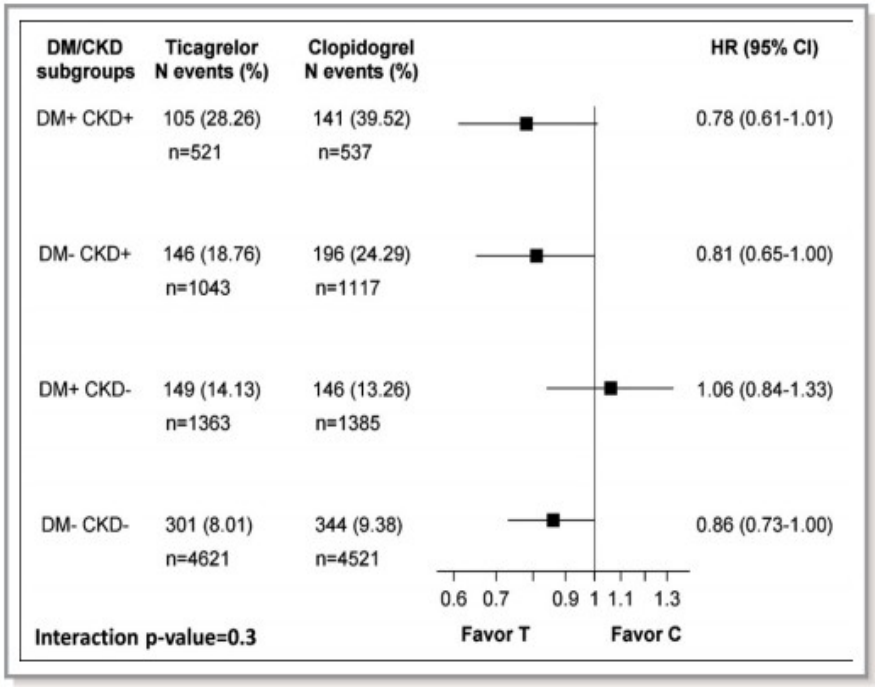
Major bleeding



DM+ CKD+	1058	729	677	625	481	334	290
DM- CKD+	2160	1531	1421	1349	1029	758	678
DM+ CKD-	2748	2166	2027	1930	1509	1090	994
DM- CKD-	9142	7607	7266	7041	5561	4114	3778

(J Am Heart Assoc. 2019;8: e011139. DOI: 10.1161/JAHA.118.011139.)

Impact of Diabetes Mellitus and Chronic Kidney Disease on Cardiovascular Outcomes and Platelet $P2Y_{12}$ Receptor Antagonist Effects in Patients With Acute Coronary Syndromes: Insights From the PLATO Trial



(J Am Heart Assoc. 2019;8: e011139. DOI: 10.1161/JAHA.118.011139.)

ESC European Society of Cardiology
European Heart Journal - Cardiovascular Pharmacotherapy (2020) **6**, 31–42
doi:10.1093/ehjcvp/pvz048
ORIGINAL ARTICLE
Acute coronary syndromes

P2Y12 inhibitors in acute coronary syndrome patients with renal dysfunction: an analysis from the RENAMI and BleeMACS projects

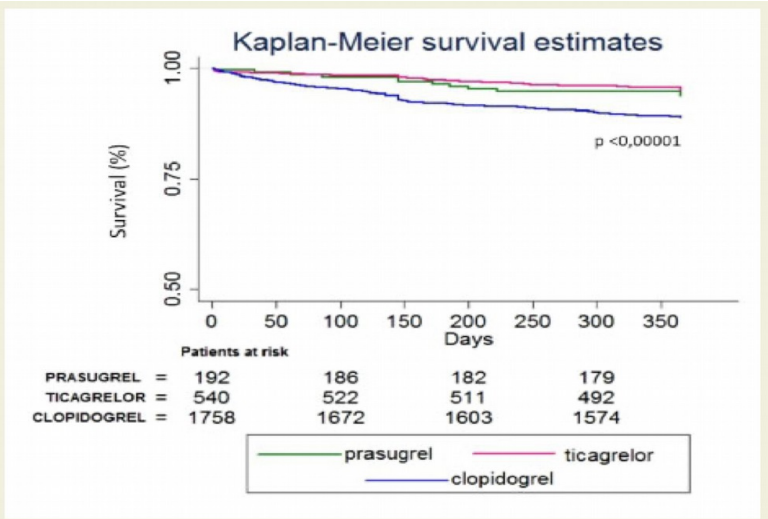


Figure 3 Survival estimates according to Kaplan–Meier analysis in patients with impaired renal function (estimated glomerular filtration rate ≤ 60 mL/min/1.73 m^2).

2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation

Diabetes mellitus

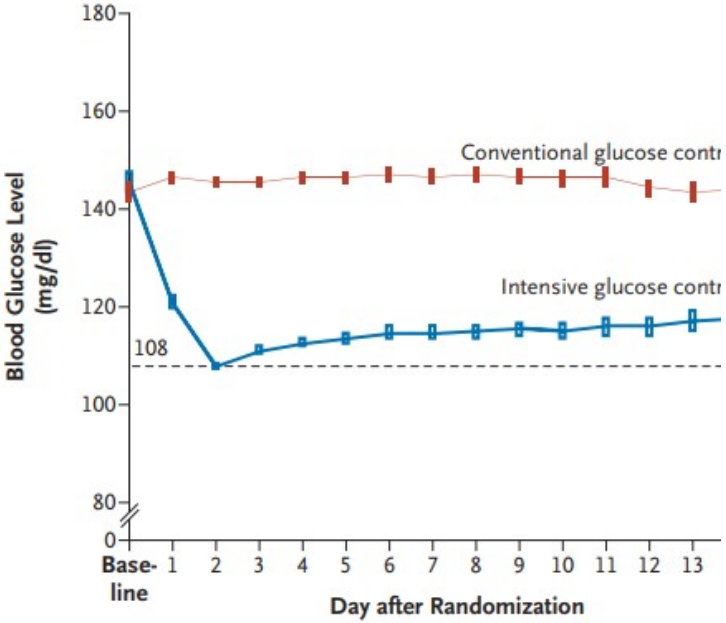
- It is not unreasonable to manage hyperglycaemia in patients with NSTE-ACS by keeping their blood glucose concentration < 200 mg/dl, while avoiding hypoglycaemia, but intensive insulin therapy should not routinely be offered unless clinically indicated

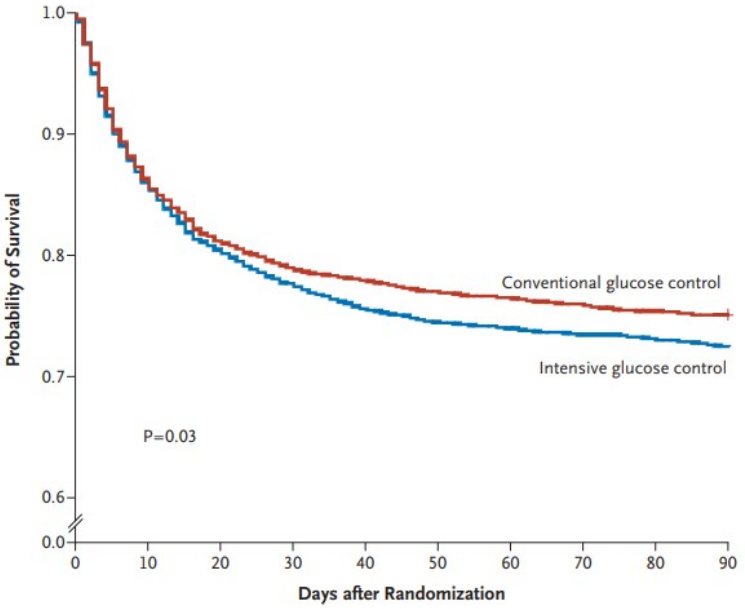
Randomized clinical studies designed to compare the effect of glucose-insulin-potassium (GIK) versus standard therapy

Clinical Trial (Year)	Number of Patients	Study Population	Admission Glycaemia	Specific Glycaemic Target	Reached Glycaemic Target (Intervention vs. Control)	Primary Endpoint	Result
ECLA-GIK (1998)	407	ACS	140 ± 15 mg/dL (7.78 ± 0.83 mmol/L; both GIK groups) vs. 143 ± 15 mg/dL (7.94 ± 0.83 mmol/L)	-	122 ± 7 mg/dL (6.78 ± 0.39 mmol/L; both GIK groups) vs. 135 ± 5 mg/dL (7.5 ± 0.28 mmol/L)	In-hospital mortality	Similar In-hospital mortality
GIPS (2003)	940	STEMI	153 mg/dL (8.5 mmol/L) in both groups	-	139 ± 10 mg/dL (7.72 ± 0.56 mmol/L) vs. 146 ± 10 mg/dL (8.11 ± 0.56 mmol/L)	30 day-Mortality	Similar 30 day-Mortality
GIPS-2 (2006)	889	STEMI (Killip Class I)	153 ± 50.4 mg/dL (8.5 ± 2.8 mmol/L) vs. 149.4 ± 45 mg/dL (8.28 ± 2.5 mmol/L)	-	-	30 day-Mortality	Similar 30 day-Mortality
CREATE-ECLA (2005)	20,201	STEMI	162 mg/dL (9 mmol/L) in both groups	-	187 mg/dL (10.39 mmol/L) vs. 148 mg/dL (8.22 mmol/L)	30 day-Mortality	Similar 30 day-Mortality
OASIS-6 GIK (2007)	2748	STEMI(14.9% vs. 14%)	-	-	-	30 day-Mortality	Similar 30 day-Mortality
IMMEDIATE (2012)	911	ACS	-	-	-	Progression to AMI, 30 day-Mortality	Similar Progression to AMI and 30 day-Mortality

Int. J. Mol. Sci. 2021, 22, 775

NICE - SUGAR





No. of Patients					
Conventional control	2995	2233	1380	909	
Intensive control	2989	2260	1428	908	562

No. at Risk				
Conventional control	3014	2379	2304	2261
Intensive control	3016	2337	2227	2182

N Engl J Med 2009;360:1283-97

COPD exacerbations in the emergency department: Epidemiology and related costs. A retrospective cohort multicentre study from the Italian Society of Emergency Medicine (SIMEU)

Characteristic	Overall (n = 4396, 34 centres) N. (%)/mean(SD)
Demographics	
Female	1706 (38.8)
Age, years	76.6 (10.6)
Medical history	
Heart failure	1162 (26.4)
Coronary artery disease	995 (22.6)
Peripheral vascular disease	502 (11.4)
Cerebrovascular disease	634 (14.4)
Diabetes without end organ damage	774 (17.6)
Diabetes with end organ damage	228 (5.2)
Moderate or severe renal disease	531 (12.1)
Connective tissue disease	97 (2.2)
Dementia	490 (11.2)
Peptic ulcer disease	245 (5.6)
Mild liver disease	177 (4.0)
Moderate or severe liver disease	25 (0.6)
Cancer	578 (13.2)
Metastatic cancer	88 (2.0)
CMI	
Class 1 (CMI 0)	1242 (28.3)
Class 2 (CMI 1–2)	1890 (43.0)
Class 3 (CMI 3–4)	833 (19.0)
Class 4 (CMI ≥ 5)	431 (9.8)

AECOPDs accounts for 0.5% of ED visits and are economically onerous.
Patients with AECOPD attending the EDs are old, frequently affected by several comorbidities, and are burdened by a high prevalence of an adverse outcome.

European Journal of Internal Medicine 51 (2018) 74–79

COPD and acute myocardial infarction

Cite this article as: Goedemans L, Bax JJ, Delgado V. COPD and acute myocardial infarction. *Eur Respir Rev* 2020; 29: 190139 [https://doi.org/10.1183/16000617.0139-2019].

In a UK registry of more than 1 million patients (among those 29 870 patients had COPD) attending primary care facilities, the prevalence of AMI was 3.5-times higher in COPD patients compared to patients without COPD (hazard ratio (95% CI) 3.53 (3.02–4.13)) [28]. A similar study performed by SCHNEIDER *et al.* [29] followed 35772 COPD patients from the moment of COPD diagnosis and an equal number of non-COPD patients for incident cardiovascular disease during follow-up. The relative risk estimate for incident AMI was 1.40-fold higher among COPD patients compared to non-COPD patients [29]. This relative risk increased up to 3.00 (95% CI 1.53–5.86) for patients with severe COPD [29].

2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: *supplementary data*

In general, oxygen administration is indicated in hypoxic patients with oxygen saturation <90% or in patients with respiratory distress. Interestingly, prior studies have suggested that hyperoxia may be harmful in some patients, presumably due to increased myocardial injury.[41] Therefore, routine oxygen administration is not recommended in cases of oxygen saturation >90%.

British Thoracic Society Guideline for oxygen use in adults in healthcare and emergency settings

B R O'Driscoll, L S Howard, J Earis and V Mak on behalf of the BTS Emergency Oxygen Guideline Development Group

If patients have COPD or other risk factors for hypercapnic respiratory failure, aim at a saturation of 88–92% pending blood gas results but adjust to 94–98% if the PCO_2 is normal (unless there is a history of respiratory failure requiring NIV or IMV) and re-check blood gases after 30–60 min, see table 4.

F13. In myocardial infarction and acute coronary syndromes, aim at an oxygen saturation of 94–98% or 88–92% if the patient is at risk of hypercapnic respiratory failure (grade D).

Beta-blockers in COPD: time for reappraisal

Editorial comment in *Eur Respir J* 2016; 48: 600–603.

Brian Lipworth[1], Jadwiga Wedzicha[2], Graham Devereux[3], Jørgen Vestbo[4] and Mark T. Dransfield[5,6]

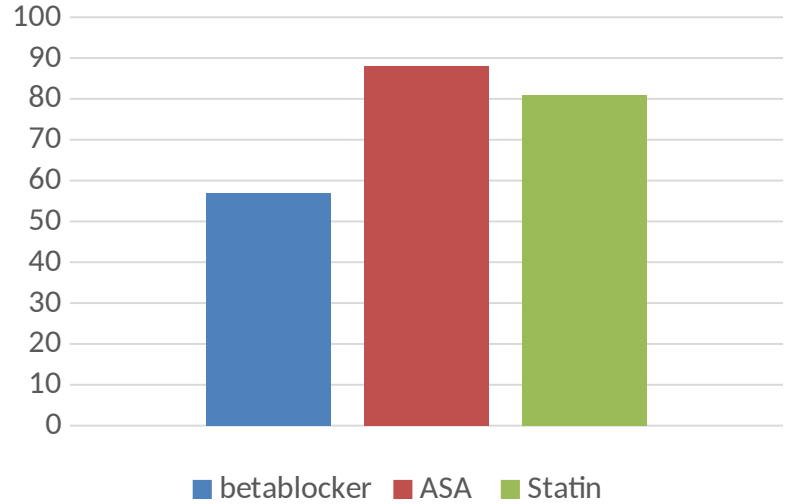
The main indications for beta-blockers in patients with COPD are post-myocardial infarction and heart failure with reduced ejection fraction. Despite clear evidence beta-blockers improve outcomes in these COPD patients they remain significantly underused due to concerns about adverse respiratory effects, even with beta-1 selective antagonists.

Meta-analyses of retrospective studies with beta-blockers in COPD have shown pooled estimates for reductions in mortality of 28% and exacerbations of 38%.

Underuse of beta-blockers by patients with COPD and co-morbid acute coronary syndrome: A nationwide follow-up study in New Zealand

- 83 435 patients aged ≥45 years, with 290 400 person-years of follow-up.

2637 patients with
≥1 ACS admission

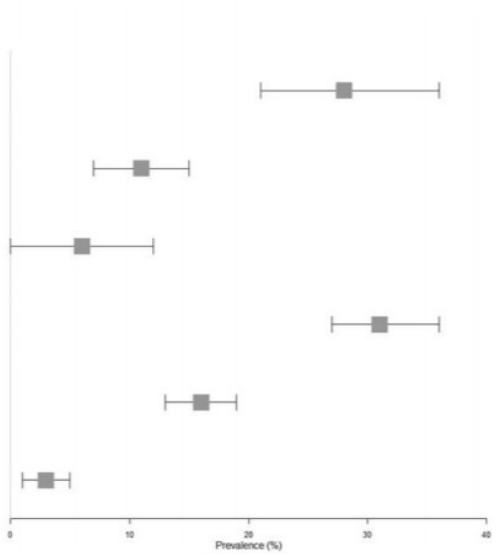


Patients with higher COPD severity were less likely to receive a beta-blocker than those with lower severity, as were those with no history of previous ACS and/or heart failure

Respirology (2020) 25, 173–182

Hypertensive emergencies and urgencies in emergency departments: a systematic review and meta-analysis

Subtype of Organ Damage	Prevalence	95% CI	I²
Ischemic Stroke	28 %	[21 - 36]	90.9 %
Haemorrhagic Stroke	11 %	[7 - 15]	87.5 %
Hypertensive Encephalopathy	6 %	[0 - 12]	99.4 %
Pulmonary Oedema / Heart Failure	31 %	[27 - 36]	77.5 %
Acute Coronary Syndrome	16 %	[13 - 19]	69.9 %
Acute Aortic Syndrome	3 %	[1 - 5]	84.8 %



Journal of Hypertension 2020, 38:1203–1210

Hypertensive emergencies and urgencies: a single-centre experience in Northern Italy 2008–2015

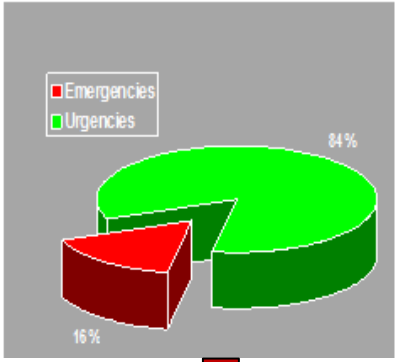
Journal of Hypertension 2019, 37:000–000

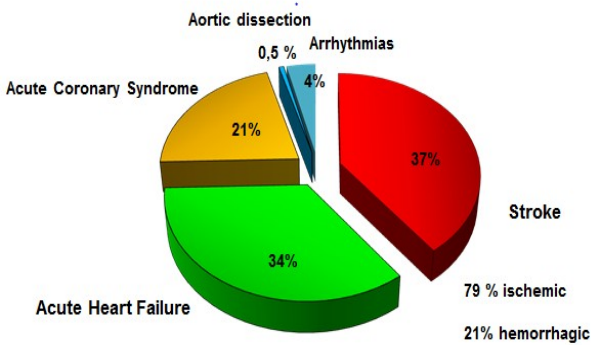
Massimo Salvetti, Anna Paini, Efrem Colonetti, Luca Tarozzi, Fabio Bertacchini, Carlo Aggiusti, Deborah Stassaldi, Claudia Agabiti Rosei, Enrico Agabiti Rosei, and Maria Lorenza Muiesan

69101 patients admitted to ED University Hospital Brescia during the year 2015

Age 70 ± 15 yrs,
range 21-99
M 41 %; females 59 %

1214 (1,75 %) patients with hypertensive emergencies or urgencies included in the study





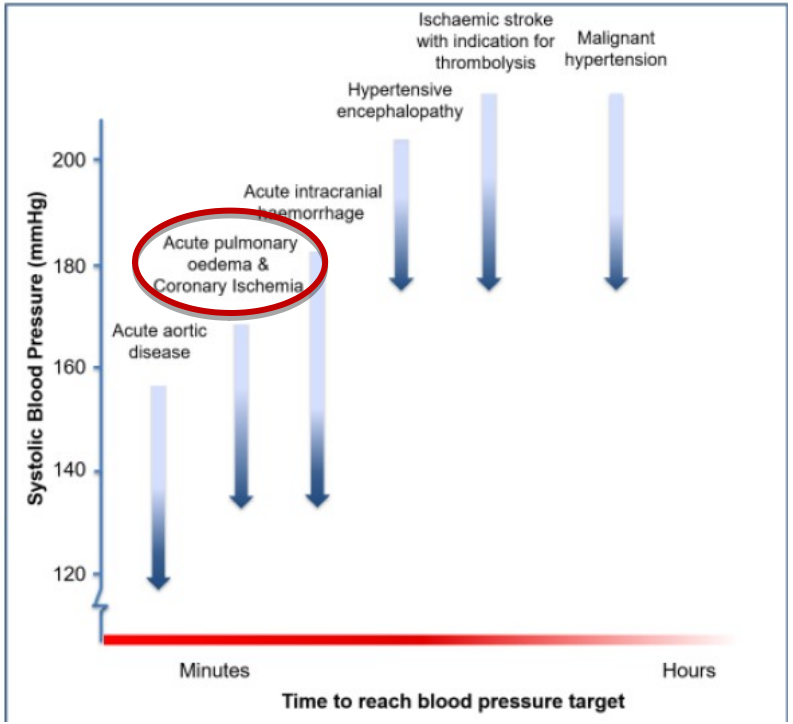
Acute HT mediated organ damage

Aorta – dissection, aneurysm

Heart – MACE, acute pulmonary oedema

Brain – stroke, HT encephalopathy

Retina & Kidneys – malignant hypertension



•ESH/ESC guidelines 2018 and ESC/ESH position paper *Eur Heart J Cardiovasc Pharmacother. 2018*

5.1 Pharmacological treatment of ischaemia

5.1.1 General supportive measures

The goal of pharmacological anti-ischaemic therapy is to decrease myocardial oxygen demand (secondary to a decrease in heart rate, blood pressure, preload or myocardial contractility) or to increase myocardial oxygen supply (by administration of oxygen or through coronary vasodilation) *European Heart Journal 2016*

Recommendations	Class[a]	Level[b]
Early initiation of beta-blocker treatment is recommended in patients with ongoing ischaemic symptoms and without contraindications.	I	B
It is recommended to continue chronic beta-blocker therapy, unless the patient is in Killip class III or higher.	I	B
Sublingual or i.v. nitrates are recommended to relieve angina;[d] i.v. treatment is recommended in patients with recurrent angina, uncontrolled hypertension or signs of heart failure.	I	C

Indication	Drugs	Goal of treatment	BP goal
Acute coronary syndrome + HT Emergency	Nitroglycerin, (sodium nitroprusside), labetalol, metoprolol, esmolol, nicardipine	Reduce cardiac workload and improve coronary perfusion	Reduce ~ 25 % of baseline BP in 3-4 hours

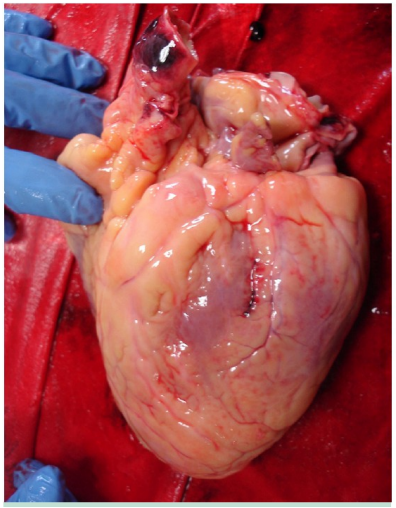
Muiesan ML et al J Cardiovasc Med 2015

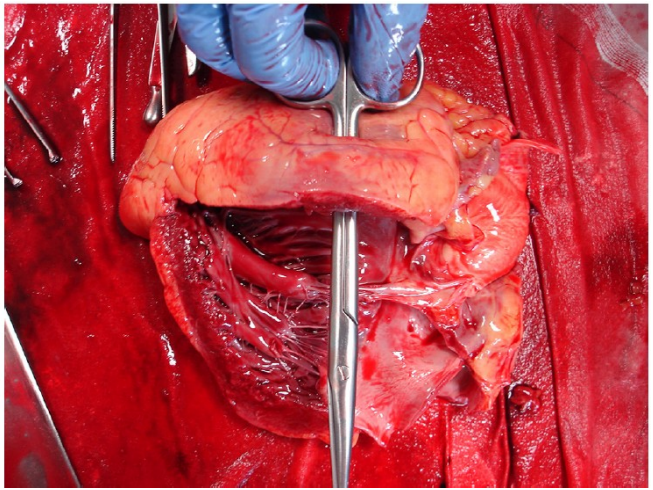
Cardiac Rupture in a Young Male Cocaine User

THE AMERICAN JOURNAL of MEDICINE®

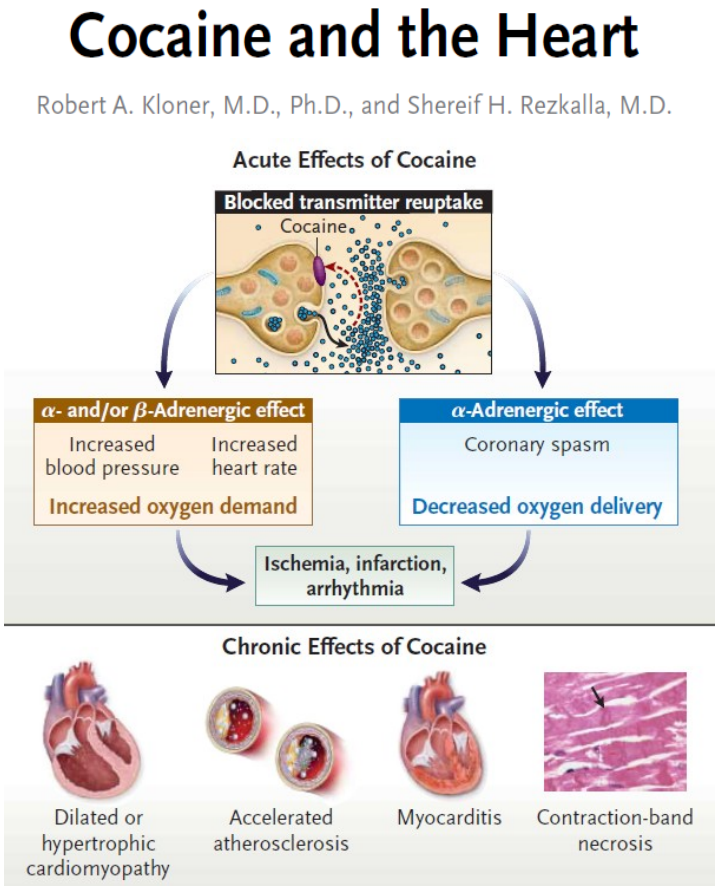
Adelaide Conti, Anna Paini, Chiara Rossetti, Marzia Bernini, Maria Lorenza Muiesan, Massimo Salvetti

A 25-year-old man was found unconscious by his wife in the bathroom of his apartment. She called emergency services and cardiopulmonary resuscitation was promptly initiated within a few minutes. The patient was intubated, transferred to the Emergency Department (ED) of a local hospital, and after 1 hour of advanced cardiac life support he was pronounced dead. His relatives reported a history of cocaine abuse; he had complained of epigastric discomfort during the previous 2 days





The American Journal of Medicine, Vol 131, No 5, May 2018



Treatment

- **nitroglycerin, oxygen, aspirin, benzodiazepines, or calcium antagonists, alpha blockers**
- **Beta-blockers should be administered with caution, since their use may worsen vasospasm** by allowing unopposed stimulation of alpha receptors.

New England Journal of Medicine, 348;6

Conclusioni

- I pazienti con SCA sono frequentemente affetti da altre malattie che condizionano l'approccio diagnostico e terapeutico
- La presenza di comorbidità dovrebbe essere sempre considerata per ottimizzare il trattamento, allo scopo di migliorare la sopravvivenza del paziente, sia per quanto riguarda la/e malattia/e preesistenti che l'evento coronarico acuto

SCOMPENSO CARDIACO nella SCA

Terapia in acuto: ossigeno

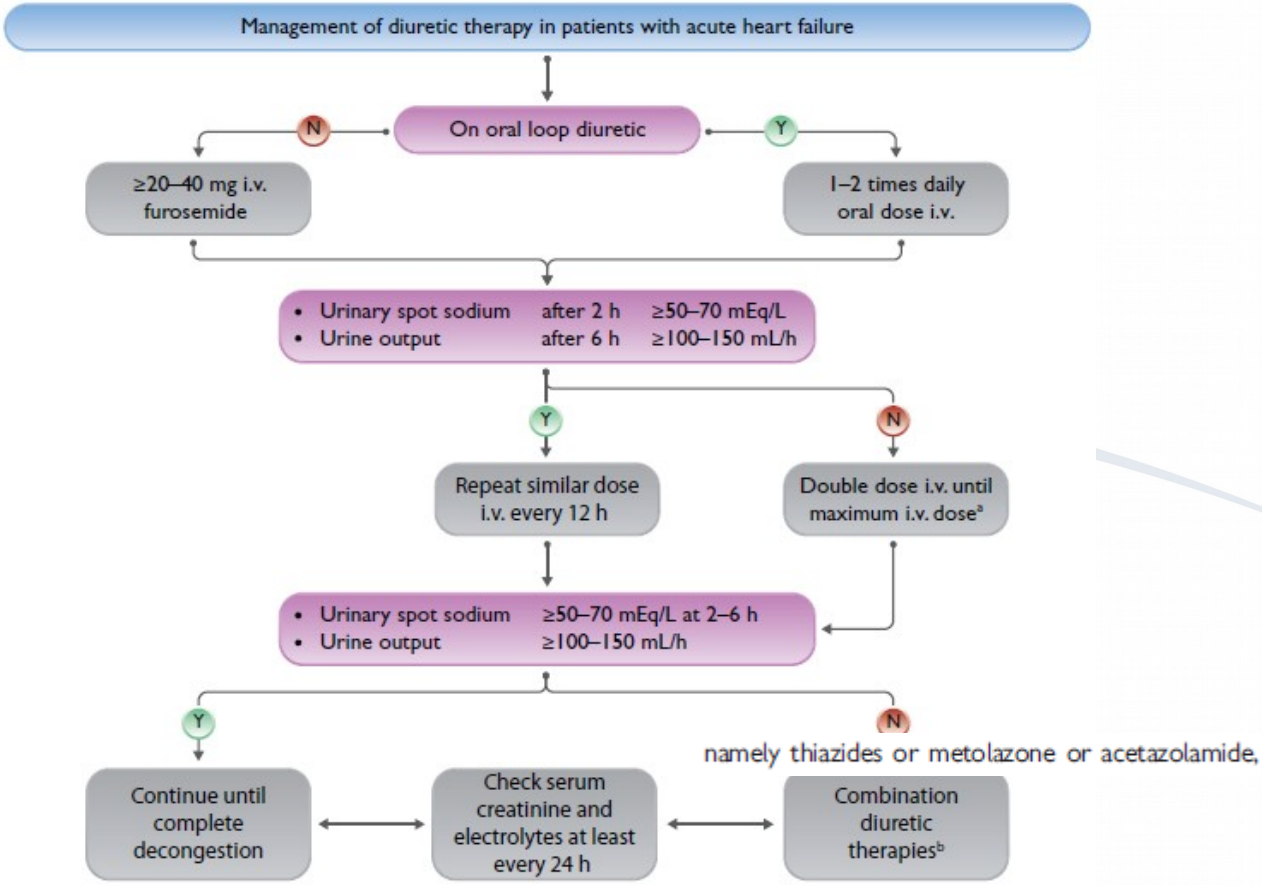
2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

Oxygen is recommended in patients with SpO_2 <90% or PaO_2 <60 mmHg to correct hypoxaemia.	I	C
Non-invasive positive pressure ventilation should be considered in patients with respiratory distress (respiratory rate >25 breaths/min, SpO_2 <90%) and started as soon as possible in order to decrease respiratory distress and reduce the rate of mechanical endotracheal intubation.[448]	IIa	B

In AHF, oxygen should not be used routinely in non-hypoxaemic patients, as it causes vasoconstriction and a reduction in cardiac output.[457]

SCOMPENSO CARDIACO nella SCA

Terapia in acuto: diuretici sì, ma quanto?



SCOMPENSO CARDIACO nella SCA

Terapia in acuto: vasodilatatori

Intravenous vasodilators may be considered to relieve AHF symptoms when SBP is >110 mmHg. They may be started at low doses and uptitrated to achieve clinical improvement and BP control. Nitrates are generally administered with an initial bolus followed by continuous infusion. However, they may also be given as repeated boluses. Nitroglycerine can be given as 1—2 mg boluses in severely hypertensive patients with acute pulmonary oedema.

Controindicata se :

- Ipotensione
- Sospetto infarto ventricolo destro
- Bradicardia o tachicardia marcate
- Utilizzo inibitori fosfodiesterasi nelle 24 ore precedenti
- Cardiomiopatia ipertrofica
- Stenosi aortica grave

SCOMPENSO CARDIACO nella SCA

Terapia in acuto: oppioidi

2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation

Severely symptomatic patients with pulmonary congestion may also need i.v. morphine to reduce dyspnoea and anxiety, but routine use is not recommended due to concerns about its safety, as it may induce nausea and hypopnea.

SCOMPENSO CARDIACO nella SCA

Terapia in acuto: inotropi

2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation

Dobutamine is the initial therapy for patients with predominant low cardiac output, whereas norepinephrine may be safer and more effective than dopamine in patients with cardiogenic shock and severe hypotension.[428]

2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

Inotropic agents		
Inotropic agents may be considered in patients with SBP <90 mmHg and evidence of hypoperfusion who do not respond to standard treatment, including fluid challenge, to improve peripheral perfusion and maintain end-organ function.[387]	IIb	C
Vasopressors		
A vasopressor, preferably norepinephrine, may be considered in patients with cardiogenic shock to increase blood pressure and vital organ perfusion.[485–487]	IIb	B

The ESC Textbook of Intensive and Acute Cardiovascular Care (2 ed.)

ACCA
Acute Cardiovascular Care Association
European Society of Cardiology

Norepinephrine should be titrated, until the systolic arterial pressure rises to at least 80 mmHg. Subsequently, IV dobutamine, due to its β2-adrenergic effects, may be given simultaneously, in an attempt to improve cardiac contractility [48].

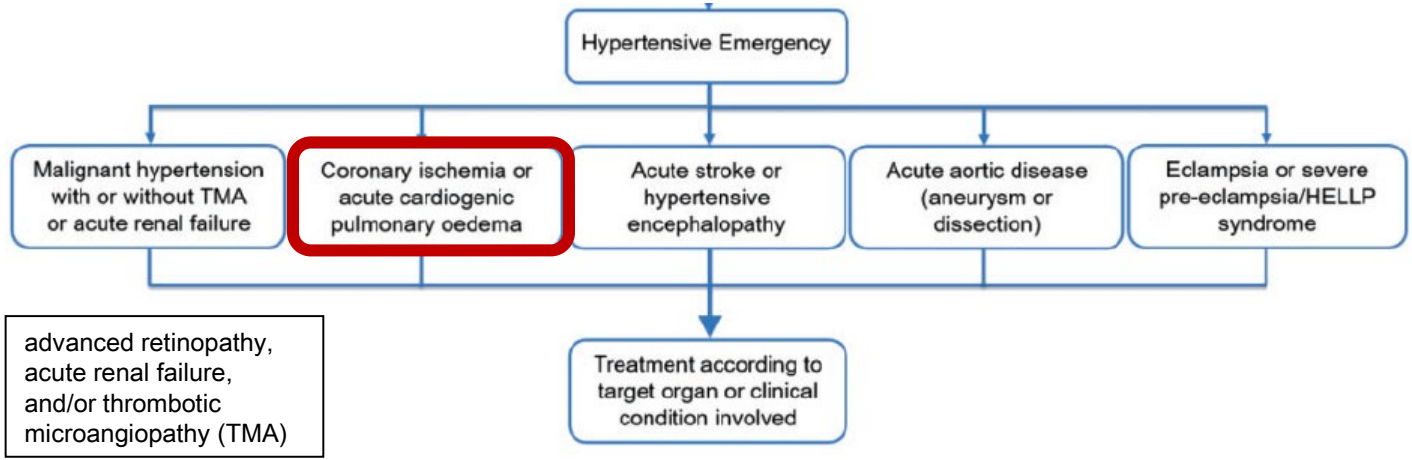
Acute heart failure

- The diagnosis of NSTE-ACS in the context of acute heart failure can be challenging because patients with acute heart failure
  - may present with chest discomfort
  - myocardial injury with troponin elevation can occur in the absence of obstructive CAD
  - the ECG may not be interpretable (bundle branch block or paced rhythm).
- Consequently, coronary angiography may be required to establish a diagnosis of NSTE-ACS

Acute HF during ACS

- The management of acute heart failure should follow current guideline recommendations.
- Emergency echocardiography should be performed to gather information about the LVEF, regional wall motion abnormalities, right ventricular function, presence of valvular heart disease, and volume loading.
- The revascularization strategy should be based on the coronary anatomy, LV function, comorbidities, functional relevance of stenoses, and estimated surgical risk according to a Heart Team consensus, and based upon current recommendations.

Stratification of hypertensive emergencies according to the condition or target organ involved



Acute and severe increases in BP can be precipitated by pheochromocytoma or by ingestion of sympathomimetics (meta-amphetamine or cocaine.)
This can result in a hypertension emergency when there is evidence of acute HMOD

van den Born BH et al, Eur Heart J Cardiovasc Pharmacother. 2018

In-hospital po/iv beta-blocker		*N*	iv/po beta-blocker (%)	Crude OR	95% CI	Adjusted OR	95% CI
eGFR	≥90	10 106	37.2	1.00	–	1.00	–
	60–89	18 485	36.4	0.96	0.92–1.01	1.04	0.98–1.09
	30–59	7340	34.9	0.87	0.82–0.93	1.13	1.05–1.21
	15–29	825	26.5	0.59	0.51–0.68	0.87	0.73–1.02
	<15/dialysis	417	25.7	0.60	0.51–0.68	0.82	0.65–1.03
Revascularization in NSTEMI		*N*	Revascularized (%)	Crude OR	95% CI	Adjusted OR	95% CI
eGFR	≥90	5607	62.8	1.00	–	1.00	–
	60–89	10 558	56.1	0.74	0.70–0.79	0.92	0.85–0.99
	30–59	4329	36.7	0.33	0.31–0.36	0.68	0.62–0.75
	15–29	510	14.3	0.10	0.08–0.13	0.28	0.21–0.37
	<15/dialysis	301	15.6	0.15	0.09–0.15	0.24	0.17–0.34
iv heparin/sc LMWH in NSTEMI		*N*	iv heparin/sc LMWH (%)	Crude OR	95% CI	Adjusted OR	95% CI
eGFR	≥90	5593	87.0	1.00	–	1.00	–
	60–89	10 494	86.3	0.92	0.84–1.01	0.99	0.90–1.10
	30–59	4307	81.3	0.66	0.59–0.73	0.87	0.77–0.99
	15–29	506	73.1	0.41	0.34–0.50	0.67	0.53–0.85
	<15/dialysis	299	66.2	0.29	0.23–0.37	0.41	0.31–0.54

BPCO e SCA

Ossigeno?

British Thoracic Society Guideline for oxygen use in adults in healthcare and emergency settings

B R O'Driscoll, L S Howard, J Earis and V Mak on behalf of the BTS Emergency Oxygen Guideline Development Group

If patients have COPD or other risk factors for hypercapnic respiratory failure, aim at a saturation of 88–92% pending blood gas results but adjust to 94–98% if the PCO_2 is normal (unless there is a history of respiratory failure requiring NIV or IMV) and re-check blood gases after 30–60 min, see table 4.

F13. In myocardial infarction and acute coronary syndromes, aim at an oxygen saturation of 94–98% or 88–92% if the patient is at risk of hypercapnic respiratory failure (grade D).

Drug	Onset of action	Duration of action	Dose	Contraindications	Adverse effects
Esmolol	1–2 min	10–30 min	0.5–1 mg/kg as bolus; 50–300 mg/kg/min as continuous infusion	History of 2nd or 3rd degree AV block (and in the absence of rhythm support), systolic heart failure, asthma, and bradycardia	Bradycardia
Metoprolol	1–2 min	5–8 h	15 mg intravenous (iv), usually given as 5 mg iv, and repeated at 5 min intervals as needed	History of 2nd or 3rd degree AV block, systolic heart failure, asthma, and bradycardia	Bradycardia
Labetalol	5–10 min	3–6 h	0.25–0.5 mg/kg; 2–4 mg/min until goal BP is reached, thereafter 5–20 mg/h	History of 2nd or 3rd degree AV block, systolic heart failure, asthma, and bradycardia	Bronchoconstriction and foetal bradycardia

DM 2

2020 ESC Guidelines N-STEMI

Patients with diabetes more frequently present with non-typical symptoms than patients without diabetes.

They more frequently have multifocal CAD, less frequently receive guideline-indicated care, and have worse clinical outcomes.

The selection of antithrombotics and an invasive strategy should not differ from those without diabetes.

Compared with clopidogrel, more potent platelet inhibitors have higher absolute risk reductions in patients with diabetes.

DM 2

2020 ESC Guidelines N-STEMI

In critically ill patients, there is a risk of hypoglycaemia-related events when using intensive insulin therapy.

It is not unreasonable to manage hyperglycaemia in patients with NSTE-ACS by keeping their blood glucose concentration <200 m/dl.

Recommendations for diabetes mellitus in non-ST-segment elevation acute coronary syndrome patients

Recommendations	Class[a]	Level[b]
It is recommended to screen all patients with NSTE-ACS for diabetes and to monitor blood glucose levels frequently in patients with known diabetes or admission hyperglycaemia.	I	C
Avoidance of hypoglycaemia is recommended.[424–427]	I	B
Glucose-lowering therapy should be considered in ACS patients with blood glucose >10 mmol/L (>180 mg/dL), with the target adapted to comorbidities, while episodes of hypoglycaemia should be avoided.[422,428–430]	IIa	B
A multifactorial approach to diabetes mellitus management, with treatment targets, should be considered in patients with diabetes and CVD.[431–436]	IIa	B
Less stringent glucose control should be considered, both in the acute phase and at follow-up, in patients with more advanced CVD, older age, longer diabetes duration, and more comorbidities.	IIa	C

ACS = acute coronary syndromes; CVD = cardiovascular disease; NSTE-ACS = non-ST-segment elevation acute coronary syndrome.
[a]Class of recommendation.
[b]Level of evidence.

DM 2

2019 ESC Guidelines **on Diabetes, Pre-Diabetes and Cardiovascular Diseases**

There is evidence that improved glycaemic control defers the onset, reduces the progression, and (in some circumstances) may partially reverse markers of microvascular complications in patients with DM.

Achieving this without detriment and with benefit to the CV system is an important challenge, particularly when selecting glucoselowering therapies to suit the individual.

Recommendations for glucose-lowering treatment for patients with diabetes

Recommendations	Class[a]	Level[b]
SGLT2 inhibitors		
Empagliflozin, canagliflozin, or dapagliflozin are recommended in patients with T2DM and CVD, or at very high/high CV risk,[c] to reduce CV events.[306,308,309,311]	I	A
Empagliflozin is recommended in patients with T2DM and CVD to reduce the risk of death.[306]	I	B
GLP1-RAs		
Liraglutide, semaglutide, or dulaglutide are recommended in patients with T2DM and CVD, or at very high/high CV risk,[c] to reduce CV events.[176,299–300,302–303]	I	A
Liraglutide is recommended in patients with T2DM and CVD, or at very high/high CV risk,[c] to reduce the risk of death.[176]	I	B
Biguanides		
Metformin should be considered in overweight patients with T2DM without CVD and at moderate CV risk.[146,149]	IIa	C
Insulin		
Insulin-based glycaemic control should be considered in patients with ACS with significant hyperglycaemia (>10 mmol/L or >180 mg/dL), with the target adapted according to comorbidities.[260–262]	IIa	C
Thiazolidinediones		
Thiazolidinediones are not recommended in patients with HF.	III	A
DPP4 inhibitors		
Saxagliptin is not recommended in patients with T2DM and a high risk of HF.[291]	III	B

ACS = acute coronary syndromes; CV = cardiovascular; CVD = cardiovascular disease; DM = diabetes mellitus; DPP4 = dipeptidyl peptidase-4; GLP1-RA = glucagon-like peptide-1 receptor agonist; HF = heart failure; SGLT2 = sodium-glucose co-transporter 2; T2DM = type 2 diabetes mellitus.

[a]Class of recommendation.

[b]Level of evidence.

[c]See *Table 7*.

DM 2 - CKD

PLATO TRIAL (Platlet Inhibition And Patient Outcomes trial)

Patients with diabetes mellitus (DM) are at increased risk of atherothrombotic events.
DM is a key risk factor for the development of chronic kidney disease (CKD), a well-known cardiovascular risk factor.

The PLATO trial was conducted from October 2006 to February 2009 and randomly assigned 18 624 patients with ST-segment–elevation myocardial infarction (MI), non-ST–segment elevation MI, or unstable angina, treated with an invasive or a noninvasive approach, to receive either ticagrelor or clopidogrel as soon as possible after admission

A post hoc analysis of the PLATO (Platelet Inhibition and Patient Outcomes) trial, was conducted to assess clinical outcomes in ACS patients according to the presence or absence of DM and CKD, as well as the differential effects of P2Y12-inhibiting therapies (ticagrelor versus clopidogrel) in these populations.

DM 2 - CKD

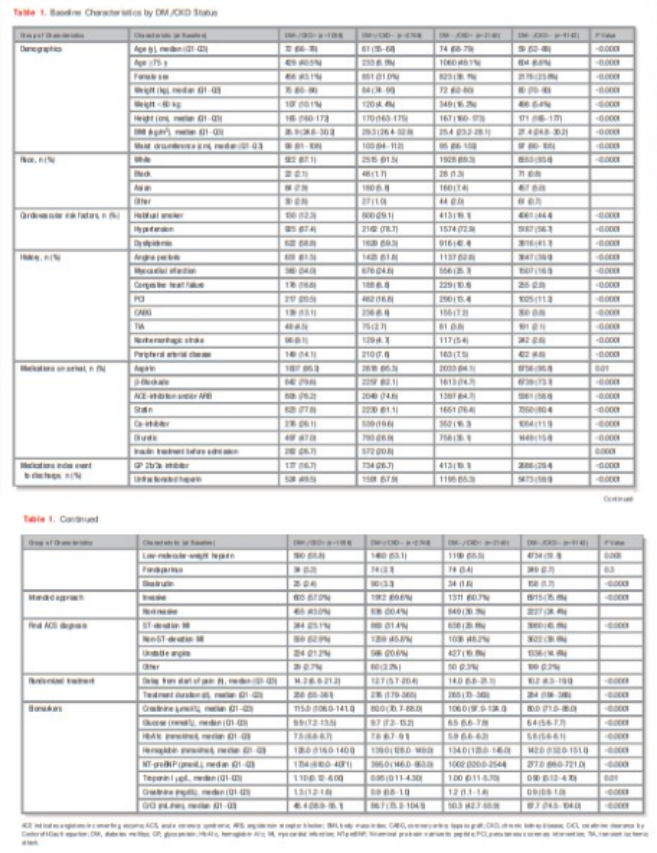
PLATO TRIAL (Platlet Inhibition And Patient Outcomes trial)

Patients randomized in PLATO with available DM and CKD status at the time of randomization were included in the present analysis. Accordingly, patients were classified into 4 groups:

DM+/CKD+ DM+/CKD DM/CKD+ DM/CKD

The primary efficacy end point was a composite of cardiovascular death, myocardial infarction, or stroke at 12 months.

The primary safety end point was PLATO major bleeding



DM 2 - CKD

PLATO TRIAL results

The concomitant presence of CKD and DM is not uncommon in patients with ACS, representing 7% of the overall study population;

Patients with CKD and DM are more likely to already have established atherosclerotic disease, more frequently present with a non-ST-elevation ACS and are more likely to be treated with a noninvasive approach

Table 1. Continued

Group of Characteristics	Characteristic (at Baseline)	DM+/CKD+ (n=1084)	DM+/CKD− (n=2740)	DM−/CKD+ (n=2149)	DM−/CKD− (n=9140)	P Value
	Low-molecular-weight heparin	590 (55.0)	1460 (53.1)	1199 (55.5)	4734 (51.8)	0.003
	Fondaparinux	36 (3.3)	74 (2.7)	74 (3.4)	369 (4.0)	0.3
	Bivalirudin	25 (2.4)	90 (3.3)	34 (1.6)	158 (1.7)	<0.0001
Intended approach	Invasive	603 (57.0%)	1912 (69.6%)	1311 (60.7%)	6815 (75.6%)	<0.0001
	Noninvasive	455 (43.0%)	836 (30.4%)	849 (39.3%)	2227 (24.4%)	
Final ACS diagnosis	ST-elevation MI	384 (23.1%)	860 (31.4%)	638 (29.6%)	3060 (40.6%)	<0.0001
	Non-ST-elevation MI	559 (52.9%)	1259 (45.6%)	1036 (48.2%)	3622 (39.6%)	
	Unstable angina	224 (21.2%)	566 (20.6%)	427 (19.8%)	1536 (16.8%)	
	Other	29 (2.7%)	60 (2.2%)	50 (2.3%)	159 (2.2%)	
Randomized treatment	Delay from start of pain (h), median (Q1-Q3)	14.2 (6.5-21.2)	12.7 (5.7-20.4)	14.0 (6.8-21.1)	10.2 (4.3-19.0)	<0.0001
	Treatment duration (d), median (Q1-Q3)	256 (55-360)	236 (179-360)	265 (35-360)	284 (98-366)	<0.0001
Biomarkers	Creatinine (μmol/L), median (Q1-Q3)	115.0 (106.0-141.0)	80.0 (70.7-88.0)	106.0 (97.0-138.0)	80.0 (71.0-88.0)	<0.0001
	Glucose (mmol/L), median (Q1-Q3)	9.9 (7.2-13.5)	9.7 (7.2-13.2)	6.5 (5.6-7.9)	6.4 (5.6-7.7)	<0.0001
	HbA1c (mmol/mol), median (Q1-Q3)	7.5 (6.6-8.7)	7.6 (6.7-9.1)	5.9 (5.6-6.2)	5.8 (5.6-6.1)	<0.0001
	Hemoglobin (mmol/mol), median (Q1-Q3)	128.0 (116.0-140.0)	139.0 (129.0-149.0)	134.0 (123.0-146.0)	142.0 (132.0-151.0)	<0.0001
	NT-proBNP (pmol/L), median (Q1-Q3)	1354 (600.0-4071)	395.0 (146.0-953.0)	1002 (320.0-2544)	277.0 (66.0-721.0)	<0.0001
	Troponin I (μg/L, median (Q1-Q3)	1.10 (0.12-6.00)	0.05 (0.11-4.30)	1.00 (0.11-5.70)	0.50 (0.12-4.70)	0.01
	Creatinine (mg/dL), median (Q1-Q3)	1.3 (1.2-1.6)	0.9 (0.8-1.0)	1.2 (1.1-1.4)	0.9 (0.8-1.0)	<0.0001
	CrCl (mL/min), median (Q1-Q3)	46.4 (38.9-56.1)	86.7 (75.3-104.5)	50.3 (42.7-60.9)	87.7 (74.5-104.0)	<0.0001

ACE indicates angiotensin-converting enzyme; ACS, acute coronary syndrome; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass graft; CKD, chronic kidney disease; CrCl, creatinine clearance by Cockcroft-Gault equation; DM, diabetes mellitus; GP, glycoprotein; HbA1c, hemoglobin A1c; MI, myocardial infarction; NT-proBNP, N-terminal pro-brain natriuretic peptide; PCI, percutaneous coronary intervention; TIA, transient ischemic

DM 2 - CKD

PLATO TRIAL outcomes

Compared with clopidogrel, ticagrelor significantly reduced the incidence of the primary end point consistently across subgroups (P interaction=0.3).

However, the absolute risk reduction (ARR) with ticagrelor versus clopidogrel was considerably higher in DM+/CKD+ patients (11.26%; adjusted HR 0.78; 95% CI 0.61–1.01) compared with DM/CKD (1.37%; adjusted HR 0.86; 95% CI 0.73–1.00)

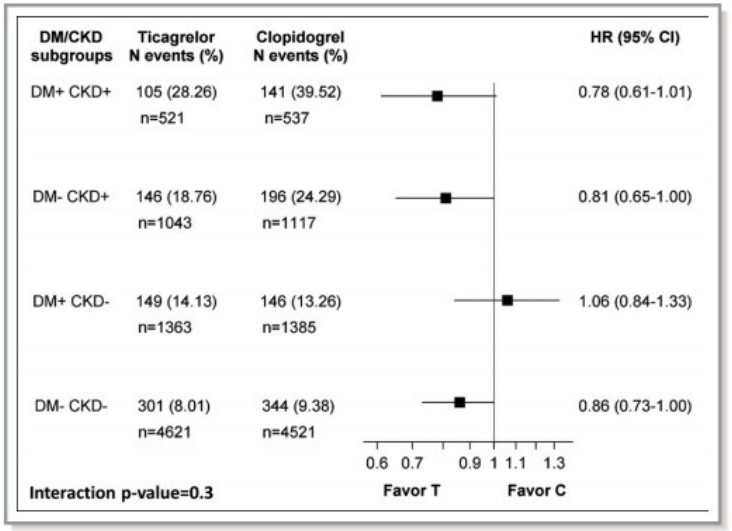


Figure 5. Hazard ratios (HR) with 95% CI for the primary composite end point (cardiovascular death, myocardial infarction, and stroke) of ticagrelor (T) vs clopidogrel (C) stratified by DM/CKD status. The model is adjusted for age, sex, body mass index, heart rate, prior myocardial infarction, hypertension, dyslipidemia, angina pectoris, smoking status, previous percutaneous coronary intervention or coronary artery bypass graft, type of acute coronary syndrome, and randomized treatment. CKD indicates chronic kidney disease; DM, diabetes mellitus.

DM 2 - CKD

PLATO TRIAL results

There was no increased risk of bleeding with ticagrelor in patients with CKD and DM as compared with the other subgroup

Table 2. Ischemic and Bleeding Outcomes According to DM/CKD Subgroup, With Poor Glycemic Control Defined by HbA1c and CKD Defined by the Creatinine-Cystatin C CKD-EPI Equation

DM/CKD Subgroup	No. of Events	No. of Patients	Event Rate (%)*	HR (95% CI)†	P Value‡
Cardiovascular death/MI/stroke					
DM−/CKD−	392	1264	6.9		<0.0001
DM+/CKD−	580	5726	10.1	1.33 (1.16–1.52)	
DM−/CKD+	123	734	16.8	1.72 (1.39–2.13)	
DM+/CKD+	263	1264	20.8	2.09 (1.76–2.49)	
Cardiovascular death					
DM−/CKD−	121	5673	2.1		<0.0001
DM+/CKD−	215	5726	3.8	1.54 (1.23–1.94)	
DM−/CKD+	65	734	8.9	2.50 (1.81–3.44)	
DM+/CKD+	155	1264	12.3	3.44 (2.64–4.48)	
MI					
DM−/CKD−	258	5673	4.5		<0.0001
DM+/CKD−	357	5726	6.2	1.24 (1.05–1.47)	
DM−/CKD+	69	734	9.4	1.60 (1.21–2.12)	
DM+/CKD+	130	1264	10.3	1.66 (1.32–2.10)	
All-cause death					
DM−/CKD−	145	5673	2.6		<0.0001
DM+/CKD−	238	5726	4.2	1.45 (1.17–1.79)	
DM−/CKD+	72	734	9.8	2.21 (1.63–2.99)	
DM+/CKD+	174	1264	13.8	3.19 (2.49–4.08)	
Stroke					
DM−/CKD−	46	5673	0.8		0.1679
DM+/CKD−	74	5726	1.3	1.43 (0.98–2.08)	
DM−/CKD+	11	734	1.5	1.15 (0.58–2.29)	
DM+/CKD+	27	1264	2.1	1.67 (0.99–2.81)	
Major bleeding					
DM−/CKD−	484	5673	8.5		0.0039
DM+/CKD−	629	5726	11.0	1.26 (1.11–1.42)	
DM−/CKD+	86	734	11.7	1.14 (0.90–1.45)	
DM+/CKD+	148	1264	11.7	1.14 (0.94–1.39)	
Non-CABG-related major bleeding					
DM−/CKD−	161	5673	2.8		0.0070
DM+/CKD−	180	5726	3.1	1.00 (0.81–1.25)	
DM−/CKD+	44	734	6.0	1.34 (0.94–1.91)	
DM+/CKD+	88	1264	7.0	1.55 (1.16–2.07)	
CABG-related major bleeding					
DM−/CKD−	367	5628	6.5		0.1678
DM+/CKD−	366	5673	6.5	1.02 (0.88–1.18)	
DM−/CKD+	44	727	6.1	0.96 (0.69–1.32)	
DM+/CKD+	96	1250	7.7	1.29 (1.01–1.65)	

The model is adjusted for age, sex, BMI, heart rate, prior myocardial infarction, hypertension, dyslipidemia, angina pectoris, smoking status, previous PCI or CABG, type of ACS define and randomized treatment. BMI indicates body mass index; CABG, coronary artery bypass graft; CKD, chronic kidney disease; CKD-EPI, chronic kidney disease epidemiology collaboration; DM, diabetes mellitus; HbA1c, hemoglobin A1c; HR, hazard ratio; MI, myocardial infarction; PCI, percutaneous coronary intervention.

*The crude event rate, [no. events/no. of subjects(×100%.

†Subgroup DM−/CKD− is the reference category.

‡P value for the effect of DM/CKD subgroup.

DM 2 - CKD

PLATO TRIAL conclusion

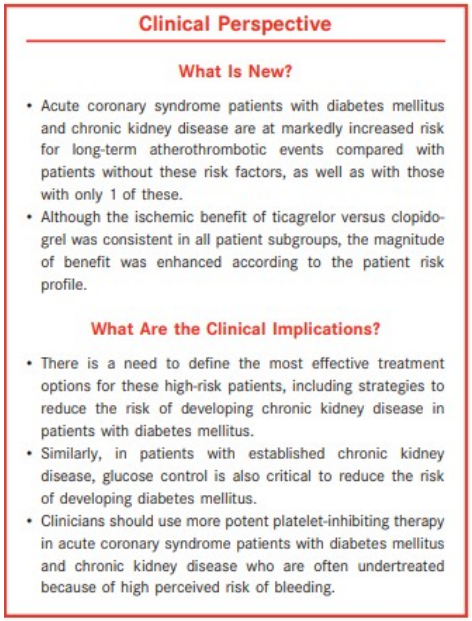
Subgroup analysis of major clinical trials have shown a reduced benefit of clopidogrel in CKD patients.

Patients with CKD are characterized by upregulation of the P2Y12 signaling pathway induced by dinucleoside polyphosphates and impaired hepatic function, which can potentially impact clopidogrel metabolism.

Ticagrelor is characterized by more potent and predictable antiplatelet effects compared with clopidogrel, which translate into better clinical outcomes in ACS patients

DM 2 - CKD

PLATO TRIAL clinical prespective



Clinical Perspective

What Is New?

- Acute coronary syndrome patients with diabetes mellitus and chronic kidney disease are at markedly increased risk for long-term atherothrombotic events compared with patients without these risk factors, as well as with those with only 1 of these.
- Although the ischemic benefit of ticagrelor versus clopidogrel was consistent in all patient subgroups, the magnitude of benefit was enhanced according to the patient risk profile.

What Are the Clinical Implications?

- There is a need to define the most effective treatment options for these high-risk patients, including strategies to reduce the risk of developing chronic kidney disease in patients with diabetes mellitus.
- Similarly, in patients with established chronic kidney disease, glucose control is also critical to reduce the risk of developing diabetes mellitus.
- Clinicians should use more potent platelet-inhibiting therapy in acute coronary syndrome patients with diabetes mellitus and chronic kidney disease who are often undertreated because of high perceived risk of bleeding.

DM is a key risk factor for the development of CKD.

One third of DM patients are found to have CKD. Therefore, with the increasing prevalence of DM, which is expected to double over the next 20 years, the prevalence of CKD is also expected to rise.

These observations underscore the need for defining the most effective treatment options for these high-risk patients, including strategies to reduce the risk of developing CKD in patients with DM.

Sodium-glucose cotransporter-2 inhibitors are new antihyperglycemic therapies known to reduce long-term decline in kidney function.

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ESC GUIDELINES NSTEMI 2020

Prevalence of **thrombocytopenia in ACS patients: 5-13%**

The presence of thrombocytopenia in ACS patients predicts significantly worse outcomes

8.5 Thrombocytopenia

Thrombocytopenia in the context of NSTE-ACS is an independent predictor of poor outcomes, including death, major bleeds, and life-threatening prothrombotic events.[167–170] Clinically significant thrombocytopenia is defined as a platelet count ≤100 000/mL or a relative drop of 50% from baseline. Causes include haemodilution, in vitro artefacts, increased platelet consumption/sequestration/destruction, and decreased platelet production.[170] Blood sampling should be in non-ethylenediaminetetraacetic acid tubes, as ethylene-diaminetetraacetic acid may lead to platelet clumping and pseudo-thrombocytopenia.[170]

2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation

- Increased risk of adverse outcomes, **regardless of the etiology of the low platelet count**, particularly death and bleeding, in this population of cardiac patients.
- **Bleeding strong independent predictor of an adverse event**
- Thrombocytopenia may be a marker for acuity of illness and often may be only an association between a low platelet count and therapeutic interventions in this population. **Treatment strategies**, both medical and mechanical, may cause thrombocytopenia.

Evaluation of thrombocytopenia in the acute coronary syndrome
William H. Matthai Jr
Current Opinion in Hematology 2010, 17:398–404

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MANAGEMENT

ESC European Society of Cardiology
European Heart Journal (2017) **38**, 3488–3492
doi:10.1093/eurheartj/ehx531

CURRENT OPINION
Acute coronary syndromes

The management of antiplatelet therapy in acute coronary syndrome patients with thrombocytopenia: a clinical conundrum

Table 2 Strategies to minimize bleeding risk in patients with significant thrombocytopenia

- Avoid non-steroidal anti-inflammatory drugs
- Avoid glycoprotein IIb/IIIa inhibitors
- Utilize a proton pump inhibitor unless contraindicated
- Aspirin should be used in low-dose form
- If a patient is already receiving a long-term anticoagulation agent, triple therapy should be avoided
- If a patient is undergoing percutaneous coronary intervention:
  - Radial approach preferred to femoral approach
  - Restrict dual antiplatelet therapy to 1 month post-stent
  - Second generation drug-eluting stent preferred to bare-metal stent

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. Risks of inpatient mortality and bleeding correlated directly with severity of thrombocytopenia and even mild thrombocytopenia (platelet nadir 100 to 149×10^9/L) was associated with increased risks of mortality [adjusted odds ratio (OR), 2.01; 95% CI: 1.69 to 2.38] and bleeding (adjusted OR, 3.76; 95% CI: 3.43 to 4.12). Every 10% decrease in platelet count was associated with increased mortality (adjusted ORs: 1.39, 95% CI: 1.33 to 1.46) and bleeding risk (adjusted OR: 1.89, 95% CI: 1.83 to 1.95). Ominously, approximately one in four patients who developed moderate/severe thrombocytopenia did not survive the hospitalization.[6] The influence of the aetiology of thrombocytopenia on prognosis and treatment has not been well investigated and warrants exploration. Liver disease in particular is associated with coagulation disorders as well and therefore may carry even greater bleeding risk in the setting of thrombocytopenia.