Diabetes & Hypertension as Risk Factors for Bad Outcomes in COVID-19

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Risk Factors For Bad Outcomes in COVID-19

Table 4 Risk factors for death.

	Uni-variable HR (95% CI)	*P* value	Multivariable HR (95% CI)	*P* value
Clinical covariates				
Age, years	1.07 (1.06–1.08)	<0.001	1.04 (1.03–1.06)	<0.001
Female sex (vs male)	0.35 (0.26–0.48)	<0.001	..	..
Smoking history (vs nonsmoking)	2.43 (1.59–3.73)	<0.001	1.84 (1.17–2.92)	0.009
Health care provider (vs non health care provider)	0.24 (0.06–0.96)	0.044	..	..
Comorbidity (Yes/No)				
ASCVD	2.56 (1.90–3.45)	<0.001	..	..
Diabetes	2.47 (1.82–3.34)	<0.001	..	..
Hypertension	2.21 (1.68–2.90)	<0.001	..	..
Cancer	2.59 (1.58–4.26)	<0.001	..	..

Lei Chen, Jianming Yu, Wenjuan He et.al. Leukemia (2020) 34:2173–2183
https://doi.org/10.1038/s41375-020-0911-0

Risk Factors in South Africa

Mortality risk (Odds Ratio)

- Age; > 50 vs < 40: 10
- Diabetes: 4-13
- HIV: 2.75
- TB: 2.58

Science

https://www.sciencemag.org/news/2020/06/hiv-and-tb-increase-death-risk-covid-19-study-finds-not-much


COVID-19
CORONAVIRUS
&
DIABETES

COVID and Diabetes/Hypertension

- No clear evidence that patients with DM and HTN have a higher risk of infection
- Clear evidence that those with DM and HTN havs
  - Higher chance of severe disease
    - Hospital admission
    - ICU admission
    - Oxygen use
    - Ventilator use
    - Death
- Ongoing debate and studies to see if those associations are causal associations (most are observational studies)

COVID-19 outcomes according to pre-existing diabetes

	Article type	Study population	Prevalence of diabetes	Outcome	Risk
Zhang et al[3]	Retrospective	258	24%	Mortality	3·64 (1·08–12·21)*
Kumar et al[4]	Meta-analysis	16 003	9·8%	Severe disease	2·75 (2·09–3·62)*
Kumar et al[4]	Meta-analysis	16 003	9·8%	Mortality	1·90 (1·37–2·64)*
Guan et al[10]	Retrospective	1590	NA	Composite†	1·59 (1·03–2·45)‡
Li et al[11]	Meta-analysis	1525	9·7%	ICU admission§	2·21 (0·88–5·57)¶
Fadini et al[12]	Meta-analysis	1687	NA	Severe disease	2·26 (0·98–4·82)‖
Fadini et al[12]	Meta-analysis	355	35·5%	Mortality	1·75‖
Petrilli et al[13]	Retrospective	5279	22·6%	Hospital admission	2·24 (1·84–2·73)*
Roncon et al[14]	Meta-analysis	1382	NA	ICU admission	2·79 (1·85–4·22)*
Roncon et al[14]	Meta-analysis	471	NA	Mortality	3·21 (1·82–5·64)*
Zhou et al[15]	Retrospective	191	19%	Mortality	2·85 (1·35–6·05)*
Zhu et al[16]	Retrospective	7337	13%	Mortality	1·49 (1·13–1·96)‡
Yan et al[17]	Retrospective	193	25%	Mortality	1·53 (1·02–2·3)‡
Sardu et al[18]	Retrospective	59	44%	Survival	0·172 (0·051–0·576)‡
Yang et al[19]	Meta-analysis	4648	NA	Severe disease	2·07 (0·88–4·82)*
Barron et al[20]	Cohort study	61 414 470	0·4% type 1 diabetes	Mortality	3·50 (3·15–3·89)*
Barron et al[20]	Cohort study	61 414 470	4·7% type 2 diabetes	Mortality	2·03 (1·97–2·09)*

ICU=intensive care unit. NA=not given. *Odds ratio (95% CI). †ICU admission, or invasive ventilation, or death. ‡Hazard ratio (95% CI). §Calculated for 1056 patients (in three of six studies). ¶Risk ratio (95% CI). ‖Rate ratio (95% CI not given).

Table 1: COVID-19 outcomes according to pre-existing diabetes

Matteo Apicella, Maria Cristina Campopiano, Michele Mantuano, et.al.

www.thelancet.com/diabetes-endocrinology Published online July 17, 2020 https://doi.org/10.1016/S2213-8587(20)30238-2

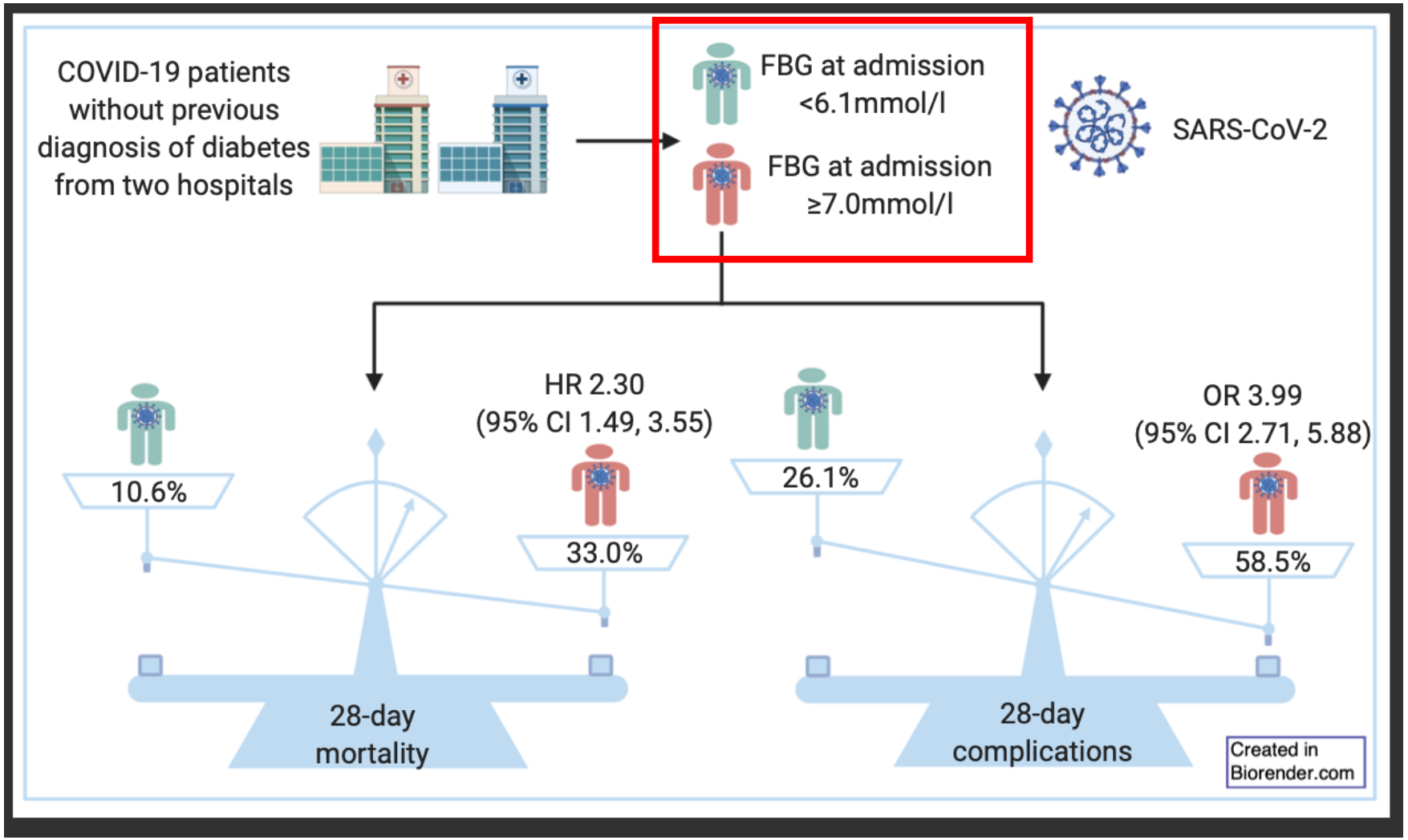
COVID-19 outcomes according to glycemic control

	Article type	Study population	Prevalence of diabetes	Parameter	Outcome	Risk
Williamson et al[7]	Cohort study	17 425 445*	10%	HbA_{1c} ≥58 mmol/mol (7·5%)	Mortality	2·36 (2·18–2·56)†
Holman et al[24]	Cohort study	265 090‡	100% type 1 diabetes	HbA_{1c} >86 mmol/mol (10%)	Mortality	2·19 (1·46–3·29)†
Holman et al[24]	Cohort study	2 889 210‡	100% type 2 diabetes	HbA_{1c} >86 mmol/mol (10%)	Mortality	1·62 (1·48–1·79)†
Sardu et al[18]	Retrospective	59	44%	Admission glycaemia >7·7 mmol/L	Survival	0·285 (0·084–0·964)†
Li et al [76]	Retrospective	269	19%	Hyperglycaemia	Mortality	1·77 (1·11–2·84)†
Zhu et al[16]	Retrospective	818	100%	Median glycaemia during hospital stay 6·4 mmol/L (IQR 5·2–7·5)	Mortality	0·13 (0·04–0·44)†
Zhu et al[16]	Retrospective	818	100%	Median glycaemia during hospital stay 6·4 mmol/L (IQR 5·2–7·5)	ARDS	0·41 (0·25–0·66)†
Zhu et al[16]	Retrospective	818	100%	Median glycaemia during hospital stay 6·4 mmol/L (IQR 5·2–7·5)	Heart injury	0·21 (0·07–0·59)†
Zhu et al[16]	Retrospective	818	100%	Median glycaemia during hospital stay 6·4 mmol/L (IQR 5·2–7·5)	Kidney injury	0·22 (0·05–1·03)†
Chen et al[28]	Retrospective	904	15%	Hyperglycaemia	Mortality	1·08 (1·01–1·16)§

ARDS=acute respiratory distress syndrome. *General practice records managed by The Phoenix Partnership. †Adjusted hazard ratio. ‡Individuals registered with a general practice in England, UK. §Adjusted odds ratio.

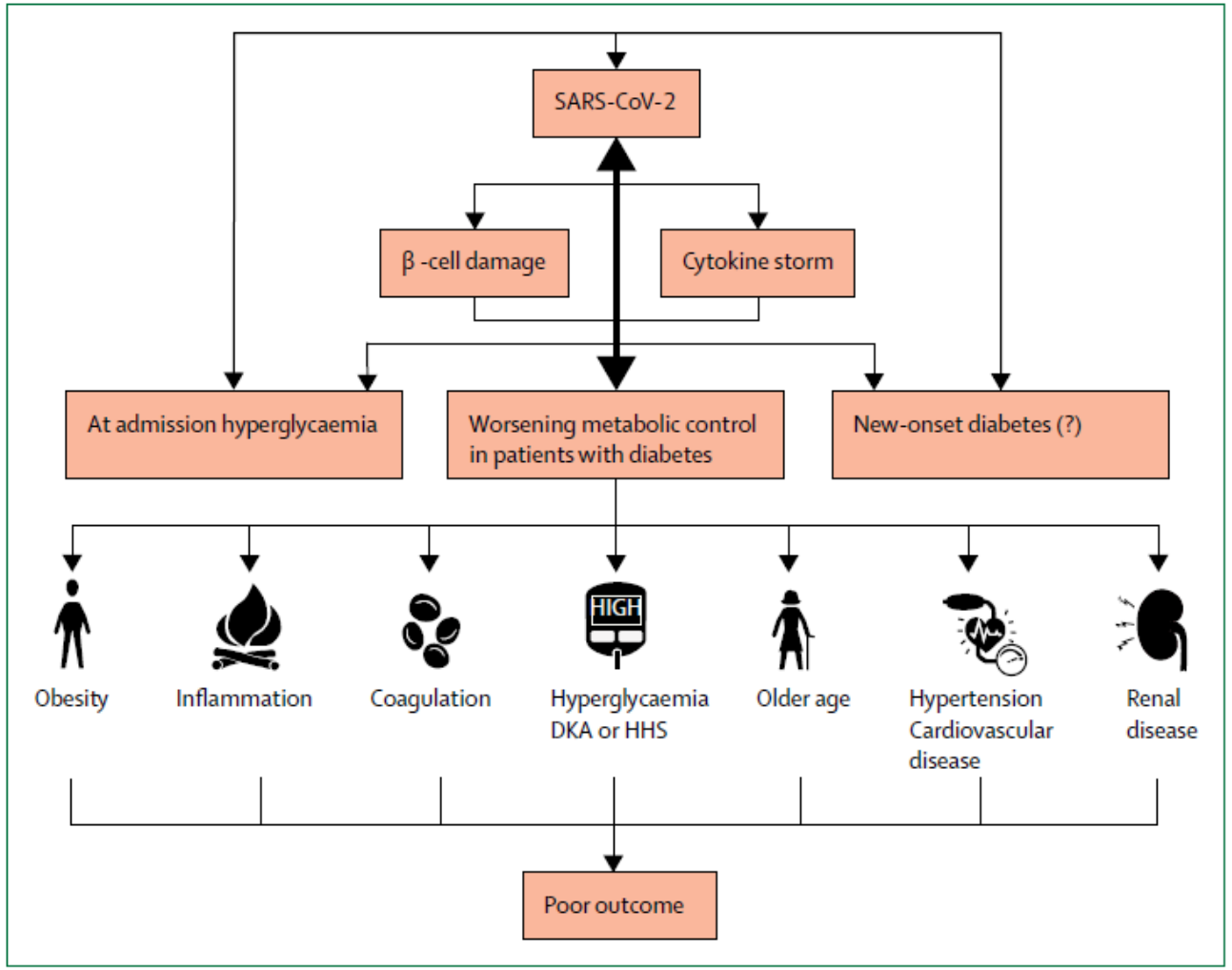
Table 2: COVID-19 outcomes according to glycaemic control

Comparing outcomes
Admission BG of < 110 mg/ dL vs > 126 mg/dL



Wang, S., Ma, P., Zhang, S. *et al. Diabetologia* (2020). https://doi.org/10.1007/s00125-020-05209-1

Synopsis of the Reciprocal Effects of Diabetes and COVID-19



Matteo Apicella, Maria Cristina Campopiano, Michele Mantuano, et.al.

Figure: Synopsis of the reciprocal effects of diabetes and COVID-19

www.thelancet.com/diabetes-endocrinology Published online July 17, 2020 https://doi.org/10.1016/S2213-8587(20)30238-2

Challenges of inpatient intensive glycemic control in COVID-19 patients

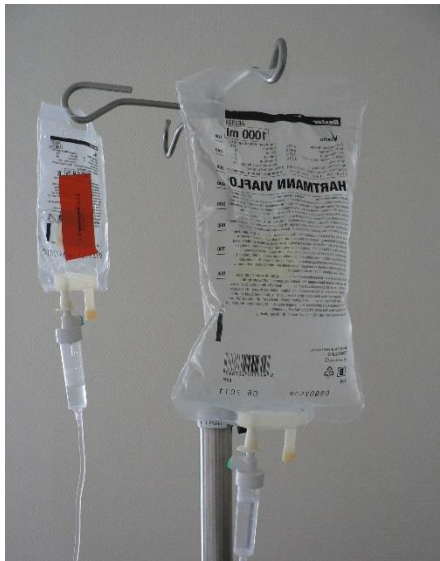
- ICU patients with severe hyperglycemia and DKA (requiring iv insulin drip)
  - Too frequent BG checks (every hour)
  - Adds to the frequency if interaction between nurse and patient (high exposure)
  - Consumes too much of PPEs
- Guidelines have been developed to manage many with SQ with less frequent BG checks and with use of continuous glucose monitoring (CGM) devices
- **Ongoing studies to find the ideal BG levels to aim for**

- **ADA COVID-19 Webinar Series**

  https://professional.diabetes.org/content-page/covid-19

- **ADA Inpatient Insulin Protocols - COVID-19**

  https://professional.diabetes.org/content-page/inpatient-insulin-protocols-covid-19



SQ Insulin DKA Protocol

EINSTEIN Albert Einstein College of Medicine | Montefiore

Authors: Shivani Agarwal MD, MPH; Jill Crandall, MD; Yaron Tomer MD

MONTEFIORE SUBCUTANEOUS INSULIN DKA PROTOCOL

This is a subcutaneous (SubQ) insulin protocol that replaces insulin drip needs for mild to moderate DKA. Procedures are adapted for COVID-related considerations of minimizing risk to staff while optimizing patient safety and health.

****CALL ENDOCRINE/DIABETES CONSULT SERVICE FOR ASSISTANCE****

DKA Diagnosis and Eligibility for SubQ Protocol:

Does patient meet ALL THREE criteria for DKA?		Meet all FIVE criteria:
1. **Hyperglycemia**: serum glucose or capillary glucose > 250 mg/dL 2. **Ketosis**: positive serum BHB or urinary ketones 3. **Acidemia**: blood (venous or arterial) gas pH ≤ 7.3 or serum bicarbonate ≤18 mEq/L	**AND**	1. Blood gas (venous or arterial) pH ≥ 7.0 2. Serum bicarbonate ≥ 10 mEq/L 3. Alert/Awake mental status 4. MAP > 65 after 1L IV fluids 5. K ≥ 3.3 mEq/L

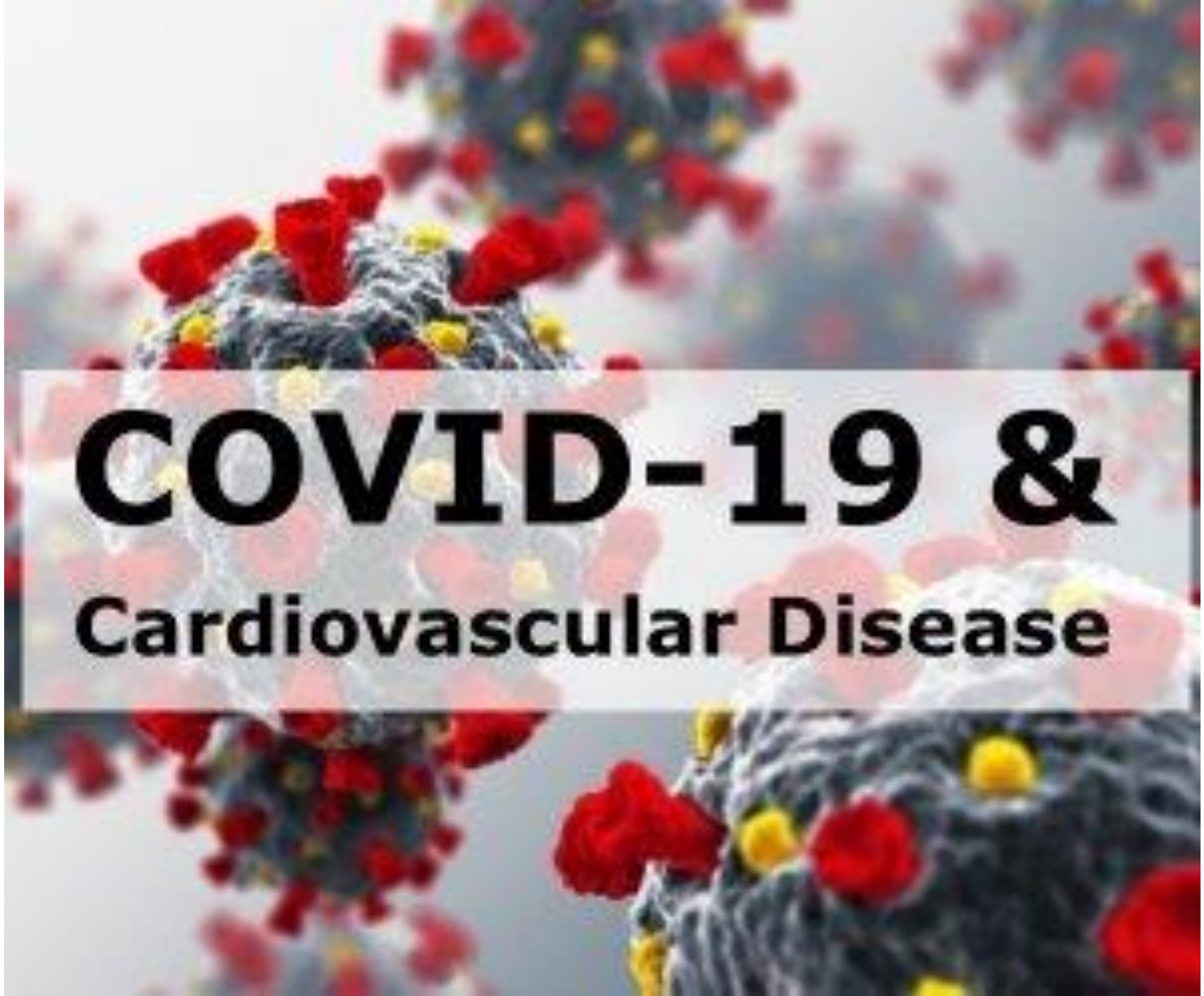
Patient can be treated according to the SubQ Pathway.

EXCLUSION for SubQ Pathway; NEED Insulin Drip

Pregnancy, Altered Mental Status, Acute CHF Exacerbation, Acute Coronary Syndrome, ESRD or CKD Stage 4 or 5, Acute Liver Failure or Cirrhosis, Anasarca, Weight >120 kg, High-dose Corticosteroids, Severe DKA (Serum HC03 <10 mEq/L or pH ≤7.1)

1. Start Basal Insulin Dose (Detemir) STAT and continue q24h (unless last dose within 12 hours):
   - **BMI ≤30 OR GFR 15-30 AND no high dose steroids→START 0.15 units/kg Detemir**
   - BMI >30 OR on high-dose steroids AND GFR>30 →START 0.2 units/kg Detemir
   - Call endocrine/diabetes consult team to verify calculated basal insulin doses over 50 units

2. Start Initial Insulin Lispro Loading Dose and Subsequent q4h dosing (STOP when pH>7.3 or serum HC03≥18):
   - Mild to Moderate DKA: Serum bicarbonate > 12 or pH > 7.15→0.2 units/kg loading dose STAT
     - Correctional doses q4h: FS ≥250 mg/dl→ 0.2 units/kg; FS<250 mg/dl→ 0.1 units/kg
   - Call endocrine/diabetes consult team for modified dosing if hypoglycemia occurs. Hold doses for FS<70.


COVID-19 &
Cardiovascular Disease

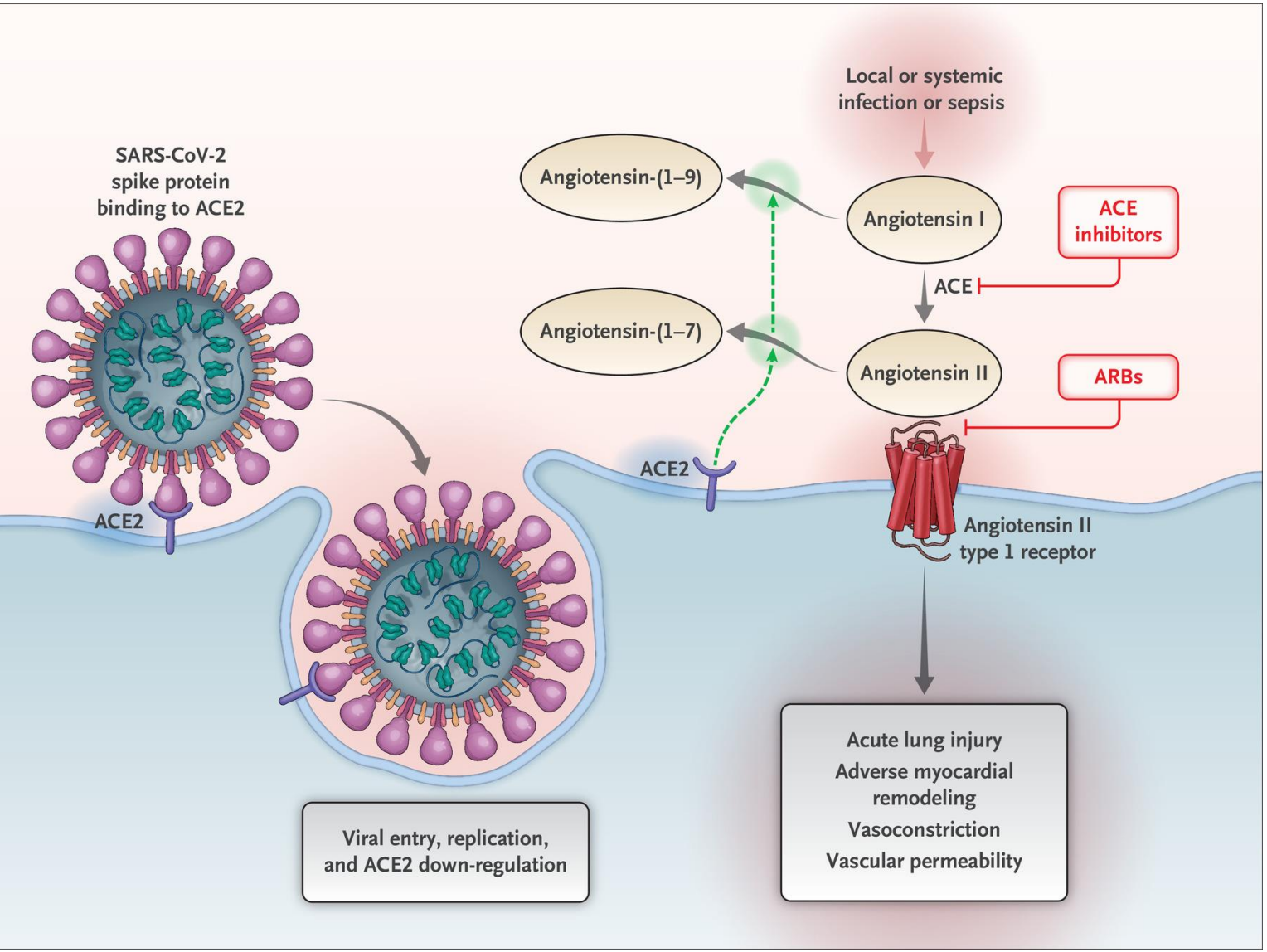
Association of HTN and Outcomes

Paper	Study Population	Proportion with HTN?	Association of HTN with outcomes?	Adjusted analysis?
Guan et al NEJM Jan 2020	N = 1099 552 Hospitals 30 Regions in China	165 (15%)	HTN: 24% in those w/ severe dz vs 14% among those w/ non-severe dz; HTN: 36% w/ 1 outcome* vs 14% w/out 1 outcome	Not done
Huang et al Lancet, Jan 2020	N = 41 Jinyintan Hospital, Wuhan	6 (15%)	NR	
Wang et al JAMA, Feb 2020	N = 138 Zhongnan Hospital, Wuhan	43 (31%)	NR	
Zhang et al Allergy, Feb 2020	N = 140 No. 7 Hospital, Wuhan	42 (30%)	HTN: 38% with severe dz 24% with non severe dz	Not done
Zhou et al Lancet, March 2020	N = 191 Jinyintan and Wuhan Hospitals	58 (30%)	48% HTN among died vs 23% HTN among survived	HT not included in adjusted model
Wu et al JAMA IM March 2020	N = 201 Jinyintan Hospital Wuhan	39 (19.4%)	ARDS: HR 1.82 (95% CI 1.13 - 2.95) Mortality HR 1.70 (95% CI 0.92 - 3.13)	Bivariate cox regression; **not** multivariable adjusted for age and other factors
Italian Report	N = 355 March 17 2020	NR	76% of patients who died had hypertension	Median age 80.5 years among dead vs 63 years among all with diagnosis
Guo et al JAMA Cardiol March 2020	N = 187 Seventh Hospital Wuhan	61 (33%)	33/52 (64%) with elevated TnT levels had HTN; ↑TnT associated with mortality	Median age 71 years among ↑TnT vs 54 years among normal TnT
Chen et al BMJ March 2020	N = 274 Tongji Hospital Wuhan	93 (34%)	48% HTN among died vs 24% HTN among survived	No adjustment for age Median age 68 years among died versus 51 years among survived
McMichael et al NEJM March 2020	N = 167 Resdents, visitors and staff at Lifecare Centre, Kirkland, WA	68 (67%) in residents 4 (8%) in staff 1 (13%) in visitors	NR	Median age Residents: 83 years Staff: 44 years Visitors: 63 years
Shi et al JAMA Cardiol March 2020	N = 416 Remnin Hospital Wuhan	127 (31%)	49/82 (60%) with elevated TnT levels had HTN; ↑TnT associated with mortality	Median age 74 years among ↑TnT vs 60 years among normal TnT
Petrilli et al MedRXiv Apr 2020	N = 4103 NYU Langone Health, New York	983 (24%)	37% HT vs 12% HT in those hospitalized vs not 40% HT vs 34% HT in those critically ill vs not	Regression analysis OR 1.23 (0.97 – 1.57) for hospitalization OR 0.95 (0.68 – 1.33) for critically ill
Bean et al MedRXiv Apr 2020	N = 205 King's College Hospital and Princess Royal University Hospital, London	105 (51%)	ICU admission/death association Unadjusted OR 1·60 (CI 0·88-3·10); p=0·12	Adjusted for age and gender (OR 1·80 (CI 0·83-3·80); p=0·14

http://www.nephjc.com/news/covidace2

Sources: Guan et al, NEJM; Huang et al, Lancet; Wang et al, JAMA; Zhang et al, Allergy; Zhou et al, Lancet; Wu et al, JAMA IM; Italian report (PDF); Chen et al, BMJ; Shi et al, JAMA Cardiol; McMichael et al, NEJM; Guo et al, JAMA Cardiol; Bean et al, MedRxiv 2020; Petrilli et al, MedRXiv 2020

Figure 1. Interaction between SARS-CoV-2 and the Renin–Angiotensin–Aldosterone System.



Shown is the initial entry of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) into cells, primarily type II pneumocytes, after binding to its functional receptor, angiotensin-converting enzyme 2 (ACE2). After endocytosis of the viral complex, surface ACE2 is further down-regulated, resulting in unopposed angiotensin II accumulation. Local activation of the renin–angiotensin–aldosterone system may mediate lung injury responses to viral insults. ACE denotes angiotensin-converting enzyme, and ARB angiotensin-receptor blocker.

ACE and ARBs tend to upregulate ACE2

Table 1: RAAS Inhibitors and COVID-19 Patient Outcomes

Author (Publication Date)	Country	N (HTN*)	Type of Study	Agent	Outcome	Endpoints
Peng et al [32] March 2, 2020	China	112 (92)	Retrospective Cohort	ACE-I/ARB	Neutral	No effect on morbidity or mortality
Meng et al. [33] March 17, 2020	China	417 (51)	Retrospective Cohort	ACE-I/ARB	Positive	Lower rate of severe disease
Huang et al. [34] March 30, 2020	China	50 (50)	Retrospective Cohort	ACE-I/ARB	Neutral	No difference in in-hospital mortality
Feng et al. [35] April 10, 2020	China	476 (113)	Retrospective Cohort	ACE-I/ARB	Positive	Increased ACE-I/ARB use in moderate vs severe COVID-19 group
Zhang et al. [24] April 17, 2020	China	1,128 (1,128)	Retrospective Cohort	ACE-I/ARB	Positive	Decreased all-cause mortality
Li et al. [36] April 23, 2020	China	1,178 (362)	Retrospective Cohort	ACE-I/ARB	Neutral	No association with severity of illness or mortality
Yang et al. [37] April 29, 2020	China	126 (126)	Retrospective Cohort	ACE-I/ARB	Neutral	Lower proportion of critically ill and lower death rate with ACE-I/ARB use
Mancia et al. [25] May 1, 2020	Italy	6,272 (3,632)	Population Based Case Control Study	ACE-I/ARB	Neutral	No association with number of patients or severe/fatal disease
Reynolds et al. [26] May 1, 2020	USA	12,594 (2,573)	Retrospective Cohort	ACE-I/ARB	Neutral	No increase in likelihood of positive test or risk of severe disease
Mehra et al. [38] May 1, 2020	Asia, Europe, North America	8,910 (2,346)	Retrospective Cohort	ACE-I/ARB	Neutral	No increased risk of in-hospital death
Mehta et al. [39] May 5, 2020	USA	18,472 (7,312)	Retrospective Cohort	ACE-I/ARB	Neutral	No association between ACE-I/ARB use and positive COVID-19 test
Conversano et al. [40] May 8, 2020	Italy	191 (96)	Retrospective Cohort	ACE-I/ARB	Neutral	ACE-I/ARB treatment not associated with increased mortality or worse clinical presentation.
de Abajo et al. [41] May 14, 2020	Spain	1,139 (617)	Population Based Case Control Study	ACE-I/ARB/ Aldosterone Antagonists/ Renin Inhibitors	Neutral	No increase in the risk of hospital or ICU admission, fatal cases

*with hypertension diagnosis and positive COVID-19 test

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https://www.acc.org/latest-in-cardiology/articles/2020/07/06/08/15/covid-19-and-hypertension

Recommendations of Professional Societies regarding ACE/ ARBs

- **ACC/AHA (April 2020)**

The American College of Cardiology and American Heart Association (ACC/AHA) notes that "there are no experimental or clinical data demonstrating beneficial or adverse outcomes with background use of ACE inhibitors [or] ARBs."[3] The statement recommends continuing these drugs if they are being prescribed for valid cardiovascular indications and advises clinicians not to add or remove them "beyond actions based on standard clinical practice."

- **Position Statement of the ESC Council on Hypertension on ACE-Inhibitors and Angiotensin Receptor Blockers (13 Mar 2020)**

The Council on Hypertension strongly recommend that physicians and patients should continue treatment with their usual anti-hypertensive therapy because there is no clinical or scientific evidence to suggest that treatment with ACEi or ARBs should be discontinued because of the Covid-19 infection.

- **Ongoing studies to find out effect of ACE and ARBs**

Summary

- Both diabetes and hypertension have been associated with bad outcomes including mortality in patients with COVID-19
- Tight glycemic control seems to be associated with better outcomes in COVID-19. Intervention trials will be needed to confirm that.
- The optimal degree of glycemic control for best COVID-19 outcomes in not known (ongoing studies).
- Some modifications of how we mange diabetes in the hospital may have to be considered in COVID-19 patients to minimize nurse exposure
- The role of ACE inhibitors and ARBs in COVID-19 infections is not known (ongoing studies).
- See outpatients with diabetes through telehealth whenever possible.