CoVID-19: Therapy Update

GA RICHARDS MBBCH PHD FCP(SA) MASSAF

Community Onset Bacterial Co-infection

- In 38 Michigan hospitals, early empiric antibacterials were prescribed to 56.6% (965/1705) of patients hospitalized with COVID-19 while 3.5% (59/1705) had a confirmed community-onset bacterial co-infection.
- Among hospitals, empiric antibacterial use varied from 27% to 84%.

Vaughn https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa1239/5895253

HCQ ± Azithro: systematic review & meta-analysis

- 839 articles: 29 met inclusion criteria: 3 RCT, 1 nonrandomized, 25 observational, including 11 with critical (these were excluded) & 14 with a serious/moderate risk of bias
- All except 1 were in hospitalized patients: n= 11 932 (HCQ), 8081 (HCQ plus azithro), 12 930 controls
- HCQ was not associated with mortality: RR 0.83 (0.65-1.06, n=17 studies) for all studies & RR 1.09 (0.97-1.24, n=3 studies) for RCTs
- HCQ plus azithro was associated with increased mortality (RR 1.27; (1.04-1.54, n=7 studies)

Fiolet Clinical Microbiology and Infection 27 (2021) 19e27

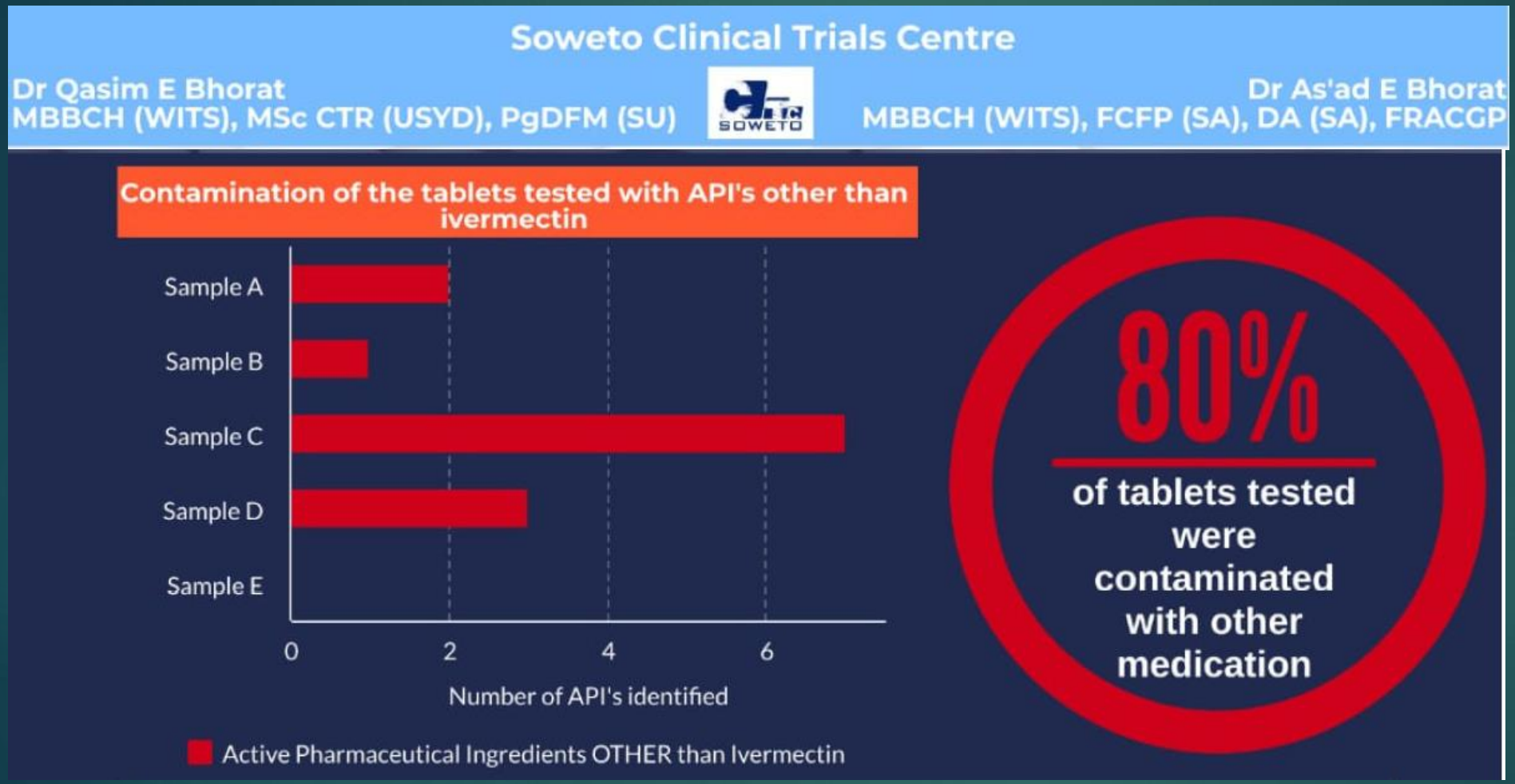
Remdesivir: Solidarity

- 405 hospitals in 30 countries; 11,266 adults randomized, 2750 allocated to Remdesivir, 954 Hydroxychloroquine, 1411 Lopinavir, 651 Interferon plus Lopinavir, 1412 only Interferon & 4088 no study drug. Compliance was 94-96% midway through treatment, with 2-6% crossover.
- Death rate ratios remdesivir vs control: RR=0.95 (0.81-1.11, p=0.50; 301/2743 active vs 303/2708 control)

WHO Solidarity trial consortium https://www.nejm.org/doi/10.1056/NEJMoa2023184

Ivermectin Studies

- Sample size of most was small
- Poor randomisation & matching of patients & controls regarding comorbidities/age
- Various doses & schedules used
- Some RCTs were open-label; neither participants nor investigators blinded
- Patients also received various concomitant medications (e.g., doxycycline, HCQ, azithro, zinc, CS), confounding assessment of efficacy or safety
- Severity of COVID-19 seldom described
- Outcome measures were not clearly defined.



APIs Identified

Paracetamol
Diclofenac
Mebeverine
Orindazole (antibiotic)
Pregabalin
Telmisartan
Hydroxyzine
Nortryptyline
Clopidogrel
Etizolam (benzo)

Ivermectin in Mild Disease

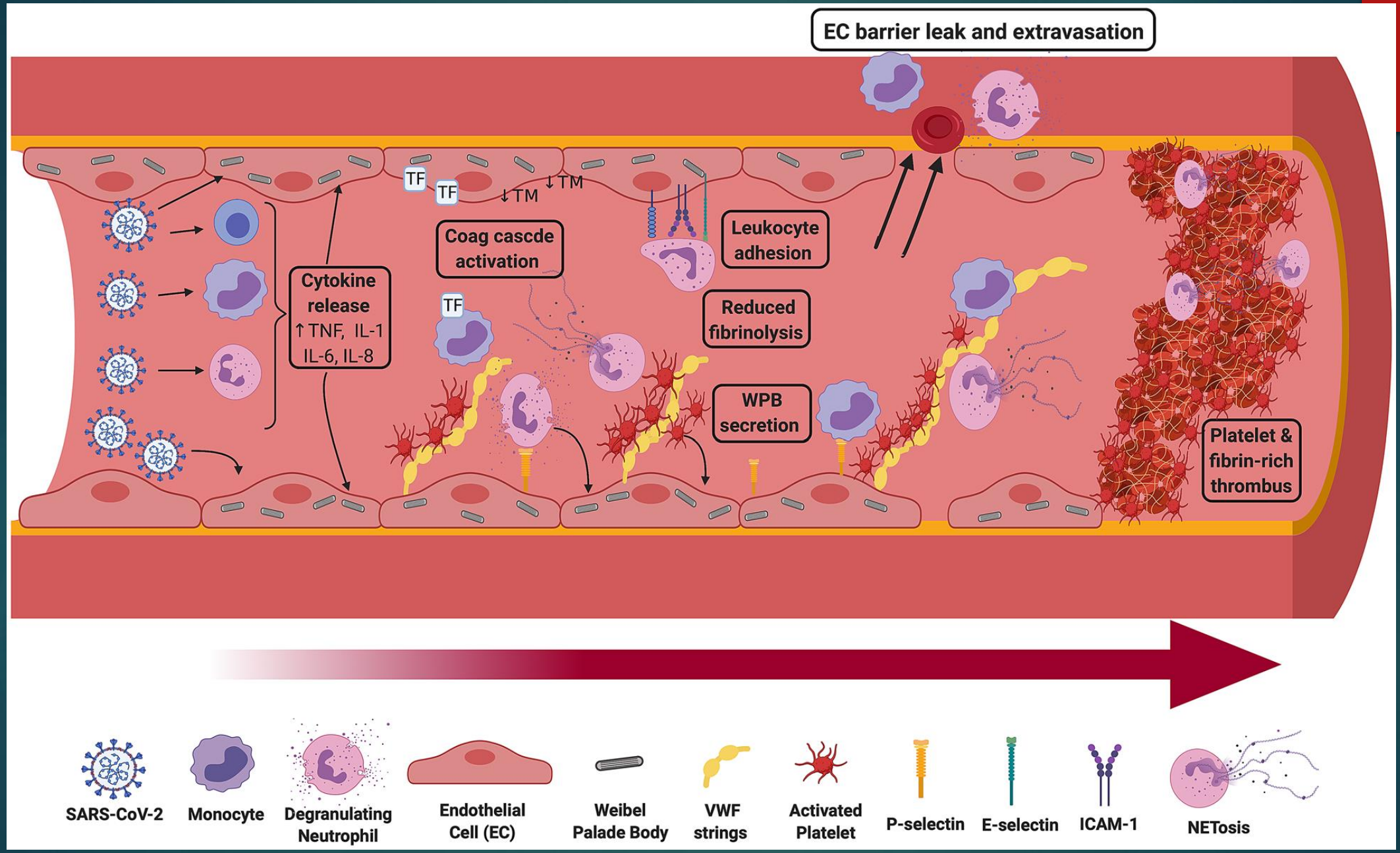
- N=400 randomised to 300µg/kg /day for 5 days (n = 200) or placebo (n = 200)
- Median age 37 [IQR 29-48]; 99.5% completed the trial
- Median time to symptom resolution: 10 days (IQR 9-13) IVM vs 12 days (IQR, 9-13) placebo; HR 1.07 [0.87 to 1.32]; P = .53
- Day 21; 82% IVM & 79% placebo had resolved symptoms.
- The most common solicited AE was headache, 104(52%) IVM & 111 (56%) placebo
- The most common SAE was multiorgan failure; 2 in each group

López-Medina JAMA. doi:10.1001/jama.2021.3071

Ivermectin Meta-analysis

- 10 RCTs (n=1173) vs SOC in 5 & placebo in 5 RCTs.
- RCTs sample size ranged from 24 to 398; mean age 26-56; disease severity mild in 8 RCTs, moderate in 1 & mild & moderate in 1
- IVM did not reduce all-cause mortality vs controls RR 1.11 (0.16-7.65), very low QoE
- IVM did not reduce LOS vs controls (MD 0.72 days (-0.86 to 2.29), very low QoE.
- AEs, severe AE & viral clearance were similar (low QoE)

Roman medRxiv preprint doi: https://doi.org/10.1101/2021.05.21.21257595;



O'Donnell Intensive Care Med https://doi.org/10.1007/s00134-021-06419-w

Anticoagulation: REMAP-CAP, ACTIV-4 & ATTACC

- Severe Covid: organ support- (HFNC, NIV, vasopressors, inotropes), randomized to therapeutic with heparin (TAC) or PAC
- 1° outcome: an ordinal scale of in-hospital mortality & days free of organ support to day 21
- N=1 074: Median organ support-free days were 3 days (IQR –1, 16) with TAC vs 5 days (IQR –1, 16) (aOR 0.87 (credible interval 0.70-1.08)
- Hospital survival: 64.3% vs. 65.3%,
- Major bleeding 3.1% with TAC vs 2.4%
- Overall no benefit

The REMAP-CAP, ACTIV-4a & ATTACC medRxiv preprint doi: https://doi.org/10.1101/2021.03.10.21252749

Anticoagulation: prophylactic

- N=4297 hospitalised patients; 3627 (84.4%) received prophylactic AC < 24 hrs of admission
- >99% (n=3600) received subcut heparin or enoxaparin
- 622 deaths occurred <30 days of hospital admission
- Using inverse probability of treatment weighted analyses, cumulative mortality at 30 days was 14.3% (13.1%-15.5%) with prophylactic AC vs 18.7% (15.1%-22.9%)
- 30 day mortality decreased 27% HR 0.73 (0.66-0.81)

Rentsch BMJ: first published as 10.1136/bmj.n311

Anticoagulation: Intermediate vs Prophylactic

- Retrospective study: n= 2785 hospitalized patients
- Intermediate (IA); enoxaparin ≥ 0.4 & < 0.7mg/kg BD or prophylaxis (PA) 30-40mg (< 0.7mg/kg) daily or 30-40mg (< 0.4mg/kg) BD: N= 1624
- Aspirin vs nil N = 1956
- Propensity score matching & MVA using markers of illness severity & other patient-specific factors
- MVA: IA vs PA: in-hospital death: HR 0.518 [0.308-0.872]
- MVA: Aspirin (N = 638) in-hospital death HR 0.522 [0.336-0.812]

Meizlish Am J Haem doi: 10.1002/ajh.26102

RECOVERY Dexamethasone-Recovery

- Preliminary statement on results of a RCT
- Dex group (n=2104) 6mg/day orally/IV x 10 days vs 4321 usual care: median number of days of dex was 6
- 28 day mortality with usual care: 41% if requiring MV, 25% with O_2 alone & 13% if neither
- Dex reduced deaths significantly: MV patients (rate ratio 0.65 [0.48-0.88] p=0.0003); O_2 alone (0.80 [0.67-0.96] p=0.0021
- *No effect if not requiring any respiratory support*.
- Prevention of 1 death/8 patients on MV & 1 in 25 requiring O_2

RECOVERY Collaborative Group*medRxiv preprint doi: https://doi.org/10.1101/2020.06.22.20137273.this

Early Corticosteroids in Acute Hypoxaemic Respiratory Failure

- 691 patients out of 882 (78.3%) received CS in hospital
- Early (in 1st 48h) vs delayed >48 h of ICU admission vs never
- Early-CS (n = 485) had lower ICU mortality (30.3% vs never 36.6% & delayed 44.2%) & lower 7-day mortality (7.2% vs never 15.2%)
- More MV-free days & decreased LOS & 2° infection
- No differences in complications between groups
- Early moderate/high dose (methylpred >1mg/kg/d or dex >0.12 mg/kg/d, pred>0.5 mg/kg/d)had better outcomes than low

Monedero et al. Crit Care (2021) 25:2
https://doi.org/10.1186/s13054-020-03422-3

Corticosteroids: Dose

- Retrospective Controlled Cohort Study
- Patients admitted with SARS-CoV-2 pneumonia
- N= 396 (46.7%) consecutive patients received 1 mg/kg/day methylpred (dex 8mg BD)or equivalent vs 67 controls.
- Global mortality was 15.1%.
- Median time to CS from symptom onset: 10 days (IQR 8 -13)
- In-hospital mortality: 13.9% (CS) vs 23.9% OR 0.51 [0.27-0.96], p= 0.044 a 41.8% reduction RRR 0.42 [0.048-0.65]

Fernández Cruz AAC 2020

Corticosteroids Dose

- Prospective triple-blinded RCT N=86 hospitalized, sat< 92
- Block randomization performed based on 2 prognostic factors; age < 55 & ≥55 & severity, sat < 85 & ≥ 85%; No differences between groups
- 2mg/kg methylpred tapered every 5 days vs dex 6mg daily x 10 days
- Methylpred group had better clinical status day 5 (4.02 vs. 5.21, p = 0.002) & 10 (2.90 vs. 4.71, p = 0.001) & overall mean score (3.909 vs. 4.873 p= .004)
- Mean LOS: 7.43 ± 3.64 & 10.52 ± 5.47 days (p = 0.015)
- Need for MV lower 18.2% vs 38.1% p = 0.040)
- Essentially for 80kg person= 160mg methylpred= 40mg dex

Ranjbar BMC Infectious Diseases (2021) 21:337 https://doi.org/10.1186/s12879-021-06045-3

CS: Dose

- Reports suggest COP & Acute Fibrinous OP (OP/AFOP) represent predominant pattern in pathological samples
- A systematic review revealed AFOP features in 26%
- CT scans often have OP features, including peripheral bilateral GGO ± consolidation or intralobular lines & atoll signs
- Rapidly progressive extensive OP requires high dose CS & critically ill Covid patients may also benefit from higher doses, especially with OP/AFOP features.

Gogali Eur Respir J 2021 https://doi.org/10.1183/13993003.00224-2021
Polak Mod Pathol 2020; 33: 2128–2138
Güneyli Diagn Interv Radiol 2020; 26: 323–332
Myall KJ Ann Am Thorac Soc 2021;18(5):799-806 doi:10.1513/AnnalsATS.202008-1002OC

REMAP-CAP & RECOVERY: Tocilizumab

- REMAP-CAP: Critically ill patients receiving Tmab on 1st day of severe illness more likely to improve: OR : 1.87 (> 1.43 with dex): NB only if given with CS (>90%)
- RECOVERY: Inclusion: n=4116: sat <92% on air or requiring O_2 & CRP ≥75 mg/L received Tmab +SOC vs SOC alone
- Tmab: 400-800mg (weight based) IVI ± 2nd 12-24hrs later
- 596 (29%)(Tmab) & 694 (33%) SOC died ≤ 28 days (rate ratio 0.86 (0.77-0.96) p=0.007
- CS & Tmab more likely to be discharged alive < 28 days (54% vs 47%); rate ratio 1.22 (1.12-1.34) p<0.0001

Wise BMJ 2020;371:m4530 http://dx.doi.org/10.1136/bmj.m4530
Horby medRxiv preprint doi: https://doi.org/10.1101/2021.02.11.21249258

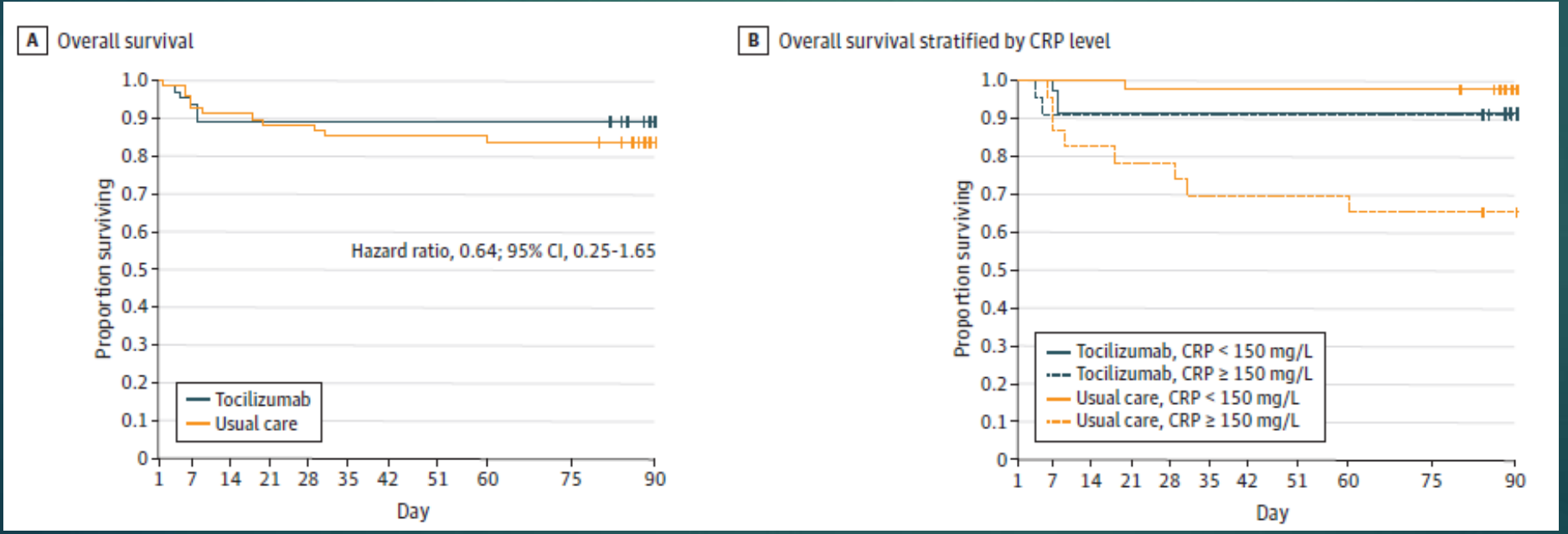
Tocilizumab: Meta-analysis

- 10 RCTs; 9 reported mortality, n=6493; 52.2% Tmab
- Tmab may reduce mortality (24.4% vs. 29.0%; OR 0.87 [0.74–1.01]; p = 0.07; I2 = 10%; but could not exclude the possibility of no difference or a small adverse effect at the 5% significance level (OR 0.87 [95% compatibility interval (CI) 0.74–1.01]; moderate quality of evidence).
- Meta-regression suggested a relationship between treatment & mortality risk, with benefit at higher levels of risk
- Tmab reduced need for MV & had benefit in a composite 2° outcome but did not reduce ICU admission.

Snow Intensive Care Med https://doi.org/10.1007/s00134-021-06416-z

Tocilizumab & Survival

- Only RECOVERY enrolled patients with elevated CRP
- There is benefit if CRP > 150 only
- With CRP >150 NIV, MV or death was 18% (Tmab) & 57% SOC (HR 0.18 (0.06-0.59)
- Likewise, 90day mortality was 9% (Tmab) & 35% (SOC) (HR, 0.18;)
- Few patients were taking CS at randomization



Mariette JAMA Internal Medicine 2021

Lenzilumab: Survival without ventilation

- Novel anti-human GM-CSF monoclonal preventing signaling
- 40.5% on HFNO or NPPV; 59.5% on low flow O_2 or room air
- Obesity (55.1%), diabetes (53.4%), CKI 14.0%, CAD 13.6%
- 93.7% received CS; 72.4% remdesivir; both 69.1%
- Likelihood of SWOV improved 54% in mITT population HR 1.54 (1.02-2.31) p=0.041 & 90% in ITT; HR 1.90 (1.02-3.52) nominal p=0.043
- SWOV improved 92% if on both CS & remdesivir; nominal p=0.0067); & 2.96 fold with CRP<150 & age <85; p=0.0003
- But: MV, ECMO, death: 15.4(Lmab) vs 21.4%: OR 0.67 (0.41-1.10) p=ns
- If CRP<150 & age<85: OR 0.32; 0.15-0.65, it was significant

Temesgen MedRxiv **doi:** https://doi.org/10.1101/2021.05.01.21256470

Convalescent Plasma: Recovery

- 28 day mortality: 1399 (24%) of 5795 in plasma & 1408 (24%) of 5763 in SOC groups died within 28 days: rate ratio 1.00 (0.93-1.07) p=0.95
- Consistent for all prespecified subgroups
- No effect on proportion discharged within 28 days: rate ratio 0.99,
- No difference in proportion meeting a composite MV or death

Horby https://doi.org/10.1016/S0140-6736(21)00897-7

Colchicine in Hospitalised Patients: RECOVERY

- N=5610 colchicine & 5730 SOC
- 1173 (21%) in colchicine & 1190 (21%) in SOC groups died within 28 days: rate ratio 1.01 (0.93-1.10) p=0.77
- Consistent results for all pre-specified subgroups
- No difference in LOHS or in those discharged alive within 28 days
- In those not on MV at baseline, no difference in a composite of MV or death

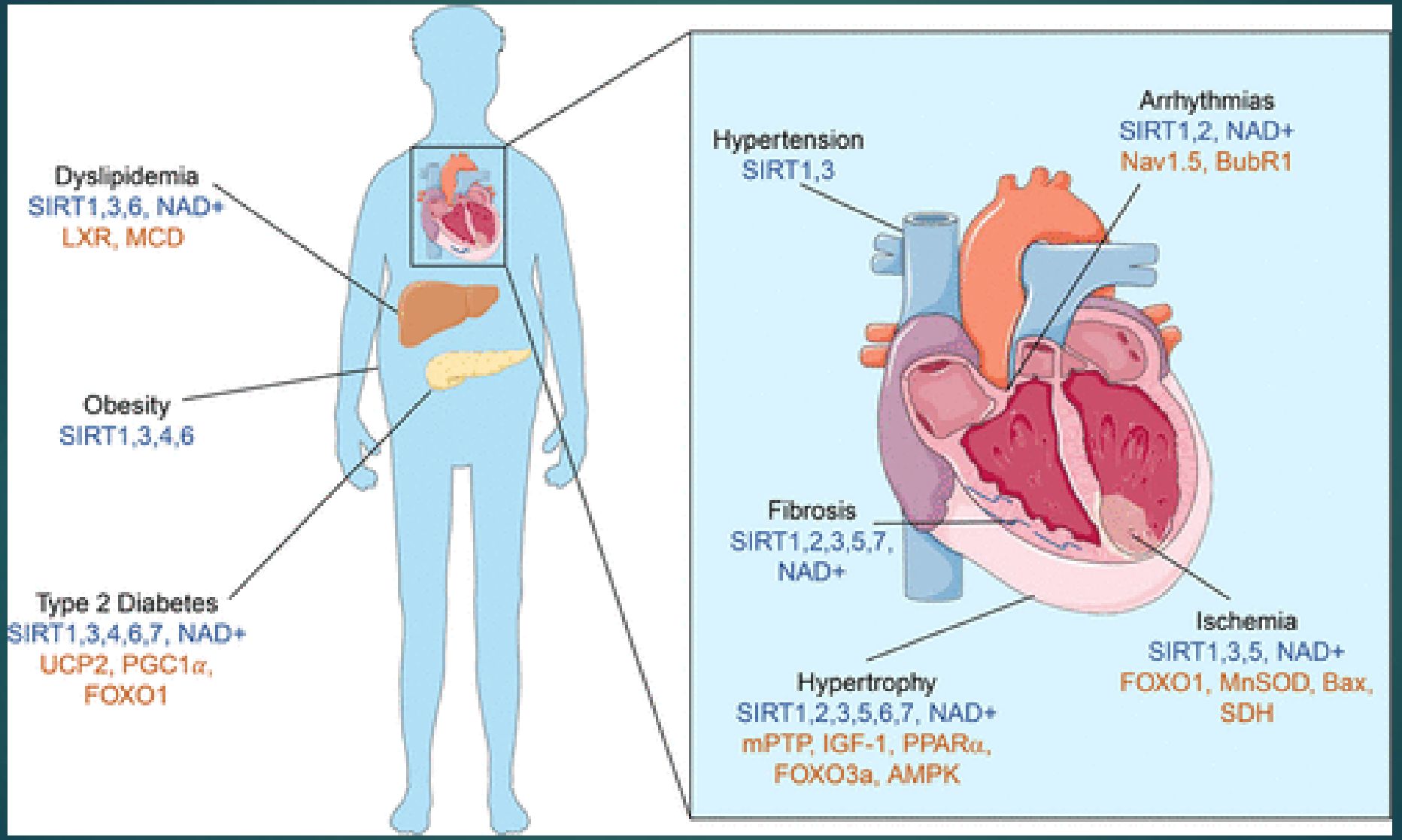
Horby medRxiv preprint doi: https://doi.org/10.1101/2021.05.18.21257267

Vitamin D

- N= 237 randomised to 1 oral dose of 200 000 IU Vit D3 or placebo mean [SD]: baseline 25-hydroxyvitamin D was 20.9 [9.2] ng/mL
- Median (IQR) LOS not different with D3 & placebo (log-rank P= .59)
- No difference for in-hospital mortality 7.6% vs 5.1%; (–4.1%to 9.2%] P= .43; ICU admission P= .30, need for MV P = .09
- Mean serum level of vitamin D significantly increased after 1 dose (44.4 vs 19.8 ng/mL) P < .001)
- There were no adverse events,

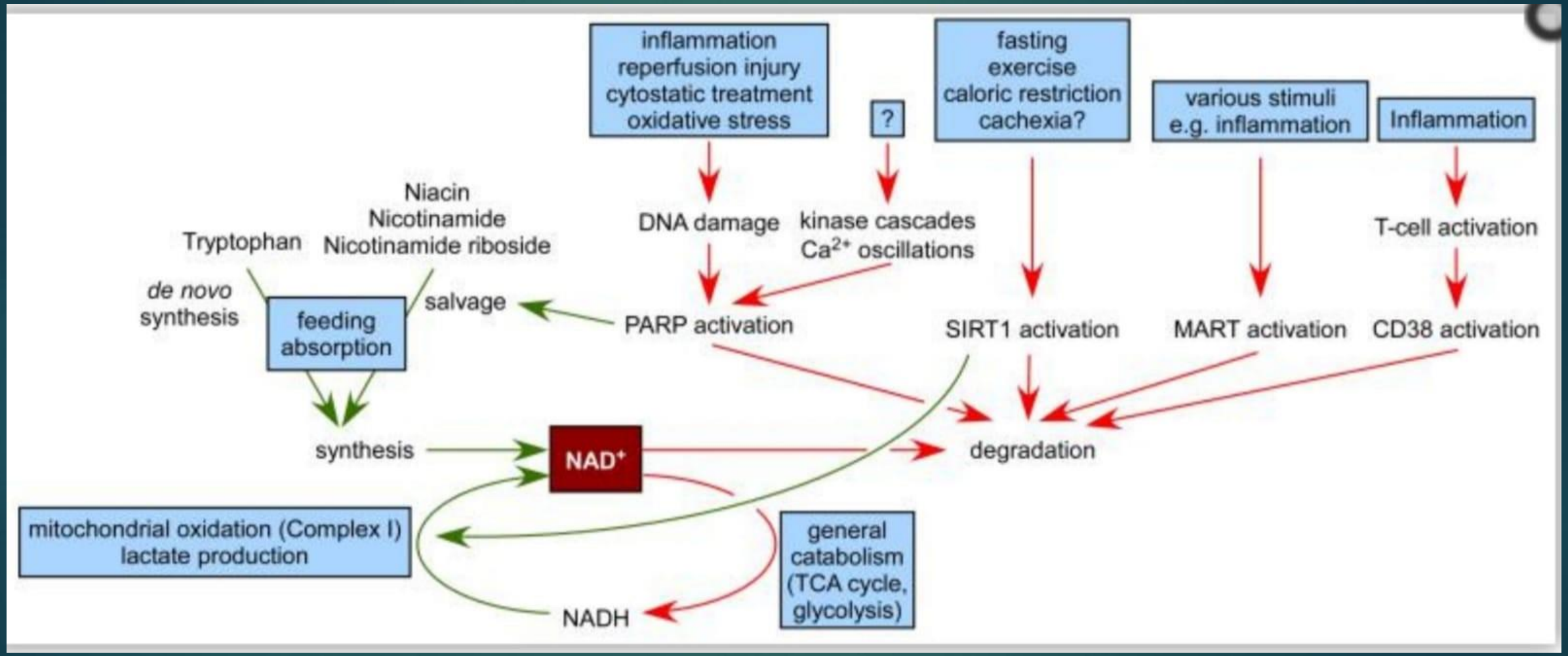
Murai JAMA. doi:10.1001/jama.2020.26848

CoVID 19 Risk factors for Poor Outcome



Kane Circulation Research 2018

Treatment of Chronic CoVID



PARP: poly ADP ribose polymerase: MART Mono ADP ribose transferases

Pathophysiology

- Symptoms may be due to NAD+ deficiency causing decreased SIRT 1 activity (silent immune regulator of T cells)
- Zn^{++} & NAD^{+} are imperative for SIRT1function which modulates TNFa, IL1b & IL6 production
- Hyperactivity of PARP1 results in depletion of cellular NAD^{+} pools, leading to ATP deficiency, energy loss & subsequent cell death.
- NAD^{+} deficiency impairs SIRT1 function & activation. Replenishment of NAD^{+} by nicotinic acid plus zinc have the potential to ameliorate the pro-inflammatory cascade

Miller, Wentzel, Richards Medical Hypotheses 2020

What Pharmacotherapy Would I Recommend

- Admission
- Zinc 20-50mg daily × 5 days
- Nicotinic acid 35-50mg daily
- Pneumonic phase:
  - No antibiotics unless PCT elevated: Beware post Tmab PCT does not rise
  - Watch for fungal & bacterial sepsis esp post Tmab
  - Anticoagulation to Xa of 0.8 if D-dimer >1: add PPI
  - CS: Dexamethasone 8mg BD x 3 then 8mg daily or equivalent
  - If CRP rising, hypoxaemia worse or needs MV: Consider methylpred 125mg BD x 3 days ±Tocilizumab 400mg stat or IVIg?
  - If remdesivir used give early with steroids in pneumonic phase