Coronavirus disease 2019 and cardiovascular implications
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The coronavirus disease 2019 (COVID-19) has important implications for the cardiovascular care of patients. COVID-19 interacts with the cardiovascular system on multiple levels, increasing morbidity in patients with underlying cardiovascular conditions and favoring acute myocardial injury and dysfunction. COVID-19 infection may also have long-term implications for overall cardiovascular health. Many issues regarding the involvement of the cardiovascular system remain controversial. Despite angiotensin-converting enzyme 2 serving as the site of entry of the virus into the cells, the role of angiotensin-converting enzyme inhibitors or AT1 blockers requires further investigation. Therapies under investigation for COVID-19 may have cardiovascular side effects. Treatment of COVID-19, especially the use of antivirals, must be closely monitored. This article is a review of the most updated literature.

Keywords: cardiovascular disease, coronavirus disease 2019, infection

Coronavirus disease 2019 and preexisting cardiovascular disease

Compared with other zoonotic coronaviruses, COVID-19 has a lower case fatality rate (2.3 vs. 9.6% and 34.4% for Severe Acute Respiratory Syndrome, SARS and Middle East Respiratory Syndrome CoronaVirus, MERS-CoV, respectively), but has resulted in many more deaths than both of these prior outbreaks combined, due to its greater infectivity and higher attack rate, leading to a larger number of infected patients. Furthermore, the case fatality rate (CFR) of this virus has been reported to rise significantly with the age, reaching 8.0% in patients aged 70–79 years and 14.8% in those aged more than 80 years. Much higher mortality rates have been recently shown in a series from the New York City area including patients older than in the Chinese series (Fig. 1).

Coronavirus disease 2019 and preexisting cardiovascular disease

Previous studies showed a relationship between cardiovascular disease (CVD) and SARS and MERS-CoV. A systematic analysis of 637 MERS-CoV cases showed that diabetes and HTN were prevalent in about 50% of the patients and cardiac diseases were present in 30% of the cases. Diabetes was seen as an independent predictor for mortality and morbidity in patients with SARS. Furthermore, the severity of the primary respiratory syndrome and risk of adverse outcomes increased in patients with preexisting CVD. A number of studies in the available literature suggest a similar association also between preexisting CVD and severe COVID-19.

A meta-analysis of six studies including 1527 patients with COVID-19 reported the prevalence of HTN, cardio...
Patients who required ICU and other acute inflammatory conditions were more likely to have these comorbidities compared with non-ICU patients. The overall proportions of HTN, cardio-cerebrovascular diseases, and diabetes were about two-fold, three-fold, and two-fold, respectively, higher in ICU/severe cases than in their non-ICU/severe counterparts. In a large study including 44,672 COVID-19 cases from Wuhan, China, increased CFR was reported in patients with CVD (10.5%), diabetes (7.3%), HTN (6.0%), all notably higher than the overall CFR of 2.3%.

Several smaller cohort studies have reported similar results suggesting higher risk for adverse events in patients with COVID-19 and CVD with a tighter association than respiratory disease itself. Notably, whereas reports outside China are limited, preliminary data from Italy suggest similar mortality rates and an elevated risk for death in patients with comorbidities.

These results suggest that comorbidities, along with age, are a major risk factor for critical patients. HTN, diabetes, and CVD may be related to the pathogenesis of COVID-19. The proinflammatory state of these conditions may predispose to COVID-19 and cause a more complicated clinical course. However, this hypothesis needs to be properly tested with adequate and powered studies.

**Coronavirus disease 2019 and cardiac injury**

During the acute phase of the infection great attention should be paid to viral infection-related cardiac injury. Patients may also develop cardiovascular complications, such as heart failure, myocarditis, pericarditis, vasculitis, and cardiac arrhythmias. The relative contribution of direct SARS-CoV-2 infection and the patient’s exaggerated inflammatory response are, however, variable and not completely clear.

Myocardial injury, evidenced by elevated cardiac biomarkers, was recognized among early cases in China. In the aforementioned study of 138 hospitalized patients with COVID-19 in Wuhan, China, cardiac injury (elevated high-sensitivity troponin I (hs-cTnI) or new ECG or echocardiographic abnormalities) was present in 7.2% of patients overall, and 22% of those required ICU care. The report from two hospitals in Wuhan documented that almost 12% of patients without known CVD had elevated troponin levels or cardiac arrest during the hospitalization. Notably, hs-cTnI was above the 99th percentile upper reference limit in 46% of nonsurvivors as opposed to 1% of survivors.

In Li et al.’s meta-analysis at least 8.0% of the COVID-19 patients suffered from acute cardiac injury. The incidence of acute cardiac injury was about 13-fold higher in ICU/severe patients compared with non-ICU/severe patients. There is strong evidence that patients with long-term coronary artery disease and those with risk factors for atherosclerotic CVD have a heightened risk of developing an acute coronary syndrome during acute infections, according to previous epidemiologic and clinical studies of influenza and other acute inflammatory conditions.

Such acute coronary events could result from the severe increase in myocardial demand triggered by infection that precipitates myocardial injury or infarction (type 2 myocardial infarction). Alternatively, circulating cytokines released during severe systemic inflammatory stress could lead to atherosclerotic plaque instability and rupture. Similarly, patients with heart failure are also prone to hemodynamic decompensation during the stress of severe infectious illnesses.

In a cohort study of 416 hospitalized COVID-19 patients, Shi et al. reported that 82 individuals (19.7%) had evidence of myocardial injury manifested by elevation of high-sensitivity troponin I (TnI) levels. Patients with myocardial injury had a significantly higher in-hospital mortality rate (51.2%) compared with those without myocardial injury (4.5%), and among those with myocardial injury, greater degrees of TnI elevation were associated with higher mortality rates.

Some authors have recently summarized that between 8 and 28% of patients with COVID-19 infections will manifest troponin elevation early in the course of the disease, reflecting cardiac injury, or stress. The presence of troponin elevation, or its dynamic increase during hospitalization, confers up to five times the risk of requiring ventilation, increases in arrhythmias such as ventricular tachycardia/ventricular fibrillation, and five times the risk for mortality. A similar proportion of patients also manifest elevations of natriuretic peptides. Troponin and brain natriuretic peptide (BNP), together with the presence of underlying CVDs or cardiovascular risk factors, are highly prognostic of requirement for ICU admission, ventilation, and death.
The pathogenesis of SARS-CoV-2 infection-related acute myocardial injury is still unknown.

According to the clinical presentation and the lab data of the disease, as well as to the pathogenesis of SARS-CoV, it can be speculated that COVID-19 may affect the cardiovascular system through the following multiple mechanisms (Fig. 2). A first cause of myocardial injury may be nonspecific mechanisms related to infection such as fever, heightened adrenergic drive, tachycardia, and hypoxemia. Hypoxemia is a hallmark of COVID-19 pneumonia and may cause myocardial ischemia and cell death. A second mechanism may be represented by direct myocardial involvement mediated via ACE2. This peptide is widely expressed not only in the lungs but also in the cardiovascular system and mediates angiotensin II breakdown into a fragment with vasodilatory properties. Coronavirus infection causes a downregulation of ACE2 with increased angiotensin II tissue levels that may directly cause tissue injury. Murine models and human autopsy samples demonstrate that SARS-CoV can downregulate myocardial and pulmonary ACE2, thereby mediating myocardial inflammation, lung edema, and acute respiratory failure. Similar mechanisms may be active at the myocardial level. Among humans, during the Toronto SARS outbreak, SARS-CoV viral RNA was detected in 35% of autopsied hearts. Recent data have also shown this SARS-CoV-2 in macrophages in the myocardium of a patient with cardiogenic shock and myocarditis during COVID-19.

Third, myocardial injury may be secondary to the cytokine storm triggered by an imbalanced response by type 1 and type 2 T-helper cells. Huang’s study noted that high concentrations of IL-1ß, IFN-γ, IP-10, and monocyte chemotactic protein-1 could be detected in patients infected with SARS-CoV-2, which might lead to activated Th1 cell responses. The study also found that ICU patients had much higher concentrations of inflammatory factors than non-ICU patients, suggesting that the cytokine storm was associated with disease severity.

Heightened systemic inflammatory and procoagulant activity can persist in survivors of hospitalization for community-acquired pneumonia long after resolution of the index infection. The clinical effects of pneumonia have been linked to increased risk of CVD up to the 10-year follow-up and it may be that COVID-19 recovered patients will experience similar adverse outcomes, with a poor quality of life.

As a consequence, attention should be given to cardiovascular protection during treatment for COVID-19 and to cardiological follow-up.
Coronavirus disease 2019 and thrombotic or thromboembolic disease

COVID-19 may predispose patients to thromboembolic disease, both in the venous and arterial circulations, due to excessive inflammation, platelet activation, endothelial dysfunction, and immobilization. Remarkably, thrombotic complications have hardly been described. In patients who develop sepsis from various infectious agents, development of coagulopathy is one of the key and persistent features which is associated with poor outcomes. The most consistent hemostatic abnormalities with COVID-19 include mild thrombocytopenia and increased d-dimer levels, which are associated with a higher risk of requiring mechanical ventilation, ICU admission, or death. These findings are consistent with the already demonstrated close connection between thrombosis and inflammation, two processes that mutually reinforce each other. Indeed, both coagulation factors (procoagulants and anticoagulants) and platelets are directly implicated in the modulation of the host immune response, displaying proinflammatory functions that are independent from their hemostatic effects.

Recently, Tang et al. assessed 183 patients with COVID-19, 21 of whom (11.5%) died. Among the notable differences between patients who died and those who survived were increased levels of d-dimer and fibrin degradation products (~3.5-fold and ~1.9-fold increase, respectively) and prothrombin time (PT) prolongation (by 14%, P < 0.001). Further, 71% of COVID-19 patients who died fulfilled the International Society on Thrombosis and Haemostasis (ISTH) criteria for DIC (disseminated intravascular coagulation), compared with only 0.6% among survivors.

Moreover, it has been shown that heparin, besides its anticoagulant effects, also displays an anti-inflammatory action, various immunomodulatory properties, and protects glycolcalyx from shedding. Despite such a tight interconnection between inflammation and hemostasis abnormalities, no good evidence is available of the efficacy/safety of heparin and/or antplatelet agents on sepsis patients, and many issues remain to be addressed, such as the appropriate timing, dosages, and administration scheme of antithrombotic drugs.

Klok et al. studied 184 patients with proven COVID-19 pneumonia admitted to the ICU. All patients received at least standard doses thromboprophylaxis, although regimens differed between hospitals and doses increased over time. The cumulative incidence of the composite outcome of venous thromboembolism (VTE) and arterial thrombotic complications was 31% [95% confidence interval (CI) 20–41%], of which computed tomography pulmonary angiogram and/or ultrasonography confirmed VTE in 27% (95% CI 17–37%) and arterial thrombotic events in 3.7% (95% CI 0–8.2%). Acute pulmonary embolism was the most frequent thrombotic complication (n = 25, 81%); no patient developed DIC. Age and coagulopathy, defined as spontaneous prolongation of the PT for more than 3 s or activated partial thromboplastin time of more than 5 s, were independent predictors of thrombotic complications.

Although the scientific community is waiting for more robust evidence from properly designed clinical trials with strong end points, the ISTH (Italian Society on Thrombosis and Haemostasis) has recently provided some recommendations, based on expert consensus, for the management of the hemostasis derangement in COVID-19 patients, including the following:

1. Measuring d-dimer, PT, and platelet count (decreasing order of importance) is recommended in all patients who present with COVID-19 infection. This may help in stratifying patients who may need admission and close monitoring or not.

2. Monitoring PT, d-dimer, platelet count, and fibrinogen can be helpful in determining prognosis in COVID-19 patients requiring hospital admission. If there is worsening of these parameters, more aggressive critical care support is warranted. If these markers are stable or improving, it gives the added confidence for stepdown of treatment if corroborating with the clinical condition.

3. Prophylactic dose low-molecular weight heparin (LMWH) should be considered in all patients (including noncritically ill) who require hospital admission for COVID-19 infection, in the absence of any contraindications (active bleeding and platelet count less than 25 × 10^9/l; monitoring advised in severe renal impairment). The benefit of this approach has recently been reported in a study including 449 patients with severe COVID-19, of whom 99 received heparin (mainly with LMWH) at prophylactic doses. Although no difference was observed in the 28-day mortality in those who received heparin compared with those who did not, if a sepsis-induced coagulopathy score of at least 4 were to be applied to the patients, anticoagulant therapy with LMWH appears to be associated with better prognosis in relation to mortality (40.0 vs. 64.2%, P = 0.029). A similar benefit was noted in those with d-dimer more than six-fold times the upper limit of normal (32.8 vs. 52.4%, P = 0.017).

4. Thromboprophylaxis should be administered for the entire duration of the hospital stay and should also be maintained at home for 7–14 days after hospital discharge or in the prehospital phase, in case of preexisting or persisting VTE risk factors (i.e. reduced mobility, BMI more than 30, previous VTE, active cancer).

5. The use of intermediate-dose LMWH (i.e. enoxaparin 4000 IU subcutaneously every 12 h) can be considered...
on an individual basis in patients with multiple risk factors for VTE (i.e. BMI more than 30, previous VTE, active cancer, etc.).

6. The use of therapeutic doses of unfractionated heparin (UFH) or LMWH, although a reasonable approach, is currently not supported by evidence outside of established diagnoses of VTE or as a bridging strategy in patients on vitamin K antagonists (VKA), and cannot be recommended as a standard treatment for all COVID-19 patients.

Coronavirus disease 2019, experimental therapies, drug interactions, and cardiovascular implications

Although currently there are no specific effective therapies for COVID-19, various pharmacologic agents are under active investigation. Drug-related cardiac injury during COVID-19 treatment is a concern. In particular, the use of antiviral drugs should be monitored. As these drugs are being studied, it is important to review the potential cardiovascular side effects and the main interactions with other cardiovascular medications (Table 1).

Antiviral therapy: Antivirals are at the forefront of medications under study for COVID-19 treatment. Ribavirin and Remdesivir are two such agents that bind to the active site on the RNA-dependent RNA polymerase on SARS-CoV-2, whereas lopinavir/ritonavir inhibits replication of RNA virus and has evidence of a synergistic effect in vitro with ribavirin.

Although ribavirin has no characterized direct cardiovascular toxicity, lopinavir/ritonavir may result in QT and PR interval on electrocardiogram, especially in patients who have a baseline abnormality (long QT) or those who are at risk for conduction abnormalities including those taking other QT-prolonging drugs. Both ribavirin and lopinavir/ritonavir have the potential to affect anticoagulant dosing; ribavirin has variable effects on warfarin dosing and lopinavir/ritonavir may require dose reductions or avoidance of cytochrome P450 (CYP)3A-mediated drugs such as rivaroxaban and apixaban.

Lopinavir/ritonavir can also influence the activity of P2Y12 inhibitors through CYP3A4 inhibition, which results in decreased serum concentrations of the active metabolites of clopidogrel and prasugrel and increased serum concentrations of ticagrelor.

Therefore, concomitant use with ticagrelor is discouraged in the United States and Canada due to excess in bleeding risk. Conversely, there is evidence that clopidogrel may not always provide sufficient platelet inhibition in the setting of concomitant administration of lopinavir/ritonavir, whereas this was not the case with prasugrel as assessed by the VerifyNow P2Y12 assay.

If P2Y12 inhibition is needed during treatment with lopinavir/ritonavir, then prasugrel can be used; however, if contraindicated (i.e. history of stroke or transient ischemic attack, low-BMI, or active pathological bleeding), a testing-guided approach (e.g. with P2Y12 platelet function assays) may be considered with alternative antiplatelet agents.

3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins) also have the potential to interact with the combination of lopinavir/ritonavir and can result in myopathy due to elevated statin levels when administered together.

Table 1 Recommendations regarding dosing and adjustment in the setting of medication interactions

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Specific interaction</th>
<th>Mechanism of drug interaction and specific dose adjustments</th>
<th>Other notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ribavirin</td>
<td>Anticoagulant</td>
<td>Unknown mechanism of action: no dosage adjustment recommended</td>
<td>Monitor INR</td>
</tr>
<tr>
<td>Lopinavir/Ritonavir</td>
<td>Warfarin</td>
<td>CYP3A4 inhibition: Apixaban should be administered at 50% of dose</td>
<td>Monitor INR</td>
</tr>
<tr>
<td></td>
<td>Anticoagulants</td>
<td>Rivaroxaban should not be coadministered</td>
<td></td>
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<tr>
<td></td>
<td>Apixaban</td>
<td>CYP3A4 inhibition: diminished effect of clopidogrel</td>
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<tr>
<td></td>
<td>Lopinavir</td>
<td>Increased effect of ticagrelor</td>
<td></td>
</tr>
<tr>
<td>Statin</td>
<td>Atorvastatin, rosuvastatin</td>
<td>CYP3A4 inhibition: Atorvastatin should be adjusted to maximum dose 10 mg/day</td>
<td></td>
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<tr>
<td></td>
<td>Lovastatin, simvastatin</td>
<td>Should be adjusted to maximum dose 20 mg/day</td>
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<tr>
<td></td>
<td></td>
<td>Lovastatin and simvastatin should not be coadministered</td>
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</tr>
<tr>
<td>Antiarrhythmics</td>
<td>QT-prolonging medication</td>
<td>P-glycoprotein inhibition: monitor digoxin level for possible dose reduction</td>
<td>Use cautiously with antiarrhythmics</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Beta blockers</td>
<td>CYP2D6 inhibition: dose reduction for beta blockers may be required</td>
<td>Use cautiously with antiarrhythmics</td>
</tr>
<tr>
<td>Chloroquine/Hydroxychloroquine</td>
<td>Metoprolol, labetalol</td>
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<tr>
<td></td>
<td>Antiarhythmics</td>
<td></td>
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<td>QT-prolonging agents</td>
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<td>Digoxin</td>
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BCRP, breast cancer resistance protein; CYP, cytochrome P450; INR, international normalized ratio; QT, QT interval on electrocardiogram. Adapted from.
Lovastatin and simvastatin, in particular, are contraindicated for coadministration with lopinavir/ritonavir due to risk of rhabdomyolysis. Other statins, including atorvastatin and rosuvastatin, should be administered at the lowest possible dose but not exceeding the maximum dose stated in the package insert while on lopinavir/ritonavir.62

In addition to antiviral medications, numerous immune-modulating and secondary medications to prevent complications that could arise from COVID-19 are currently being investigated. Chloroquine, which has been used as an antimalarial agent, blocks virus infection by increasing the endosomal pH required for virus/cell fusion, and has been demonstrated in vitro to have inhibitory activity in SARS-CoV-2.68 Chloroquine and hydroxychloroquine have the potential for intermediate-to-delayed myocardial toxicity. Risk factors include: long-term exposure (>3 months), higher weight-based dose, preexisting cardiac disease, and renal insufficiency.69

Chloroquine cardiac toxicity presents as restrictive or dilated cardiomyopathy or conduction abnormalities thought to be due to intracellular inhibition of lysosomal enzymes in the myocyte.70 In addition, due to effects of chloroquine on CYP2D6 inhibition, beta blockers metabolized via CYP2D6 (such as metoprolol, carvedilol, propranolol, or labetalol) can have increased concentrations of drugs requiring careful monitoring for heart rate and blood pressure shifts. Lastly, both agents are associated with a conditional risk of torsade des pointes in patients with electrolyte abnormalities or with concomitant use of QT-prolonging agents.

Methylprednisolone is another drug under investigation that is currently being used to treat severe cases of COVID-19 that are complicated by ARDS.71 This steroid is known to cause fluid retention, electrolyte derangement, and HTN as direct cardiovascular effects, and may also interact with warfarin via an undescribed mechanism. Clinicians are advised to observe for these drug interactions.

Finally, patient debilitation from severe COVID-19 may pose challenges in administering routine cardiovascular medications, ranging from antiplatelet therapy to beta-blockers, thus putting patients with or at risk of ischemic heart disease or heart failure at risk of further deterioration of their clinical condition.72

Anticoagulant therapy in COVID-19 patients: Direct oral anticoagulants (DOAC) represent the treatment of choice for many clinical indications, such as the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation and the prevention and treatment of VTE, whereas VKA remain the only available drugs to prevent valve thrombosis and thromboembolic events in patients with prosthetic heart valves and in those in whom DOAC are contraindicated.73–75 The development of COVID-19 syndrome in anticoagulated patients, and especially their admission to ICUs with acute severe respiratory syndrome (SARS-CoV-2) exposes them to specific problems related to their therapy, in addition to those associated with the acute viral infection.

In particular, patients on VKA show a high instability of PT international normalized ratio, specifically due to the variability of vitamin K metabolism, diet, fasting, comedinations, liver impairment, and heart failure, which leads to physicians dealing with difficulties in strictly maintaining the therapeutic range.54,65

On the other hand, DOAC interact with P-glycoprotein and/or CYP-based metabolic pathways. Many classes of drugs cause drug–drug interactions, in such a way modifying the DOAC pharmacodynamic and pharmacokinetic profile and causing a remarkable decrease or increase in their anticoagulant action. On this basis, the use of DOAC is generally discouraged in association with many classes of drug, such as antiviral drugs, rifampicin, fungostatics, and some antineoplastic agents.76 Specifically antiviral therapies strongly interact with DOAC, exposing patients to significant a increase in DOAC plasma levels.

The multiple drug–drug interactions (antiviral, antibiotics, antihypertensive, bronchodilators, immunosuppressive drugs), in addition to metabolic alterations that are induced by the acute disease, can cause unpredictable and unstable DOAC anticoagulant effect, exposing patients to the risk of uncontrolled bleeding or thrombotic complications.77

During acute COVID-19 respiratory infection the replacement of oral anticoagulant therapies (AVK and DOAC) by parenteral LMWH has been suggested to avoid the risk of over/under treatment. In hospitalized COVID-19 patients with mechanical heart valves, the oral anticoagulant therapy can be replaced by the UFH or in alternative with LMWH maintaining a strict control of anti-activated factor X at the upper limit of the therapeutic range.78,79

ACE2 and potential therapeutic implications: As the ACE2 receptor is the mechanism of entry for SARS-CoV-2, some data suggest that ACE inhibitors (ACEi) and AT1 blockers (ARB) may upregulate ACE2, thereby increasing susceptibility to the virus.4,32 In contrast, other studies show that ACEi/ARB may potentiate the lung protective function of ACE2, which is an angiotensin II inhibitor.80,81 Thus, the therapeutic implications for ACEi/ARB therapy during COVID-19 infection is unclear. Overall, there are insufficient data to suggest any mechanistic connections between ACEi/ARB therapy and contracting COVID-19 or with severity illness once infected. At this time nearly all major societies have recommended to continue the antihypertensive therapy with ACEi or ARB, given the lack of evidence currently available on their potential benefit or harm.82 To date, a
small report concerning a retrospective analysis seems to suggest that ACEIs/ARBs are not associated with the severity or mortality in patients with HTN hospitalized with COVID-19 infections. 

Conclusion
COVID-19 is an infectious disease caused by SARS-CoV-2 that has significant implications for the cardiovascular care of patients.

Cardiovascular comorbidities are common in patients with COVID-19 and may contribute to adverse early clinical outcome whereas COVID-19 infection increases the risk of cardiac disease in the short and probably in the long term.

Interdisciplinary management of severe cases, with priority for those with preexisting CVD, cardiovascular protection during the acute infection, and prolonged clinical follow-up are essential.

Conflicts of interest
There are no conflicts of interest.

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Coronavirus disease 2019 and cardiovascular implications Frattini et al. 731

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