**Supplemental Table 1. Age-related changes in the cardiovascular structure and function and their pathological consequences2,3,20**

|  |  |  |
| --- | --- | --- |
| **Parameters** | **Cardiovascular changes** | **Clinical consequences** |
| **Vascular system** | **1. Endothelial dysfunction:** * ↓ vasodilation
* ↑ eNOS uncoupling and ↓ NO bioavailability
* ↑ angiotensin II activity/signaling
* ↑ endothelin-1 levels
* ↑ plasma levels of catecholamines leading to β-adrenergic desensitization
* ↑ COX-derived eicosanoids associated with vasoconstriction (PGH2, PGFα, TxA2), but ↓ PGI2

**2. Arterial wall:*** ↑ vasoconstriction
* Hypertrophy and hyperplasia of VSMC
* ↑ arterial wall thickness/stiffness
* ↓ distensibility of elastic arteries (↑ frying of elastin fibers)
* ↑ TGF-β activity and the synthesis of interstitial collagen
* ↑ stiffness in large/medium-sized arteries
* ↓ angiogenic growth factors (VEGF, HIF1α) and capilar density

**3. Oxidative stress and inflammation:** * ↑ NADPH oxidase, uncoupled NOS and xanthine oxidase
* ↓ antioxidant capacity (glutathione peroxidase-1)
* ↓ Jun D and SIRT 1 expression
* ↑ proinflammatory cytokines (TNF-α, IL-1β, IL-6, IL-18, chemokines, adhesion molecules)
 | * ↑ peripheral vascular resistances
* ↑ SBP (afterload): ↑ LV afterload, myocardial oxygen demands and may lead to LV hypertrophy
* ↓ DBP
* ↑ pulse pressure
* ↓ DBP and coronary perfusion, favoring the development of myocardial ischemia
* ↓ aortic distensibility (↑ aortic wall stiffness)
* ↑ aorto-femoral pulse wave velocity
* Media thickening of coronary arterioles can further decrease coronary perfusion and impair vasomotion
* ↓ renal function
* ↑ vascular encephalopathy
* ↑ carotid and peripheral artery obstruction
* ↑ the prevalence of orthostatic hypotension
 |
| **Cardiac structure** | * ↑ atrial size and filling
* ↓ isinopriltes number
* ↑ myocyte hypertrophy and fibrosis
* ↑ deposition of collagen, fibrous tissue and wtTTR within the connective tissue
* ↓ cardiac contractility and relaxation
* ↑ intraventricular wall thickness and LV hypertrophy
* LV function: ↓ early diastolic peak filling rate, ↑ late LV filling; preserved end systolic volume and ejection fraction
* Cardiac valves: ↑ calcium deposition and collagen infiltration, myxomatous degeneration, fixation of valvular leaflets
 | * Left atrial dilatation that ↑ susceptibility to AF
* ↑ afterload
* ↑ LV stiffness and fibrosis
* ↑ LV mass/volume ratio
* ↑ LV dysfunction, LV systolic and diastolic volumes and heart failure
* ↑ susceptibility to HFpEF
* ↑ susceptibility to myocardial ischemia
* Hypertrophy and fibrosis impair lusitropy
* Myocardial ischemia in the hypertrophied LV can predispose to HFrEF
* Aortic sclerosis and stenosis
* ↑ mitral and aortic regurgitation
* Mitral annular calcification, aortic stenosis and sclerosis
 |
| **Electrophysiological changes**  | * ↓ pacemaker cells, fibrous infiltration of the conduction system
* Sinoatrial node: ↓ ICa,L and HCN4 mRNA, heart rate and heart rate variability
* ↓ cardiac repolarization reserve
* ↑ PR and AH intervals
* ↓ SERCA-2 expression and ↑ intracellular Ca2+ overload
* ↓ Ca2+ transient amplitude
 | * ↑ PR and AH intervals without alteration of the HV interval
* ↑ bradyarrhythmias and heart blocks (sinus node dysfunction, AV block, bundle branch block), requiring pacemaker placement
* ↑ supraventricular (atrial fibrillation) and ventricular arrhythmias and sudden cardiac death
 |
| **Response to exercise** | * ↓ autonomic response to stress and sinus baroreceptor sensitivity
* ↓ VO2max/kg weight and maximal heart rate at peak exercise and the chronotropic response to β-adrenergic stimulation
* Inability to ↑ LVEDP during exercise, ↓ cardiac reserve
* Metabolic alterations: ↓ body weight and muscle mass, ↑ intramuscular fat, sarcopenia
 | * ↓ muscle function, functional independence, mobility, and quality of life
* ↓ exercise tolerance
* ↑ pulmonary hypertension
 |

Abbreviations: AF: atrial fibrillation. AH: atrial-His interval. AV: atrio-ventricular. COX: cyclo-oxygenase. DBP: systolic blood pressure. eNOS: endothelial nitric oxide synthase. HFpEF: heart failure with preserved ejection fraction. HFrEF: heart failure with reduced ejection fraction. HIF1: hypoxia inducible factor. HCN4: hyperpolarization-activated cyclic nucleotide-gated channel 4. HV: His bundle-ventricular interval. ICaL: L-type calcium current. IL: interleukin. LV: left ventricle. LVEDP: left ventricular end-diastolic pressure. NADPH: nicotinamide adenine dinucleotide phosphate. PGH/F: prostaglandins H and F. PR: PR interval of the electrocardiogram. SBP: systolic blood pressure. SERCA2a: sarcoplasmic reticulum Ca2+ adenosine triphosphatase 2a. SIRT1: silent information regulator 1. TGF: transforming growth factor. TNFα: tumor necrosis factor alfa. TxA2: thromboxane A2. VEGF: vascular endothelial growth factor. VO2max, maximum oxygen consumptions. VSMC: vascular smooth muscle cells. wtTTR: wild-type transthyretin.

**Supplemental Table 2. Cardiovascular drugs highly metabolized in the liver or mainly eliminated by the kidneys12**

|  |  |
| --- | --- |
| **Drugs extensively metabolized in the liver** | **Drugs that mainly renally excreted\*** |
| * Analgesics: NSAIDs
* Angiotensin receptor blockers: candesartan, irbesartan
* Antianginal drugs: ivabradine, ranolazine
* Antiarrhythmics: amiodarone, dofetilide, dronedarone, flecainide, lidocaine, propafenone, quinidine, vernakalant
* Anticoagulants: apixaban, argatroban, edoxaban, rivaroxaban, VKAs (warfarin)
* Antitplatelets: clopidogrel, prasugrel, ticagrelor, vorapaxar
* β-blockers: labetalol, metoprolol, propranolol
* Calcium channel blockers
* Colchicine
* Diuretics: indapamide, torasemide
* Endothelin receptor antagonists: ambrisentan, bosentan, macitentan
* Eplerenone
* Glucose-lowering drugs: gliclazide, pioglitazone, selective sodium-glucose transporter 2 inhibitors, saxagliptin
* Guanylate cyclase inhibitors: riociguat
* Lipid-lowering drugs: ezetimibe, fibrates, statins
* Phosphodiesterase 5 inhibitors: sildenafil, taladafil, vardenafil
* Prostacyclin analogues (beraprost, epoprostenol, iloprost, treprostinil) and selective prostacyclin receptor agonists (selexipag)
* Soluble guanylate cyclase stimulators: riociguat, vericiguat
* Warfarin
 | * ACEIs: benacepril, captopril, cilazapril, enalapril, isinopril, quinapril, ramiprill
* Antiarrhythmics: dofetilide, flecainide, ibutilide, sotalol
* Antithrombotics: dabigatran, eptifibatide, fondaparinux, LMWHs, tirofiban, unfractioned heparin
* Beta-blockers: atenolol, bisoprolol, nadolol
* Digoxin
* Diuretics amiloride, chlorthalidone, furosemide, hydrochlorothiazide, metolazone, spironolactone, triamterene
* Glucose-lowering drugs: exenatide, glimepiridine, glyburide, insulin, metformin, sitagliptin
* Opioids: morphine, meperidine, oxycodone, prophoxyphene, tramadol
* Trimetazidine
 |

Abbreviations: ACEIs: angiotensin-converting enzyme inhibitors. CCBs: calcium channel blockers. LMWH: low-molecular weight heparins. NSAIDs: nonsteroidal anti-inflammatory drugs. VKAs: vitamin K antagonists.

\*: Doses should be reduced (or the drug avoided) with decreased renal function. For creatinine clearance < 15 mL/min consult the nephrologist.

**Supplemental Table S3. Most common drug-drug interactions of cardiovascular drugs in older people12,34**

|  |  |  |
| --- | --- | --- |
| **Drug** | **Interaction** | **Effects** |
| ACEIs/ARBs | ARBs or aliskiren  | Increased risk of renal dysfunction and hyperkalemia |
|  | Loop diuretics  | Hypotension\*, falls, renal impairment |
|  | NSAIDs, COX-2 inhibitors, potassium-sparing diuretics | Decreased renal function, hyperkalemia. NSAIDs can attenuate the antihypertensive effects of ACEIs/ARBs  |
|  | Aldosterone antagonists, cyclosporine, heparin, NSAIDs, potassium-sparing diuretics, tacrolimus, trimethoprim-sulfamethoxazole | ↑ risk of hyperkalemia |
| Adenosine | Dipyridamole, theophylline | Dipyridamole potentiates and theophylline antagonizes its effects |
| Alfa-adrenergic blockers | Antihypertensive drugs, phosphodiesterase 5 inhibitors | Additive BP lowering effects. Monitor BP |
| Amiodarone  | β-blockers, diltiazem, digoxin, or verapamil | ↑ risk of bradycardia and AV block. Amiodarone inhibits CYP2D6 and increases metoprolol exposure |
|  | Flecainide | ↑ flecainide exposure |
|  | Vitamin K antagonists | ↑ their anticoagulant effects |
| Antiarrhythmics (class I) | β-blockers, digoxin, diltiazem, verapamil  | ↑ the risk of bradycardia and AV block |
| Anticoagulants | Antiplatelets, NSAIDs, SSRIs, SNRIs, thrombolytics | ↑ the risk of bleeding |
| Antihypertensives | Vasodilators, antipsychotic drugs, TCAs | ↑ the antihypertensive effect |
|  | NSAIDs | ↓ the antihypertensive effect |
| Antiplatelets | Anticoagulants, SSRIs, SNRIs, NSAIDs, thrombolytics | ↑ the risk of bleeding |
| Aspirin | Anticoagulants, antiaggregants | ↑ the risk of bleeding |
|  | Ibuprofen | ↓ the antiplatelet and cardioprotective effect of aspirin |
| Beta-blockers | Glucose-lowering drugs | Masks hypoglycemia. ↑ risk of hypoglycemia with sulfonylureas |
|  | Diltiazem, verapamil | ↑ the risk ofbradycardia, AV block and hypotension |
|  | Beta-agonists,  |  |
| Bile acid sequestrants | Anticoagulants, digitalis, furosemide, gemfibrozil, hydrochlorothiazide, propranolol and tetracycline | Delay or reduce the absorption of these drugs  |
| Calcium channel blockers | β-blockers, digoxin | ↑ the risk ofbradycardia and AV block |
| Cimetidine | Amiodarone, dofetilide, flecainide, lidocaine, nebivolol, propafenone, sildenafil, theophylline, tolbutamide  | Cimetidine is a non-selective inhibitor of cytochrome P450 isoform that may increase the drug exposure of CYP substrates |
| Clopidogrel | Esomeprazole, omeprazole, statins (atorvastatin, lovastatin, simvastatin)  | ↓ the antiplatelet effect of clopidogrel. Replace omeprazole by pantoprazole. Select non-CYP3A4-metabolized statins |
|  | Glycoprotein IIb/IIIa inhibitors, heparins, NSAIDs, oral anticoagulants | ↑ the risk of bleeding |
| Cyclosporine | Diltiazem, verapamil | ↑ cyclosporine exposure and the risk of ADRs |
| Corticosteroids (oral) | NSAIDs (without PPI prophylaxis) | ↑ the risk of peptic ulcer disease and gastrointestinal bleeding |
| Dabigatran | Clarithromycin, dronedarone, verapamil | ↑ the plasma levels of dabigatran |
| Digoxin | Amiodarone, atorvastatin, canagliflozin, captopril, carvedilol, clarithromycin, cyclosporine, dronedarone, flecainide, erythromycin, omeprazole, propafenone, ranolazine, spironolactone, ticagrelor, verapamil | ↑ digoxin exposure and ADRs (nausea, confusion, bradycardia, AV block).  |
|  | Acarbose, cholestyramine, colestipol, metoclopramide, miglitol, neomycin, sucralfate, sulfasalazine | ↓ absorption of digoxin. Administer 2 h apart from digoxin |
|  | Dronedarone | ↑ risk of sudden death in patients receiving digoxin with dronedarone |
|  | Beta-blockers, diltiazem, ivabradine, verapamil | ↑ the risk of bradycardia and AVB (with beta-blockers) |
|  | Loop and thiazide diuretics | Hypokalemia ↑ the risk of digoxin intoxication |
|  |  |  |
| Direct oral factor Xa inhibitors | Potent inhibitors of P-gp and CYP3A: clarithromycin, cyclosporine, dronedarone, erythromycin, itraconazole, ritonavir, tacrolimus  | ↑ the plasma levels of apixaban, edoxaban and rivaroxaban |
| Endothelin receptor blockers | Amiodarone, amprenavir, cyclosporine, diltiazem, erythromycin, fluconazole, itraconazole,ritonavir-boosted protease inhibitors | ↑ the exposure to bosentan and the combination is not recommended. Avoid the coadministration with cyclosporine and nevirapine |
|  | Glibenclamide | ↑ risk of elevated liver aminotransferases. Avoid the combination  |
|  | Sildenafil | ↑ bosentan exposure and ↓ sildenafil exposure |
| Glucose-lowering drugs | β-blockers (nonselective), corticosteroids, thiazides | ↓ hypoglycemic effects |
|  | Warfarin | ↑ the risk of hypoglycemia in patients on glipizide, glimepiride or metformin |
| Fludrocortisone | Antihypertensive agents | Loss of BP control |
| Iron | Antibiotics (quinolones, tetracyclines), bisphosphonates, levodopa, levothyroxine, methyldopa | Decreased the oral bioavailability of these drugs |
| Lidocaine | β-blockers, cimetidine | ↑ lidocaine exposure and the risk of ADRs |
| Loop diuretics | Beta-blockers | Hyperglycemia, hypertriglyceridemia |
| Metformin | Furosemide | ↑ metformin exposure and the risk of lactic acidosis |
| Mineralocortioid receptor antagonists | Nephrotoxic drugs (aminoglycosides, cisplatin, and NSAIDs) | Worsening of renal function may occur  |
| Nitrates | Phosphodiesterase type 5 inhibitors  | ↑ the risk of severe hypotension. Separate at least 24 (sildenafil) or 48 hours (taladafil) before nitrate use |
| NSAIDs | Antihypertensives | NSAIDs ↓ the effects of some antihypertensives |
|  | Anticoagulants, antiplatelets, fibrinolytics, SSRIs | ↑ the risk of bleeding |
|  | Corticosteroids | ↑ the risk of peptic ulcer disease or gastrointestinal bleedingAvoid if possible\*. If not, provide gastrointestinal protection |
|  | Loop diuretics | NSAIDs can reduce the natriuretic effect of loop diuretics |
| Peripheral α1-blockers | Loop diuretics | ↑ the risk of urinary incontinence in older women (avoid their use) |
| Phosphodiesterase type 5 inhibitors | Organic nitrites or nitrates, α-adrenergic blockers | Contraindicated because of the increased risk of hypotension |
|  | CYP3A4 inhibitors: cimetidine, ciprofloxacin, claryrhromycin, erythromycin, itraconazole, ritonavir, saquinavir | ↑ systemic exposure of sildenafil |
| Proton pump inhibitors | Clopidogrel | ↓ bioactivation of clopidogrel and the therapeutic efficacy |
| QT prolonging drugs | QT prolonging drugs | Avoid the combination when possible |
| Sodium nitroprusside | PDE 5 inhibitors (sildenafil, tadalafil, vardenafil), riociguat, vericiguat | Avoid the combination because of the risk of hypotension |
| Soluble guanylate cyclase stimulators | Nitrates, PDE-5 inhibitors | Avoid the combination because of the risk of severe hypotension |
| Statins (atorvastatin, lovastatin, simvastatin) | Amiodarone, amlodipine, cyclosporine, digoxin, gemfibrozil, macrolides (clarithromycin, erythromycin), verapamil, warfarin | ↑ the risk of myopathy. Avoid the coadministration with cyclosporine or gemfibrozil |
| Vasodilators | Antihypertensives | ↑ the risk of hypotension |
| Verapamil, diltiazem | β-blockers, Class I AADs, digoxin | ↑ the risk of bradycardia and AVB |
| Warfarin | Amiodarone, amoxicillin, anticoagulants, antiaggregants, cimetidine, doxycycline, fluconazole, fluoroquinolones, itraconazole, lansoprazole, macrolides, NSAIDs, omeprazole, propafenone, prostacyclin, SSRIs, SNRIs, sulfonamides, trimethoprim-sulfamethoxazole, thyroxine | ↑ the INR and the risk of bleeding. Monitor the INR closely |
|  | Vitamin K, barbiturates, bosentan, carbamazepine, rifampin, sulfacrate, trazodone | Loss of anticoagulant control |

Abbreviations: AADs: antiarrhythmic drugs. ACEIs: angiotensin converting enzyme inhibitors. ARBs: angiotensin receptor blockers. ADRs: adverse drug reactions. AV: atrio-ventricular. AVB: atrio-ventricular block. BP: blood pressure. CNS: central nervous system. CYP: cytochrome P450. INR: International Normalized Ratio. LV: left ventricular. NSAIDs: nonsteroidal anti-inflammatory drugs. PDE5: phosphodiesterase type 5. P-gp: P-glycoprotein. PPIs: proton pump inhibitors. RAAS: renin-angiotensin-aldosterone system. SNRIs: selective serotonin norepinephrine re-uptake inhibitors. SSRIs: selective serotonin reuptake inhibitors. TCAs: tricyclic antidepressants. VKAs: vitamin K antagonists.

**Other references**

* Stockley IH. Stockley's Drug Interactions. 12th Edition. Ed. Preston CL. Pharmaceutical Press, London 2019

**Supplemental Table S4. Most common cardiovascular drug-disease interactions in the elderly12,34**

|  |  |
| --- | --- |
| **Disease** | **Contraindicated/non-recommended drugs** |
| **Angina pectoris** | Vasodilators, including the combination of nitrated and phosphodiesterase type-5 inhibitors  |
| **Asthma** | Avoid β-blockers in asthmatic patients |
| **Atrial fibrillation** | Adenosine, antineoplastic agents (anthracyclines, interleukin 2, mitoxantrone, paclitaxel), bisphosphonate drugs, corticosteroids, dobutamine, ivabradine, milrinone and ondansetron can induce atrial fibrillation. |
| **Bradycardia/AVB** | Higher risk with class I, II and IV AADs and digoxin. Ivabradine: higher risk of bradycardia |
| **Cardiac conduction disorders** | Class I AADs |
| **Cardiovascular disease** | COX-2 selective NSAIDs with concurrent cardiovascular disease increased risk of myocardial infarction and stroke |
| **Constipation** | Atropine, bile acid sequestrants, iron supplements, furosemide, morphine, propranolol, verapamil |
| **COPD** | Non-selective β-blockers (propranolol, carvedilol, labetalol, sotalol), propafenone and sotalol may exacerbate bronchospasm  |
| **Coronary artery disease** | Class I AADs increase the risk of proarrhythmia and sudden cardiac death. Drugs producing postural hypotension |
| **Decrease bone density** | Anticonvulsants, glucocorticoids, H2 receptor antagonists, proton pump inhibitors, thiazolidinediones |
| **Depression** | β-blockers, centrally acting antihypertensive and methyldopa can precipitate or exacerbate depression |
| **Diabetes** | β-blockers, corticosteroids, diazoxide, statins, thiazide and loop diuretics can produce hyperglycemia  |
| **Electrolyte abnormalities** | Maintain normal serum potassium (3.5–5 mmol/L) levels in patients receiving diuretics, ACEIs, and/or ARBsHypokalemia can precipitate QT-prolongation related ventricular arrhythmias and increase digitalis toxicity |
| **Falls** | Drugs (antihypertensive, vasodilators) that produce orthostatic hypotension |
| **Heart failure** | AADs (class IC and IV, dronedarone, sotalol), chemotherapy drugs (anthracyclines, bevacizumab, cyclophosphamide, lapatinib, imatinib, paclitaxel, sunitinib, trastuzumab), cilostazol, doxazosin, moxonidine, NSAIDs and pioglitazone can worsen HF in patients with poor LV function. Use with caution; dosage adjustments are necessary. |
| **Hyperkalemia** | Avoid drugs producing hyperkalemia: antifungals (fluconazole, itraconazole), non-selective β-blockers, cyclosporine, digoxin, heparin, NSAIDs, potassium-sparing diuretics, renin-angiotensin-aldosterone system inhibitors, tacrolimus |
| **Hypertension** | ↑ BP cyclosporine, corticosteroids and mineralocorticoids, nasal decongestants (phenylephrine, pseudoephedrine), erythropoietin, estrogens, NSAIDs, phentermine, tacrolimus and VEGF inhibitors |
| **Hyperuricemia** | Thiazide diuretics |
| **Hypokalemia** | ↑ the risk of life-threatening ventricular arrhythmias induced by digoxin or dofetilide |
| **Kidney disease (CrCl <30 mL/min)** | Avoid mineralocorticoid receptor antagonists.Dosage adjustment is necessary for drugs mainly excreted by the kidney or whose active metabolites are eliminated by the kidney (see Suppl Table 2). Close monitoring of renal function |
| **Liver disease** | With caution drugs that are highly metabolized in the liver (see Suppl Table 2) |
| **Metabolic syndrome** | β-blockers, thiazide diuretics |
| **Peripheral artery disease** | β-blockers (consider those with direct vasodilator properties: carvedilol, nebivolol) |
| Postural hypotension | Antihypertensive drugs, direct peripheral vasodilators, nitrates |
| **Syncope** | Avoid drugs that ↑ the risk of orthostatic hypotension. |
| **Ventricular arrhythmias** | Drugs producing hypokalemia (i.e., loop and thiazide diuretics) |
| **Venous thromboembolism** | Diuretics (loop and thiazide diuretics), erythropoietin, estrogens, SSRIs |

Abbreviations. AADs: antiarrhythmic drugs. ACEIs: angiotensin converting enzyme inhibitors. AF: atrial fibrillation. ARBs: angiotensin receptor blockers. COPD: chronic pulmonary disease. COX-2: cyclooxygenase 2. CrCl: creatinine clearance. DVT: deep venous thrombosis. eGFR: estimated glomerular filtration rate. GI: gastrointestinal. HF: heart failure. INR: international normalized ratio. LMWHs: low-molecular weight heparins. LV: left ventricular. NSAIDs: nonsteroidal anti-inflammatory drugs. PE: pulmonary embolism.P-gp: P-glycoprotein. PPIs: proton pump inhibitors. SNRIs: serotonin–norepinephrine reuptake inhibitors. SSRIs: selective serotonin reuptake inhibitors. VEGF: Vascular endothelial growth factor. VKORC1: Vitamin K epOxide Reductase Complex subunit 1. VTE: venous thromboembolism.