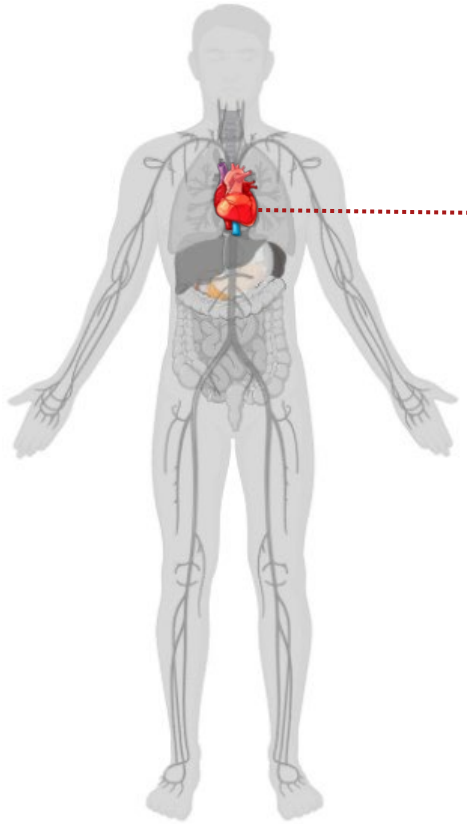
# Negative Impact of Hypercortisolism on Cardiovascular Health

# Cardiovascular consequences

## Physiological role of cortisol[1]



**Cardiovascular System**

- Cardiomyocyte survival
- Cardiac hypertrophy
- Vascular inflammation
- Blood pressure regulation

## Cardiovascular consequences of excess cortisol[2-5]

**Up to 85%**
Hypertension[2,3]

**Up to 20%**
Thromboembolic events[4]

**2x risk**
Myocardial infarction[4]

**6x risk**
Cardiac failure[4]

**Up to 100%**
Cardiovascular-related mortality[5]

1. Cruz-Topete D, et al. *Front Endocrinol*. 2020;11:347. doi:10.3389/fendo.2020.00347 2. Braun LT, et al. *Front Endocrinol (Lausanne)*. 2019;10:766. 3. Prete A, et al. *Ann Intern Med*. 2022;175(3):325-334. 4. Pivonello R, et al. *Lancet Diabetes Endocrinol*. 2016;4:611-629. 5. Javanmard P, et al. *Endocrinol Metab Clin N Am*. 2018;47:313-333.

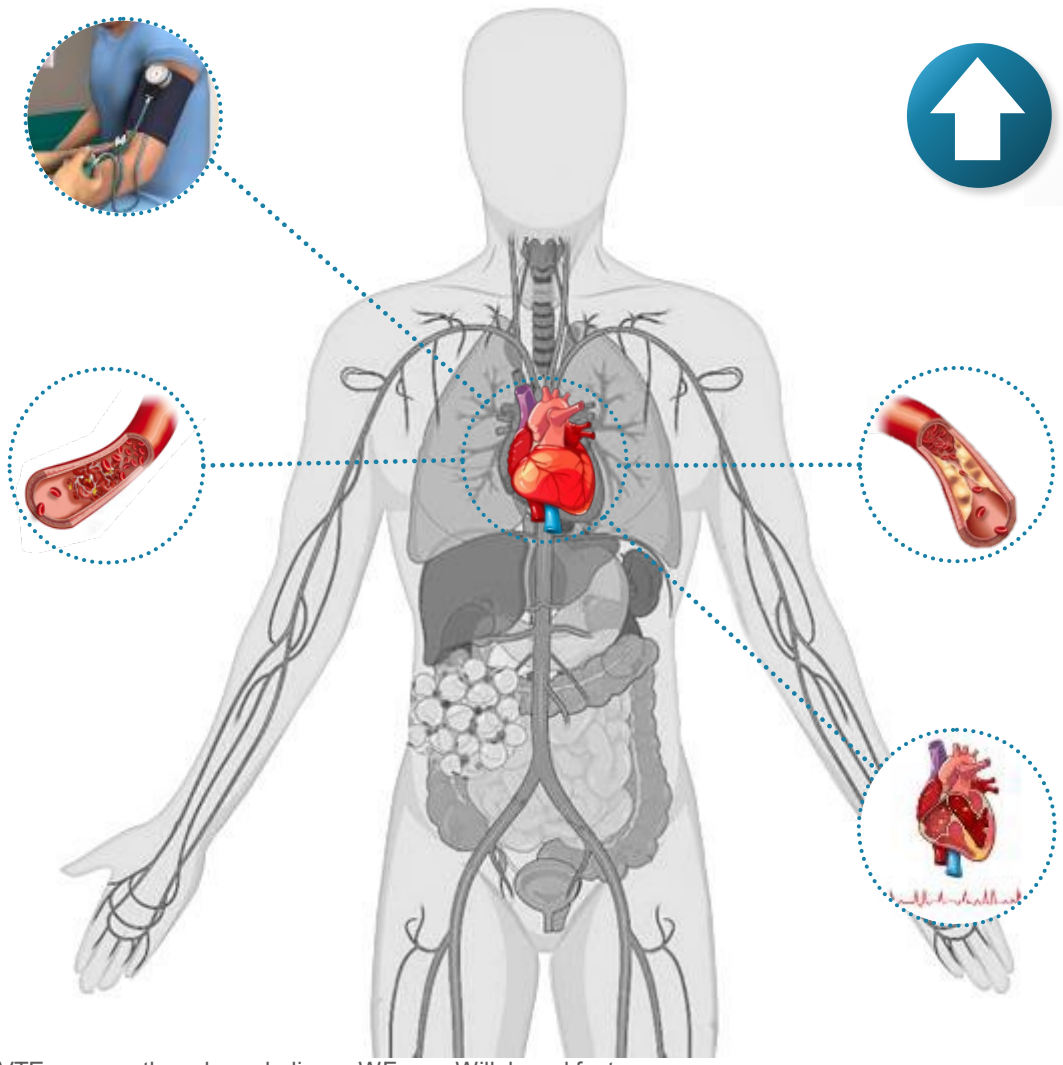
# Excess cortisol negatively impacts cardiac structure/function, blood pressure, and coagulation

## Hypertension[1]

- ↑ Renin-angiotensin system
- ↑ Mineralocorticoid activity
- ↑ Sympathetic nervous system
- ↑ Vasoconstriction

## VTE[1,2]

- ↑ FVIII
- ↑ vWF
- ↑ Fibrinogen
- ↑ PAI-1
- ↑ Inflammation[2]



**Cardiovascular risks**
**Metabolic syndrome**

## Vascular atherosclerosis[1]

Dyslipidemia
Inflammation
Insulin resistance
Impaired glucose tolerance
Diabetes mellitus
Visceral obesity

## Cardiac comorbidities[1]

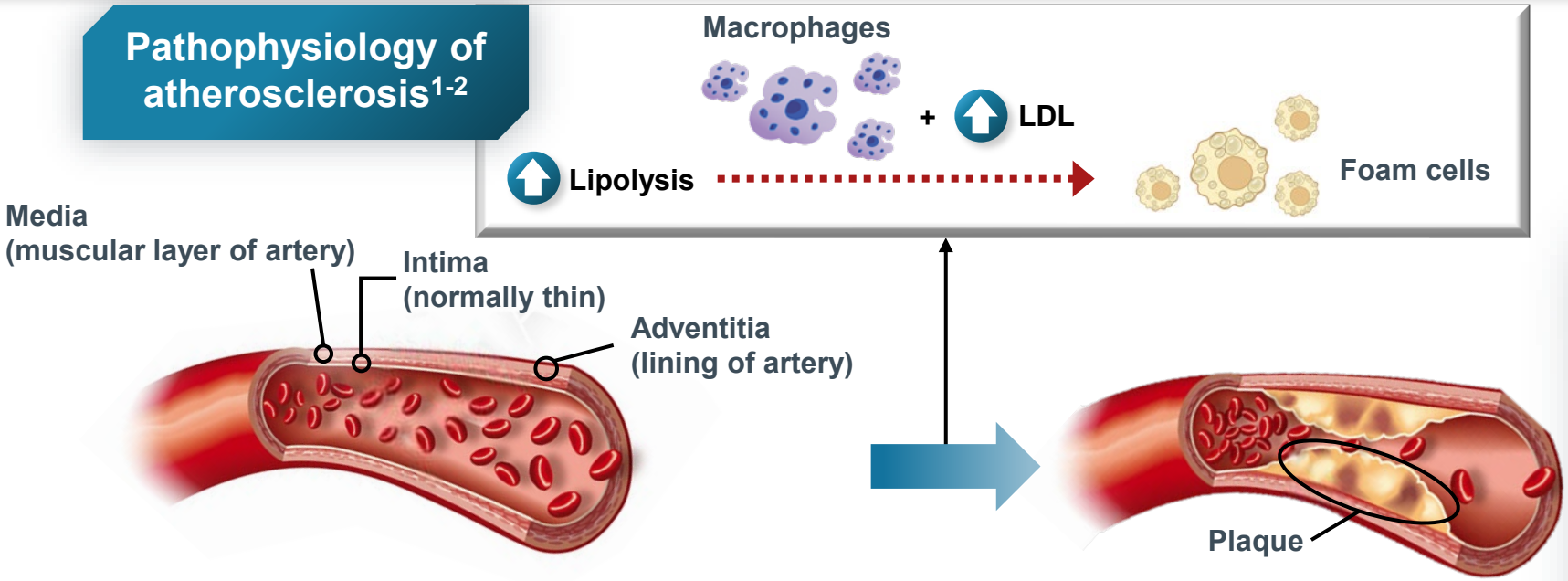
Arrhythmia
Left ventricular hypertrophy
Changes in wall thickness
Myocardial fibrosis
Hypokalemia

FVIII=factor VIII; PAI-1=plasminogen activator inhibitor-1; VTE=venous thromboembolism; vWF=von Willebrand factor.

1. Pivonello R, et al. *Lancet Diabetes Endocrinol*. 2016;4:611-629. 2. Suarez MG, et al. *J Endocr Soc*. 2019;4(2):bvz033. doi:10.1210/jendso/bvz033

# Excess cortisol increases the risk of atherosclerosis

## Pathophysiology of atherosclerosis[1-2]




## Indicators of atherosclerosis were significantly elevated in patients with CS compared with patients with essential hypertension[3]

| Variable | CS (n=30) | EH (n=35) | Control (n=30) |
|---|---|---|---|
| cIMT, mm | 0.93 (0.17)[a] | 0.81 (0.16) | 0.75 (0.24) |
| Plaque, % | 26.6[a] | 16 | 0 |
| ABI[b] (<0.9), % | 20[a] | 3 | 0 |

## Effects of excess cortisol[3,4]

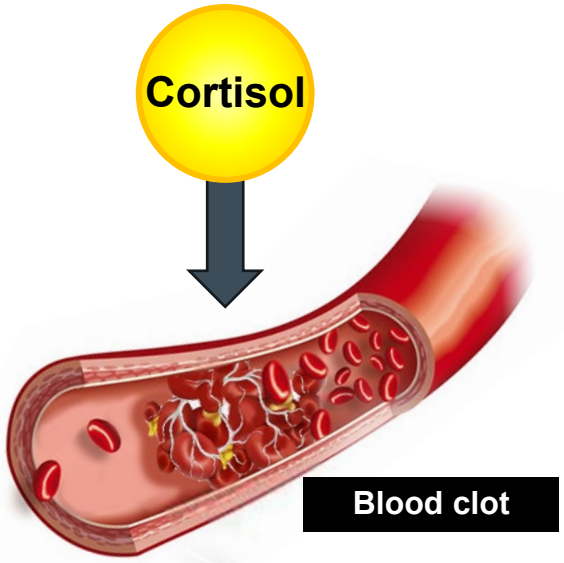
- ↑ Endothelial dysfunction
- ↑ Intima-media thickness
- ↓ Flow-mediated dilation
- ↑ VEGF
- ↑ Carotid plaques

**The risk of myocardial infarction increases 43% with every 0.163-mm increase in cIMT[4]**

ABI=ankle-brachial index; cIMT=carotid intima-media thickness; CS=Cushing's syndrome; EH=essential hypertension; LDL=low-density lipoprotein; VEGF=vascular endothelial growth factor.
[a]*P*<0.03 vs EH and healthy subject (control). [b]ABI is an indicator of generalized atherosclerosis, and low ABI has been related to an increased incidence of cardiovascular mortality.

1. van der Sluis RJ, Hoekstra M. *Mol Cell Endocrinol*. 2020;504:110728. 2. Magomedova L, Cummins CL. *Handb Exp Pharmacol*. 2016;233:73-93.
3. Petramala L, et al. *Endocrinol Metab (Seoul)*. 2015;30(4):488-493. 4. Lupoli R, et al. *Ann Med*. 2017;49:206-216.

# Excess cortisol promotes coagulation and increases the risk of thrombosis




**Odds ratio of VTE[1]**
Meta-analysis of 7142 patients with endogenous hypercortisolism

**17.82**

## Excess cortisol modulates several factors involved in coagulation[3]

| Variable | Role in coagulation | Change in patients with CS |
|---|---|---|
| **vWF** | Mediates platelet adhesion | ↑ |
| **aPTT** | Coagulation time | ↓ |
| **FVIII** | Promotes coagulation | ↑ |
| **Fibrinogen** | Promotes coagulation | ↑ |
| **PAI-1** | Inhibitor of fibrinolysis | ↑ |
| **TAFI** | Inhibitor of fibrinolysis | ↑ |
| **α2-antiplasmin** | Inhibitor of fibrinolysis | ↑ |

Excess cortisol can promote coagulation and impair fibrinolysis

- ↓ Activated partial thromboplastin time[1]
- ↑ Clot lysis time[2]

aPTT=activated partial thromboplastin time; TAFI=thrombin activatable fibrinolysis inhibitor.

1. Wagner J, et al. *Front Endocrinol (Lausanne)*. 2019;9:805. doi:10.3389/fendo.2018.00805 2. van der Pas R, et al. *Clin Endocrinol (Oxf)*. 2013;78(4):481-488.
3. Isidori AM, et al. *Eur J Endocrinol*. 2015;173:R101-R113.

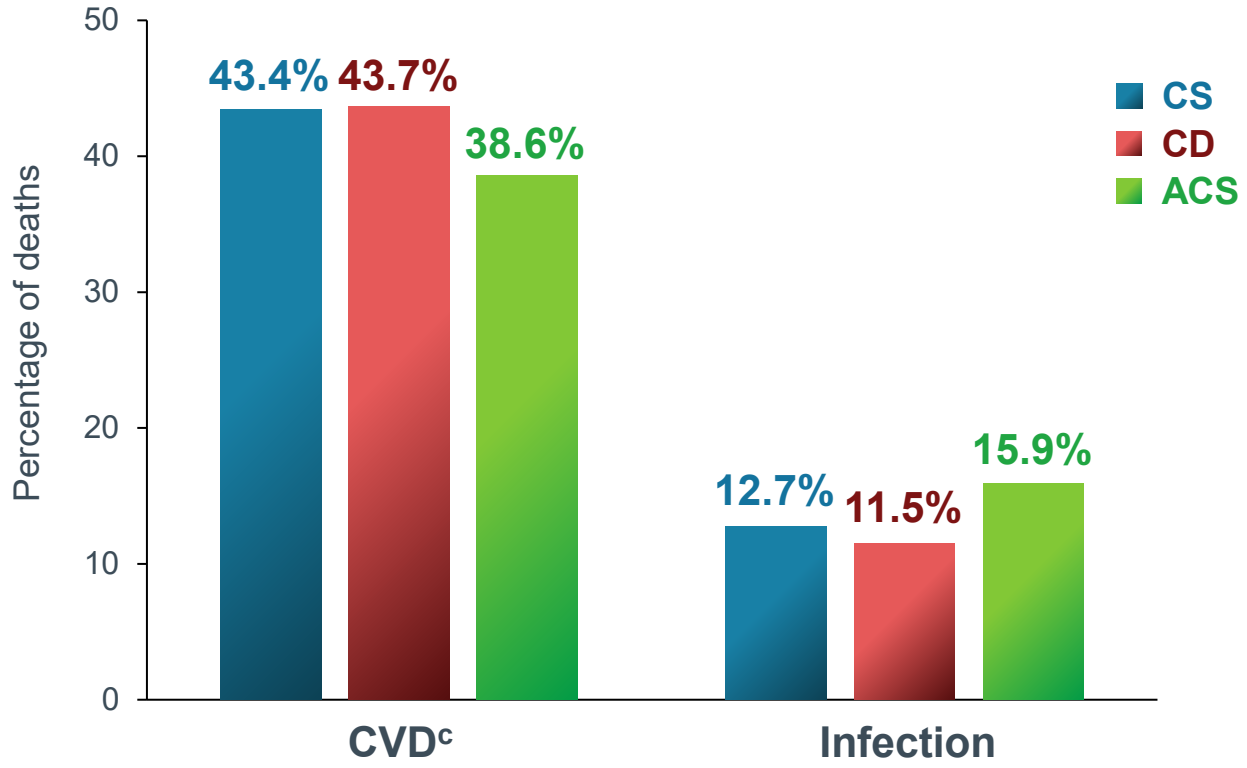
# Mortality risk: Need for timely diagnosis and treatment

## Standardized Mortality Ratio[a]

| | |
|---|---|
| **Pooled CS (CD + ACS)**<br>20 study cohorts (n=3691) | **3x** |
| **Cushing disease (CD)**<br>13 study cohorts (n=2160) | **2.8x** |
| **Active CD**<br>8 study cohorts (n=206) | **5.7x** |
| **Remission from CD**<br>8 study cohorts (n=1103) | **2.3x** |
| **Adrenal CS (ACS)**<br>7 study cohorts (n=1531) | **3.3x[b]** |

## Most common causes of death

Meta-analysis of 68 study cohorts that included 592 deaths among 7255 patients




CVD=cardiovascular disease.

[a]Represented by the number of CS deaths in the study compared to the expected number of deaths in an age- and sex-matched normal population. [b]*P*<0.1 vs SMR for pituitary CS. [c]Includes atherosclerotic heart disease, cerebrovascular disease, and venous thromboembolism.

Limumpornpetch P, et al. *J Clin Endocrinol Metab*. 2022;107(8):2377-2388.