Choosing Study Outcomes that Reflect Cardiovascular Disease: From "Biomarkers" to Burden of Disease

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Framework for Choosing "Subclinical" Outcomes To Study

- What clinical outcomes are of interest?
- What pathways to these clinical outcomes can be meaningfully examined?
- What measures provide meaningful insight into likely contribution to burden of disease?

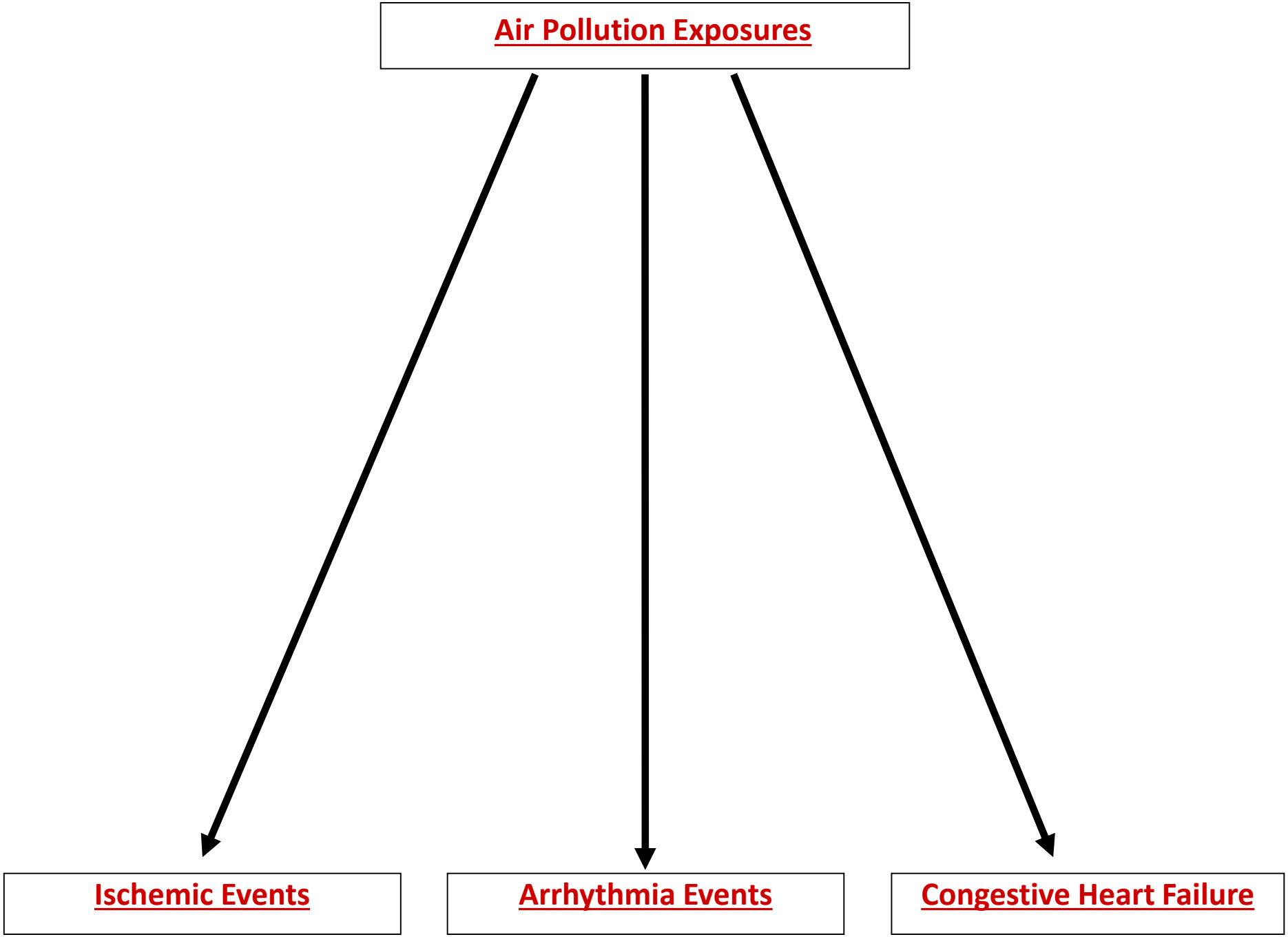
What Clinical Outcomes Are of Interest?

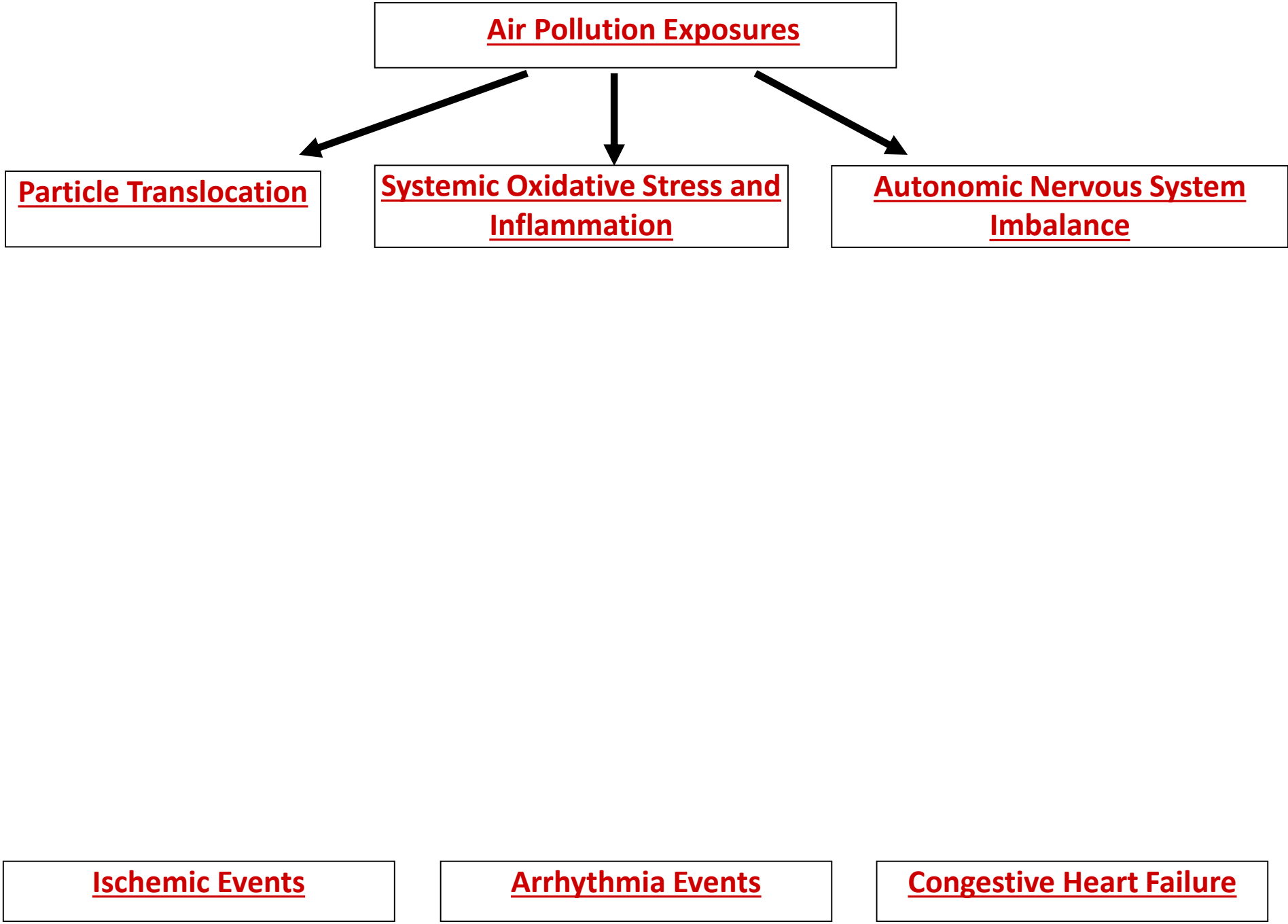
- Informed by Studies of Ambient Air Pollution:
  - Short-term Increases in Pollutant Concentration Associated with *Triggering* of Acute Cardiovascular Events
  - Long-term Concentration Gradients Associated with Increased Risk of Cardiovascular Events

- Appealing to consider common mechanisms of short- and long-term effect, though common mechanism not necessary

What pathways to these clinical outcomes can be meaningfully examined?

- Can we be informed by research into effects of ambient air pollution?


Air Pollution Exposures
Ischemic Events
Arrhythmia Events
Congestive Heart Failure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Systemic Oxidative Stress and Inflammation
Autonomic Nervous System Imbalance
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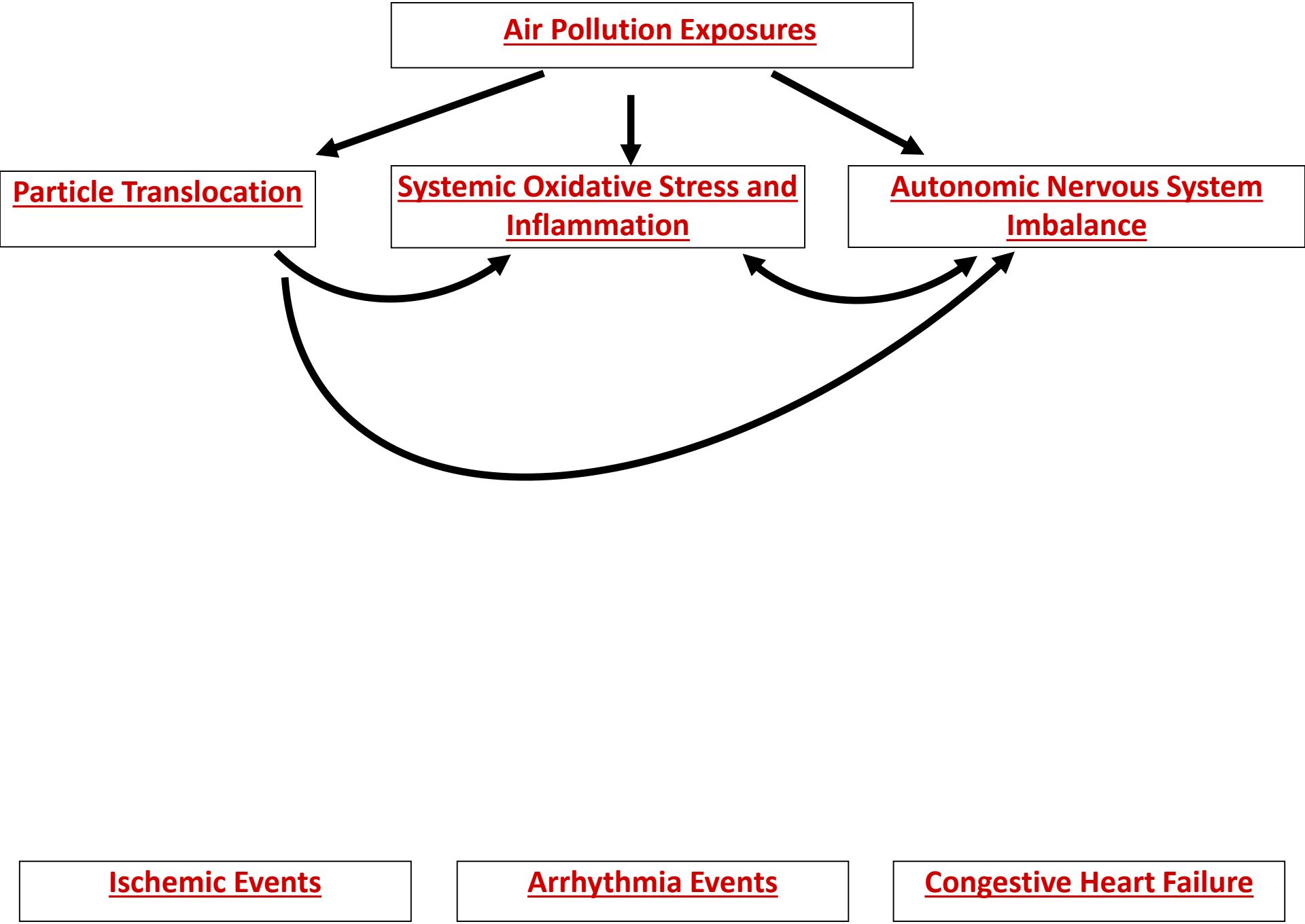
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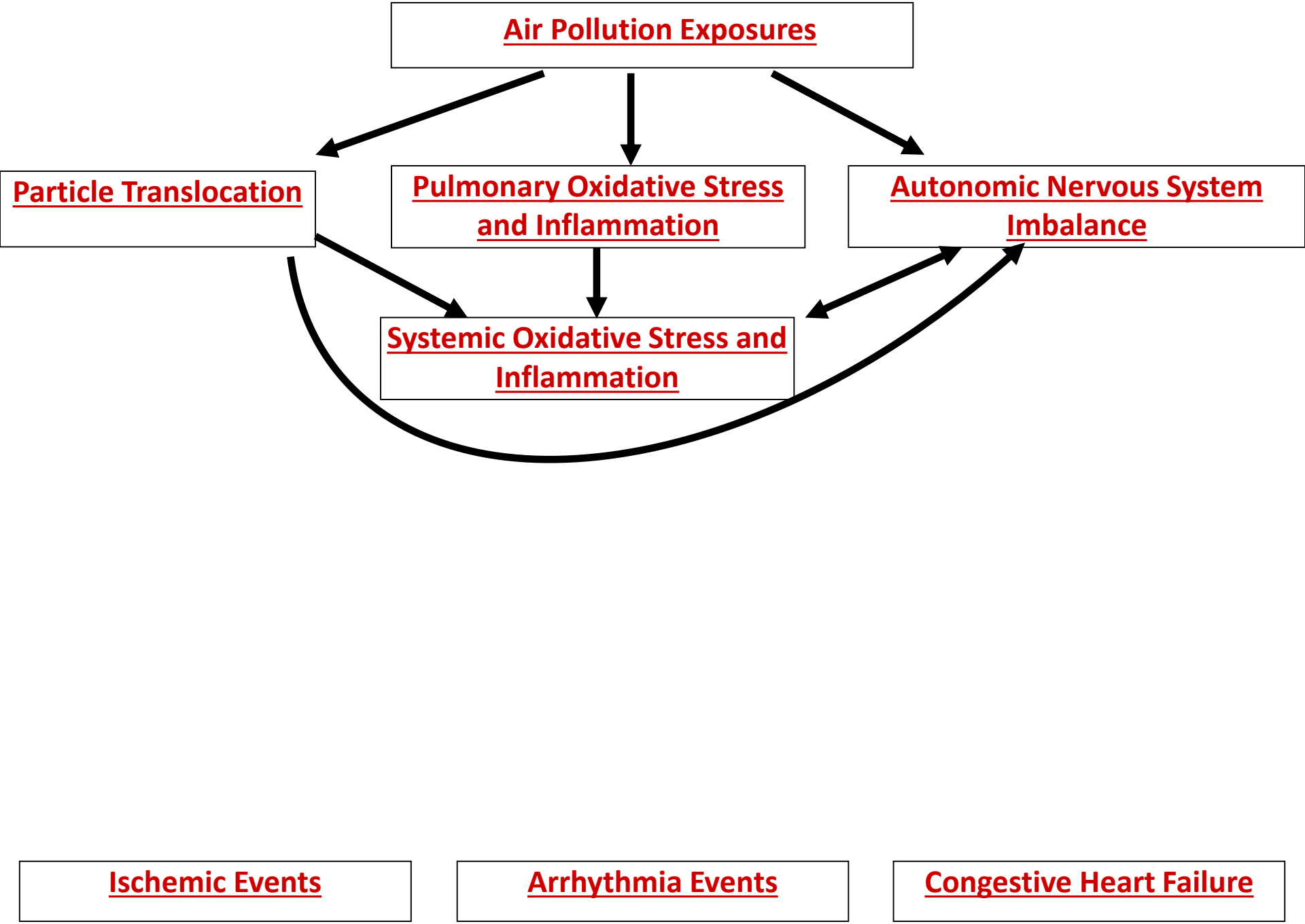
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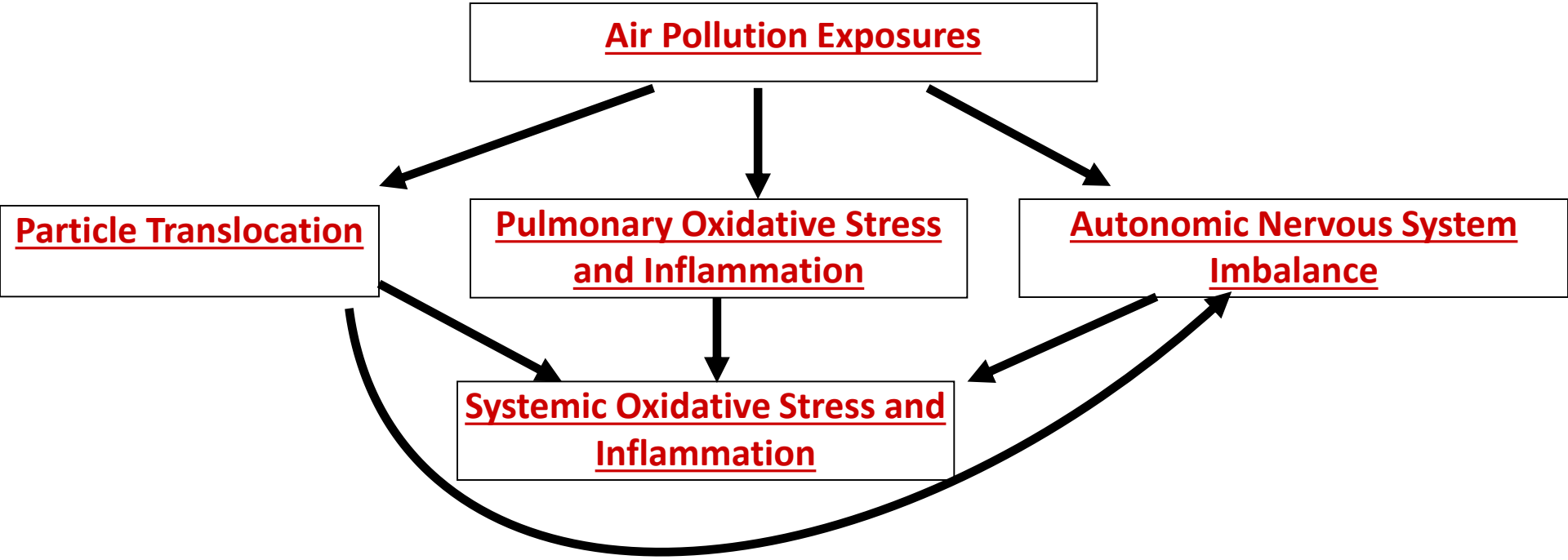
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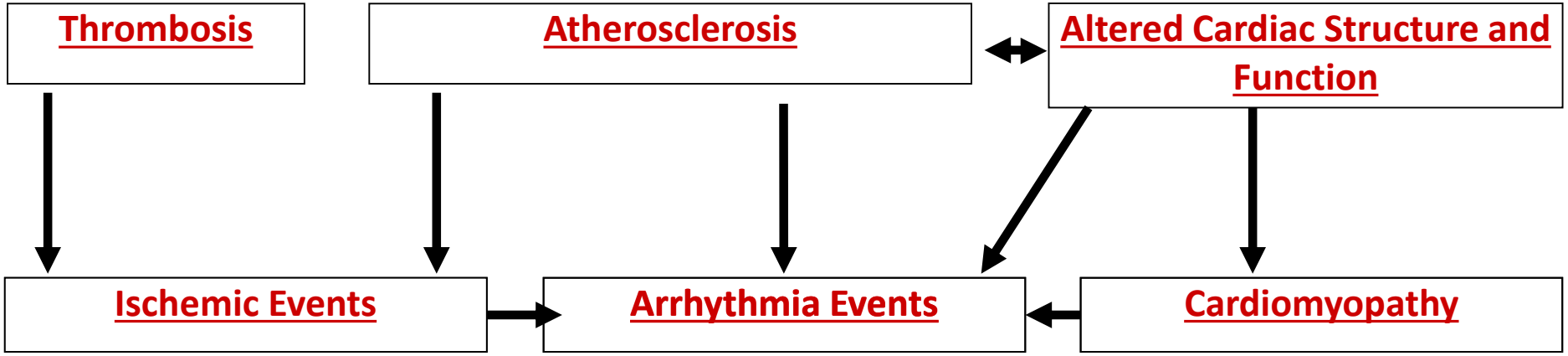
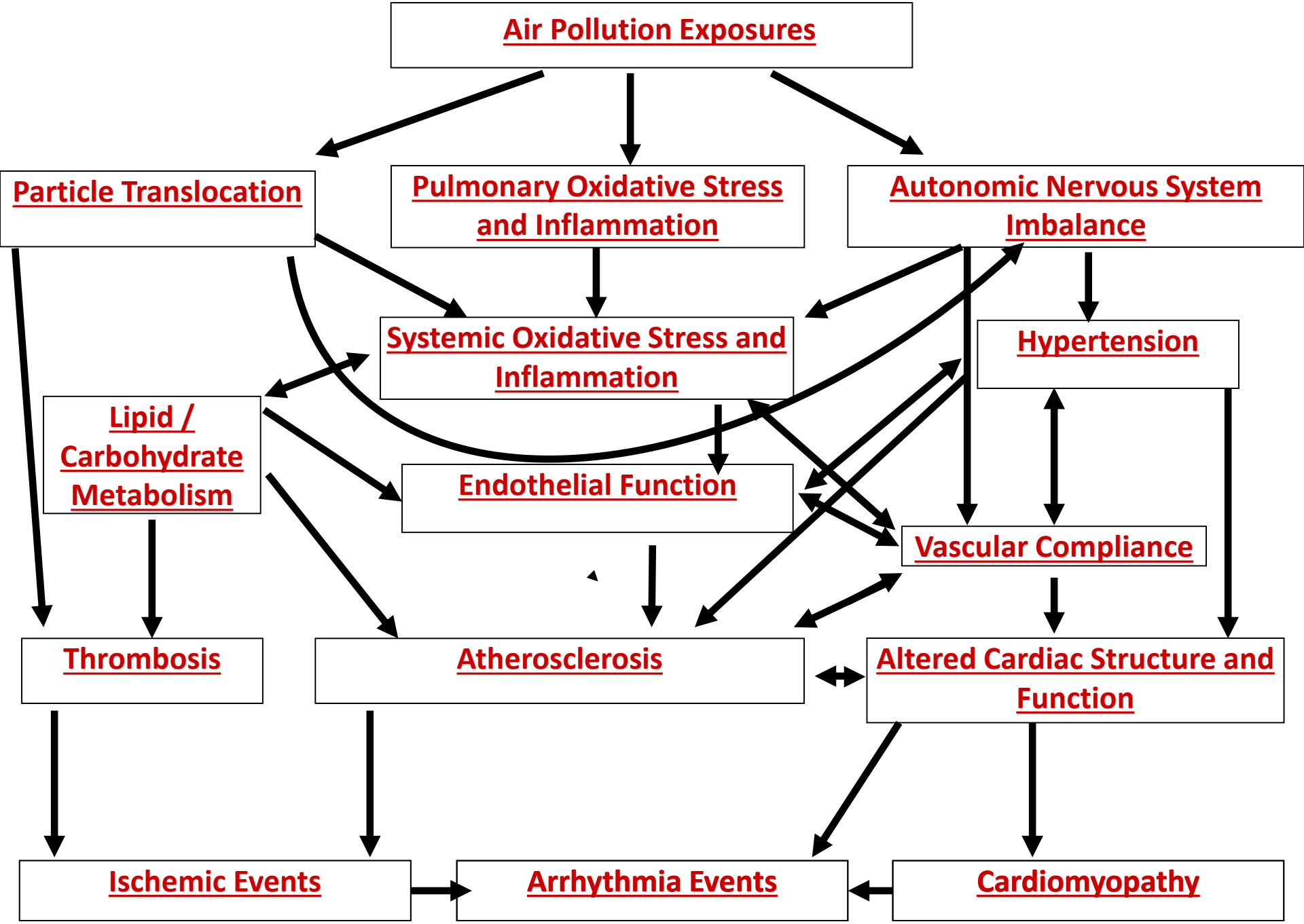

Thrombosis
Atherosclerosis
Altered Cardiac Structure and Function
Ischemic Events
Arrhythmia Events
Cardiomyopathy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Endothelial Function
Vascular Compliance
Thrombosis
Atherosclerosis
Altered Cardiac Structure and Function
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Arrhythmia Events
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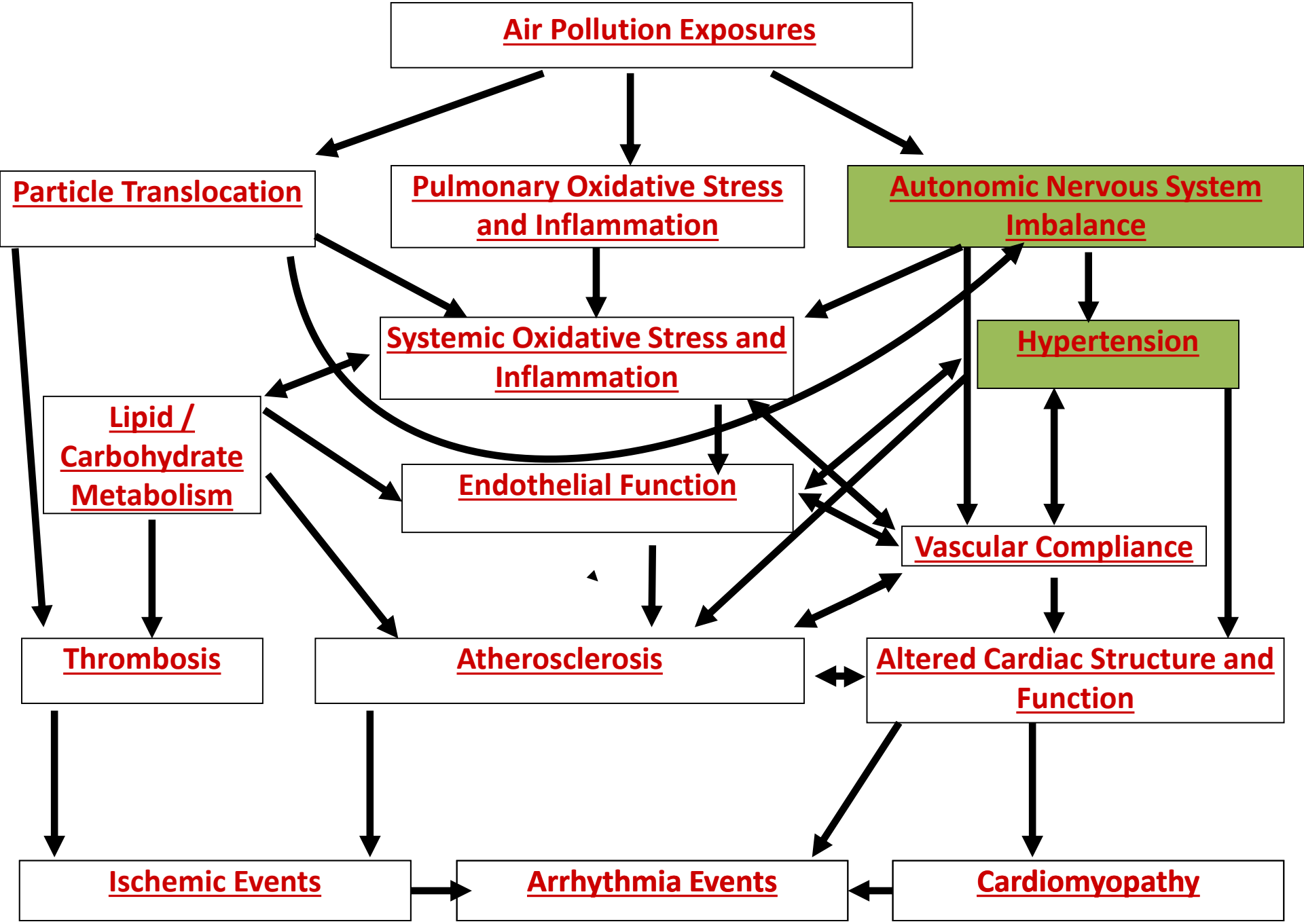
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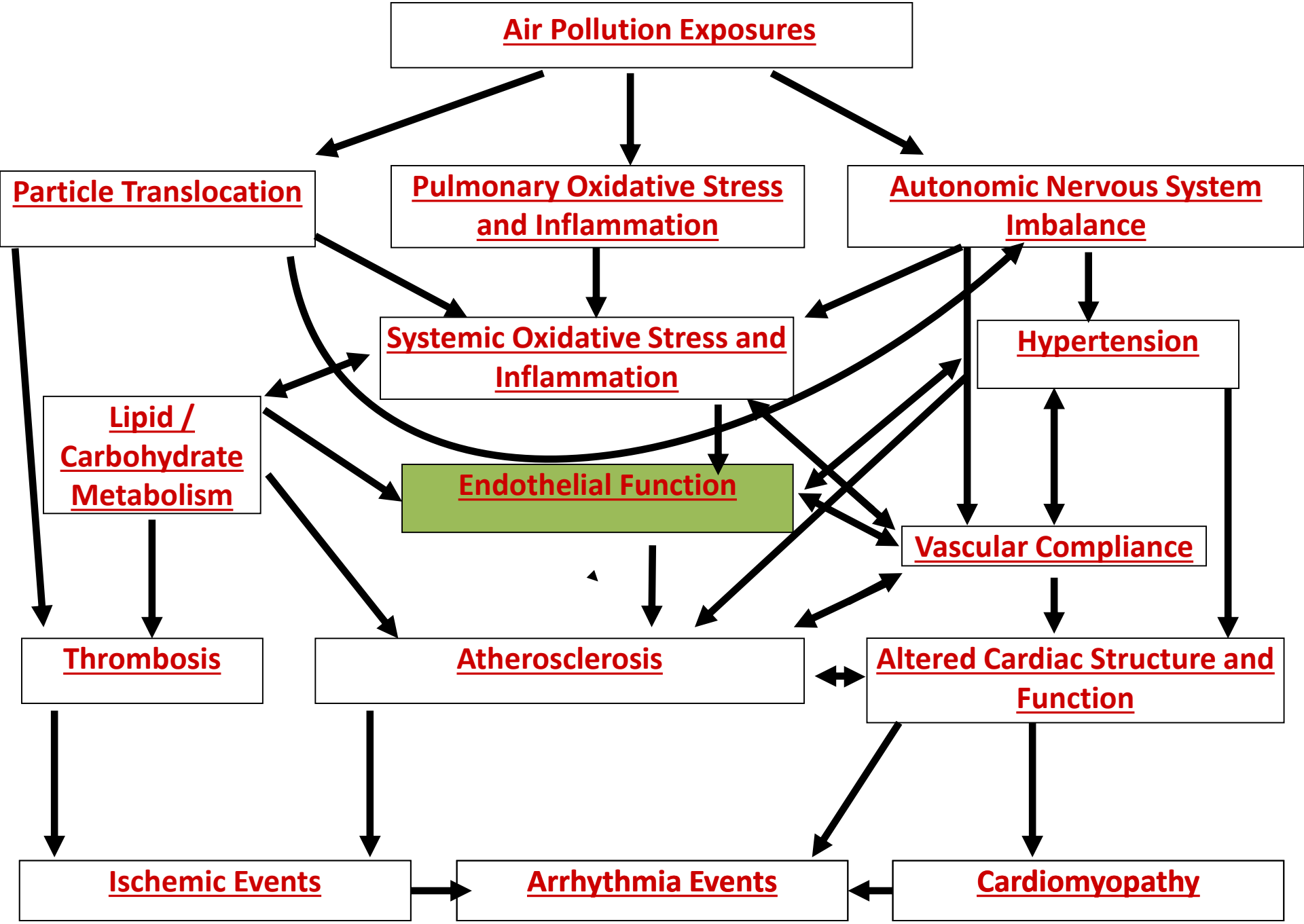
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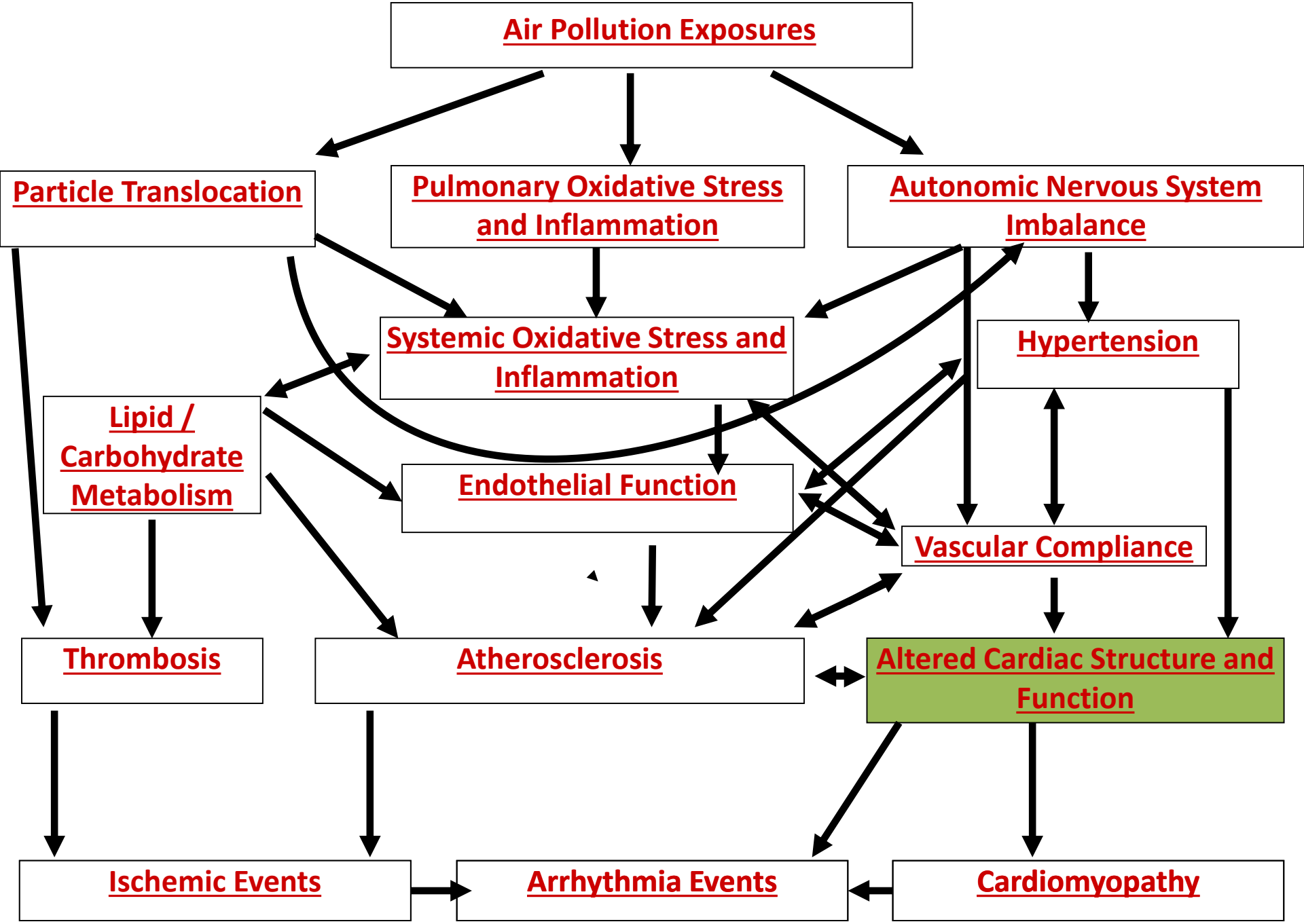
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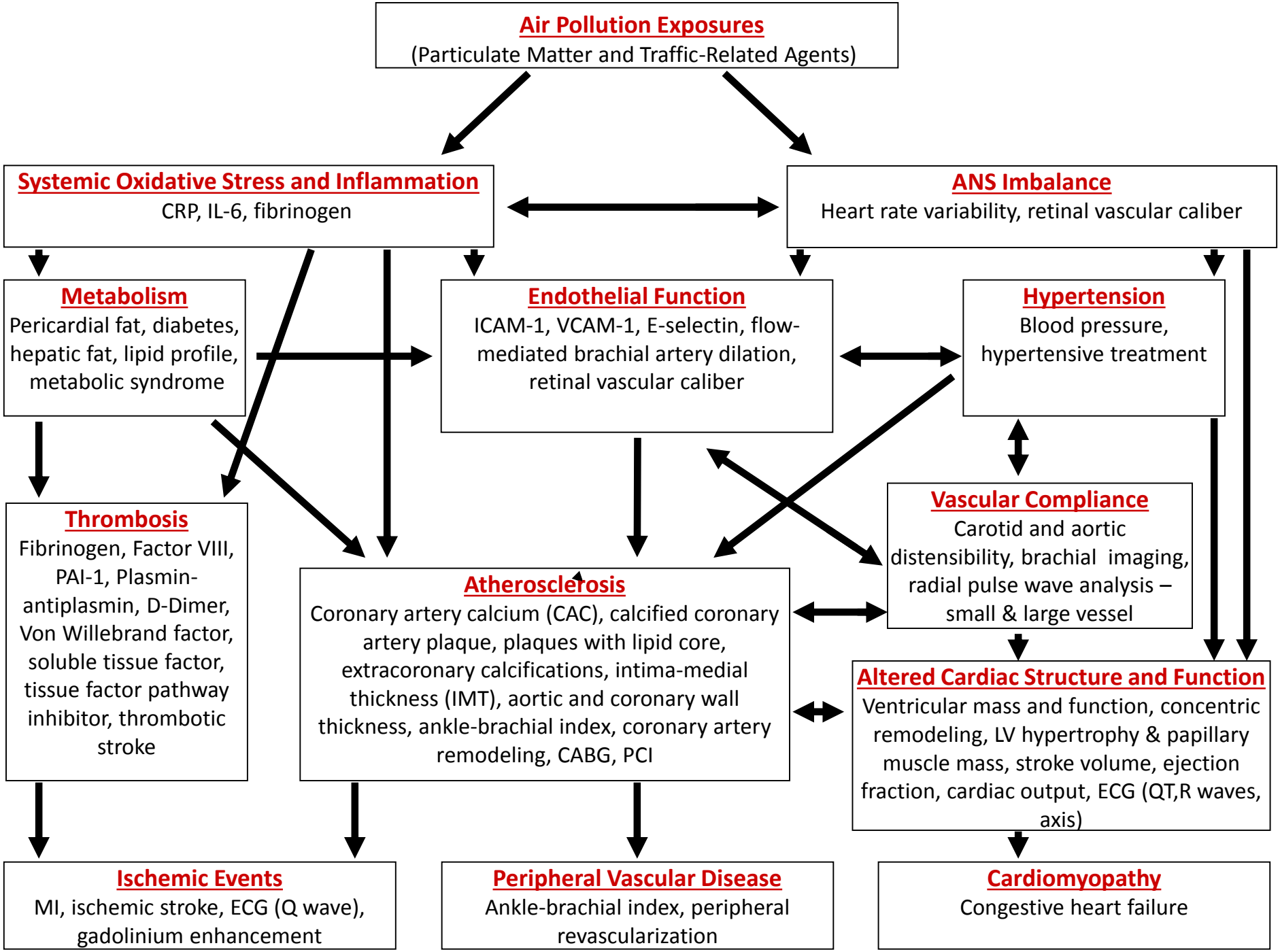
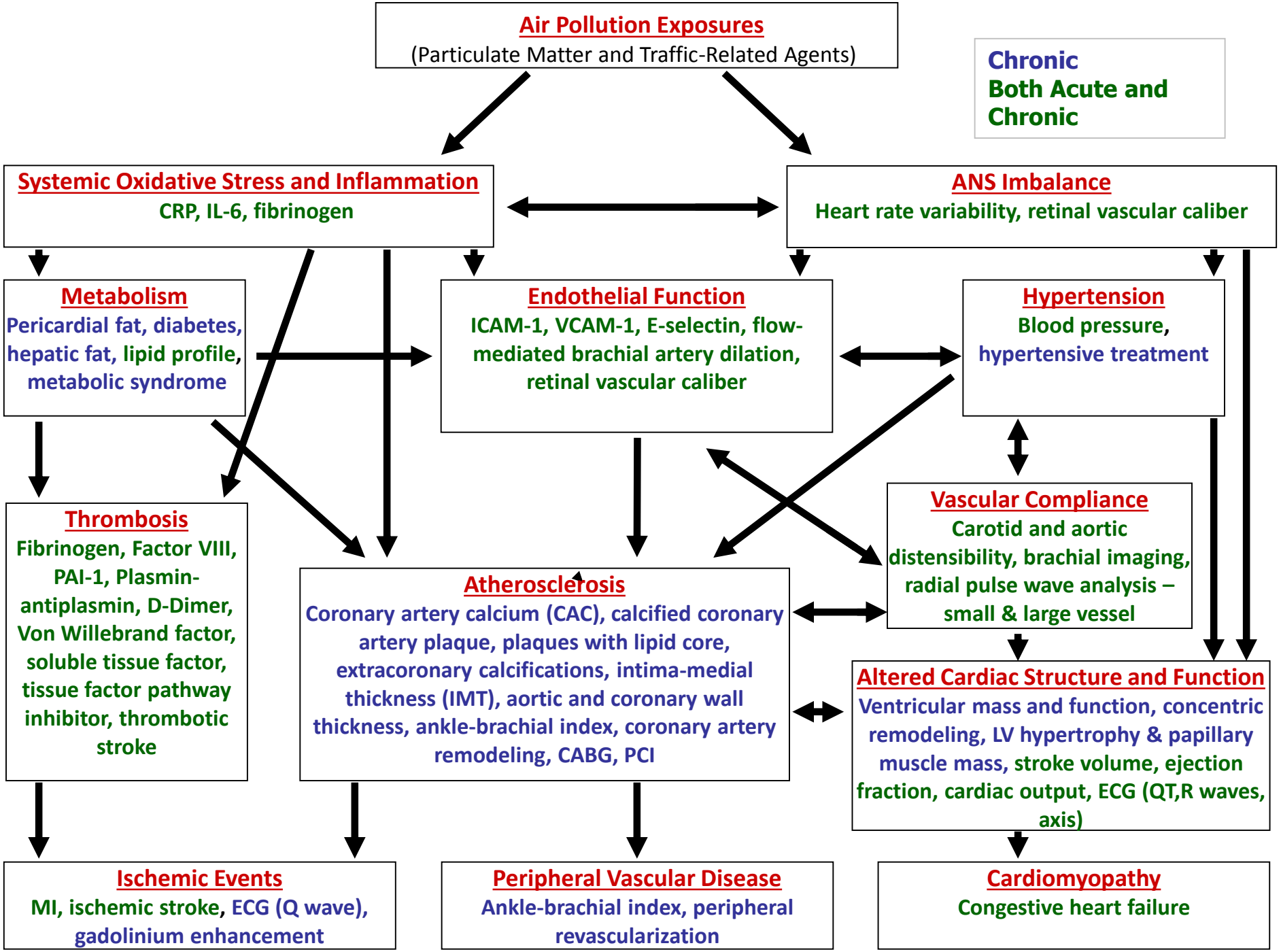

Air Pollution Exposures
(Particulate Matter and Traffic-Related Agents)
Systemic Oxidative Stress and Inflammation
CRP, IL-6, fibrinogen
ANS Imbalance
Heart rate variability, retinal vascular caliber
Metabolism
Pericardial fat, diabetes, hepatic fat, lipid profile, metabolic syndrome
Endothelial Function
ICAM-1, VCAM-1, E-selectin, flow-mediated brachial artery dilation, retinal vascular caliber
Hypertension
Blood pressure, hypertensive treatment
Thrombosis
Fibrinogen, Factor VIII, PAI-1, Plasmin-antiplasmin, D-Dimer, Von Willebrand factor, soluble tissue factor, tissue factor pathway inhibitor, thrombotic stroke
Vascular Compliance
Carotid and aortic distensibility, brachial imaging, radial pulse wave analysis – small & large vessel
Atherosclerosis
Coronary artery calcium (CAC), calcified coronary artery plaque, plaques with lipid core, extracoronary calcifications, intima-medial thickness (IMT), aortic and coronary wall thickness, ankle-brachial index, coronary artery remodeling, CABG, PCI
Altered Cardiac Structure and Function
Ventricular mass and function, concentric remodeling, LV hypertrophy & papillary muscle mass, stroke volume, ejection fraction, cardiac output, ECG (QT,R waves, axis)
Ischemic Events
MI, ischemic stroke, ECG (Q wave), gadolinium enhancement
Peripheral Vascular Disease
Ankle-brachial index, peripheral revascularization
Cardiomyopathy
Congestive heart failure


Air Pollution Exposures
(Particulate Matter and Traffic-Related Agents)
Chronic
Both Acute and Chronic
Systemic Oxidative Stress and Inflammation
CRP, IL-6, fibrinogen
ANS Imbalance
Heart rate variability, retinal vascular caliber
Metabolism
Pericardial fat, diabetes, hepatic fat, lipid profile, metabolic syndrome
Endothelial Function
ICAM-1, VCAM-1, E-selectin, flow-mediated brachial artery dilation, retinal vascular caliber
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Blood pressure, hypertensive treatment
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Hypothesized Mechanisms

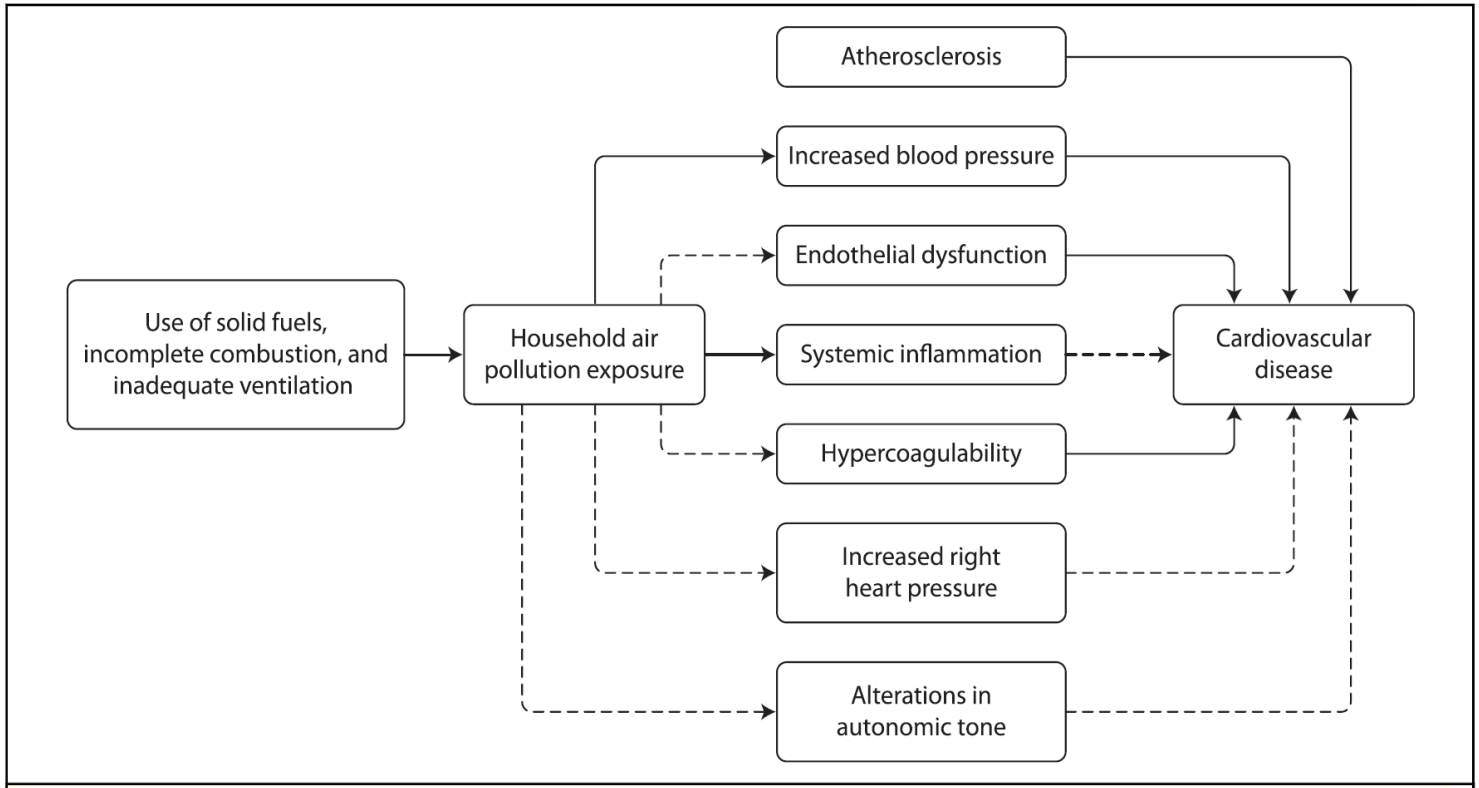


Fig. 1. Schematic representation of hypothesized mechanisms for relationship between household air pollution (HAP) and cardiovascular disease (CVD). Solid lines represent stronger evidence and dashed lines represent weaker evidence. Strong evidence for the link between HAP and surrogate outcomes means it is based on randomized controlled trials or carefully conducted observational studies with adequate control for confounders and valid exposure assessment. Strong evidence for the link between surrogate outcomes and CVD means that these markers are widely accepted as determinants of CVD. The absence of an arrow means there is no evidence of a relationship from HAP studies.

McCracken et al. *Global Heart.* 2012

What measures provide meaningful insight into likely contribution to burden of disease?

Considerations:

- What's measurable AND what is informative regarding burden of disease?
  - Insight into mechanism secondary
- What can be feasibly measured in resource-poor settings?
- What informs mechanism vs risk prediction?
- Biochemical vs functional vs structural markers of cardiovascular health and disease
- Time course of effect

What Makes an Ideal Test?

- Meaningful to be measured repeatedly in an individual
- Could be hypothesized to change in response to risk factor modification within months or years
- Clearly predictive of clinical CVD events/mortality
  - Change in measurement predicts subsequent events
- Can be measured in resource-poor settings
- Previously shown to be associated with ambient air pollution?

What Makes an Ideal Test?

- Meaningful to be measured repeatedly in an individual
  - Good reproducibility/ low test-test variability
  - Operator independent or high inter-operator reliability
  - Within person-variability < between-person variability

What Makes an Ideal Test?

- Hypothesized to change in response to risk factor modification within months or years
  - Change very quickly: heart rate, HRV, BP
  - Change less quickly: inflammatory response, endothelial function
  - Change slowly: atherosclerosis, measures of end-organ damage from risk factors

What Makes an Ideal Test?

- Clearly predictive of clinical CVD or mortality
  - Demonstrating effect could influence policy
  - Demonstrating effect could influence burden of disease estimates
  - Previously associated with ≥1 traditional cardiovascular risk factor
  - Focused on CVD prediction vs elucidating disease mechanism(s)
  - Changes inform prediction of future CVD risk

What Makes an Ideal Test?

- Can be measured in resource-poor settings
  - Technology/materials readily available
  - Low/moderate cost
  - SOP readily available or easy to develop
  - Robust to fluctuations in personnel, field conditions, infrastructure
  - For biologic samples, can be analyzed in country

EXAMPLES FROM THE LITERATURE

Markers of Cardiovascular Disease

- Cardiovascular events
  - Incident MI, stroke, cardiac death
  - Incident hypertension, diabetes, chronic kidney disease
- Biochemical
  - Inflammation
  - Oxidative stress
  - Hemostasis
  - Lipids
  - Glucose homeostasis
  - Endothelial injury
- Cardiovascular Function
  - Hemodynamics
  - Vascular reactivity
  - ECG measures
  - Myocardial strain
  - Exercise capacity
- Cardiovascular Structure
  - LV mass, hypertrophy
  - Carotid IMT

Chimney Stove Intervention to Reduce Long-term Wood Smoke Exposure Lowers Blood Pressure among Guatemalan Women

John P. McCracken,[1,2] Kirk R. Smith,[3] Anaité Díaz,[4] Murray A. Mittleman,[1,5] and Joel Schwartz[1,2]

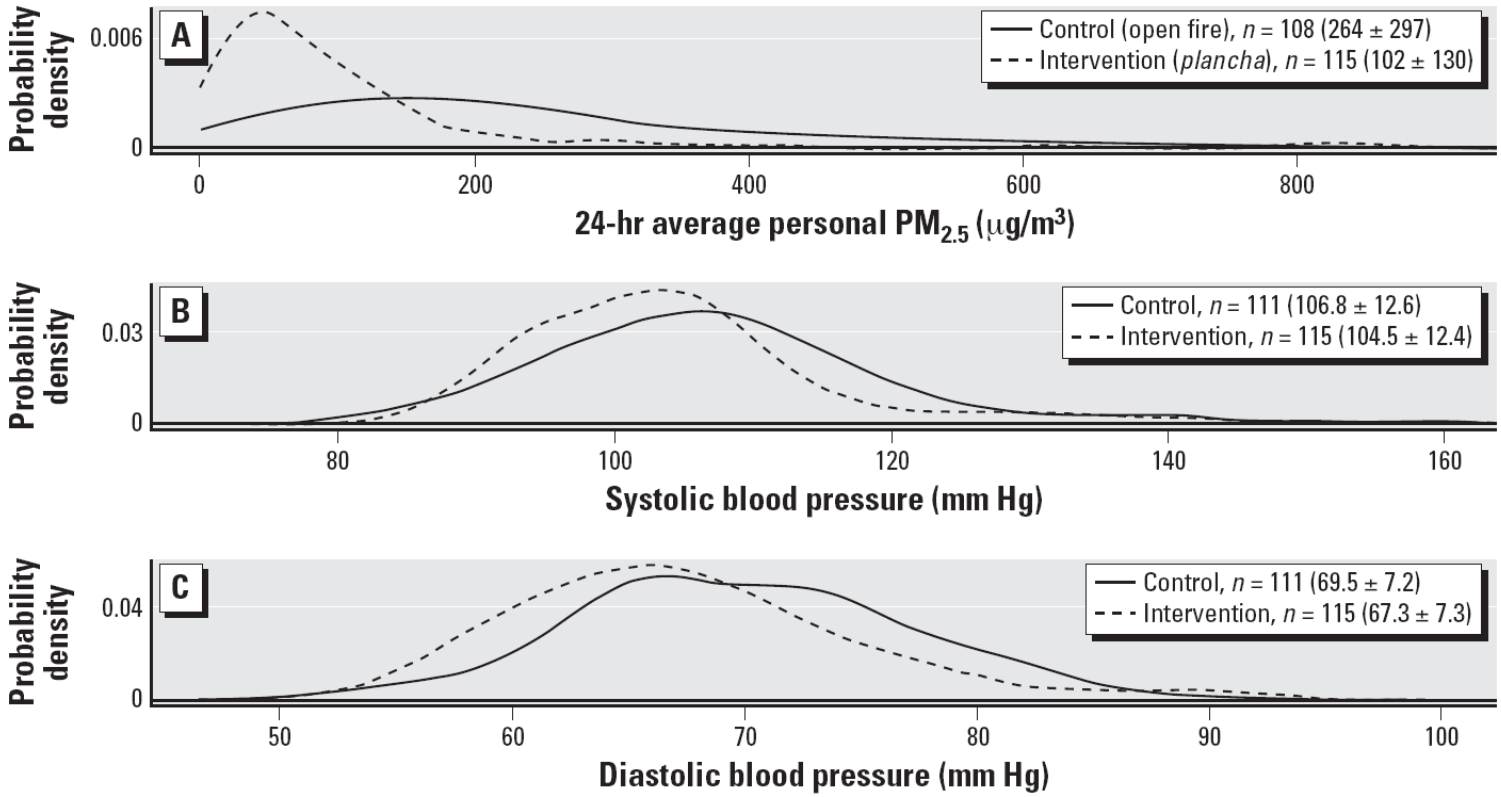
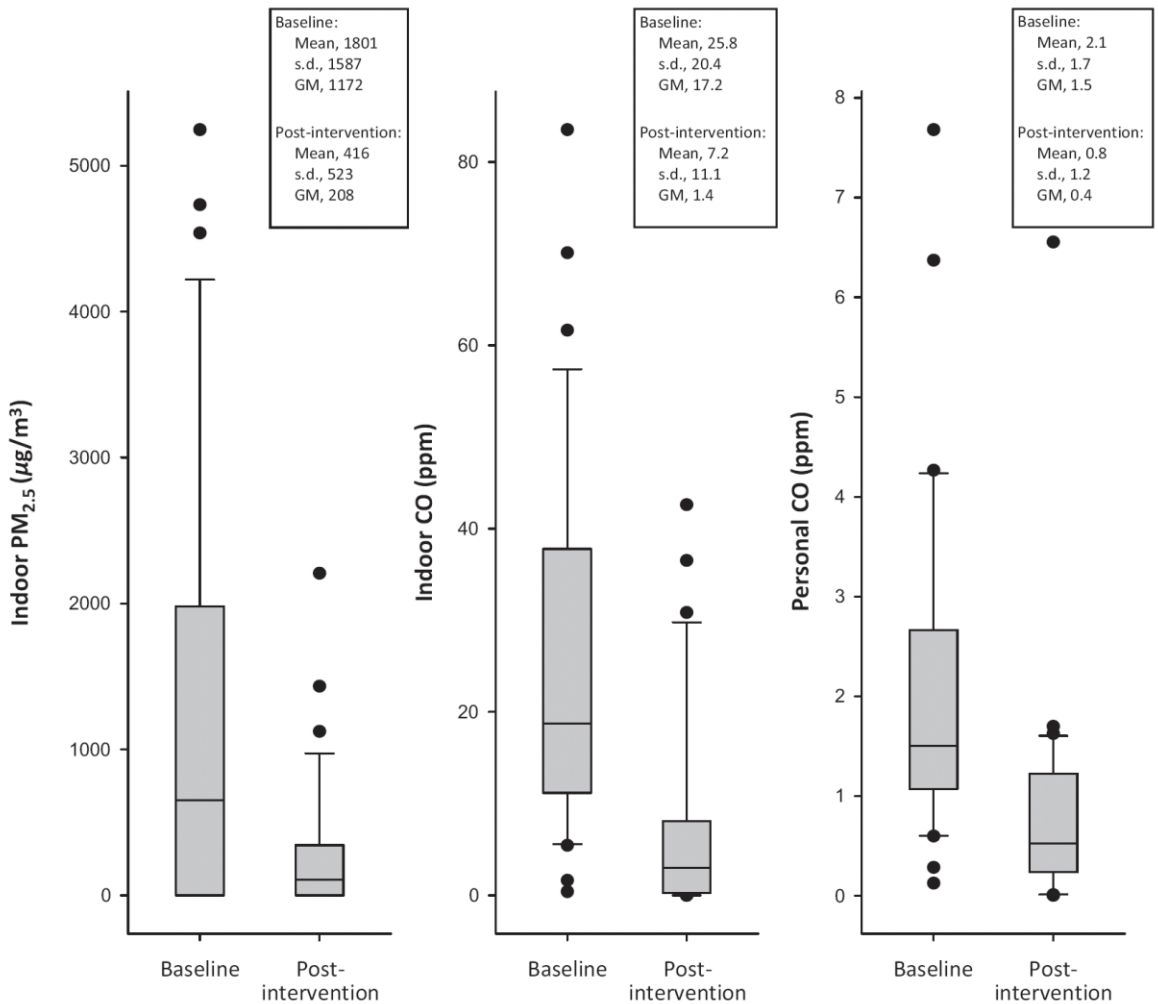


Figure 1. Between-group comparisons. Smoothed probability densities by randomized stove group (control, n = 71; intervention, n = 49) during the trial period (June 2003 through December 2004) of (*A*) 24-hr average $PM_{2.5}$; (*B*) SBP; and (*C*) DBP. Mean ± SD for each distribution shown in parentheses next to number of repeated measures (n).

McCracken et al. *EHP.* 2007

Impact of a cleaner-burning cookstove intervention on blood pressure in Nicaraguan women



Clark et al. *Indoor Air* 2013

Why is BP Interesting?

- Hypertension is the major modifiable risk factor for premature CVD
- Associated with increased risk of:
  - Heart failure (PEF, REF)
  - MI, coronary revascularization
  - Ischemic stroke, intracerebral hemorrhage
  - Chronic kidney disease, end stage renal disease
- Risks increase with SBP>115 and DBP>75

BP vs Ideal Test

- Meaningful to measure repeatedly in an individual?
- Responsive to risk factor modification within months or years?
- Predictive of clinical CVD or mortality?
- Measureable in resource-poor settings?
- Previously shown to be associated with ambient air pollution?

BP vs Ideal Test

- Meaningful to measure repeatedly in an individual? **YES, but varies within individual**
- Responsive to risk factor modification within months or years? **YES**
- Predictive of clinical CVD or mortality? **YES, long-term**
- Measureable in resource-poor settings? **YES**
- Previously shown to be associated with ambient air pollution? **YES**

Potential Extensions - ABPM

- Ambulatory BP monitoring
  - Diurnal variation in BP
  - Nocturnal BP, nighttime dipping
  - Masked hypertension, white coat hypertension
- Related to ambient air pollution (eg: Tsai et al, Hypertension, 2010)

Potential Extensions - LVH

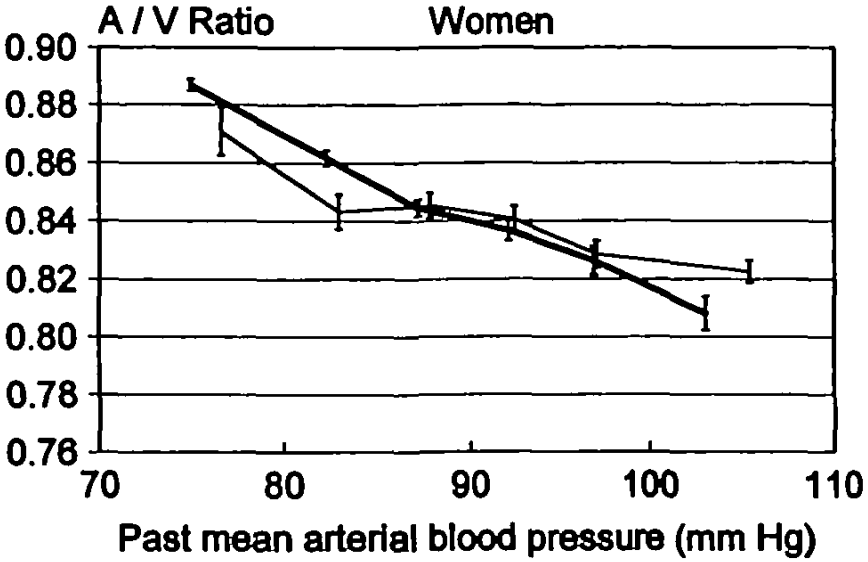
- Left Ventricular Hypertrophy
  - Early response to hypertension
  - Defined as increase in mass of left ventricle
  - Can be assessed by ECG (insensitive) or echo
  - Associated with increased risk of HF, sudden cardiac death, stroke, cardiac events
  - Reversible with treatment of hypertension
- Associated with residential proximity to roadways (Van Hee et al. AJRCCM 2009)

LVH vs Ideal Test

- Meaningful to measure repeatedly in an individual? **YES**
- Responsive to risk factor modification within months or years? **YES**
- Predictive of clinical CVD or mortality? **YES**
- Measureable in resource-poor settings? **YES**
- Previously shown to be associated with ambient air pollution? **Some evidence**

Retinal Arteriolar/Venular Diameter

- Marker of microvascular structure
- Associated with MI, stroke, CVD mortality
- Non-invasive, highly reproducible
- Associated with ambient air pollution (Adar et al. PLoS Med, 2010)



Sharrett et al. AJE 1999

Tests of Cardiovascular Function

- Vascular
  - Flow mediated dilation
  - EndoPAT
  - Pulse wave amplitude/velocity
- Cardiac
  - Inducible ischemia
  - Exercise capacity

ECG-Based Measures

- Ventricular or atrial arrhythmias
- ST-segment changes
- QT interval, markers of repolarization
- T-wave alternans
- Heart rate variability
- Heart rate turbulence
- Acceleration capacity/deceleration capacity

Intervention to Lower Household Wood Smoke Exposure in Guatemala Reduces ST-Segment Depression on Electrocardiograms

John McCracken,[1,2] Kirk R. Smith,[2] Peter Stone,[3] Anaité Díaz,[4] Byron Arana,[4] and Joel Schwartz[1]

Table 3. Odds ratios (ORs) for nonspecific ST-segment depression (30-min average ≤ –1 mm, regardless of slope) associated with chimney-stove intervention compared with open fire from two study designs: between-groups and before-and-after analyses.

	Crude		Adjusted	
Comparison	OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value
Between-groups	0.34 (0.15, 0.81)	0.015	0.26 (0.08, 0.90)[a]	0.033
Before-and-after (only control group)	0.41 (0.24, 0.70)	0.001	0.28 (0.12, 0.63)[b]	0.002

[a]Adjusted for age (quadratic), BMI (quadratic), asset index category, ever smoking, SHS, owning a wood-fired sauna, recent use of wood-fired sauna, and time of day (natural spline with 5 degrees of freedom). [b]Adjusted for age (quadratic), day of week, season (wet/dry), daily average temperature and relative humidity, daily rainfall, interactions of weather variables with season, recent use of wood-fired sauna, and time of day (natural spline with 5 degrees of freedom).

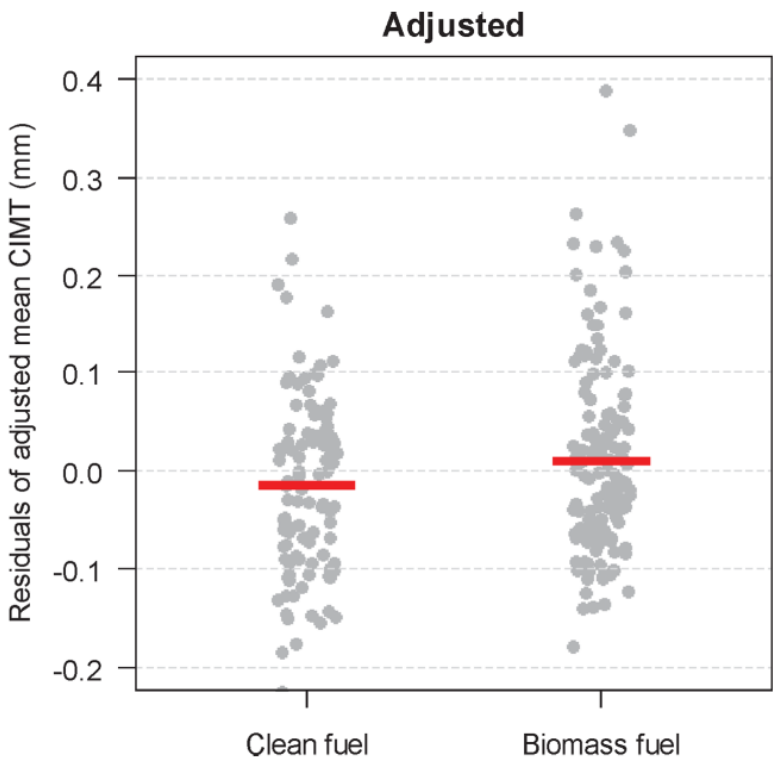
McCracken et al. *EHP.* 2011

Markers of Atherosclerosis

- Ankle brachial index
  - Easy to measure, predictive of CVD events
  - Reflects peripheral occlusive disease
- Carotid intima medial thickness
  - Harder to measure reproducibly
  - Stronger predictor of CVD events
- Coronary artery calcium
  - Probably not feasible to measure

Chronic exposure to biomass fuel is associated with increased carotid artery intima-media thickness and a higher prevalence of atherosclerotic plaque

Matthew S Painschab,[1,2] Victor G Davila-Roman,[2] Robert H Gilman,[3] Angel D Vasquez-Villar,[4] Suzanne L Pollard,[3] Robert A Wise,[1] J Jaime Miranda,[5,6] William Checkley,[1,3,5] CRONICAS Cohort Study Group



Δ=0.03
(95% CI: 0.01, 0.06)

Painschab et al. Heart 2013

CIMT vs Ideal Test

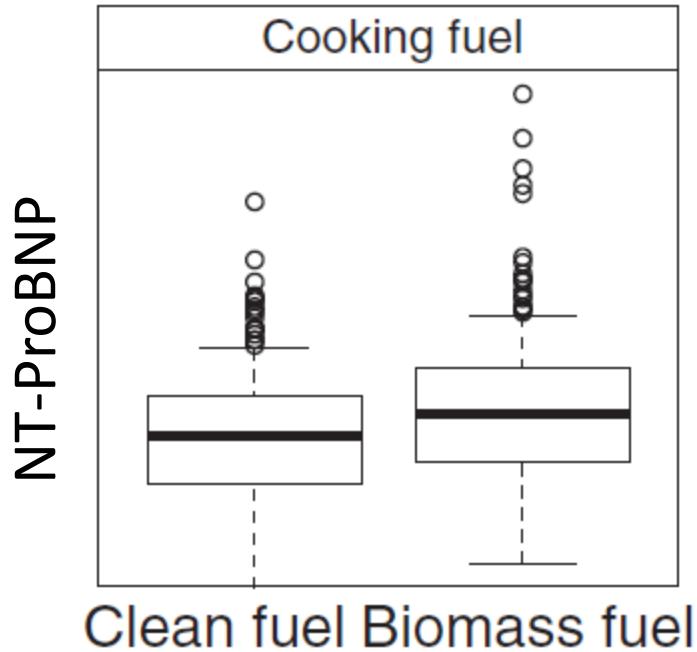
- Meaningful to measure repeatedly in an individual? **YES, over long term**
- Responsive to risk factor modification within months or years? **YES**
- Predictive of clinical CVD or mortality? **YES**
- Measureable in resource-poor settings? **Challenging to do well**
- Previously shown to be associated with ambient air pollution? **YES**

Biochemical Assays

- Inflammation
- Endothelial injury
- Oxidative stress
- Hemostasis
- Lipids
- Glucose homeostasis
- Cardiac stretch

Lack of association between chronic exposure to biomass fuel smoke and markers of right ventricular pressure overload at high altitude

Maria A. Caravedo, MD,[a] Matthew S. Painschab, MD,[a] Victor G. Davila-Roman, MD,[b] Aldo De Ferrari, MD,[a] Robert H. Gilman, MD, DTMH,[c] Angel D. Vasquez-Villar, MD,[d] Suzanne L. Pollard, MSPH,[a] J. Jaime Miranda, MD, PhD,[e,f] and William Checkley, MD, PhD[a,c,e], CRONICAS Cohort Study Group *Baltimore, MD; St. Louis, MO; and Lima, Peru*



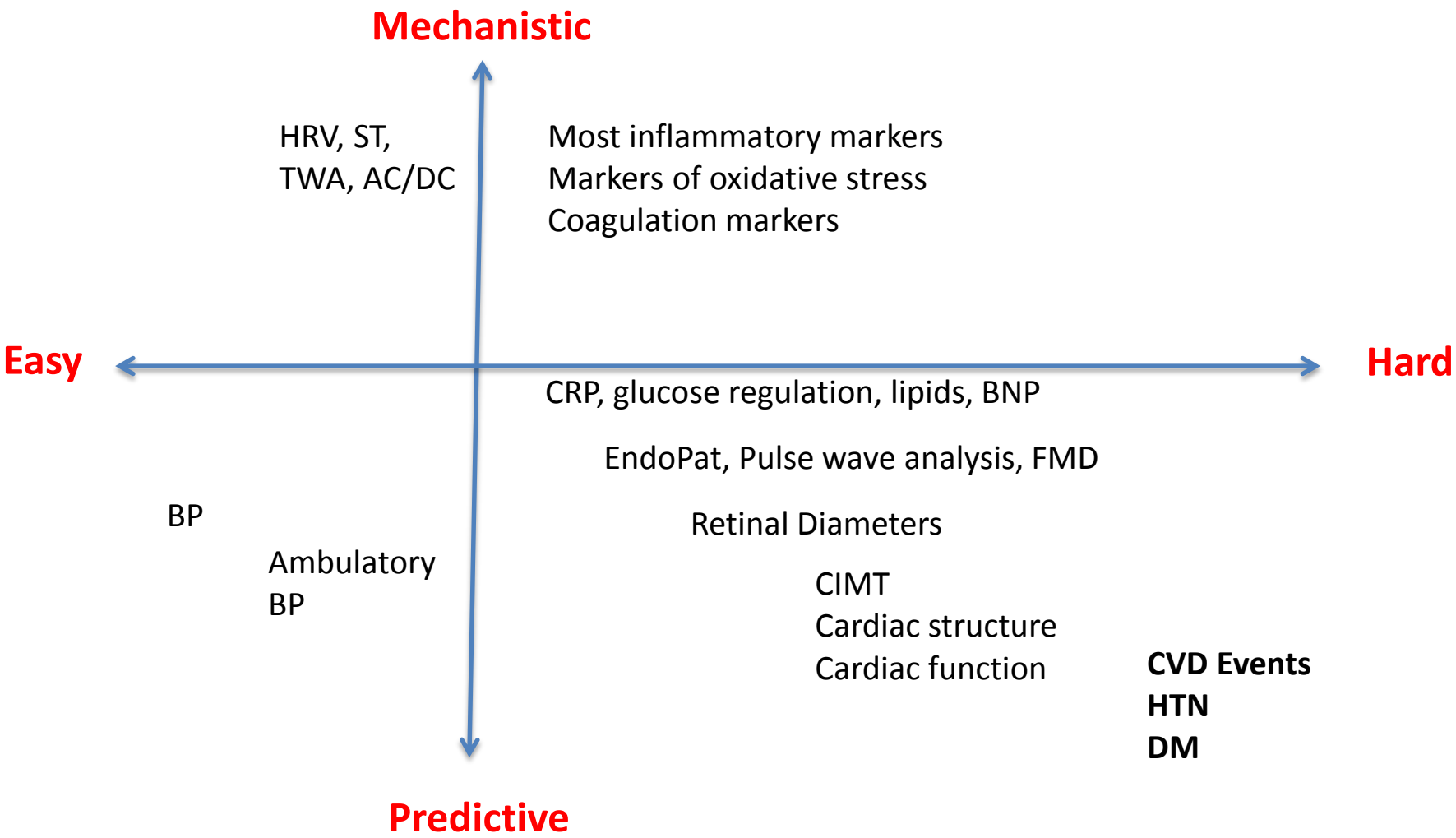
Δ=0.11
95% CI: -0.1, 0.32
p=0.31

Caravedo et al. *AHJ* 2014

BNP vs Ideal Test

- Meaningful to measure repeatedly in an individual? **YES, but highly variable over time**
- Responsive to risk factor modification within months or years? **Hours?**
- Predictive of clinical CVD or mortality? **Maybe**
- Measureable in resource-poor settings? **Maybe**
- Previously shown to be associated with ambient air pollution? **NO**

What to Measure?



Who to Study?

- Prior studies have mostly been in young, adult women without overt disease
  - Low risk for CVD events/mortality
- Some markers useful in general population
- Some markers are best suited for diseased/high risk populations
  - Eg: exercise capacity, some ECG measures
- Choice of population also affects sample size

Recommendations

- Consider potential outcomes vs ideal test
- Be clear whether goal is on prediction of CVD events/mortality or elucidation of mechanism
- Balance with what can be feasibly measured well in resource poor setting
- Consider what is the most appropriate population to study
  - Exposure, life stage, pre-existing disease