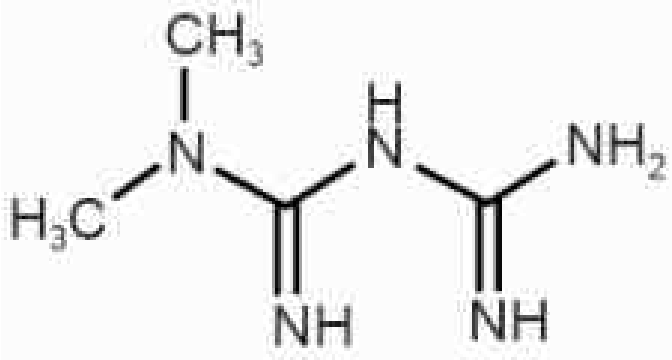
METFORMINA

biguanide sintetica



farmaco di prima linea nel trattamento del diabete di tipo 2

TRASPORTO INTRACELLULARE DI GLUCOSIO

Potenzia l'azione dell'insulina sui carrier GLUT1 e GLUT4 favorendo la captazione del glucosio da parte delle cellule

UTILIZZAZIONE DEL GLUCOSIO E METABOLISMO GLUCIDICO

Stimola la formazione di glicogeno, favorisce il metabolismo non ossidativo del glucosio e l'incorporazione del glucosio nei trigliceridi

LIVELLI PLASMATICI DI INSULINA

Aumenta la quota libera attiva, non legata a proteine, dell'insulina circolante

PRODUZIONE DI GLUCOSIO EPATICO

Inibisce la gluconeogenesi e la glicogenolisi

METABOLISMO LIPIDICO

Riduce il metabolismo ossidativo degli acidi grassi liberi con riduzione dei livelli di trigliceridi, col. tot. E del rapporto LDL/HDL

FARMACOCINETICA

Somministrazione per os (0,5 g/die – 3 g/die).

Assorbimento gastrointestinale lento e incompleto. Biodisponibilità 50-60%.

Concentrazione di picco plasmatico di 1,5-2,0µ/ml dopo circa 6h dalla somm. di una dose di 500-1000mg.

Lo steady state è raggiunto è raggiunto dopo 24-48h.

Nessun legame farmaco-proteico.

Vd 63-276L.
La metformina si distribuisce rapidamente nei tessuti dell'organismo; si accumula nella parete intestinale (concentrazione pari a 10-100 volte quella plasmatica); nelle ghiandole salivari, fegato e reni (concentrazione pari a 2-volte quella plasmatica); cuore e muscolo scheletrico (concentrazioni superiori a quelle plasmatiche).

Emivita 4-8h

Eliminazione renale per filtrazione glomerulare e per secrezione tubulare in forma immodificata.

Il 90% del farmaco è eliminato in circa 12h dalla sua somministrazione.

Controindicazioni

1) ipersensibilità;

2) diabete di tipo I, diabete mellito complicato da acidosi, infezioni e gangrena; coma e precoma diabetico;

3) insufficienza renale acuta/cronica

4) grave insufficienza epatica;

5) Età >80 anni;

6) patologie cardiovascolari che possono causare ipossia tissutale (patologia coronarica, insufficienza cardiaca cronica, scompenso cardiaco congestizio, shock), patologie vascolari periferiche;

7) malattie dell'app. respiratorio caratterizzate da ostruzione delle vie aeree

8) intossicazione alcolica acuta, alcolismo;

9) In caso di regimi alimentari fortemente ipocalorici; disidratazione.

10) insufficienza surrenalica.

EFFETTI COLLATERALI

Cardiovascolari: vasculite

Centrali: anoressia, encefalopatia

Dermatologici: (molto rari) eritema, prurito, orticaria,psoriasi.

Ematici: (rari) anemia emolitica, anemia megaloblastica.

Epatici: (segnalazioni sporadiche) test di funzionalità epatica anomali, epatite (reversibili con la sospensione della metformina).

Gastrointestinali: flatulenza nausea, vomito, alterazione del gusto (sensazione di sapore metallico), diarrea (fino al 20% dei pazienti), dolore addominale, perdita di appetito.

Metabolici: (molto rari) ipoglicemia (in particolare in pazienti anziani, debilitati), acidosi lattica, ridotto assorbimento di vitamina B12 e acido folico.

Muscoloscheletrici: mialgia.

Oftalmici: edema maculare (in associazione a glitazone).

Sistemici: lieve calo ponderale, malessere generale; (raro) polmonite associata a vasculite).

SOVRADOSAGGIO

- tossicità gastrointestinale
- acidosi metabolica
- **acidosi lattica**
- ipoglicemia

- ipovolemia
- convulsioni
- oligo-anuria
- depressione resp.
- Shock
- coma

MALA
Metformin Associated Lactic Acidosis

- pH < 7.35
- increased anion gap
- blood lactate level > 5.0 mmoles/l
- metformin plasma levels >5 µg/mL (reference range 1-2)

INCIDENZA

1-5 casi su 100,000 pazienti che ricevono metformina per anno.

TASSO DI MORTALITA': 30-50%

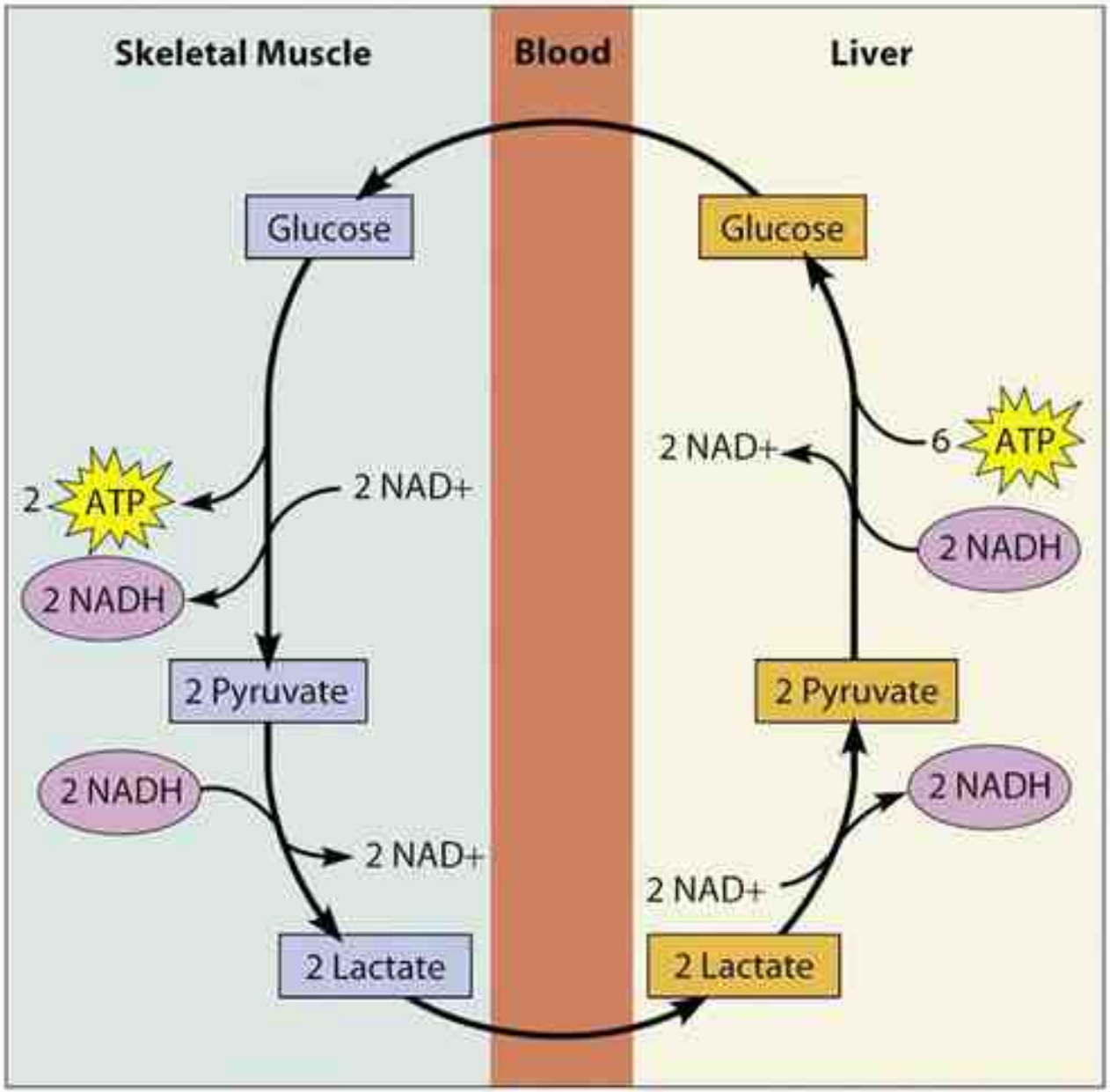
la prognosi non sembra dipendere dalla concentrazione plasmatica di metformina o di lattato.

MECCANISMI FISIOPATOLOGICI DELLA M.A.L.A.

1. La metformina promuove la **conversione del glucosio a lattato** a livello della parete intestinale.

1. La metformina determina uno **shift da un metabolismo aerobico ad uno anaerobico** con conseguente aumento dei livelli di lattato.

1. La metformina **inibisce la gluconeogenesi epatica** a partire da substrati quali lattato, piruvato e alanina, con aumento dei livelli di lattato.


Skeletal Muscle
Blood
Liver
Glucose
2
ATP
2 NAD+
2 NADH
2 Pyruvate
2 NADH
2 NAD+
2 Lactate
Glucose
6
ATP
2 NAD+
2 NADH
2 Pyruvate
2 NADH
2 NAD+
2 Lactate

Lactic Acidosis

Type A

clinical evidence of inadequate tissue perfusion or oxygenation

This includes:
- Anaerobic muscular activity (for example, exercising)
- Tissue hypoperfusion (for example, septic shock)
- Reduced tissue oxygen delivery or utilization (for example, severe anaemia)

TYPE B

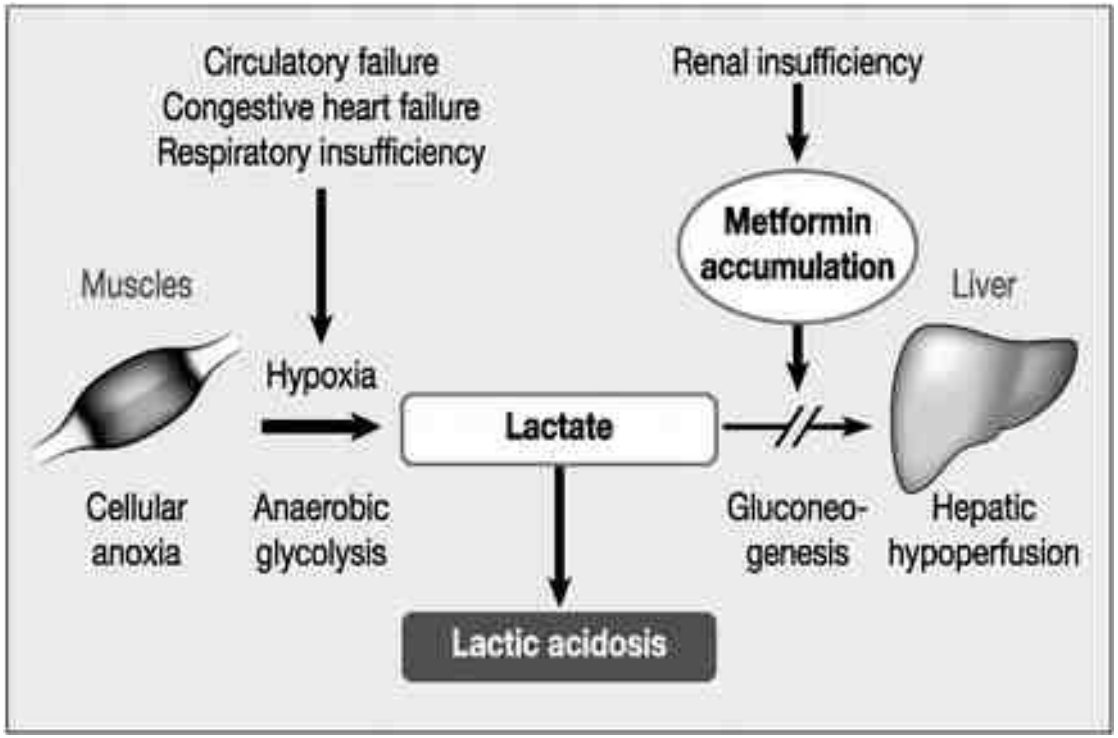
no clinical evidence of poor tissue perfusion

this is further subdivided into:
B1 – Associated with underlying diseases (for example, ketoacidosis)
B2 – **ASSOCIATED WITH SEVERAL CLASSES OF DRUGS AND TOXINS** (for example, biguanides, salicylates, isoniazid and alcohol)
B3 – Associated with inborn errors of metabolism (for example, pyruvate dehydrogenase deficiency).

Cohen R, Woods H: Clinical and Biochemical Aspects of Lactic Acidosis.
Oxford: Blackwell Scientific Publications; 1976

Sono state descritte diverse circostanze che possono aumentare il rischio di MALA:

- Aumento della formazione dei lattati da parte dei tessuti periferici in condizioni di ipossia (<u>insufficienza cardiaca e respiratoria</u>)



- Alterazione del metabolismo dei lattati per riduzione della gluconeogenesi epatica (<u>insufficienza epatica</u>)

- Aumenti drammatici dei livelli di metformina (<u>intossicazione da metformina, insufficienza renale grave</u>)

Solo un esiguo numero di articoli è stato pubblicato sulla relazione tra MALA, anestesia e chirurgia.

SPINE Volume 27, Number 22, pp E482–E484

Metformin-Associated Lactic Acidosis After Elective Cervical Spine Fusion

A Case Report

Simon C. Mears, MD, PhD* Pamela A. Lipsett, MD, FACS,† Myles D. Brager, MD,† and Lee H. Riley III, MD†

Gowardman JR, Havill J. Fatal metformin induced lactic acidosis: case report. *NZ Med J* 1995; **108**: 230–231.

Mercker SK, Maier C, Neumann G, Wulf H. Lactic acidosis as a serious perioperative complication of antidiabetic biguanide medication with metformin. *Anesthesiol* 1997; **87**: 1003–1005.

L’anestesia e la chirurgia non sono state identificate come cause specifiche di MALA, ma i pz sottoposti ad anestesia sono a rischio di complicanze peri-operatorie che possono favorire l’insorgenza di MALA (digiuno prolungato, disidratazione, ipotensione, ipoperfusione periferica, infarto, sepsi,…)

Controindicazioni

1) ipersensibilità;
2) diabete di tipo I, diabete mellito complicato da acidosi, infezioni e gangrena; coma e precoma diabetico;
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9) In caso di regimi alimentari fortemente ipocalorici; in condizioni di disidratazione
10) insufficienza surrenalica.

L’acidosi lattica associata alla metformina è un evento avverso raro ma grave .

TASSO DI MORTALITA’: 30-50%

SOSPENDERE LA METFORMINA

1) 48 ore prima della procedura che prevede l'uso di agenti di contrasto iodati e ricominciare 48 ore dopo

2) 48 ore prima dell'intervento chirurgico con anestesia generale, ricominciare 48 ore dopo o dopo la ripresa dell'alimentazione orale, comunque solo dopo che sia stata verificata una normale funzionalità renale.


METFORMINA
I PAZIENTI CHE
DEVONO ESSERE OPERATI
O SOTTOPOSTI AD ARTERIOGRAFIA,
DEVONO SOSPENDERE LA TERAPIA
48 ORE PRIMA!
E MANTENERLA SOSPESA PER
48 ORE DOPO!

Diabetic cardiomyopathy and metformin

Scuola di specializzazione in anestesia e rianimazione

Dr.ssa Barbieri Silvia

Mitochondrial Dysfunction in Diabetic Cardiomyopathy

Biochim Biophys Acta. Author manuscript; available in PMC 2012 July 1.
Published in final edited form as:
Biochim Biophys Acta. 2011 July ; 1813(7): 1351–1359. doi:10.1016/j.bbamcr.2011.01.014

Myocardial Substrate Metabolism in the Normal and Failing Heart

WILLIAM C. STANLEY, FABIO A. RECCHIA, AND GARY D. LOPASCHUK
Department of Physiology and Biophysics, School of Medicine, Case Western Reserve University, Cleveland, Ohio; Scuola Superiore Sant'Anna, Pisa, Italy; Department of Physiology, New York Medical College,
Valhalla, New York; and Department of Pediatrics, University of Alberta, Edmonton, Canada

Physiol. Rev 85; 1093-1129 2005

Diabetic cardiomyopathy: pathophysiology and clinical features

Takayuki Miki • Satoshi Yuda • Hidemichi Kouzu •
Tetsuji Miura

Published online: 28 March 2012

Heart Fail Rev 2013

- Complicanze cardiache perioperatorie 2-5%

- Esistono diversi indicatori (ASA, tipo di chirurgia, età)

Pz con DM tipo 2 sono da considerarsi pz con rischio 2 volte maggiore per lo sviluppo di complicanze cardiache perioperatorie

Si stima che nel 2030 circa 552 milioni di persone sara' affetto da DM tipo 2

Diabetic cardiomyopathy

- Concetto introdotto nel 1972 da Rubler

- Si tratta di alterazioni:
  - strutturali: fibrosi interstiziale e perivascolare, aumento dei depositi di collagene che riducono la compliance
  - funzionali: disfunzione mitocondriale

- Termine utilizzato per indicare una disfunzione ventricolare in pz diabetici anche in assenza di problemi coronarici o

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Metabolic abnormalities in the Diabetic Heart

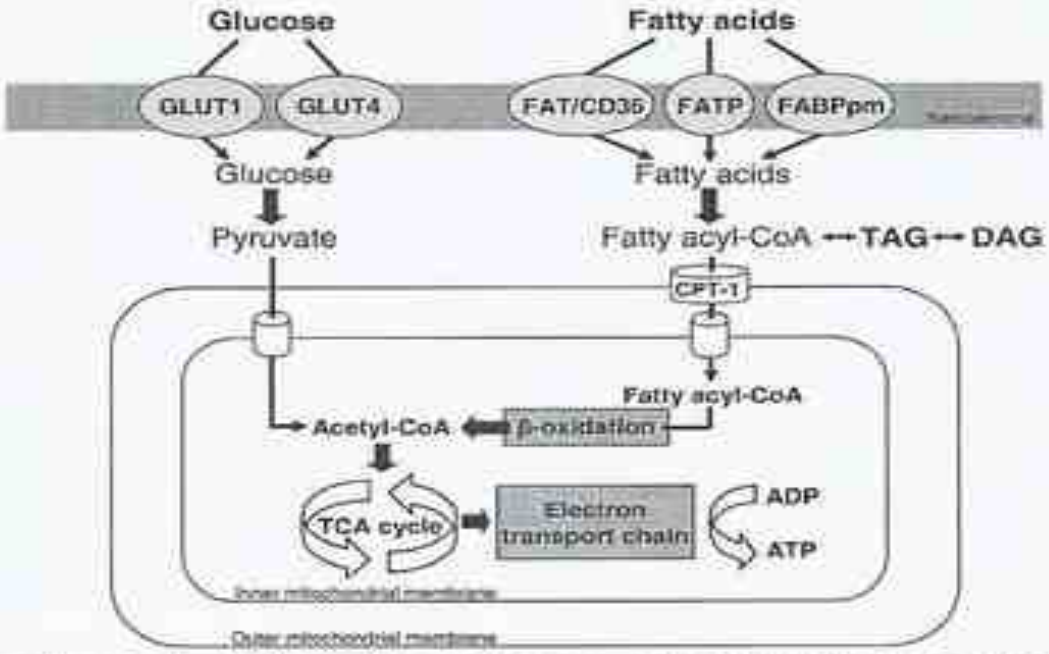

Figure 1 Glucose and fatty acid metabolism in the cardiomyocyte. Glucose uptake into the cell occurs through the glucose transporters GLUT1 and GLUT4. Once inside, glucose is broken down into pyruvate by glycolysis. Pyruvate is subsequently transported into the mitochondria and decarboxylated to acetyl-CoA. Non-esterified fatty acids are taken up through fatty acid transporter (FAT/CD36, fatty acid transport protein (FATP) and plasma membrane fatty acid binding protein (FABPpm). Intracellular fatty acids form fatty acyl-CoA and can either be esterified into triglycerides (TG) or enter the mitochondria via carnitine palmitoyl transferase (CPT-1). Fatty acyl-CoA enters the β-oxidation pathway, forming acetyl-CoA. Glucose or fatty acid-derived acetyl-CoA enters the tricarboxylic acid (TCA) cycle with entry of reducing equivalents to the electron transport chain and oxidative phosphorylation, and finally ATP is formed.

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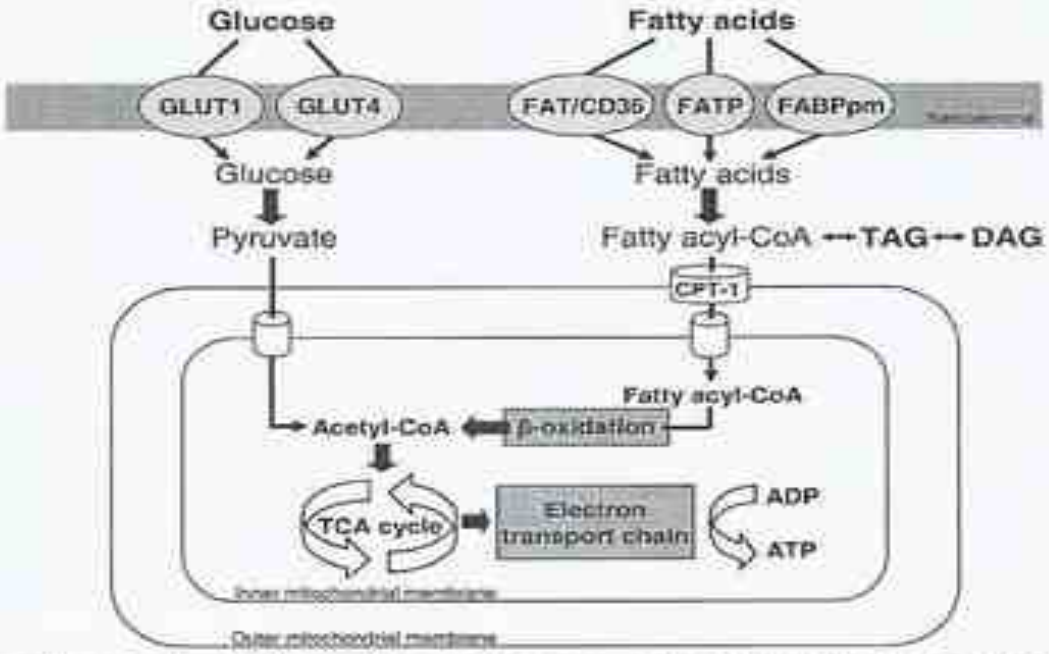

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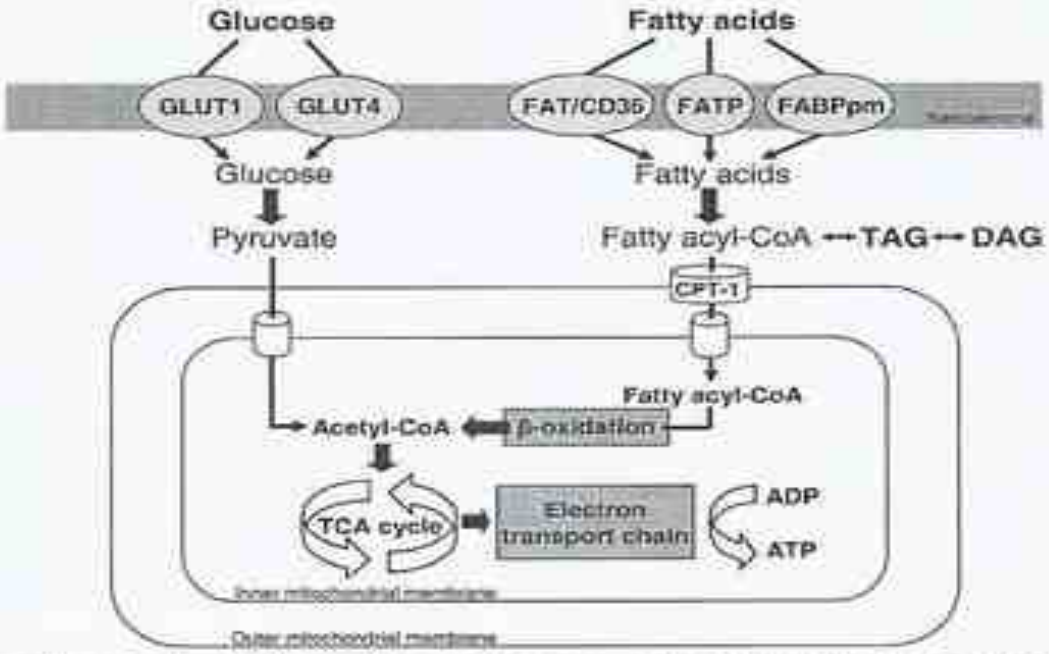

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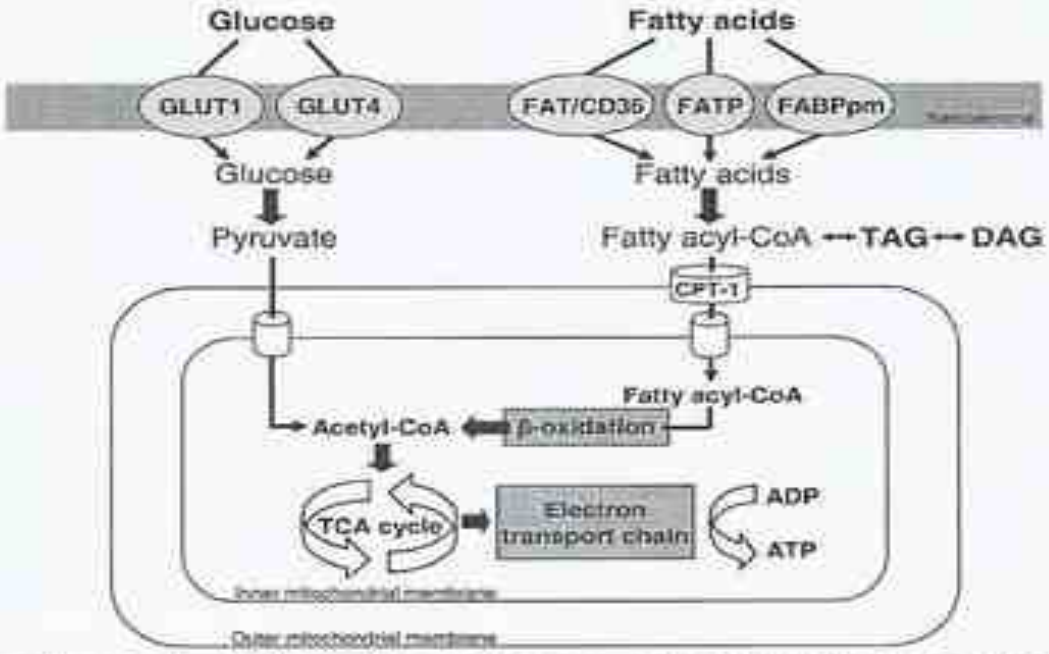

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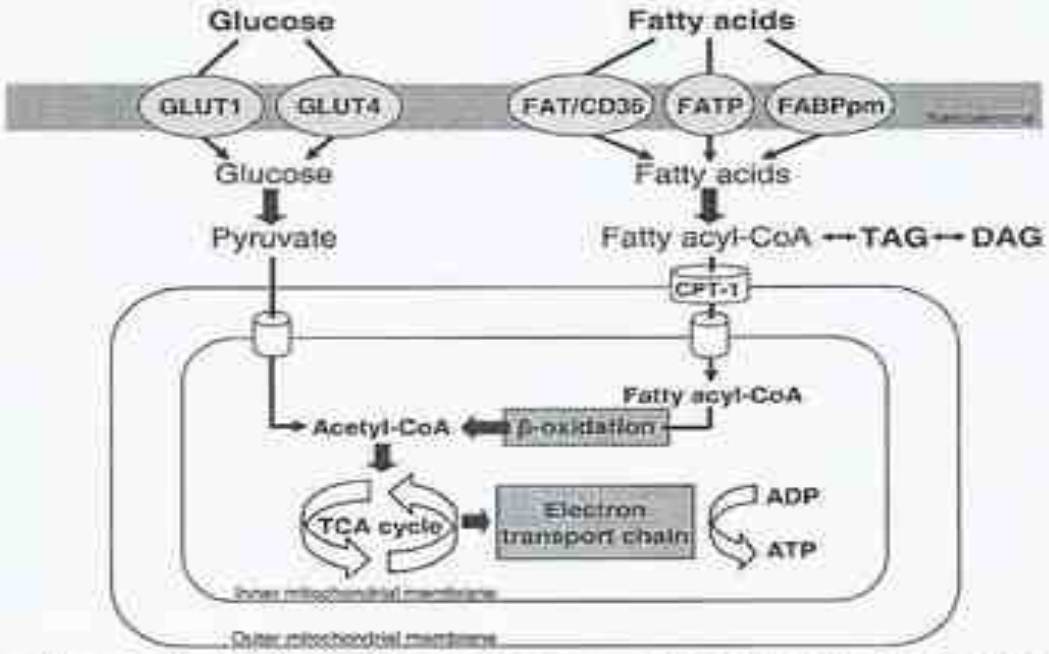

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van den Brom et al. Cardiovascular Diabetology 2013, 12:42
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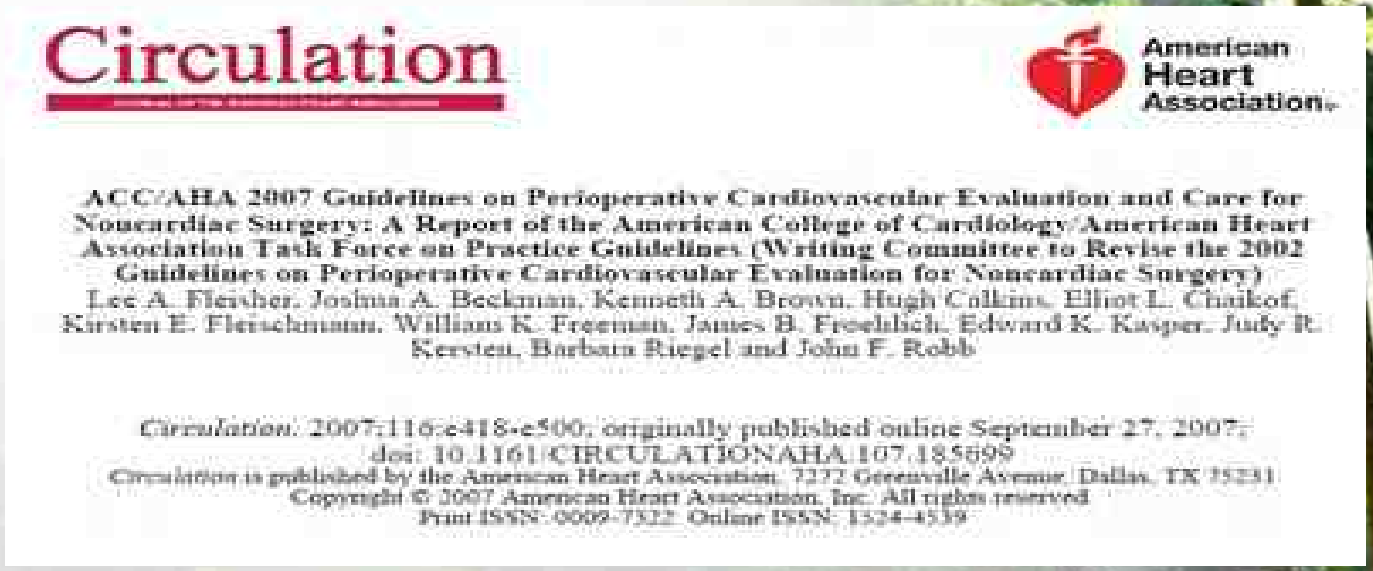
REVIEW

Open Access

Diabetes, perioperative ischaemia and volatile anaesthetics: consequences of derangements in myocardial substrate metabolism

Charissa E van den Brom[1,2*], Carolien SE Bulte[3], Stephan A Loer[3], R Arthur Bouwman[3] and Christa Boer[3]



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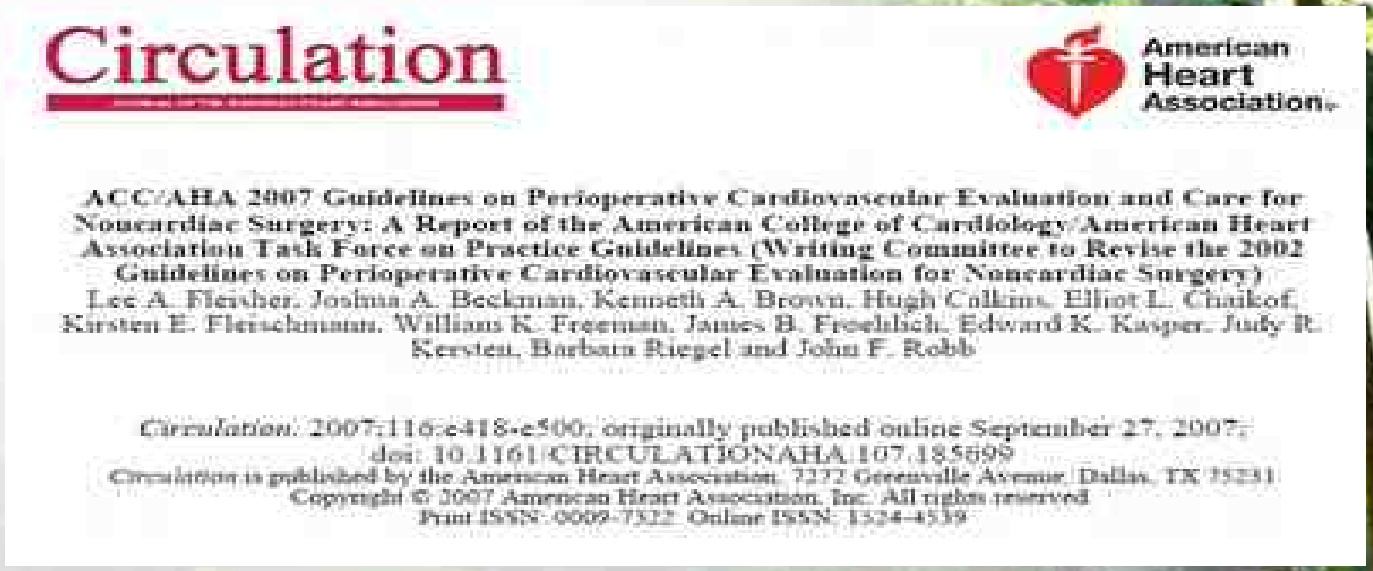

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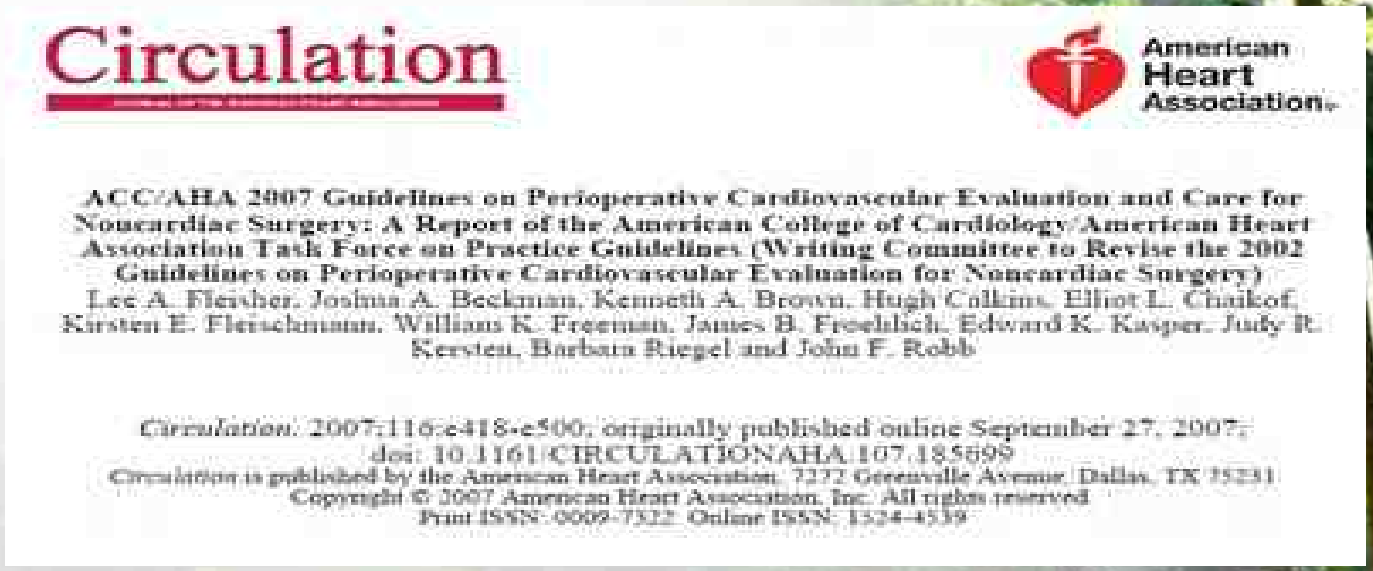

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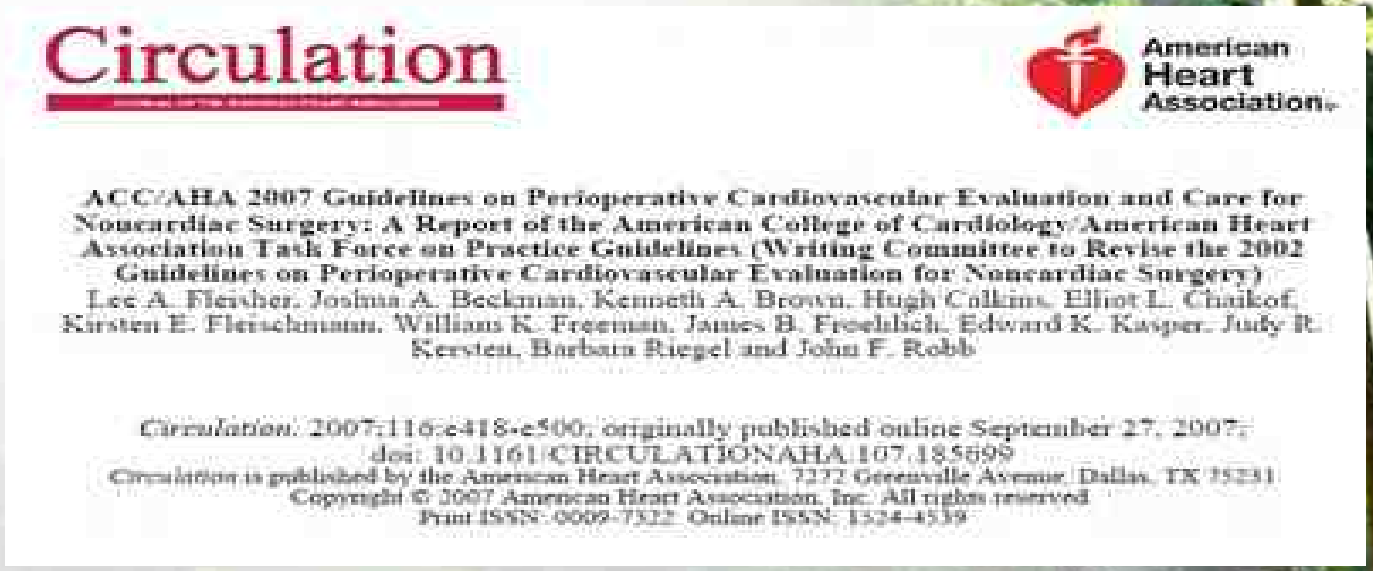

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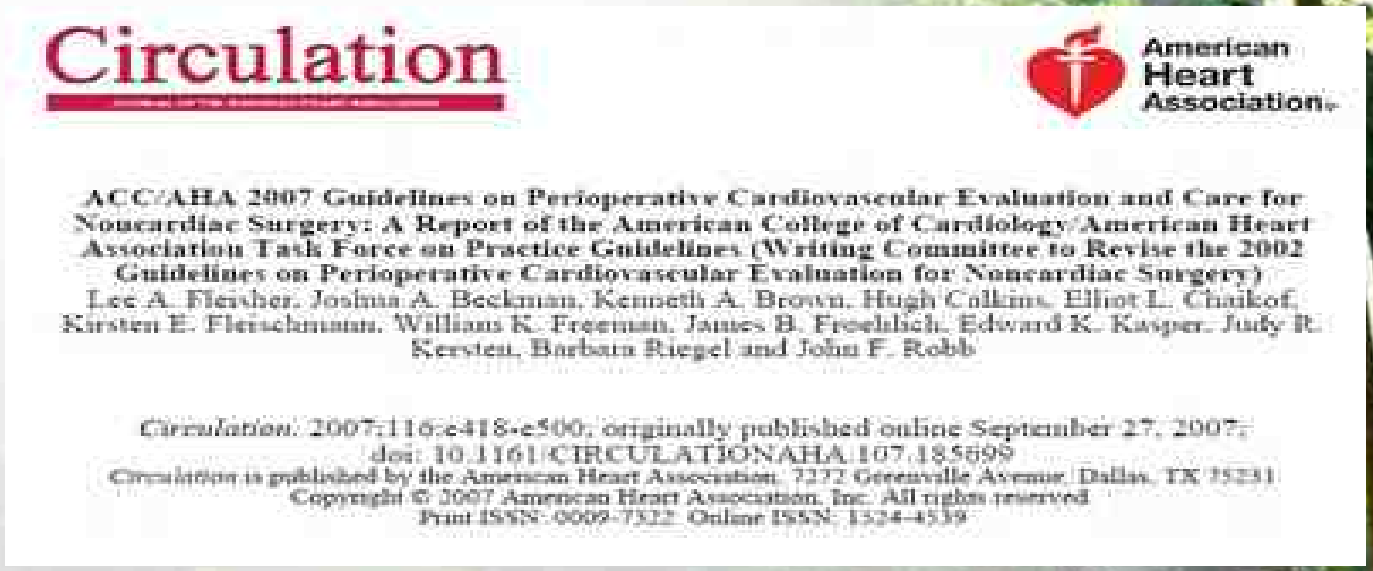

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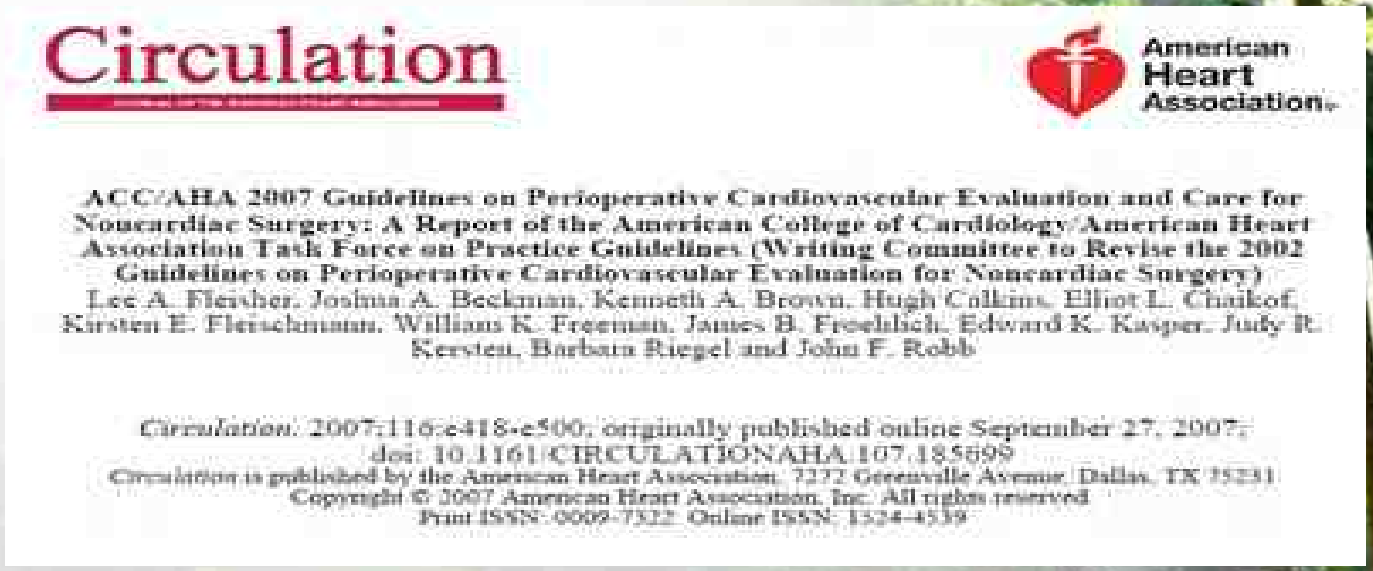

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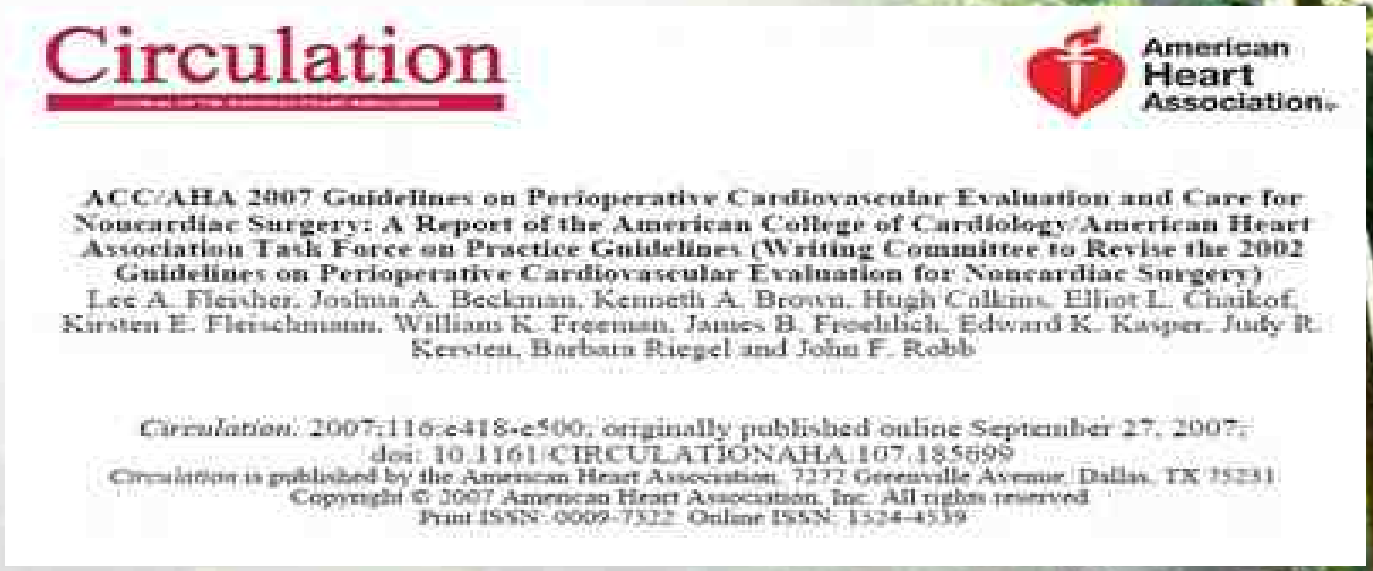

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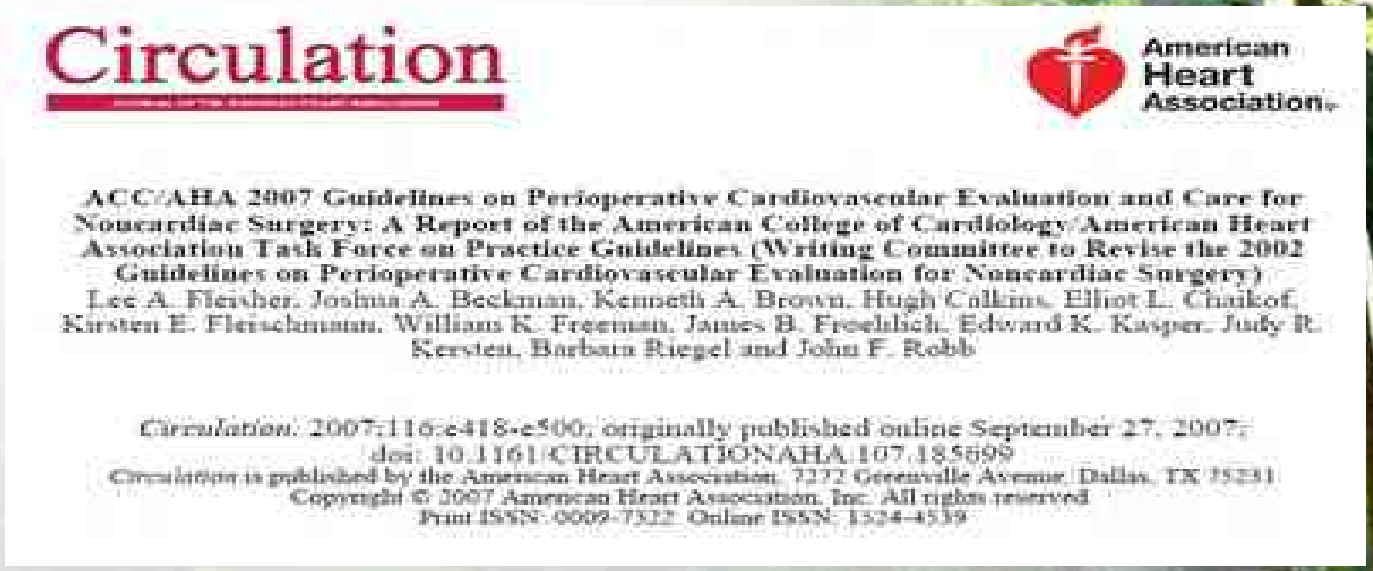

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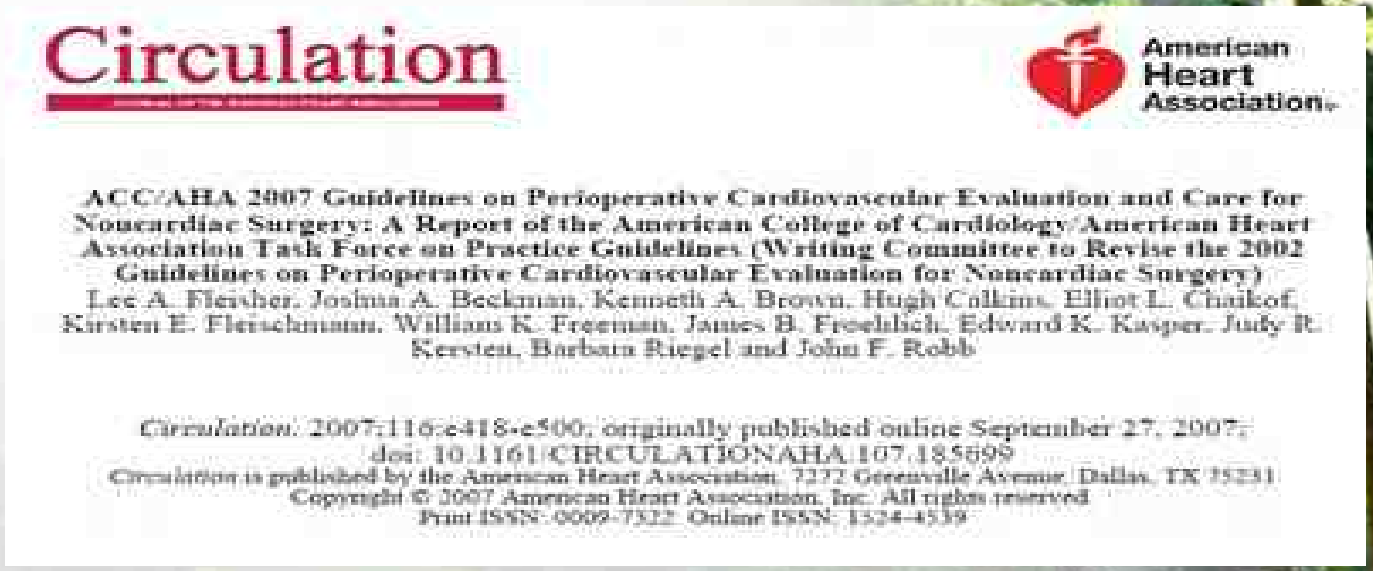

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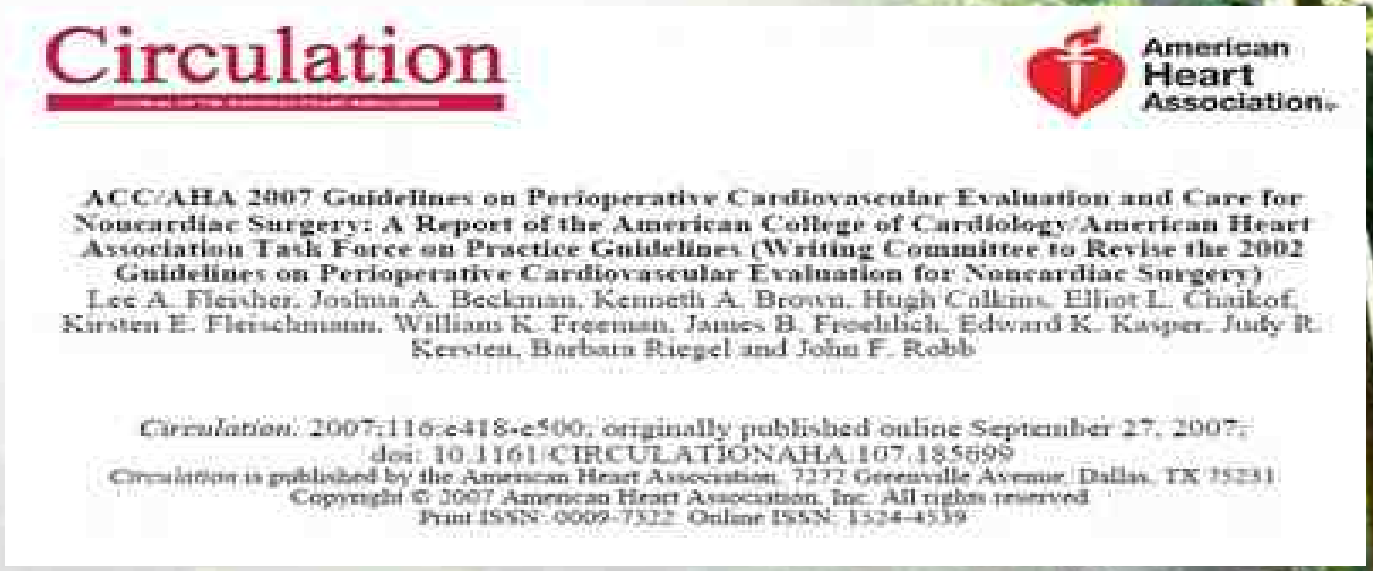

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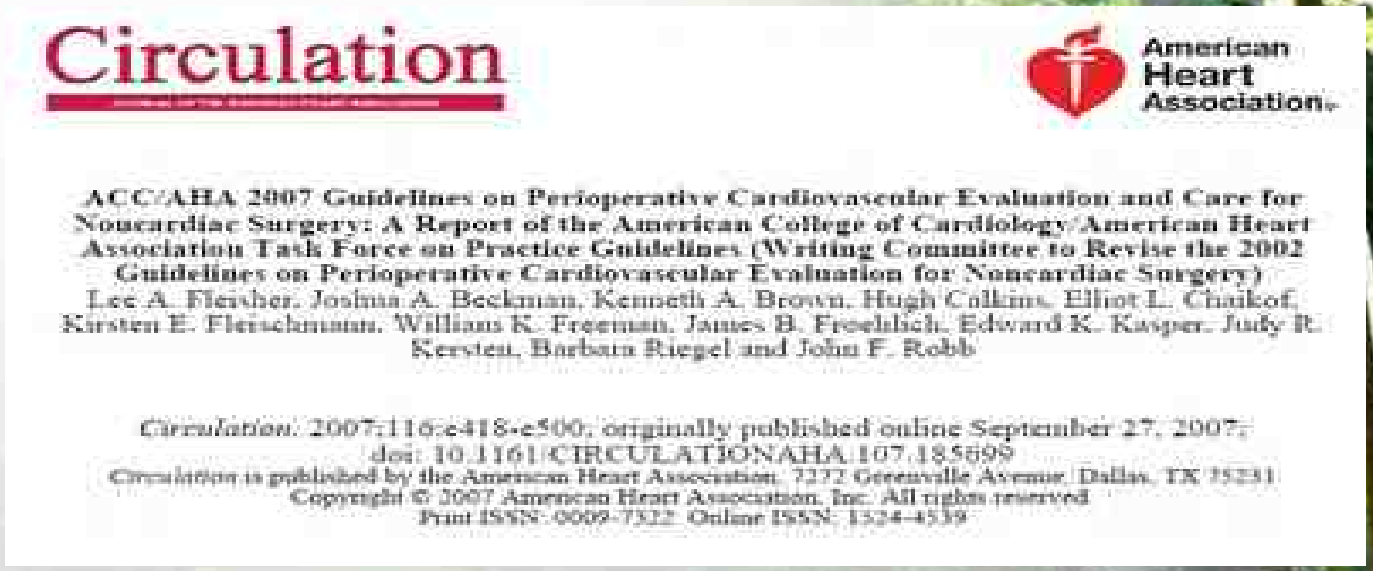

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