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Effect on Mortality of Metoprolol In Acute Myocardial Infarction A Double-Blind Randomized Trial

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Study Objective:

- Determine whether or not metoprolol would ↓ 90-Day mortality

Study Design:

- Randomized
- Placebo-controlled
- Double-Blind
- n = 1395 → 698 Metoprolol group
  697 Placebo group
- Pt's enrolled b/w 6/1976 - 1/1981

Study Population:

- Eligible Pt's: (A) Age 40-74 y.o.
  (B) Admitted in a 9-month span (during holiday times)
  Either/or (C) Chest Pain
  - acute onset
  - 30 mins. duration
  (D) EKG signs of acute MI w/ estimated onset w/in prior 48hrs.

- Exclusions:
  (1) Contraindication to β-blockade
  - Hypotension (SBP < 100)
  - Bradycardia (HR < 45)
  - HFailure (basal rales >10 cm from lung base, poor peripheral circulation + shock)
  - AvBlock
  - Asthma

② Need for β-blockers (cannot be randomized to placebo)
③ Alcoholism
④ Chronic AFib
⑤ PPM
⑥ Language Barriers
⑦ Planned / Prior CABG
⑧ Confusion
⑨ Unconsciousness
⑩ Concurrent CCB's

Study Subgroup Definitions:

Ⓐ All Patients
Ⓑ Prior MI
Ⓒ Chronic β-blockade @ entry into study
Ⓓ Age 40-69
Ⓔ Age 70-74
Ⓕ Chest Pain (Alone)
Ⓖ Chest Pain w/ EKG signs of MI
Ⓗ Chest Pain w/ : (one of the following)
- HR >90
- RR ≥28
- Rales heard ϕ more than 10cm above base

Ⓘ Previous Unconsciousness
Ⓙ Temporary Adverse Characteristics
- Hypotension (SBP <100)
- Rales more than 10cm above base

Ⓚ Definite MI : (2 of the following)
① Chest Pain @ least 15 mins duration
② Q-wave or ST-segment elevations followed by T-wave inversions in @ least 2 leads

⑤ 2 serum AST values twice normal w/ low/normal serum ALT

or

Ekg Δ's in 1 lead

or

only 1 AST value twice normal in combo w/ 1 LDH value above normal

Ⓒ Probable MI:

- Chest pain w/ : (one of the following)
  - ① T-wave inversions
  - ② ↑↑ AST in combo w/ low/normal ALT
  - ③ 1 or more ↑ LDH
  - ④ Q-wave or ST-segment elevations followed by T-wave inversions in only 1 lead

Study Protocol:

- Treatment was started ASAP after arrival
- Metoprolol 15 mg IV (5 mg IV @ 2 mins.)
  - If SBP < 90, HR < 40 or AV Block (PQ-time ≤ 0.26 s) or adverse effect possibly related to β-blockers
  - ↓ ϕ further injections

If full IV dose tolerated (15 mg IV)

50 mg PO 15 mins. after injections done then 50 mg PO @ 6 Hrs. × 48 hrs. then 100 mg PO BID

If < full IV dose tolerated

25 mg PO @ 6 H × 48 hrs. then 100 mg PO BID

(n = 32 pts. total
20 - Metoprolol group
12 - Placebo group)

- Repeat 12-lead Ekg's every AM × 72 hrs.

Study withdrawals: (statistically significant)

① Hypotension (SBP < 90) - 13 cases in placebo group
($p = 0.018$) - 29 cases in Metoprolol group

② Bradycardia (HR < 40) - 5 cases in placebo group
($p = 0.011$) - 18 cases in Metoprolol group

③ Need for β-blockers
- Angina ($p = 0.04$) - 28 cases in placebo group
- 14 cases in Metoprolol group
- Arrythmias ($p = 0.003$) - 13 cases in placebo group
- 1 case in Metoprolol group

Study Compliance:
- judged by tab counts and urine metoprolol assays
- 78% of pt's had taken >90% of their doses

Study Conclusions:
- supports early administration of β-blockers in acute MI (1st study to do so in regards to "early")
- common thread of β-blockers w/ a ⊕ effect on survival
↓
β_1-receptor blockade
- 12-Day to 90-Day mortality:
- also ↓ 42% w/ metoprolol (not really discussed as far as #'s-wise in study → just mentioned in conclusions)
- metoprolol also assoc. w/ 15% ↓ in enzyme estimated infarct size among pts tx'd w/in 12hrs after pain onset

Study 90-Day Mortality Outcomes:

(1) All Patients: Better in Metoprolol group
↓ 36% RR reduction ($p = 0.03$)

(2) ϕ History of Prior MI: ϕ significant difference

(3) History of Prior MI: ϕ significant difference

(4) Not on Chronic β-Blockade @ Entry: ϕ significant difference

(5) On Chronic β-blockade @ Entry: ϕ significant difference

(6) Age 40-69: Better in Metoprolol group
↓ 37% RR reduction ($p = 0.039$)

(7) Age 70-74: ϕ significant difference

(8) Age 40-64: ϕ significant difference

(9) Age 65-74: Better in Metoprolol group
↓ 45% RR reduction ($p = 0.032$)

(10) Definite MI: Better in Metoprolol group
↓ 34% RR reduction ($p = 0.044$)

(11) ϕ Definite MI: ϕ significant difference

90-Day Mortality
(Primary Outcome: p = 0.03)

		Outcome	No Outcome	Risk of Outcome	Risk of Outcome
Treatment (Y)	||	40	658	0.05731	=a/(a+b)
Control (X)	||	62	635	0.08895	=c/(c+d)

RR (Relative Risk) or Hazard Ratio: 0.64424
RR = (a/a+b)/(c/c+d)

RRR (Relative Risk Reduction): 35.57630%
RRR = 1-RR x100 (%)

ARR (Absolute Risk Reduction): 3.16461%
ARR = (X Risk - Y Risk) x100 (%)

NNT (Number Needed to Treat): 32
NNT = 1/ARR

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90-Day Mortality For Ages 40-69
(Secondary Outcome: p = 0.039)

		Outcome	No Outcome	Risk of Outcome	Risk of Outcome
Treatment (Y)	||	32	597	0.05087	=a/(a+b)
Control (X)	||	51	576	0.08134	=c/(c+d)

RR (Relative Risk) or Hazard Ratio: 0.62546
RR = (a/a+b)/(c/c+d)

RRR (Relative Risk Reduction): 37.45441%
RRR = 1-RR x100 (%)

ARR (Absolute Risk Reduction): 3.04653%
ARR = (X Risk - Y Risk) x100 (%)

NNT (Number Needed to Treat): 33
NNT = 1/ARR

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90-Day Mortality For Ages 65-74
(Secondary Outcome: p = 0.032)

		Outcome	No Outcome	Risk of Outcome	Risk of Outcome
Treatment (Y)	||	19	215	0.08120	=a/(a+b)
Control (X)	||	36	208	0.14754	=c/(c+d)

RR (Relative Risk) or Hazard Ratio: 0.55033
RR = (a/a+b)/(c/c+d)

RRR (Relative Risk Reduction): 44.96676%
RRR = 1-RR x100 (%)

ARR (Absolute Risk Reduction): 6.63444%
ARR = (X Risk - Y Risk) x100 (%)

NNT (Number Needed to Treat): 15
NNT = 1/ARR

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90-Day Mortality For Definite MI
(Secondary Outcome: p = 0.046)

		Outcome	No Outcome	Risk of Outcome	Risk of Outcome
Treatment (Y)	||	36	836	0.04128	=a/(a+b)
Control (X)	||	56	792	0.06604	=c/(c+d)

RR (Relative Risk) or Hazard Ratio: 0.62516
RR = (a/a+b)/(c/c+d)

RRR (Relative Risk Reduction): 37.48362%
RRR = 1-RR x100 (%)

ARR (Absolute Risk Reduction): 2.47533%
ARR = (X Risk - Y Risk) x100 (%)

NNT (Number Needed to Treat): 40
NNT = 1/ARR