Is mifepristone 200mg non-inferior to 600mg for medical abortion? Results of a meta-analysis

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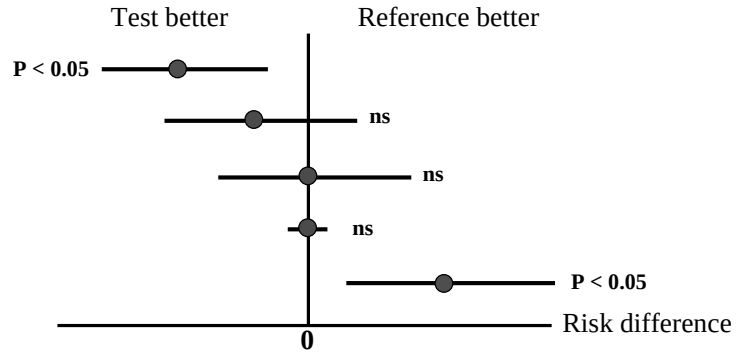
The question

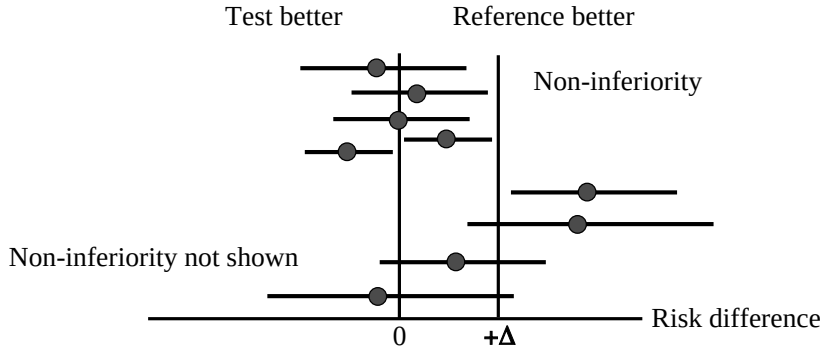
Has mifepristone 200mg the same efficacy as mifepristone 600mg for termination of pregnancy in combination with a prostaglandin administered 36 to 48 hours later?

Interpretation of a difference in an active-control trial



Conclusion: identity of the groups is impossible to demonstrate:
Absence of evidence is not evidence of absence

Non-inferiority trials



Δ = non-inferiority limit = what is consented to be lost

Comparison of mifepristone 200 mg vs 600 mg in TOP

- No non-inferiority trial comparing 200mg with 600mg
- Method
  - Choose a relevant end point
  - Determine the non-inferiority limit independently of the results of trials comparing 200 with 600mg
  - Perform a meta-analysis of the trials comparing 200 with 600mg
  - Interpret the results as a non-inferiority trial

Choice of the end point

- Success (complete abortion) is the most commonly used end point (available in all trials)
- Among failures, ongoing pregnancy is the worst situation
- It would be possible to use 200mg instead of 600mg if it was possible to conclude to non-inferiority for both success and ongoing pregnancy

Choice of the non-inferiority limit

- Background: what has been accepted by regulators to grant a marketing authorization to mifepristone
- The mean success rate varied from 92% to 96%, the mean ongoing pregnancy rate from 1% to 1.5%
- Non-inferiority limits = variation of effect accepted by the regulatory authorities
  - Success (complete abortion): -4% (absolute)
  - Ongoing pregnancy: +0.5% (absolute)
  - Same results when considering trials with misoprostol 400 mg per os (up to 49 DA) or with gemeprost 1 mg vaginally

Available studies comparing 200 with 600mg mifepristone

Study	Days amenorrhea	Mifepristone (mg)	Prostaglandin
WHO 1993	35-56	200 / 400 / 600	Gemeprost 1 mg vaginally
McKinley 1993	≤63	200 / 600	Misoprostol 600 μg per os
WHO 2000	≤63	200 / 600	Misoprostol 400 μg per os
WHO 2001	57-63	200 / 600	Gemeprost 1 mg vaginally

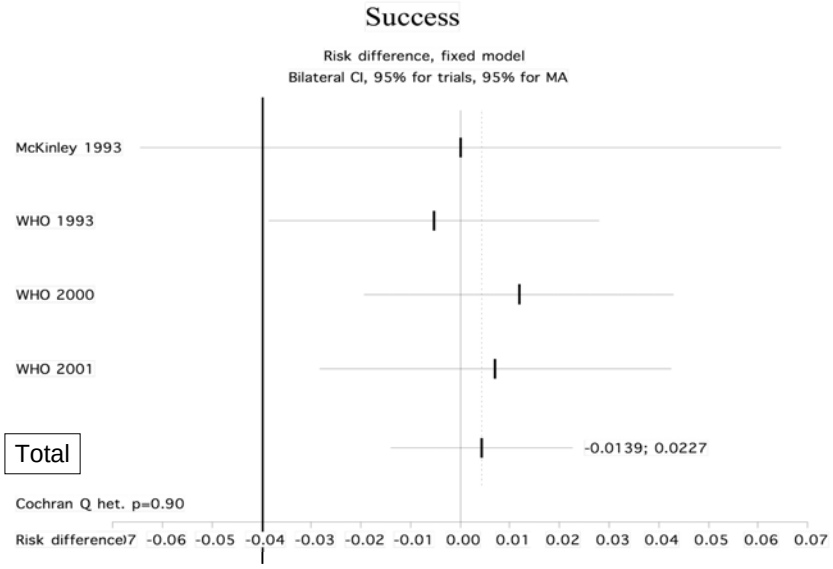
Available studies comparing 200 with 600mg mifepristone

	Dose, number of subjects	Success	Ongoing pregnancy
MCKinley 1993	200 mg 110 600 mg 110	103 103	1 0
WHO 1993	200 mg 388 600 mg 389	364 367	2 1
WHO 2000	200 mg 792 600 mg 797	707 702	22 15
WHO 2001	200 mg 449 600 mg 447	415 410	6 7

Meta-analysis

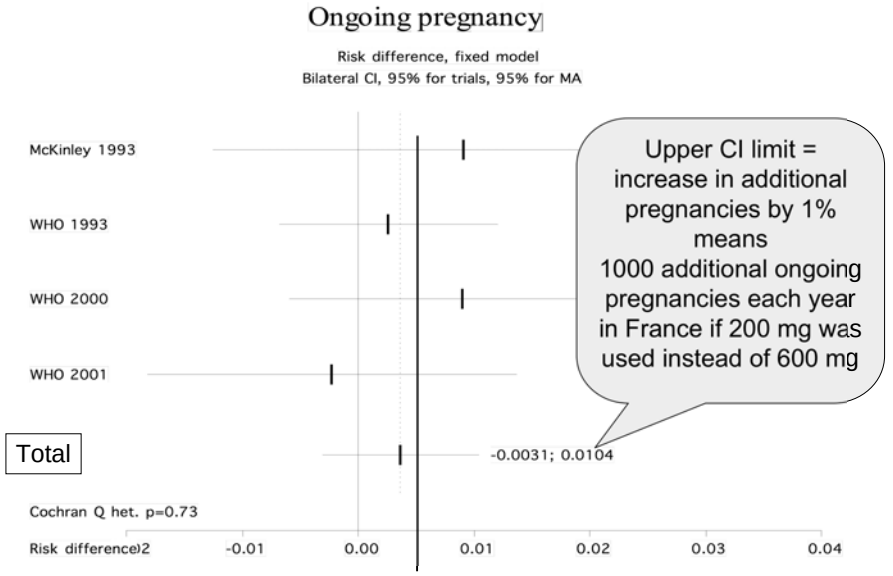
- Rate difference, fixed effect model
- Main analysis: all studies, data as published (ITT)
- Sensitivity analyses
  - Per protocol population (reconstructed from limited published information)
  - Exclusion of the McKinley study (misoprostol 600mg)
  - Restriction to subgroups with <50 DA (at the request of EMEA)

Main analysis (success)



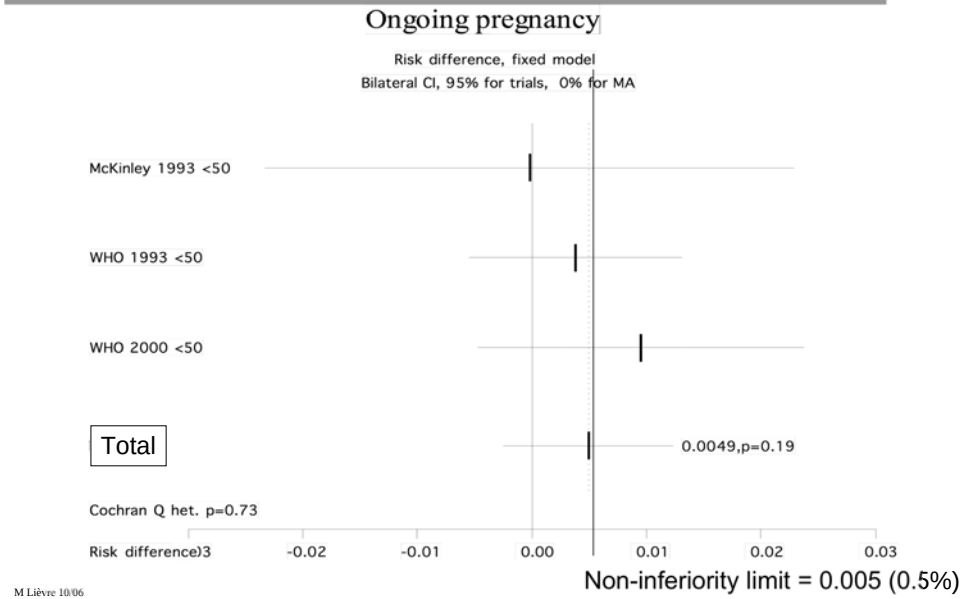
Non-inferiority limit = -0.04 (-4%)

Main analysis (ongoing pregnancy)



Non-inferiority limit = 0.005 (0.5%)

Sensitivity analysis (<50 DA, ongoing pregnancy)



Conclusion

- Non-inferiority of mifepristone 200 mg is demonstrated compared with 600 mg for “success”
- Non-inferiority of mifepristone 200 mg is not demonstrated compared with 600 mg for “ongoing pregnancy”
- Final conclusion: depends on the relative importance of “success” and “ongoing pregnancy”

I would like to thank Gilda Piaggio Pareja and Helena Von Hertzen (WHO), for having provided sub-group data of the WHO studies in women with <50 DA