Agranulocytosis in clozapine: myths and facts

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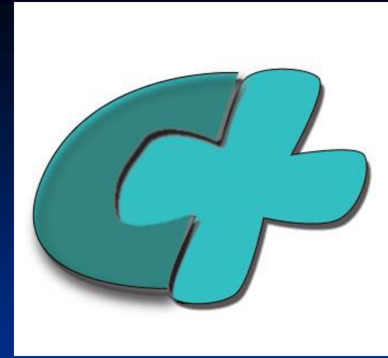
Statement of Potential Conflicts of Interest

Agranulocytosis in clozapine: myths and facts

Relating to this presentation, there are no relationships that could be perceived as potential conflict of interests.

Outline



- History and some facts
- Mortality in clozapine users
- Appraisal of WBC results
- Rechallenge after leukopenia
- Termination of WBC controls
- For all remaining questions:
  Dutch Clozapine Guideline (in English) at:
  www.clozapinepluswerkgroep.nl

Agranulocytosis: history and facts

- Incidence of agranulocytosis in Europe before mandatory WBC controls: **1 to 2% per year#**
- Incidence of agranulocytosis in clinical research for registration in the US (1989): **1.3% in the first year***
- Mortality of agranulocytosis before 1989: **32%*** (now 3-4%)
- Mortality in unexpected agranulocytosis: 16%
- Mortality caused by clozapine agranulocytosis (with controls): 1:10.000 (US) en 1:26.000 (GB)

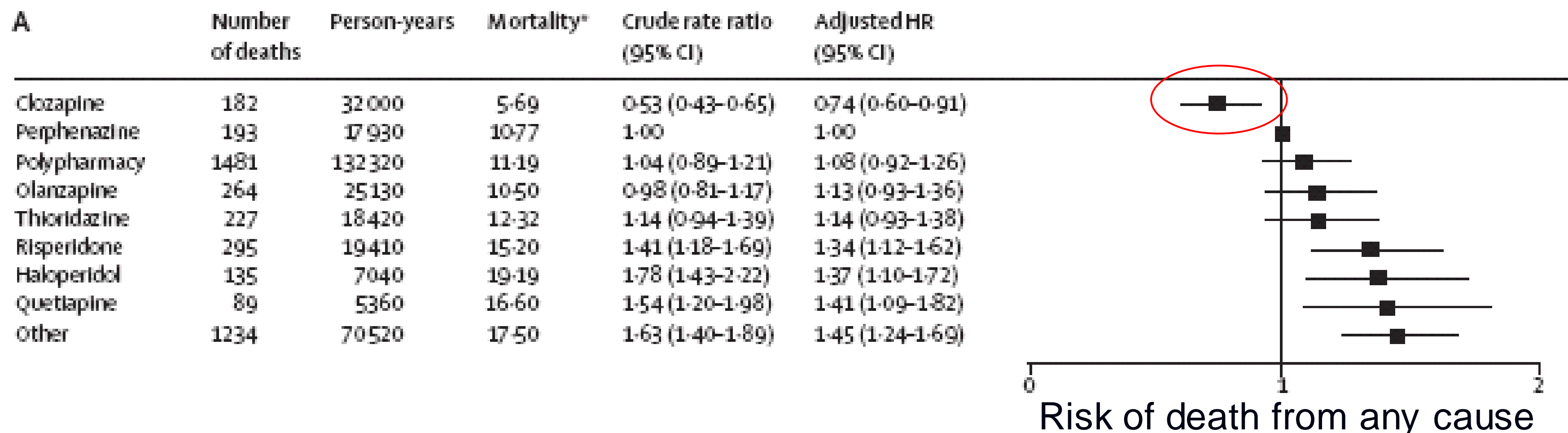
Honigfeld, et. al.(1998). J Clin Psychiatry;59 Suppl 3:3-7,

*United States package insert

Mortality in current clozapine users vs. past clozapine users

- 67,072 current and former clozapine users
- 85,399 person-years
- Lower mortality in current users
- Suicides per year: 0.039% vs. 0.219% (RR 5.67)

Walker et al. Epidemiology 1997;8:671-7.



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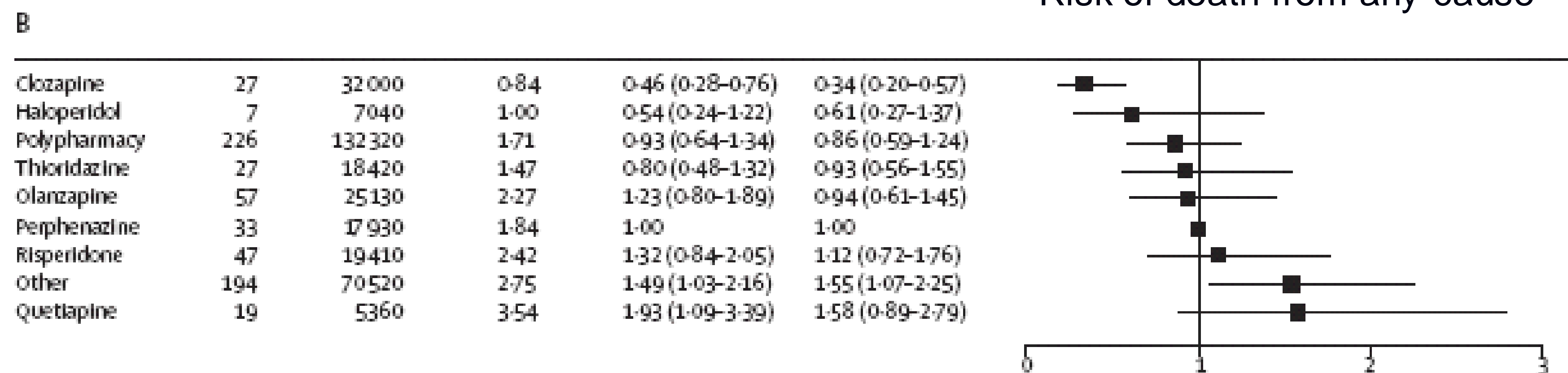
Clozapine	182	32 000	5·69	0·53 (0·43–0·65)	0·74 (0·60–0·91)
Perphenazine	193	17 930	10·77	1·00	1·00
Polypharmacy	1481	132 320	11·19	1·04 (0·89–1·21)	1·08 (0·92–1·26)
Olanzapine	264	25 130	10·50	0·98 (0·81–1·17)	1·13 (0·93–1·36)
Thioridazine	227	18 420	12·32	1·14 (0·94–1·39)	1·14 (0·93–1·38)
Risperidone	295	19 410	15·20	1·41 (1·18–1·69)	1·34 (1·12–1·62)
Haloperidol	135	7040	19·19	1·78 (1·43–2·22)	1·37 (1·10–1·72)
Quetiapine	89	5360	16·60	1·54 (1·20–1·98)	1·41 (1·09–1·82)
Other	1234	70 520	17·50	1·63 (1·40–1·89)	1·45 (1·24–1·69)



B	Number of deaths	Person-years	Mortality*	Crude rate ratio (95% CI)	Adjusted HR (95% CI)
Clozapine	27	32 000	0·84	0·46 (0·28–0·76)	0·34 (0·20–0·57)
Haloperidol	7	7040	1·00	0·54 (0·24–1·22)	0·61 (0·27–1·37)
Polypharmacy	226	132 320	1·71	0·93 (0·64–1·34)	0·86 (0·59–1·24)
Thioridazine	27	18 420	1·47	0·80 (0·48–1·32)	0·93 (0·56–1·55)
Olanzapine	57	25 130	2·27	1·23 (0·80–1·89)	0·94 (0·61–1·45)
Perphenazine	33	17 930	1·84	1·00	1·00
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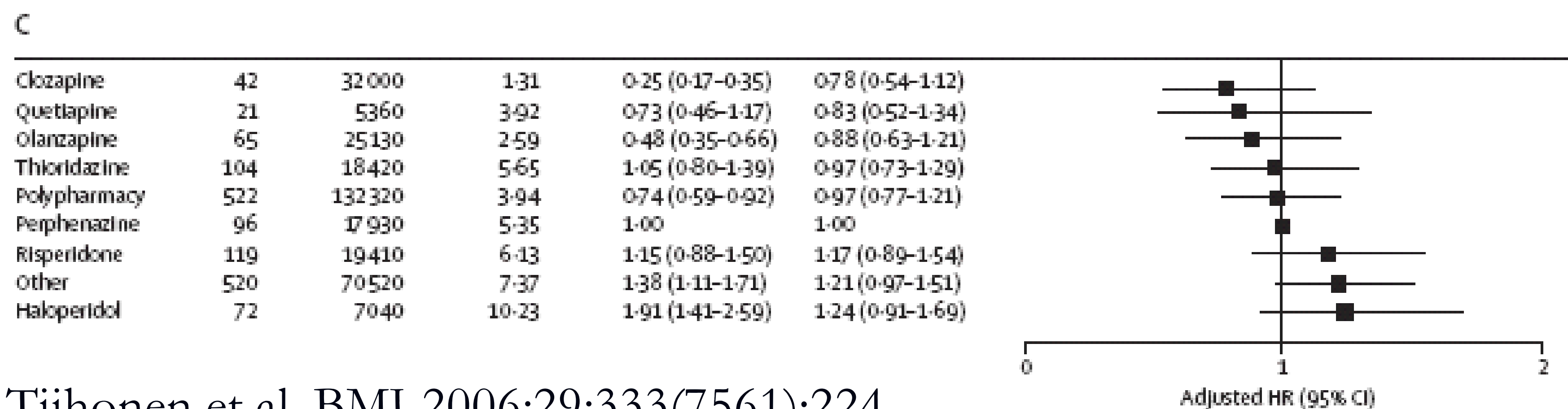

C	Number of deaths	Person-years	Mortality*	Crude rate ratio (95% CI)	Adjusted HR (95% CI)
Clozapine	42	32 000	1·31	0·25 (0·17–0·35)	0·78 (0·54–1·12)
Quetiapine	21	5360	3·92	0·73 (0·46–1·17)	0·83 (0·52–1·34)
Olanzapine	65	25 130	2·59	0·48 (0·35–0·66)	0·88 (0·63–1·21)
Thioridazine	104	18 420	5·65	1·05 (0·80–1·39)	0·97 (0·73–1·29)
Polypharmacy	522	132 320	3·94	0·74 (0·59–0·92)	0·97 (0·77–1·21)
Perphenazine	96	17 930	5·35	1·00	1·00
Risperidone	119	19 410	6·13	1·15 (0·88–1·50)	1·17 (0·89–1·54)
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Tiihonen et al. BMJ 2006;29;333(7561):224.

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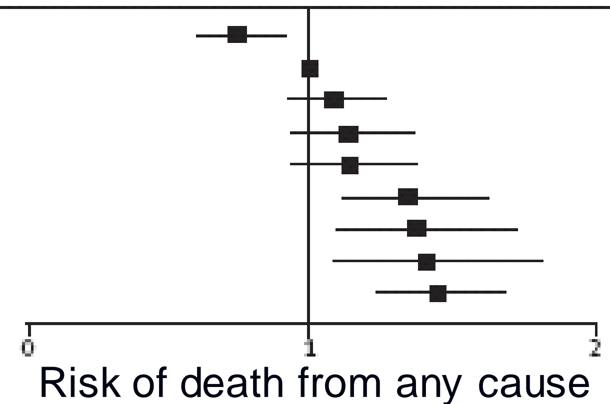

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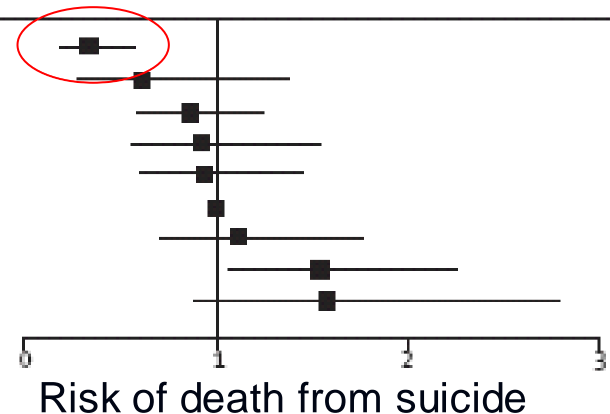

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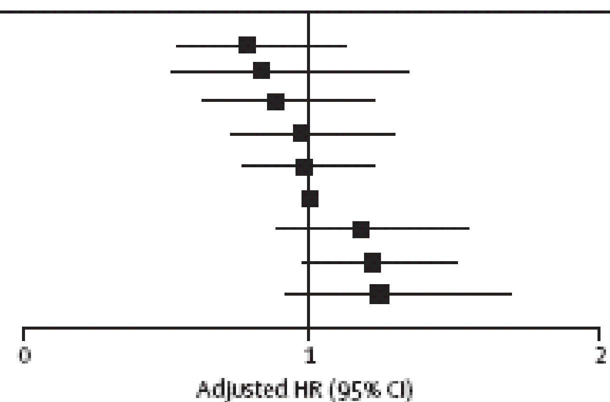

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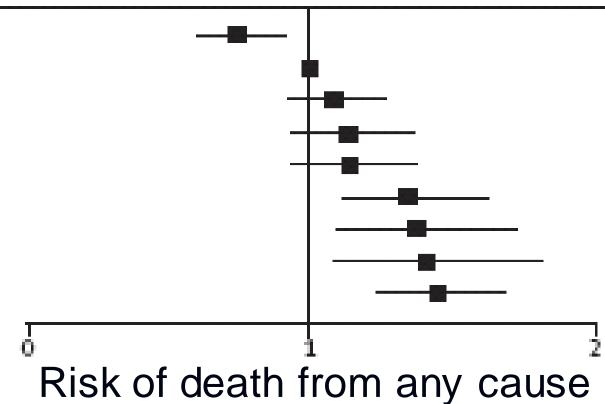

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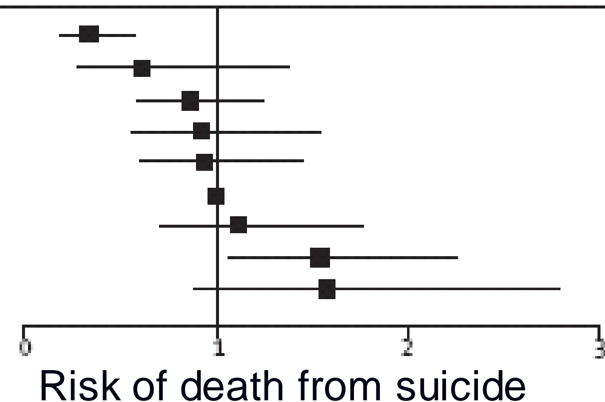

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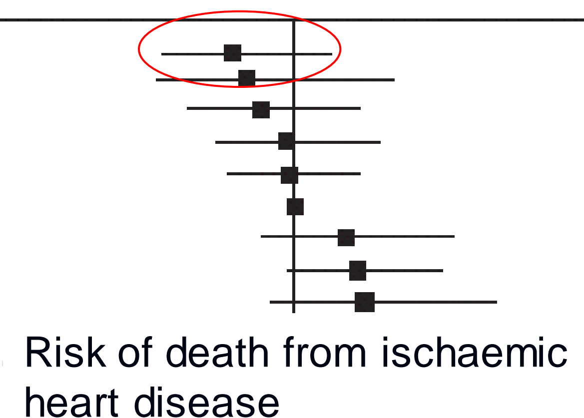

Possible confounders

- 14,754 individuals with SMI
- 879 deaths
- mortality clozapine vs. non-clozapine after adjustment: hazard ratio 0.4 (95% CI 0.2-0.7)
- mortality clozapine vs. olanzapine after adjustment: hazard ratio 0.4 (95% CI 0.2-0.8)
- True for natural and unnatural causes of death

Hayes et al. Schiz Bull 2014, in press

Types of low WBC counts

- Measurement or reporting error
- Circadian rythm
- Benign ethnic neutropenia
- Benign clozapine leukopenia (transient peripheric destruction; Hummer et al. 1992: 8/68 patients)
- malign leukopenia leading to agranulocytosis

Benign Ethnic Neutropenia (BEN)

	WBC		Neutrophils	
	BEN	Regular	BEN	Regular
Normal (green)	$> 3,0 \times 10^9$	$> 3,5 \times 10^9$	$> 1,5 \times 10^9$	$> 2,0 \times 10^9$
Lowered (amber)	$2,5 – 3,0 \times 10^9$	$3,0\text{-}3,5 \times 10^9$	$1,0\text{-}1,5 \times 10^9$	$1,5\text{-}2,0 \times 10^9$
Agranulocytosis (red)	$< 2,5 \times 10^9$	$< 3,0 \times 10^9$	$< 1,0 \times 10^9$	$< 1,5 \times 10^9$
Normal (green):	satisfactory.			
Lowered (amber):	continuation of clozapine with repeated measurement.			
Agranulocytosis (red):	immediate cessation of clozapine.			

Rajagopal Postgrad Med J 2005

Types of low WBC counts

- Measurement error
- Circadian rythm
- Benign ethnic neutropenia
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Stages of neutropenia: risks and treatment

- >1000/µl : no significant risk of infection
- 500-1000/µl : some risk of infection, treat fever like normal policlinic patient
- <500/µl (agranulocytosis): high risk of infection, nearly always clinical symptoms. Parenteral antibiotics.
- <200/µl: very high risk of (opportunistic) infections, reverse isolation, broad spectrum antibiotics

Interruption/termination of treatment with clozapine

- EMA: stop with
  Leukocytes < 3000/µl and /or
  Granulocytes < 1500/µl

- FDA: interrupt with
  Leukocytes < 3000/µl and/or
  Granulocytes < 1500 /µl

  stop with
  Leukocytes < 2000/µl and/or
  Granulocytes < 1000 /µl

Rechallenge

	failure
Leukopenia or granulopenia	38% (95% CI 26-52)
Agranulocytosis	1 of 1

- 17% of rechallenges after leukopenia/granulopenia develop agranulocytosis
- If mortality is set at 5% mortality of rechallenge (without earlier agranulocytosis) is 0.85%
- In the literature positive cases of rechallenge even after agranulocytosis

Dunk et al. Br J Psychiatry 2006;188:255-63.

Rechallenge with Lithium

- All clozapine rechallenges with lithium in one hospital compared to rechallenges from the national clozapine register
- Lithium for 1 or 2 weeks on 0.4mmol/L, then start clozapine
- Failures 21.2% vs. 4%; ARD 29.8% (95% CI 14.6-45.0)
- Unclear whether Lithium really decreases the risk of agranulocytosis
- Advice: do not rechallenge patients with agranulocytosis or severe granulopenia >2 days during the first 18 weeks, except if other possible causes

Kanaan & Kerwin J Clin Psychiatry 2006 ;67:756-60.

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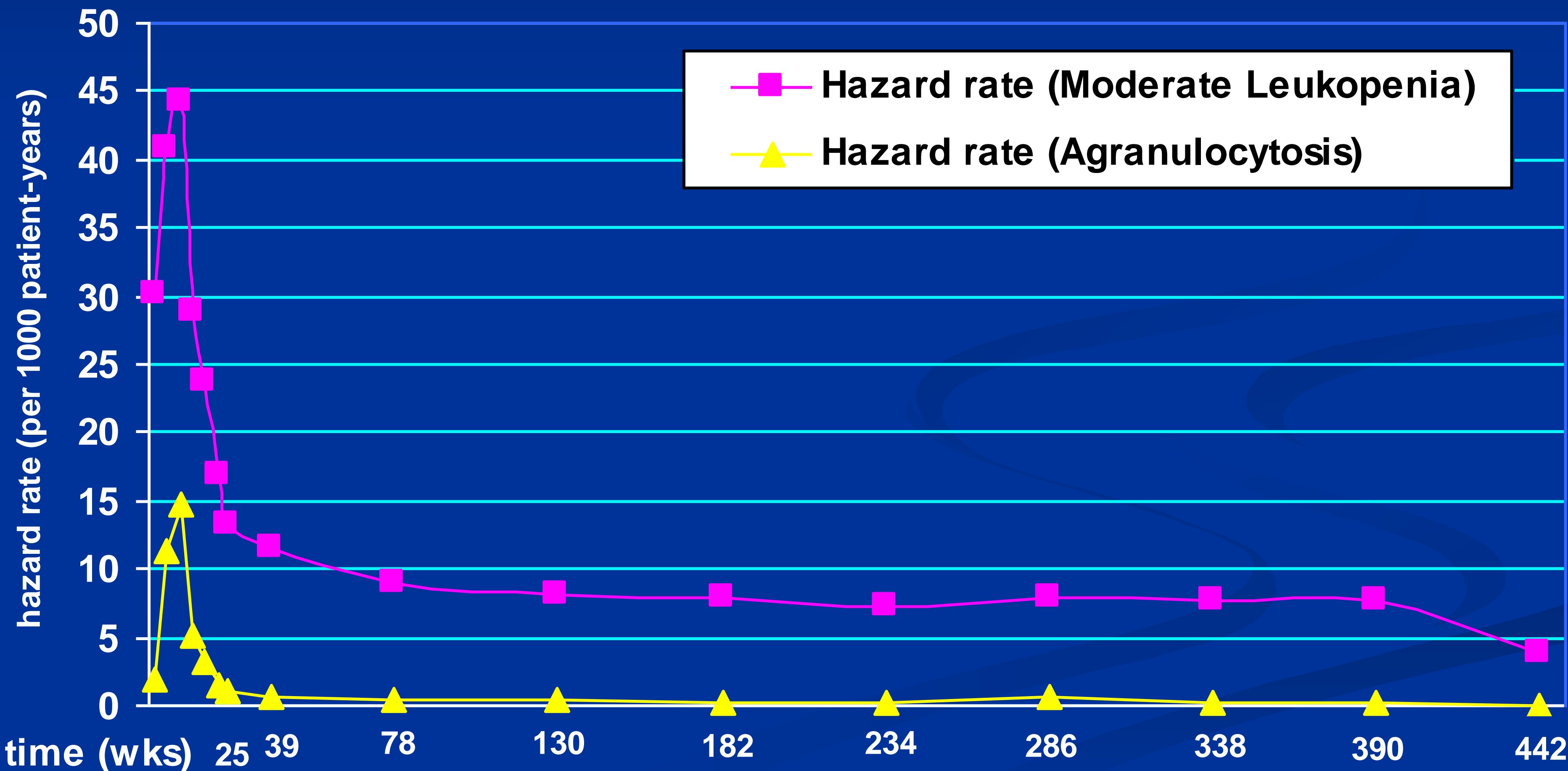
First, do no harm!

Kanaan & Kerwin J Clin Psychiatry 2006;67:756-60.

Controls for ever and ever?

- EMA and FDA: monthly WBC counts up to four weeks after termination of treatment
- Patients want to stop

Risk of moderate leukopenia and agranulocytosis



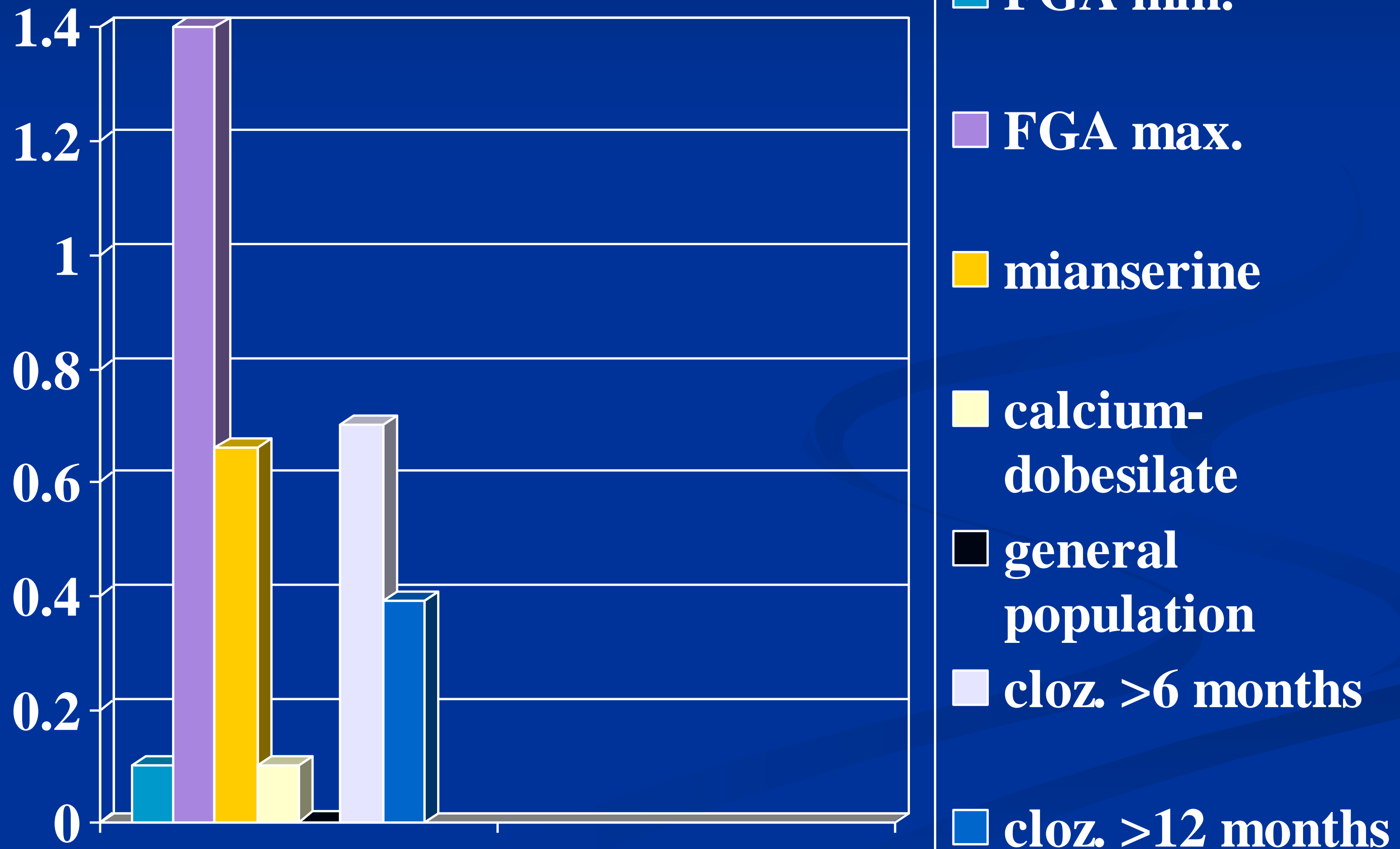
V. Kumar. FDA.gov

Incidence per 1000 patient years

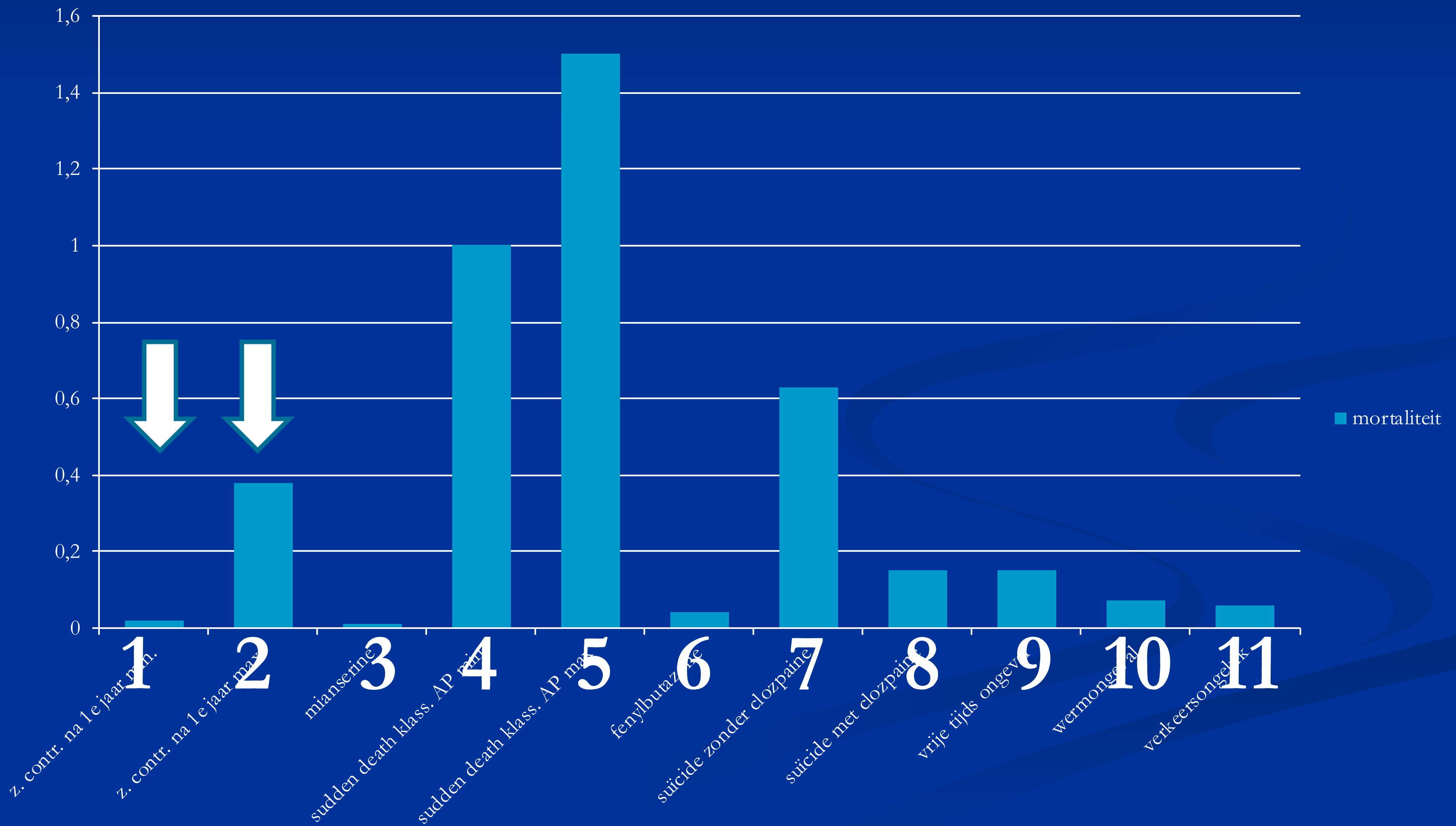
	Severe leucopenia			Agranulocytosis		
Country	<18wks	19-52 wks	>52wks	<18wks	19-52 wks	>52wks
USA	6.93	0.48	0.45	6.76	0.40	0.39
GB/Ire	33.5	4.25	2.6	24.8	1.16	0.31
Australia	12.76	1.58	0.70	8.27	2.17	0.52

V. Kumar. FDA.gov

Agranulocytosis per 1000 person years



Mortality
per 1000 person years



Mortality
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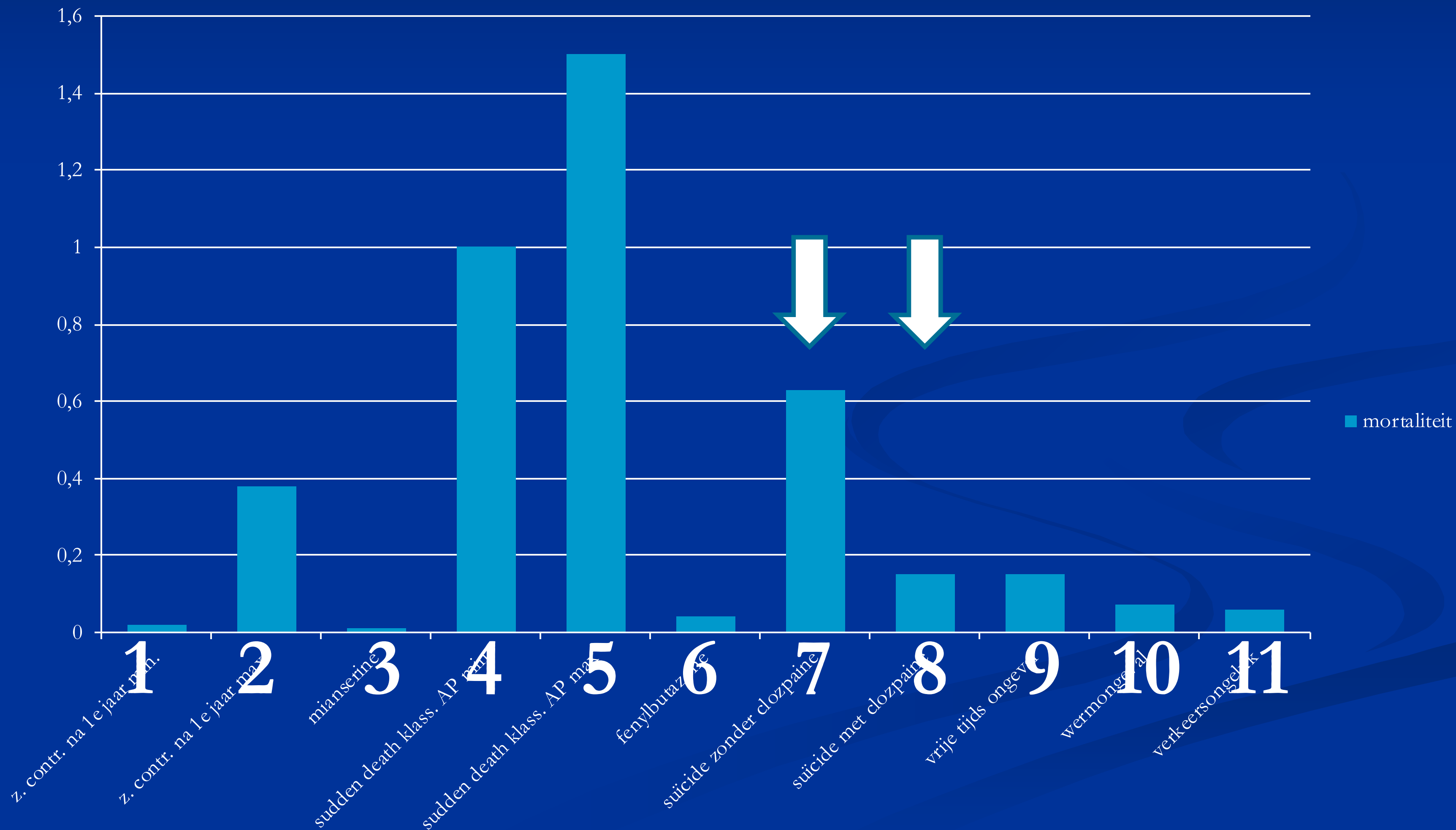

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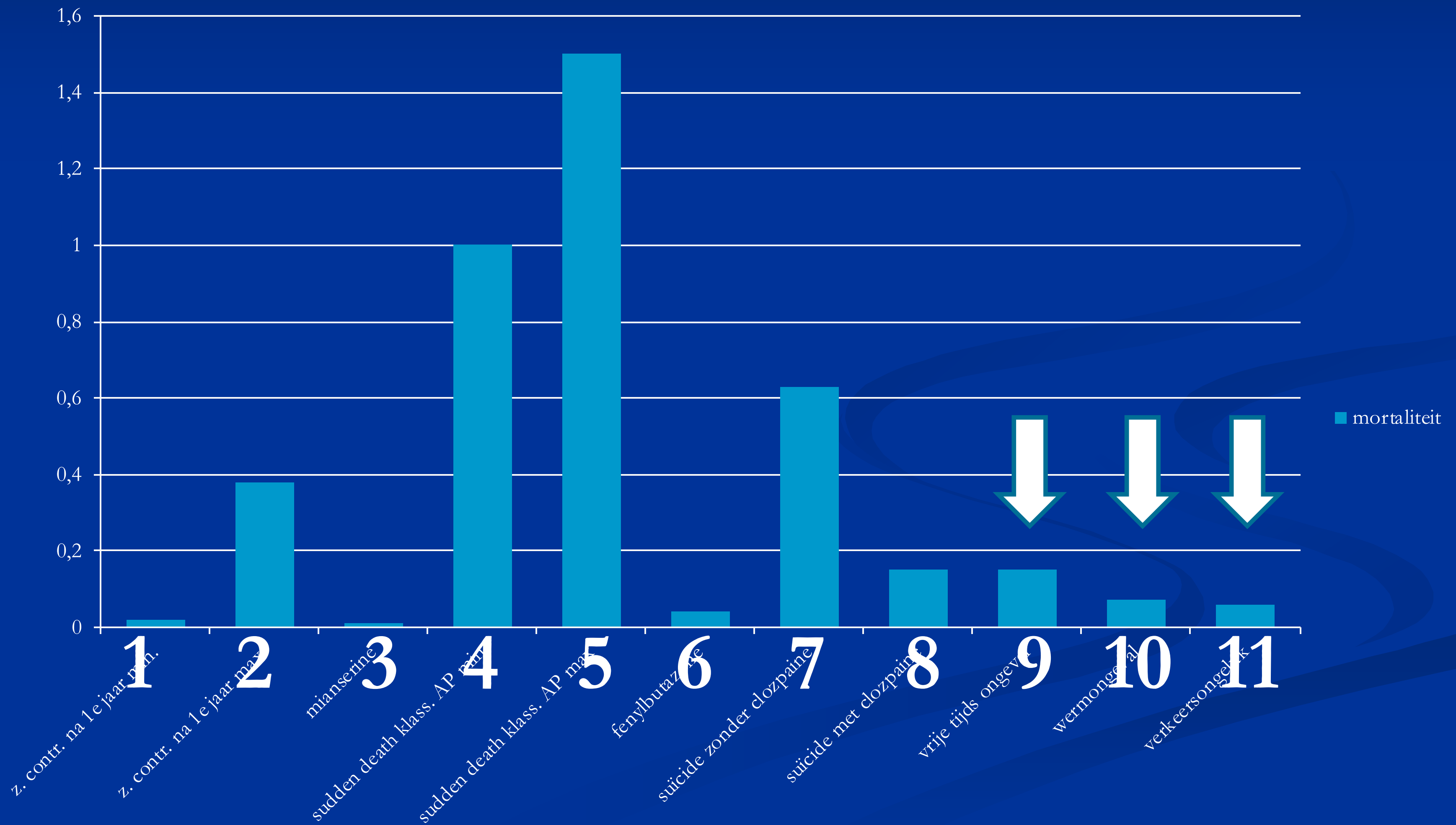

Conclusion

- Mortality GB and US resp. caused by termination of WBC controls after the 1st year: 0.46/1000 and 0.13/1000 patient-years
- If mortality of agranulocytosis is set at 5% and not 16% the risk is 0.15 and 0.04/1000 patient-years
- In the second 6 months of clozapine treatment these risks are about twice as high.

Schulte, Ann Pharmacother 2006;40:683-688

Dutch clozapine guideline

- If a mentally competent and adequately informed patient explicitly wants to stop having routine blood tests, this can be permitted after the first six months of clozapine treatment.
- However, the WBC count must still be monitored immediately if there is any clinical suspicion of agranulocytosis.
- Low frequency tests, for example four times a year, are still advisable.

Medicine
of last resort

Do not overestimate
the risks

Thank you for your attention!

For all remaining questions:
Dutch Clozapine Guideline (in English) at
www.clozapinepluswerkgroep.nl