Tolerability of Artemisinin based combination treatments - ACTs

Bob Taylor

MD (Lond), FRCP (UK), DTM&H (Lond)

Main ACTs

- Artesunate + mefloquine
- Dihydroartemisinin + piperaquine
- Artemether + lumefantrine
- Artesunate + amodiaquine
- Artesunate + sulfadoxine/pyrimethamine
- Artesunate + pyronaridine

Assessing tolerability & safety

- **Tolerability:**
  - **how much do patients complain while on the drug ?**
- **Safety:**
  - **how harmful is the drug ?**
- **Phase I studies in human normal volunteers**
- **Phase II & III studies in patients**
- **After registration:**
  - **phase IV studies**
  - **Pharmacovigilance**

Side effects of the artemisinins

- **Anaphylaxis – 1 in 2800**
- **Good CNS record in patients:**
  - **No brain pathology attributable to artemether**
  - **Hearing unaffected**
- **Bone marrow depression**
  - **Dose related neutropenia**
  - **Reduced reticulocyte counts**

Leonardi E et al. Severe allergic reactions to oral artesunate: a report of two cases. Trans R Soc Trop Med Hyg 2001;95: 182-3.
Hien TT et al. Neuropathological assessment of artemether-treated severe malaria. Lancet. 2003 Jul 26;362(9380):295-6.
Carrara VI et al. Auditory assessment of patients with acute uncomplicated Plasmodium falciparum malaria treated with three-day mefloquine-artesunate on the north-western border of Thailand. Malar J. 2008 Nov 6;7:233
Bethell D et al. Dose-dependent risk of neutropenia after 7-day courses of artesunate monotherapy in Cambodian patients with acute Plasmodium falciparum malaria. Clin Infect Dis. 2010 Dec 15;51(12):e105-14
Kongpatanakul S et al. Comparative study of dihydroartemisinin and artesunate safety in healthy Thai volunteers. Int J Clin Pharmacol Ther. 2009 Sep;47(9):579-86.

Side effects of ACTs

- *Essentially the side effects of the partner drug*
- Most mild or moderate & reversible
- Common (≥1%) / very common (≥10%):
  - Gastrointestinal
  - CNS
  - Itching +/- mild rashes
- Uncommon (<1%) / rare (<0.1%) / very rare (<0.01%):
  - Liver enzyme elevation
  - Bullous rashes
  - Psychiatric
  - Haematological
  - Cardiac

AS+MQ FDC vs. 4 ACTs in Myanmar*

- All ages
- Randomised to primaquine stat dose on D0

	AA (n=155)	AL (n=162)	AM-F (n=169)	AM-L (n=161)	DP (n=161)	N (n=808)	P
Dizziness	91 (58.7)	86 (53.1)	111 (65.7)	104 (64.6)	87 (54.0)	479 (59.3)	0.06
Nausea	27 (17.4)	28 (17.3)	33 (19.5)	30 (18.6)	28 (17.4)	146 (18.1)	0.98
Anorexia	29 (18.7)	17 (10.5)	25 (14.8)	21 (13.0)	22 (13.7)	114 (14.1)	0.34
Diarrhoea	17 (11.0)	12 (7.4)	11 (6.5)	16 (9.9)	20 (12.4)	76 (9.4)	0.32
Abdo. pain	20 (12.9)	23 (14.2)	23 (13.6)	26 (16.2)	19 (11.8)	111 (13.7)	0.83
Palpitations	35 (22.6)	25 (15.4)	38 (22.5)	41 (25.5)	32 (19.9)	171 (21.2)	0.23
Poor sleep	22 (14.2)	14 (8.6)	25 (14.8)	24 (14.9)	18 (11.2)	103 (12.8)	0.33
Headache	2 (1.29)	2 (1.23)	0	0	2 (1.24)	6 (0.74)	0.38
Vomiting 24h	7 (4.5)	6 (3.7)	9 (5.3)	16 (9.9)	10 (6.2)	48 (5.9)	0.18

DHA-PQP (n=767) vs loose ASMQ (n=381)*

- Asian children & adults
- All Low rates of reported AEs
- DHA-PQP less risk of common side effects:
  - Nausea: ~3 vs. ~ 7% x 2
  - Late vomiting: ~ 2.5 vs. ~ 6% x 2
  - Dizziness: ~ 1.4 % vs. ~ 6.3 % x 4
- Similar itching+/- mild rash ~2% both arms
- Early vomiting: 4 (0.5%) vs 0% (p=0.3)

Valecha N et al. An open-label, randomised study of dihydroartemisinin-piperaquine versus artesunate-mefloquine for falciparum malaria in Asia. PLoS One. 2010 Jul 30;5(7):e11880.

Artemether-lumefantrine vs. loose ASMQ*

- A-L less risk of common side effects:
  - Nausea
  - Late vomiting
  - Dizziness
  - Poor sleep
  - Pooled CNS signs e.g. ataxia, nystagmus
- Both drugs:
  - Transient neutropaenia <1000/µL
  - Unremarkable liver enzyme results

* Mueller EA et al. Efficacy and safety of the six-dose regimen of artemether-lumefantrine for treatment of uncomplicated Plasmodium falciparum malaria in adolescents and adults: a pooled analysis of individual patient data from randomized clinical trials. Acta Trop. 2006 Nov;100(1-2):41-53.

van Vugt M et al. Randomized comparison of artemether-benflumetol and artesunate-mefloquine in treatment of multidrug-resistant falciparum malaria. Antimicrob Agents Chemother. 1998 Jan;42(1):135-9

A-L vs. ASMQ-pooled analysis of D28 AE rates.

All cause AEs

Adverse events (after baseline but before recurrence of malaria) in more than 10% of patients receiving co-artemether, irrespective of cause (safety population)

Adverse event	% patients		
	Co-artemether		Comparator: MAS (*N*=335)
	Four-dose regimen (*N*=770)	Six-dose regimen (*N*=495)	
Total	94.9	100	99.7
Headache	83.1	95.2	95.8
Asthenia	54.0	79.6	83.3
Dizziness	63.2	72.7	83.6
Myalgia	35.5	65.3	65.7
Arthralgia	36.6	64.6	73.1
Nausea	48.1	56.8	56.1
Anorexia	71.0	55.6	70.4
Fatigue	38.7	44.6	45.4
Pyrexia	0	43.6	22.1
Sleep disorder	39.9	38.6	48.4
Vomiting	34.0	36.4	37.3
Abdominal pain	28.2	33.5	31.9
Rigors	48.8	31.9	37.9
Palpitations	28.8	29.3	45.7
Hepatomegaly	26.1	25.3	13.4
Splenomegaly	26.4	22.0	21.8
Chills	0	13.7	6.9

Drug related AEs

Adverse events (after baseline but before recurrence of malaria) in more than 1% of patients receiving co-artemether, suspected by the investigator to be drug-related (safety population)

Adverse event	% patients		
	Co-artemether		Comparator: MAS (*N*=335)
	Four-dose regimen (*N*=770)	Six-dose regimen (*N*=495)	
Total	31.3	11.3	63.0
Dizziness	8.7	3.0	29.9
Anorexia	5.5	2.8	16.7
Asthenia	5.2	2.6	14.0
Nausea	3.2	2.2	14.3
Palpitations	4.4	2.0	18.5
Myalgia	3.9	1.8	7.2
Abdominal pain	4.7	1.4	8.1
Sleep disorder	6.4	1.0	22.1
Arthralgia	4.2	0.8	8.1
Vomiting	2.1	0.8	8.7
Headache	6.8	0.6	11.9
Rigors	1.3	0.4	2.7
Diarrhoea	1.8	0.2	1.5
Fatigue	4.2	0	9.0
Pruritus	1.7	0	2.1
Paraesthesia	1.2	0	3.0

•Mueller EA et al. Acta Trop. 2006 Nov;100(1-2):41-53.

ASMQ FDC (251) vs. ASMQ (249) loose rates of early vomiting

Day	n/N	%	n/N	%	p
0	8/251	3.2	2/249	0.8	0.1
1	0/251	0	8/247	3.2	0.003
2	0/251	0	4/247	1.6	0.06

Ashley EA et al. An open label randomized comparison of mefloquine-artesunate as separate tablets vs. a new co-formulated combination for the treatment of uncomplicated multidrug-resistant falciparum malaria in Thailand. Trop Med Int Health. 2006 Nov;11(11):1653-60. PubMed PMID: 17054744.

AS+MQ fixed dose vs. loose tablets new adverse events reported first 7 days

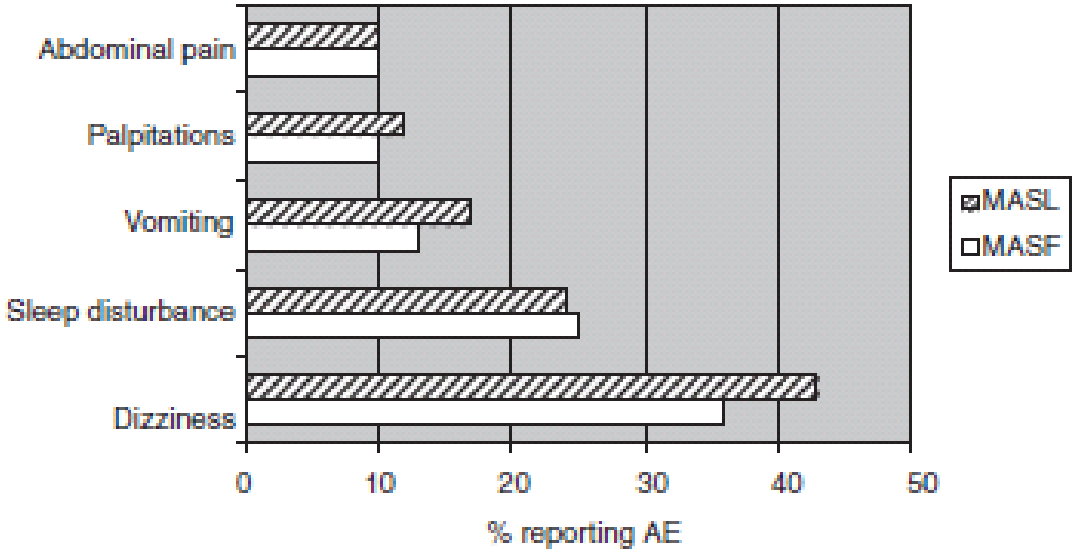
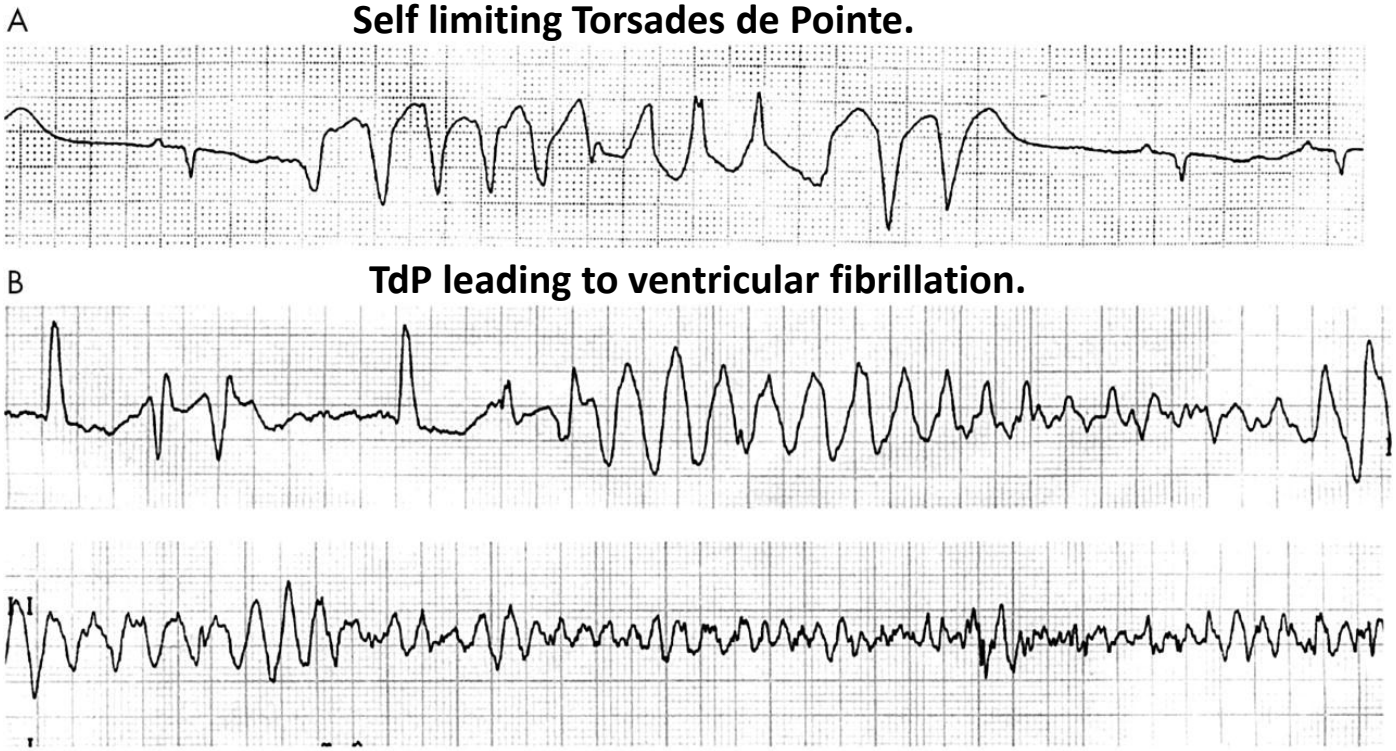


Figure 3 Adverse events absent at baseline but reported at least once before day 7. Vomiting excludes patients who vomited their drug. The numbers of symptomatic patients have been expressed as a percentage of those patients who did not report the symptom at enrolment.

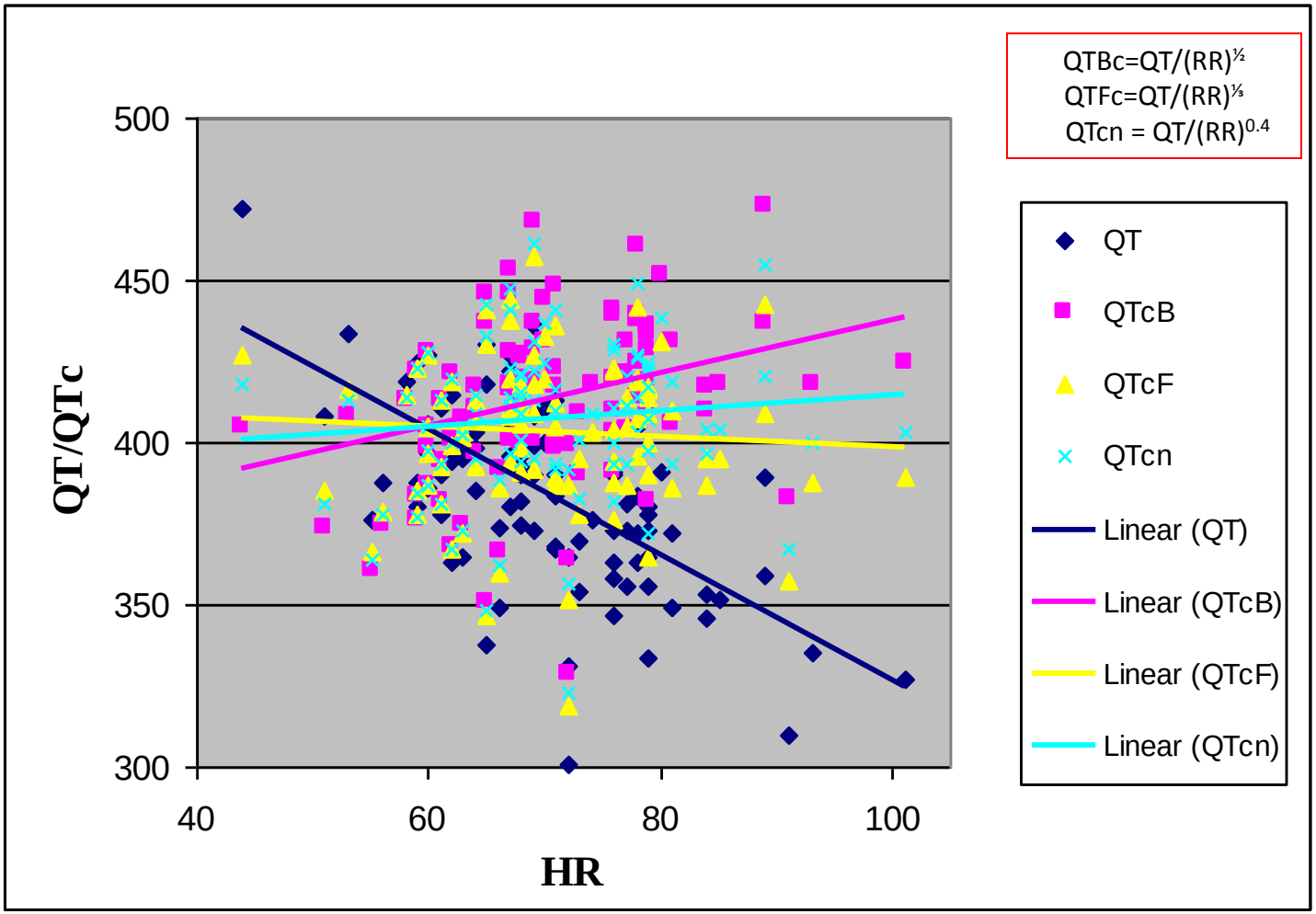
Assessing the QTc interval – potential for developing Torsades de pointe

- **Fridericia or Bazett's corrected QT interval: 12 lead ECG, 24 hour Holter monitoring**



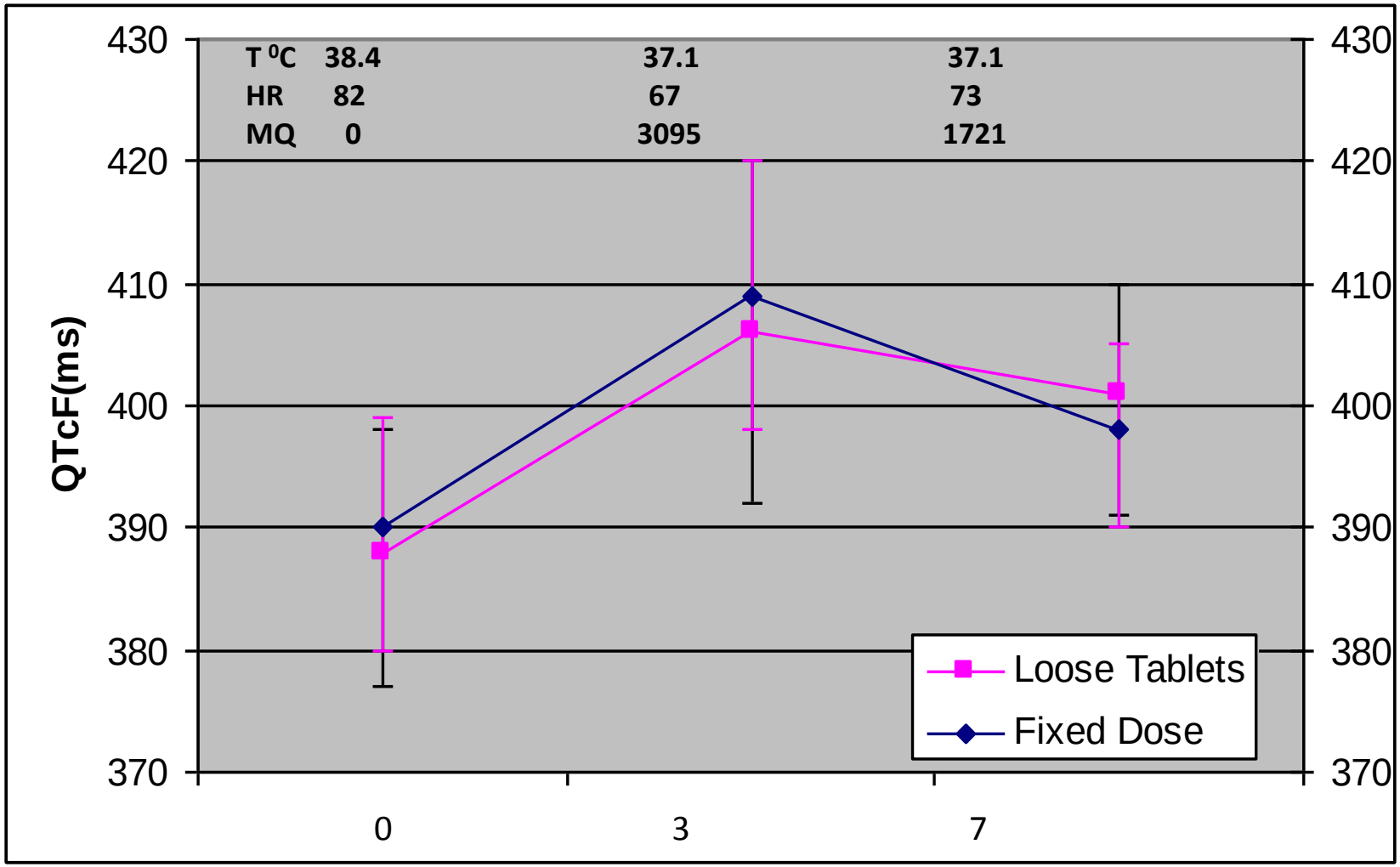
Yap, Y. G. et al. Heart 2003;89:1363-1372

QT, QTcB, QTcF, QTcn values and heart rate in AS MQ treated *P. falciparum* patients*



* Krudsood S et al. Effect of artesunate and mefloquine in combination on the Fridericia corrected QT intervals in Plasmodium falciparum infected adults from Thailand. Trop Med Int Health. 2011 Jan 10.

Mean QTcF, temperature (T), heart rate (HR), MQ concentrations (ng/ml) over time



Summary of data analyses

- Mean D3 change = 18 ms/389 ms = 4.6%
- negative association of Δ QTcF & Δ HR
- No consistent relationship: Δ QTcF & [MQ]
- Mixed effects model
  - HR only independent factor to best explain changes in QTcF
- Little or no effect of ASMQ on QT interval

QTc data other ACTs

- **DHA-PQP vs. ASMQ**
  - **D2 mean Δ QTcF: ~23 ms vs. ~15 ms**
  - **23 ms/388 ms ≈ 6%**
  - **15 ms/386 ms ≈ 4%**
- **A-L vs. ASMQ**
  - **D3 QTcB Δ: ~7 ms vs. ~11.6 ms**
  - **Baseline QTcB ?**

Valecha N et al. An open-label, randomised study of dihydroartemisinin-piperaquine versus artesunate-mefloquine for falciparum malaria in Asia. PLoS One. 2010 Jul30;5(7):e11880.

van Vugt M et al. No evidence of cardiotoxicity during antimalarial treatment with artemether-lumefantrine. Am J Trop Med Hyg. 1999 Dec;61(6):964-7.

Conclusions

- All ACTs well tolerated
- Most side effects mild or moderate & resolve
- Haematology & biochemistry
  - unremarkable
- Cardiac safety
  - good at therapeutic doses
- Different reporting rates of AEs
  - ASMQ FDC better tolerated vs. loose ASMQ
  - Few data comparing ASMQ FDC with other ACTs