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Cardiovascular safety findings in patients with rheumatoid arthritis treated with tofacitinib, an oral Janus kinase inhibitor☆,☆☆

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ABSTRACT

Objectives: Tofacitinib is an oral Janus kinase inhibitor for the treatment of rheumatoid arthritis (RA). The implications of treatment with tofacitinib on cardiovascular (CV) risk in RA are unknown. Therefore, CV adverse events (AEs), and blood pressure and lipid level changes, in tofacitinib-treated patients with RA were evaluated.

Methods: Data were pooled from six Phase (P)3 studies (24 months) and two open-label long-term extension (LTE) studies (60 months) of tofacitinib in patients with RA and inadequate response to DMARDs. Tofacitinib was administered alone or with non-biologic DMARDs. CV events, including major adverse CV events (MACE: CV death and non-fatal CV events) and congestive heart failure (CHF), were assessed by a blinded adjudication committee.

Results: Overall, 4271 patients from P3 studies and 4827 enrolled from P2/P3 studies into LTE studies were evaluated, representing 3942 and 8699 patient-years of exposure to tofacitinib, respectively. Blood pressure remained stable over time across studies. The number of investigator-reported hypertension-related AEs in tofacitinib-treated patients was low in P3 studies (Months 0–3: 2.8%; Months 3–6: 1.4%; > 6 months: 2.8%). Across studies, lipid level increases were generally observed within 1–3 months of treatment and stabilized thereafter. Patients with events (incidence rate [IR]/100 patient-years) for MACE and CHF, respectively, were: 23 (0.58) and 9 (0.23) in P3 studies, and 32 (0.37) and 8 (0.09) in LTE studies; IRs were comparable with placebo (P3) and did not increase over time (LTE).

Conclusions: Tofacitinib was associated with a low incidence of CV events in a large Phase 3 program, including LTE studies. Further long-term studies are underway.

Abbreviations: AE, adverse event; ACR, American College of Rheumatology; Apo, apolipoprotein; BID, twice daily; BP, blood pressure; CHF, congestive heart failure; CRP, C-reactive protein; csDMARD, conventional synthetic disease-modifying antirheumatic drug; CV, cardiovascular; DBP, diastolic blood pressure; DMARD, disease-modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; HDL-C, high-density lipoprotein cholesterol; IR, inadequate response; LDL-C, low-density lipoprotein cholesterol; LTE, long-term extension; MACE, major adverse cardiovascular events; MI, myocardial infarction; MTX, methotrexate; NSAID, non-steroidal anti-inflammatory drug; pt-yrs, patient-years; q2w, once every 2 weeks; RA, rheumatoid arthritis; RCT, randomized controlled trial; SAE, serious adverse event; SBP, systolic blood pressure; sc, subcutaneously; SD, standard deviation; TC, total cholesterol; TDD, total daily dose; TNFi, tumor necrosis factor inhibitor.

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Introduction

Patients with rheumatoid arthritis (RA) have an increased risk of cardiovascular (CV) disease and CV-related death compared with the general population [1–3]. CV events are reported to occur approximately a decade earlier in patients with RA compared with the general population [4,5], suggesting that RA is an independent risk factor for premature heart disease [2,6]. CV disease risk in older patients ($\geq$ 75 years) with RA was reported to be more than three-fold the Framingham-predicted risk for the general population [7], and female patients with RA have demonstrated a two-fold higher risk of myocardial infarction (MI) compared with female patients without RA [8].

The increased risk of CV disease in patients with RA appears to be linked to coronary atherosclerosis [9,10]. Studies have also suggested that the increased risk is not driven by traditional CV risk factors alone [6,11–13], and RA-associated inflammation and disease activity play a pivotal role [14,15]. The relationship between lipid levels, RA treatment, and CV risk in patients with RA is complex. Indeed, although the evidence is inconclusive, some data indicate that effective management of RA with disease-modifying anti-rheumatic drugs (DMARDs) is associated with a reduced risk of CV events, most likely due to inhibitory effects on inflammatory pathways [16,17].

Tofacitinib is an oral Janus kinase inhibitor for the treatment of RA. Tofacitinib has demonstrated efficacy and safety in patients with RA at doses of 5 and 10 mg twice daily (BID) in Phase 2 [18–22] and Phase 3 randomized controlled trials (RCTs) of up to 24 months' duration [23–28] and in long-term extension (LTE) studies with up to 72 months of observation [29,30].

During the Phase 2 studies, increases in low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) levels were observed in patients with active RA receiving treatment with tofacitinib [18,19,21,22,31]. Consequently, Phase 3 and LTE studies included adjudication of potential CV events and deaths.

The purpose of the current analysis was to evaluate the CV event rates and changes in blood pressure (BP) and lipid levels from pooled Phase 3 and open-label LTE studies of tofacitinib in patients with moderate to severe active RA.

Methods

Study design and treatment

The six double-blind, Phase 3 RCTs included in this analysis were of 6–24 months' duration, and pooled in a single data set (Table 1). Pooling was justified by the similarity of demographic and baseline disease characteristics of patients across the studies. The two open-label LTE studies (A3921024 [NCT00413699] and A3921041 [NCT00661661]) [29] (Table 1) enrolled eligible patients from two Phase 1, nine Phase 2, and six Phase 3 index studies of tofacitinib. Details on individual study designs have been published previously [23–28] and are summarized in Table 1. In all studies, patients were permitted to receive treatment with non-steroidal anti-inflammatory drugs (NSAIDs) and oral glucocorticoids, that is, $\leq$ 10 mg/day prednisone or equivalent, consistent with rheumatology practice worldwide. Dosing of tofacitinib and background DMARD therapy was required to be stable in Phase 1, Phase 2, and 3 studies. In the LTE studies, dose adjustments of tofacitinib and background DMARD therapy were permitted based on the investigator's assessment of efficacy and safety. For the purpose of the current analysis, the average total daily dose (TDD) during the LTE studies was calculated by adding all doses received by each patient and dividing by the number of days a dose was received. TDDs of $<$ 15 mg/day and $\geq$ 15 mg/day were categorized as 5 and 10 mg BID groups, respectively.

All studies were conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice Guidelines. All patients provided written, informed consent. The final protocols, amendments, and informed consent documentation were reviewed and approved by the Institutional Review Board and/or Independent Ethics Committee of each investigational site.

Patients

In Phase 3 studies, eligible patients aged $\geq$ 18 years with active moderate to severe RA were enrolled globally from North America, Europe, Latin America, Asia, and Australia. Patients eligible for enrollment in the LTE studies were aged $\geq$ 18 years (A3921024) or $\geq$ 20 years (A3921041). Key inclusion criteria are detailed in Table 1. Key exclusion criteria included: current or recent history of severe, progressive, or uncontrolled renal, hepatic, hematological, gastrointestinal, endocrine, metabolic, pulmonary, cardiac, or neurological disease; or a 12-lead electrocardiogram at screening that demonstrated clinically relevant abnormalities that might have affected patient safety or interpretation of the study results. The screening visit included an evaluation of vital signs, including blood pressure and heart rate, and fasting lipid profiles.

Cardiovascular events

Adjudicated major adverse CV events (MACE) and congestive heart failure (CHF) events were categorized and incidence rates calculated. The endpoint of MACE was defined as the composite of the following events: CV mortality (including coronary, cerebrovascular, cardiac, and non-cardiac vascular events), and non-fatal CV events (including MI and cerebrovascular events).

Measurement of lipid levels

Total cholesterol (TC), HDL-C, and triglyceride levels (fasting) were assayed using conventional analytical techniques in all studies. LDL-C levels were calculated using the Friedewald formula [32]. When triglyceride levels were $\geq$ 400 mg/dL, LDL-C was measured directly by ultracentrifugation. Plasma concentrations of apolipoprotein (Apo) A-1 and Apo B-100 were measured using immunophelometry.

Blood pressure and hypertension

For all studies, BP measurements were obtained at the screening, all study visits, and at follow-up, and were recorded to the nearest mmHg in the dominant arm after the patient had rested for $\geq$ 5 minutes. For recorded BP measurements, hypertension was defined using criteria specified in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7) [33]. By contrast, adverse events (AEs) related to hypertension were identified and reported by the investigators, then coded to preferred terms using MedDRA.

Statistical analyses

Data are reported through Month 24 for Phase 3 studies and through 60 months of observation for LTE studies. All data captured up to and including 10 April 2013 are included in this analysis. For Phase 3 studies, data are presented by Months 0–3 (placebo comparison phase), Months 3–6 (placebo advancement phase), and $>$ 6 months (tofacitinib-only phase). Data collection and analyses for LTE studies were still ongoing at the time of the

Table 1
Summary of the tofacitinib clinical studies included in this analysis: A3921024, A3921032, A3921041, A3921044 (2-year data), A3921045, A3921046, A3921064, and A3921069 (1-year data)

Study	Main inclusion criteria	Study duration	Study treatments	Background therapy	Number of patients randomized
Phase 3 studies					
ORAL Start [26] A3921069 NCT01039688	Active RA[a] MTX naïve	24 months	Tofacitinib 5 mg BID Tofacitinib 10 mg BID MTX[b]	None – monotherapy	958
ORAL Sync [25] A3921046 NCT00856544	Active RA[c] DMARD-IR	12 months	Tofacitinib 5 mg BID Tofacitinib 10 mg BID Placebo[d]	Combination with csDMARDs	795
ORAL Standard [28] A3921064 NCT00853385	Active RA[a] MTX-IR[a]	12 months	Tofacitinib 5 mg BID Tofacitinib 10 mg BID Placebo[d] Adalimumab 40 mg sc q2w	Combination with MTX	717
ORAL Scan [27] A3921044 NCT00847613	Active RA[a] ≥3 distinct joint erosions MTX-IR	24 months	Tofacitinib 5 mg BID Tofacitinib 10 mg BID Placebo[d]	Combination with MTX	797
ORAL Step [23] A3921032 NCT00960440	Active RA[a] TNFi-IR	6 months	Tofacitinib 5 mg BID Tofacitinib 10 mg BID Placebo[d]	Combination with MTX	399
ORAL Solo [24] A3921045 NCT00814307	Active RA[a] DMARD-IR	6 months	Tofacitinib 5 mg BID Tofacitinib 10 mg BID Placebo[d]	None – monotherapy	611
Long-term extension studies					
ORAL Sequel [29] A3921024			Patients from five Phase 2 studies, or from China and Japan, initiated treatment with tofacitinib 5 mg BID		
NCT00413699 A3921041 [29] NCT00661661	Active RA[e]; participation in a qualifying Phase 1, Phase 2, or Phase 3 study	Long term	Patients from the Phase 1 studies, the remaining Phase 2 studies, and Phase 3 studies initiated treatment with tofacitinib 10 mg BID, regardless of treatment assignment in the index study	Background csDMARDs or monotherapy based on the requirements of the index study	4827

ACR, American College of Rheumatology; BID, twice daily; CRP, C-reactive protein; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DMARD, disease-modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; IR, inadequate response; MTX, methotrexate; q2w, once every 2 weeks; RA, rheumatoid arthritis; sc, subcutaneously; TNFi-IR, inadequate response to tumor necrosis factor inhibitors.

[a] Diagnosis of RA based on the ACR 1987 revised criteria [59] and ≥6 tender/painful joints (68-joint count) and ≥6 swollen joints (66-joint count); ESR >28 mm/h (in local laboratory); or CRP > 7 mg/L.

[b] Starting dose of 10 mg per week that was incrementally increased to 20 mg per week by Week 8.

[c] Diagnosis of RA based on the ACR 1987 revised criteria [59] and ≥4 tender/painful joints (68-joint count) and ≥4 swollen joints (66-joint count); ESR > 28 mm/h (in local laboratory); or CRP > 7 mg/L.

[d] Patients randomized to placebo were advanced in a blinded manner to tofacitinib 5 or 10 mg BID at 3 or 6 months.

[e] Diagnosis of RA based on the ACR 1987 revised criteria [59].

current analyses and the database was unlocked (i.e., some values may change for the final, locked study database).

All safety analyses were descriptive in nature. Incidence rates (unique patients with events per 100 patient-years of observation) for adjudicated CV events were compared between treatment groups and were based on the number of patients with an event and the total exposure time censored at time of event, death, or discontinuation from the study. The 95% confidence intervals (CIs) for incidence rates were based on maximum likelihood estimation (Table 2).

In Phase 3 studies, adjudication of CV events was performed by a blinded CV Safety Endpoint Adjudication Committee (CVSEAC) comprised of three cardiologists independent of Pfizer. The adjudication process was implemented on 25 February 2009 after the completion of Phase 2 studies and before the start of Phase 3 studies but when the LTE studies were already ongoing. Therefore,

Table 2
Summary of patients from the Phase 3 and LTE studies included in this analysis

	0–6 Months	6–12 Months	12–18 Months	18–24 Months	24–30 Months	30–36 Months	36–42 Months	>42 Months
Total patients, *n*	4069	3585	3154	2442	2151	1783	1344	370
Total pt-yrs of drug exposure	1893.30	1679.63	1367.34	1128.75	966.32	772.85	406.01	34.52

LTE, long-term extension; *N*, number of patients; pt-yrs, patient-years.

Table 3
Baseline demographics in Phase 3 and LTE studies

	Phase 3 studies						LTE studies		
	Tofacitinib 5 mg BID (N = 1589)	Tofacitinib 10 mg BID (N = 1611)	Placebo → tofacitinib 5 mg BID (N = 343)	Placebo → tofacitinib 10 mg BID (N = 338)	Adalimumab 40 mg sc q2w (N = 204)	Methotrexate (N = 186)	Tofacitinib 5 mg BID (N = 1452)	Tofacitinib 10 mg BID (N = 3374)	All doses (5 and 10 mg BID) (N = 4826)[a]
Age (years)									
Mean (range)	52.5 (18–86)	51.7 (18–85)	52.8 (18–82)	52.2 (18–80)	52.5 (23–77)	48.8 (20–80)	53.1 (18–82)	53.0 (18–86)	53.1 (18–86)
≥ 65 years (%)	14.3	14.3	16.3	13.3	14.7	10.8	17.1	15.4	15.9
Gender (%)									
Male: female	17.4: 82.6	15.8: 84.2	19.0: 81.0	18.6: 81.4	20.6: 79.4	22.0: 78.0	16.8: 83.2	18.1: 81.9	17.7: 82.3
Race (%)									
White	61.4	62.5	66.8	62.1	72.5	68.3	46.6	70.5 3.2 16.3 10.0	63.3
Black	3.7	2.9	2.3	4.7	1.5	2.2	1.7	3.2	2.7
Asian	24.9	23.4	23.6	25.1	14.2	17.7	43.1	16.3	24.4
Other	10.1	11.2	7.3	8.0	11.8	11.8	8.7	10.0	9.6
Smoker (%)									
Never: current: ex-smoker	66.6: 14.7: 18.7	68.1: 17.5: 14.4	59.2: 21.1: 19.6	66.4: 17.0: 16.7	65.5: 18.5: 16.0	67.2: 21.0: 11.8	73.6: 13.3: 13.1	65.7: 18.1: 16.2	67.9: 16.8: 15.3
Mean (SD) body mass index (kg/m^2)	26.9 (6.5)	27.0 (6.3)	26.8 (6.6)	27.6 (7.1)	27.1 (5.5)	26.7 (6.1)	25.5 (5.8)	27.5 (6.5)	26.9 (6.4)
	Tofacitinib 5 mg BID (N = 1589)	Tofacitinib 10 mg BID (N = 1611)	All tofacitinib doses (N = 3200)	Placebo (N = 681)	Adalimumab 40 mg sc q2w (N = 204)	Methotrexate (N = 186)	Tofacitinib 5 mg BID (N = 1452)	Tofacitinib 10 mg BID (N = 3374)	All doses (5 and 10 mg BID) (N = 4827)
Hypertension, n (%)	369 (23.2)	358 (22.2)	727 (22.7)	145 (21.3)	49 (24.0)	33 (17.7)	365 (25.5)	735 (22.1)	1100 (23.1)
Diabetes, n (%)	130 (8.2)	127 (7.9)	257 (8.0)	48 (7.0)	16 (7.8)	8 (4.3)	107 (7.4)	243 (7.2)	350 (7.3)
Mean (SD) LDL-C (mg/dL)	114.8 (34.2)	113.3 (34.9)	114.1 (34.5)	115.8 (35.0)	117.0 (34.3)	111.5 (32.0)	111.5 (32.6)	114.2 (34.4)	113.4 (33.9)
Mean (SD) HDL-C (mg/dL)	59.4 (16.9)	59.7 (17.0)	59.6 (16.9)	59.8 (17.1)	58.6 (16.5)	55.7 (15.0)	58.7 (16.3)	59.0 (16.5)	58.9 (16.5)
Mean (SD) TC (mg/dL)	199.1 (42.4)	198.6 (42.8)	198.8 (42.6)	200.6 (41.7)	200.8 (40.3)	190.1 (39.7)	192.1 (39.6)	198.8 (41.7)	196.6 (41.2)
Mean (SD) Triglycerides (mg/dL)	124.6 (68.7)	128.6 (78.8)	126.6 (74.0)	125.2 (64.3)	126.1 (60.2)	115.2 (51.2)	113.3 (63.1)	125.5 (70.2)	121.8 (63.4)

In Phase 3 studies, patients randomized to placebo were advanced in a blinded manner to tofacitinib 5 or 10 mg BID at Months 3 or 6.
The average total daily dose (TDD) during the LTE studies was calculated by adding all doses received by each patient and dividing by the number of days a dose was received. TDDs of <15 mg/day and ≥ 15 mg/day were categorized as 5 and 10 mg BID groups, respectively.
BID, twice daily; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LTE, long-term extension; q2w, once every 2 weeks; sc, subcutaneously; SD, standard deviation; TC, total cholesterol.

[a] One subject had no demographic data at the time of the analysis.

adjudicated CV events included those that occurred during the entire Phase 3 program but only those that occurred after 25 February 2009 in the LTE studies. Exposures were calculated from either the date of randomization in Phase 3 studies or 25 February 2009 in LTE studies until the date of the event or the date of data cutoff. The use of the implementation date in the adjudication process rather than the date of randomization for determining tofacitinib exposure in the LTE studies may underestimate exposures and overestimate the actual incidence rates. This approach was selected to generate the most conservative estimates of incidence rates.

Results

Patients

In total, 4271 patients (including those receiving adalimumab, MTX, and placebo) from Phase 3 studies and 4827 patients enrolled from Phase 1, Phase 2, or Phase 3 studies into the LTE studies were included in the analyses, representing 3942 and 8699 patient-years of exposure to tofacitinib, respectively. Patient baseline demographics and clinical and laboratory data are presented in Table 3. Baseline hypertension by JNC7 criteria was present in up to approximately one-quarter of patients in both Phase 3 and LTE studies.

Major adverse cardiovascular events

In the Phase 3 studies, 23 events of MACE occurred in tofacitinib-treated patients. Incidence rates for MACE were similar for tofacitinib, placebo, and adalimumab, although considerably fewer patients were observed on adalimumab overall and the total exposure to adalimumab and number of MACE events in these patients was less than in the other treatment groups. No events were observed in the MTX treatment group (Table 4, Fig. 1A). The incidence rates for CV mortality events and MI were low and similar for tofacitinib (both doses) and adalimumab and no events were observed in the placebo and MTX treatment groups (Table 4; Fig. 1B and C). Incidence rates for non-fatal cerebrovascular accidents were low and similar for tofacitinib (both doses) and placebo; no events were observed in the adalimumab or MTX treatment groups (Table 4; Fig. 1D). The incidence rates for CHF events were low and similar with both doses of tofacitinib; there were no CHF events in the placebo, adalimumab, or MTX treatment groups (Fig. 1E). Incidence rates for adjudicated CV events were generally lower in the LTE versus Phase 3 studies (Table 4, Fig. 1A–E). Three CV deaths were reported in the LTE studies (tofacitinib 5 mg BID) (Table 4; Fig. 1B).

Lipid levels

Phase 3 studies

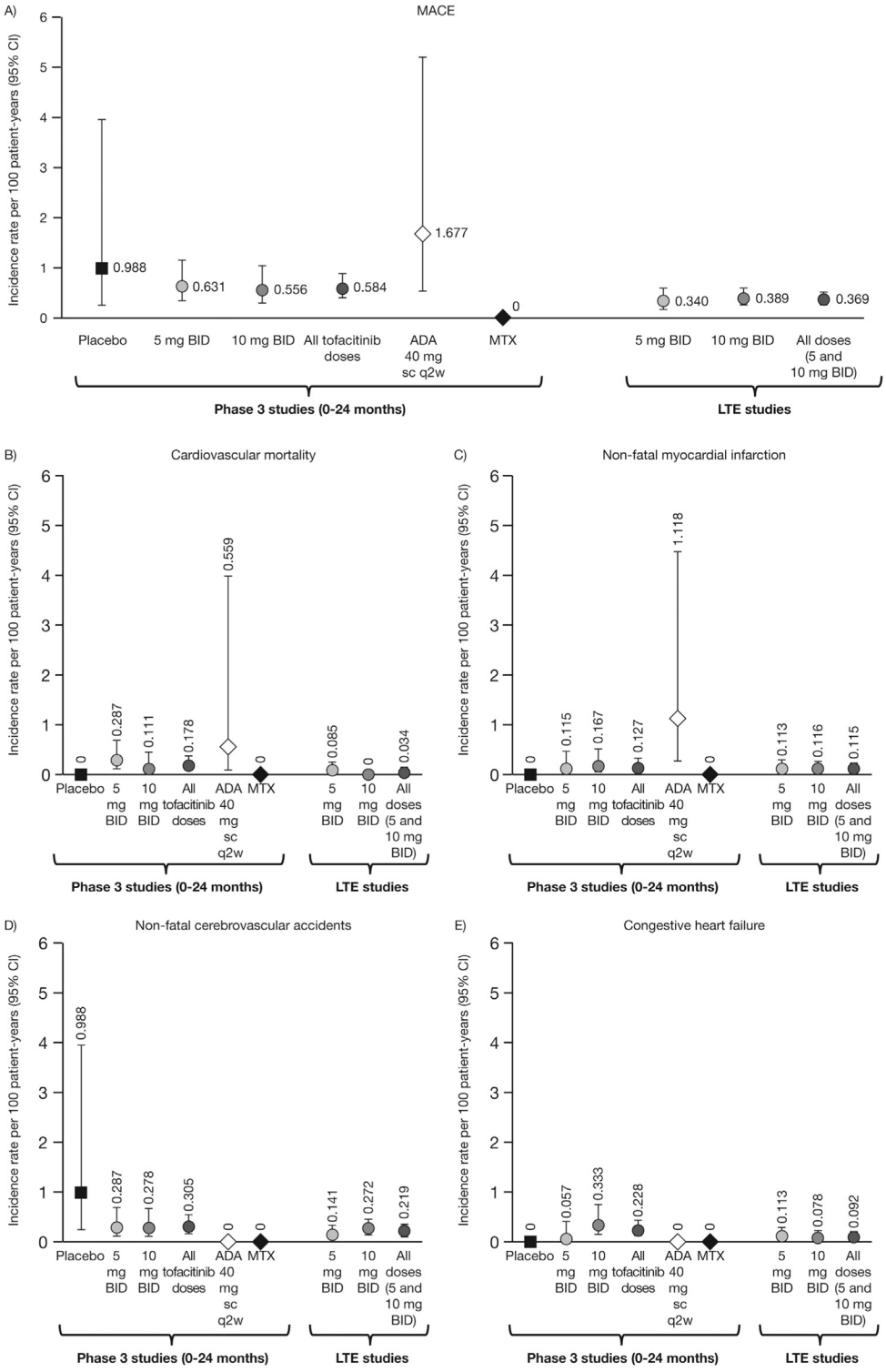
Mean LDL-C, HDL-C, TC, and triglyceride levels were similar across all treatment groups at baseline (Table 3). Mean Apo A-1 ranged from 143.7 mg/dL to 154.9 mg/dL across all treatment groups and mean Apo B-100 ranged from 93.6 mg/dL to 95.3 mg/dL. Mean percentage changes from baseline for LDL-C, HDL-C, TC, and triglycerides were greater for tofacitinib compared with placebo through Months 1–6, adalimumab through Months 1–12 (with the exception of triglycerides at Month 1), and MTX through Months 1–18 (with the exception of LDL-C at Month 1 and HDL-C at Month 15) (Fig. 2A). In patients treated with tofacitinib 5 and 10 mg BID, mean percentage changes from baseline in Apo A-1 were quantitatively similar to mean percentage changes from baseline in HDL-C values, with changes in Apo B-100 similar to LDL-C, but 7–9% lower in magnitude. Mean baseline LDL-C/HDL-C ratios were similar across all treatment groups. Small mean changes in LDL-C/HDL-C ratio occurred for tofacitinib 5 and 10 mg BID and MTX through Month 24, placebo through Month 6, and adalimumab through Month 12 (Fig. 2A).

Table 4
Exposure estimates and incidence rates for adjudicated CV events in Phase 3 and LTE studies

	Phase 3 studies (0–24 Months)						LTE studies		
	Tofacitinib 5 mg BID (N = 1589)	Tofacitinib 10 mg BID (N = 1611)	All tofacitinib doses (N = 3800)	Placebo (N = 681)	Adalimumab 40 mg sc q2w (N = 204)	Methotrexate (N = 186)	Tofacitinib 5 mg BID (N = 1452)	Tofacitinib 10 mg BID (N = 3375)	All doses (5 and 10 mg BID) (N = 4827)
Exposure, pt-yrs	1744	1800	3942	203	179	268	3538	5161	8699
MACE events (n)	11	10	23	2	3	0	12	20	32
Incidence rate per 100 pt-yrs (95% CI)	0.63 (0.35, 1.14)	0.56 (0.30, 1.03)	0.58 (0.39, 0.88)	0.99 (0.25, 3.95)	1.68 (0.54, 5.20)		0.34 (0.19, 0.60)	0.39 (0.25, 0.60)	0.37 (0.26, 0.52)
CV mortality events (n)	5	2	7	0	1	0	3	0	3
Incidence rate per 100 pt-yrs (95% CI)	0.29 (0.12, 0.69)	0.11 (0.03, 0.44)	0.18 (0.09, 0.37)		0.56 (0.08, 3.97)		0.09 (0.03, 0.26)		0.03 (0.01, 0.11)
MI events (n)	2	3	5	0	2	0	4	6	10
Incidence rate per 100 pt-yrs (95% CI)	0.12 (0.03, 0.46)	0.17 (0.05, 0.52)	0.13 (0.05, 0.31)		1.12 (0.28, 4.47)		0.11 (0.04, 0.30)	0.12 (0.05, 0.26)	0.12 (0.06, 0.21)
Cerebrovascular accidents events (n)	5	5	12	2	0	0	5	14	19
Incidence rate per 100 pt-yrs (95% CI)	0.29 (0.12, 0.69)	0.28 (0.17, 0.67)	0.31 (0.17, 0.54)	0.99 (0.25, 3.95)			0.14 (0.06, 0.34)	0.27 (0.16, 0.46)	0.22 (0.14, 0.34)
CHF events (n)			9	0	0	0			8
Incidence rate per 100 pt-yrs (95% CI)	1 0.06 (0.01, 0.41)	6 0.33 (0.15, 0.74)	0.23 (0.12, 0.44)				4 0.11 (0.04, 0.30)	4 0.08 (0.03, 0.21)	0.09 (0.05, 0.18)

In Phase 3 studies, patients randomized to placebo were advanced in a blinded manner to tofacitinib 5 or 10 mg BID at Months 3 or 6. The "All tofacitinib doses" group includes placebo patients who advanced to tofacitinib where applicable. The average total daily dose (TDD) during the LTE studies was calculated by adding all doses received by each patient and dividing by the number of days a dose was received. TDDs of $<$ 15 mg/day and $\geq$ 15 mg/day were categorized as 5 and 10 mg BID groups, respectively.

BID, twice daily; CHF, congestive heart failure; CI, confidence interval; CV, cardiovascular; LTE, long-term extension; MACE, major adverse CV events; MI, myocardial infarction; pt-yrs, patient-years; q2w, once every 2 weeks; sc, subcutaneously.



In Phase 3 studies, patients randomized to placebo were advanced in a blinded manner to tofacitinib 5 or 10 mg BID at Months 3 or 6.
The 'All tofacitinib doses' group includes placebo patients who advanced to tofacitinib where applicable.

The average total daily dose (TDD) during the LTE studies was calculated by adding all doses received by each patient and dividing by the number of days a dose was received. TDDs of <15 mg/day and ≥15 mg/day were included as 5 and 10 mg BID groups, respectively.

ADA, adalimumab; BID, twice daily; CI, confidence interval; CV, cardiovascular; LTE, long-term extension; MTX, methotrexate; q2w, once every 2 weeks; sc, subcutaneously

Fig. 1. Incidence rates for CV events in the Phase 3 and LTE studies.

LTE studies

In the LTE studies, mean baseline LDL-C, HDL-C, TC, and triglyceride levels were consistent with those seen in the Phase 3 studies (Table 3). Mean Apo A-1 values were 148.9 mg/dL for tofacitinib 5 mg BID and 153.1 mg/dL for tofacitinib 10 mg BID. Mean Apo B-100 values were 88.3 mg/dL and 94.4 mg/dL, respectively, for tofacitinib 5 and 10 mg BID. LDL-C, HDL-C, TC, and triglyceride levels in the tofacitinib 5 mg BID group did not

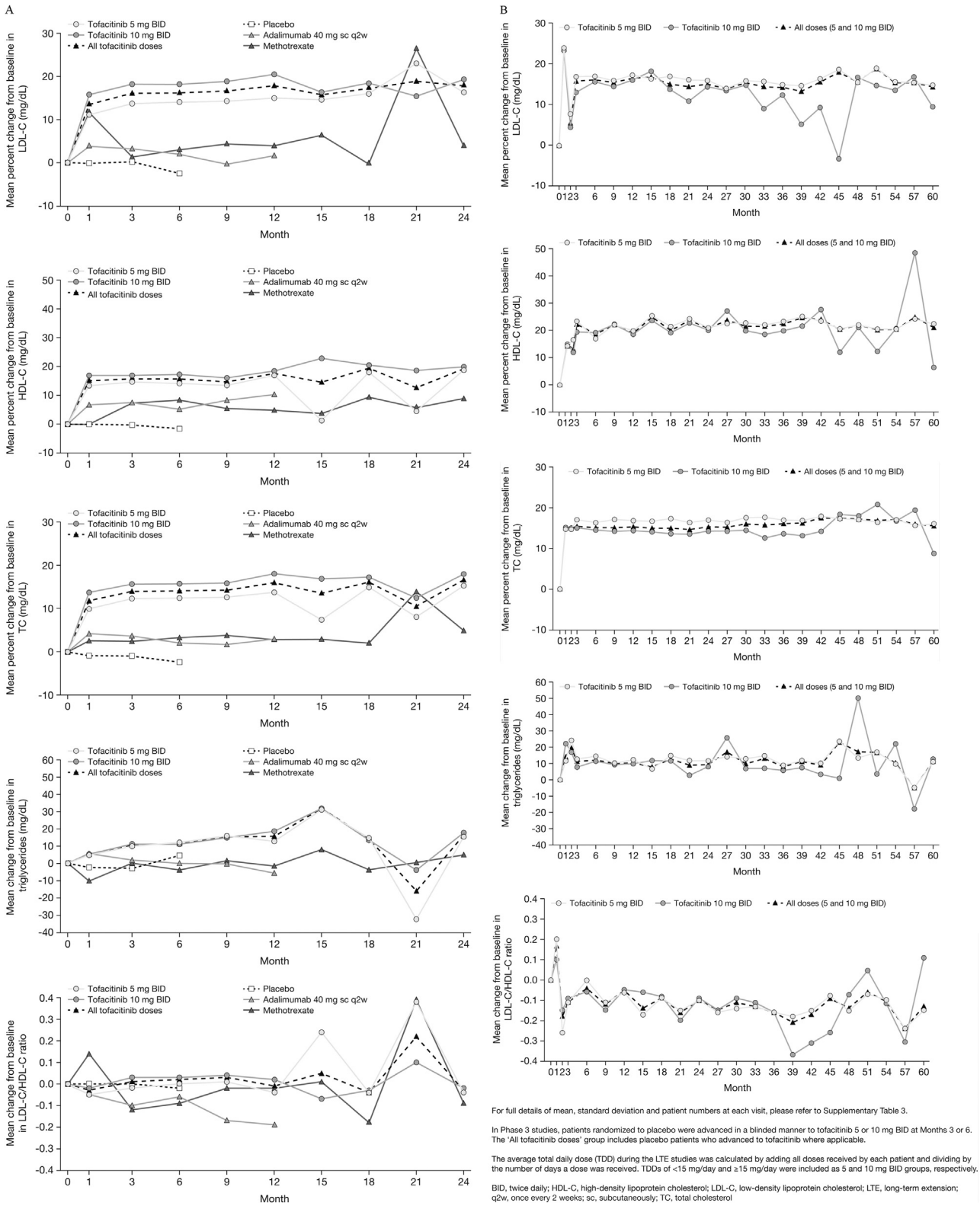


Fig. 2. Mean change from baseline in LDL-C, HDL-C, TC, triglycerides, and LDL-C/HDL-C ratio in the Phase 3 (A) and LTE studies (B).

increase further compared with the Phase 3 studies; a similar pattern was observed in the tofacitinib 10 mg BID group (Fig. 2B). Mean percentage change from baseline in Apo A-1 and Apo B-100 was highly variable for both doses of tofacitinib throughout the LTE studies, with small patient numbers at Months 1, 2, 45, 48, 51, 54, 57, and 60. The LDL-C/HDL-C ratio remained largely unchanged for tofacitinib 5 and 10 mg BID over time (Fig. 2B).

Blood pressure and hypertension

Phase 3 studies

Mean baseline systolic BP (SBP) and mean diastolic BP (DBP) were similar across all treatment groups. SBP changes were small: the mean SBP ranged from 125.6 at baseline to 125.2 at Month 3 for all tofacitinib doses (5 and 10 mg BID) and from 125.5 to 125.6

for placebo. Mean DBP ranged from 78.0 to 78.2 for all tofacitinib doses during the first 3 months and from 78.1 to 77.3 for placebo. Both SBP and DBP remained stable up to 24 months across all treatment groups.

LTE studies

Baseline measurements for SBP and DBP for patients enrolled in the LTE studies were consistent with the Phase 3 pooled data. SBP remained stable over time and ranged from 125.2 at baseline to 124.2 at Month 60 for all tofacitinib doses (5 and 10 mg BID). Mean DBP ranged from 77.8 at baseline to 77.6 at Month 60 for all tofacitinib doses. SBP and DBP remained stable over time in both tofacitinib treatment groups.

Hypertension

Across Phase 3 and LTE studies, approximately the same percentage (17–25%) of patients in the tofacitinib, adalimumab, MTX, and placebo treatment groups who were hypertensive at baseline according to JNC7 criteria continued to meet the criteria for hypertension at each visit (Supplementary Table 1). There were few reports of hypertension-related AEs in the Phase 3 and LTE studies (Table 5). In the Phase 3 studies, the number of investigator-reported AEs of hypertension was slightly higher in

Table 5
Hypertension-related adverse events in Phase 3 studies (A) and LTE studies (B)

(A)

	Tofacitinib 5 mg BID $N = 1589$	Tofacitinib 10 mg BID $N = 1611$	All tofacitinib doses $N = 3200$	Placebo $N = 681$	Adalimumab 40 mg sc q2w $N = 204$	Methotrexate $N = 186$
Up to Month 3, *n* (%)						
Blood pressure diastolic increased	0	1 (0.1)	1 (0.03)	0	0	0
Blood pressure increased	7 (0.4)	6 (0.4)	13 (0.4)	3 (0.4)	0	0
Blood pressure systolic increased	0	1 (0.1)	1 (0.03)	0	0	0
Hypertension	27 (1.7)	43 (2.7)	70 (2.2)	7 (1.0)	0	2 (1.1)
Hypertensive crisis	1 (0.1)	3 (0.2)	4 (0.1)	0	0	0
Total	**35 (2.2)**	**54 (3.4)**	**89 (2.8)**	**10 (1.5)**	**0**	**2 (1.1)**
	$N = 1824$	$N = 1836$	$N = 3660$	$N = 221$	$N = 204$	$N = 186$
Months 3 – 6, *n* (%)						
Retinopathy hypertensive	1 (0.1)	0	1 (0.03)	0	0	0
Blood pressure diastolic increased	0	0	0	1 (0.5)	0	0
Blood pressure increased	2 (0.1)	3 (0.2)	5 (0.1)	0	0	0
Blood pressure systolic increased	0	1 (0.1)	1 (0.03)	0	0	0
Hypertension	22 (1.2)	22 (1.2)	44 (1.2)	1 (0.5)	0	0
Hypertensive crisis	1 (0.1)	0	1 (0.03)	0	0	0
Total	**26 (1.4)**	**26 (1.4)**	**52 (1.4)**	**2 (0.9)**	**0**	**0**
	$N = 1429$	$N = 1443$	$N = 2872$	–	$N = 204$	$N = 186$
> 6 Months, *n* (%)						
Hypertensive cardiomyopathy	0	1 (0.1)	1 (0.03)	–	0	0
Blood pressure increased	6 (0.4)	4 (0.3)	10 (0.3)	–	0	1 (0.5)
Blood pressure systolic increased	1 (0.1)	0	1 (0.03)	–	0	0
Essential hypertension	0	0	0	–	1 (0.5)	0
Hypertension	38 (2.7)	29 (2.0)	67 (2.3)	–	2 (1.0)	1 (0.5)
Hypertensive crisis	1 (0.1)	1 (0.1)	2 (0.1)	–	0	0
Total	**45 (3.1)**	**34 (2.1)**	**79 (2.8)**	**–**	**3 (1.5)**	**2 (1.1)**

(B)

n (%)	Tofacitinib 5 mg BID $N = 1452$	Tofacitinib 10 mg BID $N = 3375$	All doses (5 and 10 mg BID) $N = 4827$
Retinopathy hypertensive	0	1 (0.03)	1 (0.02)
Blood pressure abnormal	0	1 (0.03)	1 (0.02)
Blood pressure diastolic increased	0	3 (0.1)	3 (0.1)
Blood pressure increased	22 (1.5)	34 (1.0)	56 (1.2)
Metabolic syndrome	0	2 (0.1)	2 (0.04)
Hypertensive encephalopathy	1 (0.1)	0	1 (0.02)
Accelerated hypertension	1 (0.1)	1 (0.03)	2 (0.04)
Blood pressure inadequately controlled	0	1 (0.03)	1 (0.02)
Essential hypertension	0	1 (0.03)	1 (0.02)
Hypertension	140 (9.6)	168 (5.0)	308 (6.4)
Hypertensive crisis	5 (0.3)	10 (0.3)	15 (0.3)
Systolic hypertension	0	2 (0.1)	2 (0.04)
Total	**169 (11.6)**	**224 (6.6)**	**393 (8.1)**

In Phase 3 studies, patients randomized to placebo were advanced in a blinded manner to tofacitinib 5 or 10 mg BID at Months 3 or 6. The "All tofacitinib doses" group includes placebo patients who advanced to tofacitinib where applicable.
The average total daily dose (TDD) during the LTE studies was calculated by adding all doses received by each patient and dividing by the number of days a dose was received. TDDs of < 15 mg/day and ≥ 15 mg/day were categorized as 5 and 10 mg BID groups, respectively.
BID, twice daily; LTE, long-term extension; q2w, once every 2 weeks; sc, subcutaneously.

the tofacitinib groups compared with the placebo group through Month 6.

Across Phase 3 and LTE studies, most hypertension-related AEs were graded as mild to moderate in severity by the investigators. Serious adverse events (SAEs) related to hypertension occurred in one patient in the Phase 3 studies [hypertension ($n = 1$)] and resulted in discontinuation from the study. In addition, four patients discontinued from the Phase 3 studies due to hypertension-related AEs [BP increased ($n = 2$), hypertension ($n = 1$), and hypertensive crisis ($n = 1$)]. In the LTE studies, 15 patients reported SAEs of hypertension [hypertension ($n = 8$], accelerated hypertension ($n = 1$), and hypertensive crisis ($n = 6$)] resulting in five discontinuations from the study [hypertensive crisis ($n = 4$); hypertension ($n = 1$)].

Discussion

In the current pooled analyses, which included 3942 patient-years of follow-up in the Phase 3 studies and 8699 patient-years of follow-up in the LTE studies, treatment with tofacitinib 5 or 10 mg BID was associated with a low CV event rate, despite short- and long-term increases in traditional cholesterol levels. Rates of CV events (range of incidence rates per 100 patient-years) for tofacitinib-treated patients, including MI events (0.12–0.17), CHF (0.06–0.33), and cerebrovascular events (0.28–0.29), did not increase with longer treatment duration. These rates were generally similar to rates reported in past RA studies, including studies of RA patients treated with TNFi [1,2,5,6,34–36]. In an observational study of 236 patients with RA, an IR of 3.43/100 patient-years was reported for CV events (CV-related hospitalizations, including MI, stroke or other arterial occlusive events, or arterial revascularization procedures) [6]. In a cohort study of 25,385 residents of British Colombia with RA, IRs of 5.3/1000 patient-years and 14.8/1000 patient-years were reported, respectively, for MI and for all CV events (CV-related hospitalizations, including MI, stroke, or death from CVD) [2]. In another study of 983 patients with RA recruited from a regional register, IRs of 14.0/1000 patient-years and 35.4/1000 patient-years were reported for the first CVD event in patients treated with TNFi (etanercept or infliximab) and for those without prior TNFi treatment, respectively [35]. In the LTE study of tofacitinib, more than 500 patients were treated with tofacitinib for > 3.5 years; and 57 patients were treated for 5 years.

The incidence rates for MACE events in all treatment groups (0.34–1.68) correspond to a 10-year Framingham CV risk of 6 – 10%, which is categorized as low in the general population [37]. Although the incidence rates for CV events were generally similar between treatment groups, the confidence intervals were wide due to the small number of events; therefore, differences between tofacitinib, placebo, adalimumab, and MTX cannot be excluded with certainty. When findings were compared between the Phase 3 and the LTE studies there was no increase in the incidence rate of CV events as a function of treatment duration.

Overall, the results of this study are generally consistent with those observed in other studies of DMARD therapy for RA [38,39]. Systematic literature reviews and meta-analyses of the relationship between MTX and CVD occurrence reported that MTX treatment is associated with a low risk of CVD (21% lower in patients with MTX than in those without) [38] and MI [39]. Recent data indicate that use of TNFi in patients with RA is associated with a decreased risk of CV events [16,17,40,41] and that the risk decreases further with long-term use [41]. In particular, a retrospective cohort study of 2101 patients with RA reported a lower risk of coronary artery disease in patients treated with TNFi versus those with no prior TNFi treatment [41]. Another retrospective cohort study using data from the MarketScan claims database reported that following index prescription, each additional 6 months of TNFi therapy use versus non-use reduced the risk of any CV event by 12% [42]. By contrast, NSAIDs and glucocorticoids are generally considered to impact coronary heart disease risk negatively in patients with RA [43].

Increases in serum LDL-C, HDL-C, and TC were observed within 1–3 months of tofacitinib treatment, were greater compared with placebo, adalimumab and MTX, and stabilized after Month 3; there was little change in LDL-C/HDL-C ratios. Corresponding increases in Apo A-1 and Apo B-100 levels were also noted with tofacitinib. While further studies are in progress, the analysis of the data presented in the current work does not suggest an increase in CV events associated with these lipid changes.

Similar cholesterol increases noted with tofacitinib have also been reported for other DMARD therapies, including tocilizumab [44], and have included simultaneous increases in LDL-C, HDL-C, and TC combined with little or no change in the LDL-C/HDL-C ratio [44–49]. The degree of cholesterol elevations with other DMARD therapies has varied considerably depending on the patient population, treatment response, and trial/study design.

Mean BP levels remained stable over time and there were no changes in the proportion of patients with hypertension as per JNC7 criteria. There were few reports of hypertension-related AEs during the Phase 3 and LTE studies. In the Phase 3 studies, the number of investigator-reported AEs of hypertension was slightly higher in the tofacitinib 5 and 10 mg BID groups compared with the placebo group through Month 6. No AEs related to hypertension were reported in patients treated with adalimumab up to Month 6 but did occur in patients treated with MTX during Months 1–3 and beyond Month 6. Few patients discontinued the studies due to hypertension-related AEs.

For all patients with RA, annual CV risk assessment using national guidelines is recommended [50]; however, current assessment tools and guidelines may underestimate the overall CV risk [51,52]. In this regard, a high frequency of carotid plaques were observed in patients with RA included in the category of moderate CV risk according to the modified EULAR systematic coronary risk evaluation (SCORE) [53]. Previous work has evaluated the effects of tofacitinib on the structural and functional characteristics of lipoproteins in addition to its effects on cholesterol levels [54,55]. These data support a growing body of work [56–58] that suggests the importance of the functional and structural characteristics of lipoproteins as well as levels of cholesterol in the assessment of CV risk.

In summary, the current work suggests a low incidence of CV events and CHF in patients receiving tofacitinib in both Phase 3 and LTE studies despite increases in cholesterol, including LDL-C levels. The CV event rates with tofacitinib were generally similar to those seen for placebo, adalimumab and MTX, and did not increase over time. These data are consistent with previously published CV event rates among patients with RA, including those treated with TNF inhibitors. LTE studies are ongoing and further analyses with longer observational periods are required to confirm these findings. A post-marketing surveillance study (NCT02092467) comparing the safety of tofacitinib versus TNFi with respect to MACE and malignancies is currently underway.

Competing interests

Dr. Charles-Schoeman has served as a consultant for and has received research/grant support from Pfizer Inc.

Dr. Wicker is a former employee of Pfizer Inc. He has received consultancy fees for reviewing the data presented in the manuscript and holds stock in Pfizer Inc.

Dr. Gonzalez-Gay has received consultancy fees from Pfizer Inc. Dr. Mary Boy, Dr. Andrea Zuckerman, Dr. Koshika Soma, Mr. Kenneth Kwok, and Dr. Richard Riese are employees of Pfizer Inc. Dr. Jamie Geier is an employee and shareholder of Pfizer Inc.

Appendix A. Supplementary material

Supplementary data are available in the online version of this article at http://dx.doi.org/10.1016/j.semarthrit.2016.05.014

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